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POINT OF VIEW

Recent perspectives on global epidemiology of asthma in childhood

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Abstract
New research in asthma epidemiology in children includes the development of the ISAAC programme, which has shown large variations globally in the prevalence of asthma symptoms. Time trends in the prevalence of asthma symptoms have shown a mixed picture of increases in low prevalence centres, and a plateau or even a decrease in high prevalence centres. A range of environmental factors have been studied and some potentially protective associations have been found, as well as potentially aggravating factors. Atopy has less influence on the prevalence of symptoms of asthma in low and middle income countries. Breast feeding exerts a protective effect only on non-atopic asthma in non-affluent countries. Future research should explore these areas further.
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Background

What causes asthma is a pressing question, but the answers remain elusive. Until the mid 1980s most studies of asthma had been undertaken within high income countries whose populations originated from the British Isles, and thus the broader distribution of the prevalence of asthma in the world was largely unknown.[1] Studies of the epidemiology of asthma have burgeoned since that time, reflecting world-wide concern that asthma is increasing in prevalence and is an important cause of morbidity not only in developed countries, but also in developing countries.[2] Nevertheless, the hope of identifying factors in populations which influence asthma and are amenable to interventions has not yet been fulfilled. This article summarises some key advances in epidemiological knowledge which have public health and clinical relevance.

The creation of the International Study of Asthma and Allergies in Childhood (ISAAC) was inspired by the fall of the Berlin wall in 1989 which provided a unique opportunity to compare prevalence and time trends of asthma and allergies in Eastern and Western European environments.[3,4] ISAAC also reflected an interest in the comparison of severity of asthma between English language western populations.[3] One of the scientific driving forces behind the ISAAC collaboration was the suspicion that causes of asthma in high prevalence countries might be so widespread that it would be difficult, if not impossible, to detect them by comparisons between individuals within those countries. The accessibility of the cross-sectional design studying children in a defined geographical area, coupled with a

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simple validated tool – a written core questionnaire – made ISAAC Phase One relatively straightforward to complete even in the many centres where this type of research had not been previously been undertaken.[5,6]

The standardised and coordinated approach of ISAAC enabled the collection of comparable data from children throughout the world including non-English language populations, and countries in the developing world.[3,6,7] Phase One of ISAAC represented by far the most extensive international survey of symptoms of asthma, rhinitis and eczema ever performed. ISAAC Phase One involved 700,000 children from 156 centres in 56 countries, reflecting the worldwide concern about these conditions.[8] The main comparisons used symptoms of asthma in the past 12 months self-reported by 13–14 year olds (adolescents) and reported by parents of 6–7 year olds (children). The only other comparable international survey of symptoms of asthma is the European Community Respiratory Health Survey (ECRHS)[9] which studied adults (20–44 years) mainly from European centres which generally yielded similar findings to those of ISAAC.[10]

Global variations in asthma prevalence

Key findings from ISAAC Phase One (1994–1996) included large variations in the worldwide prevalence of symptoms of asthma which were found even among genetically similar populations[8,11] suggesting that environmental factors play an important role.

Further study of the global prevalence and severity of asthma symptoms was undertaken in ISAAC Phase Three, conducted between 2000 and 2003, involving 798,685 adolescents from 233 centres in 97 countries, and 388,811 children from 144 centres in 61 countries.[12] As in ISAAC Phase One, wide variations in prevalence were found around the world. The prevalence of wheeze in the past 12 months in adolescents varied from 32.6% in Wellington (New Zealand) to 0.8% in Tibet (China), and in children from 37.6% in Costa Rica to 2.4% in Jodhpur (India). The prevalence of symptoms of severe asthma (defined as ≥ 4 attacks of wheeze, or ≥ 1 night per week sleep disturbance from wheeze, or wheeze affecting speech in the past 12 months) varied from 16% in Costa Rica to 0.1% in Pune (India) in adolescents, and from 20.3% to 0% in the same two centres in children. The reasons for such wide variations in prevalence are the subject of ongoing research.

Time trends in asthma prevalence

Most centres who undertook ISAAC Phase One repeated the study after at least five years, reflecting the large worldwide interest in time trends of prevalence. For most centres it was the first opportunity to obtain time trends information. Following reports from English language countries in the 1990s of increases in asthma prevalence from the 1980s, continuing increases in prevalence had been expected. However, ISAAC found that in most high prevalence countries, particularly the English language countries, the prevalence of asthma symptoms changed little between Phase One and Phase Three, and even declined in some cases. In contrast, a number of countries that had high or intermediate levels of symptom prevalence in Phase One showed significant increases in prevalence in Phase Three. Examples include Latin American countries such as Costa Rica, Panama, Mexico, Argentina and Chile, and Eastern European countries such as the Ukraine and Romania. Other countries with significant increases in symptom prevalence included Barbados, Tunisia, Morocco and Algeria. With the exception of India, all of the countries with very low symptom prevalence rates in Phase One reported increases in prevalence in Phase Three, although only the increases for Indonesia and China were statistically significant. The percentage of children and adolescents reported to have ever had asthma increased significantly, possibly reflecting greater awareness of this condition and/or changes in diagnostic practice. The increases in asthma symptom prevalence in locations of high population density such as Africa, Latin America and parts of Asia indicate that the global burden of asthma is continuing to rise, and at the same time the global prevalence differences are lessening.

What environmental factors are important?

The central ISAAC approach has been to study symptoms of disease *between* populations, which has naturally led to ecological analyses between symptom prevalence values and potential environmental exposures. As Rose states, "the primary determinants of disease are mainly economic and social, and therefore its remedies must also be economic and social"[13], and this has been the thrust of the ISAAC approach. If the environment of populations is important in the occurrence of asthma, rhinoconjunctivitis and eczema, as the evidence suggests it is, analyses should be at the population environmental level. As Marmot has argued, analyses of individual risk factors may be inappropriate if social environmental causes of illness are sought.[14]

Ecological analyses were therefore undertaken with ISAAC Phase One data to explore environmental factors that may have contributed to these variations by analysing the relationship between asthma symptom prevalence and many factors. Prevalence of symptoms of asthma was positively associated with GNP[15], *trans* fatty acids[16], paracetamol[17], and women smoking[18], and inversely associated with food of plant origin[19], pollen[20], immunisations[21], tuberculosis notifications[22,23], air pollution[24], and men smoking[18]. The magnitude of these associations was small. There were mixed associations with climate[25] and antibiotic sales[26].

The potential role of these associations as causative or protective factors warrants further investigation. Factors which prevent the development of asthma, rhinitis and eczema, or where there is an absence of a positive association at a population level may be as important from a public health policy viewpoint as a focus on the positive risk factors. Interventions based on small associations may have the potential for a large public health benefit[27]. As some risk factors genuinely operate at the population level, either directly causing disease, or by causing disease as effect modifiers or determinants of exposure to individual risk factors, the prediction of the health effects in an exposed population can be of primary importance.

ISAAC Phase Three explored many of these factors further with environmental questionnaires for individuals. To date

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three analyses have been published which have shown that reported paracetamol use in young children[28], truck traffic exposure[29] and antibiotic use[30] are potential risk factors which need further research.

The influence of country income and atopy

The ecological economic analysis undertaken in the ISAAC Phase Three global study of asthma prevalence[12] revealed a significant trend towards a higher prevalence of current wheeze in centres in higher income countries in both age groups, but this trend was reversed for the prevalence of severe symptoms among children with current wheeze, especially in the adolescents. Although asthma symptoms tended to be more prevalent in high income countries, they appeared to be more severe in low and middle income countries.

The influence of country income and its relationship to atopy was also explored in ISAAC Phase Two – a cross-sectional study of random samples of 8 to 12 year old children using standardised methodology. Thirty study centres in 22 countries worldwide participated, and reflected a wide range of living conditions, from rural Africa to urban Europe. The role of atopic sensitisation in determining asthma prevalence in children[31] was explored in ISAAC Phase Two. Although asthma in children is commonly described as an allergic IgE-mediated atopic disease, many children with asthma do not have an atopic constitution[32], and previous epidemiological evidence suggested that only 50% of the adult population with asthma have IgE-mediated disease. Cementing this concept further, the World Allergy Organisation has articulated the distinction between allergic and non-allergic asthma in their recent recommendations on nomenclature[33].

In this ISAAC Phase Two analysis[31] data were derived from parental questionnaires, skin prick tests, and measurements of allergen-specific IgE levels in serum. Economic development was assessed by gross national income per capita (GNI). The prevalence of wheeze in the past 12 months among centres varied from almost zero to about one in 4 children. The fraction of wheeze in the past 12 months attributable to atopic sensitisation ranged from 0% to 94%. Surprisingly, there were no associations between prevalence of current wheeze and atopic sensitisation, and only weak associations between both these measures and GNI. However, the fractions and prevalence of wheeze attributable to skin test reactivity were strongly associated with GNI. In addition, the strength of the association between current wheeze and skin test reactivity, assessed by odds ratio, increased with GNI. Thus the strength of the association between atopic sensitisation and asthma symptoms in children varies greatly between populations and increases with economic development.

In a more recent analysis from ISAAC Phase Two, any breastfeeding was associated with less wheeze in countries of all income levels.[34] However, when the types of wheeze and income of country were explored, breastfeeding was associated only with non-atopic wheeze in low and middle income countries, and showed no protective association for atopic wheeze in countries of all income levels.

Thus it appears that while the relationship between atopy and asthma is important, it may have been overemphasised by the concentration of research studies in high income countries where allergy may be a more important determinant, to the detriment of exploration of the non-allergic mechanisms of asthma. Non-allergic asthma may be a separate entity from allergic asthma and a different set of preventive strategies may be required for this type of asthma.

Further evidence of the relative weakness of the relationship between atopy and asthma was found in ISAAC Phase One. This confirmed a strong correlation between symptoms of asthma and allergic rhinoconjunctivitis, and also atopic eczema.[11] However in this cross-sectional study most children had symptoms of only one condition, and less than one in 10 symptomatic children had symptoms of all three diseases. Some of the observed lack of concurrent symptoms may be explainable by the concept of the ''allergic march'', with eczema occurring in the youngest children, followed by asthma and later by allergic rhinitis, but the lack of overlap even for ''symptoms ever'' was less than expected if the causative mechanism were the same for all three conditions.

In conclusion

The asthma epidemic experienced by developed nations over the last 30 years is now affecting developing countries as they become more urbanised. Many of the world's most populous developing countries are now showing similar increases in prevalence of asthma to those experienced in many developed countries. The size of the increases in prevalence implies a large impact on the health of populations. Environmental factors are the key to explain the variations and changes in asthma prevalence. Some global associations which could be explored by further research are the associations found in the ecological analyses. While a global ecological approach has advantages, it may miss factors of importance within regions[35–37], or combinations of variables within or between regions. Further studies could include randomised controlled trials of putative risk factors such as paracetamol exposure.[28] Examples of rapid environmental and lifestyle changes within whole societies offer potential opportunities for demonstrating the importance of community-wide determinants of ill-health, and provide a rationale for ongoing monitoring of time trends in asthma and allergic diseases in diverse populations.

Future research could study the underlying causes of non-atopic asthma in low and middle income countries with a particular emphasis on urban versus rural prevalence and severity gradients to unravel the environmental risk factors associated with urbanisation and demographic change. Critical research topics might include the impact of diet (mother and child[38]); obesity; indoor pollution (environmental tobacco smoke (ETS) and biomass fuels[39]); outdoor pollution (diesel fumes[29,40]); climate change; acute lower respiratory infections; respiratory syncytial virus; and the role of helminth parasites in allergic diseases. As asthma prevalence is rising in the most populous countries, the necessity of identifying modifiable causes has never been more pressing.

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Conflict of interest

Innes Asher is the Chairperson of The International Study of Asthma and Allergies in Childhood.

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