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Lifestyle Changes and Childhood Asthma

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Abstract In recent decades there have been marked increases in asthma prevalence in Western countries. More recently, asthma prevalence has peaked, or even begun to decline, in Western countries, but many low and middle income countries are now beginning to experience increases in prevalence (although there is no evidence of increases in prevalence in India to date). "Established" risk factors for asthma cannot account for the global prevalence increases, or the international patterns that have been observed, or the recent declines in prevalence in some Western countries. It seems that as a result of the "package" of changes in the intrauterine and infant environment that are occurring with "Westernization", we are seeing an increased susceptibility to the development of asthma and/or allergy. There are a number of elements of this "package" including changes in maternal diet, increased fetal growth, smaller family size, reduced infant infections and increased use of antibiotics and paracetamol, and immunization, all of which have been (inconsistently) associated with an increased risk of childhood asthma, but none of which can alone explain the increases in prevalence. It is likely that the "package" is more than the sum of its parts, and that these social and environmental changes are all pushing the infants' immune systems towards an increased risk of asthma.

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Introduction

Until relatively recently it was widely believed that asthma was an atopic disease caused by allergen exposure. The fundamental etiological mechanism was that allergen exposure, particularly in infancy, produced atopic sensitization and continued exposure resulted in asthma through the development of eosinophilic airways inflammation, bronchial hyper-responsiveness and reversible airflow obstruction. Asthma prevalence was increasing around the world because of changes in lifestyle and domestic building design that were increasing allergen exposure. The solution was therefore clear: to prevent asthma we needed to prevent exposure to allergens [1].

In the past two decades it has become increasingly evident that this picture is, at best, too simplistic [2]. In particular, although there are some clear cases of allergen exposure causing asthma in adults in the occupational environment, overall there is little evidence that allergen exposure is a major primary cause of asthma in children, and even some evidence that allergen exposure early in life may have a protective effect [3]. Furthermore, less than one half of asthma cases are attributable to atopy and/or eosinophilic airways inflammation, and non-allergic or non-eosinophilic airways inflammation may account for the other half [4].

Global Prevalence Patterns

Global comparisons of asthma prevalence have played a major role in this "paradigm shift" in our understanding of asthma that has occurred in the last decade. In particular, the

International Study of Asthma and Allergies in Childhood (ISAAC) [5, 6] has provided, for the first time, a picture of global patterns and time trends of asthma prevalence, and has identified the key phenomena which future research must address and attempt to explain.

Firstly, it has shown a particularly high prevalence of reported asthma symptoms in English-speaking countries, *i.e.,* the British Isles, New Zealand, Australia, the United States and Canada. This appears unlikely to be entirely due to translation problems, since the same pattern was observed with the ISAAC video questionnaire [7].

Secondly, the ISAAC survey showed that centres in Latin America also had particularly high symptom prevalence. This finding is of particular interest in that the Spanish-speaking centres of Latin America showed higher prevalences than Spain itself, in contrast to the general tendency for more affluent countries to have higher prevalence rates.

Thirdly, amongst the non-English-speaking European countries, ISAAC has found a high asthma prevalence in Western Europe, with lower prevalences in Eastern and Southern Europe. For example, there is a clear Northwest-Southeast gradient within Europe, with the highest prevalence in the world being in the United Kingdom, and some of the lowest prevalences in Albania and Greece [7]. The West–east gradient was particularly strong; in particular there was a significantly lower prevalence in the former East Germany than in the former West Germany.

Fourthly, Africa and Asia generally showed relatively low asthma prevalence. In particular, prevalence was low in developing countries such as China and Indonesia whereas more affluent Asian countries such as Singapore and Japan showed relatively high asthma prevalence rates. Perhaps the most striking contrast is between Hong Kong and Guangzhou which are close geographically, and involve the same language and predominant ethnic group; Hong Kong (the more affluent city) had a 12-mo period prevalence of wheeze of 12.4 %, compared with 3.4 % in Guangzhou (the less affluent city) [8]. In India, prevalence is relatively low, with a prevalence of wheezing in the last 12 mo in 13–14 y olds of 6.0 % compared with 8.0 % in the rest of the Asia-Pacific region, 13.8 % globally, 16.8 % in Western Europe, and 32.2 % in the United Kingdom [8].

More recently, the ISAAC study has been repeated after an interval of 5–10 y (ISAAC Phase III) [9], and this showed that asthma prevalence has peaked, and possibly even begun to decline, in Western countries, whereas increases in prevalence are now occurring in many low and middle income countries where prevalence was previously low. For example, prevalence had increased by 0.16 % per year in Africa, 0.32 % per year in Latin America, and 0.07 % per year in the Asia Pacific region, but only 0.02 % per year in the Indian subcontinent, and prevalence had decreased by 0.07 % per year in Western Europe [9]. Few of the studies focusing on time trends in asthma prevalence have studied atopic and non-atopic asthma separately, but the available evidence generally indicates that the global increases in prevalence have occurred for both atopic and non-atopic asthma [10].

"Established" Risk Factors

There is little evidence that the "established" risk factors can account for the global prevalence increases, or the international prevalence patterns that have been observed.

Family history is consistently associated with asthma [11] suggesting a genetic component. Alternatively, part of this association is likely to be due to common environmental factors shared by most family members. In any case, it is clear that *the increases* in asthma prevalence *cannot* be due to genetic factors, since they are occurring too rapidly, and the rapidity of the increases indicates that genetic factors alone are unlikely to account for a substantial proportion of asthma cases [12], although genetic susceptibility to changing environmental exposures may play a role.

Although the importance of atopy as a marker of asthma risk is well-established, in terms of assessing the reasons for the global increases in asthma prevalence, it functions more as an intermediate variable which is relevant to the assessment of causal mechanisms, rather than as a primary causal exposure [13]. In fact, standardised comparisons across populations or time periods show only weak and inconsistent associations between the prevalence of asthma and the prevalence of atopy [2], and as noted above, there is no consistent evidence that the increases in prevalence are predominantly occurring through mechanisms involving atopy. It may be that the consistent associations between atopy and asthma, but the lack of consistent associations between allergen exposure and asthma, occur because allergen exposure is not, in general, a primary cause of asthma [3]. Rather, asthmatics may have a non-specific predisposition to become sensitized to certain aeroallergens, and this may contribute to the development of asthma symptoms, but sensitization would be the consequence rather than the cause of the asthmatic predisposition. In this situation, exposure to specific allergens, such as house dust mite allergen, would not affect the risk of sensitization or asthma; rather it would merely affect which specific allergens susceptible individuals became sensitized to, and therefore which specific allergens provoked exacerbations in current asthmatics.

The global patterns of asthma prevalence are also inconsistent with the hypothesis that air pollution is a major risk factor for the development of asthma. Regions such as China and Eastern Europe where there are some of the highest levels of traditional air pollution such as particulate matter and SO_2 generally have lower asthma prevalence

than the countries of Western Europe and North America, Australia and New Zealand which have lower levels of pollution. For example, a study of the prevalence of asthma and atopy in two areas of West and East Germany [14] found that the life-time prevalence of asthma diagnosed by a doctor, and the prevalence of reported wheezing was similar in the East and West German centres, despite the considerable difference in levels of particulate air pollution. It also appears very unlikely that the international prevalence patterns can be explained by differences in smoking, or occupational exposures [11].

Allergen exposure is the risk factor that has perhaps received the most attention as a possible cause of the global increases in prevalence of asthma and allergies. In particular, it has been suggested that increases in indoor allergen exposures, through changes in lifestyle such as wall-to-wall carpeting, cold water washing, greater time spent indoors watching television, *etc.*, could account for the global increases in asthma prevalence. In fact, the evidence that allergen exposure is a major primary cause of childhood asthma is remarkably weak [3], and there is also relatively little evidence that allergen exposure levels have changed over time. The International Study of Asthma and Allergies in Childhood has consistently found uniformly high levels of asthma prevalence in centres in English-speaking countries, even though there is a wide variation in house dust mite levels across these countries [3]. In geographical areas in which house dust mite exposure is very low or absent, including desert regions and mountainous regions the prevalence of asthma is as high or even higher than that in other areas where house dust mite exposure is high [3].

The Hygiene Hypothesis and the Protective Effects of Farming

So what can explain these global patterns and time trends? The most recent candidate for an explanation is the "hygiene hypothesis". This has been prompted by evidence that overcrowding, unhygienic conditions and larger family size were associated with a lower prevalence of atopy, eczema, hayfever, and asthma [15]. An increase in infections as well as increased exposures to specific microbial agents with strong pro-inflammatory properties such as bacterial endotoxin has been proposed as an explanation for these findings [16]. Although the specific immune mechanisms are not clear, it is believed that microbial exposures may activate innate immune pathways through expression of Toll-like receptors (TLRs) and CD14. These exposures may thereby suppress T-helper-2 (TH2) cell expansion and the development of IgE-antibodies and TH2 dependent diseases, including allergic asthma, hay fever and eczema. It has, therefore, been hypothesized that increased cleanliness, reduced family size, and subsequent decreased exposures to general and infectious microbes in the past few decades could explain the increase in global asthma prevalence.

Consistent with the hygiene hypothesis recent studies have found consistently low prevalences of allergies and asthma in farmers' children both in high income countries such as Canada, the US, Australia, New Zealand and Europe and in low income countries including Mongolia and Southern Africa [17]. These protective effects for allergies and asthma have also been observed in adult farmers [17] despite the increased risks of other respiratory conditions such as COPD, reduced lung function, and farmers' lung.

The observed protective effects of farming on allergies and asthma have been particularly strong for animal contact which may be due to the associated exposures to microorganisms [17] or their components. In fact, a recent study showed that exposure to a wide variety of environmenttal microorganisms as well as exposures to specific fungal and bacterial species explained a substantial fraction of the inverse association between farm upbringing and asthma [18]. Exposures early in life including the prenatal period appear particularly protective, although continued exposure may be required to maintain optimal protection [17]. Consumption of unpasteurised farm milk has also been suggested to play a role [17] and may involve exposures to probiotic bacteria or other currently unidentified non-microbial components in farm milk.

The hygiene hypothesis has gained considerable support from asthma researchers world-wide, and has resulted in new etiologic theories, and inspired basic scientists to develop novel laboratory-based studies. However, despite great enthusiasm and rapid uptake of this new paradigm there is reason for caution [16]. In particular: (i) as noted above, at most one-half of asthma cases appear to be through allergic mechanisms (the mechanisms specifically addressed by the hygiene hypothesis), whereas the global increases in asthma prevalence appear to involve both allergic and non-allergic asthma; (ii) asthma prevalence has begun to decline in some Western countries, but there is no evidence that these countries have become less clean; (iii) there is a high asthma prevalence in Latin American countries [6, 7] which appear unlikely to have lower infection rates or less exposure to microbes than European countries such as Spain or Portugal which share the same language; and (iv) the hygiene hypothesis is generally explained as a protective effect of early exposures resulting in long-lasting health benefits, but recent studies (including studies in farming populations) suggest that exposures throughout life may be important, and that long-term continual exposure may be required to maintain optimal protection [16].

On the other hand, none of these anomalies are fatal for the hygiene hypothesis in general, but only for the very "narrow" version of it in which microbial pressure early in

life protects against atopic asthma by suppressing TH2 (or atopic) immune responses. It is possible that this very specific form of the hygiene hypothesis may be invalid, or at least incomplete, but that a more general version of the hygiene hypothesis is still valid. In particular: 1) the hygiene hypothesis is a very useful model to explain the significant protective effects of farming on asthma and allergies observed in many studies world-wide [19]; 2) the hygiene hypothesis is consistent with findings that pets in the home may protect against allergies and asthma [16]; and 3) many aspects of the hygiene hypothesis can be reproduced in mice models of allergic asthma [16]. However, although the hygiene hypothesis may be a valid explanation for some of the observed differences in asthma prevalence between populations, it is unlikely that the hygiene hypothesis on its own can explain the large asthma prevalence increases observed over the last decades, or the decline in asthma prevalence observed more recently in Western countries. Furthermore, it appears unlikely that the immunologic reactivity expressed in later life is exclusively established in early life as is often assumed in the hygiene hypothesis. As it has been previously noted [12], it is important that we consider the 'forest' of changes that occur with westernisation, as well as the specific 'trees', and that the package of changes that come with westernisation and increased hygiene may increase asthma risk, but not necessarily exclusively through an imbalance of TH_1/TH_2 immunity. New etiological theories of global asthma prevalence are therefore required that are more consistent with the epidemiological evidence and which take into account factors affecting the time trends for both allergic and non-allergic asthma.

In addition to the lifestyle changes discussed above there are several new and emerging risk and protective factors which may have followed a similar time trend as asthma prevalence and/or parallel the international pattern of asthma prevalence. These include changes in diet and paracetamol use, vitamin D levels, and obesity [20]. However, the evidence that these factors play a major role in asthma causation is still weak, and a direct link with asthma has not been well established. Further studies are therefore required to test the robustness of these observations.

Conclusions

In conclusion, until recently most studies had reported that asthma prevalence has increased in recent decades and that the magnitude of the increase had in some cases been substantial. It appears that asthma prevalence has peaked or even begun to decline in Western countries, whereas low and middle income countries are now experiencing increases in prevalence, so that they are heading towards the high prevalence situation that prevails in the West.

However, the "established" risk factors for asthma do not appear to explain the global prevalence patterns and time trends. These risk factors were "discovered" primarily on the basis of clinical studies and case reports of exacerbations in asthma patients. It is natural for physicians and patients to assume that the factors involved in secondary causation may also be important for primary causation. In fact, for most of the "established" risk factors the evidence of primary causation is relatively weak, and risk factors such as allergen exposure do not appear to explain the prevalence patterns and time trends. On the other hand, there is substantial evidence of urban/rural differences in asthma prevalence in low and middle income countries, with prevalence being lower in rural areas, together with evidence from Western countries that growing up on a farm reduces the risk of developing asthma. It seems that as a result of the "package" of changes in the intrauterine and infant environment that are occurring with "Westernization", we are seeing an increased susceptibility to the development of asthma and/or allergy [12]. There are a number of elements of this "package" including changes in maternal diet, increased fetal growth, smaller family size, reduced infant infections and increased use of antibiotics and paracetamol, and immunization, all of which have been (inconsistently) associated with an increased risk of childhood asthma, but none of which can alone explain the increases in prevalence [11]. Thus, it is important that we consider the "forest" of changes that occur with Westernization, as well as doing studies of specific "trees". It is likely that the "package" is more than the sum of its parts, and that these social and environmental changes are all pushing the infants' immune systems in the same direction. To know what that direction is, and which components of the "package" are responsible, requires that better etiologic theories of asthma are developed to replace the hygiene hypothesis, or to incorporate it as a special case.

Conflict of Interest None.

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