Aetiology of asthma

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Abstract

Asthma is complex, heterogeneous disease that is often associated with atopic sensitization in children. Asthma is believed to arise as a result of interactions in early life between environmental exposures and genetic predisposition. Estimates from twin studies suggest that asthma has a high heritable component. Large increases in childhood asthma prevalence were described in the United Kingdom and similar developed countries in the last few decades of the 20th Century. This change was too rapid to be explained by genetic shift and so there has been an intensive search for modifiable environmental factors that are causally related to the development of asthma in children. Although a large number of biologically plausible factors have been suggested, most have only modest effects on disease risk. New technologies to enable the study of genes and environment in relation to disease risk (-omics) may reveal new insights into asthma aetiology that could pave the way for primary prevention.

Keywords asthma; epidemiology; genetics; hypersensitivity; risk factors

Importance of the topic

Asthma is one of the commonest chronic diseases of childhood. An estimated 1.1 million children (1 in 11) in the UK receive current treatment for asthma and healthcare spending is approximately £1 billion (€1.24 billion; $1.60 billion) per annum for asthma in children and adults. Asthma prevalence in UK children started to rise in the early 1970s and increased until the end of the 20th Century following which there has been a plateau or even a fall in prevalence. Sequential cross-sectional studies using identical methods in comparable populations of school-aged children, notably in South Wales and Aberdeen, confirmed a contemporaneous rise in the prevalence of asthma, wheezing, eczema and hay fever. Although diagnostic shift and greater awareness of milder, previously undiagnosed cases, may have accounted for some of the apparent increase in disease prevalence, there was convincing evidence of a true increase. This temporal pattern was mirrored in other high income, industrialized (and largely Anglophone) countries. It was evident that the large change in prevalence (greater than doubling over a relatively short timescale; i.e. around a single generation) could not be explained by genetic shift and was therefore likely to be due to changing environmental exposures. Although many children with asthma will 'outgrow' their symptoms during adolescence, evidence from longitudinal studies of asthma, following children through to young adulthood suggests that the prognosis is less favourable for those with more troublesome symptoms during childhood. In the Melbourne Asthma Study, 40% of children continued to have symptoms by the age of 21 years but in the group with frequent or persistent childhood asthma this proportion rose to 80%, a pattern that was generally maintained to age 42 years. Therefore, there is an imperative to identify aetiological factors for asthma in childhood with the goal of influencing disease inception (primary prevention) or natural history (secondary prevention). This is most likely to be achieved by modifying environmental variables, modifying host responses to environment or a combination of these and the evidence suggests that such interventions need to happen in early life, including fetal development and early infancy, to be most effective.

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Epidemiology of asthma and lessons learnt

What's in a name?

In order to investigate the influence of environment on asthma development, it is best to start before the onset of asthma symptoms. Although some variables that are routinely captured, e.g. air pollution may be monitored at a site proximal to the study area, can be recorded retrospectively, many variables are time sensitive and require direct observation or else rely on retrospective recall by participants, which introduces bias. For example, women may be conscious of an association between smoking and asthma leading mothers of children with asthma to report their smoking habits differently from those whose children do not have asthma. Therefore, a large number of studies seeking clues to the aetiology of asthma have been designed as longitudinal cohort studies. Most have been observational but some have included specific interventions in a sample of the population such as allergen avoidance or dietary manipulations during infancy. This study design can be a powerful way of identifying associations of outcome with putative risk factors in the environment. However, such large epidemiological surveys have encountered difficulties in defining the endpoint, asthma. The majority of readers of this review will be very familiar with asthma presentation in their clinics. In school-aged children the diagnosis is seldom in serious doubt and a diagnosis can be confidently made on the basis of clinical history and symptom pattern, often in the absence of abnormal clinical signs. Supportive evidence from peak expiratory flow monitoring, response to bronchodilator treatment or evidence of allergic sensitization can be helpful but there is no definitive 'gold-standard' test to confirm or refute the diagnosis and certainly none that could be applied to large numbers of subjects in a population-based study. The situation is further complicated by increasing realization that asthma is not a single disease entity with some even calling for the term 'asthma' to be abandoned altogether. Several working definitions of asthma have been developed based on standardized questionnaires, the most common in current usage arising from the International Study of Asthma and Allergies in Childhood (ISAAC). More specificity can be introduced by coupling questionnaire definitions with directly measured indices, such as bronchial hyperresponsiveness, but such measures can be expensive, poorly reproducible and can exist in the absence of a clinical diagnosis of asthma. Therefore, most definitions are founded on parental reports of cardinal symptoms, primarily wheezing. A breakthrough in

understanding the implications of different patterns of wheezing in early childhood came from a longitudinal cohort study in Tucson, AZ. with the recognition that a large proportion of infant wheezing disappears by school age. This description of transient early wheezing defines a syndrome that has little in common with asthma and probably represents an airway developmental abnormality. Other wheezing phenotypes have been defined on the basis of increasingly sophisticated statistical clustering methods or by stratifying classes of wheezing by other characteristics, such as evidence of atopy or identified triggers; viral associated and multi-trigger wheeze. The objectives of discriminating between different phenotypes are fundamentally sound. As will become clear throughout this review, no single factor has been sufficiently strongly associated with asthma to begin to explain the recent rapid increase. Instead, several factors with modest effects have been reported suggesting that specific factors may be more strongly associated with only one endotype of asthma and their effects diluted at population level. Disappointingly, phenotypic sub-classifications have so far not yielded strong evidence of diversity of aetiological factors associated with different phenotypes, although there is emerging evidence that the 'severe asthma' phenotype is a distinct entity that may have specific determinants.

Temporal and geographical changes in asthma prevalence

The ISAAC study has been instrumental in demonstrating geographical variations and temporal changes in asthma prevalence. The study has used carefully constructed methods to identify comparable syndromes of asthma and allergic diseases in widely different settings. Since early reports of high and rising prevalence in rich, industrialized countries, this has levelled off or declined whereas countries with intermediate prevalence have seen continuing increases. Based on these observations, comparisons can be made between lifestyle and environment in areas of high and low asthma prevalence. Alternatively, studying contemporaneous changes in environment in countries where asthma prevalence is changing rapidly, often in concert with moves to a more 'Westernized' lifestyle among the population, may give clues to the major shifts in exposure that accompany increasing asthma prevalence. Of course, this is not a simple matter as lifestyle changes are usually multiple and inter-related, making identification of individual exposures difficult. Additionally, caution needs to be exercised in ascribing changes in two independent variables, asthma and some putative risk factor, to any *causal* relationship between them. Despite these caveats, comparisons have been made and these have yielded interesting findings. A good example of his would be the unique opportunity to examine effects on asthma and allergy prevalence following German reunification in 1990. One of the obvious attractions of this particular situation was the chance to examine changes in environment in a genetically homogenous population. The results showed a strikingly higher rate of allergic diseases in West compared with East Germany and suggested that atopic mechanisms may have been responsible for the higher levels of asthma seen in association with a Westernized lifestyle. Many factors that are prevalent in Western societies have been investigated for possible associations with asthma in epidemiological studies. These include mode of delivery, dietary patterns and specific dietary constituents, air pollutants, tobacco smoke exposure, exposure to xenobiotics, including paracetamol and antibiotics, and the presence of domestic animals in the home. Although many of these have been suggested as risk factors for the development of asthma in childhood, their effect sizes are usually modest, the results are not always replicated and their population attributable risk is small. It seems improbable that the rise in asthma prevalence reported in the last three decades of the 20th Century could be attributed to multiple risk factors changing in the same direction over the same time span, thus leading to a multiplicative effect on disease risk.

The hygiene hypothesis & beyond

One obvious difference that exists between children in resource-poor, developing countries compared with rich, Westernized countries is exposure to infections in childhood. Several studies have suggested apparent protective effects on future development of asthma and allergic disorders following early childhood infection with a variety of organisms, including measles and tuberculosis, in developing countries. In more developed countries, there has been a coincident decline in the incidence of several infectious diseases with a rise in autoimmune disorders, including asthma.

The apparent negative association between infections in early life and the development of asthma and allergic diseases is encapsulated in the hygiene hypothesis. This was postulated by Strachan in 1989 as the explanation for an observed inverse relationship between family size in childhood and hay fever in adult life. The presence of older siblings in the household of young children was reasoned to be associated with increased trafficking of infections into the home. The biological basis for the hygiene hypothesis was founded on the idea of stimulation of Th1-lymphocyte mediated immune responses by frequent infections in early life leading to suppression of Th2 mediated allergic responses. This explanation is not consistent with the concomitant rise in the prevalence Th1 mediated autoimmune diseases that accompanied the asthma epidemic and the concept of Th1—Th2 balance has been developed with greater understanding of regulation of the developing immune system. Despite some inconsistencies in observations supporting aspects of the hygiene hypothesis, there are several strands of evidence that suggest a role for interactions between microbial products and the immune system in the aetiology of asthma and allergy. Studies of rural farming communities in central Europe have reported lower incidence of allergic diseases in children brought up on farms compared with children in rural villages or urban settings. Several aspects of farm living have been investigated in attempts to identify the protective factor. These have included exposure to hay, drinking unpasteurized milk and contact with farm animals. The last of these appears to be an important constituent of the protective effect and has been associated with increased levels of environmental endotoxin, a lipopolysaccharide (LPS) that forms part of Gram-negative bacterial cell walls. Directly measured endotoxin in house dust has been reported to be negatively associated with the risk of developing allergy in childhood. Furthermore, there is evidence of interaction between endotoxin levels in the home and a functional genetic variant of the promoter region of *CD14*, a co-receptor with toll-like receptor 4 (*TLR4*) for LPS and a constituent part of the innate immune

