

Risk factors and epidemiology

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ASTHMA IN EARLY CHILDHOOD appears to result from susceptible individuals being exposed to particular environmental stimuli. In recent years, many individual risk factors have been defined and a large number of environmental factors have been identified. However, many questions relating to each of these risk factors remain, of which the most important are discussed here.

How important are genetic factors in determining susceptibility to asthma?

The increase in asthma prevalence over the past few decades is likely to be due to increased phenotypic expression of underlying genetic susceptibility to asthma. Strong environmental factors, as yet unidentified, are the most plausible explanation for this increase. Increased genetic penetration of asthma (ie, increased expression of the disease by those who have a genetic predisposition) may help researchers to identify the specific genetic changes that predispose to asthma.

Many regions of the human genome have been reported to show linkage to asthma or associated phenotypic features, but no region has been found to be associated with asthma in every study. Similarly, particular alleles of many candidate genes appear to be linked with asthma, but no allele has been shown to be associated with asthma in every population. These genome screen and candidate gene data suggest that no one allele accounts for more than 10% of the overall susceptibility to asthma.¹ Nonetheless, several polymorphisms have produced similar associations in different populations, and the results are biologically plausible and may be important in those populations. At our current state of knowledge, the most important genes implicated in genetic susceptibility to asthma include the genes coding for CD14, β_2 -adrenoreceptor, tumour necrosis factor alpha (TNF- α), and interleukins IL-4R and IL-12.

Few studies have attempted to define the genes that may be important in predisposing to asthma in early childhood. CD14 is most likely to be important, as it has a critical role in early differentiation of T_H1 and T_H2 responses. Recent preliminary data suggest that a CD14 promoter allele is associated with asthma-related phenotype from 8 to 12 years of age, making this the first genotype identified as contributing to the development of asthma at a particular age.²

Susceptibility to asthma may be higher among certain racial groups than others.³ The genetic tendency to produce T_H2 -type inflammatory responses appears to be substan-

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ABSTRACT

What we know

- No one gene is a major cause of asthma.
- Some racial groups are more at risk of asthma than others.
- Early exposure to domestic animals appears to reduce the chance of developing asthma.
- Good hygiene may increase the likelihood of asthma.
- Impaired early airway function predisposes to asthma.

What we need to know

- How do several minor genetic factors combine to increase the risk of asthma in individuals and in population groups?
- Does early exposure to allergens promote sensitisation or tolerance?
- How do viruses precipitate asthma? Can acute asthma be treated by treating viral respiratory infections?
- Does impaired early airway function predispose to asthma throughout childhood?

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tially greater in populations with longstanding ancestry in tropical regions, as evidenced by an increased prevalence of pro-inflammatory alleles in genes with T_H2 activity. Europeans have a lesser tendency to produce such responses, and people who have lived in polar regions for tens of thousands of years have the lowest level of T_H2 -type responses.⁴ These differences in allele prevalence between populations are the likely reason for race being an important risk factor for asthma in children. For example, asthma is about twice as common in African-Americans as European-Americans when all other factors are controlled for.³ Clearly, this genetic risk factor operates independently of the strong environmental factors that contribute to asthma.

Does high exposure to environmental allergens early in life promote sensitivity or tolerance?

For many years, scientists have recognised the lack of convincing evidence that avoidance of allergen exposure reduces the incidence of asthma. Recent data on developmental immunology have highlighted the dilemma of sensitisation versus tolerance. Does increased exposure to allergens early in life promote sensitisation by lowering the threshold to an allergic response, or does it increase tolerance by raising the threshold? Little is known about whether there is a period in the developmental process during which exposure to foreign proteins can promote tolerance and, if so, the age at which this occurs. Intervention studies of allergen avoidance run a reasonable risk of increasing allergic disease.

Why is living with animals good for asthma?

Several studies have shown that the presence of a cat in the family has a protective effect on the development of asthma,⁵ despite cat allergen being a recognised risk factor for provoking asthma symptoms in sensitised individuals. Living in close proximity to farm animals also has a protective effect on the development of asthma in children,⁶ and this finding has been replicated in several studies from a number of countries. A plausible mechanism may be by lipopolysaccharide stimulation producing a T_H1 shift in the balance of T_H1 and T_H2 responses.

Is good hygiene a risk factor for asthma?

The perception that asthma was less common in developing countries led to the "hygiene hypothesis".^{6,7} The problem with this hypothesis is that there are many lines of evidence that do not fit.⁸ The most extensive body of evidence against the hypothesis comes from the ISAAC study,⁹ in which asthma was found to be unexpectedly prevalent in several countries with a relatively low standard of living. In collaboration with Venezuelan colleagues, we have found high levels of pro-inflammatory alleles, IgE and asthma in people living on Coche Island, in the Caribbean, with endemic parasitic disease and poor socioeconomic conditions.¹⁰ Some epidemiological studies have reported associations between increased infection and reduced asthma, but the results are not consistent in all studies.⁷ There is still too little evidence to conclude that good hygiene itself is an important risk factor for the high levels of asthma in affluent or "westernised" societies. Important, unrecognised factors are likely to be responsible for producing high disease levels.

Can change of diet or breastfeeding decrease asthma?

Several studies have suggested that consumption of fish oil reduces the risk of developing asthma in children.¹¹ This has led to the hypothesis that omega-3 fatty acids may be responsible for these observations, and controlled trials are under way to investigate this possibility. Breastfeeding may also be associated with a change in asthma prevalence, but some studies have shown that it decreases the incidence of asthma in the general population, while others have shown that it increases asthma in the offspring of asthmatic mothers.¹²

Are physiological characteristics important risk factors for asthma in children?

Longitudinal studies beginning in infancy have identified physiological factors that predispose to asthma in early life. In the Tucson study,¹³ maximal flow at functional residual capacity ($V'_{max}FRC$) was obtained in 125 infants at a variable age after birth. A low $V'_{max}FRC$ value was found to be a risk factor for wheeze in the first three years of life, but not thereafter. In our longitudinal study,¹⁴ $V'_{max}FRC$ was measured in 253 infants at one month of age and reassessed at six and 12 years of age. We found that early

infant lung function and airway responsiveness both correlated with physiological status and clinical outcome at six years of age. In preliminary analyses of the 192 infants reassessed at 12 years of age, we have found that significant associations remain between the assessments at one month and at 12 years. We have also noted that the lung function of children diagnosed with bronchiolitis in infancy was just as abnormal before they had bronchiolitis as it was at the 12-year follow-up, suggesting that the low lung function found after bronchiolitis in other studies was pre-existing and not related to infection. These studies establish underlying physiology as a risk factor for asthma throughout childhood.

Why are viruses the most important precipitant of acute asthma?

Viral respiratory infections are the most common triggers of acute, severe asthma attacks in people with both non-atopic and atopic asthma, but how viral infections precipitate acute asthma remains unclear.¹⁵ Protection from viral infection is mainly via T_H1 pathways, yet children susceptible to asthma have a T_H2 skew. Understanding the relative balance of T_H1 and T_H2 activity at both the genetic and cellular levels in response to respiratory viral infections may well be fundamental to understanding how control of inflammation is lost and acute asthma develops.

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