

Early predictors of asthma

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A number of recent cohort and cross-sectional studies have contributed substantial knowledge to factors that influence the early development of asthma. Here, we summarize the recent evidence for the role of early life events such as prenatal factors, infections, diet and allergen exposure, and discuss the implications for future preventative strategies. *Curr Opin Allergy Clin Immunol* 2:167–173. © 2002 Lippincott Williams & Wilkins.

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Introduction

Early childhood is thought to be the most critical time for the development of atopy and asthma. For this reason, it is important to have precise information on risk factors that are most influential in early life and that predispose to later airway disease, especially any treatable or modifiable factors that alter immune function, promote airway inflammation, or inhibit normal lung development in early life. This then needs to be followed by the development of potentially effective clinical or public health preventative interventions.

The potentially modifiable predictors identified to date include environmental factors such as allergens, diet, and environmental tobacco smoke. However, non-modifiable factors such as prenatal events and infections, which influence the immune system via the intestine or via the airways, appear to be especially important. In this review, we summarize recent information on early predictors of asthma collected from cohort studies, large cross-sectional studies, and randomized controlled trials in young children. Because the early development of atopy is a strong predictor of later asthma and the development of the two mechanisms cannot be delineated, we have included information for both conditions.

Prenatal factors

Parental atopy and asthma are established factors that approximately double the risk of a child developing asthma. This risk has been further confirmed in five recent studies [1•,2,3•,4,5•]. In addition to inheritance, events during pregnancy may influence later airway disease, as shown in Table 1. In studies 1–3 [1•,6•,7•], early or threatened labour, restricted growth and malposition of the foetus were risk factors for the future development of asthma. In study 3, gestational age greater than 40 weeks compared with less than 36 weeks was a significant risk factor for atopy in adulthood. Although evidence of prenatal effects is accumulating, the mechanisms through which these events could influence the developing lung and lead to the onset of asthma are unclear. It is also unclear how prenatal factors could be altered by any interventions.

In tropical Africa, where the prevalence of wheezing in young children is low by international standards, prenatal factors such as maternal asthma, low levels of IgE at birth and malaria parasites in cord blood were strong risk factors for later asthma (Table 1, study 4) [8•]. The role of malaria in the aetiology of asthma has not been

Table 1. Summary of evidence that pre-natal factors and early signs and symptoms are predictors of asthma

Reference	Study sample	Study design	Predictor	Outcome	Odds ratio and 95% CI (bold type $P < 0.05$)
<i>Prenatal factors</i>					
1. Annessi-Maesano <i>et al.</i> [1•]	Unselected sample	Birth cohort of 4054 children	Pregnancy health complications Child illness in first week Birth weight < 2.5 kg	Asthma at 1–18 years	2.0 (1.5, 2.7) 1.4 (1.0, 2.0) 1.6 (1.1, 2.3)
2. Nafstad <i>et al.</i> [6•]	Unselected sample	Birth cohort of 2531 children	Maternal related complications Uterus-related complications Birth weight > 2.5 kg	Asthma at 4 years	1.5 (0.8, 2.7) 3.0 (1.8, 5.0) 0.7 (0.4, 1.2)
3. Pekkanen <i>et al.</i> [7••]	Unselected sample	Birth cohort of 5192 children	Gestational age ≥ 40 weeks	Atopy at 31 years	1.7 (1.2, 2.3)
4. Sunyer <i>et al.</i> [8••]	Children participating in a trial of iron supplementation and treatment for malaria	Birth cohort of 528 children	Maternal asthma Low cord blood total IgE Malaria parasite in cord blood	Persistent wheeze at 4 years	8.5 (2.7, 26.2) 4.2 (1.2, 14.3) 6.8 (1.8, 24.0)
5. Gilliland <i>et al.</i> [9]	Unselected sample	Cross-sectional study of 5762 children	Maternal smoking in pregnancy	Current asthma at 4–10 years	2.3 (1.3, 4.0)
<i>Early sensitization or symptoms</i>					
6. Illi <i>et al.</i> [2]	Children at risk of developing atopy and controls	Birth cohort of 1314 children	Early atopy and atopy at age 7 years	Current asthma at 7 years	10.1 (3.8, 26.9)
7. Haby <i>et al.</i> [3•]	Unselected sample	Cross-sectional study of 974 children	Atopy to food and inhaled allergens at 3–5 years	Recent asthma at 3–5 years	2.4 (1.5, 3.7)
8. Rhodes <i>et al.</i> [11]	Children at risk of developing asthma and atopy	Birth cohort of 73 children	Atopy to egg or milk in first year Wheeze before age 2 years	Asthma at 22 years	10.7 (2.1, 55.1) 0.3 (0.03, 1.7)

reported previously, although it seems plausible that exposure to infections via cord blood could play a role in determining future immune responses.

The role of maternal smoking in predisposing children to later illness, which has been reported extensively in the past, continues to be re-affirmed (Table 1, study 5) [9].

Early sensitization, symptoms and immune status

To date, there are no screening tests for young children that accurately predict whether asthma will develop at a later time. However, data from a small follow-up study [10] suggested that airway responsiveness in early life is a good predictor of abnormal airway function and lower respiratory symptoms at the age of 6 years. Evidence has been accumulating that symptoms of wheeze in the first 1–3 years of life are a poor predictor of subsequent asthma, but that atopy in early life is a strong predictor of future airway disease (Table 1, studies 6–9) [2,3•,11]. Those three new studies confirmed that early atopy, including cord blood IgE, is a significant predictor of current and future asthma, but that wheeze in the first 2 years of life is not predictive of later asthma [11].

As the immune system undergoes complex changes in early life, it is plausible that adverse encounters at this time could influence the programming of future immune status. In neonates, signals from the environment may

influence the important conversion of T helper cells to either a T helper type 1 or 2 phenotype, each of which produces a different profile of cytokines. Children with a T helper type 2 profile produce cytokines that are associated with allergic asthma [12], and sensitized children produce higher levels of IgE inducing T helper type 2 cytokines in response to stimulation with allergens [13]. The first 6 months of life seem to be a critical window for the initiation of T helper type 1 or 2 immunological responses that can lead to the development of atopy or non-atopy [14].

However, suggestions that increases in the prevalence of asthma have resulted from a shift in T helper type 1–2 profiles as a result of changes in infection rates are contradicted by epidemiological evidence of other immune diseases. For example, other childhood illnesses such as type I diabetes mellitus, which is mediated by T helper type 1 responses, have also increased in prevalence, rather than decreased. It is interesting that, in common with allergic diseases, type 1 diabetes mellitus often begins in early childhood and is most common in first-born children [15].

Infections

Infections are thought to play a fundamental role in the development of asthma. The hygiene hypothesis was generated from epidemiological studies that showed that children born into larger families had less atopy and fewer allergic symptoms. The proposed explanation is

that children in small families are exposed to fewer infections in very early childhood. While the relationship is strong for hay-fever, eczema, positive skin prick tests and circulating IgE, it has been inconsistent for asthma, perhaps because of the inherent problems of defining asthma phenotypes [16].

Studies 1–3 in Table 2 show direct evidence that infections are risk factors for asthma. In study 1, serious respiratory infection in early life was associated with later asthma, although this could be an early expression of developing airway inflammation [3•]. However, in study 2, bacillus Calmette–Guérin vaccination was found to have no influence on later illness [17•]. In study 3, which was a birth cohort study [18••], upper respiratory tract viral infection and repeated runny nose was negatively associated with later asthma, whereas repeated lower respiratory tract infections were positively associated with later asthma. This raises important questions about whether viral and bacterial infections play very different roles in altering the development of the immune system. It is suggested that repeated upper respiratory tract viral infections stimulate the immune system towards a T helper type 1 phenotype, thereby reducing the likelihood of subsequent asthma, but that lower respiratory

tract infections such as pneumonia, bronchiolitis or bronchitis do not have this effect.

It has also been suggested that routine immunization increases the risk of atopy, either by directly changing the course of immune development or by reducing the number of infections in early life. However, evidence that pertussis vaccine is a risk factor for the development of atopy has been inconsistent. Indeed, evidence from the International Study of Asthma and Allergies in Childhood data collected from children in 56 centres worldwide, with a median of approximately 3000 children per centre, showed a moderate negative association between pertussis vaccination and atopic symptoms [19].

Indirect evidence for the role of infections as early predictors of asthma came from studies in which exposure to siblings, day care and a farming lifestyle have been measured (Table 2, studies 4–10) [3•,4,5•,6•,7••,20•,21•]. Although the evidence was not entirely consistent, high parity, day-care attendance and living on a livestock farm generally conferred a protective effect against atopy and asthma. Whereas children who attend day care have a lower rate of development of asthma, they may have more frequent

Table 2. Summary of evidence for infections and vaccinations as predictors of asthma

Reference	Study sample	Study design	Direct evidence for role of infections and vaccination	Outcome	Odds ratio and 95% CI (bold type $P < 0.05$)
1. Haby <i>et al.</i> [3•]	Unselected sample	Cross-sectional study of 974 children aged 3–5 years	Serious respiratory infection < 2 years	Recent asthma	1.9 (1.3, 3.0)
2. Wong <i>et al.</i> [17•]	Unselected sample	Cross sectional study of 3110 children	BCG vaccination at birth	Asthma at 10 years Current wheeze at 10 years	1.2 (0.8, 1.7) 1.2 (0.8, 1.9)
3. Illi <i>et al.</i> [18••]	Children at risk of developing atopy and controls	Birth cohort of 1314 children	≥ 2 viral infections in first year Repeated lower respiratory tract infections in first 3 years	Asthma at 7 years Wheeze at 7 years Asthma at 7 years	0.5 (0.3, 0.9) 0.6 (0.4, 0.9) 3.4 (1.9, 5.9)
Reference	Study sample	Study design	Indirect evidence for role of infections	Outcome	Odds ratio and 95% CI (bold type $P < 0.05$)
4. Nafstad <i>et al.</i> [6•]	Unselected sample	Birth cohort of 2531 children	High parity	Asthma at 4 years	0.5 (0.3, 1.0)
5. Pekkanen <i>et al.</i> [7••]	Unselected sample	Birth cohort of 5192 children	High parity and farmer's child Farmer's child No siblings	Atopy at 31 years Atopy at 31 years Asthma at 31 years Atopy at 31 years Asthma at 31 years	0.5 (0.4, 0.6) 0.5 (0.4, 0.6) 0.7 (0.5, 0.9) 1.8 (1.4, 2.4) 0.9 (0.6, 1.4)
6. Ball <i>et al.</i> [20•]	Unselected sample	Birth cohort of 1035 children	Day care attendance in first year Exposure to other children	Asthma at 6–13 years Wheeze at 2 years Wheeze at 13 years	0.4 (0.2, 1.0) 1.4 (1.1, 1.8) 0.3 (0.2, 0.5)
7. Lanphear <i>et al.</i> [4]	Unselected sample	Cross-sectional study of 8257 children	Day care > 10 h/week	Diagnosed asthma < 6 years	1.6 (1.1, 2.3)
8. Haby <i>et al.</i> [3•]	Unselected sample	Cross-sectional study of 974 children	Three or more older siblings	Recent asthma at 3–5 years	0.2 (0.1, 0.7)
9. Riedler <i>et al.</i> [5•]	Unselected sample	Cross-sectional study of 3504 children	Exposure to stables and farm milk in first year	Asthma at 6–13 years Atopy at 6–13 years	0.1 (0.04, 0.5) 0.3 (0.2, 0.6)
10. Downs <i>et al.</i> [21•]	Unselected sample	Cross-sectional study of 1520 children	Lived on a livestock farm Lived on a crops farm	Recent wheeze at 7–12 years Atopy at 7–12 years Atopy at 7–12 years	0.7 (0.4, 1.0) 0.5 (0.3, 0.7) 0.9 (0.6, 1.5)

wheezing (presumably non-asthmatic) during the pre-school years [20•].

The protective effects associated with living on a farm and consuming farm milk could be explained by different exposures to infections or allergens. Clinical evidence suggested that differences in neonatal gut microflora precede the development of atopy, and that gut microflora may play a crucial role in the development of an atopic versus a non-atopic phenotype [22]. In addition, early exposure to environmental microbial matter and to animal allergens may influence early immune modulation to a T helper type 1 response [5•] with the effects appearing to continue well into adulthood [7••]. In support of this, the effects seem to occur only on livestock farms, with no evidence of a protective effect conferred to children on cropping farms [21•].

This inconsistency and complexity of evidence relating to the role of infections has cast some doubt on the simplistic hygiene hypothesis. However, controlling for confounding is problematical. For example, recent studies showed that atopic mothers tend to have fewer children [23], that high-risk children are more likely to be born into a low-risk environment [24], that day-care centres are low-allergen environments, and that allergy-prone children are at greater risk of having lower respiratory tract infections if they attend child care or have older siblings [25]. These associations may all help to explain the inverse relationship between infections and atopy or allergic symptoms.

Allergens

It is unlikely that allergens could cross the placenta and trigger immune responses before birth, even in mothers exposed to high allergen levels during pregnancy. However, allergen exposure in early infancy is an established risk factor for allergic diseases, with further evidence that exposure to high house dust mite allergen levels predisposes to atopy (Table 3) [26]. On the other hand, the evidence relating to endotoxin exposure is complicated, with exposure appearing to protect against atopic eczema but to predispose to wheezing in early life (Table 3) [27•,28•].

The digestion of food allergens and the inhalation of airborne allergen particles clearly influence the development of sensitization and airway inflammation. Recent evidence shows that persistent atopy develops in early life, initially as a food-related sensitization and subsequently as sensitization to inhalant allergens, and is a strong determinant of asthma in later childhood [29]. Atopy to ingested allergens in the first year of life [11] and sensitization to ingested allergens in early life, leading to sensitization to inhalant allergens in later childhood, are highly predictive of future asthma [2].

This progressive atopic march is thought to be a major causal factor for asthma in a large proportion of children who develop atopy in early childhood. However, an atopic march is not the only developmental path for asthma, with evidence that factors unrelated to atopy are involved in the rising prevalence of early respiratory symptoms [30].

In a recent turn of events, debate has centred on whether high exposure to allergens in very early life protects rather than predisposes to atopy in later life, as shown in studies 4–7 in Table 3. Whereas in some studies early exposure to an allergen source such as a cat appeared to cause tolerance to atopy [31], the evidence from other studies [4,32,33] was contradictory. Reverse causation (that is, asthmatic families avoiding having a cat at home) cannot be excluded in those studies. Much better evidence thus needs to be collected to support the hypothesis that high levels of exposure to allergens in early life can modify the T helper type 1 versus the T helper type 2 response and protect against the development of atopy.

Diet and other environmental exposures

Breastfeeding has been documented as a factor that protects against asthma in many studies, with further evidence accumulating as shown in Table 3, studies 7 and 8 [3•,34]. The possibility that breastfeeding may be detrimental in children of asthmatic mothers has been reported for the first time [34], and will need to be confirmed in further studies before public health messages are devised. The adverse effects of omega-6 fatty acids, parental smoking and gas appliances in the home also continue to be reported (Table 3, studies 8–11) [3•,4,35•,36].

Trials of primary prevention

To date, several randomized controlled trials of the avoidance of allergens and other environmental risk factors as a preventative measure have been conducted or are underway. Also, new ways to reduce allergen exposure significantly continue to be developed [37,38]. In a recent randomized controlled trial (Table 4, study 1) [39••], stringent house dust mite avoidance measures significantly reduced the incidence of severe wheeze but not other symptoms. However, primary outcomes from three prevention trials in progress [39••,40,41•] will not be known until the participants are much older and can have their allergic and asthmatic status measured more reliably.

It has also been suggested that probiotic milk could reduce the incidence of respiratory infections and atopy by modifying the intestinal microflora and their metabolic activities. To be effective, probiotics would need to colonize the intestine and influence T helper type 1 and 2 immune responses [42]. Studies 2 and 3 in Table 4 summarized the results of trials in which probiotics were

Table 3. Summary of evidence that environmental factors are predictors of asthma

Reference	Study sample	Study design	Allergen exposure	Outcome	Odds ratio or *relative risk and 95%CI (bold type $P < 0.05$)
1. Huss <i>et al.</i> [26]	Asthmatic children enrolled in large multicentre clinical trial	Cohort of 1041 children	High level of house dust mite exposure	Atopy at 5–12 years	9.0 (5.4, 15.1)
2. Park <i>et al.</i> [27•]	Children at high risk of developing asthma	Birth cohort of 499 children	High level of endotoxin in house dust	Repeated wheeze at 1 year	1.6 (1.0, 2.4)
3. Gehring <i>et al.</i> [28•]	Unselected sample	Cohort of 1884 term, normal weight neonates	High level of endotoxin from mother's mattress	Atopic eczema at 6 months	0.5 (0.3, 0.9)
4. Nafstad <i>et al.</i> [32]	Unselected sample	Birth cohort of 2531 children	Exposure to pets in early life	Wheeze at 6 months	2.4 (1.4, 4.0)
5. Remes <i>et al.</i> [33]	Unselected sample	Birth cohort of 1246 healthy babies	≥ 2 dogs in house during infancy	Eczema at 0–6 months	0.7 (0.5, 0.9)
			≥ 2 cats in house during in infancy	Asthma at 4 years	0.7 (0.5, 1.0)
				Atopy at 6 years	1.0 (0.6, 1.6)
6. Lanphear <i>et al.</i> [4]	Unselected sample	Cross-sectional study of 8257 children	Dog in household	Diagnosed asthma <6 years	1.6 (1.1, 2.3)
<i>Diet</i>					
7. Wright <i>et al.</i> [34]	Unselected sample	Birth cohort of 1246 infants	Exclusive breastfeeding	Recurrent wheeze <2 years	0.5 (0.2, 0.9)
			Exclusive breastfeeding and maternal asthma	Recurrent wheeze at 6 years	5.7 (2.3, 14.1)
8. Haby <i>et al.</i> [3•]	Unselected sample	Cross-sectional study of 974 children	Breastfed	Recent asthma at 3–5 years	0.4 (0.2, 0.7)
			High intake polyunsaturated fats		2.0 (1.2, 3.6)
9. Bolte <i>et al.</i> [35•]	Unselected sample	Cross-sectional study of 2348 children aged	Polyunsaturated margarine consumption	Atopy at 5–14 years	1.3 (1.0, 1.7)
				Rhinitis symptoms at 5–14 years	1.8 (1.1, 2.8)
<i>Other environmental exposures</i>					
10. Lanphear <i>et al.</i> [4]	Unselected sample	Cross-sectional study of 8257 children	Environmental tobacco smoke	Diagnosed asthma <6 years	1.8 (1.2, 2.6)
			Gas cooking or heating		1.8 (1.0, 3.2)
11. Ponsonby <i>et al.</i> [36]	Unselected sample	Birth cohort study of 498 children	Gas cooking or heating	Atopy	1.7 (1.4, 2.8)*

Table 4. Preventative interventions demonstrated in randomized controlled trials

Reference	Study sample	Study design	Intervention	Outcome	Size of effect odds ratio and 95% CI
1. Custovic <i>et al.</i> [39••]	Babies at high risk of developing asthma	Randomized controlled trial from pregnancy	Stringent house dust mite reduction measures versus no intervention	Eczema	1.1 (0.8, 1.5)
				Wheeze without cold	0.6 (0.3, 1.2)
2. Hatakka <i>et al.</i> [43••]	Healthy children attending day care	Randomized controlled trial in children aged 1–6 years	Milk with or without added probiotics given daily	Severe wheeze	0.2 (0.2, 1.0)
				Lower respiratory infections	0.8 (0.5, 1.1)
3. Kalliomaki <i>et al.</i> [44••]	Babies of mothers with eczema at least in a first degree relative	Randomized controlled trial from birth	Probiotic capsules given to babies and prenatally to mothers versus no intervention	Atopic eczema at 2 years	0.5 (0.3, 0.8)

given in early life [22,43••]. The interventions had an encouraging influence in reducing the rates of both respiratory infections and atopic eczema. The results suggested that four or five mothers and their babies who attend day care need to be treated to prevent one incident case of eczema. The attraction of giving probiotics in milk is that it is a simple intervention to administer and has no adverse side-effects.

Conclusion

The major value of collecting risk factor data is to develop early interventions to prevent asthma from developing in young children. Airway development is largely complete in term babies, but the alveoli develop and multiply until the third year of life and continue to grow into adulthood [44••]. Therefore, interventions that reduce adverse prenatal or early postnatal factors, which

affect alveolar growth or the consequent development of lung function, will reduce the probability of children developing asthma.

To devise preventative strategies, we need a more thorough understanding of the predictors of airway inflammation and the point at which asthma begins to develop. We also need better information to enable clinicians to predict which children would most benefit from early preventative treatment. However, recent studies indicated that the relationship between prenatal events, infections, early exposure to allergens, and the later development of asthma is extremely complex. To improve effectiveness in future trials, we need better information to target the group most at risk. Whether genetic studies will contribute to this remains to be seen. We also need more detailed information about the interactions that obviously occur between the timing of environmental exposures and the priming of the immune system.

At this time, we must continue to test novel preventative methods to establish their efficacy. However, early interventions aimed at altering the balance between T helper type 1 and 2 responses in early childhood may cause more problems than they solve [45]. Although trials of primary prevention are expensive and involve long-term follow-up before effectiveness can be measured, they are the only strategy that can be used to determine whether environmental manipulations, the control of infections, or early treatments can reduce the incidence of asthma in the next generation of children.

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- of special interest
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