

# Is prevention of childhood asthma possible?

## Allergens, infections and animals

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THE RECENT INCREASE in prevalence of asthma and wheeze in children is likely to reflect changes in environmental exposure to allergens. Primary prevention appears to be the most promising means of reducing the burden of asthma. To develop effective prevention strategies, we need to identify potential risk factors, understand how these factors lead to disease, and test specific interventions in prospective studies.

### Risk factors for asthma

Epidemiological studies have implicated a number of risk factors associated with asthma. However, whether these factors actually cause disease or are merely associated with it remains uncertain. To confirm causation requires the use of prospective intervention studies.

In this article, the roles of allergen sensitisation and exposure, infections, farm animal exposure and smoking in the development of asthma are discussed. The roles of breastfeeding and gut flora are discussed elsewhere (*see page S78*<sup>1</sup>).

### Allergen sensitisation and exposure

Cross-sectional studies have suggested that atopic sensitisation is associated with increased prevalence and severity of asthma.<sup>2,3</sup> Sensitisation to house-dust mite (HDM) is strongly associated with childhood asthma,<sup>4</sup> and sensitisation to other allergens (cat, dog, mould) is associated with asthma in some communities.<sup>4</sup> However, a recent cohort study failed to demonstrate a relationship between early indoor allergen exposure and the prevalence of asthma, suggesting that sensitisation to allergen and the development of childhood asthma are determined by independent events.<sup>5</sup> Prospective intervention studies on allergen exposure have demonstrated a reduction in wheezing under one year of age but no effect on later childhood asthma.<sup>6</sup> Application of HDM avoidance measures from birth reduced the incidence of severe wheezing illness in the first year of life but not at age four years. In other words, avoidance of HDM may delay, rather than prevent, the development of asthma. Alternatively, HDM avoidance may prevent asthma in a subgroup of children, such as those who develop wheeze in infancy.

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### ABSTRACT

#### What we know

- Epidemiological studies have identified a number of factors associated with increased incidence of asthma. These include allergen sensitisation and exposure, reduced exposure to infections and to farm animals in early childhood, and maternal smoking.
- These factors may represent "true" risk factors for asthma or may be merely associated factors that do not in themselves cause asthma.
- The "hygiene hypothesis" has been proposed as one mechanism by which infections may protect against asthma.
- Current recommendations for the primary prevention of asthma include exclusive breastfeeding for the first six months of life, avoidance of maternal smoking during pregnancy and infancy, and reducing the levels of house-dust mite in some environments.

#### What we need to know

- What are the mechanisms by which specific risk factors and prevention strategies lead to or protect from asthma?
- How do genetic and environmental factors interact to increase the risk of asthma?

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The issue of pet allergens is more complex. Paradoxically, some cross-sectional studies suggest that increased exposure to cats and dogs may be associated with reduced sensitisation and a lower incidence of pet allergy or asthma.<sup>7,8</sup> However, other studies have not found a protective effect of early exposure to pets on sensitisation or asthma development.<sup>9</sup>

Prospective cohort studies have also produced conflicting findings. Hesselmar et al reported a lower incidence of asthma at age 12–13 years in children exposed to a cat or dog in the first year of life.<sup>10</sup> Remes et al reported reduced frequency of wheeze at 12 years in children with a history of dog exposure in infancy.<sup>11</sup> On the other hand, no protective effect was observed for cat exposure in the Remes study, and Custovic et al failed to show any relationship between pet ownership at birth and the incidence of wheezing at one year.<sup>12</sup> A systematic review concluded that exposure to pets increases the risk of asthma and wheezing in *older* children (> 6 years) but not *younger* children (< 6 years).<sup>13</sup>

The findings for HDM suggest that allergen sensitisation may be an associated factor rather than a direct risk factor for asthma, and that other, "upstream" risk factors may be responsible for both increased sensitisation to allergens and

the onset of asthma. If environmental allergens do not directly determine the development of asthma, allergen avoidance as a primary prevention strategy is unlikely to significantly reduce the incidence of asthma.

The reported protective effect of pet ownership on the development of asthma has generated great interest and warrants further investigation, but it is unlikely that this protective effect is a direct result of allergen exposure. It is more likely that other factors related to pet ownership have an influence on underlying immunoregulation, perhaps along the lines of the "hygiene hypothesis" or through induction of tolerance.

### **Infections — the hygiene hypothesis**

There is an inverse association between infectious burden in early life and the development of atopy and asthma. Children who have frequent respiratory infections and pneumonia have a lower prevalence of asthma.<sup>14,15</sup> In southern Italy, military students who were seropositive for hepatitis A (considered to be an indicator of poor hygiene) had a significantly lower prevalence of allergic sensitisation and atopic diseases (including asthma) than peers with no antibodies to hepatitis A.<sup>16</sup> Such findings suggest that increased exposure to infections in infancy may protect against the development of asthma.

Several investigators have proposed the "hygiene hypothesis" as a mechanism by which these protective effects are produced.<sup>17</sup> The hygiene hypothesis postulates that reduced exposure to environmental influences (such as infections) that produce a  $T_H1$ -type immune response has led to a persistence of "fetal" immune responses that are  $T_H2$ -skewed, and that persistence of  $T_H2$ -type responses has led to increased susceptibility to allergic disease.<sup>18</sup> During early childhood there is a transition from the fetal  $T_H2$  cytokine phenotype to the adult  $T_H1$  cytokine phenotype. The timing of this transition is influenced by both environmental and genetic factors. Microbial exposure is thought to be the major environmental trigger for the maturation of immune responses in the newborn.

There is conflicting evidence on the role of respiratory syncytial virus (RSV) infection in asthma. Long-term follow-up studies suggest that RSV infection is not directly associated with the development of atopic asthma, and that infants who experience recurrent wheezing following RSV infection have an underlying premorbid respiratory abnormality that predisposes them to the development of recurrent wheezing.<sup>19</sup>

### **Exposure to farm animals**

Epidemiological studies suggest that exposure to a farming environment confers protection against atopy and allergic diseases, including asthma.<sup>20</sup> Exposure to farm animals has been the factor most closely linked with these effects. The mechanism for this association is not yet understood, but it may involve either an induction of  $T_H1$ -type responses in line with the hygiene hypothesis, or, alternatively, the induction of immune tolerance.

### **Smoking**

Exposure to cigarette smoke significantly increases the risk of wheezing illness in early childhood, but probably does not increase the risk of atopic asthma later in life.<sup>21-23</sup> In a large prospective study of asthma and wheezing in childhood, maternal smoking was associated with wheezing in the first three years of life, but not with asthma and allergies at six years of age.<sup>21</sup> Maternal smoking during pregnancy is also a risk factor for transient wheezing in infancy that does not proceed to development of asthma.<sup>24</sup>

### **Other issues in prevention**

#### **What is the population at risk?**

Identification of the population at risk is an important aspect of prevention. Given the heterogeneity of childhood asthma, different phenotypes may respond to different interventions. There is evidence that different intervention strategies will be effective in different disease groups.<sup>11</sup> Delineating which strategies are effective in individual patient populations and when they should be implemented for maximum effect will be important.

#### **What is the time frame in which preventive interventions can be effective?**

The development of atopy may already be determined at the time of birth.<sup>25</sup> The subsequent manifestation of allergic disease is likely to be determined by environmental influences in early infancy. This suggests that early intervention may be most effective in prevention of asthma. Nevertheless, it is important to determine the time frame in which preventive strategies can still be effective. Do prevention strategies need to be in place before the onset of allergic sensitisation? Can an intervention prevent the development of asthma if implemented after the onset of other allergic conditions (eg, food allergy, eczema)? Different approaches may be effective at different times during gestation through to early childhood.

#### **What recommendations for prevention can be made now?**

Current evidence supports only a limited number of recommended interventions for the prevention of asthma:

- Breastfeeding for the first six months of life (*see page S78*<sup>1</sup>).
- Avoidance of smoking during pregnancy and during infancy (although it is likely that this would mainly affect transient wheeze in infancy rather than atopic asthma in later childhood).
- Reducing exposure to HDM allergen in environments where HDM levels are high. (However, it is not clear whether this will influence wheezing beyond the first year of life or asthma in later childhood.)

Based on our current knowledge, no firm recommendations can be made regarding pet allergens. There is no clear

evidence that avoidance of pets is either beneficial or detrimental for the development of asthma.

### Where to from here?

Our current knowledge of strategies for primary prevention of asthma remains limited. Breastfeeding for the first 3–6 months of life is the only intervention that has been demonstrated in prospective studies to reduce the incidence of asthma (see page S78<sup>1</sup>). The impact of allergen avoidance on disease prevalence has been disappointing. Other strategies directed at influencing underlying immune mechanisms may be more worthwhile (eg, promoting T<sub>H</sub>1-type responses or inducing tolerance).

We need a more detailed understanding of gene–environment interactions. Individual asthma susceptibility genes may require different environmental interactions for overt manifestation of asthma. That is, different environmental risk factors may operate in different individuals to cause disease. Furthermore, different patient populations may respond differently to specific interventions, based upon genetic differences. The timing and nature of preventive approaches may need to be tailored to specific patient populations.

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