

Seminar

Epidemiology of childhood asthma

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Asthma is a growing medical concern at the end of the 20th century. Better understanding of the pathogenesis of risk factors for this disease has not reduced the prevalence of childhood asthma, which appears to be increasing. This review highlights recent studies of the epidemiology of childhood asthma, risk factors associated with the development and persistence of the illness, and strategies which may contribute to its control.

Definitions and prevalence of childhood asthma

Despite several carefully worded statements during the past decade we do not have a definition of asthma that is applicable to all cases, even in childhood. This difficulty reflects not only the lack of a single biological marker or clinical test for asthma but also the variable expression of symptoms, multiple aetiological factors, heterogeneous responses to treatment, and differing outcomes. Current "definitions" are in fact descriptions of the characteristics of the disease—for example, the 1995 Global Initiative in Asthma definition (panel 1).¹

Different descriptions and outcomes of childhood wheezing were clearly delineated in a longitudinal study of infants born to parents registered in a health maintenance organisation in Tucson, Arizona, USA.² Of 826 children followed up from birth to age 6 years, 49% developed "early", "late", or "persistent" wheezing. The 20% with early transient wheezing (occurring before age 3 and remitting before age 6) had reduced airway calibre in the first year of life. Development of wheezing in these children was strongly correlated with exposure to maternal smoking but not to maternal asthma. In contrast, children whose wheezing began between age 3 and 6 (late wheezers) or those wheezing began before age 3 but persisted to age 6 (persistent wheezers) characteristically had clinical features of atopy, high IgE levels, positive skin tests, and a strong family history of asthma, but did not have reduced lung function in early life. Hence children whose wheezing symptoms abated before age 3 may have a disease of different pathogenesis, with different long-term implications.

Studies of prevalence have relied heavily on questionnaires. Lately these have been supplemented by measurements of pulmonary function and of airway responsiveness to challenge with methacholine, histamine, cold air, or ultrasonically nebulised saline. A definition of asthma permitting comparisons of

Panel 1: 1995 Global Initiative in Asthma definition¹

"Asthma is a chronic inflammatory disorder of the airway in which many cells play a role, in particular mast cells, eosinophils, and T lymphocytes. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and/or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible either spontaneously or with treatment. The inflammation also causes an associated increase in airway responsiveness to a variety of stimuli."

populations in epidemiological studies was proposed by Toelle et al, who reported "current asthma" if the patient had had symptoms (wheezing, chest tightness, recurrent cough) in the previous 12 months and had a positive airway responsiveness test.³ Patients fulfilling these criteria had more symptoms, greater variability in flow rates, more atopy, and required more treatment than those with symptoms but not airway responsiveness or the small group with airway responsiveness and no symptoms.

The International Study of Asthma and Allergies in Childhood (ISAAC), a worldwide study of the prevalence of childhood asthma and respiratory symptoms in the age-groups 6–7 years and 13–14 years, has brought uniformity into data collection, as far as language allows.⁴ Prevalence rates for wheezing among 13–14-year-olds reported from representative countries are shown in panel 2. Phase 2 of ISAAC will include measurements of lung function, airway responsiveness, and atopy which will further help elucidate differences and similarities among populations.

Genetic risk factors

Asthma is a complex genetic disorder with a high population prevalence compared with other genetic pulmonary disorders where mendelian characteristics are much more readily observed (eg, cystic fibrosis). This complexity suggests either polygenic inheritance (more than one gene responsible for the disease in a given individual) or genetic heterogeneity, where different combinations of genes determine asthma in different individuals.

The importance of genetic susceptibility to asthma is highlighted in a retrospective study of 5864 Norwegian twins aged 18–25.⁵ The relative risk of asthma developing among twins whose co-twins had a history of asthma compared with those whose co-twin had not was 17.9 (95% CI 10.3–31.0) for identical twins but only 2.3 (1.2–4.4) for fraternal twins, despite the shared environment. In this study, 75% of the variation in propensity to asthma was explained by genetic effects.

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Panel 2: **Prevalence (%) among 13–14-year-olds for wheezing in previous year, and for wheezing four or more times per year, in representative countries participating in ISAAC**

Country	Wheeze in previous year	Wheeze ≥ 4 /yr
Australia (Adelaide)	29	12
UK (west Sussex)	29	7
New Zealand (Wellington)	28	8
Germany (Bochum)	20	4
Spain (Barcelona)	14	· ·
Norway (Oslo)	13	· ·
Hongkong	12	4
Singapore	10	2

In an intensive search for the “asthma gene” investigators have used atopy and airway responsiveness as surrogate markers of the phenotype of asthma rather than using asthma symptoms. Possible loci of atopy genes have been identified on chromosomes 11q, 14, and 5.⁶ Among children and grandchildren of probands with asthma, serum IgE was strongly correlated in sibling pairs concordant for airway responsiveness, suggesting coinheritance, but airway hyperresponsiveness was not correlated with serum IgE.⁷ The investigators suggested the coexistence of one or more genes on chromosome 5q31 to q33 causing susceptibility to asthma. Other investigators reported transmission of atopy at chromosome 11q only through the maternal line.⁸ Different groups have been unable to confirm some identified “asthma” or “atopy” loci⁹ and the genetic markers for asthma remain to be conclusively identified.

While genetic factors are clearly important in determining the risk of development of asthma, environmental factors are still likely to be the primary determinants of expression of disease. Differences in asthma between urban and rural populations, and studies in migrating populations who develop more airway responsiveness and more atopy when changing environments (eg, Tokelauan Islanders migrating to New Zealand) indicate a dominant role for environmental factors.¹⁰ Similarly the increase in prevalence over the past three decades is much too great to be attributed to genetic variations. However, identification of genetic markers of asthma may allow screening of high-risk children, permitting better targeting of avoidance measures such as reducing exposure to allergens and tobacco smoke. At present the only reliable marker of the “at risk” infant is a parental, especially maternal, history of asthma and atopy.

Environmental risk factors

In utero and neonatal

Several characteristics of pregnancy have been reported to influence the likelihood of development of childhood asthma. Mothers under 20 years old had a 3·5-fold increased risk of having a child with asthma compared with mothers over age 30,¹¹ this being possibly related to lower birthweights and reduced lung function. Among inner city African-American children, those who developed asthma had lower birthweights and their mothers were more likely to have smoked during pregnancy (odds ratio [OR] 2·8) and to have had less weight gain during pregnancy (OR 3·4) and less antenatal care (OR 4·7).¹² Low birthweight and prematurity have been found to be risk factors in some studies but not others. Male sex is a risk factor in most studies.

Maternal smoking during pregnancy is a consistent risk factor for early childhood asthma.^{12–14} In a UK cohort, the smoking of 15 cigarettes or more daily during pregnancy was associated with childhood asthma (OR 1·39)¹³ and among Australian newborn babies lower lung function was independently associated with maternal smoking of more than 10 cigarettes a day during pregnancy.¹⁴

Additional risk factors have been identified in the neonatal period. In the UK national cohort study, the risk of asthma in children was associated with antepartum haemorrhage, early threatened labour, malpresentation of the fetus, the use of opioids in labour, and caesarean section and with neonatal illness in the first week of life.¹⁵

The genetic propensity to allergic responsiveness may be influenced by environmental factors in very early infancy when neonatal T-cells are primed in directions favouring dominance of Th₁ or Th₂ type of T helper cell. The initial priming of the T-cell to respond to allergens probably occurs late in gestation, and early neonatal allergen exposures reinforce the T-cell switching to Th₂, with production of cytokines promoting IgE antibody synthesis which, if persistent, may lead to asthma.¹⁶ Children with maternal allergen exposure who develop a dominance of Th₂ cells and atopy have down-regulated interferon- γ production, which may be the explanation for the development of asthma by allowing Th₂ cytokine predominance and resultant atopy.¹⁷

Recent studies have shown an inverse relation between asthma and response to tuberculin. Those children with a positive tuberculin response to BCG had reduced production of IgE, a Th₁ cytokine profile, and less asthma.¹⁸ Production of Th₂ cells, which release cytokines IL-4 and IL-5 leading to allergic inflammation, probably predisposes the infant to more persistent disease. Interventions to prevent asthma, by stopping the switch to Th₂ or by encouraging Th₁ cell production, might include reduced maternal exposure to allergens, adjuvant stimulation of the infant immune system, and, possibly, allergen-specific immunoprophylaxis early in the course of the disease, rather than when asthma is established. Reduction of neonatal exposures to known allergens is logical, especially since the Th₁/Th₂ switch seems to happen within weeks of birth.¹⁹

Early childhood

Exposure to the housedust mite (*Dermatophagoides pteronyssinus*), development of positive skin tests, and continuing exposure to allergens in early infancy all increase the risk of asthma. In one study of 67 children selected as being at risk because of a family history of atopy all but one of the 17 who developed asthma by age 11 had been exposed to housedust mite at a concentration of *Der* p1 > 10 μ g/g of dust at age one. The age at first wheezing episode was inversely related to the level of exposure at age one, especially in atopic children.²⁰ In another recent study of 1314 newborn babies in Germany, children found to be sensitised to housedust mite or cat allergen during the first 3 years of life had had higher levels of exposure to housedust mite (median 868 *vs* 210 ng/g) and cat (150 *vs* 64 ng/g) allergen concentrations in carpet dust from their home compared with non-sensitised children.²¹ Children with a positive family history required less exposure to develop sensitisation than those with a negative family history.

Panel 3: **Allergen-specific RR (95% CI), adjusted for sensitivity to other allergens, for development of asthma symptoms, airway hyperresponsiveness, and for concurrent symptoms and hyperresponsiveness, compared with non-sensitivity to that particular allergen, among 714 New Zealand children studied longitudinally**

Allergen	Asthma symptoms	Airway hyperresponsiveness	Concurrent symptoms and airway hyperresponsiveness at same age
Rye grass pollen	1.29 (0.86–1.92)	0.96 (0.57–1.62)	1.33 (0.69–2.58)
Housedust mite	1.94 (1.29–2.92)*	4.45 (2.69–7.36)*	6.71 (1.21–13.38)*
Cat fur	2.27 (1.20–4.30)*	2.66 (1.42–4.98)*	4.19 (2.11–8.31)*
<i>Alternaria</i>	0.67 (0.31–1.46)	0.55 (0.22–1.36)	0.78 (0.29–2.13)
Dog fur	1.49 (0.59–3.77)	2.51 (1.04–6.06)*	3.68 (1.43–9.49)*
<i>Cladosporium</i>	1.21 (0.37–3.98)	1.11 (0.38–3.21)	0.71 (0.22–2.34)
<i>Aspergillus fumigatus</i>	7.15 (1.40–36.44)*	6.63 (1.79–24.49)*	13.76 (3.19–59.45)*

Source: from data in ref 27. *RRs significant when CI excludes unity.

In an interesting report from the Tucson study, children who had a lower-respiratory-tract infection without wheezing in the first 3 years of life had lower serum IgE levels months and even years after the incident, whereas in those in whom it was measured, IgE levels before the non-wheezing lower-respiratory-tract infections were normal. The prevalence of positive skin tests was lower in children with a non-wheezing lower respiratory infection than in children who did not have such an infection in the first 3 years.²² This suggests the immune response to a viral infection may influence the pattern of response to subsequent allergic stimulation, and that view is supported by the finding that interferon- γ production by peripheral blood mononuclear cells was higher in children who had a non-wheezing lower-respiratory-tract infection.

Maternal smoking has been held responsible for 380 000 excess cases of childhood asthma and wheezing among US children, or 7.5% of all symptomatic children.²³ The OR for children of smokers having wheezing illness was 1.36, and it was higher in children under the age of 2. The effect of maternal smoking is almost always reported to be greater than that of paternal smoking. Environmental tobacco smoke exposure is associated with increased wheezing, airway responsiveness, morbidity, the need for treatment, and the likelihood of allergen sensitisation.²⁴ However, in the Tucson study parental smoking was primarily a risk factor for childhood cough without wheezing, while male sex, maternal allergy, wheezing, lower-respiratory-tract illnesses and high IgE levels were risk factors for cough with wheezing.²⁵

The influence of family income has been debated. While children from poorer families may have a higher prevalence of wheezing, children from better-off families are more likely to receive a diagnosis of asthma and treatment for asthma, reflecting different levels of access to health care. The higher prevalence of childhood wheezing in low-income groups may be confounded by parental smoking.

Attendance at day care increased the OR for lower-respiratory-tract illnesses from 1.36 to 2.0, and a history of parental asthma increased the rate even further. Day-care attendance was associated with a three-fold risk in wheezing illness in children under 2 years of age.²⁶

Later childhood and adolescence

Several cross-sectional and longitudinal studies have examined the characteristics of asthma in schoolchildren. Asthma is consistently strongly related to atopy, especially to housedust mite and pets, notably cats. In New Zealand housedust mite and cat sensitivity were the

strongest risk factors for symptoms suggesting asthma and/or airway hyperresponsiveness²⁷ (panel 3). In Australia the risk of housedust mite sensitised children having current asthma doubled with every doubling of *Der* p1 levels in their environment.²⁸

In a longitudinal study in Danish children aged 7–17, the prevalence of atopy to housedust mite increased from 14% to 26% over 6 years. Among those with no symptoms in 1986 risk factors for developing asthma by 1992 were asymptomatic airway hyperresponsiveness (OR 3.8), positive housedust mite skin test (OR 2.6), wheezy bronchitis before age 2 (OR 3.8), and rhinitis or eczema (OR 2.8). No relation between asthma and active or passive smoking was found.²⁹ Among German and Austrian children studied on four occasions 1 year apart, housedust mite sensitisation was a risk factor not only for prevalence and persistence of asthma symptoms but also for new asthma (OR 2.3), as was parental atopy (OR 2.1). On the other hand, sensitivity to animal dander, the presence of hayfever or eczema, a low gestational age, and male sex all increased the risk of persistence of childhood asthma but not of development of new asthma.³⁰

Although air pollution has been proposed as increasing the risk of childhood asthma strong supportive data are lacking. On the contrary, studies comparing children in former East and West Germany have suggested that lifestyle factors have led to significantly higher rates of allergy and asthma in West German children than has air pollution in East Germany, which is associated more with symptoms of chronic bronchitis. Questionnaire surveys and cold-air challenges in children age 9–11 revealed more airway hyperresponsiveness in the west but more bronchitis in the east.³¹ When sensitisation to housedust mite, cats, and pollens was taken into account, region of residence was no longer significant in determining prevalence of asthma. Indoor air pollution from coal burning does not seem to be a risk factor. In 9–11-year-old children in Bavaria, Germany, the presence of coal fires in the home reduced risks of atopy, hayfever, and airway hyperresponsiveness compared with other forms of heating.³²

Cultural differences, including diet, can influence childhood asthma. Among 8–11-year-old British children of white and Asian descent, white children had higher risks of airway hyperresponsiveness but a lower risk of atopy.³³ Asian children eating a fully Asian diet had an OR for airway responsiveness of 0.31, compared with 0.88 among those eating a mostly Asian diet, and 0.99 among those eating a mixed Asian and English diet. The ORs for atopy for these three groups were, respectively, 1.22, 1.47, and 1.78. Among Australian children

increased consumption of oily fish containing greater than 2% fat was associated with a reduced OR for asthma (0.26 [0.09–0.72]).³⁴

The influence of environmental tobacco smoke in mid-childhood is less strong than it is in infancy. Increased exacerbations of asthma were noted in children exposed to passive smoking, urinary cotinine being the marker of exposure.³⁵ A dose-response has been described, with a 14% increase in childhood wheezy bronchitis when the mother smoked more than four cigarettes per day but a 49% increase when smoking exceeded 14 cigarettes daily.³⁶ Children with wheezing who were exposed to environmental tobacco smoke through childhood showed progressive impairment of lung function between ages 9 and 15 whereas lung function returned towards normal in wheezing children not exposed.³⁷ A relation between smoking and allergy has been postulated. Children with atopic dermatitis were more at risk for asthma if the mother smoked, whereas children without dermatitis were not influenced by parental smoking.³⁸

Natural history

Studies of outcome in childhood asthma can be grouped according to selection of the initial population. Follow-up of patients seen in private practice or in asthma clinics linked with a major hospital show significantly poorer outcomes than do longitudinal studies of general populations, reflecting the more severe asthma of children referred to hospital or a specialist. Among children seen at a university hospital asthma clinic in Gröningen, Netherlands, 43% still had symptoms 16 years later. Predictors of adult asthma were a low forced expiratory volume in 1 s (FEV₁) in children and airway hyperresponsiveness, with a clear relationship between degree of responsiveness and persistence of asthma. Of those with PC₁₀ histamine (concentration of histamine causing 10% reduction in FEV₁) below 2 mg/mL 65% had symptoms as adults, compared with 40% of those with a PC₁₀ of 2–8 mg/mL and 33% of those with a PC₁₀ above 8 mg/mL.³⁹ In Copenhagen, Denmark 70 of 85 children aged 5–15 years were followed up 10–12 years later.⁴⁰ Despite improvement in lung function and less severe symptoms 86% had had symptoms within the previous 12 months as adults and most required treatment. Blair⁴¹ reviewed 267 children initially seen in his UK general practice at age less than 12. 20 years later only 28% were symptom-free, 24% had minimal symptoms, 27% had had remission for more than three years but had relapsed as adults, while 21% had had no remission lasting more than 6 months.

Longitudinal population studies have been conducted over periods from 6 to 28 years. In Tasmania, Australia, 8600 7-year-old children were assessed by questionnaire and spirometry in 1968 and a representative sample of this cohort was reviewed at age 29–32.⁴² Among those with reported asthma at age 7 only 26% were symptomatic as adults. Current asthma in adulthood was associated with a later age of onset, more frequent attacks, and a greater number of attacks. Significant risk factors for persistence of asthma into adulthood included female sex, eczema, low lung function, and maternal or paternal asthma, and a personal history of childhood asthma.

In a 28-year follow-up in Melbourne, Australia, children aged 7 were reviewed every 7 years, with 86% retention of the cohort at age 35.⁴³ Of the original,

randomly selected population cohort, 50% of those with childhood wheezing symptoms were asymptomatic at age 35, 15% had infrequent symptoms (wheezing in the previous three years but not in the previous three months), and 20% persistent symptoms (at least once per week in the previous three months). There was a higher rate of persistence among those who had been given the label of asthma at age 7, only 30% of whom were symptom-free, while 20% had infrequent symptoms, 18% frequent, and 32% persistent symptoms. Risk factors for persistence of asthma to age 35 included multiple episodes before the age of two years, the presence of eczema, atopy, and a low FEV₁, but not the age of onset of symptoms.

These and other longitudinal studies indicate that children with mild disease generally outgrow their asthma, whereas those with more severe disease, more marked airway hyperresponsiveness, greater degree of atopy, and a family history of atopy and asthma tend to have persistent disease.⁴⁴ Although childhood asthma is more common among boys persistence is more common in females.

Increasing prevalence

Studies in the same populations over time suggest that the prevalence of both wheezing and diagnosed asthma has increased. In Aberdeen, UK, 7-year-old children were studied in 1964 and again in 1989, during which interval the prevalence of wheezing had doubled from 10% to 20% and diagnosed asthma had risen from 4% to 10%.⁴⁵ The prevalence of hayfever and eczema had approximately doubled, suggesting the increase in asthma and wheezing resulted from increased atopy in the childhood population. There was a greater tendency to label wheezing as asthma in the 1989 survey, a strong reason for comparing wheezing symptoms rather than diagnosed asthma in longitudinal or repeated studies. Of more than 20 sequential studies, none have shown a decrease in asthma prevalence with time.

The reasons for this increase in asthma and atopy have been debated.⁴⁶ Lifestyle changes, with increased atopy related to increased exposure or allergen load, perhaps influenced by air pollution and exposure to environmental tobacco smoke, have been a major focus of attention. Loss of protection against development of atopy (eg, by reduced breast feeding, lower antioxidant intake, or increased salt intake) has also been postulated. A lower frequency or severity of early childhood infections may have a role too; the reduced stimulus to Th₁ cytokine production leads to dominance of the pro-inflammatory Th₂ cytokines involved in asthma.

Prevention

Several messages from the above studies point to recommendations that might decrease the burden of illness from asthma. Reduction in exposure to allergens, especially in the early months after birth and even in utero, may favourably alter the Th₁/Th₂ priming of the immune system influencing IgE production, and thus reduce the risk of allergic sensitisation, especially in children at high risk because of a family history. Exposure to environmental tobacco smoke in utero and after birth is a significant risk factor for development of wheezing, for persistence of wheezing, and for worsening lung function in childhood asthma. Continued avoidance

of allergen exposure during childhood may reduce the incidence of asthma on mid-childhood and changes in antioxidant intake are now being studied. The role of viral and other infections on the immune system and the possibility of "vaccinating" against asthma are intriguing research questions.

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Further reading

Definitions and prevalence of asthma

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