Paediatric origins of adult lung disease • 6

Series editors: P Sly, S Stick

Paediatric origins of adult lung disease

E von Mutius

There is substantial evidence that morbidity due to asthma is on the increase in western affluent countries.¹ The increases in the prevalence of asthma have, however, only been reported in children and young adults, whereas no major increase in the prevalence of asthma has been found in adults. In an Australian study investigating the time trends from 1982 to 1992, a doubling both in the prevalence of wheeze and airway hyperresponsiveness was seen in children.² In contrast, in a similar survey of adults from 1981 to 1990 the prevalence of recent wheeze increased only in subjects under 30 years of age.³ Moreover, the prevalence of airway hyperresponsiveness had not increased at all, even among atopic adults. The prevalence of asthma and airway hyperresponsiveness was higher in Australian children than in adults, and the severity of airway responsiveness was higher in atopic children than in atopic adults. Likewise, Yunginger and colleagues in the USA performed a study using a population based computer linked medical diagnosis system to identify individual medical records with diagnoses of asthma.⁴ These authors found an increase in the incidence of asthma between 1964 and 1983 which was entirely accounted for by increased incidence rates in children and adolescents aged 1–14 years.

These observations point towards the importance of childhood years for the development of asthma. In fact, Yunginger and colleagues showed that incidence rates were highest in infants of less than one year of age, particularly in boys. Between one and four years of age the incidence rates decreased, but were still much higher than in older age groups.

The development of wheezing illnesses follows a certain pattern over the childhood years. In a prospective, longitudinal, population based survey, the Tucson Children's Respiratory Study in the USA, wheeze was reported at some time from birth up to the age of six years in about half of a random sample of children enrolled as newborn infants.⁵ European population studies estimated somewhat lower numbers of 15–32% of children wheezing in the first five years of life.^{6,7} Different patterns of wheezing phenotypes emerged from these surveys. A significant proportion of children start wheezing early in life but usually have no reports of wheezing at six years of age or later.⁵ This form of wheezing was associated

with a good prognosis and showed no association with a parental history of asthma, with atopic symptoms, or with the production of IgE in the child. In turn, a significant reduction in pulmonary function soon after birth before any wheezing illness had occurred was found in this group of infants. These results suggest that smaller airway calibre or other abnormalities of airway size and lung tissue predispose some infants to the development of wheezing illnesses early in life.

In many infants wheezing episodes early in life are, however, related to a predisposition to develop asthma in later childhood. In the Tucson cohort a subgroup of children showed recurrent episodes of wheeze from birth up to the age of six years.⁵ These infants had normal lung function and cord-serum IgE levels postnatally, but had developed significantly higher IgE levels at nine months of age and atopic sensitisation to a panel of aeroallergens at the age of six years. This condition was furthermore associated with a parental history of asthma and the occurrence of eczema in the child. In this group, pulmonary function was within normal limits in the first year of life but decreased by the age of six years. More boys than girls were affected.

The distinction between these two groups is not only relevant for the detection of individual risk factors related to different wheezing phenotypes in epidemiological surveys, but seems particularly important for the management of these infants. In clinical practice, however, the unequivocal separation of transient from persistent wheeze in the first years of life is only partly achieved by using criteria such as those proposed through findings of epidemiological studies—that is, a family history of asthma and early signs of atopy in the child. Several authors have therefore sought early markers of wheezing outcomes. Martinez and colleagues observed that the acute immune response of infants with persistent wheezing differs from that of children with transient wheeze.⁸ During the acute phase of wheezing lower respiratory tract illnesses, children who will eventually continue to wheeze had significant increases in total serum IgE. Such a reaction was not observed in transient wheezers or in those who had non-wheezing lower respiratory tract illnesses.

Furthermore, the persistent wheezers differed from both other groups in their eosin-

University Children's
Hospital, Munich,
Germany
E von Mutius

Correspondence to:
Dr E von Mutius, Dr von
Haunersche Kinderklinik,
Klinikum Innenstadt,
Lindwurmstrasse 4, D-80337
München, Germany
erika.von.mutius@
ll-i.med.uni-muenchen.de

nophilic response to acute infectious episodes. While normal infants respond with eosinopenia to acute infectious episodes, the children with continuing wheezing did not show any changes in their eosinophil counts. Not only eosinophils, but also their product, eosinophil cationic protein (ECP), assessed in the serum may indicate the prognosis of wheezy infants. Recent studies have suggested that circulating levels of ECP at the time of an acute wheezing episode are significantly higher in infants who will go on to develop recurrent wheezing than in those whose wheezing episodes will remit with time.^{9, 10} In the study by Villa and colleagues⁹ the probability of continuing wheezing two years after an initial visit at age 2–4 was almost three times greater in children with ECP values >20 µg/l (OR 2.9; 95% CI 1.4 to 5.9, $p < 0.001$). Whether measurements of soluble interleukin (IL)-2 receptor have a similar predictive value remains to be seen.¹¹

Early origins of asthma

In childhood a strong link has been found between atopic sensitisation and asthma. In clinical studies most asthmatic children are atopic.¹² The strength of this association may, however, be attributable to population selection whereby more severe asthmatics, usually followed in tertiary referral centres, may tend to be more atopic than other children with asthma. On a population level a significant link between childhood asthma and atopy is still seen.¹³ When comparing prevalences of asthma and atopy over different areas worldwide, however, a wide range of distributions and associations is found.¹⁴ In some regions such as China the prevalence of atopy is as high as 40%, whereas the occurrence of asthma is exceedingly low. In other areas such as Australia and the USA both asthma and skin test reactivity are in the highest quartiles of the distribution. These observations indicate that the association between atopy and asthma may not be as strong as clinical studies have suggested. Earlier reports have, in fact, estimated that only about one third of asthma is attributable to atopy.¹⁵

In many studies sensitisation to mites has been implicated as the most potent risk factor for the development of childhood asthma.^{16–18} Others, however, have found that sensitisation to other allergens such as cats, dogs, cockroaches, or moulds is similarly associated with asthma and bronchial hyperresponsiveness (BHR).^{18–20} Australian investigators¹⁸ studied the relation between atopy, asthma and BHR in three populations of children living in different climatic areas of the country. Each study area was characterised by different exposure levels to house dust mites and moulds, respectively. The associations between sensitisation to each of these allergens, BHR, and asthma differed in each area and were strongest for the locally most prevalent allergen.

The type of allergic sensitisation is, however, not the only characteristic link between atopy and asthma. The age of onset of atopic sensitisation also relates to both conditions. Peat and colleagues have reported that only early

atopy—defined as sensitisation to any allergen before the age of eight years—was associated with the prevalence of wheeze and asthma, whereas atopy developing thereafter was only related to hay fever but not to wheeze.¹³

To understand these relations better it is also important to consider the natural course of atopy which equally has a distinct pattern over childhood years. Sensitisation to food allergens develops first and is followed by the development of sensitivity towards inhalant allergens.²¹ As with wheezing illnesses, atopy may be a transient phenomenon vanishing around the second to third birthday. It may be clinically manifest as atopic dermatitis related to food allergy but will not result in an increased risk of inhalant allergy and asthma at school age. However, persistent sensitisation developing early in life as food related IgE production and continuing as sensitisation towards inhalant allergens is a strong determinant of asthma.²² The early incidence of atopy is probably part of this characteristic pattern. In the MAS study twice as many children who, at the age of seven years, were diagnosed as having asthma or who presented with airway hyperresponsiveness had measurable IgE antibodies towards food allergens at the age of one year compared with non-asthmatic children.²³ These findings suggest that some common underlying process may determine both the timing of sensitisation and the incidence of asthma. Risk factors for the development of asthma may therefore also result in an earlier onset of IgE production towards environmental allergens, most probably towards food allergens.

It seems unlikely that environmental exposure to allergens, mostly food allergens in the first years of life, may activate such underlying predisposition. Rather, factors which impair or induce the maturation of the immune system and which early in life may also involve lymphatic structures in the gastrointestinal tract may determine the development of asthma. There is also no convincing evidence that exposure to house dust mite or cat allergens is a causal factor for the development of childhood asthma. This notion is supported by the results of two surveys investigating the prevalence of asthma in children raised in mite-free environments.^{24, 25} In both studies asthma was no less common in non-exposed children than in their peers brought up in mite infested areas. Furthermore, recent studies suggest that exposure to cats and dogs early in life is inversely related to the development of asthma.^{26, 27} Once atopic sensitisation and asthma are manifest, however, exposure to allergens may well aggravate symptoms and contribute to the progression of the disease.

If it is correct that the level of allergen exposure is not a major determinant in the development of childhood asthma, why is it that atopic sensitisation to hen's eggs and house dust mites is so strongly associated with asthma? Factors that influence the early development of an immune response skewed towards an IgE and eosinophilic response may be relevant. Several recent studies have suggested that newborn infants who either have a hereditary predispo-

sition to allergies or who go on to develop early sensitisation show defective interferon gamma responses to non-specific mitogens by peripheral blood mononuclear cells.^{28–29} Whether this property is also characteristic of those who develop childhood asthma is unknown to date, but will probably be addressed by ongoing long term follow up studies. The recent findings by Prescott and coworkers may also shed some light.³⁰ They reported that Th2 skewed responses to environmental allergens are present in almost all newborn infants. Over the first 18 months immune deviation towards a Th1 skewed immunity developed in non-atopic infants, whereas in atopic subjects a defective increase in interferon gamma production counterbalancing the postnatal Th2 responsiveness was observed. Thus, the development of early sensitisation which is a characteristic of childhood asthma may be a marker of an underlying defect in the maturation of a normal immune response affecting both the manifestation of atopy and of asthma.

Progression of asthma into adolescence and adulthood

Little is known about the progression of asthma from childhood through adolescence. Clinical studies have reported that up to 80% of asthmatics lose their symptoms during puberty.^{31–33} In a cohort study of Australian schoolchildren³⁴ studied at the age of 8–10 years and again at the age of 12–14 years, the persistence of BHR into adolescence was related to its severity at school age, to the atopic status of the child, and to the occurrence of asthma in the parents. The majority of children showing a slight or mild degree of BHR lost their increased response at 12–14 years of age, whereas only 15.4% of children with severe or moderate BHR at school age were normoreactive as adolescents. Whether the decline in reported symptoms is real or subject to increasing denial of illness by children reaching puberty remains to be clarified. The concomitant decrease in BHR may favour the hypothesis of a real decrease in the activity of the disease.

Recent findings suggest that the decline in the prevalence of asthma during the adolescent years may also be attributable to the disappearance of the clinical expression of one particular wheezing phenotype mainly associated with viral infections. A recent report from the longitudinal Tucson Birth Cohort Study showed that lower respiratory tract illnesses caused by respiratory syncytial virus (RSV) and other viruses were associated with a diminishing risk of recurrent wheezing during school years.³⁵ A fourfold increased risk at the age of six years subsequently reduced to no risk at the age of 13. Furthermore, the occurrence of viral lower respiratory tract illnesses was unrelated to the development of atopic sensitisation. Thus, virus associated wheezing may have a better prognosis than atopy related asthma.³⁶ Children with the atopic wheezing phenotype may, in turn, develop more severe disease and will probably belong to the subgroup with continuing wheezing during adolescence.

The findings of the British national childhood development study, a longitudinal survey of all people in England, Scotland and Wales born during one week in 1958, may help in understanding the course of asthma incidence throughout childhood into early adult life.³⁷ A history of wheezing illnesses assessed at ages seven, 11, 16, 23, and 33 years was available in almost 6000 subjects. Only 5% of symptomatic subjects had persistent wheeze at all times, whereas most subjects (60%) had a relapsing course. Over half of the subjects who wheezed before the age of seven years and who reported wheezing in the previous year at the age of 33 had been free of attacks for seven years from the age of 16 to 23; 35% of wheezing subjects at the age of seven reported complete remission after adolescence. The incidence at age 17–33 was strongly associated with active cigarette smoking.

Determinants of ventilatory function over time in asthmatic subjects

Decrements in baseline lung function may result from repeated or progressive inflammatory changes of the airway epithelium associated with exposure to allergens, viral infections, or environmental tobacco smoke (ETS) leading to increased airway tone and airway remodelling. A longitudinal Australian survey following subjects over a 28 year period revealed that those with frequent and persistent asthma before the age of seven years continued to have abnormal lung function in mid adult life (age 35 years).³⁸ However, those with infrequent wheeze associated with symptoms during presumed viral respiratory tract infections at the age of seven had no evidence of airways obstruction in mid adult life. In this study the level of pulmonary function already differed between the groups at the age of seven, thereafter tracking along the previously set level. Likewise, a low level of pulmonary function together with airway hyperresponsiveness in childhood (ages 5–14 years) was significantly associated with a lower level of forced expiratory volume in one second (FEV₁) at the age of 22–32 years in asthmatic subjects in a Dutch university hospital outpatient department.³⁹

In the British Birth Cohort Study lung function at the age of 34–35 years was also dependent on a previous history of wheezing.⁴⁰ Young adults who outgrew their childhood wheezing generally had similar ventilatory function to their peers who have never wheezed. In contrast, young adults who continued to wheeze had poorer baseline spirometric values than healthy control subjects. The ventilatory function deficit was reported to be progressively greater if the wheezing started at an earlier age and continued throughout adolescence.

These observations might be explained in two not mutually exclusive ways. The persistence of childhood wheezing may result in a progressive loss of ventilatory function or, alternatively, impaired lung growth and early lung damage in children with persistent wheeze may predict the long term prognosis of wheezing. Although decrements in baseline lung

function were apparent among children with persistent wheeze as early as at 6–7 years of age.^{5, 38} Measurements of the FEV₁/FVC ratio in three prospective studies^{41–43} showed a worsening over time among children with persistent wheeze, asthma, or airway hyperresponsiveness. Since, in the British Birth Cohort Study, ventilatory function was particularly poor if the wheeze persisted throughout childhood and adolescence and was only partially reversible after salbutamol inhalation, progressive irreversible airflow obstruction may result from a chronic disease process.

Early influences on adult lung function

Early childhood infections were identified as early predictors of adult pulmonary function in non-asthmatic subjects.^{44–47} A challenging difficulty in assessing the importance of respiratory infections as a risk factor for adult ventilatory function and chronic obstructive disease is determining whether an acute respiratory illness is an infectious process or a non-infectious exacerbation of pre-existing obstructive airway disease. Symptoms such as cough and dyspnoea are non-specific and can be associated with either infectious or non-infectious processes. Several authors have studied the effects of childhood respiratory infections, although few have used longitudinal study designs. Gold and colleagues followed spirometric measures prospectively for eight years in a population of children in East Boston⁴⁸ and found that a prior history of pneumonia was associated with a slower rate of increase in FEF_{25–75} in boys but not in girls. Shaheen and coworkers^{44, 45} assessed the relation of several childhood respiratory illnesses, as documented in health visit records, to lung function in adults aged 67–74 years and found a significant reduction in FEV₁ and the FEV₁/FVC ratio, particularly in men, suggesting an obstructive ventilatory defect in subjects who were diagnosed with pneumonia before the age of two years.⁴⁴

The adverse effects of pneumonia in the first years of life were confirmed in another longitudinal British study following subjects from birth up to the age of 34–35 years.⁴⁷ Independent of a history of asthma or wheezing, pneumonia before the age of seven years was associated with reduced ventilatory function (FEV₁ and FVC) whereas a history of whooping cough had no effect. In this survey a reduction in lung size was mainly seen as the FEV₁/FVC ratio was unaffected. It remains unclear, however, whether childhood pneumonia causes a loss of adult lung function or whether pneumonia is more common in children who have poorer lung function before the disease. It seems conceivable that infants with impaired lung function at birth who manifest as transient early wheezers may belong to this sensitive group.

Several studies have consistently shown an adverse effect of exposure to ETS on childhood pulmonary function. A recent meta-analysis has furthermore concluded that there is evidence to suggest that passive smoking is causally related to decrements in lung function

in children, although the magnitude of the effect is relatively small at a population level.⁴⁹ The susceptibility to ETS may, however, vary substantially between individuals but the factors contributing to the risk of particular subgroups are so far unknown. In a large population cohort of New Zealand children observed from nine to 15 years of age, parental smoking was associated with persistent but mild and non-progressive impairment of the FEV₁/FVC ratio in boys, an effect that was present at the time lung function measurements were first made at the age of nine years.⁵⁰ Girls were not affected. In children with reported wheeze or asthma, exposure to ETS had progressive, more serious, and clinically significant effects on the FEV₁/FVC ratio in adolescents of both sexes, causing a mean reduction of 4% by the age of 15 in boys and of 2% in girls. Likewise, in the Tucson cohort boys exposed to parental smoking who had low lung function at the age of 10 years showed definite changes over the 13 year observation period.⁵¹ Their FEV₁ grew more slowly between the ages of 13 to 16. Similarly, the rates of decline of the FEV₁/FVC and the FEF₅₀/FVC ratios were increased. No effect was seen among girls.

Transient early wheezing is strongly determined by maternal smoking during pregnancy.⁵ In two prospective studies forced expiratory flow levels were found to be significantly reduced in infants of smoking mothers compared with non-exposed children.^{52–55} Since lung function testing had been performed shortly after birth, the findings suggest that maternal smoking impairs airway development in utero causing smaller airways at birth. These reductions are of clinical relevance since in both surveys they were related to the development of wheezing lower respiratory tract illnesses during the first years of life.^{53, 54} Thus exposure to ETS, either as passive exposure through smoking parents or in the active form thereafter, is a strong determinant of lung function impairment which in turn may favour the development of chronic obstructive pulmonary disease (COPD) in adult years.

Conclusions

Adult respiratory disease may have its roots in early childhood. For asthma most cases arise in the first four years of life, although new incidence of asthma also occurs during adolescence and adulthood. In childhood, asthma begins very early and risk factors for the inception of the disease may affect an individual in utero or in the first years of life. A defect in the maturation of certain immune responses may contribute to the development of asthma and of characteristic features strongly associated with asthma such as early atopic sensitisation to food or inhalant allergens. Asthma has a highly variable course over childhood and adolescent years. Predictors of progression of the illness over puberty into adulthood are the severity of the illness, the presence and severity of atopy, and the uptake of active cigarette smoking. Decrement in pulmonary function, either present at birth or acquired in childhood

through exposure to ETS or uptake of active smoking during adolescence, may be related to the development of COPD. Whether infectious respiratory illnesses early in life are merely a reflection of pre-existent obstructive airway disease or affect the growing lung and induce persistent decrements in ventilatory function favouring the clinical manifestation of COPD awaits further elucidation.

- 1 von Mutius E. The rising trends in asthma and allergic disease. *Clin Exp Allergy* 1998;28:45–9.
- 2 Peat JK, Gray EJ, Mellis CM, *et al.* Differences in airway hyperresponsiveness between children and adults living in the same environment: an epidemiological study in two regions of New South Wales. *Eur Respir J* 1994;7:1805–13.
- 3 Peat JK, Haby M, Spijker J, *et al.* Prevalence of asthma in adults in Busselton, Western Australia. *BMJ* 1992;305:1326–9.
- 4 Yunginger JW, Reed CE, O'Connell EJ, *et al.* A community-based study of the epidemiology of asthma. Incidence rates, 1964–1983. *Am Rev Respir Dis* 1992;146:888–94.
- 5 Martinez FD, Wright AL, Taussig LM, *et al.* Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133–8.
- 6 Strachan DP. The prevalence and natural history of wheezing in early childhood. *J R Coll Gen Pract* 1985;35:182–4.
- 7 Park ES, Golding J, Carswell F, *et al.* Preschool wheezing and prognosis at 10. *Arch Dis Child* 1986;61:642–6.
- 8 Martinez FD, Stern DA, Wright AL, *et al.* Differential immune responses to acute lower respiratory illness in early life and subsequent development of persistent wheezing an asthma. *J Allergy Clin Immunol* 1998;102:915–20.
- 9 Villa JR, Garcia G, Rueda S, *et al.* Serum eosinophilic cationic protein may predict clinical course of wheezing in young children. *Arch Dis Child* 1998;78:448–52.
- 10 Koller DY, Wojnarowski C, Herkner KR, *et al.* High levels of eosinophilic cationic protein in wheezing infants predict the development of asthma. *J Allergy Clin Immunol* 1997;99:752–6.
- 11 Clough JB, Keeping KA, Edwards LC, *et al.* Can we predict which wheezy infants will continue to wheeze? *Am J Respir Crit Care Med* 1999;160:1473–80.
- 12 Zimmerman B, Feanny S, Reisman J, *et al.* Allergy in asthma. *J Allergy Clin Immunol* 1988;81:63–70.
- 13 Peat JK, Salome CM, Woolcock AJ. Longitudinal changes in atopy during a 4-year period: relation to bronchial hyperresponsiveness and respiratory symptoms in a population sample of Australian schoolchildren. *J Allergy Clin Immunol* 1990;85:65–74.
- 14 Woolcock AJ, Peat JK. Evidence for the increase in asthma worldwide. In: *The rising trends in asthma*. Ciba Foundation Symposium 206. Chichester: Wiley, 1997: 122–34.
- 15 Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999;54:268–72.
- 16 Peat JK, Tovey E, Toelle BG, *et al.* House dust mite allergens. A major risk factor for childhood asthma in Australia. *Am J Respir Crit Care Med* 1996;153:141–6.
- 17 Platts-Mills TAE, Thomas WR, Aalberse RC, *et al.* Dust mite allergens and asthma: report of a second international workshop. *J Allergy Clin Immunol* 1992;89:1046–60.
- 18 Peat JK, Woolcock AJ. Sensitivity to common allergens: relation to respiratory symptoms and bronchial hyperresponsiveness in children from three different climatic areas of Australia. *Clin Exp Allergy* 1991;21:573–81.
- 19 Burrows B, Sears MR, Flannery EM, *et al.* Relations of bronchial responsiveness to allergy skin test reactivity, lung function, respiratory symptoms, and diagnoses in thirteen-year-old New Zealand children. *J Allergy Clin Immunol* 1995;95:548–56.
- 20 Gergen PJ, Turkeltaub PC. The association of individual allergen reactivity with respiratory disease in a national sample: data from the second National Health and Nutrition Examination Survey, 1976–80 [NHANES II]. *J Allergy Clin Immunol* 1992;90:579–88.
- 21 Sigurs N, Hattveig G, Kjellman B, *et al.* Appearance of atopic disease in relation to serum IgE antibodies in children followed up from birth for 4 to 15 years. *J Allergy Clin Immunol* 1994;14:551–9.
- 22 Nickel R, Kulig M, Forster J, *et al.* Sensitisation to hen's egg at the age of twelve months is predictive for allergic sensitisation to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol* 1997;99:613–7.
- 23 Illi S, von Mutius E, Wahn U and the MAS Study Group. Among asthmatic children atopy starts very early in life. *Eur Respir J* 1999;14:S175.
- 24 Charpin D, Birnbaum J, Haddi E, *et al.* Altitude and allergy to house-dust mites. A paradigm of the influence of environmental exposure on allergic sensitization. *Am Rev Respir Dis* 1991;143:983–6.
- 25 Sporik R, Ingram JM, Price W, *et al.* Association of asthma with serum IgE and skin test reactivity to allergens among children living at high altitude. Ticking the dragon's breath. *Am J Respir Crit Care Med* 1995;151:1388–92.
- 26 Hesselmar B, Aberg N, Aberg B, *et al.* Does early exposure to cat or dog protect against later allergy development? *Clin Exp Allergy* 1999;29:611–7.
- 27 Svanes C, Jarvis D, Chinn S, *et al.* Childhood environment and adult atopy: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999;103:415–20.
- 28 Liao SY, Liao TN, Chiang BL, *et al.* Decreased production of IFN gamma and increased production of IL-6 by cord blood mononuclear cells of newborns with a high risk of allergy. *Clin Exp Allergy* 1996;26:397–405.
- 29 Martinez FD, Stern DA, Wright AL, *et al.* Association of interleukin-2 and interferon-gamma production by blood mononuclear cells in infancy with parental allergy skin tests and with subsequent development of atopy. *J Allergy Clin Immunol* 1995;96:652–60.
- 30 Prescott SL, Macaubas C, Smallacombe T, *et al.* Development of allergen-specific T-cell memory in atopic and normal children (see comments). *Lancet* 1999;353:196–200.
- 31 Park ES, Golding J, Carswell F, *et al.* Preschool wheezing and prognosis at 10. *Arch Dis Child* 1986;61:642–6.
- 32 Nicolai T, Illi S, von Mutius E. Dampness at home in childhood is a risk factor for bronchial hyperactivity in adolescence. *Thorax* 1998;53:1035–40.
- 33 Balfour-Lynn L. Childhood asthma and puberty. *Arch Dis Child* 1985;60:231–5.
- 34 Peat JK, Salome CM, Sedgwick CS, *et al.* A prospective study of bronchial hyperresponsiveness and respiratory symptoms in a population of Australian schoolchildren. *Clin Exp Allergy* 1989;19:299–306.
- 35 Stein RT, Sherrill D, Morgan WJ, *et al.* Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354:541–5.
- 36 von Mutius E, Illi S, Hirsch T, *et al.* Frequency of infections in the first years of life and risk of asthma, atopy and airway hyperresponsiveness among schoolage children. *Eur Respir J* 1999;14:4–11.
- 37 Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ* 1996;312:1195–9.
- 38 Oswald H, Phelan PD, Lanigan A, *et al.* Childhood asthma and lung function in mid-adult life. *Pediatr Pulmonol* 1997;23:14–20.
- 39 Grol MH, Gerritsen J, Vonk JM, *et al.* Risk factors for growth and decline of lung function in asthmatic individuals up to the age 42 years. *Am J Respir Crit Care Med* 1999;160:1830–7.
- 40 Strachan DP, Griffiths JM, Johnston IDA, *et al.* Ventilatory function in British adults after asthma or wheezing illness at ages 0–35. *Am J Respir Crit Care Med* 1996;154:1629–35.
- 41 Kelly WJW, Hudson I, Raven J, *et al.* Childhood asthma and adult lung function. *Am Rev Respir Dis* 1988;138:26–30.
- 42 Weiss ST, Tosteson TD, Segal MR, *et al.* Effects of asthma on pulmonary function in children. A longitudinal population-based study. *Am Rev Respir Dis* 1992;145:58–64.
- 43 Sherrill D, Sears MR, Lebowitz MD, *et al.* The effects of airway hyperresponsiveness, wheezing and atopy on longitudinal pulmonary function in children: a 6 year follow-up study. *Pediatr Pulmonol* 1992;13:78–85.
- 44 Shaheen SO, Barker DJP, Shiell AW, *et al.* The relationship between pneumonia in early childhood and impaired lung function in late adult life. *Am J Respir Crit Care Med* 1994;149:616–9.
- 45 Shaheen SO, Barker DJP, Holgate ST. Do lower respiratory tract infections in early childhood cause chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 1995;151:1649–52.
- 46 Silverman EK, Speizer FE. Risk factors for the development of chronic obstructive pulmonary disease. *Med Clin North Am* 1996;80:501–22.
- 47 Johnston IDA, Strachan DP, Anderson HR. Effect of pneumonia and whooping cough in childhood on adult lung function. *N Engl J Med* 1998;338:581–7.
- 48 Gold DR, Tager IB, Weiss ST, *et al.* Acute lower respiratory illness in childhood as a predictor of lung function and chronic respiratory symptoms. *Am Rev Respir Dis* 1989;140:877–84.
- 49 Cook DG, Strachan DP, Carey IM. Parental smoking and spirometric indices in children. *Thorax* 1998;53:884–93.
- 50 Sherrill DL, Martinez FD, Lebowitz MD, *et al.* Longitudinal effects of passive smoking on pulmonary function in New Zealand children. *Am Rev Respir Dis* 1992;145:1136–41.
- 51 Lebowitz MD, Sherrill D, Holberg CJ. Effects of passive smoking on lung growth in children. *Pediatr Pulmonol* 1992;12:37–42.
- 52 Hanrahan JP, Tager IB, Segal MR, *et al.* The effect of maternal smoking during pregnancy on early infant lung function. *Am Rev Respir Dis* 1992;145:1129–35.
- 53 Tager IB, Ngo L, Hanrahan JP. Maternal smoking during pregnancy. Effects on lung function during the first 18 months of life. *Am J Respir Crit Care Med* 1995;152:977–83.
- 54 Tager IB, Hanrahan JP, Tosteson TD, *et al.* Lung function, pre and post natal smoke exposure, and wheezing in the first year of life. *Am Rev Respir Dis* 1993;147:811–7.
- 55 Wright AL, Holberg C, Martinez FD, *et al.* Relationship of parental smoking to wheezing and nonwheezing lower respiratory tract illnesses in infancy. Group Health Medical Associates. *J Pediatr* 1991;118:207–14.