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Are There Long Term Consequences for Acute Respiratory Infection in Childhood?

JF ***PRICE***

Abstract Injury to the growing lung may influence the development of chest disease in the later life. Three potentially harmful factors are passive smoking, premature birth and acute lower respiratory tract infection. These factors contribute to the spectrum of wheezing in early childhood but probably make a relatively small impact on the prevalence of asthma in adults. They may however increase vulnerability to COPD by affecting normal development of lung function in childhood and adolescence. Young adults who have been exposed to cigarette smoke since foetal life, were of low birthweight or who contracted severe bacterial or viral lower respiratory infection as young children, frequently show persisting airways obstruction. This is not reversible with a bronchodilatator and suggests a failure to attain maximal lung function. Exposure to tobacco products also increases vulnerability to respiratory infection in childhood. The cycle is carried to the next generation through smoking in pregnancy.

Key words Children; Prematurity; Respiratory infection; Smoking

Introduction

Many diseases of adults have their origins in childhood and it is likely that growth and nutrition in fetal and early post-natal life influence the development of adult disease. For example Barker and colleagues have shown that high levels of IgE antibody and therefore vulnerability to allergy is associated with disproportionate fetal growth. This association persists even when social class and smoking are discounted.[1] It is also possible that injury to the growing lung might influence the development of chest disease in adulthood. I will discuss three potentially harmful factors, passive smoking, premature birth and acute lower respiratory tract infection, and consider whether they increase the risk of asthma, chronic obstructive pulmonary disease (COPD) or bronchiectasis.

Asthma is diagnosed much more frequently in childhood that at any other time and there is abundant evidence to link childhood asthma with adult asthma. Passive smoking, extreme premature birth and acute viral bronchiolitis in infancy each have a clear relationship with wheezing illness in early childhood. However the association with asthma persisting into adulthood is less obvious. Traditionally COPD has been regarded as a disease of middle aged men who are heavy smokers and work in areas of high environmental pollution. However women are also affected and only 10% to 15% of heavy smokers develop COPD. Other factors must be selecting a minority of smokers and some non-smokers to be afflicted by the condition. COPD is less common than asthma but has a much higher mortality. Although nearly six times as many people have asthma as have COPD, the standardised mortality rate for COPD is 20 times that of asthma (Table 1). Therefore it is important to determine all the factors which increase vulnerability to COPD and to find out whether at least some of them date back to childhood.

Passive Smoking

Some recent laboratory based and epidemiological

Table 1 Prevalence and death rates from asthma and chronic obstructive pulmonary disease (COPD)

	Asthma	COPD
Diagnosed/ treated	>3.4 m	0.6 m
Deaths per year	1347	26,630
Mortality rate/ million	27	546

England and Wales 1998 (Total population = 48.7 million)

King's College Hospital, London, UK

JF **PRICE** *MD, FRCP, FRCPCH*

Correspondence to: Professor JF **PRICE**

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studies have helped to clarify the relationship between exposure to the products of tobacco smoke and respiratory illness in childhood. Lung function testing in newborn infants is now safe and reproducible. Thus it is feasible to evaluate the effects of passive smoke exposure on the growing lung before birth. Lodrup-Carlsen and her colleagues in Oslo measured compliance of the respiratory system (CRS) in newborn infants who had been exposed to different levels of the products of tobacco smoke *in utero*. Those infants exposed to both active (mother) and passive (other household members) smoke had the values for CRS which were significantly lower than in infants who were not exposed to either active or passive smoke.[2] An Australian group assessed bronchial responsiveness using maximum flow at Functional Residual Capacity (Vmax FRC) derived from partial expiratory flow volume curves. Measurements were made within a few weeks of birth. Airway responsiveness was increased in babies of mothers who smoked during pregnancy compared with infants of non-smoking mothers and was comparable to that in infants of atopic mothers.[3]

A prospective study of over 1000 babies born in Tuscon, Arizona has provided valuable new information about wheezing illness in childhood. The study included an analysis of the relationship between passive smoke exposure and wheezing in the first six years of life. Exposure to tobacco smoke was positively associated with transient episodes of wheezing which had resolved by the age of three years. The children who showed this pattern of transient early wheezing had relatively low values for Vmax FRC in the neonatal period. Passive smoke exposure was also positively associated with wheezing illness that persisted beyond the age of six years. These children tended to be atopic and to have raised levels of serum IgE.[4] Strachan and Cook in a series of review articles made meta-analyses of studies that investigated the relationship between passive smoking and respiratory illness in childhood. Their results emphasise the increased risk of respiratory illness in children exposed to passive smoking with the highest odds ratio in families where both parents smoke.[5] They analysed 25 papers that contained quantitative information about the relationship between asthma in childhood and passive smoking. The odds ratio in children where either parent smoked was consistently above one with a pooled odds ratio of 1.3.[6] The positive association between passive smoke exposure and wheezing illness weakened with age the pooled odds ratio falling from 1.31 in children under six years to 1.13 in children older than six years. Moreover the high incidence of wheezing in smoking households was mainly viral associated wheezing in non-atopic children.[7] This suggests passive smoke exposure may not be an important factor increasing the prevalence of atopic asthma that starts in childhood and persists to adulthood.

Both passive and active smoking adversely effect the attainment of maximum lung function in adolescence. Lung function reaches a plateau that is sustained for several years before a gradual decline throughout adult life.[8] Continuous exposure to tobacco products in early childhood leads to a small but significant reduction in maximum attained FEV1 of 1% to 5%. Most of this effect is probably the result of ante-natal exposure.[9] A larger effect on FEV1 follows the uptake of active smoking. In the UK about a quarter of 15 to 16 year olds "smoke cigarettes regularly" according to one survey.[10] The reduction in maximal attained lung function as a result of active smoking in adolescence amounts to 5% to 10%.[11] Many children of parents who smoke will emulate their parents with a cumulative effect on the development of lung function. Since tracking of lung function is consistent throughout adult life early exposure to tobacco smoke even if not accompanied by active smoking might contribute to the development of COPD in middle age.

Premature Birth

The relationship between chronic lung disease of prematurity (CLD), atopy and asthma is a complicated one. A large study carried out in Wisconsin and Iowa, USA has helped to clarify these relationships. Detailed information about atopy and asthma was collected in 723 infants born with birth weight <1501 g who survived more than 30 days and 106 full term controls. The diagnosis of asthma and use of asthma treatment at the age of five years was investigated in a representative subgroup of 257 of the very low birth weight (VLBW) children. The conclusions drawn from the study were (1) that parents with a family history of asthma were more likely to give birth to a premature VLBW infant, (2) a family history of asthma was not associated with CLD, (3) CLD was associated with asthma in childhood.[12] Recurrent wheezing occurs in at least half of babies born prematurely who develop CLD. However because extreme prematurity is rare such babies make a relatively small contribution to wheezing illness in infancy. They comprise not more than 1% of the total population of all wheezy infants. Of those babies with CLD who survive the prevalence of wheeze declines with age.[13,14] By the age of seven years wheezing is no more common in low birth weight children than in those born at term.[15] Some of the low birth weight children will have an atopic family background and would have been at risk of developing asthma anyway. Prematurity and CLD may therefore make relatively little additional contribution to the prevalence of wheezing illness in adolescence and adulthood.

High resolution CT scanning has provided valuable information about lung and airway architecture in older

children and adults who had CLD. The scans show marked distortion of lung architecture with scarring and air trapping but bronchiectasis is rarely if ever seen.[16] With improved survival of VLBW infants data is accumulating about the development of lung function as these children grow up. Northway and colleagues studied 26 young adults (average age 18 years) born at a mean of 33 weeks gestation with birth weights averaging 1800 grams, who had a history of CLD. Compared with adults who were either born at a similar gestation but did not develop CLD or who were born at full term, these 18 year olds showed a marked reduction in FEV1, lung hyperrinflation and increased bronchial reactivity.[17] The abnormalities demonstrate a failure to attain maximal FEV1 and resemble the lung function abnormalities characteristic of COPD. The study reflects the long term effect on lung function of CLD acquired in the 1960s and early 1970s. Infants of much lower birthweight are now surviving and more recent data provides information about their development of lung function. Pulmonary function tests in 31 children aged seven to 11 years born at a mean of 28 weeks gestation (range 25 to 35 weeks) detected abnormal diffusing capacity and reduced FEV1. These changes were seen both in survivors of CLD and survivors who were of similar gestation but did not require ventilation or develop CLD.[18] The results suggest that structural changes in the lung and lung airways persist in VLBW infants irrespective of whether or not they have CLD. The significance of these findings to the evolution of lung function in adulthood is not yet known but raises the question whether survivors of extreme prematurity are at increased risk of COPD in later life.

Acute Lower Respiration Infection

In 1986 it was estimated that acute respiratory infection (ARI) caused 4 million child deaths each year, 2.6 million deaths in infants and 1.4 million deaths in children aged one to four years.[19] Although this stimulated vaccination programmes and new projects designed to recognise and treat pneumonia with simple and inexpensive regimes, the mortality from ARI in young children in developing countries has probably declined very little.[20] In developed countries mortality rates from pneumonia in children are relatively low. Nevertheless radiographically defined pneumonia accounts for 13% of all infectious illness in children less than two years of age.[21]

With adequate oxgenation and hydration and appropriate use of antibiotics, most children will make a good recovery from ARIs. However there are indications that ARI in childhood is associated with long term abnormalities in lung function. In a study which utilised meticulous nursing records dating back to the 1920s, FEV1 and FVC was reduced in men aged 59 to 74 years of age who had a history of pneumonia or bronchitis in childhood. The study included only a small number of cases of pneumonia and it is surprising that a similar association between pneumonia and reduced lung function was not seen in women. Moreover the inclusion of "bronchitis" raises the question as to that some of the subjects had asthma.[22,23] Despite these reservations the study generated the hypothesis that ARI in childhood might predispose to or predict COPD in middle age.

Support for this hypothesis comes from a much larger prospective study that was part of the British National Child Development Study, 1958 Cohort. The evidence derives from1392 adults followed up from their birth during one week in 1958. At the age of seven years a past history of pneumonia was elicited by interview questionnaire in 193 of the subjects. At the age of 34 to 35 years spirometry was done in these subjects and compared with lung function data obtained in 1199 subjects with no history of respiratory illness before the age of seven years. FEV1 and FVC were significantly lower in young adults with pneumonia before the age of seven years than in those with no childhood pneumonia. The analysis was adjusted for gender, height and smoking. The association between reduced lung function and childhood pneumonia was unaffected by a history of wheezing (Table 2) and FEV1 did not improve after treatment with salbutamol. In other words the deficit represented a loss of attainment of maximum adult lung function which was not attributable to asthma.[24] Once again the question arises "are these young adults at increased risk of COPD in middle age". An important issue not resolved by this study is whether the deficit in young function predated, or was a consequence of pneumonia in childhood. The size of the deficit was not related to the age of acquisition of pneumonia. If pneumonia was the primary cause of the reduction in FEV1 one might expect the abnormality to be greatest in those children who contracted pneumonia at a very young age.

The majority of severe pneumonia is caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*.[25] However the commonest cause of acute lower respiratory

Table 2 Reduction in FEV1 in 34 to 35 years old adults with a history of pneumonia before the age of seven years: data is compared with FEV1 in adults of the same age with no history of pneumonia in early childhood

Pneumonia	n	Difference in FEV1	(95%)	p
- all subjects	193	-102	(73)	0.006
- current wheeze	74	-119	(133)	0.08
- never wheezed	57	-155	(122)	0.01

(Adapted from Johnston et al. N Engl J Med 1998;338:581-7)

infection in early childhood is the Respiratory Syncytial Virus (RSV). About 1% of infants born in the UK are admitted to hospital with acute viral bronchiolitis with or without evidence of pneumonia and over 80% is due to RSV. In healthy term infants the mortality is very low. However many babies have persistent respiratory symptoms after an episode of viral bronchiolitis. During the two years following hospital admission for acute bronchiolitis up to 75% of children have further wheezing illnesses[26] and many show persisting lung function abnormalities.[27] However the prevalence of wheezing falls as the children grow older. Ten years after acute bronchiolitis wheezing illness in children admitted to hospital in infancy with RSV positive bronchiolitis had dropped to between 22% and 34%.[28,29] Most studies of the outcome of RSV infection in early childhood have focused on those admitted to hospital. A recent prospective study has examined the odds ratio for wheezing in children who acquired RSV infection with lower respiratory tract symptoms in the first two years of life, but were not sufficiently unwell to be hospitalised. The odds ratio for infrequent and frequent wheezing at the age of six years was 3.2 and 4.3 respectively. However the risk of wheezing illness decreased as the children grew older and by the time they were thirteen there was no increased risk of infrequent or frequent wheeze.[30] In the same study the number of thirteen years olds with previous RSV lower respiratory illness who were atopic was no higher than in a control group. This confirms observations made in 3 other prospective controlled studies of children admitted to hospital with acute viral bronchiolitis.[28,29,31] Only one similarly designed study has suggested a higher prevalence of atopy in children who have had acute bronchiolitis. This was a carefully controlled study but the follow up period was much shorter than in the other studies and the children were hospitalised with severe bronchiolitis. Babies with a personal or family history of atopy are more likely to be severely affected by RSV bronchiolitis than those with a non-atopic family background. Perhaps this influenced the result.[32]

Whereas there is controversy as to whether wheezing or atopy is a consequence of RSV lower respiratory infection in infancy, there is strong evidence that RSV bronchiolitis is followed by persisting abnormalities of lung function. Three prospective controlled trials have all shown a significant degree of airways obstruction 10 to 11 years after viral bronchiolitis in infancy (Table 3).[28-30] The changes are independent of past or current wheezing and of atopy. A further report of lung function tests in subjects aged 16 to 22 years with a past history of viral bronchiolitis showed reduced flow at low lung volumes even in those who had no abnormal respiratory symptoms.[33] The abnormalities of lung function bear some resemblance to the changes seen in adults who had pneumonia in early childhood and hint at a possible similar link with COPD. The question, as with childhood pneumonia, is which comes first, the changes in lung function or the lower respiratory tract infection. An Australian report has suggested that Vmax FRC is reduced in neonates who subsequently develop severe RSV lower respiratory infection.[34] An alternative hypothesis is that severe RSV infection in infancy is the result of genetically determined variation in immune response to infection. Hull and his colleagues in Oxford have described a polymorphic variant in the IL-8 promoter region. In a family based study they suggest there may be increased likelihood of transmission of the "high IL-8" allele to infants with severe RSV bronchiolitis.[35] This preliminary report opens up new possibilities for investigating the variation in severity of illness following respiratory infection in childhood.

Adenoviruses are a less common cause of bronchiolitis and pneumonia in childhood but adenovirus lower respiratory tract infection more often results in severe lung injury. In western countries adenovirus infection accounts for between 4% and 22% of acute lower respiratory infection in children requiring hospital admission.[36] In Argenina and Chile adenovirus (commonly Type 7H) is the second most frequent viral pathogen detected in children hospitalised for ARI, RSV being the most common.[37] Fifty nine per cent of viral pneumonia in China is caused by adenovirus, mainly Type 7.[38] The risk of long term injury to the lung may be as high as 60% following severe adenovirus pneumonia in childhood.[39] Long term consequences include bronchiolitis obliterans, bronchiectasis, fibrosis and the Swyer James syndrome,[40] a hypoplastic, hyperlucent lung which may contain areas of bronchiectasis.[41] Why certain strains of adenovirus are so virulent and damaging to the growing lung is not understood. High levels of Interleukin-6, Interleukin-8, Tumour Necrosis Factor alpha and the presence of adenovirus specific immune complexes in the circulation

Table 3 RSV lower respiratory tract infection and atopy - prospective controlled trials

Study	Ref.	Hospital	FU	Atopy	
				Method	Increased
Sims (1978)	31	Yes	8	History	no
Pullen (1982)	28	Yes	10	SPT	no
Noble (1997)	29	Yes	10	SPT	no
Stein (1999)	30	No	11	SPT	no
Siggurs (1995)	32	Yes	3	IgE	yes

SPT= skin prick test to common inhaled allergens

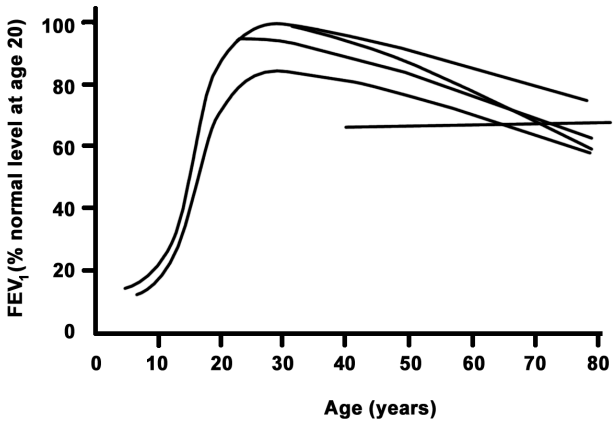
FU= number of years after acute RSV lower respiratory tract infection

suggest that host variation in immune response may play a part in determining severity.[42]

Conclusion

Inhaling the products of tobacco smoke, extreme prematurity and severe viral lower respiratory tract infection acquired in early childhood, contribute to the spectrum of wheezing illness in childhood. However these factors probably make a relatively small impact on the prevalence of asthma in adults.

Adolescents and adults who have been exposed to cigarette smoke since fetal life, were VLBW babies or who contracted severe lower respiratory infection as young children, show persisting airways obstruction which differs from asthma and is not reversible with a bronchodilator. In young adults these abnormalities apparently cause few symptoms. However they indicate a failure to attain maximal lung function. In 1991 Rijcken[8] proposed a model to describe increased vulnerability to COPD using hypothetical tracking curves for FEV1 (Figure 1). The factors to which I have referred could operate within this model. Intrauterine passive smoking affects airway function at birth and exposure to tobacco products also increases vulnerability to respiratory infection in childhood. There is an association between respiratory infection in early childhood and impairment of lung function. Uptake of active smoking may have an additive effect on attainment of adult lung function and if continued could accelerate the rate of decline. The cycle is carried to the next generation through smoking in pregnancy. An additional factor not yet quantified but of great potential importance is genetically determined immune variation influencing the nature of the inflammatory response to respiratory infection.



Increased risk of COPD may result from:

- Abnormally slow increase in FEV1 in childhood
- Failure to attain maximal FEV1 in adolescence
- Abnormally rapid decline in FEV1 during adulthood

Figure 1 Mechanisms increasing the risk of COPD

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