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Early-life events

Introduction

Key points

- Major early-life risk factors for respiratory disease include abnormal antenatal lung growth, low birthweight, prematurity and bronchopulmonary dysplasia, passive smoke exposure and viral infections.
- Abnormal antenatal lung development is common and has a high mortality risk.
- Low birthweight and prematurity are key risk factors for respiratory disease.
- Tobacco smoke exposure, during pregnancy and after birth, can have respiratory repercussions throughout childhood, and is a risk factor for asthma and infectious illness.
- Respiratory viral infections in early childhood can have a long-term impact on childhood lung function and asthma or wheezing.

Infants born very prematurely can require supplementary oxygen for many months. Rehospitalisation is common in the first 2 years after birth and the majority of admissions are for respiratory disorders. Rehospitalisation is particularly increased in infants with bronchopulmonary dysplasia (BPD) who require supplementary oxygen for more than 28 days after birth, and in infants who have a respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) (see chapter 16). Respiratory symptoms continue to be common in schoolchildren who were born prematurely, and the most severely affected remain symptomatic in adulthood; an adverse outcome that may be more common in females. Prematurely born infants, particularly those who wheeze at follow-up, have evidence of airway obstruction (raised airway resistance and gas trapping) in the first 2 years after birth. Their lung function improves with increasing age, but even in adolescence there is evidence of airflow limitation in those who had had BPD, particularly in those with ongoing recurrent respiratory symptoms. Gas transfer abnormalities and airway hyperreactivity have also been described, and fixed airway obstruction has been reported in young adults who had severe BPD.

It is more than 20 years since it was first reported that airway function was diminished in adults born with low birthweight and it was speculated that

> *Respiratory symptoms continue to be common in schoolchildren who were born prematurely; the most severely affected remain symptomatic in adulthood*

pre-natal nutrition might program fetal lung growth. Low birthweight, however, is only one of a number of early-life factors that might influence respiratory disease in children and adults; other factors potentially include breastfeeding, post-natal weight gain, maternal paracetamol use during pregnancy, maternal obstetric complications, and indoor and outdoor air quality. This chapter will focus on the major risk factors.

Abnormal antenatal lung growth

Abnormal antenatal lung growth, which may result in pulmonary hypoplasia (incomplete lung development), is common: it has been reported to be present in 15–20% of early neonatal deaths. The mortality rate is high, particularly if the abnormal growth has occurred either as a consequence of oligohydramnios with rupture of the membranes between 14 and 19 weeks of gestation, or in association with a congenital diaphragmatic hernia (CDH). It may be primary, but more usually occurs as a consequence of a variety of problems, which can largely be divided into those conditions that reduce intra-thoracic space, fetal breathing movements or amniotic fluid volume. It is also found in association with trisomy 18 and 21. Pulmonary hypoplasia may have a genetic basis, as the condition occasionally occurs in twins and families. Both pre- and post-natal malnutrition can adversely affect lung growth. Vitamin A is essential for normal alveolar development and vitamin A deficiency decreases alveolar septal development.

Antenatal interventions

Determining whether a fetus has an important chromosomal abnormality is key to providing appropriate counselling to parents regarding antenatal intervention with the aim of promoting lung growth. In the first trimester, however, both amniocentesis and chorion villus sampling have been associated with an excess of infant respiratory symptoms and abnormal lung function at follow-up.

Antenatal interventions that aim to prevent abnormal antenatal lung growth include: amnio-infusion, which can facilitate ultrasound examination but has not been shown to improve lung growth; and thoraco-amniotic shunting, which results in effective drainage of pleural effusions, facilitating resuscitation, but is usually performed too late

There are modifiable risk factors of respiratory disease in those with low birthweight: for instance, smoking has been reported to be more prevalent in low-birthweight adults

in pregnancy to influence lung growth. *In utero* surgical repair of CDH has been attempted, but a more promising technique is obstruction of the normal egress of fetal lung fluid by placing a balloon in the trachea.

Pre-natal antioxidant supplementation might be expected to influence fetal lung growth and development, and to reduce the oxidative stress implicated in the development of BPD. However, follow-up of infants entered into a randomised trial did not demonstrate improved infant respiratory outcome following maternal high-dose vitamin C and E supplementation.

Low birthweight

Children and adults with a low birthweight have been reported to be at increased risk of wheezing, respiratory infection and lung function abnormalities. This is true regardless of whether the low birthweight was the result of *in utero* growth retardation or premature birth. Despite antenatal and post-natal prophylaxis, small-for-gestational age infants, compared with those born with an appropriate birthweight for their gestational age, had worse neonatal and infant respiratory outcomes. There are modifiable risk factors of respiratory disease in those born with low birthweight: for instance, smoking has been reported to be more common in low birthweight adults.

Prematurity and BPD

Prematurely born infants, particularly those who had BPD, are at increased risk of chronic respiratory morbidity. BPD is diagnosed in infants who are dependent on oxygen for at least 28 days after birth. Prematurely born infants are classified at 36 weeks' post-menstrual age as having mild, moderate or severe BPD according to their respiratory support requirement at that date. In the past, infants who developed BPD had frequently suffered severe respiratory failure, necessitating both high inflating pressures and supplementary oxygen. Nowadays, BPD can occur in very prematurely born infants who initially had minimal or even no signs of lung disease: the so-called 'new' BPD. In new, compared with 'old', BPD, there is less interstitial fibrosis, but there is an arrest in acinar development resulting in fewer and larger alveoli; there is also a reduction in the number of arteries. It has been suggested that abnormal

vascular development may lead to abnormalities in lung growth and that new BPD is a maldevelopment sequence resulting from interference with or interruption of normal developmental signalling for terminal maturation and alveolarisation of the lungs of very pre-term infants.

BPD has a multi-factorial aetiology (figure 1). It can occur in infants born at term who had severe respiratory failure, but it is commonest in very prematurely born infants. It was originally thought that BPD was caused by oxygen toxicity: prematurely born infants are deficient in antioxidant enzyme systems at birth and have low levels of antioxidants, making them more vulnerable to oxygen toxicity. High airway pressures have been associated with the development of BPD, with an inverse relationship between carbon dioxide levels and BPD development. Volutrauma in the first minutes after birth may be injurious to the lungs. BPD is commoner in infants who develop a patent ductus arteriosus, particularly if this is temporally related to infection. Chorioamnionitis can increase the risk of BPD, but only if associated with 'other hits' such as post-natal infection and a requirement for mechanical ventilation for more than 7 days. Some infants have a family history of BPD and certain genetic polymorphisms have been associated with the development of BPD.

Tobacco smoke exposure

Antenatal smoke exposure is an important risk factor for increased respiratory symptoms and lung function abnormalities in infants and children. In children less than 2 years of age, the risk for lower respiratory illness has been found to be increased by 72% if the mother smoked. Although the observed increase in risk is lower in older children, parental smoking may nevertheless account for

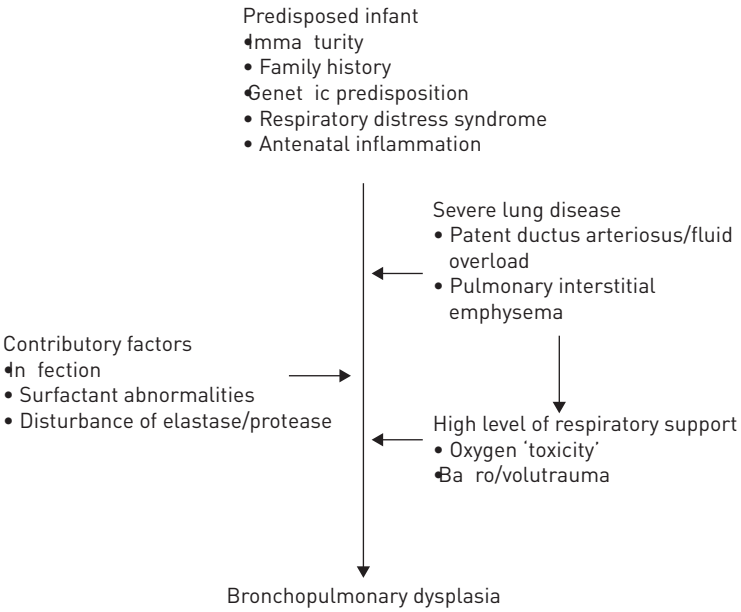

Figure 1 – The multifactorial aetiology of bronchopulmonary dysplasia. Reproduced and modified from Rennie *et al*., 2005, with permission from the publisher.

Infants less than 6 weeks old	
Pre-term birth	
Chronic illness	
	Bronchopulmonary dysplasia
	Other chronic lung disease
	Congenital heart disease
	Neurological disease
	Immunodeficiency
Maternal factors	
	Asthma
	Smoking during pregnancy
Environmental factors	
	Poverty
	Over-crowding
	Passive smoking

Table 1 – Risk factors for severe respiratory syncytial virus infection. Modified from Greenough and Broughton, 2005.

approximately 20% of all asthma in childhood. Maternal environmental tobacco smoke (ETS) exposure during the third trimester of pregnancy is associated with asthma and allergy-related symptoms in pre-school children. Certain infants may have a genetic susceptibility to the adverse effects of environmental smoke exposure, both maternal during pregnancy and in infancy. Antenatal smoking exposure has been demonstrated in some, but not all, studies to have an adverse effect on lung function in infancy. In older children, antenatal smoke exposure has been associated with a reduction in airway function. The effects of passive smoking exposure vary with genetic factors, sex, race and exposure to other pollutants. Exposure to ETS and subsequent active smoking both aggravate symptoms and have a negative effect on lung function. Passive smoke exposure in the first 3 months after birth also increases the risk of hospital admission for infectious illness. The association is strongest in the first 6 months after birth, but in vulnerable groups, such as prematurely born infants, the association has been shown to hold through to 8 years of age. Bronchiolitis also occurs more frequently in infants of mothers who smoke. Exposure in later childhood to ETS is associated with increased respiratory symptoms, although the effect appears to diminish with increasing age of the child.

Antenatal smoking exposure may have a more deleterious effect than passive smoke exposure after delivery. Analysis

of the British Births Survey data bank revealed that the incidences of admissions to hospital for a LRTI in the first 5 years after birth and of episodes of bronchitis were 2.3% and 14.1%, respectively, in infants of nonsmokers, 3.1% and 18.2% in infants whose mothers smoked only after birth, but 5.9% and 18.9% in infants whose mothers smoked only during pregnancy.

Viral infections in infancy

RSV is the most common respiratory pathogen in early childhood, with most children having had a RSV infection by 2 years of age. The majority of children suffer only a coryzal illness (common cold symptoms) requiring no medical intervention, but others develop bronchiolitis or RSV pneumonia requiring hospital admission and even intensive care. There are a number of risk factors for severe RSV infection (table 1) and therefore for increased respiratory illness at follow-up. Numerous studies have demonstrated that RSV infection in otherwise healthy infants born at term is associated with long-term respiratory sequelae. However, the effect appears to decrease with increasing age: in one cohort, although significantly more children who had had RSV LRTI wheezed up to 5 years of age compared to controls, there was no significant difference in children aged 5–10 years. Other studies report an increase in asthma in adults following RSV infection in infancy. However, the results of studies assessing bronchial hyperreactivity or allergic sensitisation following RSV infection in children born at term are conflicting. In prematurely born children who had BPD, hospitalisation due to RSV infection in the first 2 years after birth was associated with increased healthcare utilisation and associated costs up to 7 years of age. Lung function abnormalities at follow-up following RSV LRTI have been described in both term and prematurely born children.

The fact that 30–50% of children with viral-induced wheezing in infancy go on to develop asthma suggests that viral respiratory infections cause airway damage, promoting airway remodelling, leading to asthma. There is, however, evidence to suggest that infants who have symptomatic RSV LRTIs may have pre-existing diminished lung function, particularly small-airway abnormalities. In one study, however, the results were not significant and virology results were only available for the two infants who were hospitalised. Follow-up of the cohort highlighted that lung function level at 11 years of age was similar to the pre-infection level, suggesting that the infection had not had an adverse effect. In prematurely born infants, a higher resistance of the respiratory system at 36 weeks' post-menstrual age has been associated with more wheeze at follow-up following RSV LRTI and, in a larger cohort, with a greater requirement for RSV hospitalisation. Some single nucleotide polymorphisms (SNPs) have been associated with an increased risk of severe RSV infection as indicated by a need for hospitalisation. In addition, SNPs in genes coding for interleukin (IL)-8, IL-19, IL-20, IL-13, mannose binding lectin, interferon (IFN)-γ and RANTES (regulated upon activation, normal T-cell expressed, and secreted) have been associated with wheeze following RSV LRTI in term-born infants.

There is evidence that other respiratory viral infections may be associated with chronic respiratory morbidity in childhood. The chronic lung damage that can result

“30–50% of children with viral-induced wheezing in infancy go on to develop asthma, which suggests that viral respiratory infections cause airway damage, promoting airway remodelling, leading to asthma”

from adenovirus infection in young children has frequently been reported. Asthma has been reported to be significantly more common in 5-year-old children who had been admitted to hospital with either human metapneumovirus (hMPV) or RSV bronchiolitis in infancy. Prematurely born infants with either a hMPV LRTI or a RSV LRTI have been found to be more likely to cough and wheeze at follow-up and have lung function abnormalities, particularly a higher airway resistance.

It may be that the impact of other viruses, particularly rhinovirus (RV), is even greater than that of RSV. Among children at increased risk of developing allergies and asthma, the most significant risk factor for the development of pre-school childhood asthma was the occurrence of a symptomatic RV illness during infancy. In another study, out of 14 respiratory viruses, RV was most likely to be associated with recurrent wheezing at 12 months in infants who had been hospitalised for their first episode of bronchiolitis.

A number of hypotheses have been put forward to explain the association of RV wheezing illnesses and asthma development. These include that predisposition by allergic sensitisation reduces IFN responses in infants with asthma. As a consequence, there is increased viral replication and impaired barrier function due to smoke exposure, pollution and/or virus infection, which again leads to enhanced viral replication, greater illness severity and airway damage. A ‘double hit hypothesis’ for atopy and viral infection has been proposed as, in the Perth Birth Cohort, there was an increase in the odds ratio of developing asthma at age 6 years in patients with a greater number of viral respiratory infections in the first year after birth who were atopic. In that cohort, RV was the most common pathogen associated with an acute respiratory infection in the first year after birth. Prospective follow-up of another cohort demonstrated that allergic sensitisation preceded RV wheezing but the converse was not true. Hence, the researchers suggested that the timing and plausible mechanisms by which allergic sensitisation led to more severe RV illness supported a causal role for allergic sensitisation in that developmental pathway.

It has been suggested that the development of asthma may be related to immature immune responses to respiratory viruses and that the timing of the viral respiratory infection is an important predictor of asthma. In the Tennessee Database study, infants born 4 months prior to the winter virus peak were 30% more likely to have asthma

than infants born 12 months before the winter virus peak. Viral infections, RV in particular, can activate a number of pro-inflammatory and airway remodelling pathways that might have deleterious effects on the rapidly growing airways of young children. There may also be a functional predisposition to RV-associated wheeze, as an increased risk of wheeze has been reported in infants with a higher pre-infection resistance of the respiratory system.

Wheezy bronchitis

Although children with wheezy bronchitis achieved normal lung function in early adulthood, when they were re-examined at age 45–50 years they had undergone a more rapid decline in lung function than controls. If such a rate of decline were to persist, it may predispose to the development of chronic obstructive pulmonary disease (COPD) in later life. COPD development is also related to indoor and outdoor pollutants.

Conclusion

There are many early-life risk factors for respiratory disease in children and adults, a number of which are preventable. It is important that prospective parents receive better advice about the adverse effects smoking could have on their infant. Effective prophylactic agents against respiratory viruses, particularly rhinovirus, need to be developed and evaluated appropriately. Invasive antenatal interventions, therapeutic or diagnostic, should only be introduced into routine clinical care after their impact on the infant has been carefully evaluated. Further, randomised trials with the outcome of respiratory status at follow-up are required to determine the best management of very prematurely born infants.

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