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REVIEW

# The respiratory consequences of preterm birth: from infancy to adulthood

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## Abstract

Survival of preterm-born infants, especially at extremes of prematurity (less than 28 weeks gestation), is now common, particularly in the developed world. Despite advances in neonatal care, short-term respiratory morbidity, termed bronchopulmonary dysplasia (also called chronic lung disease of prematurity), remains an important clinical outcome. As survival during the neonatal period has improved, preterm-born individuals are now entering childhood, adolescence and adulthood in far greater numbers, and adverse longer-term respiratory outcomes following birth at an immature stage of lung development are becoming increasingly apparent. In this article, we shall review the background of the major respiratory complications in the neonatal period, bronchopulmonary dysplasia, and the current evidence regarding its prevention and management. In addition, we shall review the emerging literature on the respiratory morbidity experienced in childhood, adolescence, and adulthood by preterm-born survivors, with reduced lung function and a risk of developing chronic obstructive pulmonary disease in early adult life. As this population of preterm-born individuals increases, an understanding of the respiratory consequences of preterm birth will become increasingly important not only for neonatologists, paediatricians and paediatric pulmonologists but also for physicians and healthcare professionals involved in the care of adults who were born preterm.

Key words: Bronchopulmonary dysplasia; Chronic lung disease of prematurity; Chronic obstructive pulmonary disease; Lung function; Prematurity; Spirometry

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## Introduction

Preterm birth is defined by the World Health Organization as birth occurring before 37 weeks of completed gestation, with extreme prematurity defined as birth before 28 weeks of gestation (World Health Organisation, 2019). Currently, the rate of preterm birth worldwide is estimated at 11%, with marked geographical variation (Blencowe et al, 2012). It appears to be increasing globally, especially in industrialised nations, where delivery at earlier gestation may be induced for fetal or maternal reasons, and where healthcare resources are available to care for these vulnerable infants. In developed countries, rates of preterm birth range from 5% in European nations to 12% in the USA (Blencowe et al, 2012). Preterm birth has a significant healthcare-related economic impact, not only during the initial neonatal unit admission but also with increased healthcare use during childhood and adolescence, with those born at the most immature gestational ages generating the highest cost (Kim et al, 2022).

The survival of preterm-born infants has improved significantly over the last 30 years with advances in modern antenatal care and neonatal intensive care, with survival approaching 90% for even those born at the most extremely immature gestations (i.e., <28 weeks post-menstrual age, post-menstrual age (PMA)) (Stensvold et al, 2017). Despite continuing improvements in mortality, survivors still experience a considerable burden of long-term morbidity, and while the impact of prematurity on neurodevelopmental outcomes has been appreciated for many years, the long-term impact of preterm birth on lung function and respiratory morbidity is becoming increasingly evident (Kotecha et al, 2022). In this review, in addition to discussing the major early respiratory morbidity following preterm birth, bronchopulmonary dysplasia (BPD), we shall also discuss the longer-term respiratory consequences of preterm birth in infancy and beyond. An awareness of the

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life-long impact of preterm birth, and the consequent risk of respiratory morbidity, is becoming increasingly important not only for neonatologists, paediatricians and paediatric pulmonologists but also for physicians and healthcare professionals in adult services, as the extremely preterm-born population is increasingly surviving into adulthood and will require vigilance and monitoring.

## Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (also called chronic lung disease of prematurity), a major respiratory complication of preterm birth, was first described by Northway et al (1967) as injury to the airways and lung parenchyma characterised by heterogeneous fibrosis, epithelial damage, smooth muscle hyperplasia, hyperinflation and atelectasis secondary to positive pressure ventilation and high fractions of inspired oxygen administered over the first few weeks of life. This cohort of 13 infants with a mean gestational age at birth of 34 weeks with a mean birthweight of 2234 g had high mortality. Since then, the management of preterm infants has greatly evolved, including introduction of specifically designed neonatal ventilators, routine administration of antenatal maternal corticosteroids and early treatment with exogenous pulmonary surfactant. The result of these interventions, among others, means that infants born at increasingly immature gestations, and therefore increasingly immature stages of lung development, are now surviving. Consequently, the clinical and pathological presentation of BPD has changed, becoming a disease predominantly of those born extremely preterm or with extremely low birthweight (<1000 g). Rather than injury to relatively well-developed lungs in the first description of BPD (Northway et al, 1967), contemporary BPD is a disease characterised by dysfunctional lung development. Histological observations from animal models and infants who have died from BPD now demonstrate a more homogenous lung disease of alveolar simplification, whereby the alveoli appear larger, but fewer in number, with decreased septation and impaired growth of the pulmonary microvasculature (Thébaud et al, 2019). An imaging study of surviving preterm infants with BPD demonstrates a variable and heterogeneous disease of lung hyper expansion, cystic emphysema, interstitial fibrosis and variable airway and microvasculature injury (Higano et al, 2018). Despite ongoing advances in neonatal medicine, the incidence of BPD is continuing to rise, unlike many other neonatal outcomes (Stoll et al, 2015), likely related to the improved survival of infants born at increasingly immature gestational ages.

### Risk factors for the development of bronchopulmonary dysplasia

Prematurity and birthweight are the most important risk factors for the development of BPD, with the incidence being inversely proportional to both (Stoll et al, 2010). Whether there is a genetic predisposition to BPD is uncertain and although twin studies have demonstrated that genetic factors may play a role in the susceptibility to BPD, study sample sizes have generally been small, and identifying candidate genes has been so far unsuccessful. The pathogenesis of BPD appears to be multifactorial, with both ante- and post-natal factors increasing the risk of developing BPD (Figure 1) (Chakraborty et al, 2010), with pulmonary inflammation being a common mechanism by which the lung is injured and the normal lung development trajectory altered (Chakraborty et al, 2010; Thébaud et al, 2019). This inflammatory cascade can be initiated in the immediate post-partum period, where initial respiratory support in the delivery room can injure the preterm lung during the transition from fluid-filled lungs to air-breathing (Thébaud et al, 2019).

Early respiratory morbidity in the form of neonatal respiratory distress syndrome (RDS) is the commonest diagnosis immediately following preterm birth and results from a combination of pulmonary structural immaturity and endogenous pulmonary surfactant deficiency (Chakraborty et al, 2010; Thébaud et al, 2019). The resulting respiratory failure often necessitates the use of invasive mechanical ventilation, and risks ventilator-induced lung injury (barotrauma and volutrauma) which causes pulmonary injury and inflammation and is itself a risk factor for subsequent development of BPD. The advent of specifically designed ventilators for neonates, including those delivering volume-targeted ventilation, has reduced the degree of lung injury and risk of developing BPD (Klingenberg et al, 2017), although current practice prioritises initial use of non-invasive respiratory support

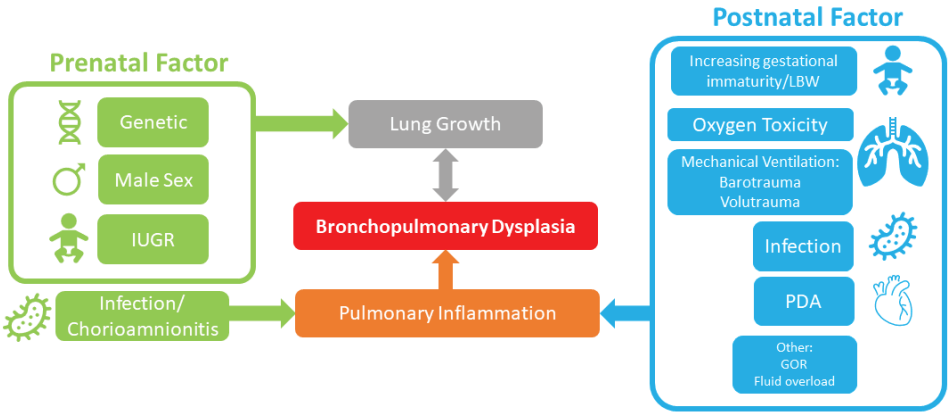


**Figure 1.** Diagram of risk factors for the development of bronchopulmonary dysplasia (adapted from Chakraborty et al, 2010). IUGR: Intrauterine growth restriction. LBW: Low birth weight. PDA: Patent ductus arteriosus. GOR: Gastro-oesophageal reflux.

**Table 1. National Institute of Child Health and Human Development, 2001 and 2016 workshop definitions of bronchopulmonary dysplasia**

| **NICHHD, 2001 Workshop definition** | | |
|---|---|---|
| **Gestational age** | **<32 weeks** | **≥32 weeks** |
| Assessment timepoint | 36 weeks PMA or discharge home | >28 days but <56 days postnatal age/at discharge home |
| Treatment with supplementary oxygen for 28 days plus | | |
| Mild BPD | Breathing room air | |
| Moderate BPD | Need for <30% supplementary oxygen | |
| Severe BPD | Need for ≥30% oxygen and/or positive pressure respiratory support | |
| **NICHHD, 2016 Workshop revised definition for moderate/severe BPD** | | |
| Treatment with supplementary oxygen for 28 days plus requiring respiratory support at 36 weeks PMA | | |
| Grade I | ■ nCPAP, NIPPV or HFNC ≥3 litres/min with $FiO_2$ 0.21<br>■ NC 1 to <3 litres/min, hood $O_2$ with $FiO_2$ 0.22 – 0.29<br>■ NC <1 litres/min with $FiO_2$ 0.22 – 0.70 | |
| Grade II | ■ IPPV with $FiO_2$ 0.21<br>■ nCPAP, NIPPV or HFNC ≥3 litres/min with $FiO_2$ 0.22 – 0.29<br>■ NC 1 to <3 litres/min, hood $O_2$ with $FiO_2$ ≥0.30<br>■ NC <1 litres/min with $FiO_2$ 0.70 | |
| Grade III | ■ IPPV with $FiO_2$ >0.21<br>■ nCPAP, NIPPV or HFNC ≥3 litres/min with $FiO_2$ ≥0.30 | |
| Grade IIIa | Death between 14 days of postnatal age and 36 weeks owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities | |

*NICHHD, 2001 BPD Classification (Modified from Am J Respir Crit Care Med. 2001 Jun;163(7):1723–1729) NICHHD, 2016 BPD Classification (Modified from J Pediatr. 2018;197:300–308).*

*NICHHD: National Institute of Child Health and Human Development. BPD: bronchopulmonary dysplasia. PMA: post-menstrual age. nCPAP: nasal continuous positive airway pressure, NIPPV: non-invasive intermittent positive pressure ventilation, IPPV: Invasive positive pressure ventilation, HFNC: High-flow nasal canulae, NC: Nasal cannula, $FiO_2$: fraction of inspired oxygen.*

wherever clinically possible (Course and Chakraborty, 2020). Pulmonary immaturity and RDS also often necessitate the use of supplementary oxygen therapy, which although often life-saving, precipitates oxidative stress and injury in the immature lungs (Morty, 2018). While the routine use of antenatal maternal administration of corticosteroids and

early exogenous pulmonary surfactant replacement therapy have decreased mortality and early respiratory morbidity, they have had little impact on rates of BPD (Simpson et al, 2023). Postnatal infections, sepsis, and the consequent systemic inflammatory response, especially from conditions such as necrotising enterocolitis, have also been associated with an increased risk of developing BPD (Thébaud et al, 2019). A Patent ductus arteriosus (PDA) is a common finding following preterm birth and has been associated with an increased risk of BPD, due to the left-to-right shunting of blood to the pulmonary vasculature, fluid overload, pulmonary hypertension and damage to the pulmonary vasculature and parenchyma. Numerous treatment strategies to close the PDA to prevent BPD have been investigated, but despite numerous randomised controlled trials, none so far have shown any clinical benefits (Gupta et al, 2024).

## Diagnosis of bronchopulmonary dysplasia

Bronchopulmonary dysplasia is an unusual disease in that it is defined by its treatment with supplemental oxygen, as opposed to a diagnostic test or histopathological appearance. The diagnostic criteria for BPD have evolved as the disease process has changed with advances in neonatal intensive care. Currently, the most widely used definition internationally is from the National Institute of Child Health and Human Development (NICHHD) workshop, published in 2001, which defines BPD as a requirement for supplemental oxygen for at least the first 28 days of life, with severity defined when the preterm-born infant born at less than 32 weeks gestation reaches 36 weeks PMA, as detailed in Table 1. For infants born at or over 32 weeks gestation, assessment for severity is made at 56 days of life. This classification system acknowledges that some infants needing supplemental oxygen therapy for 28 days of age but not at 36 weeks PMA may also have underlying residual lung pathology (Jobe and Bancalari, 2001). There have been further attempts by the NICHHD in 2016 to improve upon the definition, acknowledging the introduction of newer modalities of respiratory support, including heated and humidified high-flow nasal cannula therapy, to grade moderate and severe BPD more precisely (Higgins et al, 2018) (Table 1). Further attempts to classify severe BPD have focused on extensive phenotyping to determine whether parenchymal injury, pulmonary hypertension or mixed patterns predominate (Wu et al, 2020), with the aim to prognosticate outcomes over infancy, with significant pulmonary hypertension carrying a high risk of early mortality.

## Treatment of bronchopulmonary dysplasia

Without effective interventions to prevent preterm birth at present, most treatment strategies have focused on reducing exposure to risk factors associated with the development of BPD (Table 2) (Thébaud et al, 2019; Schmidt et al, 2006; Darlow et al, 2016; Doyle et al, 2006; Baud et al, 2016). Limiting the use of mechanical ventilation (especially endotracheally intubated invasive ventilation) (Course and Chakraborty, 2020), caffeine administration (to prevent apnoea of prematurity) (Schmidt et al, 2006), and postnatal administration of corticosteroids (Simpson et al, 2023) have all been shown to modestly reduce the risk of developing BPD. Important questions remain about the optimal type, dose, route and timing of corticosteroid administration, as, although early high-dose dexamethasone (<7 days of life) significantly reduced the development of BPD, it carried an unacceptably high risk of poorer neurodevelopmental outcome and cerebral palsy at 2-years of corrected age. Late (>7 days of life), low-dose dexamethasone (Doyle et al, 2006) and early use of hydrocortisone (Baud et al, 2016) have been investigated and appear safer from a neurodevelopmental perspective, but appear to be less effective in preventing the development of BPD. Vitamin A, which is important for lung development, has been shown to reduce the risk of developing BPD without significant systemic side effects, but regular three-times per-week intramuscular administration is challenging in preterm infants with low muscle mass, and enteral administration appears ineffective (Darlow et al, 2016); therefore, Vitamin A has not become routinely established in clinical practice.

For established BPD, there remain few therapeutic options, and international guidelines acknowledge the lack of robust evidence, e.g., for inhaled therapy, to guide management, including therapeutic options during childhood for preterm-born infants discharged from the neonatal unit (Duijts et al, 2020). Supplemental oxygen remains the mainstay of

treatment and infants with moderate/severe BPD often require home oxygen on discharge, which can help optimise growth and prevent the development of pulmonary hypertension. While increasing numbers of extremely preterm infants survive and current treatments to prevent the development of BPD have only modest benefits, further research into optimal management of infants with established BPD is urgently needed.

## Respiratory consequences of preterm birth in infancy and childhood

Until recently, most studies have focused on the longer-term respiratory outcomes for preterm-born individuals who had a neonatal diagnosis of BPD. The assessment of BPD severity at 36 weeks corrected gestational age was originally chosen as it provided the highest positive predictive value for respiratory morbidity over the first 2 years of life (Shennan et al, 1988). Although challenging to perform, lung function tests in infants suggest that over the first 12 months of life, those with severe BPD can develop obstructive, restrictive or mixed lung function deficits, which are likely to be related to impaired alveolar growth, small airways disease and gas trapping (Shepherd et al, 2018). In addition, infants with BPD are at heightened risk of sleep-disordered breathing and sleep hypoxaemia, which can be clinically silent (Moyer-Mileur et al, 1996). A small proportion of infants with severe BPD will require long-term positive pressure ventilation, due to significant parenchymal disease and/or larger airway disease, including tracheobronchomalacia (Hysinger et al, 2017) or subglottic stenosis due to prolonged periods of endotracheal intubation and invasive mechanical ventilation. In these cases, tracheostomy can provide a safe, secure airway and optimise ventilation efficiency.

**Table 2. Interventions to prevent bronchopulmonary dysplasia (adapted from Thébaud et al, 2019)**

| Intervention | Rationale | Findings |
|---|---|---|
| 'Gentle' ventilation strategies | Reduces ventilator-induced lung injury (volutrauma/barotrauma) which leads to pulmonary injury and inflammation | Modest improvements in BPD with the use of targeted tidal volume ventilation and non-invasive respiratory support |
| Targeting lower oxygen saturations | Avoiding high oxygen levels reduces oxygen-mediated inflammation | Targeting saturations between 91–95% reduces mortality without increasing BPD risk |
| Less invasive surfactant therapy | Avoids the need for endotracheal intubation and mechanical ventilation for administration | Early studies promising, but larger prospective studies required |
| Caffeine | Prevents apnoea of prematurity, which aids weaning of mechanical ventilation and reduces extubation failure | Recommended for routine use in all preterm infants <34 weeks PMA (Schmidt et al, 2006) |
| Vitamin A | Preterm infants are vitamin A deficient<br>Vitamin A required for normal lung development | Modest improvements seen in BPD rates, but repeated intramuscular administration difficult in preterm infants (Darlow et al, 2016) |
| | **Glucocorticoids** | |
| Dexamethasone | Targets pulmonary inflammation | Early use (<7 days of life) reduces BPD but increases the risk of poor neurodevelopmental outcomes. Low-dose regimes used for ventilator-dependent infants >7 days old (Doyle et al, 2006) |
| Hydrocortisone | Targets pulmonary inflammation | Early use (<7 days of life) may reduce BPD but the risk of intestinal perforation (Baud et al, 2016). Longer-term neurodevelopmental outcomes are currently unclear |
| Budesonide mixed with exogenous pulmonary surfactant | Targets pulmonary inflammation directly and reduces systemic side effects | Only small-scale studies are available but with promising results for reducing BPD<br>Larger studies are required |

Infants with BPD are at higher risk of severe lower respiratory tract infections, especially over the first 2 years of life. These infections are typically viral, with respiratory syncytial virus (RSV) and rhinovirus being common causative agents. Up to 50% of infants with BPD will require re-hospitalisation in the first 2 years of life for respiratory illness (Bhandari and Panitch, 2006), with RSV infection being particularly severe in those with a history of BPD. Often these infants will need intensive care unit admission thereby resulting in markedly increased healthcare costs (Deshpande and Northern, 2003). Many centres routinely use the anti-RSV monoclonal antibody palivizumab, usually targeting high-risk preterm infants, including those with BPD (Quinn et al, 2021). Given its half-life, palivizumab is administered monthly over the winter season. The newer monoclonal antibody, nirsevimab, with an extended half-life only requires a single administration per RSV-season. In addition to evidence of efficacy in term and near-term infants, recently nirsevimab has also been shown to be effective in reducing hospital admissions for RSV infection in preterm-born infants (Domachowske et al, 2022).

Bronchopulmonary dysplasia is associated with pulmonary vascular remodelling leading to the development of secondary pulmonary arterial hypertension, which can, if left untreated, precipitate right-sided heart failure. Pulmonary arterial hypertension in infants with BPD

**Table 3. Published meta-analyses of lung function studies comparing preterm-born survivors and term controls performed during childhood, adolescence and adulthood**

| Study | Age range | Group comparison | Study group (n) | Control group (n) | Lung function | |
|---|---|---|---|---|---|---|
| | | | | | Parameter | Result |
| Kotecha et al (2022) | 3–52 years | Preterm (<37 weeks) vs Term, mean (95% CI) | 7094 | 17,700 | $\%FEV_1$ | –9.2 (–10.4 to –8.0) |
| | | BPD vs Term, mean (95% CI) | 1736 | 2827 | $\%FEV_1$ | –15.9 (–17.6 to –14.2) |
| | | No BPD vs Term, mean (95% CI) | 2133 | 2562 | $\%FEV_1$ | –5.8 (–7.1 to –4.5) |
| Gibbons et al (2023) | 3–52 years | Preterm (<37 weeks) vs Term, SMD (95% CI) | 5501 | 12,648 | $FEV_1/FVC$ | –0.56 (–0.68 to –0.45) |
| | | BPD vs Term, SMD (95% CI) | 1326 | 1851 | $FEV_1/FVC$ | –0.87 (–1.02 to –0.71) |
| | | No BPD vs Term, SMD (95% CI) | 1606 | 1727 | $FEV_1/FVC$ | –0.45 (–0.62 to –0.27) |
| Du Berry et al (2022) | 5–25 years | Moderate-late preterm (32 to <37 weeks) vs Term, z-score mean difference (95% CI) | 847 | 8209 | $FEV_1$ | –0.22 (–0.35 to –0.09) |
| | | | | | FVC | –0.23 (–0.4 to –0.06) |
| | | | | | $FEV_1/FVC$ | –0.11(–0.20 to –0.03) |
| | | | | | $FEF_{25-75}$ | –0.27 (–0.41 to –0.12) |
| Doyle et al (2019a) | 16–33 years | Very preterm (<32 weeks) vs Term, z-score mean difference (95% CI) | 935 | 722 | $FEV_1$ | –0.78 (–0.96 to –0.61) |
| | | | | | FVC | –0.25 (–0.40 to –0.10) |
| | | | | | $FEV_1/FVC$ | –0.74 (–0.85 to –0.64) |
| | | | | | $FEF_{25-75}$ | –0.88 (–1.12 to –0.65) |
| Lillebøe et al (2024) | 17–33 years | Extremely preterm (<28 weeks), mean (95% CI) | 879 | N/A | $FEV_1$ (z-score) | –1.05 (–1.21 to –0.90) |
| | | | 858 | | FVC (z-score) | –0.45 (–0.59 to –0.31) |
| | | | 648 | | $FEV_1/FVC$ | 79.54 (77.71 to 81.38) |

*BPD: bronchopulmonary dysplasia. $FEV_1$: forced expiratory volume in 1 second. $\%FEV_1$ percentage predicted forced expiratory volume in 1 second. FVC: Forced vital capacity. $FEF_{25-75}$: Forced expiratory flow between 25–75% of maximal expiration. SMD: Standardised mean difference. CI: confidence interval.*

is associated with high mortality in the first 2 years of life (Farrow and Steinhorn, 2012). Maintaining oxygen saturations >95% for infants with pulmonary arterial hypertension can potentially prevent progression of the disease. Sildenafil (a phosphodiesterase-5 inhibitor, which induces vasodilation by acting on the nitric oxide pathway) is commonly used in the management of pulmonary arterial hypertension to reduce pulmonary blood pressure, however, there is a lack of robust data on its long-term use in pulmonary arterial hypertension with infants with BPD (Hansmann et al, 2021).

Beyond infancy, preterm-born individuals have a heightened risk of poor respiratory outcomes in childhood and adolescence (**Table 3**) (Kotecha et al, 2022; Gibbons et al, 2023; Du Berry et al, 2022; Doyle et al, 2019a; Lillebøe et al, 2024). Again, most of the published work to date has focused on individuals who had a neonatal history of BPD. A recent large systematic review and meta-analysis of 86 studies demonstrated that across a wide range of ages (3 to 52 years old) preterm birth was associated with a 9.2% (95% confidence interval 8 to 10.4%) reduction in percent precited forced expiratory volume in 1 second ($FEV_1$), that was consistent across the age ranges studied. This deficit increased to 15.2% (95% confidence interval 14.2 to 17.6%) reduction for those with a history of mild or moderate/severe BPD in infancy (Kotecha et al, 2022). The studies included in this analysis spanned a wide range of years, with subjects born between 1961 and 2017, with most subjects studied in either childhood or adolescence. Meta-regression analysis demonstrated that these spirometry deficits improved with time for those who had BPD in infancy, perhaps reflecting advances in neonatal care. There also appeared to be geographical variation in these outcomes, with Scandinavian countries having better outcomes than Western European countries and the United States of America. Whether these differences are due to population differences including genetic, environmental, or wider socio-economic factors, or methodological variations related to study methods or population selection requires further investigation. There is also a need for robust studies from cohorts outside of these developed nations.

While most focus has been on those who had a neonatal diagnosis of BPD, it has become apparent that even those born preterm who did not have any neonatal intensive care or BPD in infancy, or are born at later gestations, are at risk of developing significant respiratory disease in later life. The UK-based Respiratory Health Outcomes in Neonates (RHiNO) study examined lung function in over 500 preterm-born school-aged children born at 34 weeks or less in gestation and who had experienced contemporary neonatal care. In this cohort, gestational immaturity at birth and a history of Intrauterine growth restriction (IUGR) were better predictors of childhood lung function deficits than a history of BPD (Hart et al, 2022). Data from the large Avon Longitudinal Study of Parents and Children (ALSPAC) cohort demonstrated that spirometry impairments were present at 8–9 years of age not only in those born at 32 weeks or less of gestation, regardless of BPD status, but also in those born in the moderate preterm category (33–34 weeks gestation), whereas those born late preterm (35–36 weeks gestation) had similar lung function measures as those born at term. By 14–17 years of age, although these spirometry deficits appeared to have generally improved, the moderate preterm group still had significantly reduced values for mid-expiratory airflow measurements (Forced expiratory flow between 25–75% of maximal expiration ($FEF_{25-75}$)) and the ratio between $FEV_1$/ Forced vital capacity (FVC) when compared to those born at term (Kotecha et al, 2012). Given that with modern neonatal care, BPD is a disease predominantly seen in those born <28 weeks gestation, these studies suggest that late preterm birth can adversely impact lung function in childhood regardless of early neonatal interventions and outcomes. Another systematic review and meta-analysis collating data on over 1600 moderate-late preterm-born individuals, who were predominantly school-aged children and adolescents, showed modest, but persistent deficits for $FEV_1$, FVC, $FEV_1$/FVC and $FEF_{25-75}$ when compared to both term-born controls and internationally standardised reference values (Global Lung Initiative), highlighting that individuals born moderate-late preterm are not achieving adequate peak lung function in early adulthood (Du Berry et al, 2022).

## Respiratory consequences of preterm birth in adulthood

With advances in neonatal care and improving survival over the last 30 years, more preterm-born individuals, including those born extremely preterm, are now reaching adulthood, with the respiratory consequences of prematurity in adulthood now becoming increasingly apparent (Table 3) (Kotecha et al, 2022; Gibbons et al, 2023; Du Berry et al, 2022; Doyle et al, 2019a; Lillebøe et al, 2024). An individual participant meta-analysis of spirometry from 11 cohort studies including over 900 preterm-born individuals (mean gestational age of 28 weeks and 1054 g birthweight) with a mean age of 21 years showed significant impairments to expiratory flows ($FEV_1$ z-score −0.78, 95% confidence interval −0.96 to −0.61, $p \leq 0.001$, and $FEF_{25-75}$ z-score −0.88, −1.12 to −0.65, $p < 0.001$) and increased likelihood of pattern of obstructive spirometry when compared to term-born controls (Doyle et al, 2019a). Most of these individuals were born before the routine use of antenatal maternal corticosteroids and exogenous surfactant replacement therapy. Longitudinal studies of preterm-born individuals from childhood to adulthood (aged 25 years) born at <28 weeks gestation in the post-surfactant era have demonstrated persistent deficits in $FEV_1$ (mean z-score −0.97, 95% confidence intervals −1.23 to −0.71, $p < 0.001$) and airway obstruction, which appears more pronounced in those with a previous history of BPD, when compared to term-born individuals (Doyle et al, 2019b). Another meta-analysis has recently shown that preterm-born individuals with a history of BPD appear to develop an increasingly obstructive pattern as they age (Gibbons et al, 2023). These findings have also been supported by another recent meta-analysis of data from 16 studies of lung function in adults born at <28 weeks gestation, finding a mean $FEV_1$ deficit of 14% (or one z-score), and a mean $FEV_1$/FVC near the lower limit of normal. These findings were more pronounced in those with a history of BPD. Interestingly, the authors found no difference between those born before and after the introduction of pulmonary surfactant replacement (Lillebøe et al, 2024).

However, these findings are not exclusive to extremely preterm-born individuals. A longitudinal study of moderate-to-late (32 to <37 weeks gestation) preterm-born young adults (aged 16 and 24 years at each respective assessment) demonstrated smaller, but persistent deficit in $FEV_1$ (mean z-score −0.28, 95% confidence intervals −0.56 to −0.01, $p$=0.05) in males and obstructive spirometry patterns in both sexes when compared to term-born controls, regardless of smoking status (Lundberg et al, 2024). It is becoming increasingly apparent that preterm-born individuals appear to be at heightened risk of early respiratory decline in young adulthood, regardless of neonatal history of BPD or smoking status. Those individuals with the most significant lung disease will likely develop chronic obstructive pulmonary disease (COPD) in early adulthood, with consequent concerns regarding early respiratory morbidity and mortality.

## Conclusion

Over the last 30 years, as mortality has decreased markedly after preterm birth, especially in those born extremely preterm below 28 weeks gestation, it has become apparent that birth at an immature stage of lung development places survivors at increased risk of long-term respiratory morbidity, throughout childhood and in adulthood. With decreased attainment of peak lung function in early adulthood, a significant proportion of these individuals are at risk of developing COPD sooner than their term-born counterparts. While there have been many efforts to reduce the risk of developing BPD in the neonatal period, those with any positive impact have at best had modest effects. Future research must now turn to understanding the biological mechanisms underlying prematurity-associated lung disease in both early and later life and developing appropriate interventions to maximise the peak lung function attainment in early adulthood and preserve lung function to prevent premature decline. There will be an increasing role for adult healthcare services in caring for the respiratory health of the preterm-born population as long-term survival from preterm birth continues to improve.

## Key points

- As survival from preterm birth improves, the short- and long-term respiratory outcomes of delivery at an immature stage of lung development are becoming increasingly recognised.
- Bronchopulmonary dysplasia remains an important outcome in the neonatal period, but there are few effective treatment options to prevent its development.
- Management of established BPD remains supportive, aiming to prevent complications (including pulmonary arterial hypertension) and the need for re-hospitalisation due to vial respiratory tract infection.
- It is increasingly well recognised that as preterm-born individuals survive into childhood and adulthood, a significant proportion experience reduced lung function, and are at risk of early development of COPD.
- Future research should prioritise understanding the pathological mechanisms underlying prematurity-associated lung disease and developing treatments to maximise and maintain respiratory health.

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## Availability of data and materials

No original data or materials were created as part of this review.

## Author contributions

CWC, EAK, KC and SK contributed to the design of the review. CWC and SK drafted the original manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics approval and consent to participate

Not applicable.

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