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Understanding the Short- and Long-Term Respiratory Outcomes of Prematurity and Bronchopulmonary Dysplasia

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Abstract

Bronchopulmonary dysplasia (BPD) is a chronic respiratory disease associated with premature birth that primarily affects infants born at less than 28 weeks' gestational age. BPD is the most common serious complication experienced by premature infants, with more than 8,000 newly diagnosed infants annually in the United States alone. In light of the increasing numbers of preterm survivors with BPD, improving the current state of knowledge of long-term respiratory morbidity for infants with BPD is a priority. We undertook a comprehensive review of the published literature to analyze and consolidate current knowledge of the effects of BPD that are recognized at specific stages of life, including infancy, childhood, and adulthood. In this review, we discuss both the short-term and long-term respiratory outcomes of individuals diagnosed as infants with the disease and highlight the gaps in knowledge needed to improve early and lifelong management of these patients.

Keywords: bronchopulmonary dysplasia; respiratory outcomes; preterm birth

At a Glance Commentary

Scientific Knowledge on the Subject: Currently, there is no comprehensive review of what is known about the short- and long-term respiratory morbidity associated with prematurity and bronchopulmonary dysplasia (BPD). With contemporary improvements in treatment and technology, more infants born prematurely are surviving with poorly understood respiratory sequelae that will present unique challenges to pediatric and ultimately adult pulmonary providers.

What This Study Adds to the Field: This review provides both clinicians and researchers with a comprehensive understanding of the range of pulmonary outcomes for survivors of BPD. In reviewing the literature, we have also summarized the research gaps in this field.

The significant associations of preterm birth with adult health have become increasingly recognized through epidemiological research and clinical observations (1–3). Complications of preterm birth (<37 completed weeks of gestation) are most often seen in very preterm infants (28–31 wk gestation) and extremely preterm infants (<28 wk gestation) (4), although it is increasingly recognized that even modestly preterm infants are at increased risk of adverse health and developmental outcomes.

Preterm birth predisposes individuals to the development of chronic respiratory disease in adulthood, including asthma and chronic obstructive pulmonary disease (COPD) (5). Worldwide, it has been estimated that more than 15 million babies (11% of live births) are born preterm. Health complications associated with preterm birth have recently been implicated as the cause of 36% (1.03 million) of neonatal deaths. Rates of preterm birth are increasing in most countries with reliable

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data (6). In 2010, it was estimated that the rate of preterm births in the United States was 12%, accounting for 42% of all preterm births in developed regions (7), and approximately 90% of preterm infants survive (8). Infants born most preterm, during the late canalicular or saccular stage of lung development, have the greatest burden of early respiratory disease, putting them at greatest risk for later pulmonary morbidity. Indeed, despite medical advances in neonatal care that have led to improvements in survival of extremely preterm infants, the prevalence of the neonatal chronic lung disease, known as bronchopulmonary dysplasia (BPD), has not diminished (9); BPD remains the most common complication of extreme prematurity.

The respiratory system undergoes significant growth and development during the third trimester of fetal life and throughout the first year of infancy. Lung volume and function continue to increase in healthy children, reaching a maximum in their late twenties, and then steadily decline with age (5). However, in those who have experienced early lung injury or maldevelopment during infancy, respiratory symptoms may appear earlier in life, even in the absence of other illness, leading to a reduction in peak lung growth. The outcome of poor lung development depends on the type and severity of the insult as well as the lung developmental stage at which it occurs (4). Factors that may result in poor lung development include inadequate nutrition or specific nutrient deficiencies, maternal alcohol consumption, tobacco smoke exposure, respiratory infections, and exposure to environmental pollution (10). However, preterm delivery is the most common cause of abnormal lung development and can lead to lifelong sequelae.

In 1967, Northway and colleagues first described BPD as a chronic pulmonary disorder occurring in preterm infants with severe respiratory distress syndrome who had been exposed to aggressive mechanical ventilation and high concentrations of inspired oxygen (11). Infants presented with persistently abnormal lung fields on chest radiograph, and histopathological changes included interstitial thickening, lung fibrosis, and airway epithelial metaplasia and smooth muscle hypertrophy (11). After the increased use of antenatal steroids for lung maturation and the development of exogenous surfactant replacement therapy, the severity of infant lung disease decreased and survival of preterm newborns improved, particularly at lower gestational ages. These medical advancements resulted in the evolution of the disorder to a new form of the condition that predominantly occurs in the most premature infants. BPD, in the contemporary era of perinatal care, is characterized by persistent decreases in alveolar counts, with enlarged alveoli, leaving an overall reduction in the surface area available for gas exchange, and is thus considered a consequence of disrupted or arrested lung development. Currently, the most commonly used clinical definition of BPD is the need for supplemental oxygen at 36 weeks' corrected gestational age, often referred to as the Shennan definition (12). Newer definitions incorporating a physiological test of room air saturation at 36 weeks and a severity grade based on the extent of respiratory support required have also been proposed and used clinically and for research purposes (13–15).

BPD develops in approximately 10 to 40% of very low birth weight (VLBW) and extremely low birth weight born infants, respectively, with 5,000 to 10,000 new cases in the United States each year, depending on the definition applied (16). Although mortality attributable to BPD has declined over the past decade (17), BPD places a significant demand on health services (16) and constitutes a significant health burden far beyond the neonatal period. With persisting lung impairment, survivors may be at risk for developing chronic obstructive physiologic impairments, such as fixed airflow obstruction and hyperinflation, later in life. However, beyond prematurity, the role of different neonatal factors, events, or treatments in the development or persistence of pulmonary changes in later life is poorly understood. In light of the increasing numbers of survivors of BPD and the lack of clear knowledge of the etiology of BPD sequelae in later life, the goal of this paper is to review the published literature to determine the effects of BPD at different stages of the life course. This review focuses on respiratory outcomes of premature infants and the impact that a diagnosis of BPD has on these later outcomes.

Methods

An electronic search of MEDLINE and EMBASE was conducted using the following key words: "premature infants," "respiratory outcomes," "chronic lung disease," "wheezing," "outcomes," "asthma," "adult," and "bronchopulmonary dysplasia." These keywords were iteratively entered to identify all relevant literature. Further searches were then conducted based on references cited in the retrieved articles, and additional studies were identified. Titles and abstracts were included based on a checklist of selection and exclusion criteria. The search was not time limited. However, only studies published on or after the year 1990 were included in this review; these studies largely focus on children born after the routine use of antenatal glucocorticoids and availability of surfactant. The initial selection criteria included studies involving human subjects and survivors of preterm birth. Articles were included if they provided primary data on the respiratory outcomes of individuals at various stages of life. These papers were categorized according to the following subgroups: first 5 years of life, school-aged children (6–18 yr), and adulthood (older than 18 yr). Literature reviews, commentaries, metaanalyses, and systematic reviews were excluded. Only articles published in English with full text versions available were included. All studies cited in this paper were identified and abstracted by the authors.

Results

Overall, 61 publications met inclusion criteria (18–78) and are summarized in Table 1.

First 5 Years of Life

Seventeen papers were identified that evaluated pulmonary outcomes of preterm infants within the first 5 years of life (21, 26, 27, 30, 31, 33, 40, 46, 47, 51, 55, 58, 61, 64, 65, 73, 74). Varying definitions of BPD were used in these studies, with some defining BPD as persistent oxygen use at 28 days of age and others defining BPD based on an assessment at 36 weeks postmenstrual age. Studies varied in study design, evaluations, and study end points used to measure pulmonary outcomes in children younger than 5 years old. Eight

Table 1. Premature Infants with Bronchopulmonary Dysplasia and Respiratory Outcomes: Selected Studies, Grouped by Age of Outcome

Study, Location	Study Objective	Outcome Definition	Study Design and Sample Size	Findings	Comments
Outcome measured within the first 5 yr of life					
Baraldi *et al.* (1997) (27), Italy	Evaluate the physiologic course of pulmonary function in infants with bronchopulmonary dysplasia	Diagnostic criteria for BPD included: birth weight < 1,250 g, ventilator dependence of at least 10 d, need for continuous supplemental oxygen for >28 d, and abnormal chest radiograms at 1 mo of age.	Cohort N = 24 All infants included had BPD.	Although pulmonary mechanics of BPD survivors improve during the first years of life, reaching the range of normal values, at 2 yr of age they still present a substantial airway function impairment as revealed by the low FEFs.	Pulmonary mechanics and FRC were evaluated at 3, 6, 9, 12, and 24 mo.
Evans *et al.* (1998) (30), United States	To evaluate the associations between family history of asthma, low birth weight, and respiratory disease at birth, in infancy, and in early childhood	Radiographic evidence of BPD and use of supplemental oxygen at 30 d of life was termed as "BPD diagnosis." BPD severity was also assessed.	Case–control/cohort study N = 1,007 neonates Cases (n = 723) were neonates born with birth weight < 1,501 g, and control subjects (n = 106) were full term.	Of cases, 29.4% showed radiographic evidence of BPD and 25.4% were diagnosed with BPD. Two indicators of BPD/CLD were found to be significantly associated with bronchodilator use: radiographic evidence of BPD at age 25–35 d up to age 2 yr and with asthma between ages 2–5 yr. Infants with radiographic evidence of BPD or who received supplemental oxygen at 36 wk postconceptional age were significantly more likely to use bronchodilators in the first 2 yr of life and to have asthma after the first 2 yr.	The Newborn Lung Project, multicenter study. Data on outcomes associated with infants with BPD were only assessed for this review.
Fakhoury *et al.* (2010) (55), Houston, Texas	Measure lung function in a cohort of children with BPD during their first 3 yr of life	Chest radiographic findings consistent with BPD diagnosis and required oxygen beyond 28 d of life or 36 wk gestation was defined as BPD diagnosis.	Prospective longitudinal cohort study N = 44 All infants included had BPD.	Children with BPD were found to have low partial expiratory flow, measured by VmaxFRC. No significant improvements were seen over time. During the first 3 yr of life, children with BPD show significant abnormalities with airflow limitation according to lung function testing, with no improvements.	Partial expiratory airflow was measured at 6, 12, and 24 mo.

(Continued)

Table 1. (*Continued*)

Study, Location	Study Objective	Outcome Definition	Study Design and Sample Size	Findings	Comments
Farstad *et al.* (1995) (74), Germany	To evaluate impairment of cardiopulmonary function at 50 and 120 wk corrected age in premature infants with and without BPD	BPD was defined as neonatal respiratory distress syndrome requiring mechanical support, persistent respiratory insufficiency with oxygen dependency at 28 d of age, and abnormal chest radiograms at the same age.	Case–control N = 37 Cases (n = 23) were infants with severe respiratory distress syndrome diagnosed with BPD, and control subjects (n = 14) were low birth weight without BPD.	Respiratory system resistance was initially increased, especially in the BPD group, but improved gradually. $\dot{V}$maxFRC ml/s indicated severe peripheral obstruction (flow $<$ 84 ml/s) in 16/20 infants with BPD and in 7/12 control infants at 50-wk corrected age. At 120 wk, control patients did not suffer from severe peripheral pulmonary obstruction (flow $<$ 120 ml/s), whereas this was still found in 5/13 infants with BPD.	Measurements were taken at 50 and 120 wk of age.
Filbrun *et al.* (2011) (58), Michigan	Assess longitudinal changes in pulmonary function in infants with a history of BPD over the first 3 yr of life	BPD was defined as lung disease resulting from mechanical ventilation and oxygen therapy in infants born prematurely who require oxygen at 36 wk PMA.	Longitudinal cohort N = 18 infants All infants included had BPD.	Eighteen infants underwent two lung function studies. Spirometry demonstrated significant reductions in FEV in 0.5 s (76.0 $\pm$ 15.9% predicted; *Z* score, -2.13 ± 1.69), FEF at 75% of expired FVC (54.8 $\pm$ 31.1%, -3.58 ± 2.73), and $FEF_{25–75\%}$ (67.8 $\pm$ 33.3%, -1.79 ± 1.76).	Significant airflow obstruction and modest restriction demonstrated
Grégoire *et al.* (1998) (31), Montreal, Canada	Determine if very preterm infants are at high risk of morbidities at 18 mo	BPD was defined as oxygen dependence at 28 d or 36 wk gestational age.	Case–control retrospective cohort study N = 217 infants Control: neonatal comparison group, not oxygen dependent at 28 d (n = 76); cases: BPD-1: received O_2 28 d, not at 36 wk (n = 48) and BPD-2: received O_2 at 36 wk (n = 93)	Children with BPD-1 were similar in outcomes measured (growth, general health, and respiratory causes) to the control group. Children with BPD-2 were similar to control but had more days of readmissions for respiratory problems (6.3 vs. 2.0 for the control group and BPD-1).	Outcome measures included: growth, persistent respiratory problems, surgery, hospitalizations, and neurodevelopmental impairments.
Hofhuis *et al.* (2002) (73), the Netherlands	To evaluate $\dot{V}$maxFRC in VLBW infants with chronic lung disease, treated with high-frequency oscillation ventilation or conventional mechanical ventilation	Outcome defined as VLBW ($<$1,250 g), need for mechanical ventilation for at least 7 d after birth, need for continuous supplemental oxygen at 28 d and/or at 36 wk gestational age, and chest radiogram at 1 mo of age typical for CLD	Prospective cohort study N = 36 All infants included had chronic lung disease/ BPD.	At 6 and 12 mo, mean $\dot{V}$maxFRC was significantly below normal. Between 6 and 12 mo, there was a mean reduction in $\dot{V}$maxFRC (*Z* score) of 0.5 ($P < 0.001$). VLBW infants with CLD have decreased $\dot{V}$maxFRC, which worsens during the first year of life.	Participants born between January 1998 and September 1999 from same hospital

(*Continued*)

Table 1. (*Continued*)

Study, Location	Study Objective	Outcome Definition	Study Design and Sample Size	Findings	Comments
Hsieh *et al.* (2007) (47), Taiwan	Verify whether BPD is a risk factor for asthma in VLBW infants during their early childhood	BPD was defined as the need for supplemental oxygen at 36 wk PMA with typical radiologic changes, gestational age $<$ 32 wk, and weight of $<$1,500 g.	Retrospective cohort study N = 168 All infants included were preterm with a gestational age $\leq$ 32 wk, weight $<$ 1,500 g.	BPD was found in 31 premature children (18.5%). Children with BPD had significantly higher prevalence of childhood asthma than children without ($P < 0.001$).	Neonates admitted to the hospital from January 1995 to December 2001. Outcome measured at average age of 4.8–5.6 yr
Jacob *et al.* (1998) (33), Quebec, Canada	Evaluate long-term pulmonary sequelae of survivors of BPD	BPD criteria: premature birth at $\leq$34 wk gestational age and requirement for supplemental oxygen for at least 1 mo after term	Case–control study N = 30 Cases: with BPD; control subjects: premature but without BPD	Subjects with BPD had a mean FEV_1 of 64 $\pm$ 21% predicted (4 had an $FEV_1 < 50\%$ predicted) compared with 85 $\pm$ 11% ($P < 0.01$) for the preterm children in the control group. Severe BPD may result in moderate to severe long-term abnormalities.	Outcomes were measured at a mean age of 1.1 yr. Due to the therapeutic era, none of the children had received surfactant therapy.
Mallory *et al.* (1991) (21), Missouri	Evaluate maximal expiratory flow volume in infants with previous tracheostomy with moderate to severe BPD	BPD criteria: neonatal respiratory distress requiring mechanical ventilator support, persistent respiratory insufficiency with oxygen dependency at 28 d of age, and abnormal chest radiograms at 1 mo	Longitudinal study N = 11 All infants included had previous moderate to severe BPD.	In patients with moderate to severe BPD, vital capacity is moderately decreased but catches up to normal levels by 36 mo of age. These findings suggest that in BPD neither obstruction of the smaller intrathoracic airways nor bronchial hyperreactivity resolves during the first 3 yr of life.	Very small sample. No comparison. Two groups: Group A, ventilated $<$5 mo; Group B, ventilated $\geq$10 mo.
Ng. *et al.* (2000) (40), Hong Kong, China	Asses long-term sequelae of individuals who suffered from BPD at birth	Preterm infants with $<$32 wk gestation and documented oxygen dependency for $>$28 postnatal days	Retrospective cohort study N = 55 All participants had BPD at infancy.	Forty-four percent of children demonstrated symptoms of current asthma. Children with BPD had a significantly higher risk than the general population of developing current asthma (OR, 4.7; 95% CI, 3.4–6.5; $P < 0.0001$).	Mean age at assessment was 5.4 yr.
Pramana *et al.* (2011) (61), Bern, Switzerland	Describe the burden of respiratory disease in groups of preterm infants with and without BPD	BPD was defined as supplemental oxygen requirement for at least 28 d.	Prospective birth cohort study N = 126 All infants included were preterm, 78 with and 48 without BPD.	Eighty percent experienced cough; 44% experienced wheeze. Cough in preterm infants is as common as in term infants, whereas wheeze and inhalation therapy occur more often in VLBW and survivors of BPD.	Patients taken from one hospital born between 1999 and 2006. Outcome was measured 12 mo after birth.

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Table 1. (*Continued*)

Study, Location	Study Objective	Outcome Definition	Study Design and Sample Size	Findings	Comments
Robin *et al.* (2004) (46), Chicago, Illinois	Examine lung function in infants with history of prematurity and BPD	BPD defined as preterm birth with O_2 at 36 wk PMA	Case–control study Cases: n = 28, history of prematurity and BPD Control subjects: n = 41, healthy full-term infants	Fifty percent of cases had a history of recurrent wheezing. Participants with history of BPD had decreased FEF compared with control subjects. FRC, RV, and RV/TLC were increased in cases. Infants with a history of BPD have pulmonary function abnormalities characterized by mild to moderate airflow obstruction and air trapping.	Age at study, 68.0 ± 35.6 wk
Sanchez-Solis *et al.* (2012) (64), Spain	Determine if lung function is different between preterm infants with and without BPD	BPD and severity of BPD (mild/moderate/severe) defined per NICHD/NIH workshop	Case–control study Cases: n = 43, history of prematurity and BPD Control subjects: n = 32, history of prematurity	*Z* scores of $FEV_{0.5}$, $FEF_{50\%}$, $FEF_{75\%}$, $FEF_{85\%}$, $FEF_{25-75\%}$ and gestational age were lower in cases than in control subjects. BPD was associated with significantly lower flows. BPD is associated with an additional decrease of lung function during the first 2 yr of life in infants bom preterm.	Lung function was measured at chronological age range of 2–28 mo.
Schaubel *et al.* (1996) (26), Ontario, Canada	Evaluate the effect of certain characteristics on asthma incidence during age 0–4 yr	BPD was assessed retrospectively and was identified through ICD9 codes.	Retrospective cohort N = 16,207, all births between April 1984 and March 1985	A total of 1.4% (n = 228) were diagnosed with BPD. Prematurity (OR = 1.34) and birth weight < 1,500 g (OR = 211) in the presence (OR = 2.95) or absence (OR = 1.61) of BPD were significantly associated with preschool asthma.	Data available from 1984–1989
Schmalisch *et al.* (2012) (65), Berlin, Germany	Compare functional lung development after discharge between VLBW infants with and without BPD	BPD criteria: preterm birth or birth weight < 1,500 g and needed supplemental oxygen at 26 wk PMA	Case–control study N = 55, preterm infants Cases: n = 29, with BPD Control subjects: n = 26, without BPD	Both V_T and $\dot{V}_E$ were significantly lower in cases than in control subjects. $\dot{V}$maxFRC increased rapidly over time in both cases and control subjects. Somatic growth of some lung functional parameters lags in former infants with BPD; the lung function of such infants develops in line with that of infants without BPD when a body weight correction is applied.	Comprehensive lung function assessment was performed at 50, 70, and 100 wk.

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Table 1. (*Continued*)

Study, Location	Study Objective	Outcome Definition	Study Design and Sample Size	Findings	Comments
Vrijlandt *et al.* (2007) (51), the Netherlands	Investigate the respiratory health of preterm infants with BPD at preschool age	BPD was defined as the need for continuous supplemental oxygen at 28 d combined with radiographic manifestation.	Case–control study Cases: n = 77, prematurely born children both with BPD (n = 41) and without BPD (n = 36) Control subjects: n = 73, healthy full-term infants	Cases with BPD reported significantly more hospital admissions because of RSV than cases without BPD. Children with BPD could be distinguished from children without BPD based on a higher resonant frequency and a lower mean reactance.	Outcome measured between 3 and 5 yr of age.
Outcome measured between 6–18 yr (school age)					
Aquino *et al.* (1999) (36), United States	Correlated high-resolution inspiratory and expiratory CT findings with pulmonary function results in older children with BPD	Inclusion criteria for participants included a previous diagnosis of BPD. BPD diagnosis was retrospectively assessed, and, as such, a clear definition was not specified by authors.	Prospective study N = 26 All patients included had a clinical history of BPD.	Ninety-two percent of participants had abnormal CT findings; 24 patients had evidence of air trapping in expiratory CT scans; 69% had abnormal functional residual capacity. Abnormal pulmonary function correlated significantly with abnormal decreases in density, air trapping on expiratory CT, and architectural distortion.	Small sample size. Broad range of ages; average age of participants was 10 yr.
Blayney *et al.* (1991) (20), Canada	Evaluate the natural history of BPD	BPD was defined as a respiratory disorder after acute neonatal injury with incomplete recovery as determined by clinical, radiologic, and blood gas tension abnormalities beyond 28 d of age.	Prospective cohort study N = 50 Follow up: n = 32 All patients included had a clinical history of BPD.	Participants had expected rate of lung growth between 7–10 yr of age, based on normal increase in FEV. Evidence of significant residual lung dysfunction. Those with BPD and normal lung function at age 7 yr, had normal lung growth; those with evidence of mild to moderate lung disease have continued lung growth or repair, or both, during their school years.	Small sample size. Infants who developed BPD after premature births were investigated.
Broström *et al.* (2010) (54), Sweden	To examine the impact of the severity of BPD on pulmonary morbidity at school age	Diagnosis of BPD was based on the need for supplementary oxygen at 28 d of age.	Follow-up/case–control study Total: N = 60; all included were VLBW Cases: n = 32, preterm with BPD Control subjects: n = 28, preterm non-BPD	Severity of BPD (graded at mild, moderate, and severe) was positively correlated with days on ventilator, CPAP, and duration of days on supplemental oxygen. Significantly more parents of children with BPD suffered from asthma. All children with BPD showed some evidence of impaired lung function. All children diagnosed with BPD are potentially at risk of developing COPD later in life.	Study population: Neonatal Care Unit of Sachsska Children's Hospital between 1992 and 1997. Followed up at age 6–7 yr.

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Table 1. (*Continued*)

Study, Location	Study Objective	Outcome Definition	Study Design and Sample Size	Findings	Comments
Cazzato *et al.* (2013) (66), Bologna, Italy	To assess lung function outcome at school age of VLBW children	BPD was diagnosed based on the need for supplementary oxygen for >28 d of postnatal age.	Case–control study Cases: n = 48; 22 with BPD Control subjects: n = 46, healthy term infants	No differences were found in lung function between VLBW children (no BPD vs. BPD) with the exception of a significantly higher RV/TLC ratio in the BPD subgroup (mean difference, 7.0%; 95% CI, 0.4–13%; $P = 0.03$).	Study population obtained from single tertiary center during 1996–1999.
Doyle *et al.* (2001) (41), Melbourne, Australia	To determine the respiratory health in adolescence of children of birth weight < 1,501 g and to compare the results with normal control subjects	BPD was defined as clinical signs of respiratory distress with an abnormal chest X-ray and an oxygen requirement after 28 d of age.	Prospective cohort, case–control Cases: n = 210 Control subjects: n = 60, healthy term infants (>2,499 g weight)	Lung function was normal at 14 yr of age for all groups. Preterm children with BPD had significantly lower values for variables reflecting flow than children without BPD.	Looked at children at the age of 14 yr who had a history of preterm birth. No matching was conducted. Sample was taken from one hospital.
Doyle *et al.* (2006) (49), Melbourne, Australia	To determine the relationship between lung function in late adolescence and BPD	BPD criteria were infants who required assisted ventilation, had respiratory distress, required oxygen at 28 d of age, and had an abnormal chest radiograph at or after 28 d.	Retrospective cohort study N = 147 All participants included were VLBW.	Twenty-two percent of the cohort had BPD. VLBW with BPD in the newborn period have poorer lung function in late adolescence than those without BPD, and their lung function may be deteriorating at a more rapid rate.	Subjects were hospitalized from 1977–1982 at birth. Outcome was measured at average age of 18.9 yr.
Doyle *et al.* (1996) (24), Australia	To determine the relationship between lung function at 11 yr of age and BPD in VLBW subjects	BPD was diagnosed in those who required intermittent positive pressure ventilation in the neonatal period, had respiratory distress and were still on oxygen at 28 d of age, and had an abnormal chest X-ray.	Case–control cohort study N = 154 All participants included were VLBW. Cases (n = 15) with BPD Control subjects group I (n = 41) ventilation but no BPD; control subjects group II (n = 64), no ventilation, no BPD	VLBW children with BPD in the newborn period have poorer lung function at 11 yr of age than other surviving VLBW children without BPD, although few have lung function abnormalities in the clinically significant range.	Outcome was measured at age 11.
Farooqi *et al.* (2011) (57), Sweden	Determine the impact of BPD, brain injury, and ROP on 11-yr outcomes in infants born at <26 wk gestation	BPD was defined as a need for supplemental oxygen at PMA (gestational age + postnatal age) 36 wk.	Cohort study N = 247 All participants included had BPD	BPD was not independently correlated with poor outcome at age 11.	Asthma/wheezing was not a major outcome. Poor outcome was defined as combined end point of death after 26 wk.

(Continued)

Table 1. (*Continued*)

Study, Location	Study Objective	Outcome Definition	Study Design and Sample Size	Findings	Comments
Fawke *et al.* (2010) (56), United Kingdom and Ireland	Assess respiratory morbidity at 11 yr in children born extremely preterm	BPD was defined as receiving supplemental oxygen at 36 wk PMA (gestational age + postnatal age).	Case–control/cohort study N = 343 Cases (n = 182) were born extremely premature. Control subjects (n = 161) were healthy term-born infants	Spirometry was obtained in both cases and control subjects. A total of 129 cases had prior diagnosed BPD. Cases showed more chest deformities and respiratory symptoms than control subjects. Twice as many cases had asthma (25 vs. 13%, $P < 0.01$) than control subjects. After extremely preterm birth, impaired lung function and increased respiratory morbidity persist into middle childhood, especially among those with BPD.	Extremely premature infants (≤25 wk gestation) with BPD were compared to extremely preterm infants without BPD and term infants.
Filippone *et al.* (2003) (43), Italy	To obtain longitudinal data on lung function measurements obtained during infancy and at school age of those who suffered from moderate/severe BPD at birth	BPD was defined as clinical signs of respiratory distress, chest radiograph abnormalities, and oxygen dependence at 28 d of life.	Longitudinal cohort study N = 18 All participants were previously diagnosed with moderate to severe BPD at infancy.	FEV_1 and $FEF_{25–75\%}$ at school age were lower than normal in 15 of 18 children, and both showed a significant positive correlation with the VmaxFRC at 24 mo of age ($r = 0.68$ and 0.85, respectively).	Assessment of respiratory function during infancy can help to identify children with BPD at risk of incomplete recovery of respiratory function during childhood.
Giacoia *et al.* (1997) (28), Oklahoma	Investigate the health outcomes of school-aged children with BPD	BPD was defined as need for supplemental oxygen, ventilator dependency, or both at or beyond 36 wk of postconceptional age and diagnostic clinical and radiologic findings on chest radiographs.	Case–control study N = 36 Cases (n = 24) were split into two groups (n = 12) with BPD and (n = 12) preterm, without BPD. Control subjects (n = 12) were term.	Cases with BPD: decreased FEV_1 and decreased $FEF_{25–75\%}$ of VC and decreased MEF at 50% VC compared to age-matched control subjects. Subclinical pulmonary dysfunction in cases with BPD persists at school age.	2 groups of cases: 12 preterm without BPD and 12 with BPD
Gross *et al.* (1998) (32), Syracuse, New York	Assess long-term pulmonary outcome of a regional cohort of children born preterm	BPD was defined as dependence on supplemental oxygen at 35 wk postconceptional age.	Case–control study N = 204 Cases (n = 96) were all preterm; group was split into BPD (n = 43) and non-BPD (n = 53). Control subjects (n = 108) were term.	Participants were evaluated at age 7 yr. Cases with BPD had more airway obstruction than both groups (significantly reduced mean FVC, FEV_1, and $FEF_{25–75\%}$ VC; all $P < 0.001$).	Preterm infants with BPD were compared with both preterm without BPD and term infants.

(Continued)

Table 1. (*Continued*)

Study, Location	Study Objective	Outcome Definition	Study Design and Sample Size	Findings	Comments
Guimarães *et al.* (2011) (59), Portugal	Asses pulmonary function and prevalence of atopy in school-aged children who were VLBW and to compare those who had BPD to those who did not	BPD was diagnosed based on dependence on supplementary oxygen at 36 wk of gestational age.	Cohort study N = 77 All participants were preterm. Cohort split into BPD (n = 13) and without BPD (n = 64)	Atopy was observed in 30.5% of patients with BPD and 26.6% of patients without BPD. Lung function tests showed airway obstruction in 15.4% of BPD and in 15.6% of no BPD. Overall, no significant differences in lung function between patients with and without BPD at school age.	Small group of patients with BPD
Hacking *et al.* (2013) (75), Australia	To determine if respiratory function at age 8 yr in extremely low birth weight or extremely preterm children remains worse than normal birth weight and term control subjects	BPD was defined as clinical signs of respiratory distress with an oxygen requirement at 36 wk PMA.	Case–control/cohort study N = 400 Cases (n = 201) included extremely low birth weight/extremely preterm births Control subjects (n = 199) included term births	Respiratory function was measured at 8 yr and compared with previous cohorts born in 1991–1992. Within cases, children who had BPD in the newborn period had significant reductions in both the FEV_1 and $FEF_{25–75\%}$ compared with those who did not have BPD. At age 8 yr, cases had significantly abnormal lung function compared with control subjects.	Cases were born in 1997 and compared to previous cohorts born in 1991–1992 (control subjects).
Hakulinen *et al.* (1996) (25), Finland	Determine the extent to which BPD affects the diffusing properties of lung tissue in childhood	BPD criteria were as follows: requirement for intermittent positive pressure ventilation during first week of life and for a minimum of 3 d, clinical signs of chronic respiratory disease persisting more than 28 d, requirement for supplementary oxygen beyond age 1 mo, and chronic changes in chest X-ray at 1 mo.	Retrospective case–control study N = 51 Cases (n = 31) were premature with birth weight $<$ 1,250 g Control subjects (n = 20) were matched for age and term born	Of the cases, 65% were diagnosed with BPD. Spirometry demonstrated reduced flow rates in both BPD and non-BPD cases. Thoracic gas volumes measured with a body plethysmograph were similar in both control subjects and cases. Structural changes in lung tissues always persist in children who are born preterm with or without BPD.	Thirty-one prematurely born children were examined at age 7–11 yr; 20 out of 31 met the criteria for BPD.
Hakulinen *et al.* (1990) (18), Finland	Measure pulmonary function and respiratory morbidity in school-aged children born preterm	BPD was defined as the need for supplementary oxygen for $>$28 d and by chronic changes on chest X-ray.	Case–control study N = 72 Cases (n = 42) were all preterm. Control subjects (n = 30) were full term at birth.	Of the cases, 10 had BPD and 19 had neonatal respiratory treatment but no BPD. Children with BPD had lower specific airway conductance and larger RV than the full-term control group, but there were no significant differences in spirometric measurements. BPD group had higher respiratory morbidity during first 2 yr of life.	Neonatal lung disease may be a more important determinant of abnormal pulmonary function at a later age than prematurity alone.

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Table 1. (*Continued*)

Study, Location	Study Objective	Outcome Definition	Study Design and Sample Size	Findings	Comments
Halvorsen *et al.* (2004) (44), Norway	Determine respiratory health and lung function status in a cohort of young preterms approaching adulthood	BPD was defined according to requirement for supplemental oxygen at ⩾28 postnatal d (mild) and ⩾36 wk (severe) PMA.	Case–control study N = 92 Cases (n = 46) were all preterm births. Control subjects (n = 46) were all full-term at birth.	Of the cases, 36 were diagnosed with BPD. Diagnosis of asthma or use of asthma inhaler was significantly more prevalent among cases. PEF and FEV were decreased in preterms. FEV_1 was reduced by 580 ml/s in subjects with history of BPD.	Gestational age of ⩽28 wk or birth weight ⩽ 1,000 g was defined as preterm. Babies born between 1982–1985 were considered for study.
Hennessy *et al.* (2008) (52), London, United Kingdom	Identify respiratory morbidity and risk factors in the EPICure cohort over first 6 yr	BPD was defined as receiving required supplemental oxygen at 36 wk PMA.	Prospective cohort study N = 308 All infants included were preterm.	A total of 236 children were followed to 6 yr. Respiratory symptoms and medication use were more prevalent at 30 mo and 6 yr in children with BPD than in those without. Children without BPD (n = 60) were not significantly different from their classmates but had consistently higher prevalence of poor respiratory health.	Participants born at ⩽25 wk gestation in 1995 were followed up at 30 mo and 6 yr of age.
Kaplan *et al.* (2012) (62), Israel	Determine the long-term pulmonary outcome of extremely premature infants	BPD was defined as lung disease requiring oxygen supplementation at 28 d and severity graded by oxygen requirement at a corrected gestational age of 36 wk.	Case–control study N = 76 Cases (n = 53) were all preterm. Control subjects (n = 23) were term.	BPD cases: 21 were mild, 7 were moderate. Sixty percent of the preterm subjects wheezed at age < 2 yr compared with 13% of the control subjects ($P < 0.001$). Pulmonary outcome was encouraging at mid-childhood.	Cases were preterm/BPD and control subjects were term. Follow up was done at a mean age of 10 yr.
Konefał *et al.* (2013) (67), Poland	Assess whether school-aged spirometry and lung volumes of premature infants with/without BPD differ from term neonates	BPD was defined as the need for supplemental oxygen for at least 28 d and radiographic findings in chest X-rays.	Case–control study N = 148 Cases n = 38 (no BPD)/20 (BPD) all preterm Control (n = 90) were term-born infants.	No statistically significant differences between the spirometric parameters in preterm infants with and without BPD were found. All investigated parameters were significantly lower in both ventilated groups compared with term control subjects, with the exception of ERV%, which was significantly higher.	Outcome was measured at 9–10 yr.

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Table 1. (*Continued*)

Study, Location	Study Objective	Outcome Definition	Study Design and Sample Size	Findings	Comments
Korhonen *et al.* (1999) (37), Finland	Evaluate the impact of BPD and VLBW on respiratory morbidity	BPD was defined as the need for oxygen supplementation and typical radiological findings in chest X-rays.	Case–control study N = 274 Cases (n = 143) were all preterm. Control subjects (n = 131) were term born.	Thirty-six cases were diagnosed with BPD at infancy. Children with BPD suffered respiratory infections and needed antibiotic courses more frequently than term control subjects. Respiratory morbidity did not significantly differ between BPD and non-BPD cases.	Questionnaire was administered to parents of children aged 2–8 yr.
Korhonen *et al.* (2004) (45), Finland	Assess respiratory outcome and its predictors during the surfactant era in VLBW schoolchildren with and without BPD	BPD diagnosis criteria were the requirement of supplemental oxygen and chest X-ray findings typical of BPD.	Case–control study N = 102 Cases (n = 68) were preterm infants. Control subjects (n = 34) were term born.	Fifty percent of cases were diagnosed with BPD at infancy. Compared with control subjects, the BPD cases had lower FEV_1, higher ratio of RV:TLC, and higher airway resistance. Birth weight, neonatal respiratory morbidity, and later environmental factors appear to affect the respiratory outcome of VLBW children.	Outcome was measured at 7–8 yr of age.
Korhonen *et al.* (2014) (70), Finland	Evaluate the inflammatory activity in plasma and exhaled air in VLBW BPD survivors at school age	BPD diagnosis was defined by radiographic findings in chest X-rays and need for oxygen supplementation at 36-wk corrected gestational age.	Case–control study N = 59 Cases (n = 40) were all preterm. Control subjects (n = 19) were nonasthmatic term born.	Twenty-one cases were former VLBW children with radBPD. There were no significant differences between the groups in any of the inflammatory markers measured. Five (25%) children with radBPD and 2 (11%) children without BPD reported asthma (P = 0.058). The inflammatory activity seems to decrease by school age in VLBW BPD survivors.	Outcomes measured at 6–14 yr of age. Background data were obtained from both patient records and parental questionnaire.
Landry *et al.* (2011) (60), Quebec, Canada	Describe the outcomes of individuals with preterm birth complicated by BPD	BPD was defined as the need for supplemental oxygen for at least 28 d.	Retrospective cohort study N = 322 All included were preterm with BPD.	Outcomes associated with initial severity of BPD: hospital readmissions in first 2 yr of life, presence of developmental delay, and FEV_1 and FVC on pulmonary function tests in patients 8–15 yr	Hospital records were used.

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Table 1. (*Continued*)

Study, Location	Study Objective	Outcome Definition	Study Design and Sample Size	Findings	Comments
Logie *et al.* (2012) (63), Australia	Relate mid-childhood respiratory function with neonatal variables in children born at ⩽32 wk	BPD was defined as the need for supplemental oxygen for at least 28 d and radiographic findings in chest X-rays.	Case–control study N = 121 Cases (n = 84) were preterm. Control subjects (n = 37) were term born.	Sixty-three percent of cases were diagnosed with BPD. Children with BPD had increased respiratory resistance and reactance, and reduced FEV_1 and $FEF_{25–75\%}$ compared with children born preterm without BPD and control subjects. Children born ⩽32 wk gestational age with BPD had worse lung function than preterm children without BPD.	Four lung function tests were performed.
Malmberg *et al.* (2000) (39), Helsinki, Finland	Investigate the association between AHR and fractional exhaled NO with school-aged children with VLBW	VLBW infants: born prematurely (birth weight < 1,500 g and/or gestational age < 30 wk)	Case–control study N = 67 Cases (n = 49) were preterm. Control subjects (n = 18) were term.	VLBW children had well-preserved lung function but significantly increased AHR. History of BPD had no effect on F_{ENO} levels. In VLBW children there is a relationship between AHR and F_{ENO} but only in atopic children.	Outcome was measured at school age.
Mitchell *et al.* (1998) (34), United States	Evaluate the effect of BPD on alveolar surface area in school-aged children	BPD criteria included history of neonatal respiratory distress, exposure to mechanical ventilation, radiographic features consistent with BPD, and dependence on supplemental oxygen at ⩾4 wk of postnatal age.	Case–control study N = 30 Cases (n = 20) were all preterm. Control subjects (n = 10) were term.	Fifty percent of cases were diagnosed with BPD. C_2H_2 transfer corrected for body surface area was lower in BPD group than cases without BPD and control subjects. With exercise, C_2H_2 transfer did increase. Soluble gas transfer at rest and during acute exercise is reduced in children who survived BPD.	Outcomes were measured using treadmill exercise studies and at age 6–9 yr.
Northway *et al.* (1990) (19), United States	Determine long-term outcomes for infants with BPD	BPD diagnosis was defined as having received mechanical ventilation and oxygen supplementation at 4 wk of age.	Case–control study N = 105 Cases (n = 52) were all preterm. Control subjects (n = 53) were term.	Sixty-eight percent of cases had airway obstruction; 24% of cases had fixed airway obstruction; 52% of cases had reactive airway disease. Most adolescents and young adults who had BPD in infancy have some degree of pulmonary dysfunction.	Outcome measured in adolescents/young adults born between 1964–1973.

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Table 1. (*Continued*)

Study, Location	Study Objective	Outcome Definition	Study Design and Sample Size	Findings	Comments
Palta *et al.* (2001) (42), United States	Assess risk factors for respiratory symptoms of VLBW-born children	VLBW was defined as weight $\leq$ 1,500 g.	Case–control study N = 508 Cases (n = 384) were all VLBW Control subjects (n = 154) were term.	Thirty-two cases were diagnosed with BPD. BPD, family history of asthma, smoking in the household, and patent ductus arteriosus were predictive of wheezing in the previous 12 mo. In this sample, there was a dramatic decrease in wheezing symptoms at age 8 yr among children with BPD at 25–35 d of age.	Cases were 8 yr old and control subjects were 8–10 yr old. Rates of asthma were compared to world rates and rates in Canada.
Parat *et al.* (1995) (22), Paris, France	Evaluate long-term pulmonary function of premature infants with and without BPD	BPD was defined as respiratory difficulties during the first 2 wk of life and significant clinical, radiologic, and blood gas tension abnormalities at a 28-d postnatal age.	Case–control study N = 24. All patients included were preterm. Cases (n = 15) were diagnosed with BPD. Control subjects (n = 9) did not have BPD.	BPD group had significantly higher total lung resistance. FEV and FEV_1/FVC were lower in BPD. Prematurity and BPD are followed by long-term airway obstruction and a mild degree of exercise intolerance. Prematurity without BPD may be followed by a milder degree of airway obstruction.	Control group was of same characteristics but born at term. Outcome was measured in late childhood.
Pelkonen *et al.* (1997) (29), Helsinki, Finland	Evaluate bronchial liability and responsiveness in prematurely born children with and without histories of BPD	Criterion of BPD was being still oxygen dependent at the age of 36 postconceptional wk.	Case–control study N = 51 Cases (n = 29) were all preterm. Control subjects (n = 22) were term.	Forty-one percent of cases were diagnosed with BPD. Spirometric values (except FEV_1/FVC) were significantly lower in BPD group than non-BPD group. All spirometric values were significantly lower in both preterm groups than in the control group born at full term ($P < 0.01$).	Sample taken from one hospital. Outcome was measured at 8–14 yr of age.
Sadeghi *et al.* (1998) (35), United States	Compare pulmonary function tests of children with BPD and asthma	BPD diagnosis criteria were gestational age of $<$35 wk at birth, history of mechanical ventilation, and supplemental oxygen requirements at 28 d.	Case–control retrospective study N = 43 Cases (n = 11) were diagnosed with BPD. Control subjects (n = 32) were diagnosed with asthma.	Pulmonary function of children with BPD who are still symptomatic after 5 yr of age is different from age-matched children with asthma, and the children with BPD demonstrate significant inspiratory flow limitations.	Follow up was measured between 5–8 yr of age. Control subjects were height matched to cases.

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Table 1. (*Continued*)

Study, Location	Study Objective	Outcome Definition	Study Design and Sample Size	Findings	Comments
Santuz *et al.* (1995) (23), Italy	Assess long-term pulmonary function of school-aged children who survived BPD	Diagnosis of BPD was made according to the criteria of Bancalari *et al.* (81). Chest radiographs at the end of the first month of life showed the featuring criteria of BPD as described by Northway *et al.* (11).	Case–control study N = 28 Cases (n = 12) had a history of BPD. Control subjects (n = 16) were term.	FVC, FEV_1 and $FEF_{25–75\%}$ were significantly lower among cases compared with control subjects. Cases performed a test indicative of reduced aerobic power. Asymptomatic school-aged survivors of BPD show evidence of striking disturbances in ventilatory response to exercise and reduced aerobic capacity.	Outcomes were measured in children aged 6–12 yr. Control subjects and cases were matched for age, height, weight, and physical activity.
Vom Hove *et al.* (2014) (71), Leipzig, Germany	Assess long-term pulmonary outcome in preterm-born VLBW children with and without BPD	BPD was defined as administration of supplemental oxygen beyond 36 wk gestational age.	Case–control study N = 56 Cases (n = 28) were preterm with BPD. Control subjects (n = 28) were preterm without BPD.	Preterm-born children with a history of BPD are significantly more likely to have lung function abnormalities, such as airway obstruction and respiratory symptoms, at school age compared with preterm-born children without BPD.	Medical history was evaluated by questionnaire.
Outcomes measured older than 18 yr (adulthood)					
Gibson *et al.* (2014) (76), Australia	To report lung function data in adulthood of VLBW survivors compared with normal birth weight control subjects and in those who had BPD compared with those without BPD	BPD was defined as infants with signs of respiratory distress and oxygen dependency beyond 28 d with classic chest X-ray changes of stage 3 or 4 BPD beyond 28 d of age.	Longitudinal cohort study/ case–control study (subanalysis) Cases (n = 87) were all VLBW. Control subjects (n = 20) were term.	Twenty-four cases were diagnosed with BPD at infancy. Both groups with birth weight $<$ 1,501 g had significant reductions in airflow compared with control subjects. Those with BPD had reductions in airflow compared with those without BPD, within the VLBW cohort. Survivors of VLBW continued to have airway obstructions in their mid-20s compared with control subjects; obstruction was most pronounced in BPD survivors.	Two case groups, one of birth weight $<$ 1,000 g and the other birth weight 1,000–1,500 g.

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Study, Location	Study Objective	Outcome Definition	Study Design and Sample Size	Findings	Comments
Gough *et al.* (2014) (69), Belfast, United Kingdom	Investigate respiratory outcomes of survivors of BPD	BPD was defined as the requirement for supplemental oxygen at >28 postnatal d and radiographic changes and severity according to oxygen requirements at 36 wk PMA.	Case–control study N = 151 Cases (n = 96) were all born preterm. Control subjects (n = 55) were born term.	Fifty-eight percent of cases were diagnosed with BPD. BPD cases were twice as likely to report wheeze and three times more likely to use asthma medication than control subjects. BPD adults had significantly lower FEV_1 and $FEF_{25–75\%}$ of FVC than both the non-BPD cases and control subjects (all $P < 0.01$).	Sample taken from one hospital. Patients included were born between 1978–1993.
Howling *et al.* (2000) (38), Canada	Review the CT appearances of adult survivors of BPD	Patients for this study were identified by reviewing the clinical records of patients with BPD who survived to adulthood. BPD was characterized using the following criteria: patients underwent mechanical ventilation and low birth weight.	Retrospective case–control N = 15 Cases (n = 5) were diagnosed with BPD. Control subjects (n = 10) were term-born infants.	Multifocal areas of reduced lung attenuation were the main findings on CT and were present in all five patients with BPD. Pulmonary function abnormalities consisted of airway obstruction and air trapping. Airway obstruction, present in 80% (4/5) of cases, was manifested by decreases in FEV_1 and MEF at 50% of VC. Air trapping was observed in all cases.	In all cases, BPD had been preceded by respiratory distress syndrome. Control subjects were matched for age and sex.
Lovering *et al.* (2014) (77), United States	Test the hypothesis that adult survivors of preterm birth with and without BPD with reduced exercise capacity demonstrate respiratory limitations	BPD was defined by the use of supplemental oxygen therapy for >28 d.	Cohort study N = 55 n = 35 were preterm; 20 with BPD and 15 without BPD. n = 20 were born at term.	Severe dyspnea and leg discomfort associated with critical constraints on V_T expansion may lead to reduced exercise tolerance in adults born very or extremely preterm, whether or not their birth was complicated by BPD and despite differences in expiratory flow limitation. Adults born very or extremely preterm have respiratory limitations to exercise similar to patients with COPD.	Ventilatory measurements were made on all patients before and after exercise.

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Study, Location	Study Objective	Outcome Definition	Study Design and Sample Size	Findings	Comments
Vollsæter *et al.* (2013) (68), Bergen, Norway	Assess the development of spirometric lung function variables from childhood to adulthood after extreme preterm birth	BPD was defined if supplemental oxygen was required at 28 postnatal d.	Population-based cohort Studies/case–control study Cases (n = 83) were all preterm. Control subjects (n = 67) were term.	Sixty-three cases were diagnosed with BPD. Airway obstruction was present from mid-childhood to adulthood after extreme preterm birth, most evident after neonatal BPD. Lung function indices were tracking similarly in the preterm and term-born groups.	Participants were recruited from two different cohorts. Lung function was assessed at 10 and 18 yr for one cohort and at 18 and 25 yr for the second cohort.
Vrijlandt *et al.* (2005) (48), the Netherlands	Study the prevalence of respiratory symptoms in adults born prematurely, differences between those who did and did not develop BPD at infancy	BPD was defined as clinical signs of respiratory distress, with an abnormal chest X-ray and an oxygen requirement after 28 d of age.	Prospective cohort study; nationwide follow-up study N = 690 n = 508 had a gestational age of ⩽32 wk. n = 182 had a gestational age of >32 wk.	A total of 111 (8.2%) developed BPD. Prevalence of doctor-diagnosed asthma was significantly higher in female ex-preterms than in the general population; study shows a higher prevalence of asthma, wheeze, and shortness of breath in the prematurely born young adults.	Main outcome measures: Presence of wheeze, shortness of breath, asthma, hay fever, and eczema using the ECRHS questionnaire.
Vrijilandt *et al.* (2006) (50), the Netherlands	Determine long-term effects of prematurity on lung function and exercise capacity in ex-preterms compared with healthy peers	BPD was identified by the need for oxygen for >28 d and by chronic changes on the chest X-ray.	Prospective cohort study N = 90 n = 42 were low birth weight. n = 48 were term.	Twenty-one percent of participants were survivors of BPD. No significant differences in lung function and exercise parameters were found between preterms with and without BPD.	Project on Preterm and Small for Gestational Age Children (POPS) Dutch study. Small sample size.
Wong *et al.* (2008) (53), Perth, Australia	To describe the functional and structural pulmonary sequelae of moderate and severe BPD in a population of adult survivors	BPD was defined as birth weight < 1,500 g and continued dependence on supplementary oxygen after 36 wk PMA.	Prospective cohort study N = 21 All participants were survivors of BPD.	Young adult survivors of moderate and severe BPD may be left with residual functional and characteristic structural pulmonary abnormalities, most notably emphysema.	Small study sample. Subjects were born between 1980 and 1987 and required supplemental oxygen.
Wong *et al.* (2011) (72), Perth, Australia	To describe the structural pulmonary sequelae of BPD in adulthood	BPD was defined as birth weight < 1,500 g and continued dependence on supplementary oxygen after 36 wk PMA.	Prospective cohort study N = 51 All participants were survivors of BPD.	Abnormal findings were seen in 50 (98%), the most common of which were subpleural triangular opacities (94%), linear opacities (90%), air trapping (65%), and emphysema (47%).	Median age = 20 yr.

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Table 1. (*Continued*)

Study, Location	Study Objective	Outcome Definition	Study Design and Sample Size	Findings	Comments
Vollsæter *et al.* (2015) (78), Norway	To compare respiratory health and lung function in a population-based birth cohort of extremely preterm born young adults to matched control subjects	BPD was defined if supplemental oxygen was required at 28 postnatal d.	Case–control study N = 90 Cases (n = 45) were born extremely preterm. Control subjects (n = 45) were born full term.	Cases′ respiratory measures, FEV_1, $FEF_{25–75\%}$, and FEV_1/FVC were reduced compared with control subjects. Changes in lung function were similar between cases and control subjects. Deficits in lung function were minor in cases; however, lung function abnormalities persisted from 18 to 25 yr.	

Definition of abbreviations: AHR = airway hyperresponsiveness; BPD = bronchopulmonary dysplasia; CI = confidence interval; CLD = chronic lung disease; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; CT = computed tomography; ECRHS = European Community Respiratory Health Survey; ERV = expiratory reserve volume; FEF = forced expiratory flow; $FEF_{25–75\%}$ = forced midexpiratory flow; ICD9 = International Classification of Diseases, 9th revision; MEF = maximal expiratory flow; NICHD/NIH = National Institute of Child Health and Human Development/National Institutes of Health; OR = odds ratio; PMA = postmenstrual age; ROP = retinopathy of prematurity; RV = residual volume; radBPD = severe radiographic BPD; TLC = total lung capacity; $\dot{V}maxFRC$ = maximal flow at FRC; VLBW = very low birth weight.

studies used case–control methods (26, 30, 33, 46, 51, 61, 64, 65, 74), five were longitudinal prospective cohort studies (21, 27, 55, 58, 73), and the remaining studies used retrospective cohort designs (26, 31, 40, 47). Overall, it was found that in the first 5 years of life, children with a diagnosis of BPD showed signs of substantial airway functional impairment as exhibited by abnormal measures of FEV, VC, and FRC.

Several studies measured pulmonary function longitudinally in infants and young children with a history of BPD over varying periods of time (21, 27, 55, 58, 74). Infant pulmonary function testing using the raised volume rapid thoracoabdominal compression technique demonstrated significant airflow obstruction (21, 46, 58). Abnormalities in forced expiratory flow were shown to persist over time, revealing substantial airway functional impairment that persisted even when clinical course improved. In addition, measurements of lung volumes showing a modest reduction in TLC, an increase in FRC, and an increase in residual volume to TLC ratio (RV/TLC) were consistent with a significant degree of ongoing gas trapping (27, 33, 46, 64, 73). In the studies that measured bronchodilator response, only one-third of patients had improvement in airflow limitation after administration of bronchodilator (45, 54). Interestingly, infants using bronchodilators and inhaled steroids showed a significantly higher mean FRC (55). When pulmonary mechanics were longitudinally measured in one study, a progressive improvement in passive respiratory system compliance and resistance was observed in the first year of life and at 24 months of age (26).

Significant somatic growth retardation is evident in former preterm infants with BPD. In one study, infants with above average somatic growth showed greater improvements in lung function with longitudinal assessments (57). Additionally, after adjusting for differences in weight, V_T and $\dot{V}_E$, children with a diagnosis of BPD appear to develop similarly to children without BPD (58, 65). Evidence of catch-up during the first 15 months of life was only found when tidal breathing parameters, V_T and $\dot{V}_E$, were measured in this study population (65). The reasons for the poor growth of former preterm infants with BPD are multifactorial and include increased caloric demands and decreased nutrient intake.

Although several studies have identified that children with a diagnosis of BPD are at a higher risk of developing poor pulmonary outcomes later in life, other studies have shown no significant difference between the pulmonary outcomes (cough, wheezing, rehospitalization, and inhalation therapy) of VLBW infants (birth weight $<$ 1,500 g) with and without BPD (61). BPD was strongly associated with continued bronchodilator use up to age 2 years, with persistent wheezing between ages 2 and 5 years, and with an asthma diagnosis later in childhood (30). Similar evaluations also identified BPD as an independent risk factor for the development of asthma later on in childhood (26, 40, 47); asthma was more prevalent in groups of survivors with BPD when compared with healthy term children (47).

School-aged Children (6–18 yr)

Overall, 34 studies were identified that evaluated the long-term effects of BPD in school-aged children (18–20, 22–25, 28, 32, 34–37, 39, 41–45, 49, 52, 54, 56, 57, 59, 60, 62, 63, 66, 67, 70, 71, 75). These studies were of mixed study designs and evaluated different outcomes; however, each study was able to provide some measure of the pulmonary outcome(s) of children with a diagnosis of BPD. Again, variable definitions of BPD were used. The majority of studies (n = 26) used case–control study design (18, 19, 22, 23, 25, 28, 29, 32, 34, 35, 37, 39, 41, 42, 44, 45, 54, 56, 59, 62, 63, 66, 67, 70, 71, 75), and the remaining used either retrospective (n = 4) or prospective (n = 4) cohort study designs (20, 24, 36, 43, 49, 52, 57, 60).

To evaluate the natural history of BPD, a number of studies evaluated pulmonary function testing in BPD survivors (19, 20, 22, 28, 29, 32, 35, 43–45, 59, 60, 63, 66, 67, 71, 75). Spirometric measurements of airflow obstruction, including FEV_1 and forced midexpiratory flow of VC ($FEF_{25–75\%}$), were consistently found to be decreased at school age in BPD survivors, compared with term control subjects. In contrast, measurements of TLC and FRC were normal or only modestly reduced, although a persistence in the RV/TLC ratio was more pronounced and suggestive of air trapping. Only a few studies measured diffusion but suggested an impairment of diffusing capacity in BPD survivors. Overall, there were mixed results as to whether children with a history of VLBW and BPD exhibited any difference in lung function when compared with children with a history of VLBW but without BPD. Doyle and colleagues demonstrated through two different analyses that former VLBW infants with BPD have decreased lung function compared with those without BPD (24, 49), although Cazzato and colleagues found no differences in lung function between VLBW infants (no BPD vs. BPD), with the exception of a significant higher RV/TLC ratio in the BPD subgroup (66). There also may be differences in lung function in infants born in earlier eras. Comparison of lung function at 8 to 9 years in two cohorts born in 1991 to 1992 and 1997 demonstrate no significant differences between infants with BPD but lower lung function in the earlier cohort among those infants without BPD (75). Hakulinen and colleagues reported in a small cohort of 31 children born prematurely that the diffusing capacity of the lung for carbon monoxide (D_{LCO}) did not differ in those with a history of BPD and those without a history of BPD; however, D_{LCO} values in both prematurely born study groups were significantly lower than control subjects born at term. Thoracic gas volumes were similar in all groups (25). These results suggested that structural changes can persist for years in children who are born very preterm whether or not they have BPD.

Structural changes were identified in survivors of preterm birth with or without BPD. High-resolution computed tomography (CT) of the chest was used to study the association between changes in lung function and structural changes in the lungs of children with BPD. Such evaluations found that children with BPD showed abnormalities on high-resolution CT and suggest that children diagnosed with BPD are potentially at risk of developing COPD later in life due to the widespread involvement of the peripheral airways (54). Interestingly, children with a history of BPD and normal lung function at age 8 years had normal lung growth (20).

A number of studies also linked BPD to respiratory outcomes in school-aged children, although physiologic and radiographic abnormalities were not always accompanied by clinical symptoms. One recent study highlights

the extreme of phenotype among children born at 25 weeks' gestation or less and studied again at age 11 years in the EPICure study. In these children, respiratory symptoms were more common than in age-matched full-term control subjects, with twice as many (25 vs. 13%; $P < 0.01$) children having a current diagnosis of asthma (55). The authors also reported that less than half of those with impaired lung function were receiving any medication.

Adulthood (Older than 18 yr)

With the increase in longevity of infants with BPD into adulthood, it is of critical significance to study the effects of this disease of infancy on adult-age respiratory impairments. Ten papers were identified that studied the long-term effects of BPD at birth in adults (38, 48, 50, 53, 68, 69, 72, 76–78). For the purpose of this review, adulthood is defined as older than 18 years of age. Five of these studies were case–control and five were prospective cohort studies. Several methods were used to assess respiratory outcomes in these adults who had BPD as infants.

Spirometry was measured in half of these studies (53, 68, 69, 76). Adults with BPD consistently exhibited significantly lower FEV_1 and $FEF_{25–75\%}$ than both preterm cases without BPD and term control subjects. Using the European Community Respiratory Health Survey, adults with a history of BPD were twice as likely to report wheeze and three times as likely to use asthma medications as full-term control subjects (69). In a national cohort from the Netherlands, the prevalence of doctor-diagnosed asthma was significantly higher in women with a history of BPD than in term control subjects (24 vs. 5%, $P < 0.001$). Additionally, women with a history of BPD reported higher rates of shortness of breath during exercise than term control subjects (43 vs. 16, $P = 0.008$) Interestingly, in this study, the prevalence of reported symptoms in men with a history of BPD was comparable to term control subjects, indicating that preterm birth was not a risk factor for long-term respiratory symptoms in men (48). Emphysema, defined radiographically as areas of very low attenuation containing no perceptible parenchymal anatomy, was also reported to be common among young adult survivors of moderate and severe BPD, as assessed by chest CT (53, 72). A recent study that measured ventilator and sensory responses in adult survivors of preterm birth and BPD with reduced exercise tolerance showed severe dyspnea and leg discomfort to be associated with critical constraints on V_T expansion, despite differences in expiratory flow limitation in those with BPD (77). Although each of these studies in former preterm adults focused on different outcomes, each study consistently confirmed that adults who had a diagnosis of BPD continued to experience respiratory symptoms and lung function impairments into adulthood.

Conclusions

Advances in perinatal management and therapy have resulted in improved survival of extremely premature infants. In the postsurfactant era, BPD has different pathophysiological underpinnings, resulting in different clinical and radiographic manifestations in the neonatal intensive care unit than the previously defined "classic BPD." The ways in which these differences influence both clinical course and pulmonary function later in childhood and adulthood are poorly understood.

This comprehensive review of respiratory outcomes in survivors of prematurity includes studies published on or after 1990 and thus mostly focuses on those born in the postsurfactant era. Despite the number of published studies, there can be significant variation in the observed short- and long-term pulmonary outcomes after premature birth due to a number of confounding factors, including heterogeneous study populations and term control subjects as well as the use of ambiguous terminology and shifting definitions. Survivors of BPD have impaired respiratory function compared with full-term control subjects, highlighting the potential link between altered early-life lung development and chronic lung diseases in adulthood. In general, these differences were less apparent when comparing children born prematurely with BPD to those born prematurely without BPD and suggest that the current definitions of BPD (defined as an oxygen requirement at 36 wk) do not fully capture the mechanisms of and risk factors for long-term pulmonary morbidity in premature infants.

Measurements of airway obstruction were consistently noted to be reduced in BPD survivors; this pattern of airway obstruction was observed with infant pulmonary function testing and persisted across all age groups. Impairments in lung volumes and diffusion were modest and observed less consistently, despite the fact that the "new BPD" is considered to be the consequence of arrested lung development and is characterized by persistent decreases in alveolar counts, with enlarged alveoli, leaving an overall reduction in the surface area available for gas exchange. The absence of a significant restrictive defect in these studies suggests that premature infants may experience significant alveolar surface area catch-up growth. How extreme prematurity results in airway obstruction is not well understood, but it is possible that premature birth or hyperoxic exposure alters the innate immune response that ultimately mediates airway responses. One can also speculate that insults during the late canalicular or early saccular stage of lung development also impact the conducting branches that form the airways. The development of newer imaging techniques may allow more precise measurements of airways and facilitate longitudinal studies to correlate structural changes in premature infants with long-term pulmonary outcomes. Although this review focuses on studies published in the postsurfactant era, two papers cited (19, 24) include infants born in the 1960s and 1970s before the routine use of surfactant and report a greater degree of fixed airway obstruction compared with more recent studies.

The pattern of airway obstruction noted in BPD survivors correlated with the clinical observation of wheezing and an increased prevalence of physician-diagnosed asthma that persisted across all age groups. Even the use of bronchodilators and inhaled corticosteroids in the first year of life correlated with elevated FRC, suggesting that air trapping is an early feature resulting in clinical symptoms. Clinically diagnosed asthma in this patient population likely represents a more complex phenotype and pathophysiology that incorporates a combination of obstructive, restrictive, and diffusion defects. Understanding why some premature infants with BPD go on to develop a wheezing phenotype and others do not may aid in developing primary

prevention strategies for chronic pulmonary morbidity that results from prematurity. In addition, we need to better understand how evolving neonatal management strategies alter pathologic and physiologic changes in the developing lung. We also need to identify and understand the causal risk factors, aside from prematurity, that could be targeted to prevent the long-term sequelae of lung disease of prematurity. Most of the longitudinal asthma cohorts that follow "at-risk" enriched populations of atopic families or infants with severe bronchiolitis exclude infants born prematurely, so the impact of atopy and respiratory infections as well as environmental insults of tobacco smoke exposure and environmental pollution on the development of asthma are poorly characterized in BPD survivors. Last, we need to have a better understanding of the genetic factors that contribute to the heritability associated with BPD. Although a number of candidate genes have been linked to BPD, a recent population-based genome-wide association study failed to identify any genomic loci associated with moderate to severe BPD at the genome-wide significance level (79), indicating that multiple genes and pathways likely contribute to BPD.

Additional studies are needed to understand the short- and long-term respiratory outcomes of prematurity and BPD. The Premature and Respiratory Outcomes Program (PROP), a longitudinal birth cohort of 835 infants at six centers in the United States, has a primary goal to identify biomarkers (biochemical, physiological, and genetic) and clinical variables that are predictive of pulmonary status in preterm infants at 1 year corrected age (80). This well-phenotyped birth cohort of premature infants with and without BPD has the promise to advance our understanding of the magnitude and time course of changes in pulmonary function of premature infants into adulthood. Retention of this cohort and additional cross-sectional studies of children with asthma that do not exclude premature infants are needed to better understand respiratory morbidity after prematurity and to develop appropriate treatment for these infants. The incorporation of large-scale genomic data in these approaches may yield clues to genes and pathways that are common to BPD and asthma, but like asthma, BPD is almost certainly a polygenic disease with important gene–environment interactions that determine risk. The identification of novel biologic targets may ultimately allow for the development of new therapies and approaches targeting this vulnerable population of preterm infants. ■

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