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# Preterm Birth and Long-Term Pulmonary Function

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## 1. Introduction

### 1.1 Lung development

To understand the pathophysiology and the outcome of chronic lung disease of infancy, it is essential to understand normal lung development and the host of cofactors that will interfere with both antenatal and postnatal lung development. Lung growth starts in utero and continues to early adolescence going through different phases (Burri, 2006). The embryonic phase, between the 4<sup>th</sup> and 7<sup>th</sup> week, begins with the formation of a groove in the ventral lower pharynx and a bud at the lower part of the groove. After further elongation and subdivision of the bud, the two main bronchi are formed. Between the 7<sup>th</sup> and 16<sup>th</sup> week of gestation, known as the pseudoglandular phase, the air conducting trees continue to subdivide to form the terminal bronchioles. During the canalicular phase from the 17<sup>th</sup> to the 26<sup>th</sup> week of gestation, airway branching is complete with the formation of the primitive saccules. It is also during this phase that the cuboidal epithelium lining the saccules differentiates into type I and type II pneumocytes with concomitant increases in peripheral mesenchyme vascularization. From 27 weeks onwards, during the saccular phase, the lung will begin to prepare for birth with thinning of the connective tissue, secondary septation subdividing the sacculi into smaller subunits or alveoli and the presence of a single capillary layer characteristic of mature alveoli (Hislop et al., 1986; Langston et al., 1984; Post & Copland, 2002). Alveoli continue to increase in number until and beyond birth. At 29 weeks gestation, there are approximately 30 million alveoli and this will increase to some 150 million alveoli by term, one third to half the adult number (Hislop et al., 1986; Langston et al., 1984).

### 1.2 Chronic lung disease of infancy

Chronic lung disease of infancy (CLDI) is a heterogeneous group of diseases that usually evolves from an acute newborn respiratory disorder. These disorders, such as respiratory distress syndrome secondary to preterm birth, meconium aspiration, sepsis, persistent pulmonary hypertension, congenital heart disease and their subsequent treatments, may predispose the infant to the development of CLDI. Bronchopulmonary dysplasia (BPD), the most significant long-term pulmonary complication of preterm birth (Eber & Zach, 2001) was initially defined as the continued dependence on supplementary oxygen for greater than 28 days postpartum (Northway, 1979). However, BPD has been redefined as we

approach a new era of survivors of extreme preterm birth due to important advances in all aspects of neonatal care including surfactant treatment, new ventilator strategies, improved nutrition and other treatments leading an increase in incidence of live preterm birth (Tracy et al., 2007). However, despite these treatments, the overall incidence of BPD has not changed over the past decade (Smith et al., 2005). The 'new BPD' is defined as the need for supplemental oxygen for at least 28 days after birth, and its severity is graded according to the respiratory support required at 36 weeks post-natal age for infants born at gestational ages of less than 32 weeks (Jobe & Bancalari, 2001).

### **1.3 Pathogenesis of BPD**

Old BPD was characterized by diffuse airway damage, alternating areas of overinflation with atelectasis, fibrosis and smooth muscle hypertrophy and prominent vascular hypertensive lesions. Pathologically, the new BPD is different. Unlike the original form of the disease, this 'new' BPD develops in extreme preterm newborns who may have only required minimal ventilator support and low inspired oxygen concentrations during the early postnatal days (Rojas et al., 1995). However, the birth of the extremely immature infant leads to an interruption of alveolarization at a very early stage, with fewer, larger alveoli with subsequent alveolar capillary hypoplasia as a prominent feature. It is important to briefly consider the factors implicated in the pathogenesis of BPD. It is well recognized that those treatments that are necessary for the survival of the preterm infant, such as antenatal steroids, mechanical intermittent positive pressure ventilation (IPPV) and oxygen therapy, may further affect normal pulmonary vascular and alveolar development (Hislop, 1997; Hislop et al., 1987; Rojas et al., 1995). Choriomnitis, post natal infection and patent ductus arteriosus are also implicated in BPD (Speer, 2006; Watterberg et al., 1996). Abnormalities of gene expression for surfactant synthesis, vascular development and inflammatory regulation are thought to play a role in the development of the new BPD (Bhandari et al., 2006). Although the diagnosis of BPD identifies most patients at increased risk for long-term respiratory sequelae, there is no linear relationship between respiratory support early in life and subsequent respiratory outcome (Greenough, 2006). Indeed, infants with BPD may have a full clinical and functional recovery, and late respiratory symptoms and pulmonary function abnormalities may appear even in young adults who did not require prolonged oxygen supplementation in the neonatal period (Narang et al., 2008).

The aim of this chapter is to review the long-term follow-up of respiratory outcomes in adolescents and adults who were born premature with and without chronic lung disease and will focus on the current available data on respiratory symptoms, pulmonary function, exercise capacity and on structural lung disease. Unless otherwise stated in the manuscript and the tables, all the studies reviewed with BPD subjects refer to the 'old BPD.'

## **1.4 Long-term respiratory outcome following preterm birth**

### **1.4.1 Respiratory symptoms**

#### **1.4.1.1 Childhood**

In infancy, there is a wealth of evidence indicating that subjects who are born premature are symptomatic with cough, wheeze and recurrent chest infections in mid-childhood (Chan et al., 1989b; McLeod et al., 1996; Mitchell & Teague, 1998; Palta et al., 2001; Rona et al., 1993) with evidence of an increased rate of hospitalization in the first 2 years of life for a respiratory illness (Mahon et al., 2007).

Multiple studies have been undertaken to look for predictors of wheezing and asthma diagnosis in preterm children (Greenough et al., 2005; Grischkan et al., 2004; Holditch-Davis et al., 2008). Most of these studies were based on questionnaires not validated in preterms with a lack of a universal definition for wheeze and asthma. However, low birth weight per se may predispose to an increased risk of wheeze and lower lung function which may increase the likelihood of a wheezing response to viral infections in early childhood (Greenough et al., 2005; Lewis et al., 1995). Other risk factors for wheeze and asthma in later life in preterm children include male sex (Palta et al., 2001) and African-American ethnicity (Kumar et al., 2008). Despite the increased risk of wheezing in preterms, there is a balance of evidence showing improvement of respiratory symptoms with age.

#### 1.4.1.2 Adolescence and adulthood

**See Table 1.** Adolescents (defined here as >12 years of age) and young adults, who were preterm either with or without subsequent BPD have excess respiratory symptoms, including cough, wheeze and asthma (Halvorsen et al., 2004; Narang et al., 2008). In one of the oldest studies to date, Northway et al (Northway et al., 1990) studied a group of young adults, mean age 18.3 years (mean birth weight of 1.9kg), with a previous history of BPD. They had a history of more wheezing, episodes of pneumonia and long-term medication use when compared with non-ventilated BPD babies. In one of the most recent studies with longitudinal follow up from childhood to adulthood, preterm infants (mean birth weight of 1.4 kg), the majority of whom had no history of BPD, there was an excess of respiratory symptoms (either cough, wheeze or asthma) compared with controls, 27% vs. 8%, respectively (Narang et al., 2008). Of significance the overall prevalence of respiratory symptoms in this cohort had decreased with time (Narang et al., 2008). Interestingly, the presence of respiratory symptoms did not necessarily translate to abnormal pulmonary function, an increase in the prevalence of airway hyper-responsiveness or an abnormal exercise tolerance (Narang et al., 2008). However, in a recent population-based case-control study, low birth weight (LBW, less than 1500 g, gestational age not given) did translate to increased hospitalization rates in adulthood (Walter et al., 2009). Specifically, LBW adults aged 18–27 years had 83% higher odds of hospitalization for asthma, respiratory infections and respiratory failure as young adults when compared with those who were of normal birth weight (Walter et al., 2009). Similarly, using inhaled corticosteroids (ICS) as a surrogate marker of respiratory symptoms and asthma, a national cohort study in Sweden, found that ICS use increased with the degree of immaturity at birth (Vogt et al., 2011). By contrast, Vrijlandt et al. (Vrijlandt et al., 2006) did not observe an excess of respiratory symptoms, however, the questionnaire focused only on previous and current history of asthma and no recurrent hospitalization data were given. Therefore, the true prevalence of respiratory symptoms may be under-represented in this cohort. It must also be considered that the variability of respiratory symptoms between the studies may be attributed to the use of different definitions. The term ‘asthma’ is used very imprecisely and furthestmost studies do not employ objective cough monitoring (Archer & Simpson, 1985; Falconer et al., 1993; Munyard et al., 1994). Only the international study of asthma and allergies in children (ISAAC) questionnaire (Asher & Weiland, 1998) has been rigorously validated, and the sensitivity, reproducibility and validity of other questionnaires are not known. However, even the use of the ISAAC questionnaire in a preterm population may be debatable since it was not exclusively designed or validated for this unique population.

Author	Age (years)	Number of Subjects	BW (g)	Gestation (weeks)	Number of Controls	Methods	Results
Anand et al. (Anand et al., 2003)	15.0	128 [BPD=8]	1249	30.7	128	Questionnaire	28% had cough# 31% had wheeze# 19% had asthma#
Doyle et al. (Doyle et al., 2006)	18.9	147 [BPD=33]	<1500	<32	37	Use of bronchodilator for wheeze= asthma	22% had asthma#
Halvorsen et al. (Halvorsen et al., 2004)	17.7	46 [BPD=36]	1014	27.3	46	ISAAC Questionnaire	35% had history of asthma#
Narang et al. (Narang et al., 2008)	21.7	60 [BPD=7]	1435	31.5	50	Questionnaire	27% had either cough, wheeze or asthma #
Northway et al. (Northway et al., 1990)	18.3	26 [all BPD]	1894	33.2	26 no-BPD 53 term	Questionnaire	Respiratory symptoms persisted in 23%#
Vrijlandt et al. (Vrijlandt et al., 2006)	19.0	42 [BPD=9]	1246	30.0	48	Questionnaire	No excess history of current asthma
Wong et al. (Wong et al., 2008)	19.0	21 [all BPD]	895	27 (24-30)	None	Questionnaire	71% had either wheeze/cough/SOB

BW=birth weight; g =grams; BPD = bronchopulmonary dysplasia; SOB = shortness of breath.  
All values are mean unless otherwise indicated. # Increased when compared with controls.

Table 1. Studies in adolescence seeking associations between prematurity and subsequent reported respiratory symptoms.

## 1.4.2 Pulmonary function

### 1.4.2.1 Childhood

In infants, Friedrich and colleagues using the raised volume rapid thoracic compression (RVRTC) technique showed that even healthy asymptomatic preterm infants have low expiratory flows with normal expired volume measured from a point near total lung capacity to residual volume, thus suggesting that lung growth is proportional to somatic growth in preterm infants (Fawke et al., 2010). The low expiratory flow measurements observed in these preterm infants is thought to be secondary to improper airway development and a reduction in airway caliber secondary to inflammation and/or airway thickening (Friedrich et al., 2006). In childhood, several studies have now documented abnormal pulmonary function in those born preterm, with evidence of significant airflow obstruction, with the mean forced expired volume in 1 second (FEV<sub>1</sub>) values between 70% and 80% of the predicted levels (Baraldi et al., 1991; Chan et al., 1990; McLeod et al., 1996; Mitchell & Teague, 1998). Recently, the extremely premature infant cure (EPICure) study assessed pulmonary function in children at an average age of 11 years following preterm birth. They found that preterms compared to controls had higher residual volume (RV) and RV/total lung capacity (TLC), lower FEV<sub>1</sub> and lower forced vital capacity (FVC) z scores compared with controls, the effect being more pronounced in preterms with a history of BPD compared with those preterms without a history of BPD (Fawke et al., 2010).

Author	Age (years)	Number of Subjects	BW (g)	Gestation (weeks)	Number of Controls	Methods	Results	Significance
Anand et al. (Anand et al., 2003)	15	128 [BPD=8]	1249	30.7	128	Spirometry	FVC % = 109.5 FEV <sub>1</sub> % = 94.9 FEF <sub>25-75%</sub> % = 88.1# FEV <sub>1</sub> /FVC % = 87.0#	#p<0.001 compared to controls
Doyle et al. (Doyle et al., 2006)	18.9	147 [BPD=33]	<1500	<32	37	Spirometry Lung volumes	BPD group data only FVC % = 98.4 FEV <sub>1</sub> % = 81.6# FEF <sub>25-75%</sub> % = 57.5\$ FEV <sub>1</sub> /FVC % = 73.9# RV % = 108.7 TLC % = 99.6	#p< 0.05 compared to controls \$ p<0.05 compared to no-BPD group
Halvorsen et al. (Halvorsen et al., 2004)	17.7	46 [BPD=36]	1014	27.3	46	Spirometry Plethysmography	Data for the moderate to severe BPD group FVC % = 101.0 FEV <sub>1</sub> % = 87.8 FEF <sub>75%</sub> % = 78.4# RV % = 123.5 TLC % = 108.3	#p< 0.001 compared to controls
Narang et al. (Narang et al., 2008)	21.7	60 [BPD=7]	1435	31.5	50	Spirometry	FVC % = 96.4 FEV <sub>1</sub> % = 92.6 FEF <sub>25-75%</sub> % = 78.6	p=NS compared to controls
Northway et al. (Northway et al., 1990)	18.3	26 [all BPD]	1894	33.2	26 no-BPD 53 term	Spirometry Plethysmography	FVC % = 96.8# FEV <sub>1</sub> % = 74.8# FEF <sub>25-75%</sub> % = 46.5# TLC % = 108.6	#p< 0.01 compared to controls \$ p<0.01 compared to no-BPD group
Vrijlandt et al. (Vrijlandt et al., 2006)	19.0	42 [BPD=9]	1246	30.0	48	Spirometry Whole body plethysmography	FVC % = 97.7# FEV <sub>1</sub> % = 95.4# FEF <sub>75%</sub> % = 75.3# FEV <sub>1</sub> /FVC % = 82.2# RV % = 99.4 TLC % = 100.1	#p<0.01 compared to controls
Wong et al. (Wong et al., 2008)	20.3	21 [all BPD]	895	27	None	Spirometry Lung volumes	FVC % = N/A FEV <sub>1</sub> % = 89.0 FEF <sub>25-75%</sub> % = 63.7 RV % = 95.8 TLC % = 106	

All values are mean data unless otherwise indicated. Unless otherwise stated, the spirometry data given are for the entire pre-term cohort. All spirometry values shown are % predicted unless otherwise indicated. BW, birth weight; g, grams; BPD, bronchopulmonary dysplasia; FVC, forced vital capacity; FEV<sub>1</sub>, forced expired volume in one second; FEF<sub>25-75%</sub>, forced expiratory flow at 25-75% of forced vital capacity; FEF<sub>75%</sub>, forced expiratory flow at 75% of forced vital capacity; NS, non-significant; RV, residual volume; TLC, total lung capacity.

Table 2. Lung function in adolescence and adulthood following preterm birth.

Many studies have now observed that the main risk factors cited for impaired lung function in ex-preterm children are intermittent positive pressure ventilation (IPPV), prolonged oxygen therapy, male sex and maternal smoking (Chan et al., 1990; McLeod et al., 1996; Mitchell & Teague, 1998).

#### 1.4.2.2 Adolescence and adulthood

There are fewer studies that have now documented pulmonary function in adolescence and adulthood (see Table 2). Furthermore, there is a paucity of relevant longitudinal data. Whether 'catch-up' growth of pulmonary function occurs from mid-childhood to adulthood is highly debated. In the longest follow-up to date, Northway and colleagues (Northway et al., 1990) found that the mean percentage predicted FEV<sub>1</sub>, FVC and forced mid-expiratory flow at 25% to 75% of FVC (FEF<sub>25-75</sub>) were significantly lower in the BPD group compared with the preterm and term controls. BPD was considered the major risk factor for reduced airflow as there was no apparent association with neonatal variables. However, the small numbers of subjects, relatively high birth weights (mean > 1800 g) and maturity (mean gestational age >33 weeks) in the BPD preterm groups may have resulted in the lack of any association. It must also be borne in mind that in the present day, those considered to be at high risk of respiratory morbidity probably did not survive in the late 1960s. In more recent studies in adolescents, Anand and colleagues after adjusting for self-reported smoking both in the subjects and their mothers, found a reduction in FEF<sub>25-75</sub> in their very low birth weight group (defined as less than 1500 g) compared with the controls, suggesting distal airflow obstruction (Friedrich et al., 2006). However, distal airflow obstruction was not associated with either low birth weight, respiratory support or BPD; the key risk factor cited was preterm birth per se (Friedrich et al., 2006). Interestingly, Halvorsen and colleagues (Halvorsen et al., 2004) also observed a lower FEV<sub>1</sub> when compared with controls, with the discrepancies in pulmonary function increasing significantly with the increasing severity of BPD. Doyle and colleagues (Doyle et al., 2006) found that pulmonary function was mostly normal in the three groups they studied, term, preterms with BPD and preterms without BPD. However, a significantly greater proportion of children with BPD compared with those preterm children without BPD had a clinically important reduction in their mean percentage predicted FEV<sub>1</sub> (81.6 and 92.9, respectively) and FEV<sub>1</sub>/FVC ratios (73.9 and 83.2, respectively). It should be noted that the mean percentage predicted FEF<sub>25-75</sub> in the Doyle study was lower than that of the preterm group studied by Anand et al (Anand et al., 2003). The different conclusions may be due to the different reference values used, again underscoring the need for appropriate controls. Similarly, Vrijlandt and colleagues (Vrijlandt et al., 2006) demonstrated pulmonary function values that were within normal range in their ex-preterm population, most of whom did not have BPD. However, the percentage predicted values of FVC, FEV<sub>1</sub> and FEV<sub>1</sub>/FVC were lower than that in the controls, the majority of who were medical students, which might select for a healthier and higher socioeconomic class population and reflect the results observed. In a more recent study and one of the largest longitudinal follow-up studies from birth to adulthood, there was evidence of airway obstruction in children aged 7-9 years (Chan et al., 1989b). This same cohort in adulthood did not show any significant differences between FEV<sub>1</sub>, FVC and FEF<sub>25-75</sub> when compared with controls, implying catch-up growth (Narang et al., 2008). The authors were also able to show some evidence of tracking, in that mid childhood spirometry was predictive of adult values (relationship between z scores for FEV<sub>1</sub> in childhood and adulthood was  $p < 0.001$  and  $r^2 = 0.34$ ) (Narang et al., 2008). However, the low incidence of

BPD and maternal smokers, both risk factors for poorer airway function, may have created a bias towards improved airway function in adulthood (Northway et al., 1990).

### **1.4.3 Airway Hyperresponsiveness (AHR)**

#### **1.4.3.1 Childhood**

Atopy and AHR are thought to be associated, even in asymptomatic subjects (Boulet et al., 1983; Sears et al., 1991). It is debated whether AHR, which was repeatedly reported to occur in long-term survivors of BPD, is a consequence of BPD or contributes to the pathophysiology of BPD in genetically predisposed patients following preterm birth (Northway et al., 1990; Wohl, 1995). In one study reported baseline spirometry was significantly reduced in BPD and non-BPD groups compared with term controls, and the provocative dose of histamine to cause a 15% fall in FEV<sub>1</sub> (PD15) was lower in the BPD compared with the non-BPD preterm group (Pelkonen et al., 1997). There was a strong association between respiratory symptoms and AHR (Chan et al., 1989a). In young adults with a history of BPD, AHR was more prevalent in the BPD than the ex-preterm no-BPD population and further, AHR was not related to respiratory symptoms, atopy, or a family history of asthma (Northway et al., 1990). In the Hammersmith cohort, increased AHR was seen in 71% of the index study group, compared with 43% of controls ( $p < 0.01$ ) (Chan et al., 1989a). There was a significant association between a personal or family history of asthma and increased AHR in both the index study group and controls and further, for the index study group, there was also an association between AHR and duration of oxygen treatment (Chan et al., 1989a). Increased AHR in the index study group was also observed more in those subjects with a positive skin-prick test to house dust mite, grass pollens, or cat fur ( $p < 0.01$ ), although skin-prick tests were not performed in the control group (Chan et al., 1989a). However, to elucidate the pathophysiological basis for the increased prevalence of AHR in the index study group, 35 of the mothers of the index study group also underwent a histamine challenge. Using the same protocol, 8.6% of mothers of the index study group had a PD15 (using histamine) of 3.9 mmol, which was similar to the 10.5% reported in an adult population using the same methods to determine AHR. In a second study, 15 subjects participated in a double-blind, placebo controlled, crossover design with 4-week-long treatment periods with inhaled steroids or placebo. There was no significant difference in respiratory symptom score, baseline airway function, or airway response to histamine between the two treatment periods. From these studies, the authors concluded that abnormal AHR was related to abnormal pulmonary development and not to an effect of chronic inflammation or maternal factors. However, the authors assumed that any preexisting inflammation would be steroid-sensitive, which may not necessarily be true.

#### **1.4.3.2 Adolescence and adulthood**

There are very few studies assessing AHR in ex-preterm adolescents and young adults. In a longitudinal follow up study involving 52 subjects from the Hammersmith cohort (Chan et al., 1989a), there was no significant difference in the prevalence of AHR in the index study group compared with controls (23% vs 19% respectively,  $p = \text{NS}$ ). The finding of a decrease in AHR prevalence in this study is similar to that of a larger longitudinal study with more than 800 subjects, in which AHR declined from childhood to adolescence, paralleling the increase in lung function during this period (Forastiere et al., 1996).



#### 1.4.4 Exercise capacity

Because cardiopulmonary limitations may not be clinically evident while the child is at rest, exercise testing may be useful in children born preterm and who developed BPD to determine the presence and extent of any dysfunction of gas exchange secondary to alveolar growth impairment. During exercise, cardiac output may increase fivefold as a result of increases in both heart rate and stroke volume; minute ventilation may increase 25-fold in healthy individuals, depending on the intensity of the exercise. Carbon monoxide transfer ( $DL_{CO}$ ) increases by up to 50% during exercise, because of recruitment and distension of the pulmonary capillaries, particularly in the upper parts of the lung. Maximum oxygen consumption ( $VO_2$  max) is the best index for aerobic capacity and is the gold standard for cardiorespiratory fitness (ATS/ACCP, 2003). It is related to oxygen availability and provides information regarding aerobic metabolism in response to exercise stress.

##### 1.4.4.1 Childhood

During mid-childhood, there are conflicting data regarding exercise performance in ex-preterm children. Some have demonstrated normal exercise ability (Baraldi et al., 1991; Jacob et al., 1997; Northway et al., 1990) while others have shown abnormal cardiopulmonary responses to exercise (Bader et al., 1987; Mitchell & Teague, 1998). Some explanations for the variability seen between these studies include different methods of exercise testing, differing exercise protocols and variation in the motivation of study subjects. The EPICure study demonstrated that ex-preterm subjects had baseline lower tidal volumes, lower oxygen consumption, lower anaerobic threshold, lower minute ventilation and 20% lower workload; however, these changes were not associated with a significant reduction in oxygen saturation but were associated with an increased likelihood of self-reported difficulties in breathing during exercise (Welsh et al., 2010).

##### 1.4.4.2 Adolescence and adulthood

**See Table 3.** In the only adult study to date that has assessed both exercise performance as well as gas transfer at both rest and exercise (using an incremental protocol and a cycle ergometer), there were no significant differences in exercise capacity between the ex-preterm subjects and controls (Narang et al., 2009). Interestingly, the main abnormal findings were that ex-preterm subjects in adulthood had reduced  $DL_{CO}$  and effective pulmonary blood flow ( $Q_{peff}$ ) at rest, which normalized during exercise and was again reduced after a recovery period. These results do not suggest true alveolar capillary hypoplasia as  $DL_{CO}$  was appropriate for  $Q_{peff}$  (Narang et al., 2009). Vrijlandt et al. in their study of 42 adults reported resting and exercise data also using an incremental protocol with a cycle ergometer (Vrijlandt et al., 2006). They too found a significantly low  $DL_{CO}$  at rest compared with controls, 88% and 96% predicted, respectively ( $p = 0.003$ ). However, the  $DL_{CO}$  values were not corrected for  $Q_{peff}$  or body surface area, both important determinants of  $DL_{CO}$ , and significantly, there were no  $DL_{CO}$  measurements undertaken during exercise or during recovery, thus posing difficulties with the interpretation of these results. Furthermore, this ex-preterm group reached a 15% lower workload than healthy peers; however, closer analyses of the results suggest that the ex-preterm subjects may have muscular deconditioning accounting for these results (Vogt et al., 2011). Indeed, these ex-preterms also reported fewer hours of exercise per week than the control subjects, which might explain their lower level of fitness (Vogt et al., 2011). In a group of adolescents assessed at 17 years of age using a step test and muscle strength tests, there were significant differences in motor performance in the

Author	Age (years)	Number of subjects	BW (g)	Gestation (weeks)	Number of controls	Methods	Results
Narang et al. (Narang et al., 2009)	21.7	60 [BPD=7]	1435	31.5	50	1) VO <sub>2</sub> max using cycle ergometer 2) Acetylene rebreathing to determine Q <sub>peff</sub> .	No difference in exercise capacity between ex-preterm subjects and controls. Decreased DL <sub>co</sub> compared to controls but normal DL <sub>co</sub> during exercise.
Vrijlandt et al. (Vrijlandt et al., 2006)	19.0	42 [BPD=9]	1246	30.0	48	1) Incremental exercise test using cycle ergometer	W <sub>max</sub> 15% lower in ex-preterms. Decreased DL <sub>co</sub> compared to controls.
Rogers et al. (Rogers et al., 2005)	17.3	53	720	26	31	1) Step test 2) Muscle strength tests 3) Activity-lead questionnaire	Decreased aerobic capacity, muscle strength and activity level.

BW, birthweight; g, grams; BPD, bronchopulmonary dysplasia; VO<sub>2</sub> max, maximum oxygen consumption; Q<sub>peff</sub>, effective pulmonary blood flow; DL<sub>co</sub>, transfer factor for carbon monoxide; W<sub>max</sub>, maximum workload. All values are mean data unless otherwise indicated.

Table 3. Exercise capacity in adolescents and adulthood following preterm birth.

ex-preterm group compared with healthy term subjects reflected in aerobic capacity, strength, endurance, flexibility, and activity level (Rogers et al., 2005). However, similar to the study by Vrijlandt et al., the differences in fitness and physical activity were possibly related to the interaction of effects of preterm birth on the motor system, together with a more inactive lifestyle (Vrijlandt et al., 2006). Burns and colleagues (Burns et al., 2009) compared 54 non-disabled ex-preterms aged 11-13 years (mean birth weight of 769 grams and mean gestational age of 26.6 weeks) with 55 children born at term. Ex-preterm adolescents had significantly lower motor coordination, 72.2% compared with 21.8% of the control group (Vogt et al., 2011). VO<sub>2</sub> max calculated from a 20m Shuttle Run test, was lower in the ex-preterm group compared with the controls ( $p = 0.001$ ).

### 1.5 Structural lung disease

In 1967, Northway based his BPD description on chest x-rays giving chest imaging a central role in diagnosing BPD. However, despite that, there is still a lack information in regards to structural abnormalities in ex-preterm children and adults with and without BPD (See Table 4). High resolution computed tomography (HRCT) images of the chest have been reported to be abnormal and thus useful in the diagnosis of BPD (Howling et al., 2000; Oppenheim et al., 1994). In one cohort of children with a median age of 10 years, 20/26 (77%) of the subjects had reduced lung attenuation (Aquino et al., 1999). The children had abnormalities of pulmonary function, which we now understand to be associated with BPD (median FEV<sub>1</sub> was 64% predicted) which correlates with abnormal HRCT findings. Aukland et al. studied HRCT images in 72 ex-preterm subjects which included two birth cohorts, children (mean

age 10 years) and adults (mean age 18 years) (Auckland et al., 2006). Their main abnormal findings were linear and triangular opacities, gas trapping and mosaic perfusion, especially in the 56/72 (78%) survivors with severe BPD, which represented subjects with old and new BPD (Auckland et al., 2006). No subject had evidence of emphysema. The same authors also demonstrated a reduction in FEV<sub>1</sub> in subjects with a high HRCT chest score (Wong et al., 2008). Subjects with hypoattenuation had a lower FEV<sub>1</sub> than those without hypoattenuation (mean FEV<sub>1</sub> 80.9% vs. 89.8%, respectively) (Auckland et al., 2006). Increased number of days with oxygen treatment also predicted an increase in the total HRCT score (Wong et al., 2008). In a more recent study of adults only, all with a previous history of BPD, simultaneous pulmonary function and HRCT chest evaluation was undertaken (Wong et al., 2008). The main abnormal finding, observed in 84% of the subjects, was the presence of emphysema, the severity of which also correlated with abnormal z scores for FEV<sub>1</sub> in this population ( $p < 0.001$  and  $r^2 = 0.50$ ) (Baraldi et al., 1991). Other HRCT abnormalities included architectural distortion, bronchial wall thickening and gas trapping. The presence of emphysema could not be predicted by perinatal or postnatal factors or a personal history of smoking. The differences in the findings with the study by Auckland et al. (Auckland et al., 2006) may be attributed to the fact that the study by Wong et al. (Wong et al., 2008) represents a group of adults who were highly selected, constituting 19 subjects (14%) with severe perinatal disease from the original cohort of 133 subjects. These subjects all had moderate/severe BPD compared to the other studies that had included ex-preterm subjects with no or mild BPD. The lack of correlation with perinatal factors may be due to the fact that perinatal factors become less important with age or simply that the study was under-powered to seek such associations. However, what is clear is that structural abnormalities, as determined by HRCT scans, do exist in an ex-preterm population, even in the absence of overt clinical disease. More intriguing is the association of radiological findings with perinatal data. Further studies are required to delineate factors, perinatal or otherwise, that impact on the structure of the immature lungs.

Author	Age (years)	Number of subjects	BW (g)	Gestation (weeks)	Methods	Results
Wong et al. (Wong et al., 2008)	19.0	19 [all BPD]	895	27	Expiratory and inspiratory HRCT chest	84% had emphysema 36% had gas trapping 42% had bronchial wall thickening
Aquino et al. (Aquino et al., 1999)	5-18	26	900	28	Expiratory and inspiratory HRCT chest	77% reduced lung attenuation 92% had gas trapping
Auckland et al. (Auckland et al., 2006; Auckland et al., 2009)	40 adults (Age 18.0) 32 children (Age 10.0)	72 [BPD=56]	991	27.2	Expiratory and inspiratory HRCT chest	72% linear capacity 58% triangular capacity 26% gas trapping 13% mosaic perfusion 10% bronchiectasis * Higher (abnormal) HRCT significantly associated with increased number of days with oxygen treatment.

BW, birthweight; g, grams; BPD, bronchopulmonary dysplasia; HRCT, high resolution computed tomography. All values are mean data unless otherwise indicated.

Table 4. Studies assessing structural lung disease in adolescence and adulthood following preterm birth.

## 2. Summary and implications

Following preterm birth, there is evidence for respiratory symptoms in infancy and childhood. While these symptoms do improve with time, the evidence does suggest that respiratory symptoms in ex-preterm subjects remain prevalent in adulthood. With regards to pulmonary function, the studies suggest evidence for catch-up growth and normalization of pulmonary function from childhood to adulthood in ex-preterm subjects without BPD. However, pulmonary function abnormalities appear to persist in those who had a more severe neonatal course and who had a diagnosis of BPD. Exercise capacity, although not overtly abnormal, may be affected by the reduced physical activity levels of ex-preterm subjects. It is postulated that the reduced  $DL_{CO}$  at rest observed in the studies may suggest the prolonged influence of antenatal programming (Narang et al., 2009). Certainly, pulmonary circulatory abnormalities have been observed in adult subjects with a transient history of lung injury secondary to persistent fetal circulation in the neonatal period (Sartori et al., 1999). These subjects, with normal pulmonary artery pressure at rest, demonstrated an exaggerated pulmonary artery pressure increase at high altitude compared with controls (Sartori et al., 1999). Structural lung disease, as determined by HRCT scans are prevalent in these subjects and further, are associated with pulmonary function abnormalities. What are the likely explanations for the respiratory morbidity of ex-preterm subjects in adulthood? It is certainly likely to be multifactorial. It is plausible that there is sustained vulnerability of the airways secondary to a host of factors related to preterm birth. Additionally, there is disruption of normal lung development as a result of preterm birth and the subsequent adaptation to extra-uterine life. This adverse disruption may be exacerbated by perinatal factors, particularly prolonged oxygen requirement and subsequent development of BPD, both of which have been identified as causal in functional and structural respiratory sequelae. It is unclear how oxygen mediates these effects. The prolonged use of oxygen in this vulnerable population may represent the final common pathway of a cascade of events related to preterm birth and lung injury. Alternatively, neonatal factors such as oxygen therapy become less important and it is possible that a host of environmental influences such as smoking dominate on more vulnerable airways. However, while it is virtually impossible to unpick the relationship between the environment, perinatal factors and prematurity on adulthood respiratory function, other investigators have demonstrated that BPD infants are particularly susceptible to lower respiratory illnesses in childhood and that these may be related to chronic airflow obstruction in adulthood (Samet et al., 1983). The improvement in pulmonary function observed may be a result of increased lung volumes as seen with somatic growth or indeed physiologic remodeling of the airway. Or could it simply be that the studies describing apparent normalization of lung function do not truly reflect 'catch-up' of lung growth? Perhaps, the results merely reflect decreased sensitivity of spirometry in this age group. Spirometry has long been known to be insensitive to distal airway obstruction until the very late phases. Sophisticated methods to assess lung ventilation and lung growth, such as the lung clearance index (LCI), a marker of ventilation inhomogeneity, may be necessary to provide more accurate information (Aurora et al., 2005). However, in one recent study assessing lung function using both spirometry and LCI in ex-preterm children aged 11 years, spirometry was more discriminative than LCI in detecting pulmonary function abnormalities (Lum et al., 2011). Recently, hyperpolarised gas MRI has demonstrated regional ventilation abnormalities in young cystic fibrosis patients with normal lung function (Bannier et al., 2010) and is known to be particularly sensitive to

early changes in emphysema (Yablonskiy et al., 2009). Perhaps, the non-invasive longitudinal assessment of lung growth with the use of labeled carbon monoxide (Rosenthal & Bush, 1998; Rosenthal & Bush, 1999) and hyperpolarized gases in magnetic resonance may provide further answers with regard to lung growth and ventilation abnormalities (Eberle et al., 2001).

### **3. Chronic lung disease of prematurity and chronic obstructive pulmonary disease in adulthood**

It is important to consider the long-term implications of abnormal functional and structural lung disease for survivors of preterm birth in adulthood. Specifically, is BPD a significant risk factor for chronic obstructive pulmonary disease (COPD)? It has long been hypothesized that COPD has its origin in fetal life (Stein et al., 1997). Additional childhood risk factors for COPD in adulthood include maternal smoking, maternal genetics, history of asthma, respiratory infections, environmental pollution and childhood nutrition (Bush, 2008; Franssen et al., 2008; Stein et al., 1997). Similarly, poorer lung function in ex-BPD subjects is associated with childhood respiratory infections and asthma. Indeed, BPD and COPD share some similar pathophysiological features; both disorders are subject to oxidant stress, inflammation and accelerated cell death resulting in complex distal lung injury. Although there are no studies evaluating lung function in BPD subjects in old age, BPD and subsequent impaired pulmonary function in adulthood, whether latent or overt, could result in an accelerated decline in ventilatory reserve that could further increase the risk of COPD like phenotype in later life. Loss of pulmonary function may be further accelerated in smokers as smoking is a well-known risk factor for a steeper age-related decline in pulmonary function and subsequent emphysema (Fletcher & Peto, 1977). The high prevalence of emphysema observed in HRCT scans in one study (Wong et al., 2008) is of greater concern given that up to 50% of preterm survivors smoke in adulthood (Doyle et al., 2006; Narang et al., 2008).

Thus it would not be unreasonable to assume that survivors of preterm birth are likely to be a cohort of subjects prone to COPD. Hence until preterm birth and its complications cease to be a problem, the prevalence of COPD or COPD like phenotype is likely to increase in the next few decades.

### **4. Conclusions and future directions**

The respiratory sequelae associated with preterm birth can no longer be a cause for concern just for pediatricians. Adult physicians will need to become increasingly aware of the long-term consequences of preterm birth, with recognition of both functional and structural lung disease associated with prematurity, as a reduced respiratory reserve could increase the risk of a COPD-like phenotype in later life. Further, because impaired airway function in adult life is an important and independent indicator of mortality risk (Barker et al., 1991), continued surveillance of these subjects into late adulthood, particularly of the active smokers, will be vital. Finally, as the etiology of chronic lung disease of prematurity remains elusive, the burden of chronic lung disease in infancy, childhood and adulthood both to the individual and in health care resources is significantly high. Thus, large long-term longitudinal studies are urgently required with subjects recruited antenatally not only to evaluate structural and functional lung disease but also to delineate the pathogenesis,

diagnosis and subsequent clinical management of lung disease of prematurity, specifically the 'new BPD.' However, future research must not be unifocal. We now understand that there is no linear relationship between neonatal factors and subsequent respiratory sequelae and that prematurity in the absence of both neonatal disease and treatments may result in long-term respiratory morbidity. Therefore, the ultimate priority for future research must be to determine preventative factors to diminish preterm birth.

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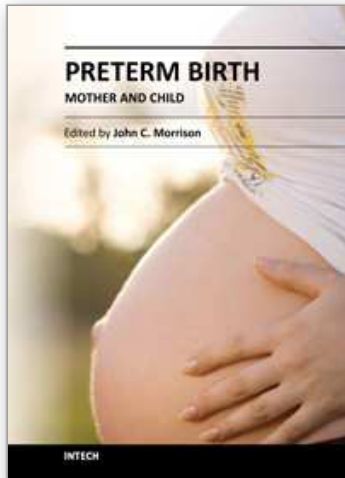
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## **Preterm Birth - Mother and Child**

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While there are many studies and books regarding preterm birth, both the obstetric and in the neonatal/pediatric literature, what is missing is the integration of data from obstetrics through neonatal course and into pediatrics as the neonate transverses childhood. A continued dialogue between specialties is essential in the battle against preterm birth in an attempt to relieve the effects or after-effects of preterm birth. For all of our medical advances to date, preterm birth is still all too common, and its ramifications are significant for hospitals, families and society in general.

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