Looking beyond bronchopulmonary dysplasia: prematurity-associated lung disease and its phenotypes

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Key Points: implications for practice

- **The concept**: prematurity-associated lung disease (PLD) provides a unifying framework to describe the heterogeneous respiratory consequences of preterm birth
- **Phenotypes**: several distinct phenotypes of PLD have been delineated - prematurity-associated obstructive lung disease (POLD), prematurity-associated preserved ratio of lung impairment (pPRISm), and prematurity-associated dysanapsis (pDysanapsis) - each with unique developmental determinants and pathophysiological mechanisms
- **Differential diagnoses**: in young adults presenting with atypical asthma, COPD, or unexplained respiratory symptoms, clinicians should consider a history of preterm birth and the possibility of prematurity-associated lung disease (PLD)
- **Phenotype diversity**: PLD encompasses distinct phenotypes (POLD, pPRISm, pDysanapsis), each with unique developmental origins and pathophysiology, requiring different clinical considerations
- **Avoid misclassification**: failure to recognise PLD may lead to misdiagnosis, inappropriate labelling (e.g., “asthma” or “early COPD”), and suboptimal treatment strategies
- **Tailored management**: awareness of PLD phenotypes can guide precision approaches, inform long-term monitoring, and stimulate referral into research or specialist care pathways

Abstract:

Preterm birth is increasingly recognised as a determinant of chronic respiratory disease across the life course. This first article in the series on prematurity-associated lung disease (PLD) introduces the concept of PLD as a unifying framework for the diverse pulmonary consequences of preterm birth. Historically, most attention has focused on extremely preterm infants (<28 weeks' gestation) who develop bronchopulmonary dysplasia (BPD), yet not all infants with BPD experience long-term morbidity. Conversely, those born very (28-31 weeks), moderate (32-33 weeks), or late (34-36 weeks) preterm also demonstrate increased respiratory risk. Multiple factors beyond BPD - including gestational age and intrauterine growth restriction - contribute to PLD development. Recently described PLD phenotypes include prematurity-associated obstructive lung disease (POLD), prematurity-associated preserved ratio impaired spirometry (pPRISm), and prematurity-associated dysanapsis (pDysanapsis). Each reflects distinct early-life exposures and mechanisms, with differing implications for prognosis. Defining these phenotypes provides a foundation for personalised monitoring and targeted therapeutic strategies.

Introduction

Preterm birth is defined by the World Health Organisation as birth occurring before 37 weeks' completed gestation.[1] Preterm birth is often classified into extremely (<28 weeks), very (28-31 weeks), moderate (32-33 weeks) and late (34-36 weeks) gestation; and term birth often into early- (37-38 weeks) and late-term (≥39 weeks) births.[2] Over thirteen million infants were born preterm in 2022, constituting approximately 10% of all births. Of these, approximately 1.5% were born before 32 weeks' gestation, often requiring specialist neonatal care.[3] Rates of preterm birth have remained unchanged over the last decade, with marked geographic variation. Most of the burden of preterm birth occurs in sub-Saharan Africa and southern Asia.[3] In contrast, in developed countries, the gestational age for infants receiving intensive care, especially in high income countries, has decreased to 22 weeks of completed gestation,[4-6] although mortality and morbidity remain high for this extremely immature group.[4]

Preterm birth results in infants delivered at an early stage of lung growth and development, with the degree of immaturity increasing with decreasing gestation. As a result, neonatal respiratory distress syndrome is common after birth, especially in extremely preterm-born infants due to surfactant deficiency, developmentally immature lungs and immature breathing control. Despite optimal obstetric management including antenatal administration of maternal corticosteroids to mature the fetal respiratory system, exogeneous surfactant treatment, invasive or non-invasive mechanical ventilation, and supplementary oxygen therapy,[7] a significant proportion will develop the neonatal lung disease bronchopulmonary dysplasia (BPD, also called chronic lung disease of prematurity (CLD)), defined by the need for ongoing supplementary oxygen and/or positive-pressure respiratory support. Although there are many definitions for BPD, a commonly used one assesses severity based on supplementary oxygen requirements and/or supportive mechanical ventilation at 28 days of age and at 36 weeks' postmenstrual age (PMA).[8,9] It has long been established that BPD is associated with future lung disease when compared with term-born controls, although not all survivors of BPD develop lung disease in later life. Importantly, it is increasingly recognised that preterm birth

at later gestations (especially moderate to late preterm birth, which account for the greater proportion of preterm births), in whom the diagnosis of BPD is uncommon, are also at risk of future lung disease when compared with their term-born counterparts.[10]

This article forms the first in a three-part series on prematurity-associated lung disease (PLD). The series introduces and develops the concept of PLD as a life-course condition. In this opening paper, we define PLD and its distinct phenotypes, providing a conceptual framework for future research and clinical care. The second paper synthesises current evidence on long-term outcomes and lung function trajectories after preterm birth, linking these outcomes to the proposed PLD phenotypes and highlighting major knowledge gaps.[11] The third paper addresses management and monitoring, outlining available therapeutic options, follow-up strategies from infancy through adulthood, and priorities for multidisciplinary care.[12] Each paper can be read independently, but together they present a coherent narrative: from definition, to natural history, to treatment and monitoring of PLD. This integrated approach is novel, since no prior reviews have conceptualised PLD as a distinct, life-long lung disease entity, nor outlined how phenotyping can inform research, clinical care, and future intervention strategies.

Search Strategy and Selection Criteria

The search strategy from our recent systematic review[10] was updated to include the search terms for six databases for lung function after preterm birth but focussed on identifying studies of lung dysfunction beyond BPD to identify other risk factors of lung disease including intrauterine growth restriction and gestational age, as described in the appendix (Pages 2 – 7). Publications in any language and conference abstracts were included. The resulting articles were reviewed and those relevant are included in this review.

Risk factors for respiratory disease after preterm birth

The most important risk factor for development of lung disease after preterm birth is gestational age at birth which reflects the immaturity of the developing lung. Lung immaturity *per se* can lead to adverse future lung disease but is often compounded by noxious exposures both before (e.g. antenatal maternal tobacco smoking, chorioamnionitis, social status, intrauterine growth restriction (IUGR)) and after birth (e.g. invasive and non-invasive respiratory support, supplementary oxygen, infection), resulting in both short- and long-term respiratory consequences for lung growth, affecting both the upper and lower airways and also the parenchyma. Discussed below are other main risk factors for the development of lung disease in the future.

Bronchopulmonary dysplasia

BPD has received the greatest attention as a risk factor for future lung disease including into adulthood. Undoubtedly, infants who are born extremely preterm at <28 weeks' gestation are at the greatest risk of developing lung disease during the neonatal period, as they are delivered at late canalicular/early saccular stage of lung development. Since a significant proportion of these infants will require respiratory support with exogeneous surfactant, supplemental oxygen and invasive or non-invasive respiratory support (latter two interventions are considered injurious to the under-developed lung), it is perhaps not surprising that many of these infants progress to develop BPD. BPD was initially described Northway and colleagues in 1967, in infants born moderately preterm at 34 weeks' gestation and birthweight of 2·234 kg.[13] They described prolonged need for supplemental oxygen and lung fibrosis in infants who died from BPD. Since this description, especially after the routine use of antenatal maternal corticosteroids, exogenous surfactant and more gentle non-invasive ventilation, the current infants most at-risk of developing BPD are those born at <28 weeks' gestation. Post-mortem findings of the current infants who die from BPD are more of decreased alveolar development rather than lung fibrosis.[14] The pathogenesis of BPD is multifactorial, with many risk factors identified including lower gestation, chorioamnionitis, male sex, IUGR, exposure to higher fractions of inspired oxygen, ventilator-induced lung injury, postnatal sepsis, patent

ductus arteriosus and poor postnatal somatic growth.[2,15] Various definitions have been created to define BPD, with the 36 weeks' PMA age commonly used to define the need for oxygen or respiratory support.[8] Importantly, excellent home oxygen and follow up programs have been developed in many countries so that these infants with BPD, who require supplemental oxygen, can be managed in suitable home environments to encourage improved neurodevelopment and somatic growth. These programmes generally have multi-disciplinary input, especially whilst the infants continue to have respiratory disease or related co-morbidities, but follow up beyond two years' PMA is generally *ad hoc*, mostly confined to those who require on-going medical care. Current and proposed longer term management and follow up programs in both children and in adults are described in more detail by Duijts and colleagues in their review.[12]

Lung disease after very, moderate and late preterm birth

Far less acute lung disease is noted in moderately or late preterm-born infants, during the neonatal period when compared with extremely preterm-born infants, requiring far less respiratory support and supplemental oxygen, with a diagnosis of BPD being very uncommon in these groups. Since these infants are generally admitted to neonatal units to establish feeding, with few requiring intensive care, follow up by the neonatal team is generally confined to those who have on-going medical need. Long term surveillance to identify lung function deficits is virtually unheard of. However, as described below, significant long-term lung disease is associated with very, moderate and late preterm birth, or even after early term birth at 37-38 weeks' gestation (Figure 1).

Intrauterine growth restriction

IUGR underpins much of the fetal programming hypothesis which is associated with many long-term diseases including of the respiratory system (e.g. chronic obstructive pulmonary disease, COPD), cardiovascular disease and with all-cause mortality.[16] IUGR, defined by WHO as birthweight below the 10th centile after adjustment for gestation and sex, is common

in preterm-born infants occurring due to maternal, fetal or placental factors, which often lead to delivery of preterm infants. IUGR is associated with numerous adverse events in the neonatal period, including greater rates of BPD when compared to infants born at similar gestation without IUGR.[17] Furthermore, IUGR in preterm-born (including those born moderately preterm) and term-born infants is associated with increased symptoms and decreased lung function in childhood and beyond when compared with subjects born with normal birthweights.[18,19] It is clear that IUGR is associated with adverse longer term respiratory outcomes but has received less attention than BPD, despite it being on the causal pathway to the development of lung disease in the future.[17]

Studies of preterm-born school-aged children with IUGR have shown consistent reductions in forced expiratory volume in one second (FEV_1) when compared with preterm-born individuals without IUGR,[20,21] an association that persists even after adjustment for BPD.[20] Meta-analysis of adult lung function data, from ages 18 to 58 years, has also demonstrated positive association between birthweight and forced vital capacity (FVC) and the FEV_1/FVC ratio, although the majority of participants included in the studies were born at term.[22] It, therefore, appears that factors affecting antenatal lung growth are strong predictors of respiratory morbidity in both children and in adults.

Other risk factors for lung disease after preterm birth

Besides the important risk factors of gestational age, BPD and IUGR, there are many other risk factors which can lead to the development of PLD (Figure 1). These include antenatal factors such as maternal tobacco smoking and ambient pollution exposure, chorioamnionitis, intrauterine infections including by *Ureaplasma* spp., male sex, and postnatal factors such as exposure to higher fractions of inspired oxygen, ventilator-induced lung injury, postnatal sepsis, patent ductus arteriosus and fluid overload.[2] From infancy onwards, exposure to postnatal cigarette smoking and ambient indoor and outdoor pollution as well as viral infections in infancy are important risk factors to the development of lung disease in child/adulthood. Co-

morbidities such as gastro-oesophageal reflux and neurodevelopmental abnormalities can worsen lung disease via micro-aspiration.

Long-term outcomes after preterm birth

Since the 1990s, there have been many studies assessing lung function, especially by spirometry, most frequently comparing preterm-born children and young adults with and without BPD against term-born controls. However, despite development of BPD being strongly associated with lower gestation, these studies generally do not adjust for gestational age differences between the BPD and no BPD groups. Nevertheless, these studies have identified the significant decreases in lung function which occur after preterm birth with lung function deficits increasing with decreasing gestations. Several systematic reviews have collated the data from such studies (recent ones summarised in Table 1). The recently updated systematic review and meta-analysis including over seven thousand preterm-born subjects aged 3 to 52 years reported an overall deficit of 9·2% percent predicted FEV_1, and deficits of 16% regardless of whether BPD was diagnosed at 28 days of age (milder end) or at 36 weeks' PMA (moderate/severe end) when compared with term-born controls.[10] Interestingly, the systematic review showed geographical differences, with Scandinavian countries faring better than other high-income regions including western European countries, North America and Australasia, suggesting genetic factors maybe important. An extension of the systematic review showed that there may be increasing airway obstruction with age. However, caution is required as these data are obtained cross-sectionally (thus not accounting for any medical progress) rather than from longitudinal observations (see Du Berry and colleagues in this series[11]).[23,24]

In recent years, it has been increasingly recognised that not all survivors of BPD develop lung disease; equally, it is now recognised that many who were born at very and moderately preterm, as well as early term gestations, are at future risk of developing lung disease despite uncommonly requiring any neonatal intensive care after birth. A UK-based cohort study of 8-9 year old children noted that those born moderately preterm (33-34 weeks' gestation) had

significantly lower lung function when compared with term-born subjects, with the decrements being similar to those who were born ≤32 weeks' gestation, despite receiving little or no neonatal intensive care after birth.[25] A recent meta-analysis of fifteen studies of moderate-late preterm-born individuals (from 32 to <37 weeks' gestation) also reported lung function deficits and impairment of expiratory airflows when compared with term-born controls (Table 1).[26] Similarly, early term birth is also associated with increased respiratory symptoms in preschool and school aged children.[27] A Scandinavian data linkage study of over 1·6 million births (5% preterm) between 1967 and 1999, with current age of 18-50 years, using ICD-10 codes for asthma and chronic obstructive pulmonary disease (COPD), showed a gradient of increasing respiratory disease with decreasing gestation (Figure 2).

These data suggest that the relative immaturity of the lung at birth is a significant risk factor for the development of PLD, which is, however, exacerbated by interventions in the neonatal period, particularly respiratory support, which causes barotrauma or volutrauma. The greatest concern is that preterm-born children who develop lung disease in childhood are now considered candidates for premature development of COPD in early adult life, often exacerbated by unmonitored exposure to cigarette smoke and ambient pollution in adulthood, a powerful argument for longer term follow up of these vulnerable group of patients.[28]

Development of the concept of prematurity-associated lung disease (PLD)

It is now evident that many other risk factors associated with prematurity, including gestational age, BPD and IUGR, can contribute to development of lung disease in future years. Due to the small sizes of individual preterm cohorts (due to low rates of preterm birth in most high-income countries of between 5% and 8%), there are few large studies specifically designed to prospectively study, for instance, the effect of relevant life factors in the development of PLD. The recent RHiNO study prospectively recruited over 550 preterm-born (born at ≤34 weeks' gestation) and 200 term-born children, aged 7 - 12 years to evaluate, amongst several other prospective questions, the association of early and current life factors with spirometry deficits

of %FEV_1 ≤85%. As anticipated, a diagnosis of BPD, IUGR and gestational age (but not other early/current life factors including male sex) were associated with lung deficits at school age in univariable regression analyses. However, including these three factors in multivariable regression modelling, only gestational age and IUGR remained significant but not BPD, which was related to gestation but not to low %FEV_1 once adjustments were made for gestation and IUGR in mediation analyses (Appendix Page 9).[29] It is, therefore, apparent that there are many risk factors which predispose preterm-born individuals to longer term respiratory morbidity. These include those with a neonatal diagnosis of BPD and acknowledge that degree of gestational immaturity at birth including those born late or moderately preterm, together with adverse antenatal factors, such as IUGR and chorioamnionitis, also have significant influence on later lung function and health.

To encompass all risk factors for future development of lung disease after preterm birth, we have promoted the concept of "prematurity-associated lung disease" (PLD) from infancy to adulthood to encompass the respiratory morbidity reported as a consequence of preterm-birth at any gestation and to also encompass other important risk factors such as BPD, IUGR, noxious exposures, viral infections, etc.[29-31] As mentioned above, currently, follow up of preterm-born infants in most countries is generally confined to the extremely preterm population, usually up to two years of age, with follow up of very and moderately preterm groups confined to those who had significant neonatal respiratory disease, which excludes the majority of these groups. Thus, a management plan to follow up from the neonatal unit through childhood to adulthood is required, if we are to identify children with PLD as early as possible, and to enhance understanding of the underlying mechanisms of PLD. Thereby, targeted interventions can be introduced, tested and developed to intervene early to prevent the long-term adverse consequences of PLD, including the premature development of COPD. Suggestions of management plans and follow up to adulthood of PLD are reviewed by Duijts et al.[12] Given the lifelong consequences of PLD, it was surprising to note in one survey from the UK that no pulmonologist practicing in adults and only 25% of paediatric pulmonologists

enquired about early life factors, including neonatal admission or diagnosis of BPD, in their clinical practice.[32] Defining PLD as early as possible would include the most important risk factor of prematurity inherently within the definition, thus is likely to result in inquisition in the future by health professionals, including those caring for adults with lung disease, of important early life factors such as neonatal care.

The strength in pulmonology is the publication of normal reference ranges by the Global Lung Initiative against which spirometry of subjects with PLD can be assessed and compared to reference values.[33] However, as with several respiratory diseases, notably asthma, there are several underlying mechanisms which result in the clinical syndrome of asthma but each of these endotypes is often associated with a different clinical phenotype. In PLD, such phenotypes are very likely to exist given the wide range of exposures that a preterm-born child or adult may have been exposed to, ranging from antenatal events such as chorioamnionitis and maternal smoking, to neonatal interventions such as respiratory support and supplemental oxygen, as well as viral infections, exposures to cigarette smoking and pollution. The concept of phenotypes of PLD are described next.

Phenotypes of prematurity-associated lung disease

In adults with lung disease, several phenotypes, often based on spirometry (so can be used in routine clinical practice), have been described including obstructive patterns of lung disease, preserved ratio of impaired spirometry (PRISm) and dysanapsis. The airway obstruction may be responsive to bronchodilators or may be fixed. Such descriptions are limited after preterm birth largely due to the availability of small sample sizes of preterm-born populations. Obstructive spirometry patterns have been described in both cross-sectional and longitudinal studies of preterm-born individuals,[34] including those who had BPD in infancy.[23] In a systematic review, the preterm population with lung disease, including those who previously had BPD, fractional exhaled nitric oxide (FE_{NO}) was not increased.[35] Lack of discrimination by methods such as FE_{NO} may not be due to the technique itself but could be due to lack of

discrimination of the underlying lung disease. Phenotypes of PLD have recently been described in the preterm-born cohort[30] (Figure 3) using the following to define the phenotypes:

- POLD-Reversible: FEV1 <LLN; FEV1/FVC ratio <LLN; bronchodilator response ≥10%
- POLD-Fixed: FEV1 <LLN; FEV1/FVC ratio <LLN; bronchodilator response <10%
- pPRISm: FEV1 <LLN; FEV1/FVC ratio ≥LLN
- pDysanapsis: FEV1 ≥LLN; FEV1/FVC <LLN
- LLN: Lower limit of normal (<5th percentile) in GLI reference ranges

The definition of PLD can, therefore, be described as a preterm-born subject who falls into one of these spirometry patterns, which can be established as early as five years of age from when spirometry is reliable. Newer techniques, such as oscillometry, which can be used from infancy onwards, have the potential to identify PLD much earlier and permit more satisfactory longitudinal studies as discussed by Du Berry et al in ths series.[11] By using these definitions, lung disease or PLD is significantly greater in preterm-born children when compared with term-born children: 123/544 (22·6%) of preterm-born (at ≤34 weeks' gestation) children aged 7-12 years in the above study had one of the phenotypes of PLD compared with 18/195 (9·2%) term-born children (OR 2·87, 95% CI 1·70, 4·86, p<0·0001)[30]. Clearly, the burden of lung disease, even by early school age after preterm-birth, is sufficienty significant to raise alarm bells especially when it is nearly three times greater than in term-born children. A significant proportion of these children will not have received any intensive care during the neonatal period. Whilst these phenotypes are pragmatic so can be used in the clinic, it will be important to delineate the structural, immune and infective processes which underpin each phenotype (Appendix Page 8).

Prematurity-associated Obstructive Lung Disease

Obstructive spirometry patterns have previously been described in preterm-born individuals[36] including those who had BPD in infancy.[23] Prematurity-associated obstructive lung disease (POLD) has been defined as both FEV_1 and FEV_1/FVC ratio <LLN,[30] in line with other obstructive lung disease such as COPD.[37] Within POLD, there are at least two sub-types (Figure 3), those who respond to a bronchodilator (predicted percent FEV_1 increase of >10% following a bronchodilator), termed POLD-reversible, and those who do not, termed POLD-fixed. These two subtypes are differentially associated with early-life factors, with both POLD-reversible and POLD-fixed being associated with a history of BPD, but POLD-reversible also being associated with IUGR (Appendix Page 8). Whether POLD is initially reversible to bronchodilators and progresses to an irreversible phenotype is speculative. Despite the previous reports of a lack of increased FE_{NO} in BPD groups,[35] POLD-reversible was associated with increased FE_{NO}, whereas FE_{NO} was low in the preterm and term control groups (Figure 4). Neither of the two POLD phenotypes was associated with positive skin prick testing, but whether eosinophilic lung inflammation is associated with this increased FE_{NO} is speculative requiring further evaluation. In addition to identifying the clinical phenotypes, it will be important to identify treatable traits of PLD.[38] Inevitably, some of these preterm-born individuals in the POLD group will develop classic (atopic) asthma but given the far greater prevalence of obstructive disease in the preterm group when compared to the term-born group (OR 5·89, 95%CI 1·80, 19·24), it is likely that the underlying pathological process is specifically associated with prematurity. Credence is given to this speculation by recent oscillometry studies demonstrating a tendency to peripheral airways disease in the POLD group with increased airway resistance, particularly at lower frequencies, and impaired reactance, indicative of reduced lung compliance.[39] Whilst this finding has also been seen in oscillometry studies of uncontrolled asthma,[40] data from a recent intra-breath oscillometry study of POLD reported increased resistance and reactance throughout the respiratory cycle,[41] unlike other obstructive respiratory disease, such as asthma and COPD, where the expiratory component of the cycle is more affected than the inspiratory component (Appendix Page 10),[42,43] especially at zero-flow states (i.e. end-expiration in comparison to end-inspiration). These

observations suggest that the nature of obstructive lung disease in POLD is different when compared to other obstructive airway diseases. In a hyperpolarised ^{129}Xenon magnetic resonance imaging study, marked ventilation abnormalities were observed in the POLD group when compared to the pPRISm and preterm and term control groups.[44] Whether these ventilation abnormalities can be reversed by adequate treatment e.g. a combination of inhaled corticosteroids and long acting beta$_2$ agonist, which improved percent predicted FEV_1 in one study, is unknown.[45]

Prematurity-associated Preserved Ratio Impaired Spirometry

Preserved ratio impaired spirometry (PRISm) in adult populations has been linked with increased risk of all-cause mortality, progression to COPD, and cardiovascular disease.[46,47] Limited studies have reported the PRISm phenotype in children including those who are born preterm. pPRISm in the above RHiNO study[30] was defined as FEV_1 of less than LLN and FEV_1/FVC ratio greater than LLN. On oscillometry and MRI studies, pPRISm findings appear to be intermediate between the POLD and preterm and term controls for the former, with similar homogeneous ventilation without any ventilation defects, albeit with smaller lungs than in preterm and term controls for the latter. Although identification of pPRISm and the other phenotypes by using spirometry circumvents the need for lung volume measurements as would be required for identifying restrictive/obstructive disease, it is clear that once PLD has been diagnosed, specialist assessments including lung volumes, detailed imaging and other specialist investigations such as gas exchange assessments may be required at specialists centres for those with significant PLD including those with restricted physical activity due to significant respiratory symptoms or those with significant exercise limitation. No early life factors were associated with pPRISm except borderline significant association with body mass index (Appendix Page 8). Bronchodilator response is limited in this group. Little is presently known about the natural history and evolution of this phenotype in preterm-born children, but since PRISm in adults is associated with obesity, increased adiposity and tobacco smoke exposure, these should be actively discouraged in this group of preterm-born children.[47] In

longitudinal studies of PRISm in the adult population, there appears to be variable phenotype progression, with some individuals showing persistent PRISm spirometry deficit, whilst some revert to normal spirometry patterns.[48] Those who revert to normal spirometry have similar long-term outcomes to those who never developed PRISm. However, given the early life deficits of lung function associated with PLD, the concern is that long term trajectories are likely to be associated with the persistent PRISm phenotype, which is associated with significant long-term morbidity including COPD. Besides avoidance of known risk factors, which additional treatments may benefit this group is currently unknown.

Prematurity-associated Dysanapsis

Dysanapsis has been described since the 1970s,[49] and is generally considered to represent a discrepancy between airway calibre and lung volume. This is thought to be related to discordant lung growth, although definitions have been debated.[50] Within the PLD context, prematurity-associated dysanapsis (pDysanapsis) was identified using the ERS recommendations[51] with $FEV_1 \geq LLN$ and $FEV_1/FVC < LLN$.[30] Findings for pDysanapsis appear to be intermediate for the POLD and pPRISm groups, with a third having significantly increased FE_{NO}, and 40% responding to bronchodilators (Appendix Page 8). Body Mass Index (BMI) and postnatal weight gain are also associated with pDyanapsis.[30] There is a suggestion that prematurity and a history of BPD may predispose to pDysanapsis, and that a dysanaptic respiratory pattern may evolve into an obstructive one as individuals age.[50] Dysanapsis in adults has been associated with later progression to emphysema[52] and COPD[53] in retrospective studies. How pDysanapsis evolves over time in preterm-born individuals requires further study.

In summary, the concept of PLD and its phenotypes is important as it embraces the many risk factors which lead to the development of lung disease after preterm birth. The description of the different phenotypes is the first step to identifying the subgroups of subjects with PLD who have specific underlying mechanisms and may be amenable to specific treatments. With in

depth studies of these phenotypes, further refinement is required of this concept to better investigate the disease process to understand why there is continuing lung disease when the initial “injury” of preterm birth occurred so many years previously. Importantly, the presence of the word “prematurity” within PLD will already identify the most important risk factor to pulmonology specialists caring for both children and adults, an important development especially as very few adult or paediatric pulmonology experts ask about early life events, including if their patient was born preterm or with low birthweight, in their clinical practice [32].

Endotypes of Prematurity-associated Lung Disease

Mechanistic studies of BPD

In comparison to other chronic respiratory diseases, such as asthma, COPD and cystic fibrosis, there are limited studies examining the biological mechanisms, especially after discharge from the neonatal unit, that underpin the development of lung disease after preterm birth. These few studies have largely focused on the BPD group at school age suggesting the possibility of neutrophilic lung inflammation, increased oxidants and lack of an association with FE_{NO} as noted above. Airway histology from individual adolescent survivors of BPD shows thickening of the basement membrane, with lymphocytic infiltration of the airway wall.[54] High resolution computed tomography scans have demonstrated significant structural airway abnormalities, with air-trapping, bullae and atelectasis.[55,56] But these studies are all limited by very small sample sizes, selection bias and lack of suitable samples to analyse.

More recent studies have utilised more relevant samples such as bronchoalveolar lavage from young preterm-born adults.[57] Additionally, newer technologies including mass spectrometry-based proteome and metabolome analysis are only starting to be used in preterm-born populations. One study using non-invasively collected airway samples (exhaled breath condensate) in school-aged survivors of BPD, showed deficits in structural proteins related to cell adhesion (desmosomes) and cytoskeletal structure, with increased abundance of

detectable free cytokeratins.[58] Reduction in desmosomes has previously been related to increased airway inflammation in *in vitro* studies,[59,60] with increased abundance of cytokeratin in EBC also observed in adult patients with lung injury.[61] Alterations to the EBC metabolome has also implicated oxidative injury in childhood and adolescent survivors of BPD, with reduced quantities of metabolites involved with glutathione synthesis (a potent airway antioxidant),[62] and higher levels of 8-isoprostane,[63] both of which are suggestive of oxidative stress. However, studies have thus far failed to find an association between changes in oxidative stress mechanisms and current lung function. Alterations in T-lymphocyte biology have also been noted in bronchoalveolar lavage fluid from preterm-born adults, with alteration in CD4+/CD8+ ratios associated with BPD and increased proportion of CD8+ lymphocytes being negatively associated with lung function.[57] The mechanistic studies of BPD have so far suggested that there appears to be persistent structural lung changes as well as an active inflammatory process, with a suggestion of increased oxidative stress. These studies provide proof of principle of disordered lung structure and of an active inflammatory process continuing in preterm-born subjects with lung disease. How they relate to underlying phenotypes is only just being described.

Mechanistic studies of phenotypes of PLD

One study of preterm-born (<30 weeks' gestation) school-aged children from the peri-surfactant era (a small minority of whom were diagnosed with BPD) demonstrated reduced serum CD4+ counts and CD4+/CD8+, with a weak association seen with bronchial hyper-responsiveness.[64] Another series of studies have analysed the proteome and metabolome to generate a series of hypothesis generating observations which require confirmation by identification of individual pathways as summarised in Figure 5. The airway proteome in PLD showed protease/anti-protease imbalance related to low lung function, with decreased abundance of secretory leukocyte peptidase inhibitor and Annexin A1,[58] which have also been noted in the study of early neonatal lung injury.[65,66] The urinary proteome in the POLD group has demonstrated alterations in proteins associated with neutrophil activity, as well as an

increased abundance of matrix metalloprotease-9 (MMP-9),[67] which has also been demonstrated in the early urine proteome of neonates who later develop BPD.[68] The urinary metabolome in POLD also shows alterations in both glutathione metabolism, suggesting oxidant/antioxidant imbalance, and the β-oxidation of fatty acids,[69] which has previously been observed in studies of adults with COPD. In addition, higher proinflammatory cytokines in EBC for the POLD group have been noted in a preliminary study when compared with preterm-born controls.[70] For the pPRISm group, study of the urine proteome revealed alterations in protein abundances associated with inflammation, T-lymphocyte activity and possibly the differential activation of CD4+ and CD8+ T-lymphocytes.[67] Changes in CD4+/CD8+ T-lymphocyte counts have been reported in adults with BPD[57] and COPD,[71] suggesting an overlap between the two. Whilst a PRISm phenotype in adults has been associated with some genetic polymorphisms, the biological mechanisms underlying PRISm in adults are as yet unknown,[72] and how they relate to the mechanisms so far seen in pPRISm will require further study.

Many of these studies should be considered preliminary and hypothesis generating but provide a platform for future direction to identify the underlying mechanisms associated with the different phenotypes of PLD. It is also unclear why preterm-born subjects have an active inflammatory phase in later life given that the insult of preterm birth at an early stage of lung development occurred so many years previously. Understanding these mechanisms will be paramount to drive the optimal management of preterm survivors who develop PLD.

Conclusions:

PLD provides an overarching concept which embraces all survivors of preterm birth who develop lung disease including those who do and do not develop BPD. By identifying subgroups of PLD, i.e. clinical phenotypes which can be identified easily in community settings, the individual trajectories associated with each phenotype can now be studied together with their associated outcomes including COPD and other respiratory diseases. In young adults presenting with atypical asthma, COPD, or unexplained respiratory symptoms,

clinicians should consider a history of preterm birth and the possibility of prematurity-associated lung disease (PLD). Furthermore, the underlying structural, immune, inflammatory or infective processed can also be studied. The future challenges are to develop appropriate national or international cohorts which can address many of these questions, especially as it is important to ensure study of adequately sized preterm-born populations.

Author Contributions:

SK conceptualised the article. CWC composed the first draft with guidance from SK and AB, with the final manuscript reviewed by all authors.

Declaration of interest:

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