Unravelling the respiratory health path across the lifespan for those born too soon

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Abstract:

Many survivors of preterm birth will have abnormal lung development, reduced peak lung function, and potentially an increased rate of physiological lung function decline; each of which places them at increased risk of chronic obstructive pulmonary disease (COPD) early in life. Current rates of preterm birth indicate that by the year 2040, around 50 years since the beginning of the surfactant era, over 700 million individuals will have been born prematurely – a number that will continue to compound by ~15 million annually. This Personal View aims to put this emerging health crisis on the radar for the respiratory community. We also detail the potential underlying mechanisms of prematurity-associated lung disease and propose a novel way of considering lung disease after preterm birth, utilising a multidimensional model to determine individual phenotypes of lung disease.

Key Messages:

- *Worldwide, ~15 million infants are born preterm each year. While their survival rates are increasing, not enough is known about their life-long respiratory health, particularly for those born extremely preterm (EP; <28 weeks' gestation). The first large groups of survivors born EP since the introduction of exogenous surfactant into clinical practice in the early 1990s are only now approaching mid-adulthood.*
- *Cohort studies show that survivors of preterm birth have more expiratory airflow deficits during childhood than their term-born peers and fail, on average, to reach normal "peak" lung function during early adulthood.*
- *Poorly reversible airflow obstruction is a common characteristic in this population, and consequently, chronic obstructive pulmonary disease (COPD) is now considered a potential major outcome of preterm birth.*
- *Survivors of preterm birth have limited evidence-based treatment options available for improving pulmonary health following discharge from the neonatal intensive care unit. Current therapies, such as inhaled corticosteroids and long-acting bronchodilators, show some promise, but robust clinical trials are required. Research focusing on the development of early and effective interventions is required to prevent an avalanche of lung disease in the near future.*

- *A detailed understanding of the mechanisms underpinning prematurity-associated lung disease is currently lacking. For example, we do not know if lung disease after preterm birth represents a current active (inflammatory) airway disorder, compounding any previous structural injuries. Elucidating the underlying mechanisms remains a priority.*

- *We propose the existence of clinical phenotypes of prematurity-associated lung disease, which can be described using a multidimensional "wheel-and-spoke" model. The model describes phenotype profiles of an indeterminate number of traits, each represented by a spoke in the wheel, which can be expanded or discarded as new evidence comes to light.*

- *Clinical phenotyping may be the first step toward appropriate treatment of prematurity-associated lung disease and could alter the trajectory of the disease. This approach may be particularly important for those at a higher risk of developing premature chronic airflow obstruction.*

Search strategy: References for this review were identified through a Scopus search for articles published between January 1990 and March 2023 by use of the search terms (TITLE-ABS-KEY (preterm) OR TITLE-ABS-KEY (bronchopulmonary AND dysplasia)) AND (TITLE-ABS-KEY (lung AND function) OR TITLE-ABS-KEY (pulmonary AND function) OR TITLE-ABS-KEY (respiratory AND function)). Articles were also identified through the authors personal files. Searches were limited to the English language.

Introduction:

Worldwide, ~15 million infants are born preterm each year (< 37 weeks' gestation).[1] Over 80% of preterm births are moderate to late preterm born (MLP; 32 to ≤ 37 weeks); fewer are very preterm born (VP; 28 to < 32 weeks) and even fewer are extremely preterm born (EP; < 28 weeks' gestation). Due to modern perinatal care practices, a larger proportion of these infants now survive to discharge than in previous generations.[2] Even amongst the highest-risk infants, those born EP, survival rates approach 90% if intensive care is offered after birth.[3] Despite the significant advances in management, preterm birth remains the second most common cause of neonatal death across the world. In addition, preterm survivors experience a broad range of morbidities throughout their lives, including conditions of the central nervous, metabolic, and cardiopulmonary systems, at significantly higher rates than those born at term (≥ 37 weeks' gestation). Consequently, gestational age is inversely associated with mortality from infancy to mid-adulthood. [4] Relative to full-term birth, the adjusted hazard ratios for mortality associated with gestational age in a Swedish national cohort study were 2·04 (0·92-4·55) for extremely preterm, 1·48 (1·17-1·87) for very preterm, and 1·22 (1·07-1·39) for late preterm, at ages 30-45 years.[4]

The economic burden on healthcare systems and families is also substantial. The total lifetime healthcare costs for each EP infant surviving to discharge is estimated to be more than US $ 500,000, with 72% incurred after the "acute" first year of life.[5] Limited evidence points to considerable respiratory morbidity across the lifespan in preterm survivors, including respiratory symptoms, structural abnormalities of the lung, and suboptimal lung function. Indeed, preterm birth is gaining increasing recognition as a significant contributor to the early origins of adult lung disease.[6]

Here, we review our current understanding of the respiratory problems that affect survivors of preterm birth, placing a significant subset of individuals at risk of poor lung health across their lifespan. We also review current interventions with potential to alter their lifelong respiratory trajectories. In doing so, we propose the existence of clinical phenotypes of prematurity-associated lung disease (PLD) for those discharged from the neonatal intensive care unit (NICU). Further, we propose that determining an individual's PLD phenotype is the key to designing optimal clinical management approaches to prevent later adult respiratory disease in survivors of preterm birth. Finally, we consider the clinical implications of prematurity over the lifespan of preterm birth survivors. We identify areas in need of urgent multidisciplinary investigation to drive the field forward and improve the lung health trajectories for those born too soon.

Risk factors of poor long-term lung health

Most research towards understanding the long-term respiratory outcomes of preterm birth has, thus far, been focused on bronchopulmonary dysplasia (BPD; also called chronic lung disease of prematurity, CLD). BPD is a major respiratory complication in the NICU for infants born preterm. BPD was first described in 1967 by Northway, reporting respiratory outcomes of 13 preterm infants born at a (relatively mature) mean gestation of 34 weeks, and mean birthweight of 2234 g.[7] These infants exhibited lung fibrosis and emphysematous changes. BPD has evolved dramatically since then, being now predominantly observed in those born EP or extremely low birthweight (ELBW; <1000 g birthweight). The evolution in BPD pathology was brought about by substantial improvements in clinical practice during the 1980s and 1990s, including antenatal maternal administration of corticosteroids, exogenous surfactant after birth to treat respiratory distress, and gentler forms of mechanical ventilation. These improvements translated to substantial increases in survival rates, particularly for those born EP/ELBW; the survival rate to two years of age for those born ELBW in the state of Victoria in 1979-80 was only 25%, rising to 73% by 1997, less than 20 years later.

Currently, there is no specific test to diagnose BPD. Rather it is a classification determined by the degree of respiratory support required by an infant at certain time-points. For many years, supplemental oxygen therapy for more than 28 days after birth and respiratory support at 36 weeks' postmenstrual age (PMA) were used to define BPD and its severity.[8] Others have suggested using respiratory support at 36 weeks PMA, or oxygen/respiratory support at 40 weeks PMA, as alternative criteria for the diagnosis of BPD and its severity, based on predictive values of BPD for respiratory or neurodevelopmental problems in early childhood.[9,10]

Based on the definitions above, however, BPD is a diagnosis specific to the neonatal period, used to identify infants with a particularly troublesome clinical course during their first few weeks and months after birth. As such, BPD should be treated as a risk factor for later lung problems, while appreciating that other early-life factors, such as allergic sensitisation,[11] lower respiratory tract infections[12] and tobacco and air pollution exposure,[13] drive gene-environment interactions and play an overtly influential role in determining lung function and severity of respiratory disease across the lifespan.

It is worrying that BPD is still used to label a complex lung condition decades after survivors have left the NICU, largely ignoring other risk factors. The extent to which BPD independently predicts more important respiratory outcomes into school-age and beyond remains to be determined. Importantly, many survivors born preterm who never developed BPD, particularly those born MLP, are increasingly recognised to be at risk of developing future lung disease. Additional risk factors include male sex, gestational age, intrauterine growth restriction, chorioamnionitis, maternal smoking during pregnancy, passive smoke exposure through childhood, era of birth, and early or severe respiratory

viral infection. It is time to establish a nomenclature that adequately describes the lung disease experienced by survivors of preterm birth across their entire lifespan. We urge the International Respiratory Societies to act. Within this article, we will use prematurity-associated lung disease (PLD) to described those with lung disease after preterm birth, regardless of BPD diagnosis. See Panel 1 for definitions.

Potential lung health trajectories across the lifespan (The expiratory airflow trajectome)

When defined by expiratory airflow (FEV_1), normal lung function follows an established trajectory throughout the lifespan; increasing during childhood and adolescence, reaching a peak in the early-mid-20s, thereafter followed by a gradual physiological decline with age.[14] The age-related decline in expiratory airflow usually proceeds unrecognised in most people.[15] This lifespan trajectory, however, can vary between individuals and is influenced by multiple factors, including genetic predisposition, antenatal fetal, maternal, or placental factors, early life exposures and airborne exposures (notably tobacco smoke exposure).

Based on our understanding of the expiratory airflow trajectome, and its modifiers, we might anticipate that the "normal" trajectome is altered in survivors of preterm birth, due to potential modifiers occurring at all phases of the trajectome (See Figure 1), and in unique combinations for each individual. Some key features of the altered trajectome across each developmental phase are detailed below for survivors of preterm birth:

1) *Genetic:*

   GETomics is a recently proposed concept that proposes inherited genetic variants and gene-environment interactions to be drivers of later-life respiratory disease[16] [ref]. These complex interactions occur across the entire lifespan, with environmental exposures continuously interacting with the genome through epigenetic modifications. It is possible that preterm birth incurs detrimental epigenetic changes early in life, altering cellular trajectories and subsequent lung development and aging.

2) *Antenatal:* Infants born preterm can be exposed to an adverse intrauterine environment, including in-utero tobacco exposure from maternal smoking, chorioamnionitis and its accompanying inflammation, or fetal growth restriction, which sometimes necessitates preterm birth. Consequently, we may anticipate that the trajectome starts at a lower level in some infants born preterm compared withinfants born at term who have been free of antenatal complications. Antenatal conditions might, therefore, prime an alternate life-course trajectome.

3) *The Neonatal Intensive Care Unit (NICU):* Preterm infants are often exposed to lifesaving, but potentially injurious (and pro-inflammatory) treatments in the NICU, including supplemental oxygen and mechanical ventilation. The increased use of non-invasive respiratory support over recent decades has not improved long term respiratory outcomes.[17] Other NICU exposures, such as disruption of the circadian rhythm, also potentially impact on normal lung growth and development. Consequently, the trajectome of preterm infants further away from that of infants not requiring any NICU interventions.[18]
4) *Childhood:* As a collective, children born preterm have expiratory flow limitation when compared with term-born controls.[19] Children born preterm often have additional exposures during early life. For example, rehospitalisation rates for severe acute respiratory illnesses (largely due to respiratory viruses) are ~7 times higher than for term-born infants, with increased risk of infection-related rehospitalisation continuing until at least 18 years of age.[20]
5) *Adolescence:* Post-pubertal adolescents are a generally understudied group. The effect of puberty on lung development together with risk factors described in "Childhood" above is largely unknown for those born preterm. However, this is also a period of development often associated with the initial uptake of smoking or vaping, which may further affect long term lung trajectories.
6) *Early adulthood:* Evidence to date suggests that a significant proportion of this population does not reach its expected peak of adult lung function, with most deficits observed amongst those born VP and EP.[21] With an abundance of early life exposures and altered lung growth, it is entirely conceivable that expiratory airflow decline might start at a younger age for those born preterm, compared with the general population. Indeed, approximately half of all COPD cases are thought to arise from low peak and normal rate of decline.[22]
7) *Late adulthood:* For survivors of preterm birth, concrete evidence regarding the nature of this decline-phase is lacking. However, a lifetime of adverse conditions may result in a steeper decline in the expiratory airflow trajectome in those born preterm than the term-born population. Even with a normal rate of decline over subsequent years, those born preterm are likely destined for higher rates of COPD in later life than those born at term.

In addition to the points above, the impact of socioeconomic disadvantage cannot be understated as an important modifier of the expiratory airflow trajectome across the entire lifespan in this population. Socioeconomic disadvantage is associated with lower lung function across the wider population. For example, at 45 years of age, an estimated 4–5 years of healthy lung function was lost according to socioeconomic disadvantage in a recent European multicohort study.[23] These associations remained after controlling for respiratory health risk factors, including smoking,

sedentary behaviour, obesity and known cardiovascular and respiratory disease. Given that estimates from Europe indicate an almost 50% higher prevalence of preterm birth among the least educated, compared with most educated mothers, the role of socioeconomic disadvantage is likely to be compounded among those born preterm.[24]

Even today, the lifelong lung health trajectories after preterm birth remain uncharted territory, as the first large groups of studied survivors are only now approaching mid-adulthood. This is particularly true for infants born EP, where the rates of survival past the neonatal period have significantly increased in the post-surfactant era.[25,26] The following sections will describe our current understanding of i) the growth and development phase, ii) attainment of the peak, and iii) the physiological aging phase of the expiratory airflow trajectome, as they it relate to survivors of preterm birth. The vast majority of evidence to date is cross-sectional, and not longitudinal. Further, the most available data are for those who developed BPD in infancy.

Expiratory airflow obstruction across the lifespan in survivors of preterm birth.

The growth phase of the trajectome: childhood and adolescence

Cross-sectional studies of lung function in children and adolescents surviving preterm birth consistently report the presence of PLD, characterised by expiratory airflow obstruction with reductions in FEV_1, ratio of FEV_1 to forced vital capacity (FVC), and forced expiratory flows (e.g., FEF_{25-75}). A recent systematic review and meta-analysis of these studies in both children and adults, spanning the pre-and post-surfactant eras, showed that overall, % predicted FEV_1 was decreased by an absolute 9.2% in the preterm group (N=8,294 preterm), compared with 17,700 term born individuals.[19] This study reported that FEV_1 deficit was constant with age, and therefore suggested that the deficit is fixed in early life, with no relative deterioration of lung function with increasing age.

The limited longitudinal data available, however, suggest that children born VP may experience increasing airway obstruction, as defined by a reduction in FEV_1/FVC over time, and/or a reduced rate of rise in FEV_1 throughout the growth phase of their trajectome. A longitudinal cohort of Australian children born ≤32 weeks gestation during the surfactant era showed that all measures of expiratory airflow obstruction (FEV_1, FEV_1/FVC and FEF_{25-75}) shifted at least -0.1 z-scores further away from the normal healthy term trajectory annually between 4 and 12 years of age.[27] Another Australian cohort, an EP/ELBW group born on the cusp of the surfactant era, demonstrated increasing airway obstruction between 8 and 18 years with a mean FEV_1/FVC decrease of -0.27 (95% CI -0.54 to -0.01) during this period,[28] but no further deterioration between 18 and 25 years.[29] In contrast, longitudinally studied cohorts from Norway suggest that lung function trajectories of EP survivors track in parallel with term

controls, albeit significantly lower than the term trajectories.[30] A particular strength of these three studies is the inclusion of (also serially measured) term born comparator groups to elucidate if growth trajectories differ between preterm and control groups. Findings are, however, similar across studies not including a term comparator group with consistent reports of increasing airway obstruction in both Swedish and United States cohorts of preterm survivors throughout childhood and adolescence.[31,32] Throughout these longitudinal studies, several factors have been associated with increased shift away from the normal growth trajectory over time including earlier gestation, increased length of supplemental oxygen and mechanical ventilation in the NICU, neonatal BPD diagnosis, passive or active cigarette smoking, and maternal asthma. Decreased rate of FEV_1 rise was also noted in children from the United States with black African or Northeast Asian ancestry, compared with European ancestry. Additionally, in a study including lung imaging, children with bronchial wall thickening on chest CT (i.e. inflammatory changes) had an FEV_1 z-score decline of –0·61 (95% CI –1·03 to–0·19; p=0·005) more than those without bronchial wall thickening, potentially suggesting an ongoing inflammatory component to progressive PLD. [27]

The peak of the trajectome: young adulthood.

Most survivors of preterm birth do not reach their expected peak adult expiratory airflow. A recent individual participant data meta-analysis derived from 11 studies of 935 survivors born either <32 weeks' gestation or with birthweight <1500 g, compared with 722 controls born at term (≥37 weeks' gestation) or of normal birthweight (>2499 g) reported expiratory flow rates at a mean age of 21 years.[21] Mean z-scores for expiratory flow were reduced in the preterm group compared with controls (e.g., FEV_1 mean difference –0·78 [95% confidence interval [CI] –0·96 to –0·61]). Moreover, 24% of the preterm group had FEV_1 values in the clinically important range of <5th centile, compared with only 7% of the controls (odds ratio 4.16, 95% CI 2.99 to 5.78). Of note, survivors born preterm who had BPD in the newborn period had even lower expiratory flows than those who did not, by -0.88 SD (95% CI -1.05 to -0.78) for FEV_1. Most of the survivors from these 11 studies had been born before 1990, and only 15% had been treated with exogenous surfactant. Subsequent studies in adult populations born preterm in the 1990s, when surfactant therapy was clinically available, have provided evidence of similar findings. These studies have revealed even greater disparities in z-scores between preterm and control groups in instances where the preterm group were more immature; specifically with gestation <28 weeks, or with birthweight <1000 g (-0.97 (95% CI -1.23 to -0.71 for FEV_1) [29] or <26 weeks (-1.31 (95% CI -1.61 to -0.98)) for FEV_1.[33] In another recent report of expiratory airflow in adulthood of survivors who were born <1500 g birthweight in 1986, before surfactant was available, the reduction in FEV_1 was less pronounced for the preterm group compared with controls (-0.54 SD (95% CI -0.83 to -0.26)).[34] Interestingly, in these three latter studies, among the preterm groups, the mean difference

between those who had and those who did not have BPD was approximately the same (-0.66, -0.78, and -0.85, respectively), and was similar to the differences between BPD and non-BPD groups in the meta-analysis above. Moreover, even though differing criteria were used to define BPD between the various studies listed above, it is still an important early marker for reduced expiratory airflow in early adulthood. However, it is important to note that it is not only adults born preterm with a prior diagnosis of BPD who experience reductions in expiratory airflow, as preterm survivors without BPD also had a mean reduction in FEV_1 z-score ranging from -0.50 SD to -1.05 SD in the studies described above.[21,29,33,34] In young adults born preterm, childhood respiratory admissions (severe acute respiratory infections) are associated with lower peak lung function (mean FEV1/FVC z-score -0.61; 95% CI –1.02, -0.21) compared with those not hospitalised; this reduction was greatest in those with BPD (-0.74 z-scores, 95% CI -1.24, -0.24).[12]

The decline phase of the trajectome: Beyond the 20s

We currently lack robust information about the decline phase for those born preterm and surviving beyond early adulthood, since the first large groups of studied survivors are only now approaching mid-adulthood. However, with such significant reductions in expiratory airflow at the expected peak in the early 20s, development of early onset poorly reversible airflow obstruction characteristic of COPD has long been postulated as an outcome for some of these young adults.[35,36] Indeed, the Lancet Commission towards the elimination of COPD recently defined a subtype of COPD related to early life origins, particularly prematurity.[6] Longitudinal studies after preterm birth extending beyond the fourth decade of life are needed to investigate this important question in more detail. To date, a limited number of longitudinal studies have traced lung function after preterm birth beyond the early 20s. Some report tracking of lung function parallel to the normal trajectome, at lower volumes, while others report deterioration of function compared with terms.[17,33,37-39] Recently, Bårdsen et al. reported expiratory airflow measures from 10 to 35 years of age based on data from three population-based cohorts born EP in three consecutive decades. They noted parallel tracking to matched term-born controls, albeit with significantly lower trajectories in the preterm-born group.[30] Age-related decline commenced at a similar age in preterm and term-born populations, and the rate of the decline between 25 and 35 years did not differ between the term and preterm groups, although the BPD group had a non-significant steeper decline. Notably, 44 (30%) of the EP group compared with 7 (5%) of the term-born group fulfilled the spirometry criteria for COPD. Trachsel *et al*. followed 14 individuals born at approximately 32 weeks' gestation during the late 1960s/early 1970s and found that mean z-scores for FEV_1 remained stable at -1.8 during the period from 18 to 38 years, but there was a tendency for increasing hyperinflation. However, it should be noted that no term-controls were included in this study.[40]

It is not only individuals born at <32 weeks' gestation who have reduced expiratory airflow, but also those born MLP. Despite accounting for a large proportion of the global population, substantially less research has been conducted on the long-term health outcomes of infants born MLP compared with survivors of EP and VP birth. Although children born MLP were historically considered to be of similar physiological maturity to their term-born peers, data from the last decade suggest that MLP birth is associated with reductions in expiratory airflow, increased cardiometabolic risk and impaired neurodevelopment.[41-44] In 2022, a meta-analysis of long-term expiratory airflow data from 847 children and adults born MLP reported mean z-score reductions of -0.22, -0.11 and -0.27 for FEV_1, FEV_1/FVC and $FEF_{25-75\%}$ when compared with 8,209 term-born controls; highlighting that even MLP survivors as a group are also failing to attain peak expiratory airflow by early adulthood.[45]

Emerging data suggest that survivors of moderate preterm (32 to <35 weeks' gestation) birth experience accelerated decline in expiratory airflow trajectories during the fifth and sixth decade of life. Investigators from the Tasmanian Longitudinal Health Study noted that FEV_1 and FEV_1/FVC of adults born moderate preterm declined annually by -8.7 ml (95% CI -25.1 to 7.6 ml) and -0.21% (95% CI -0.50% to 0.08%) more than those born at term.[46]

"Other" lung function tests to understand prematurity-associated lung disease across the lifespan.

There is a paucity of data on pulmonary function outcomes beyond studies of expiratory airflow in preterm populations (e.g., gas diffusion, oscillometry, static lung volumes and ventilation inhomogeneity). However, the existing studies do show a tendency for reduced lung diffusing capacity,[47,48] altered peripheral respiratory system mechanics (i.e. a "stiffer" lung) and hyperinflation,[49] with the most pronounced findings observed in those born at the earliest gestations.[21] Conflicting results are, however, common but future systematic reviews collating current published data may provide guidance on which tests may offer diagnostic and prognostic value for those with PLD. One study has reported serial measurements of these techniques in a VP born population. This longitudinal study showed deterioration in gas exchange (diffusing capacity of the lungs for carbon monoxide; DLCO) and peripheral lung mechanics (respiratory system reactance; Xrs_5) over time in childhood (between 4 and 12 years). [27]

Lung imaging across the lifespan in survivors of preterm birth.

Imaging studies using high resolution CT techniques have suggested lasting structural injuries, although the extent of the findings varies substantially, particularly between studies of survivors from the pre- and post-surfactant eras.[50,51] Linear and triangular subpleural opacities, areas of decreased attenuation and bronchial wall thickening are the most commonly reported abnormalities in preterm children, while some studies in adults have reported these findings in addition to substantially higher

rates of emphysema.[52] To date, there are no studies with serial chest CT scans in survivors of preterm birth and so we remain uncertain about any potential resolution or deterioration of structural lung damage over the lifespan.

MRI scanning, including with use of newly developed routines focused on ventilation and perfusion defects and the inert gases helium and xenon, promise to evaluate the structure in far greater detail than has been possible thus far.[53,54]

Current understanding of the mechanisms underpinning prematurity-associated lung disease.

A systematic review, in which 20/22 studies were from paediatric populations, suggested that those born preterm were more responsive to bronchodilator than the term born population, particularly those with neonatal BPD.[55] In short, approximately 30% of children born VP have a significant bronchodilator response. However, studies assessing responsiveness to beta agonists in adults born preterm generally report persistent airflow limitation (PAL).[49] This creates a significant challenge in clinical practice since PAL meets the diagnostic criteria for COPD, yet COPD is a condition traditionally defined by susceptibility to inhaled respiratory exposures and is associated with ongoing pulmonary inflammation.[56] At present, it is unclear if lung disease after preterm birth is a consequence of previous structural injuries, and/or a current active (inflammatory) airway disorder, with bronchospasm playing an important role.

In support of early injury, a wide range of molecular pathways driving neonatal lung disease have been proposed (See figure 2), including dysregulated immune modulation,[57-60] cellular injury and repair,[61-63] genetic polymorphisms,[64-66] growth factor signalling,[67,68] and extracellular matrix remodelling.[69-71] However, further research is needed to better understand what risk factors, treatments or host determinants trigger these molecular changes and how they interplay to result in PLD later in life.

Whilst neonatal injuries are likely to have strong implications for the future lung health of survivors born preterm, recent reports of potential lung function decline suggest active mechanisms cannot be disregarded. There is no evidence that allergy, atopy or eosinophilic inflammation are important elements[72] (as they often are in asthma), and studies including analyses of FeNO (a marker of eosinophilic inflammation) generally report levels similar to term-born controls.[33,49,73,74] However, recent data suggest that interventions with ICS can modulate FeNO in this population.[75,76] Increased pulmonary inflammatory markers and neutrophil counts have, however, been reported in some studies highlighting that inflammation, if present, is generally considered to be neutrophilic rather than eosinophilic.[73,77,78] Oxidative stress may similarly be present, with elevated 8-isoprostane levels in exhaled breath condensate in a small study of preterm born adolescents[79] and reports of systemic mitochondrial dysfunction in adults.[80] Tissue remodelling and fibrosis may occur consequent to or in

parallel with inflammatory changes, resulting in worsening airway obstruction.[81] Um Bergstrøm et al. found that young adults born preterm, with a history of neonatal BPD, have a T-cell subset pattern in the airways resembling features of COPD, findings compatible with a hypothesis that CD3+CD8+ T-cells also may be involved in mechanisms behind PLD, at least in a subset of individuals.[82] Additional proposed mechanisms underpinning active disease in survivors born preterm include altered immune programming, microbiome dysbiosis, epithelial abnormalities, accelerated cellular ageing, and host genetics.[82-88] External exposures, including tobacco smoke, air pollution and repeated viral respiratory infections, may similarly initiate cellular injury and remodelling, resulting in worsening of existing lung disease.[89-91]

Limited data exist to draw firm conclusions about underlying mechanisms associated with PLD; although it is clear that numerous active pathways and pathologies are implicated (see Figure 2 for summary). Additional studies focusing on these pathways using relevant airway sampling, such as that reported by Um- Bergström, are needed to enhance our understanding of PLD and will be crucial for optimising future care and therapeutic management of this vulnerable population.

Prevention or treatment for prematurity-associated lung disease?

Prevention

Preventing prematurity, is clearly the best way to prevent long term respiratory sequalae from PLD but has been an unrealistic goal to date, with rates of preterm births rising in many parts of the world. “A recent Lancet series on “Small Vulnerable Newborns” offers promise on the way forward to preventing preterm birth in low and middle-income countries.[92] However, the interventions proposed may not have much effect in reducing the rates of BPD in infants born VP, since most infants who survive long enough to develop BPD are born in high-income countries.

Preventing BPD through using gentler techniques of respiratory support for infants born preterm is a priority for neonatal paediatricians. However, thus far there is little evidence of success; rates of BPD may be increasing and expiratory airflows deteriorating in survivors born EP in more recent eras.

Several treatments given soon after birth, including caffeine and postnatal corticosteroids, prevent BPD, and also improve expiratory airflow in survivors in later childhood. However, studies of expiratory airflow into adulthood are lacking to determine the longevity of these benefits. Moreover, there are other complications associated with postnatal corticosteroids to prevent BPD that limit their applicability.Treatment

To date, there are limited studies investigating treatment options for PLD. Recent guidelines on clinical management of preterm graduates after discharge from the neonatal unit by the European

Respiratory Society (ERS),[93] and American Thoracic Society (ATS),[94] highlighted the lack of objective evidence on how to treat these individuals in both childhood and adulthood. Registry-based studies show that 26% of preschool aged children and 13% of school-aged children who were born preterm have been prescribed anti-asthmatic drugs.[95] However, there is wide variation with reported usage of such drugs and some studies of those born VP report ~40 % of the population to be prescribed asthma medications.[27] Similarly, young adults born VP are more than twice as likely to have an inhaled corticosteroid (ICS) prescribed, compared with those born at term.[96] There is limited evidence on the use of bronchodilators in those with PLD, resulting in both the ATS and ERS recommending inhaled short-acting bronchodilators (SABA) only for the subgroup of patients that experience asthma-like symptoms and/or had recurrent hospital visits. The use of long-acting B2-agonists (LABA) or muscarinic antagonists (short-acting and long-acting, SAMA, LAMA) was not evaluated.

The evidence for the efficacy of ICS in children and adolescents born preterm is also limited. Outside the context of a robust diagnosis of asthma, both the ERS and ATS guidelines recommend against routine treatment with ICS, apart from a potential trial in those individuals with recurrent respiratory symptoms. Since the publication of the separate ERS and ATS guidelines, two randomised controlled trials have emerged. The first study compared ICS alone (N=18) or ICS in combination with LABA (N=17) with placebo (N=13) in preterm-born school children with FEV_1 ≤85%.[75] A significant improvement in $\%FEV_1$ was noted in the group of patients treated with ICS and LABA vs. placebo, but not when comparing ICS only to placebo. While no conclusions could be made regarding the usefulness of LABA only (which does not have sufficient safety data in children), this study provides evidence that existing treatments may be efficacious in children. The second study compared an ICS alone (N=87) to placebo (N=83) in a non-selective groups of children (6 to 12 years) born < 32 weeks gestation. This study showed only modestly improved FEV1 when treated with ICS for 12 weeks. However, clinically relevant improvements were observed in a subset (23%) of children, particularly those with a pre-treatment bronchodilator response.[76] While ICS may improve short-term expiratory airflow for some survivors of preterm birth, the long-term efficacy remains unknown. There is a clear need for adequately powered clinical trials assessing existing drugs such as ICS and LABA in addition to others such as azithromycin, which has crept into clinical practice to treat many preterm born survivors without a shred of evidence for efficacy.

Further studies of potential treatments for those with already established PLD are essential. Other, non-pharmaceutical interventions may offer some benefit too, such as exercise to improve cardiopulmonary function, although none have yet been evaluated in this population. Further, as BPD has been shown to be just one potential risk factor for future poor lung health, inclusion criteria for trials need to extend beyond just BPD. On the same note, objective markers for treatment initiation

beyond the presence of symptoms should be considered, as this patient group tend to be less likely to report symptoms compared with individuals with asthma with the same level of lung function.[97,98] Given the heterogeneity of PLD, it is plausible that the choice of treatment regimens and the evaluation of response should be based on the phenotype and underlying mechanisms rather than one size fits all approach.

Phenotypes of lung disease following preterm birth

There has been a significant interest in attempting to define phenotypes of lung disease in survivors of preterm birth to better understand the disease. Such definitions range extensively from presentations of neonatal BPD, to the pathology and physiology observed throughout childhood and into adulthood.[99-101] While there is variation in the description of these phenotypes, common characteristics such as small airway obstruction, anatomical disturbances including emphysema, peripheral lung disease, and pulmonary vascular disease are maintained. What is apparent from physiological and imaging studies and histopathology samples[102] is that survivors of preterm birth often have multiple reported phenotypes occurring simultaneously, with specific phenotypes likely interacting with one another, hampering the ability to describe an individual's disease by a single phenotype.[103] When considering how to approach this, there are valuable lessons to be learnt from other major obstructive lung diseases, such as COPD and asthma. Both recent The *Lancet* commissions on COPD and asthma have argued that the physiological definitions of COPD and asthma are outdated due to the complex and varying mechanisms which underpin the morbidity and mortality associated with the respective diseases.[6,104] Further, the new COPD GOLD document for the first time includes a COPD classification to recognise developmental influences on later COPD, particularly the influence of preterm birth (COPD-D).[22] We now argue that phenotypes of PLD should also be viewed with a multidimensional model.

To elucidate these overlapping heterogeneous respiratory pathologies observed after preterm birth we have adapted the "wheel-and-spoke" model, first proposed by Chapman *et al.,* in asthma, to identify phenotypes associated with PLD.[105] This model (Figure 3) describes phenotype profiles of an indeterminate number of traits, each represented by a spoke in the wheel, with the extent of abnormality marked by the distance from the centre of the wheel. Time is placed on a z-axis to acknowledge how these traits and profiles change over time. The overall phenotype profile is created by considering the impact each trait has on the individual, and temporal changes are observed with the dotted profile. The traits on the model presented in Figure 3 represent examples only, with any number of spokes able to be added or removed as deemed relevant as more evidence is generated.

There are advantages of adopting such a model, which will increase our ability to understand and manage the lung disease that follows preterm birth. For instance, currently no clear guidance exists on which individuals warrant pulmonary follow-up after preterm birth. Indeed, most survivors of preterm birth will not have expiratory airflow measured unless they are in research studies, since few (if any) dedicated clinical services exist from childhood to adulthood for this at-risk group. If phenotype profiles can be developed to identify which early life traits are linked to severe lung disease later in life, we have the potential to identify at-risk individuals early, with an aim to optimise their subsequent trajectories.

Profiles could also be created to provide tailored treatment options within this population, where there is a limited understanding as to who may respond to therapeutic options currently available.[75] The concept of "treatable traits" is now widely used across asthma and COPD.[106] Each spoke in our model potentially represents a treatable trait, and could be used to target treatments to individuals born preterm as more evidence about each trait as relevant to PLD comes to light. Additionally, as we enter an era of precision medicine, where most of the new therapies for airway disease in the last decade target mechanistic pathways, the potential exists to link profiles to certain underpinning mechanisms, understanding how these endotypes translate into disease, and what pathways can be targeted by future therapies. Such applications must be taken into consideration when directing future research, recognising that a holistic approach which identifies factors outside of single measures of lung function is necessary to advance our understanding of PLD.

Concluding remarks and future directions

PLD represents the earliest form of all chronic respiratory disease, with clear long-term health implications in a large and growing population of individuals. Research studies have shown that adults born preterm have substantial reductions in expiratory airflow in their early 20s, which is the age at which expiratory airflow typically peaks. Even with a normal physiological rate of decline over subsequent years, they are likely destined for higher rates of chronic respiratory disease in later life compared with those born at term. As outlined in the Lancet Commission on COPD and international GOLD guideline, non-tobacco related factors including preterm birth are set to overtake tobacco as the leading cause of COPD within the next two decades. However, most adults who were born preterm with reduced expiratory airflow are not under medical surveillance and would generally not have lung function measured (unless participating in research studies). The lack of robust data makes it difficult to generalise results to all survivors born preterm and as we have outlined in this opinion piece, significant gaps remain in our knowledge. For example: Who is at highest risk of PLD? Which modifiable risk factors can alter the trajectory of PLD? What mechanisms are driving the ongoing

pathology? And, what are the best therapeutic options for this group? Even if reduced expiratory airflow is observed in those surviving preterm birth, there are few evidence-based treatment strategies, apart from avoiding noxious insults such as tobacco smoking and other environmental pollutants, that will prevent later respiratory disease in adult life. It has been over a decade since the World Health Organisation released its landmark report on preterm birth, recognising the extent of preterm birth as a public health problem. Yet, despite this report, no targeted investment exists in improving the health outcomes of this vulnerable population.

As the population of individuals surviving preterm birth continues to grow, we have a deep sense of urgency to avoid an impending tidal wave of respiratory disease, as survivors of preterm birth enter adult life. A unified, collaborative, and global approach is needed to target future research within this field and to prioritise research questions.

The establishment of the European Respiratory Society's PELICAN (Prematurity's Effect on the Lungs In Children and Adults Network) in 2020 offers an exciting future prospect.[107] PELICAN is a network of researchers, clinicians, and consumer advocates worldwide with the overarching objective to understand the pulmonary consequences of surviving preterm birth and the natural history of lung disease across the life course. PELICAN also aims to determine which modifiable factors are associated with the progression of lung disease within this vulnerable population via data sharing to expedite the collaborative research effort. The usefulness or otherwise of any such modifiable factors can then be evaluated in randomised controlled trials, subject to adequate resources being available.

We must use lessons learnt over the past several decades in COPD and asthma to increase our understanding of the consequences of preterm birth and pool our resources to improve our power to answer these questions. Of course, none of this will be easy, but now is the time for the paediatric and adult respiratory experts to acknowledge the impending problem and fund the required research. Current preterm birth and survival rates indicate that approximately 14.5 million preterm birth survivors will reach adulthood every year. By 2040, around 50 years since the beginning of the post-surfactant era, it is anticipated that over 700 million adults will be at risk of preterm associated lung disease – a number that will continue to compound annually. We need solutions before the epidemic of adults born preterm with reduced expiratory airflow swamps the resources available to treat COPD in later life.

References

1. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 2012; **379**(9832): 2162-72.
2. Cao G, Liu J, Liu M. Global, Regional, and National Incidence and Mortality of Neonatal Preterm Birth, 1990-2019. *JAMA Pediatr* 2022; **176**(8): 787-96.
3. Stensvold HJ, Klingenberg C, Stoen R, et al. Neonatal Morbidity and 1-Year Survival of Extremely Preterm Infants. *Pediatrics* 2017; **139**(3).
4. Crump C, Sundquist J, Winkleby MA, Sundquist K. Gestational age at birth and mortality from infancy into mid-adulthood: a national cohort study. *Lancet Child Adolesc Health* 2019; **3**(6): 408-17.
5. van Katwyk S, Augustine S, Thebaud B, Thavorn K. Lifetime patient outcomes and healthcare utilization for Bronchopulmonary dysplasia (BPD) and extreme preterm infants: a microsimulation study. *BMC Pediatr* 2020; **20**(1): 136.
6. Stolz D, Mkorombindo T, Schumann DM, et al. Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. *Lancet* 2022; **400**(10356): 921-72.
7. Northway WH, Jr., Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med* 1967; **276**(7): 357-68.
8. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001; **163**(7): 1723-9.
9. Jensen EA, Dysart K, Gantz MG, et al. The Diagnosis of Bronchopulmonary Dysplasia in Very Preterm Infants. An Evidence-based Approach. *Am J Respir Crit Care Med* 2019; **200**(6): 751-9.
10. Isayama T, Lee SK, Yang J, et al. Revisiting the Definition of Bronchopulmonary Dysplasia: Effect of Changing Panoply of Respiratory Support for Preterm Neonates. *JAMA Pediatr* 2017; **171**(3): 271-9.
11. Belgrave DCM, Granell R, Turner SW, et al. Lung function trajectories from pre-school age to adulthood and their associations with early life factors: a retrospective analysis of three population-based birth cohort studies. *Lancet Respir Med* 2018; **6**(7): 526-34.
12. Smith EF, Hemy NR, Hall GL, Wilson AC, Murray CP, Simpson SJ. Risk factors for poorer respiratory outcomes in adolescents and young adults born preterm. *Thorax* 2023; **In Press**.
13. Yu Z, Merid SK, Bellander T, et al. Associations of improved air quality with lung function growth from childhood to adulthood: the BAMSE study. *Eur Respir J* 2023; **61**(5).
14. Agusti A, Faner R. Lung function trajectories in health and disease. *Lancet Respir Med* 2019; **7**(4): 358-64.
15. Jakeways N, McKeever T, Lewis SA, Weiss ST, Britton J. Relationship between FEV1 reduction and respiratory symptoms in the general population. *Eur Respir J* 2003; **21**(4): 658-63.
16. Agusti A, Melen E, DeMeo DL, Breyer-Kohansal R, Faner R. Pathogenesis of chronic obstructive pulmonary disease: understanding the contributions of gene-environment interactions across the lifespan. *Lancet Respir Med* 2022; **10**(5): 512-24.
17. Doyle LW, Carse E, Adams AM, et al. Ventilation in Extremely Preterm Infants and Respiratory Function at 8 Years. *N Engl J Med* 2017; **377**(4): 329-37.
18. Bentsen MH, Markestad T, Oymar K, Halvorsen T. Lung function at term in extremely preterm-born infants: a regional prospective cohort study. *BMJ Open* 2017; **7**(10): e016868.
19. Kotecha SJ, Gibbons JTD, Course CW, et al. Geographical Differences and Temporal Improvements in Forced Expiratory Volume in 1 Second of Preterm-Born Children: A Systematic Review and Meta-analysis. *JAMA Pediatr* 2022; **176**(9): 867-77.
20. Miller JE, Hammond GC, Strunk T, et al. Association of gestational age and growth measures at birth with infection-related admissions to hospital throughout childhood: a population-based, data-linkage study from Western Australia. *Lancet Infect Dis* 2016; **16**(8): 952-61.
21. Doyle LW, Andersson S, Bush A, et al. Expiratory airflow in late adolescence and early adulthood in individuals born very preterm or with very low birthweight compared with controls

born at term or with normal birthweight: a meta-analysis of individual participant data. *Lancet Respir Med* 2019; **7**(8): 677-86.
22. Venkatesan P. GOLD COPD report: 2023 update. *Lancet Respir Med* 2023; **11**(1): 18.
23. Rocha V, Fraga S, Moreira C, et al. Life-course socioeconomic disadvantage and lung function: a multicohort study of 70 496 individuals. *Eur Respir J* 2021; **57**(3).
24. McHale P, Maudsley G, Pennington A, et al. Mediators of socioeconomic inequalities in preterm birth: a systematic review. *BMC Public Health* 2022; **22**(1): 1134.
25. Kitchen WH, Ryan MM, Rickards A, et al. Changing outcome over 13 years of very low birthweight infants. *Semin Perinatol* 1982; **6**(4): 373-89.
26. Owen LS, Manley BJ, Davis PG, Doyle LW. The evolution of modern respiratory care for preterm infants. *Lancet* 2017; **389**(10079): 1649-59.
27. Simpson SJ, Turkovic L, Wilson AC, et al. Lung function trajectories throughout childhood in survivors of very preterm birth: a longitudinal cohort study. *Lancet Child Adolesc Health* 2018; **2**(5): 350-9.
28. Doyle LW, Adams AM, Robertson C, et al. Increasing airway obstruction from 8 to 18 years in extremely preterm/low-birthweight survivors born in the surfactant era. *Thorax* 2017; **72**(8): 712-9.
29. Doyle LW, Irving L, Haikerwal A, Lee K, Ranganathan S, Cheong J. Airway obstruction in young adults born extremely preterm or extremely low birth weight in the postsurfactant era. *Thorax* 2019; **74**(12): 1147-53.
30. Bardsen T, Roksund OD, Benestad MR, et al. Tracking of lung function from 10 to 35 years after being born extremely preterm or with extremely low birth weight. *Thorax* 2022; **77**(8): 790-8.
31. Um-Bergstrom P, Hallberg J, Thunqvist P, et al. Lung function development after preterm birth in relation to severity of Bronchopulmonary dysplasia. *BMC Pulm Med* 2017; **17**(1): 97.
32. Levin JC, Sheils CA, Gaffin JM, Hersh CP, Rhein LM, Hayden LP. Lung function trajectories in children with post-prematurity respiratory disease: identifying risk factors for abnormal growth. *Respir Res* 2021; **22**(1): 143.
33. Hurst JR, Beckmann J, Ni Y, et al. Respiratory and Cardiovascular Outcomes in Survivors of Extremely Preterm Birth at 19 Years. *Am J Respir Crit Care Med* 2020; **202**(3): 422-32.
34. Yang J, Kingsford RA, Horwood J, et al. Lung Function of Adults Born at Very Low Birth Weight. *Pediatrics* 2020; **145**(2).
35. Wohl ME. Bronchopulmonary dysplasia in adulthood. *N Engl J Med* 1990; **323**(26): 1834-6.
36. Bolton CE, Bush A, Hurst JR, Kotecha S, McGarvey L. Lung consequences in adults born prematurely. *Postgrad Med J* 2015; **91**(1082): 712-8.
37. Vollsaeter M, Roksund OD, Eide GE, Markestad T, Halvorsen T. Lung function after preterm birth: development from mid-childhood to adulthood. *Thorax* 2013; **68**(8): 767-76.
38. Gibson AM, Reddington C, McBride L, Callanan C, Robertson C, Doyle LW. Lung function in adult survivors of very low birth weight, with and without bronchopulmonary dysplasia. *Pediatr Pulmonol* 2015; **50**(10): 987-94.
39. Moschino L, Stocchero M, Filippone M, Carraro S, Baraldi E. Longitudinal Assessment of Lung Function in Survivors of Bronchopulmonary Dysplasia from Birth to Adulthood. The Padova BPD Study. *Am J Respir Crit Care Med* 2018; **198**(1): 134-7.
40. Trachsel D, Brutsche MH, Hug-Batschelet H, Hammer J. Progressive static pulmonary hyperinflation in survivors of severe bronchopulmonary dysplasia by mid-adulthood. *Thorax* 2012; **67**(8): 747-8.
41. Kotecha SJ, Watkins WJ, Paranjothy S, Dunstan FD, Henderson AJ, Kotecha S. Effect of late preterm birth on longitudinal lung spirometry in school age children and adolescents. *Thorax* 2012; **67**(1): 54-61.
42. Thunqvist P, Gustafsson PM, Schultz ES, et al. Lung Function at 8 and 16 Years After Moderate-to-Late Preterm Birth: A Prospective Cohort Study. *Pediatrics* 2016; **137**(4).

43. Yoshida-Montezuma Y, Sivapathasundaram B, Brown HK, et al. Association of Late Preterm Birth and Size for Gestational Age With Cardiometabolic Risk in Childhood. *JAMA Netw Open* 2022; **5**(5): e2214379.
44. Cheong JL, Doyle LW, Burnett AC, et al. Association Between Moderate and Late Preterm Birth and Neurodevelopment and Social-Emotional Development at Age 2 Years. *JAMA Pediatr* 2017; **171**(4): e164805.
45. Du Berry C, Nesci C, Cheong JLY, et al. Long-term expiratory airflow of infants born moderate-late preterm: A systematic review and meta-analysis. *EClinicalMedicine* 2022; **52**: 101597.
46. Bui DS, Perret JL, Walters EH, et al. Association between very to moderate preterm births, lung function deficits, and COPD at age 53 years: analysis of a prospective cohort study. *Lancet Respir Med* 2022; **10**(5): 478-84.
47. Vrijlandt EJ, Gerritsen J, Boezen HM, Grevink RG, Duiverman EJ. Lung function and exercise capacity in young adults born prematurely. *Am J Respir Crit Care Med* 2006; **173**(8): 890-6.
48. Satrell E, Clemm H, Roksund OD, et al. Development of lung diffusion to adulthood following extremely preterm birth. *Eur Respir J* 2022; **59**(5).
49. Vollsaeter M, Clemm HH, Satrell E, et al. Adult respiratory outcomes of extreme preterm birth. A regional cohort study. *Annals of the American Thoracic Society* 2015; **12**(3): 313-22.
50. Wong PM, Lees AN, Louw J, et al. Emphysema in young adult survivors of moderate-to-severe bronchopulmonary dysplasia. *Eur Respir J* 2008; **32**(2): 321-8.
51. Aukland SM, Rosendahl K, Owens CM, Fosse KR, Eide GE, Halvorsen T. Neonatal bronchopulmonary dysplasia predicts abnormal pulmonary HRCT scans in long-term survivors of extreme preterm birth. *Thorax* 2009; **64**(5): 405-10.
52. Wong PM, Lees AN, Louw J, et al. Emphysema in young adult survivors of moderate-to-severe bronchopulmonary dysplasia. *Eur Respir J* 2008; **32**(2): 321-8.
53. Elders B, Tiddens H, Pijnenburg MWH, Reiss IKM, Wielopolski PA, Ciet P. Lung structure and function on MRI in preterm born school children with and without BPD: A feasibility study. *Pediatr Pulmonol* 2022; **57**(12): 2981-91.
54. Chan HF, Smith LJ, Biancardi AM, et al. Image Phenotyping of Preterm-Born Children Using Hyperpolarized (129)Xe Lung Magnetic Resonance Imaging and Multiple-Breath Washout. *Am J Respir Crit Care Med* 2023; **207**(1): 89-100.
55. Kotecha SJ, Edwards MO, Watkins WJ, Lowe J, Henderson AJ, Kotecha S. Effect of bronchodilators on forced expiratory volume in 1 s in preterm-born participants aged 5 and over: a systematic review. *Neonatology* 2015; **107**(3): 231-40.
56. Global strategy for prevention, diagnosis and management of COPD: 2023 report. https://goldcopd.org/2023-gold-report-2/.
57. Pagel J, Twisselmann N, Rausch TK, et al. Increased Regulatory T Cells Precede the Development of Bronchopulmonary Dysplasia in Preterm Infants. *Front Immunol* 2020; **11**: 565257.
58. Lao JC, Bui CB, Pang MA, et al. Type 2 immune polarization is associated with cardiopulmonary disease in preterm infants. *Sci Transl Med* 2022; **14**(639): eaaz8454.
59. Melville JM, Moss TJ. The immune consequences of preterm birth. *Front Neurosci* 2013; **7**: 79.
60. Prince LR, Maxwell NC, Gill SK, et al. Macrophage phenotype is associated with disease severity in preterm infants with chronic lung disease. *PLoS One* 2014; **9**(8): e103059.
61. Been JV, Zimmermann LJ, Debeer A, Kloosterboer N, van Iwaarden JF. Bronchoalveolar lavage fluid from preterm infants with chorioamnionitis inhibits alveolar epithelial repair. *Respir Res* 2009; **10**(1): 116.
62. Looi K, Evans DJ, Garratt LW, et al. Preterm birth: Born too soon for the developing airway epithelium? *Paediatr Respir Rev* 2019; **31**: 82-8.
63. May M, Strobel P, Preisshofen T, Seidenspinner S, Marx A, Speer CP. Apoptosis and proliferation in lungs of ventilated and oxygen-treated preterm infants. *Eur Respir J* 2004; **23**(1): 113-21.

64. Kwinta P, Bik-Multanowski M, Mitkowska Z, Tomasik T, Legutko M, Pietrzyk JJ. Genetic risk factors of bronchopulmonary dysplasia. *Pediatr Res* 2008; **64**(6): 682-8.
65. Hadchouel A, Decobert F, Franco-Montoya ML, et al. Matrix metalloproteinase gene polymorphisms and bronchopulmonary dysplasia: identification of MMP16 as a new player in lung development. *PLoS One* 2008; **3**(9): e3188.
66. Holst D, Garnier Y. Preterm birth and inflammation-The role of genetic polymorphisms. *Eur J Obstet Gynecol Reprod Biol* 2008; **141**(1): 3-9.
67. Oak P, Hilgendorff A. The BPD trio? Interaction of dysregulated PDGF, VEGF, and TGF signaling in neonatal chronic lung disease. *Mol Cell Pediatr* 2017; **4**(1): 11.
68. Been JV, Debeer A, van Iwaarden JF, et al. Early alterations of growth factor patterns in bronchoalveolar lavage fluid from preterm infants developing bronchopulmonary dysplasia. *Pediatr Res* 2010; **67**(1): 83-9.
69. Thibeault DW, Mabry SM, Ekekezie, II, Truog WE. Lung elastic tissue maturation and perturbations during the evolution of chronic lung disease. *Pediatrics* 2000; **106**(6): 1452-9.
70. Thibeault DW, Mabry SM, Ekekezie, II, Zhang X, Truog WE. Collagen scaffolding during development and its deformation with chronic lung disease. *Pediatrics* 2003; **111**(4 Pt 1): 766-76.
71. Sweet DG, McMahon KJ, Curley AE, O'Connor CM, Halliday HL. Type I collagenases in bronchoalveolar lavage fluid from preterm babies at risk of developing chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 2001; **84**(3): F168-71.
72. Halvorsen T, Skadberg BT, Eide GE, Roksund O, Aksnes L, Oymar K. Characteristics of asthma and airway hyper-responsiveness after premature birth. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology* 2005; **16**(6): 487-94.
73. Course CW, Kotecha S, Kotecha SJ. Fractional exhaled nitric oxide in preterm-born subjects: A systematic review and meta-analysis. *Pediatr Pulmonol* 2019; **54**(5): 595-601.
74. Baraldi E, Bonetto G, Zacchello F, Filippone M. Low exhaled nitric oxide in school-age children with bronchopulmonary dysplasia and airflow limitation. *Am J Respir Crit Care Med* 2005; **171**(1): 68-72.
75. Goulden N, Cousins M, Hart K, et al. Inhaled Corticosteroids Alone and in Combination With Long-Acting beta2 Receptor Agonists to Treat Reduced Lung Function in Preterm-Born Children: A Randomized Clinical Trial. *JAMA Pediatr* 2022; **176**(2): 133-41.
76. Urs RC, Evans DJ, Bradshaw T.K., et al. Inhaled corticosteroids to improve lung function in children born very preterm (Preterm Inhaled CorticoSteroid Intervention- PICSI): A randomised, placebo-controlled trial of fluticasone propionate. *The Lancet Child & Adolescent Health* 2023; **In press**.
77. Teig N, Allali M, Rieger C, Hamelmann E. Inflammatory markers in induced sputum of school children born before 32 completed weeks of gestation. *J Pediatr* 2012; **161**(6): 1085-90.
78. Siltanen M, Wehkalampi K, Hovi P, et al. Preterm birth reduces the incidence of atopy in adulthood. *J Allergy Clin Immunol* 2011; **127**(4): 935-42.
79. Filippone M, Bonetto G, Corradi M, Frigo AC, Baraldi E. Evidence of unexpected oxidative stress in airways of adolescents born very pre-term. *Eur Respir J* 2012; **40**(5): 1253-9.
80. Kumari S, Barton GP, Goss KN. Increased mitochondrial oxygen consumption in adult survivors of preterm birth. *Pediatr Res* 2021; **90**(6): 1147-52.
81. Castro-Rodriguez JA, Saglani S, Rodriguez-Martinez CE, Oyarzun MA, Fleming L, Bush A. The relationship between inflammation and remodeling in childhood asthma: A systematic review. *Pediatr Pulmonol* 2018; **53**(6): 824-35.
82. Um-Bergstrom P, Pourbazargan M, Brundin B, et al. Increased cytotoxic T-cells in the airways of adults with former bronchopulmonary dysplasia. *Eur Respir J* 2022; **60**(3).
83. Rofael SAD, McHugh TD, Troughton R, et al. Airway microbiome in adult survivors of extremely preterm birth: the EPICure study. *Eur Respir J* 2019; **53**(1).
84. Hillas J, Evans DJ, Ang S, et al. Nasal airway epithelial repair after very preterm birth. *ERJ Open Res* 2021; **7**(2).

85. Shui JE, Wang W, Liu H, et al. Prematurity alters the progenitor cell program of the upper respiratory tract of neonates. *Sci Rep* 2021; **11**(1): 10799.
86. Henckel E, James A, Konradsen JR, et al. A Novel Association between YKL-40, a Marker of Structural Lung Disease, and Short Telomere Length in 10-Year-Old Children with Bronchopulmonary Dysplasia. *Children (Basel)* 2021; **8**(2).
87. Siezen CL, Bont L, Hodemaekers HM, et al. Genetic susceptibility to respiratory syncytial virus bronchiolitis in preterm children is associated with airway remodeling genes and innate immune genes. *Pediatr Infect Dis J* 2009; **28**(4): 333-5.
88. Hamvas A, Feng R, Bi Y, et al. Exome sequencing identifies gene variants and networks associated with extreme respiratory outcomes following preterm birth. *BMC Genet* 2018; **19**(1): 94.
89. Becnel D, You D, Erskin J, Dimina DM, Cormier SA. A role for airway remodeling during respiratory syncytial virus infection. *Respir Res* 2005; **6**(1): 122.
90. Andersson CK, Iwasaki J, Cook J, et al. Impaired airway epithelial cell wound-healing capacity is associated with airway remodelling following RSV infection in severe preschool wheeze. *Allergy* 2020; **75**(12): 3195-207.
91. Churg A, Tai H, Coulthard T, Wang R, Wright JL. Cigarette smoke drives small airway remodeling by induction of growth factors in the airway wall. *Am J Respir Crit Care Med* 2006; **174**(12): 1327-34.
92. Lawn JE, Ohuma EO, Bradley E, et al. Small babies, big risks: global estimates of prevalence and mortality for vulnerable newborns to accelerate change and improve counting. *Lancet* 2023; **401**(10389): 1707-19.
93. Duijts L, van Meel ER, Moschino L, et al. European Respiratory Society guideline on long-term management of children with bronchopulmonary dysplasia. *Eur Respir J* 2020; **55**(1).
94. Cristea AI, Ren CL, Amin R, et al. Outpatient Respiratory Management of Infants, Children, and Adolescents with Post-Prematurity Respiratory Disease: An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med* 2021; **204**(12): e115-e33.
95. Damkjaer M, Loane M, Urhoj SK, et al. Preterm birth and prescriptions for cardiovascular, antiseizure, antibiotics and antiasthmatic medication in children up to 10 years of age: a population-based data linkage cohort study across six European regions. *BMJ Open* 2022; **12**(10): e061746.
96. Vogt H, Lindstrom K, Braback L, Hjern A. Preterm birth and inhaled corticosteroid use in 6- to 19-year-olds: a Swedish national cohort study. *Pediatrics* 2011; **127**(6): 1052-9.
97. Um-Bergstrom P, Hallberg J, Pourbazargan M, et al. Pulmonary outcomes in adults with a history of Bronchopulmonary Dysplasia differ from patients with asthma. *Respir Res* 2019; **20**(1): 102.
98. Bozzetto S, Carraro S, Tomasi L, Berardi M, Zanconato S, Baraldi E. Health-related quality of life in adolescent survivors of bronchopulmonary dysplasia. *Respirology* 2016; **21**(6): 1113-7.
99. Collaco JM, McGrath-Morrow SA. Respiratory Phenotypes for Preterm Infants, Children, and Adults: Bronchopulmonary Dysplasia and More. *Ann Am Thorac Soc* 2018; **15**(5): 530-8.
100. Cassady SJ, Lasso-Pirot A, Deepak J. Phenotypes of Bronchopulmonary Dysplasia in Adults. *Chest* 2020; **158**(5): 2074-81.
101. Logan JW, Lynch SK, Curtiss J, Shepherd EG. Clinical phenotypes and management concepts for severe, established bronchopulmonary dysplasia. *Paediatr Respir Rev* 2019; **31**: 58-63.
102. Liu N, Cummings OW, Lagstein A, Hage CA, Chan KM, Zhang C. Lung Transplantation for Bronchopulmonary Dysplasia in Adults: A Clinical and Pathologic Study of 3 Cases. *Am J Surg Pathol* 2020; **44**(4): 509-15.
103. Simpson SJ, Logie KM, O'Dea CA, et al. Altered lung structure and function in mid-childhood survivors of very preterm birth. *Thorax* 2017; **72**(8): 702-11.
104. Pavord ID, Beasley R, Agusti A, et al. After asthma: redefining airways diseases. *Lancet* 2018; **391**(10118): 350-400.
105. Chapman DG, King GG, Robinson PD, Farah CS, Thamrin C. The need for physiological phenotyping to develop new drugs for airways disease. *Pharmacol Res* 2020; **159**: 105029.

106. McDonald VM, Fingleton J, Agusti A, et al. Treatable traits: a new paradigm for 21st century management of chronic airway diseases: Treatable Traits Down Under International Workshop report. *Eur Respir J* 2019; **53**(5).
107. Simpson SJ, Hallberg J, Collaboration PCR, Members of the PSSCa. The PELICAN (Prematurity's Effect on the Lungs In Children and Adults Network) ERS Clinical Research Collaboration: understanding the impact of preterm birth on lung health throughout life. *Eur Respir J* 2021; **57**(4).

Panel 1: Key Terms and definitions. The following terms and definitions are proposed in this opinion piece to describe and propose approaches to understanding the nature and origins of lung disease after preterm birth.

Bronchopulmonary dysplasia (BPD):
Traditionally, a term used to describe the radiological changes seen in infants born preterm during their neonatal intensive care stay. The contemporary diagnosis is most commonly defined by the requirement for respiratory support at 36 weeks' postmenstrual age, and severity can be graded from mild to severe, determined by the level of respiratory support required at that time. Often used interchangeably with chronic lung disease of prematurity.

Prematurity-associated lung disease (PLD):
A chronic lung disease that has occurred following preterm birth. PLD is characterised by abnormal structural, physiological, clinical, and/or inflammatory respiratory phenotypes seen among survivors of preterm birth. PLD encompasses the broad implications of preterm birth on later-life respiratory health irrespective of bronchopulmonary dysplasia diagnosis during infancy.

Chronic obstructive pulmonary disease (COPD):
A clinical syndrome characterised by chronic respiratory symptoms (e.g. dyspnoea, cough, sputum production and/or exacerbations) and structural (e.g. emphysematous) or functional pulmonary abnormalities, or a combination of both, attributable to one or several underlying mechanisms that may overlap with or differ from pathological mechanisms associated with bronchopulmonary dysplasia and/or prematurity-associated lung disease. A hallmark of COPD is progressive airflow obstruction.

The preterm expiratory airflow trajectome:
The range of potential expiratory airflow trajectories (FEV_1) across the lifespan of a preterm survivor, with attained peak and subsequent rate of decline dependant on pre- and post-natal factors common to preterm birth - such as gestational age, intrauterine growth restriction, bronchopulmonary dysplasia, prematurity associated lung disease, increased early life viral infections, tobacco and environmental exposures.

Phenotype profile:
A disease attribute or combination of attributes that describe differences between patients. We propose a multidimensional model of prematurity-associated lung disease, that takes into consideration various measurable traits of disease, including structural, physiological, mechanistic and clinical factors. This approach will allow the creation of a profile that describes the impact of the disease on the individual and allows for characterisation of disease progression over time - thereby accounting for potential changes in the relative contributions of these factors throughout an individual's lifespan.

Figure 1. Potential expiratory airflow trajectomes for those born preterm. A series of potential expiratory airflow trajectories are shown for those born preterm, compared to "normal" term (green) over the lifespan. Many survivors of preterm birth will have abnormal lung development, reduced peak lung function, and potentially an increased rate of decline; each of which places them at increased risk of chronic respiratory disease.

Figure 2: Potential mechanisms underpinning our current understanding of prematurity-associated lung disease. While we lack robust evidence about the mechanisms underpinning poor lung health in those surviving preterm birth, there are likely to be both intrinsic factors and extrinsic factors, and some interplay between them. For example, the underdeveloped lungs of preterm babies are often subject to lung injury after preterm birth, which likely results in structural, molecular and systemic changes. There is interaction between these factors, and this interaction will change over time and in the presence of new exposures. Each individual's expiratory airflow trajectory will be affected, either positively or negatively, by their changes, influences and exposures.

Figure 3: Wheel-and-spoke model of phenotype profiles.

Spokes represent proposed components of a phenotype classification system with the magnitude of impairment indicated by distance from centre of the wheel. Spokes can be added or subtracted as new evidence emerges. Each spoke represents a potential treatable trait. A) 3-dimensional model showing temporal changes in profiles with time on Z-axis. Hypothesised profiles are represented by shaded areas and show three different time points. B) 2-dimensional models demonstrating hypothetical phenotype profiles at different stages of life.