Bronchopulmonary dysplasia and extremely preterm birth: time for a broader perspective on long-term outcomes

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From birth to adulthood, prematurity-associated lung disease requires lifelong multidisciplinary awareness and follow-up. Strong personalised care is needed to meet the broad respiratory and extrapulmonary needs of preterm-born individuals. https://bit.ly/4pQikdK

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Abstract

Bronchopulmonary dysplasia is a hallmark respiratory complication of prematurity and remains a major health determinant of individuals born very preterm. Its impact, however, extends far beyond the neonatal period and far beyond the lungs. Children, adolescents and adults born very preterm often follow diverse developmental trajectories that diverge from typical postnatal growth. These trajectories often display early airflow limitation, as well as features of increased cardiovascular vulnerability and altered multisystemic profiles. Although common respiratory labels such as asthma are often applied to these patients, evidence highlights distinct pathobiological mechanisms rooted in arrested alveolar and vascular growth, with a possible contribution from persistent airway inflammation and oxidative stress. Extrapulmonary involvement, including cardiovascular, neurodevelopmental, neurosensory, renal and metabolic domains, further shapes long-term outcomes and should be systematically integrated into long-term monitoring. Yet, despite improving survival and growing recognition of this multisystemic burden, current evidence remains insufficient to design a dedicated, holistic, multidisciplinary follow-up programme tailored to the diverse subgroups of preterm-born individuals. Increasing awareness among healthcare professionals of the long-term implications of prematurity is essential to ensure that these patients receive appropriate and coordinated attention. Emerging lines of research, spanning new preventive and therapeutic options, advanced imaging, mechanistic studies, and long-term cohort designs, hold promise in elucidating the biological determinants of disease. Integrating these insights into clinical pathways, together with sustained implementation of family-centred care models, will be crucial to optimise organ function trajectories, delay deterioration and ultimately improve the quality of life of the growing population of survivors of prematurity.

Introduction

Every year, a small but significant number of infants enter the world far ahead of schedule, so fragile that their earliest breaths are a testament to human tenacity. These extremely low gestational age neonates (ELGANs), born before 28 weeks' gestation, represent the greatest challenges and triumphs in neonatal medicine. Advances in perinatal intensive care have steadily improved survival, yet for those who make it through, survival is only the first step in a much longer journey.

Beyond the neonatal intensive care unit (NICU) lies an evolving landscape of health, development and adaptation. Recent evidence highlights higher healthcare resource use among ELGANs during childhood, with growing and persistent health needs extending into adolescence and adulthood [1].

The long-term outcomes of these infants are woven from a complex tapestry including a respiratory burden, associated with cardiovascular, metabolic, neurodevelopmental, nephrological, auxological and nutritional comorbidities, and psychosocial adjustments. Some children defy odds and flourish, while others bear persistent vulnerabilities that shape their lives in subtle or profound ways. Among these, bronchopulmonary dysplasia (BPD) remains the most common legacy, often shaping the health trajectories of those born too soon into adulthood. In this review article, we explore their journey, examine what is known about the sequelae of extreme prematurity (EP) and their long-term respiratory and multisystemic trajectories.

We conducted a literature search in PubMed and Google Scholar (last updated November 2025) using terms related to "preterm birth", "bronchopulmonary dysplasia" and "long-term outcomes". We prioritised cohort studies, systematic reviews and meta-analyses on respiratory and extrapulmonary sequelae of BPD and EP. Additional references were identified through citation screening.

Prematurity-associated lung disease

Among the long-term morbidities of EP, respiratory sequelae stand out as the most investigated and clinically relevant. The immature lung, eventually predisposed by intra-uterine growth restriction and other pre-natal noxae and exposed to the *ex utero* environment [2, 3], faces a cascade of inflammatory, ventilatory and oxidative stresses that disrupt alveolarisation, bronchial and vascular development, reframing prematurity-associated lung disease (PLD) as a continuum that begins before birth and evolves through life [4]. What was once termed the "classic/old" BPD of the pre-surfactant era, characterising moderately preterm infants requiring prolonged invasive ventilation and high oxygen support, has evolved into a multifaceted entity, the "new-BPD" characterised by an arrested alveolar and vascular development with less inflammation and fibrosis [5, 6]. Moreover, BPD is now recognised to mark the most respiratory-compromised infants within a broader group showing varying degrees of persistent lung derangement, collectively termed PLD [7, 8].

Despite major advances in neonatal care, the burden of chronic respiratory morbidity persists. Understanding the factors that shape disease trajectories from childhood into adulthood, whether improving or worsening, is essential to guide timely interventions and optimise the lifelong respiratory outcomes of EP.

Origins and clinical evolution of lung disease in preterm-born individuals

The reduced lung function of ELGANs stems from the profound lung immaturity at birth. At this developmental stage, between the canalicular and saccular, lungs are abruptly exposed to supraphysiological oxygen levels, ventilatory support and other stressors. This results in disrupted lung development, limiting the formation of the alveolar–capillary surface. The resulting impairment in gas-exchange function inevitably leads to prolonged respiratory support and oxygen supplementation, extending NICU stays and imposing considerable emotional and logistical burdens on families. Despite these challenges, most ELGANs are discharged off respiratory support. This apparent recovery may create the impression that the pulmonary consequences of EP have resolved. However, an underlying respiratory vulnerability persists and these children remain at higher risk of severe lower respiratory tract infections (*e.g.* respiratory syncytial virus), often resulting in hospital readmissions, intensive care need and increased respiratory-mortality risk during the first years of life [9]. These infections may also interfere with the ongoing lung development, further compromising the long-term pulmonary potential [10]. After an early phase marked by an alveolar disease, respiratory impairment grows into a predominantly obstructive pattern [7, 10–12]. This evolution is referred as dysanapsis, an inadequate out-of-phase growth of the airways relative to alveolar development. The latter may show some catch-up growth during childhood (neoalveolarisation) [13–16]. Yet our understanding of the respiratory pathobiology in long-term survivors of BPD and EP remains limited, as relatively few studies have investigated the underlying biological mechanism especially beyond the neonatal period. To gain insight into this, Galderisi *et al*. [17] examined bronchial histopathology in adolescent survivors of severe BPD. Thickened airway basement membranes with lymphocytic infiltrates and signs of immature neoangiogenesis without T-helper lymphocytes or eosinophils suggested the presence of active processes. These findings were reinforced by bronchoalveolar lavage analyses from the LUNAPRE cohort, which confirmed that young preterm-born adults (PBAs) with a history of BPD display airway $CD8^+$ T-cell patterns [18, 19]. Beyond early determinants of lung damage, exposure to tobacco smoke, vaping and environmental pollutants appear to further affect lung growth and function, with disproportionately greater impact in those born preterm, whose pulmonary reserve and repair capacity are already reduced. This is particularly concerning given that active smoking has been reported in up to 50% of individuals within some cohorts of PBAs [20].

The lungs of preterm survivors grow through adolescence and young adulthood sharing similarities with asthma and COPD. Survivors of EP frequently exhibit increased rates of wheezing, airway hyperreactivity and frequent asthma-drug prescriptions [12]. Up to ∼20% of adolescents born very preterm meet diagnostic criteria for asthma, supporting the notion of overlapping respiratory phenotypes between PLD and asthma [21], but only 30% of them show bronchodilator reversibility during childhood and young adulthood [22]. However, longitudinal studies reveal structural, biological and functional alterations suggesting that the "preterm lung" is a distinct entity from asthma [23]. Airflow limitation, air trapping, an impaired response to bronchodilators and airway $CD8^+$ T-cell patterns suggest a physiological parallel between PLD and an evolving chronic obstructive phenotype [24, 25], as suggested by Simpson *et al.* [11]. However, unlike classical COPD, inflammation and fibrosis are less prominent and the underlying mechanism reflects developmental rather than degenerative processes. Recognising this distinct aetiotype is crucial, as it suggests that lung function decline may begin decades earlier [26]. As a consequence, the Global Initiative for Chronic Obstructive Lung Disease has proposed PLD as a COPD subtype related to prematurity [27], while a *Lancet* commission has similarly identified a COPD aetiotype of early-life origin, particularly associated with prematurity [28]. As such, PLD represents the COPD endotype with the earliest origin and the longest duration [29].

Lung function impairment

Although pulmonary mechanics of EP survivors improve during early childhood, an airway impairment persists [30]. As mentioned, the sequential phenomena affecting alveolar and airway development throughout childhood shape a composite physiological scenario that can translate functionally into complex phenotypes. At this regard, Cousins *et al.* [31] characterised this complexity among preterm-born children based on forced expiratory volume in 1 s (FEV_1), FEV_1/forced vital capacity (FVC) ratio, bronchodilator responsiveness and fractional exhaled nitric oxide.

Through the transition into early adulthood and up to 53 years, it is now established that extremely PBAs fail to achieve their full respiratory potential [3, 24, 32–35]. Although this limitation is particularly pronounced among those who were diagnosed with BPD, even those without this diagnosis exhibit measurable, though milder, impairments in pulmonary function [24]. Two recent meta-analyses confirmed the lifelong persistence of reduced FEV_1 in extremely PBAs. However, they offered different perspectives on disease evolution; one reported an almost fixed FEV_1 deficit across ages, while the other suggested a gradual decline in FEV_1/FVC as a possible marker of a progressive disease [34, 36].

The majority of evidence on respiratory outcomes in extremely PBAs cohorts is based on cross-sectional analyses, whereas only a small portion comes from long-term follow-up of longitudinal cohorts, which are valuable for assessing their later lung function trajectory. An early or accelerated decline in function may serve as an early marker identifying those that are now considered candidates for premature development of COPD in early adult life [37]. In the Padova BPD study, we are assessing longitudinally since birth the lung function of a group of subjects born very preterm (<32 weeks' gestation) with BPD [38]. Follow-up evaluations showed the persistence of reduced FEV_1, with 65% of participants remaining below 80% of the predicted value during young adulthood (24 years of age) and showing no late catch-up. This cohort has now reached 30 years of age and a trend toward a faster decline in respiratory function was observed (figure 1), consistent with the findings of Gibbons *et al.* [11, 34].

Many of the cited studies have evaluated lung function in individuals born before or around the introduction of surfactant therapy. The generalisability of their results to more recent cohorts is therefore debated, as advances in neonatal care may have positively influenced respiratory outcomes. Conversely, the increased survival of more immature and fragile infants could have exerted an opposite effect on overall population results. These aspects were recently examined by Bårdsen *et al.* [39], who compared three cohorts of 18-year-old ELGANs born across consecutive decades. They found that, although lung function deficits relative to term controls remained largely stable, significant improvements in the z-scores of FEV_1, FEV_1/FVC and forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$) were evident in the most recent (1999–2000) BPD subgroup. While some cohorts suggest modest improvements of lung function in more recent eras, other authors, such as Doyle *et al.* [40], report stable or even worsening outcomes among BPD survivors, the latter option possibly beginning even during childhood as shown by Simpson *et al.* [11]. Overall, meta-analytic evidence indicates no clear or sustained improvement since the introduction of surfactant therapy [32, 36, 40, 41].

Treatment options

So far, inhaled corticosteroids (ICS) have been tested in children and adolescents born preterm with inconsistent results. A statistically significant improvement of lung function was observed only when ICS

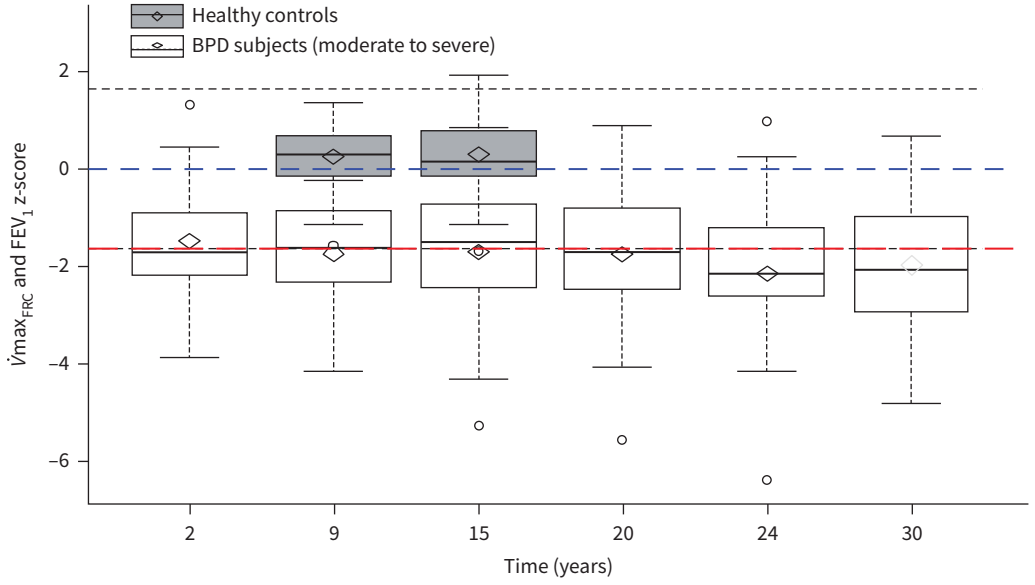

FIGURE 1 The Padova bronchopulmonary dysplasia (BPD) study: 30 years of follow-up. Box-and-whisker plots of the time course of the airway function parameters (maximal forced expiratory flow at functional residual capacity ($\dot{V}max_{FRC}$) and forced expiratory volume in 1 s (FEV_1) z-score) between 2 and 30 years of age. $\dot{V}max_{FRC}$ was measured at 2 years and FEV_1 was measured at 9, 15, 20, 24 and 30 years (white boxes). The grey boxes report the FEV_1 values for a matched control group of healthy children who were prospectively followed from 9 to 15 years of age. Values are given as z-scores. The boundaries of the boxes represent the 25th and 75th percentiles, respectively, and whiskers represent the nonoutlier ranges. The median value is indicated by the line that bisects the boxes and the mean is indicated by the diamond. Circles represent the outlier values. Horizontal dashed lines represent the 5th (red line), 50th (blue line) and 95th (grey line) percentiles of the normal z-score distribution. V.A. Ferraro, Department of Woman's and Child's Health, University of Padova, Padova, Italy; personal communication.

were combined with inhaled long-acting β_2-agonists (LABAs) in a small randomised controlled trial, but whether this translated into any actual improvement in respiratory symptoms is not known [42, 43]. According to URS *et al.* [44], a greater benefit from ICS treatment in children born very preterm is seen among those with a positive bronchodilator response. These findings suggest that treatment response depends on the individual disease phenotype. Although ICS may transiently improve expiratory airflow in some survivors of preterm birth, their long-term efficacy remains uncertain. This may reflect a specific underlying pathobiology, sustained by other possible contributors such as a non-eosinophilic inflammatory profile [23, 24] and chronic angiogenetic abnormalities [17]. Differently to asthma, ICS are therefore unlikely to be the optimal option, since their target is the eosinophilic inflammation characteristic of type-2 asthma [26, 42, 45–47].

At present, no evidence-based interventions or recommendations exist for PLD after childhood [44]. To be noted, no studies have evaluated in BPD survivors the potential effectiveness of long-acting muscarinic antagonists (in combination with ICS and LABA) and the new biologic treatments currently under evaluation in patients with COPD [27]. Due to limited evidence, international societies currently advocate a pragmatic, individualised approach, recommending a short therapeutic trial before considering any long-term prescription [48, 49]. In this context, a more personalised treatment strategy, forcedly diverging from the "one-size-fits-all" approach, is increasingly needed. The "treatable traits" framework has been proposed to help identify actionable targets and the patient subgroups (phenotypes) most likely to benefit [50], thereby advancing the development and testing of new interventions [18, 47]. However, rather than relying solely on cross-sectional assessments of respiratory function, there is an urgent need for studies evaluating possible options to stabilise or improve lung trajectories, with the goal of reducing the risk of early COPD and preventing the development of low trajectories.

Additional functional tests and chest imaging

The assessment of lung function after EP has traditionally relied on spirometric measures, but evidence about other investigations is growing.

Static lung volumes assessed by plethysmography at 11 years of age showed persistent overinflation, evidenced by increased residual volume (RV) and elevated RV/total lung capacity ratios in former extremely preterm children compared with term-born controls, further supporting the concept that PLD is predominantly an obstructive disease [51]. Several studies evaluated the lung clearance index by the multiple breath washout technique showing increased ventilation inhomogeneity following preterm birth [52–55]. The forced oscillation technique has also been used, revealing higher respiratory resistance and lower reactance in preterm neonates followed up to 36 weeks of postmenstrual age, findings consistent with peripheral airway obstruction and reduced elastic properties of the respiratory system [56–58]. Comparable results were observed in preschool children born very preterm, regardless of whether they had been diagnosed with BPD [59, 60].

The diffusing capacity of the lung for carbon monoxide (D_{LCO}) was found to be persistently reduced in individuals born extremely preterm, showing a positive correlation with gestational age [61]. This reduction has been confirmed in several studies involving very-low-birth-weight (<1500 g) preterm individuals, both with and without BPD [62], and was sometimes more pronounced in those affected [63]. Further understanding of the mechanisms underlying these observations emerges from mechanistic studies. Using a combined assessment of D_{LCO} and alveolar volume, PLD subjects at 1 year of age exhibited decreased D_{LCO} but normal alveolar volume, suggesting an impairment of alveolar development [64]. Sørensen *et al.* [65] further investigated this aspect evaluating nitric oxide diffusing capacity (D_{LNO}). D_{LNO} has been proposed as an alternative measure of alveolar membrane function, as D_{LCO} may also be influenced by erythrocytic properties and pulmonary microcirculation. Their data show greater relative impairment of the alveolar membrane compared to the alveolar capillary circulation, with the lowest D_{LNO}/D_{LCO} ratio in the BPD subjects, indicating primary alveolar membrane impairment in these patients. Interestingly, the preterm-born individuals without BPD had significantly greater D_{LNO}/D_{LCO} ratio compared to controls and BPD subjects, suggesting a possible vascular disease in this population. Overall, longitudinal data on diffusing capacity show no evidence of catch-up or decline up to 25 years of age compared with term-born controls [66]. In Bårdsen *et al.*'s [39] work, D_{LCO} showed an amelioration across birth decades both in extremely PBAs and controls; however, the observed trend may reflect differences in equipment, test procedures and software, or environmental factors (*e.g.* maternal smoking or second-hand exposure).

As previously outlined, fractional exhaled nitric oxide has been used to investigate airway inflammation in PLD, consistently showing low to normal levels, thereby confirming the noneosinophilic nature of airway inflammation [46, 67]. Nonetheless, evidence points to the persistence of an active oxidative and inflammatory process, involving airway $CD8^+$ T-cell infiltration as well as lipid metabolic derangements in the exhaled breath condensate of BPD subjects compared with healthy controls [18, 68].

The persistence of a parenchymal disease was evidenced also in imaging studies both using computed tomography (CT) and magnetic resonance imaging (MRI). High-resolution CT scans revealed abnormalities such as opacities, air trapping and mosaic perfusion in 81–93% of preterm-born individuals assessed at 10 and 18 years of age [69]. Similar findings have been reported in cohorts born in the post-surfactant era [70], with structural alterations already detectable within the first year of life, suggesting their potential use as early phenotyping tools [71]. Several CT scoring systems have been proposed to predict clinical respiratory outcomes, but none has yet been adequately validated or proven superior to the others [72]. MRI is a recent advancement in lung evaluation, enabling a radiation-free imaging, from NICU admission onward. MRI has proven to be a valuable tool for identifying lung abnormalities and a possible predictor of respiratory needs [73] and respiratory function parameters [74, 75]. Not least, MRI was capable of detecting the lung vascular pathology [76].

New therapeutic options and disease models for PLD

It is now evident that there is an urgent need for new early therapeutic/preventive options for PLD, as these would improve the respiratory health of PBAs, but possibly lead to a multisystemic benefit. In fact, the need for support to neonatal research is a crucial topic in the field [77]. In this landscape, novel research directions are attempting to act upstream on the developmental origins of the disease, with pleiotropic multisystem effects. Experimental therapies, such as insulin-like growth factor-1 infusion, surfactant protein-D and allogeneic umbilical mesenchymal cells, and their derived extracellular vesicles, currently investigated for the prevention of BPD, have shown encouraging effects on lung development and even on neurodevelopmental outcomes in preclinical models [78–81].

An effective implementation of these new options requires early identification of the patients who would benefit most. This has now been explored using noninvasive techniques such as lung ultrasound. This technique applied in the first weeks of life has proven useful to predict BPD in very preterm infants [82],

especially when combined with measures of gas exchange [83], with initial evidence of a possible predictive capability also for respiratory outcomes in the first 2 years of life [84]. Omics sciences are also emerging as valuable tools to unravel the underlying pathogenetic pathways of BPD and identify possible early biomarkers [3, 85, 86].

In parallel, new technologies are expanding the possibilities for precision medicine. Lung organoids, including patient-derived models, are emerging as a promising tool to study disease mechanisms and to test pharmacological and non-pharmacological therapies in a personalised manner [87]. Despite their still limited clinical translation, these models may soon allow individualised prediction of treatment efficacy and toxicity, addressing some of the aspects lacking in other experimental models [88].

The short- and long-term systemic sequelae: beyond the lungs

PLD can no longer be regarded as an isolated pulmonary condition. The disease can be accompanied by a spectrum of multisystem comorbidities that share many of the same perinatal risk factors and pathogenic mechanisms, beyond prematurity itself (figure 2). These comorbidities not only coexist with PLD but tend to be more prevalent and severe in infants with more advanced disease. Despite the known risks, there remains inadequate awareness of these possible long-term multisystemic complications [89].

While the severity of prematurity and low birth weight are not interchangeable in terms of health effects, infants born with very low birthweight (VLBW) are indeed at higher risk of developing PLD and represent the most frequently followed-up population worldwide. Therefore, this group has been used to broadly analyse long-term sequelae and to explore whether respiratory disease may influence morbidities in other

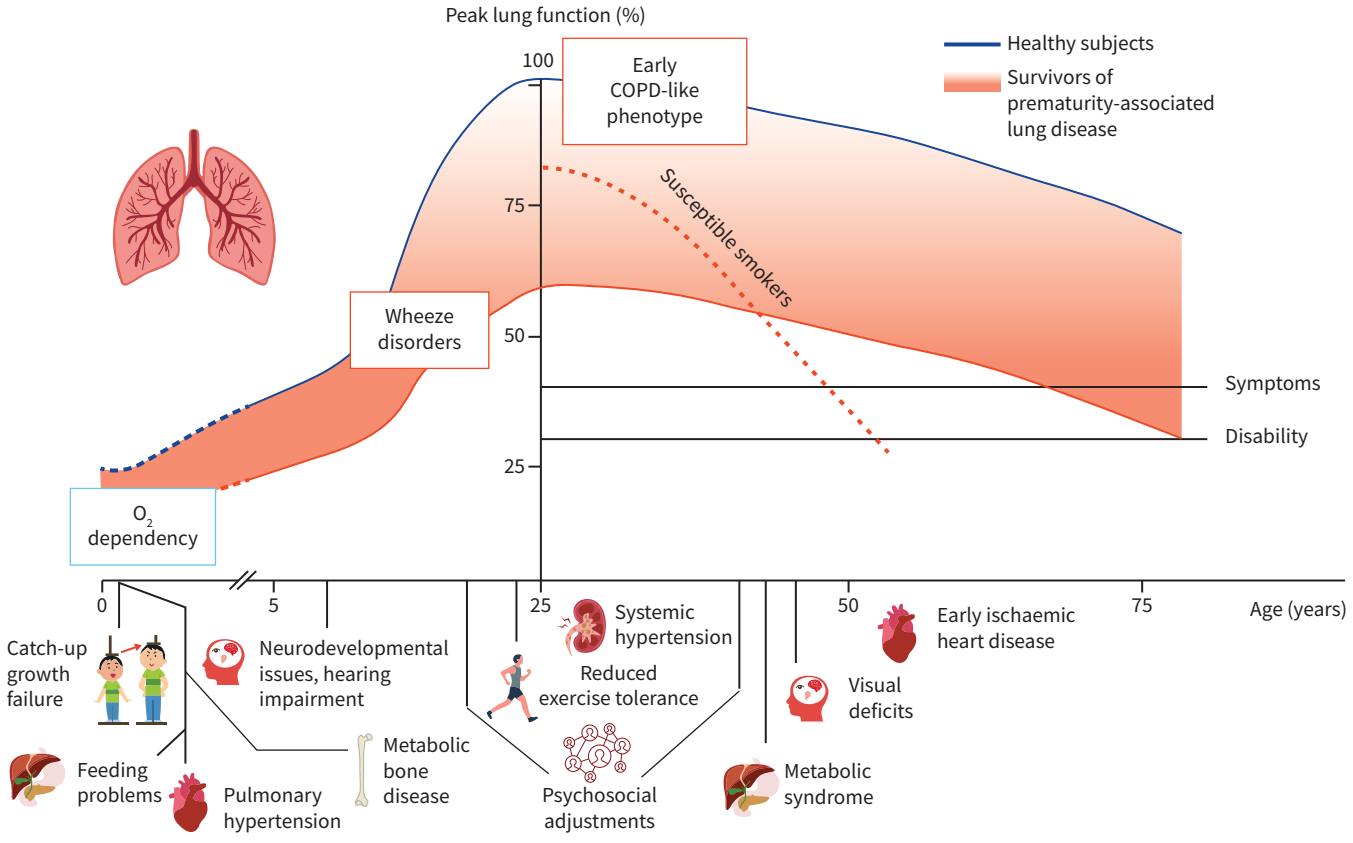

FIGURE 2 Prematurity-associated lung disease (PLD)-related multimorbidity throughout the lifespan. Trajectories of prematurity multimorbidity are greatly influenced by respiratory function. Lower peak lung function values are associated with higher risk of wheeze disorders and a new COPD-like phenotype. A multidisciplinary follow-up, involving pneumologists, respiratory therapists, cardiologists, neurologists, endocrinologists, otolaryngologists, psychologists and ophthalmologists, is needed to provide comprehensive support for PLD and associated comorbidities. Throughout the lifespan of individuals born preterm, paediatric and adult pulmonologists play a pivotal role in fostering continuity of care, uniting specialists, families and patient support groups around a shared vision of long-term holistic treatment. Modified from [24].

organ systems. Table 1 provides an overview of recent evidence from longitudinal follow-up cohorts of VLBW preterm-born individuals assessed in adulthood.

Cardiovascular sequelae

The cardiovascular system also bears the imprint of EP. The abrupt transition from fetal to postnatal circulation occurs when the myocardium and micro/macrovasculature are at an early developmental stage [90]. Premature exposure to systemic pressures, fluctuating oxygen levels, patent ductus arteriosus and interventions such as corticosteroid therapy may leave lasting structural and functional changes, creating a lifelong "preterm cardiovascular imprint" that predisposes to cardiometabolic disease later in life. As long-term survival improved, recognising and characterising these cardiovascular consequences has become increasingly important. On this basis, national guidelines (*e.g.* Canadian) are now suggesting routine echocardiographic monitoring in EP survivors [91].

The most known cardiovascular consequence of EP is pulmonary hypertension (PH) usually associated with BPD (BPD-PH), that may be present at a mild/subclinical degree in 40–50% of subjects born extremely preterm [90, 92]. These individuals may experience acute pulmonary pressure increases triggered by noxae such as respiratory infections, anaesthesia or causes of hypoxia or hypercapnia (*e.g.* airway obstruction, fever). Despite a long-term mortality rate of up to 40%, about 80% of infants with BPD-PH show resolution by 2 years, possibly due to catch-up growth [93]. A smaller subgroup, however, experiences persistent PH throughout childhood and may require pharmacological treatment with agents like phosphodiesterase inhibitors (*e.g.* sildenafil) or endothelin receptor antagonists (*e.g.* bosentan).

Apart from BPD-PH, preterm birth itself constitutes an independent, nonmodifiable risk factor for cardiovascular disease later in life [94]. Gestational age is inversely correlated with adult mortality, particularly from cardiovascular causes, and with the risk of heart failure and ischemic heart disease [95, 96]. This risk, although less pronounced, persists among moderately preterm subjects [97]. As noted earlier, birth interrupts the process of cardiomyocyte differentiation and hyperplasia, limiting the lifelong myocyte size and number. Hence, preterm individuals have smaller hearts with less binucleated myocytes. This contributes to an altered geometry, affecting contractile function and overall performance [94].

MRI and advanced echocardiographic techniques (*e.g.* speckle-tracking and four-dimensional imaging) have facilitated the recognition of a distinct preterm cardiovascular phenotype, characterised by altered biventricular mass, reduced arterial diameter and increased stiffness, which may ultimately lead to myocardial fibrosis and elevated vascular resistance [98]. Of note, some studies have reported associations between reduced expiratory flows in preterm-born individuals and later cardiovascular or metabolic abnormalities [99, 100], reframing spirometry as a potential integrative biomarker of multi-organ health [101].

Against this background of nonmodifiable risks, it is crucial to prevent additional modifiable burdens such as smoking, obesity, dyslipidaemia, hypertension and diabetes. Many of these can be mitigated through healthy lifestyles and regular physical activity. Nevertheless, individuals born extremely preterm often engage less in physical activity because their reduced exercise capacity, reflecting respiratory and cardiovascular limitations, further impacts their quality of life [102–106]. Encouragingly, structured exercise appears beneficial: preterm children and young PBAs showed improvements in exercise tolerance, capacity and cardiopulmonary performance across recent trials [107, 108].

Long-term renal involvement

Glomerulogenesis is incomplete in preterm neonates, resulting in reduced nephron endowment. Although glomerulogenesis may briefly continue after birth, the nephrons formed postnatally often develop under noxious factors, leading to structural and functional abnormalities. These alterations may underlie an increased risk of chronic kidney disease (CKD) [109]. Long-term follow-ups have inconsistently found significant differences in estimated glomerular filtration rate (eGFR) between adults born very preterm or with VLBW and term-born controls up to the third decade [53, 99]. Nonetheless, the risk is particularly relevant in subgroups such as growth-restricted infants, who show lower eGFR. Hence, international experts in obstetrics, neonatology and nephrology have raised awareness of the lifelong risk of CKD among individuals born with VLBW or EP [110]. Overall, monitoring of renal function in these high-risk groups appears warranted. Hypertension may arise as a consequence of increased intraglomerular pressure and sustained hyperfiltration stress compensating for the oligonephronia [109]. Indeed, young PBAs have been found to exhibit reduced renal volume, higher urine creatinine-to-albumin ratios and elevated circulating angiotensin II levels. These alterations were significantly associated with higher systolic and diastolic blood pressure [111]. Particular attention should be given to PBAs presenting with hypertension

TABLE 1 Updates from the past 5 years on follow-up cohorts reaching adult age of very low birthweight (VLBW) preterm-born individuals

Cohort (country) Sample population at last update [References]	Age (years) at last follow-up; birth year	Main outcomes	Main results	Extrapulmonary evaluations
LUNAPRE cohort (Sweden) **20 BPD (O_2 >28 days) *versus* 22 former preterm without BPD *versus* 24 asthma *versus* 24 controls** **[19, 171–175]**	Average age of 20 at last follow-up; 1992–1998	Sphingolipids and oxylipins in BALF	Significant sex-related alterations in the airway lipid profile of BPD survivors	No
		Bronchial epithelial gene expression	Molecular sex differences are present in BPD, involvement of diverse biological mechanisms	No
		Mucins 5AC and 5B in the large airways	Preterm-born adults with and without BPD displayed similar levels	No
		T-cell profile in the large airways	Higher lymphocyte and $CD8^+$ T-cells proportion in bronchial wash in BPD, $CD8^+$ proportion correlating with obstruction	No
		Structural abnormalities by HRCT	In the BPD group: higher linear/triangular subpleural opacities, local hypoattenuation, architectural distortion, bronchial wall thickening, air trapping	No
		Urinary metabolomics	Sex-specific urinary eicosanoid profiles in the BPD survivor group	No
Combined **HeSVA cohort (Finland)** **plus** **NTNU LBW Life cohort (Norway)** **137 participants *versus* 158 term-born controls** **29 BPD (O_2 >28 days)** **20 BPD (according to Northway definition)** **[113, 120, 142, 176, 177]**	Mean age of 36 at last follow-up; 1978–1985 and 1986–1988	Spirometry	VLBW participants had significantly lower values in all main outcomes (FVC, FEV_1, FEV_1/FVC, $FEF_{25–75\%}$ and $FEF_{75\%}$), compared with controls The differences were more pronounced among those with BPD-VLBW VLBW participants were more likely to report use of any obstructive airway disease medication and were more likely to report an attack of asthma BPD-VLBW participants have significantly faster decline of FVC and FEV_1 z-scores compared with their term-born peers VLBW participants who reported a history of smoking had a faster decline in FEV_1/FVC and FEV_1/FVC z-scores VLBW participants had lower educational attainment than controls	Educational attainment
		Pattern reversal electroretinogram, visual evoked potential, best corrected visual acuity	No relationship was found between electrophysiologic responses and best corrected visual acuity No separate analysis on BPD subjects	Ophthalmologic measures
		Refraction, visual acuity and fields, contrast sensitivity, IOP, self-reported vision-targeted health status; foveal and parafoveal thickness; optic disc optical coherence tomography	VLBW adults had a lower visual acuity score than controls VLBW adults also had lower contrast sensitivity, lower self-reported vision-targeted health status Refraction, visual fields and IOP were similar between groups Two VLBW participants were blind None had been treated for retinopathy of prematurity The foveal area was thicker in VLBW adults; thinner in the parafoveal areas of the macula A moderate decrease of the optic disc neural rim and peripapillary retinal nerve fibre layer thickness was frequently seen in VLBW adults Findings were not related to reduced visual acuity No separate analysis on BPD subjects	Ophthalmologic measures
		Overall motor abilities; fine and gross motor abilities	PBAs with VLBW had poorer overall, fine and gross motor abilities than term-born adults Substantial difficulties persist into mid-adulthood No separate analysis on BPD subjects	Neurology: motricity

Continued

TABLE 1 Continued

Cohort (country) Sample population at last update [References]	Age (years) at last follow-up; birth year	Main outcomes	Main results	Extrapulmonary evaluations
HeSVA cohort (Finland) **160 VLBW subjects *versus* matched term-born controls** **[143, 148, 149, 178, 179]**	Mean age of 22; 1978–1985	DNA methylation	Differentially methylated CpG-sites suggesting an epigenetic signature of preterm birth in PBAs	No
		Body composition by DEXA	VLBW adults had a more centralised fat distribution, as well as lower appendicular muscle mass	Cardiometabolic risk
		Body composition assessed by eight-polar bioelectrical impedance	VLBW adults had lower lean body mass than controls, mostly attributable to shorter height This has been proposed as a possible contributor to lower insulin sensitivity and muscular fitness found in VLBW survivors, predisposing to functional limitations with increasing age	Cardiometabolic risk
		Oral glucose tolerance test, cardiometabolic blood biomarkers	After adjusting for confounders, VLBW adults showed higher 2-h glucose than their siblings Also, fasting and 2-h free fatty acids were higher No statistically significant differences were found regarding insulin resistance, atherogenic lipid profiles or liver tests No separate analysis on BPD subjects	Endocrine/ cardiometabolic risk
		Actigraphy-derived data on the timing, duration and quality of sleep	VLBW adults displayed an earlier chronotype than siblings The findings were emphasised in VLBW participants born SGA Findings were maintained at 30 years of age, which suggests that the earlier chronotype is an enduring individual trait not explained by shared family factors No separate analysis on BPD subjects	Sleep
ESTER (Finland) Preterm Birth Study cohort **753 adults (149 born very or moderately preterm <34 GWs)** **[122, 158, 180]**	Mean age of 23.3 in 2009–2011 (last evaluation)	Peak height velocity (cm·year^{-1}) and age at peak height velocity	Timing of pubertal growth and age at menarche or voice break were similar in participants born preterm and at term No separate analysis on BPD subjects	Endocrine (puberty)
		Cogstate® test (associate and visual learning, psychomotor and executive function, spatial memory efficiency, visual and working memory, attention, and emotional cognition)	In tests on visual memory and executive function, the early preterm and VLBW groups had lower efficiency (*i.e.* performed the test slower) than full term AGA participants VLBW and late preterm AGA participants also had more errors than the full-term and AGA group PBAs as a group showed similar cognitive performance to their full-term peers in all other subtests No separate analysis on BPD subjects	Cognitive function
		Testosterone and sex hormone binding globulin; free androgen index; hirsutism, oligomenorrhoea	Women born <34 GWs exhibited higher testosterone and higher free androgen index than controls after adjusting for confounding factors Increased odds ratios for having PCOS No separate analysis on BPD subjects	Endocrine
HeSVA cohort+ESTER cohort (Finland) **[181]**	Mean age of 29.6 in 2014–2017	Magnetic resonance imaging from the liver, abdomen, tibia	VLBW adults displayed similar adipose tissue volumes and hepatic triglyceride content as their term siblings The VLBW group displayed less unsaturation in subcutaneous abdominal adipose tissue No separate analysis on BPD subjects	Cardiometabolic risk
The Northern Finland Birth Cohort 1966 (Finland) **125 <37 GWs *versus* 2673 term** **[182]**	Age of 46 at evaluation; 1966	Recurrent musculoskeletal pain	Preterm birth and SGA were not associated with adult multisite musculoskeletal pain No separate analysis on BPD subjects	Pain
NTNU LBW Life cohort (Norway) **45 VLBW-born adults plus 68 term-born** **[183]**	32; 1986–1988	Short Form 36-item Health Survey at 32 years of age	For both physical and mental component summaries there was an overall decline in HRQoL from 20 to 32 years of age in the VLBW group, even in absence of disabilities	Quality of life measures

Continued

TABLE 1 Continued

Cohort (country) Sample population at last update [References]	Age (years) at last follow-up; birth year	Main outcomes	Main results	Extrapulmonary evaluations
New Zealand VLBW cohort (New Zealand) **229 VLBW-born adults *versus*** **100 term-born controls** **[53]**	28 at assessment; 1986	Growth, renal, cardiac, lung function, vision, dental, cognitive and neuropsychological function, social, cranial MRI	VLBW adults were shorter and lighter compared with controls; no differences in the fasting lipid profile, fasting insulin, glycated haemoglobin, insulin resistance measures Nonsignificant increase in the rate of metabolic syndrome Systolic blood pressure significantly higher in VLBW males In VLBW adults, the left ventricular mass, volume and right ventricular dimensions were reduced No differences in serum creatinine, eGFR or urinary albumin:creatinine ratio VLBW adults had significantly reduced mean global grey matter volume and nonsignificantly reduced mean white matter volume VLBW adults who had ROP had reduced visual acuity compared with VLBW adults without ROP and controls Substantial gap in IQ, lower rates of tertiary education/training Increased airways obstruction, reduced gas exchange efficiency and increased ventilatory inhomogeneity; tendency to exercise less often and less vigorously	Multisystem evaluation
		Spirometry, plethysmography, D_{LCO}, single-breath nitrogen washout	An obstructive spirometry pattern was identified in 35% VLBW subjects *versus* 14% controls, with the majority showing mild obstruction Within the VLBW group, subjects with BPD showed significant reduction in FEV_1, FEV_1/FVC and $FEF_{25–75\%}$, and increases in RV, RV/TLC, and phase III slope for single-breath nitrogen washout, *versus* subjects without	No
Research on European Children and Adults Born Preterm+Adults Born Preterm International Collaboration Consortia (HeSVA+NTN+NZ VLBW+ESTER+AYLS) **[160, 184, 185]**	22–28; 595 VLBW *versus* 1049 controls	Fertility IQ, moderate-to-vigorous physical activity	VLBW is not associated with lower fertility in young adults Irrespective of neurosensory impairments and IQ, adults born very preterm/VLBW, especially women, reported less moderate-to-vigorous physical activity than their term-born peers No separate analysis on BPD subjects	Reproductive health Physical activity/ cardiometabolic risk
		Mental health (Achenbach system of empirically based assessment adult self-report)	Associations between mental health, pain and tiredness in adults are independent of gestational age or birthweight Results were maintained when adjusting for physical activity	Mental health
PREMATURITAS cohort (Poland) **12 <28 GWs; 40 28–34 GWs; one patient with BPD** **[54]**	Mean age of 21.6	Spirometry, plethysmography, oscillometry, multiple breath nitrogen washout, F_{ENO}, lung ultrasound, HRQoL, mental health measures	Higher ventilation inhomogeneity <28 GWs at birth	Quality of life and mental health measures
POPs (Netherlands) **370 <32 GWs and/or VLBW** **[124, 159]**	35 at last evaluation; 1983	Short Form 6-Dimension at age 35 to assess multi-attribute utility scores and domain-level functioning (ambulation, dexterity, cognition, vision, hearing, speech, emotion and pain)	Three groups were evaluated: VLBW-only, very preterm-only and combined Specific domain-level differences emerged in early adulthood At 19 years, the VLBW-only group reported significantly better speech functioning At 28 years, the very preterm-only group had better hearing, while the VLBW-only group had worse ambulation By 35 years, these inter-group differences were no longer statistically significant Female sex was a consistent predictor of poorer outcomes in several domains No separate analysis on BPD subjects	Quality of life measures
		Reproductive rate, fertility, and pregnancy complications	POPS-35 participants had less children than their peers; they reported more problems in conception and pregnancy complications, including a three times increased risk of hypertension during pregnancy	Reproductive health
AYLS+ESTER preterm birth study+EPICure study +BLS+HeSVA+two Danish cohorts **[186]**	Birth year: 1983–1985; 1983–1985, 1995, 1986, 1978–1985, 1974–1976; 1980–1982, respectively	Personality using the Five-Factor Model	Very preterm/VLBW participants scored lower on extraversion and openness and higher on neuroticism and agreeableness than term-born participants after adjusting for sex and parental education Within the very preterm/VLBW group, those with BPD scored lower on extraversion and higher on neuroticism, with similar findings after removing participants with neurosensory impairments	Personality

Continued

TABLE 1 Continued

Cohort (country) Sample population at last update [References]	Age (years) at last follow-up; birth year	Main outcomes	Main results	Extrapulmonary evaluations
UKOS (UK) **150 participants from the initial cohort of 797 infants <28 GWs** **[187–192]**	24–28 ; 1998–2001 UKOS *versus* control	Lung function tests, cardiac ultrasound, exercise assessments, inflammatory cell and biomarker profiling and airway microbiome assessment	No results yet	Cardiopulmonary outcomes
	16–19 (mean 18) Male *versus* females	Lung function testing (spirometry, oscillometry, diffusion capacity, lung clearance index and plethysmography), a shuttle sprint test for exercise capacity, and a respiratory symptoms questionnaire	Substantial differences in the percentage of participants with lung function below the 5th centile: males had poorer mean $FEF_{75\%}$, $FEF_{50\%}$, $FEF_{25-75\%}$, FEV_1/FVC ratio, D_{LCO} and D_{LCO}/V_A compared with females and the differences remained significant after adjusting for neonatal factors and age Exercise capacity and self-reported exercise both significantly better in males than females No significant differences by sex in the prevalence of either wheeze or asthma	Exercise capacity
	16–19 (mean 18) BPD *versus* those without BPD	As above [188]	At 16–19 years, those with a history of BPD had poorer airway function (FEV_1, $FEF_{75\%}$, $FEF_{50\%}$, $FEF_{25-75\%}$, FVC, D_{LCO}) These differences remained significant after adjusting for sex, gestational age and maternal smoking When excluding those who had received postnatal corticosteroids, differences remained significant in FEV_1, FVC and $FEF_{75\%}$ No significant differences in exercise capacity or respiratory symptoms between those with and without BPD	Exercise capacity
	16–19 (mean 18 years) HFOV *versus* conventional ventilation	Spirometry, diffusion capacity	Across the population, deterioration in lung function was associated with male sex, white ethnicity, lower gestational age at birth, postnatal corticosteroids, oxygen dependency at 36 weeks postmenstrual age and lower birthweight, but not ventilation mode	No
	16–19 (mean 18) IUGR *versus* AGA	As above [188]	After adjustment for BMI, the mean FEV_1/FVC, $FEF_{75\%}$, $FEF_{25-75\%}$, FRC_{pleth} and RV_{pleth} were poorer in those who had IUGR After further adjustment for BPD and postnatal corticosteroid use, only the difference in RV_{pleth} z-scores remained statistically significant Exercise capacity was lower in those with IUGR and this was more pronounced in males	Exercise capacity
	16–19 (mean 18 years) Dexamethasone *versus* no postnatal steroids	Spirometry, diffusion capacity, plethysmography	The majority of results were significantly lower in those who received dexamethasone Lung function reduced as the number of courses of dexamethasone increased Between 11 and 14 years and 16 and 19 years, lung function improved in the unexposed group, but $FEF_{75\%}$ and FEV_1 deteriorated in those who had received postnatal corticosteroids	No
TAHS cohort (Australia) **1445 preterm and term newborns** **[35]**	53	Spirometry, diffusing capacity, bronchodilator test	Very-to-moderate preterm birth was significantly associated with an increased risk of COPD at age 53 years, lower D_{LCO} and $FEF_{25-75\%}$ Very-to-moderate preterm birth was also associated with lower post-bronchodilator FEV_1/FVC ratio, only among smokers Compared with term birth, late preterm birth was not associated with lower FEV_1/FVC ratio or COPD	No
Western Australian Lung Health in Prematurity cohort (Australia) **127 participants ⩽32 GWs (81 with BPD) *versus* 41 term-born controls** **[193]**	16–23	Spirometry, diffusing capacity for the lung, whole body plethysmography, multiple breath washout, fractional exhaled nitric oxide and oscillometry, chest CT	Compared with controls, young PBAs had greater airflow obstruction, gas trapping and ventilation inhomogeneity, abnormalities in gas transfer and respiratory mechanics Greater structural abnormalities, respiratory symptoms and inhaled medication use A previous respiratory admission was associated with airway obstruction Similarly, respiratory symptom burden was increased in the preterm group with a respiratory admission, as was peribronchial thickening and bronchodilator responsiveness Atopy, maternal asthma and tobacco smoke exposure did not influence lung function or structure at 16–23 years	Respiratory symptom burden

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TABLE 1 Continued

Cohort (country) Sample population at last update [References]	Age (years) at last follow-up; birth year	Main outcomes	Main results	Extrapulmonary evaluations
EPICure study (UK and Ireland) **129 <26 GWs** **[194, 195]**	19; 1995	Presence of metabolic syndrome, BMI and systolic blood pressure	Metabolic syndrome was present in 8.7% of extremely preterm participants at 19 years Compared with subjects without metabolic syndrome, those with metabolic syndrome tended to have a smaller size at birth and a greater increase in weight z-scores from term to 2.5 years BMI at 19 years was positively related to growth from 2.5 to 6.0 years; an inverse association with birthweight z-scores was found in the lower socioeconomic status group Central systolic blood pressure was positively related to growth from 2.5 to 6.0 years	Endocrine: metabolic syndrome
		Spirometry, haemodynamics, functional capacity and markers of inflammation	Compared with controls, the extremely PBA was significantly impaired on all spirometric parameters and had lower F_{ENO} despite a higher proportion with bronchodilator reversibility Exercise capacity was significantly impaired All respiratory parameters were worse after neonatal BPD and respiratory function differences were similar at 11 and 19 years Central systolic and diastolic blood pressures increased more quickly during adolescence in the extremely preterm group	Exercise capacity, blood pressure
		Height, weight, head circumference and BMI	Extremely preterm individuals were on average 4.0 cm shorter and 6.8 kg lighter with a 1.5 cm smaller head circumference relative to controls at 19 years Extremely preterm participants grew faster in weight and in head circumference, but with no catch-up in height For the extremely preterm group, because of weight catch-up between 6 and 19 years, BMI was significantly elevated at 19 years to +0.32 SD; proportion of subjects with BMI >25 $kg \cdot m^{-2}$ and >30 $kg \cdot m^{-2}$ were similar to the control group Extremely preterm and control participants showed similar pubertal development in early adolescence, which was not associated with height at 19 years Growth through childhood was related to birth characteristics and to neonatal feeding practices	Endocrine: height, weight, pubertal growth
German cohort **212 born very preterm or with VLBW and 202 term-born controls** **[160]**	Up to 35; 1985–1986	Cumulative incidence of having the first alive child (fertility)	Fertility was lower among those born very preterm or with VLBW throughout the follow-up The association of very preterm and VLBW with lower fertility was significant during the late (>30 years) but not early (<30 years) reproductive window; no association after adjusting for neonatal and sociodemographic factors	Reproductive health

AGA: appropriate for gestational age; AYLS: Arvo Ylppö Longitudinal Study; BALF: bronchoalveolar lavage fluid; BLS: Bavarian Longitudinal Study; BPD: bronchopulmonary dysplasia; BMI: body mass index; CD8: cluster of differentiation 8; CT: computed tomography; DEXA: dual-energy X-ray absorptiometry; D_{LCO}: diffusing capacity of the lung for carbon monoxide; eGFR: estimated glomerular filtration rate; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC; $FEF_{50/75\%}$: forced expiratory flow at 50%/75% of FVC; F_{ENO}: exhaled nitric oxide fraction; FEV_1: forced expiratory volume in 1 s; FRC_{pleth}: functional residual capacity measured by plethysmography; FVC: forced vital capacity; GW: gestational week; HeSVA: Helsinki Study of Very Low Birth Weight Adults; HRCT: high-resolution computed tomography; HRQoL: health-related quality of life; HFOV: high-frequency oscillatory ventilation; MRI: magnetic resonance imaging; IOP: intraocular pressure; IQ: intelligence quotient; IUGR: intrauterine growth restriction; PBA: preterm-born adult; PCOS: polycystic ovary syndrome; POPs: Project On Preterm and Small for Gestational Age Infants; ROP: retinopathy of prematurity; RV: residual volume; RV_{pleth}: residual volume measured by plethysmography; SGA: small for gestational age; TAHS: Tasmanian Longitudinal Health Study; TLC: total lung capacity; V_A: alveolar volume.

and other features of metabolic syndrome, as these may identify the subgroup at highest risk for early cardiovascular complications [94].

Neurodevelopmental outcomes and social results

Preterm birth interrupts the normal brain development, with a large spectrum of perinatal injuries and abnormal stimuli potentially leading to an aberrant maturation [112]. Due to the wide-ranging long-term effects of altered neurodevelopment, neonatal follow-up programmes emphasise the timely identification of impairments, to enable early physiotherapy and rehabilitation. Recent findings from long-term follow-up cohorts show that PBAs with VLBW may exhibit deficits in fine and gross motor function extending into mid-adulthood [113]. PLD has been recognised as an adjunctive risk for late persisting cognitive and executive function impairment and lower intelligence quotient (IQ) scores [114–118]. Even with a normal IQ, functional deficits may influence these individuals' learning activities and performance in tasks with higher cognitive workload [119]. Young PBAs also show disadvantages in overall educational attainment [53, 120], steady employment and engagement in romantic relationships. Reassuringly, while childhood cognitive deficits tend to remain stable through adolescence [121], their impact on daily lives appears to diminish, with cognitive performance and self-perceived executive functioning similar to their full-term peers and education and social gaps narrowing by the third decade [53, 122, 123].

Another important aspect is that long-term outcomes within this heterogeneous population follow distinct trajectories. A recent study differentiated the effects of immaturity and fetal growth restriction, separately and in combination, on early and mid-adulthood health-related quality of life across several domains (*e.g.* ambulation, dexterity, cognition, speech) [124]. The same complexity probably applies to psychological functions. Extremely PBAs have been shown to perform less optimally across a range of neuropsychological tests. The specific psychological adjustments, however, are shaped by multiple factors, including postnatal environmental influences [125].

It should also be noted that, regardless of the presence of neurodevelopmental morbidities, survivors of prematurity may be subject to epilepsy in adulthood [126].

Mental health

Individuals born preterm emerge as more vulnerable to psychiatric difficulties [127–129]. Childhood attention deficit hyperactivity disorder becomes increasingly frequent with decreasing birth weight and gestational age [130]. Survivors of prematurity often display other behavioural symptoms such as introversion, anxiety, inattention, rigidity and lower risk-taking propensity [131–133]. Social interactions and communication might be impaired for those showing autism spectrum symptoms [133]. PBAs are at higher risks for affective disorders, anxiety, panic disorders and nonaffective psychosis [129, 134, 135]. Together, this behavioural and emotional phenotype could prevent one individual from developing a well-integrated and socially engaged personality in adulthood. Nevertheless, as these findings are largely derived from national registry data [127, 129], they still require further investigation. Evidence from several longitudinal cohort studies in fact shows no excess of mood or anxiety disorders in early adulthood [136]. Long-term psycho-morbidities have not yet been considered as a meaningful outcome among patients with PLD.

Neurosensory function

Low birthweight infants are at increased risk for both auditory and visual impairments [137]. Inflammation, chronic hypoxia, oxidative stress and ototoxic medications further heighten this risk in patients with PLD. In the largest population study, PLD was the most significant predictor for bilateral hearing loss [138]. Population-based studies also show a reduction of visual acuity, visual fields and contrast sensitivity in young PBAs with VLBW, even after excluding subjects with previous retinopathy of prematurity [139]. Visual–motor integration was also affected [140], with increased rates of strabismus and nystagmus [141]. However, recent long-term follow-up data extending to mid-adulthood highlight the need for a nuanced interpretation of ophthalmologic findings in this population, as many frequent differences from controls are not directly linked to actual deficits [142].

Prematurity-related endocrinologic and metabolic traits

Preterm birth and a small size for gestational age have been associated, albeit infrequently, with a range of endocrine and metabolic disturbances. Among the ∼10% of individuals who fail to achieve catch-up growth, treatment with growth hormone may enhance linear growth. Nevertheless, longitudinal follow-up cohorts consistently report reduced adult stature in this population [143–147], often accompanied by lower lean mass, reduced muscle-to-fat ratio and a more centralised fat distribution [143, 148]. These features may contribute to decreased insulin sensitivity, although evidence in this regard remains inconsistent [53, 149]. Preterm birth has been linked to chronic disturbances of lipid and glucose metabolism [150],

and to an increased prevalence of metabolic syndrome [151]. Each degree of prematurity appears to confer proportionally higher risks of type 1 and type 2 diabetes [152, 153], hypertension, and elevated low-density lipoprotein cholesterol levels [154, 155], associations that are only partly explained by genetic and environmental factors [153, 154].

Finally, both thyroid dysfunction and metabolic bone disease have been associated with EP. Premature birth has been independently linked to hypothyroidism later in life [156] and extremely PBAs exhibit lower bone mineral density at the age of peak bone mass [157].

Pubertal timing is largely comparable between individuals born preterm and at term; however, women born very preterm may exhibit altered androgen profiles with an increased risk of polycystic ovary syndrome [158]. While fertility is generally preserved in early adulthood, VLBW individuals may experience reduced fecundity and a higher risk of pregnancy complications later in the fourth decade of life, including an increased incidence of gestational hypertension [159, 160].

Feeding difficulties and gastroenterological consequences

Feeding problems during early childhood are well recognised among premature children, owing to their profound impact on growth and family management dynamics [161]. Functional gastrointestinal disorders, including infantile colic, rumination syndrome, constipation and infant dyschezia, are more prevalent in preterm infants than in term controls, possibly reflecting maturational differences [162]. The lower the gestational age, the higher the use of anti-acid medications for gastro-oesophageal reflux disease among PBAs [163], who also show increased odds of eosinophilic oesophagitis.

The liver also bears the imprint of preterm birth. Beyond the common parenteral nutrition-related cholestasis, evidence links prematurity and low birthweight to a higher risk of nonalcoholic fatty liver disease [164]. This tendency appears especially pronounced in preterm-born individuals who experience accelerated postnatal weight gain [165]. Those who developed necrotising enterocolitis in the NICU show even higher rates of gastrointestinal disorders, such as diarrhoea, abdominal pain, inflammatory bowel symptoms, bowel obstruction, adhesions, malabsorption and, in the most severe cases, short bowel syndrome [166].

360-degrees care and the need for including families

The family plays a central role in the long-term care of extremely preterm infants, particularly during stable and chronic phases of disease. While acute conditions in the NICU, such as severe respiratory failure, sepsis or necrotising enterocolitis, require highly specialised, technology-driven care with a central role of neonatologists and other specifically trained professionals, family involvement becomes increasingly important as infants transition toward clinical stability and long-term follow-up. Health trajectories are shaped not only by medical interventions but also by the emotional, psychological and practical support provided by parents and caregivers. Family-centered care, promoting parental involvement in decision-making, skin-to-skin contact in the first weeks of life, and early nurturing interactions, has been shown to improve neurodevelopmental outcomes, reduce parental stress and strengthen the parent–infant bond. Supporting families through education, psychosocial support and structured rigorous follow-up is therefore an essential component of care. To further develop effective support strategies, the involvement of parent associations, national and international foundations and other stakeholders is decisive. These collaborative efforts would help to better understand the needs and challenges faced by families of preterm-born children and to inform the development of more tailored and effective support interventions. Importantly, emerging evidence indicates that the perspectives of individuals born preterm may positively differ from those of their parents over time [167]. As survival into adolescence and adulthood increases, incorporating the voices and lived experiences of survivors themselves is becoming essential to inform long-term care priorities and outcome measures.

Towards an integrated and personalised management of PLD-related multimorbidity

Given the current heterogeneity of terminology used to describe respiratory disease related to prematurity, including BPD [8], chronic lung disease, chronic lung disease of prematurity [50], chronic pulmonary insufficiency of prematurity [168] and PLD, efforts toward harmonising and standardising nomenclature are warranted, as they would facilitate comparison across studies, improve communication among clinicians and researchers, and ultimately enhance both research quality, clinical care and overall awareness toward the disease. The concept of PLD was consequently suggested as a life-course unifying framework for the diverse pulmonary consequences of preterm birth [37].

Moreover, despite the increasing understanding of the multisystemic nature of BPD and its long-term sequelae, current evidence remains insufficient to design a dedicated, holistic and multidisciplinary follow-up strategy for former preterm patients. We are still unable to accurately identify which subgroups would benefit the most from specific monitoring programmes, nor can we reliably predict which complications are most likely to emerge. Recently, a Swedish group proposed that preterm birth should be recognised as a chronic condition that requires long-term follow-up [95], that should encompass a multispecialty approach. Early identification of at-risk individuals, coupled with timely preventive and rehabilitative interventions, would indeed be essential to improve organ function trajectories, particularly respiratory and to limit or delay their premature decline.

These aspects are part of a larger project named PELICAN Clinical Research Collaboration launched by the European Respiratory Society with the objective to harmonise cross-sectional and longitudinal datasets globally, to describe the impact of preterm birth on lung health trajectories over its life course and to determine which neonatal and lifetime exposures contribute to the progression of lung disease in this vulnerable population [169].

To address some of these gaps, the "treatable traits" approach has been recently proposed [50] as a pragmatic framework to disentangle the heterogeneity of long-term outcomes in preterm-born individuals. This strategy, focusing on measurable and modifiable clinical or biological characteristics rather than diagnostic labels, could guide tailored interventions and generate new evidence on mechanisms and therapeutic targets within this population. Another aim of this strategy would be to promote awareness of prematurity-related disease and its comorbidities among adult-care specialists and general practitioners. There is still poor recognition of the lifelong consequences of preterm birth and PLD, and management remains fragmented across different providers, with minimal coordination between paediatric and adult care services. Notably, no specific guidelines exist for the follow-up and management of adults with PLD, frequently leading to a loss of monitoring continuity during the transition of cares. An integrated pathway connecting paediatric and adult respiratory (and beyond) services is, on this basis, increasingly necessary.

Given the interconnection between pulmonary disease severity and long-term systemic health, preventing or attenuating early lung injury could ultimately enhance overall quality of life and reduce the burden of comorbidities. With the exception of the potential advances of new therapeutic options mentioned above, neonatal clinical and preclinical research in this field is progressing slowly, with no major innovations in neonatal care over the past decade. Advancing this area would clearly benefit from stronger support and collaboration among all stakeholders, to accelerate research and development aimed at innovating and improving care for neonates, particularly those born extremely preterm [77].

Furthermore, while evidence on the effectiveness of standard treatments in patients with a history of prematurity remains scarce, there is ample documentation of the profound psychosocial impact of preterm birth on self-perception, quality of life and caregiver well-being [170]. It therefore appears both necessary and beneficial to engage patients and caregivers in the process of identifying the most impactful and modifiable traits of each prematurity-related morbidity, as well as those arising from their combination. A collaborative partnership with patients and other stakeholders would be essential to define meaningful care pathways, ensure adherence to lifestyle modifications and ultimately translate emerging knowledge into improved long-term outcomes.

Questions for future research

- Future work should reinforce multidisciplinary continuity of care and expand awareness of the multisystem burden carried by preterm-born individuals.
- Integrating global longitudinal datasets within a treatable-traits framework may unravel cross-system interactions, isolate exposures that drive disease progression and reveal actionable targets to guide holistic long-term care.
- A deeper understanding of the pathogenesis underlying the long-term outcomes of preterm birth will enable the development of new preventive or therapeutic strategies aimed at improving the maturation of the lungs and of other organs.

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