Moderate-to-late prematurity: understanding respiratory consequences and modifiable risk factors

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Given the short- and long-term respiratory risks associated with prematurity, all preterm infants, regardless of gestational age or BPD history deserve respiratory follow-up care.
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Abstract

As survival rates of preterm infants have increased due to advances in perinatal care, focus has shifted towards the profound long-term effects of prematurity. An extensive amount of evidence has shown increased susceptibility to chronic illnesses among preterm infants. While the onset of such conditions typically emerges during adulthood, their roots trace back to the early stages of life. Much of this interest has been directed towards short- and long-term consequences of extreme and very preterm birth. However, it has become apparent that, despite a limited risk of complications during the neonatal period, the moderate and late preterm population suffers from an increased likelihood of morbidity during the course of life. Considering the higher prevalence of moderate and late preterm births compared to extreme and very preterm births, understanding and investigating their health outcomes is essential to address the broader impact of prematurity. In this review, we will discuss the impact of moderate and late prematurity on lung development, function and how environmental factors impose these individuals to increased risk for respiratory morbidity during the course of life. We describe interventions during early life that may protect the moderate-to-late preterm population from adverse lung development and further deterioration by addressing modifiable risk factors.

Introduction

Every year, approximately 15 million infants are born preterm (*i.e.* before 37 completed weeks of gestation), putting the current global preterm birth rate at 11% [1]. Most preterm births occur between 32 and 37 weeks of gestation, also called moderate to late prematurity. Common short-term complications associated with moderate-to-late prematurity are well known and include respiratory morbidities, increased susceptibility to infections, hypoglycaemia, hyperbilirubinaemia and feeding difficulties. However, moderate-to-late prematurity is also linked to long-term risks that are less widely recognised by patients, caregivers and healthcare providers. These include chronic respiratory, cardiovascular and metabolic diseases, as well as cognitive, behavioural and emotional impairments [2–4].

It has become increasingly clear that both short- and long-term respiratory morbidity and impaired pulmonary function are not limited to extremely and very preterm infants diagnosed with bronchopulmonary dysplasia (BPD). Instead, respiratory morbidity and impaired pulmonary function are more prevalent in all preterm infants when compared to term-born individuals [5]. Gestational age at birth and intrauterine growth restriction have been shown to better predict pulmonary function in childhood than meeting BPD criteria [6]. Therefore, the respiratory consequences of preterm birth should be considered as a spectrum of disease [7].

To address this, the terms "post-prematurity respiratory disease" (PPRD) and "prematurity-associated lung disease" (PALD) have been introduced to encompass all individuals born prematurely who may have never received supplemental oxygen during the neonatal phase or otherwise do not meet the criteria for BPD but are confronted with respiratory morbidity after neonatal discharge [8, 9]. Acknowledging the respiratory burden associated with preterm birth is essential for optimising both prevention and management. Given the overlap between PPRD and PALD, this review will use PALD to represent respiratory morbidity in preterm infants.

Regarding the clinical management of PALD, the European Respiratory Society (ERS) guideline only focuses on the long-term management of children diagnosed with BPD and does not currently specify the management of infants and children otherwise diagnosed with PALD [10]. The American Thoracic Society (ATS) released a guideline outlining recommendations for PPRD in an outpatient setting [8]. However, neither guideline addresses crucial preventive measures related to environmental exposures that may further impact respiratory health and development in preterm infants.

In this narrative review, we will first discuss the effects of moderate-to-late prematurity on lung development and function and the respiratory consequences experienced throughout life. Next, we will explore the adverse and beneficial effects of environmental factors on respiratory health, while providing a comprehensive framework to optimise the respiratory wellbeing in moderate-to-late preterm infants.

Search strategy

To find relevant publications in peer-reviewed journals, the following databases were addressed: Cochrane, Google and PubMed. Search methods were combined according to the sections of this review (prematurity-associated lung disease, post-prematurity respiratory disease, bronchopulmonary dysplasia, (moderate–late) prematurity, preterm birth, lung development, short- and long-term respiratory disease, lung function, air quality, tobacco smoke exposure, *etc*.) Search results were evaluated to ensure they addressed the research question. Citation tracking was used to find additional relevant literature.

Respiratory consequences of moderate-to-late prematurity

Lung development and preterm birth

Moderate-to-late preterm infants have been underrepresented in research, with most studies focussing on very or extremely preterm infants diagnosed with BPD. Consequently, there is a significant gap in understanding the mechanisms of pulmonary injury related to preterm birth and perinatal factors in this population. This section reviews current evidence on mechanisms potentially involved in PALD.

Moderate-to-late preterm infants are born during the saccular stage of lung development [11]. Despite a significant expansion of the most terminal airways when compared to the canalicular stage, the effectiveness of the still immature gas-exchange interface remains constrained due to the limited overall surface area of the underdeveloped lungs, restricted capillary function and insufficient surfactant production. As a consequence, infants born moderate-to-late preterm often encounter respiratory complications such as transient tachypnoea of the newborn and infant respiratory distress syndrome (IRDS) [12].

Perinatal factors play a crucial role in impaired pulmonary maturation. Factors including pre-existing maternal disease, placental dysfunction, other pregnancy-related complications and exposure to antenatal steroids can disrupt the balance between oxidative stress and antioxidant defence systems [13]. Oxidative stress plays a key role in respiratory morbidity, initiating acute inflammatory damage in IRDS [14, 15]. The formation of reactive oxygen species (ROS) increases epithelial permeability for immune cells, allowing for a pro-inflammatory environment within the airway lumen. Activated immune cells continue to release ROS, cytokines, chemokines and cytotoxic agents, perpetuating inflammation and oxidative stress, which further promote lung injury. Hyperoxia further exacerbates damage in the lungs by inducing epithelial and endothelial injury and cell necrosis [16, 17]. Preterm infants, including those born moderate-to-late preterm, have immature antioxidant defences, making them more vulnerable to oxidative stress than full-term infants, especially with added stressors such as supplemental oxygen or inflammation [18–20].

Evidence has shown that increased oxidative stress in the respiratory system of preterm infants is not limited to the neonatal phase. During adolescence, oxidative stress, measured by 8-isoprostane levels, is higher in individuals born preterm when compared to term controls. Interestingly, no differences in 8-isoprostane levels between adolescents born preterm (<32 weeks) with and without BPD were found [21]. This implies that continued or chronic oxidative stress in the respiratory system is not solely related to BPD, but to prematurity itself and therefore may play a key role in the aetiology of PALD.

Recent studies have revealed a relationship between airway microbiome composition in preterm infants and the risk of BPD [22–25]. Microbial metabolites may induce an inflammatory environment by release of pro-inflammatory cytokines [26, 27]. Additionally, *in vitro* studies have found that pro-inflammatory mediators and cytokines were reduced upon exposure to *Lactobacillus*-derived factors [28, 29]. This evidence points towards an immunomodulatory role of the microbiome, suggesting that the composition of the microbiome could influence the severity and progression of inflammatory conditions, particularly in the context of respiratory health [30, 31].

Preterm infants have a unique exposome compared to term-born individuals, with factors such as chorioamnionitis, caesarean delivery, neonatal admission, perinatal antibiotics and formula feeding influencing microbiome colonisation [32]. Based on the proposed associations with BPD, microbiome dysbiosis may be an important risk factor for the development of PALD. Other mechanisms that play a significant role in the development of BPD, such as genetic factors, mitochondrial dysfunction, impaired repair mechanisms and cellular ageing, have not yet been investigated in PALD [33–37].

All preterm infants are at risk of sustaining lung injury during the perinatal period. Mechanisms associated with BPD, including structural immaturity, chronic inflammation, oxidative stress and microbiome dysbiosis may be implicated in PALD. However, significant gaps in our understanding of the preterm lung and other potential contributing factors to PALD persist, highlighting the need for further research into factors impacting the respiratory health of preterm infants.

Infancy and childhood: respiratory tract infections, wheezing and asthma

During the first years of life, rehospitalisation rates due to respiratory problems are two to four times greater than in term infants and are predominantly caused by viral lower respiratory tract infections (LRTIs) [38–41]. Apart from a higher incidence rate of LRTIs, moderate-to-late preterm infants also require prolonged hospital stays and endure a more severe course of disease, resulting in more admissions to the paediatric intensive care unit (OR 3.83, 95% CI 2.28–6.45) when compared to term infants [42]. Moderate-to-late preterm infants appear to get infected with respiratory viruses at an earlier median age, which may contribute to increased disease severity and duration of hospital stay [43, 44].

Increased susceptibility to severe viral respiratory tract infections and earlier onset may be explained by a smaller airway calibre, impaired respiratory development, ongoing inflammation and reduced innate and adaptive immunity in moderate-to-late preterm infants [45]. Incomplete maternal transfer of immunoglobulin G may contribute to increased vulnerability to early infections [46]. Microbiome dysbiosis further affects immune programming resulting in a prolonged relative immune deficiency [47]. Several genetic factors affecting the modulation of innate and adaptive immune responses in respiratory syncytial virus (RSV) infections have been found to play an important role in preterm infants [45, 48, 49]. LRTIs during the first years of life also bear potential long-term consequences [50, 51]. Several studies have shown strong associations between early life rhinovirus and RSV infections and the subsequent development of wheezing illnesses and asthma [45, 52–55].

Although studies have shown associations between early life RSV infections and wheezing during early childhood, causality has not been identified [56]. The outcome of several RSV prophylaxis studies, especially in preterm infants, supports a potential causal relationship [57, 58]. A randomised controlled trial (MAKI-trial) in moderate-to-late preterm infants showed a significant reduction of almost 50% in wheezing episodes during the first year of life after RSV prophylaxis [58]. A systematic review concluded no overall statistically significant benefits of monoclonal antibody therapy on the risk of recurrent wheezing and asthma. However, subgroup analysis showed a significant reduction (relative risk 0.35, 95% CI 0.14–0.86) in the development of wheezing and asthma in moderate-to-late preterm infants (32–36 weeks) [54]. Despite the indicative findings concerning the effects of RSV prophylaxis on subsequent wheezing, the MAKI trial found no significant reduction in physician-diagnosed asthma at 6 years of age or lung function regardless of prophylaxis [59]. Two Japanese studies in moderate-to-late preterm infants showed similar results to the MAKI trial and found no significant reduction of physician-diagnosed asthma during follow-up periods of 6 and 10 years [60, 61]. Data from immunological studies show that there is an important role for genetic and environmental factors, which may contribute to the short- and long-term morbidity following RSV infections in individuals born preterm [45, 62–65].

Although the effect of RSV prophylaxis on disease severity in moderate-to-late preterm infants has been shown, the debate regarding the clinical relevance to specific patient groups and cost-effectiveness is far from over [66]. Passive immunisation using palivizumab in moderate preterm infants, intended to prevent RSV infections and wheezing during the first year of life, has not been found to be cost-effective [67].

However, the potential long-term effects of RSV LTRIs were not addressed in this study. With the recent approval of nirsevimab and a maternal RSV vaccine (Abrysvo) in the European Union, prevention strategies addressing both short- and long-term effects of RSV infection may undergo significant changes in the near future as more research emerges [68, 69].

Long-term consequences such as recurrent wheezing and asthma are not uniquely related to early life RSV infections. During the last decades, multiple systematic reviews have assessed the impact of preterm birth on wheezing disorders and childhood asthma. Jaakkola *et al*. [70] reported an increased risk for all preterm infants (OR 1.07, 95% CI 1.072–1.075). However, after accounting for study heterogeneity, the summarised odds ratio was 1.366 (95% CI 1.303–1.432). Been *et al*. [71] conducted a meta-analysis of over 1.5 million children, confirming an overall increased risk of wheezing disorders (unadjusted OR 1.71, 95% CI 1.57–1.87; adjusted OR 1.46, 95% CI 1.29–1.65) in preterm infants compared to term infants. Further supporting these findings, Sonnenschein-van der Voort *et al*. [72] showed that preterm birth was associated with a higher risk of preschool wheezing (pooled OR 1.34, 95% CI 1.25–1.43) and school-age asthma (pooled OR 1.40, 95% CI 1.18–1.67), independent of birth weight. More recently, Pulakka *et al*. [73] identified long-term associations between preterm birth and obstructive respiratory diseases during early and mid-adulthood. Interestingly, their findings demonstrated a gradual association between gestational age at birth and the risk of developing chronic obstructive airway diseases in adulthood ($p<0.001$). This study also found that even those born late preterm (34–36 weeks) had an increased risk of asthma (Finland: OR 1.17, 95% CI 1.05–1.30; Norway: OR 1.26, 95% CI 1.20–1.33) and COPD (Norway: OR 1.41, 95% CI 1.22–1.63). These associations remained consistent even after adjusting for maternal health, lifestyle factors and perinatal events.

There has been a considerable debate whether respiratory morbidity after premature birth and recurrent wheezing and asthma are synonymous entities [74–76]. While preterm birth is associated with airway obstruction and bronchial hyperresponsiveness, the underlying mechanisms may differ [76]. A systematic review found that preterm infants, with or without BPD, had fractional exhaled nitric oxide (F_{ENO}) values comparable to those of term-born controls [77]. This suggests that, despite similarities in symptoms, eosinophilic airway inflammation is unlikely to be the primary cause respiratory morbidity in preterm infants.

A recent study used spirometry to identify four distinct PALD phenotypes. The four phenotypes included an obstructive phenotype, with further classification in reversible or fixed, prematurity-associated preserved ratio of impaired spirometry (PRISM), and dysanapsis, each exhibiting unique characteristics in bronchodilator response, measured F_{ENO} concentrations and early life characteristics [78]. In a subsequent study, researchers investigated the urinary proteome, an emerging biomarker source in lung disease that reflects metabolic and inflammatory processes associated with respiratory pathology. Findings demonstrated that children in the obstructive phenotype group had elevated proteins related to neutrophil and macrophage activity, whereas children in the PRISM group showed elevated proteins related to ongoing inflammation and T-lymphocytes. This variability in proteomic expression underscores the heterogeneity of pathophysiological mechanisms in PALD, highlighting the need for a personalised approach in managing and understanding lung disease in preterm populations [79].

As the underlying mechanisms of PALD are still unclear, evidence for optimal treatment options is currently lacking. Both the ERS and ATS guidelines recommend a trial of short-acting beta-2 agonists when encountering recurrent respiratory symptoms [8, 10]. Routine use of inhaled corticosteroids (ICS) is not advised; however, based on several registry-based cohort studies, ICS are more frequently prescribed to preterm infants when compared to term infants [80, 81]. Little is known about the effectiveness of ICS in PALD. The PICSI trial reported no significant lung function improvements with ICS alone in children born very preterm [82]. However, another randomised controlled trial in children aged 7–12 years old (born <34 weeks) found significant lung function improvements in ICS-naive children. This study also found that the use of ICS in combination with long-acting beta-2 agonists resulted in significant lung function improvements [83].

Regarding respiratory issues, moderate-to-late preterm individuals represent a heterogeneous group, with some experiencing no respiratory problems during childhood, while others face significant respiratory complications. The key challenge, however, lies in identifying those at risk for (long-term) respiratory disease and ensuring appropriate diagnostics and therapeutic care. Recent evidence suggests that PALD is a heterogeneous condition, warranting personalised treatment. Future research should focus on uncovering its underlying mechanisms and developing targeted therapeutic approaches.

Effects on lung function during childhood and adulthood: setting sail towards COPD?

In addition to exhibiting respiratory symptoms, moderate-to-late preterm infants experience impaired pulmonary function at various ages [84–87]. A recent systematic review showed that children and young adults born moderate-to-late preterm have worse expiratory airflow compared to those born at term [87].

These findings are important as lung function during early life acts as a predictor for lung function during adulthood. Functional vital capacity (FVC) and forced expiratory volume in 1 s steadily increase before lung function peaks at around 20–25 years of age. Subsequently, both measures decline with age due to physiological lung ageing [88]. Research has found that all individuals born prematurely are at risk of lung function trajectories below the anticipated normal range (figure 1). Deficits in pulmonary function may arise from inadequate growth and development, a shortened plateau phase or an increased rate of decline in lung function due to accelerated lung aging or factors inflicting damage [89].

Subnormal trajectories are associated with an increased risk of developing COPD during adulthood [90–92]. A recent study with a median follow-up period of 53 years concluded that individuals born moderate to very preterm had a significantly higher risk of COPD and obstructive lung function deficits [93]. Registry data from Norway and Finland showed that the odds of obstructive airway disease in individuals born moderate-to-late preterm were two to nearly four times higher than in the reference population born at full term [73].

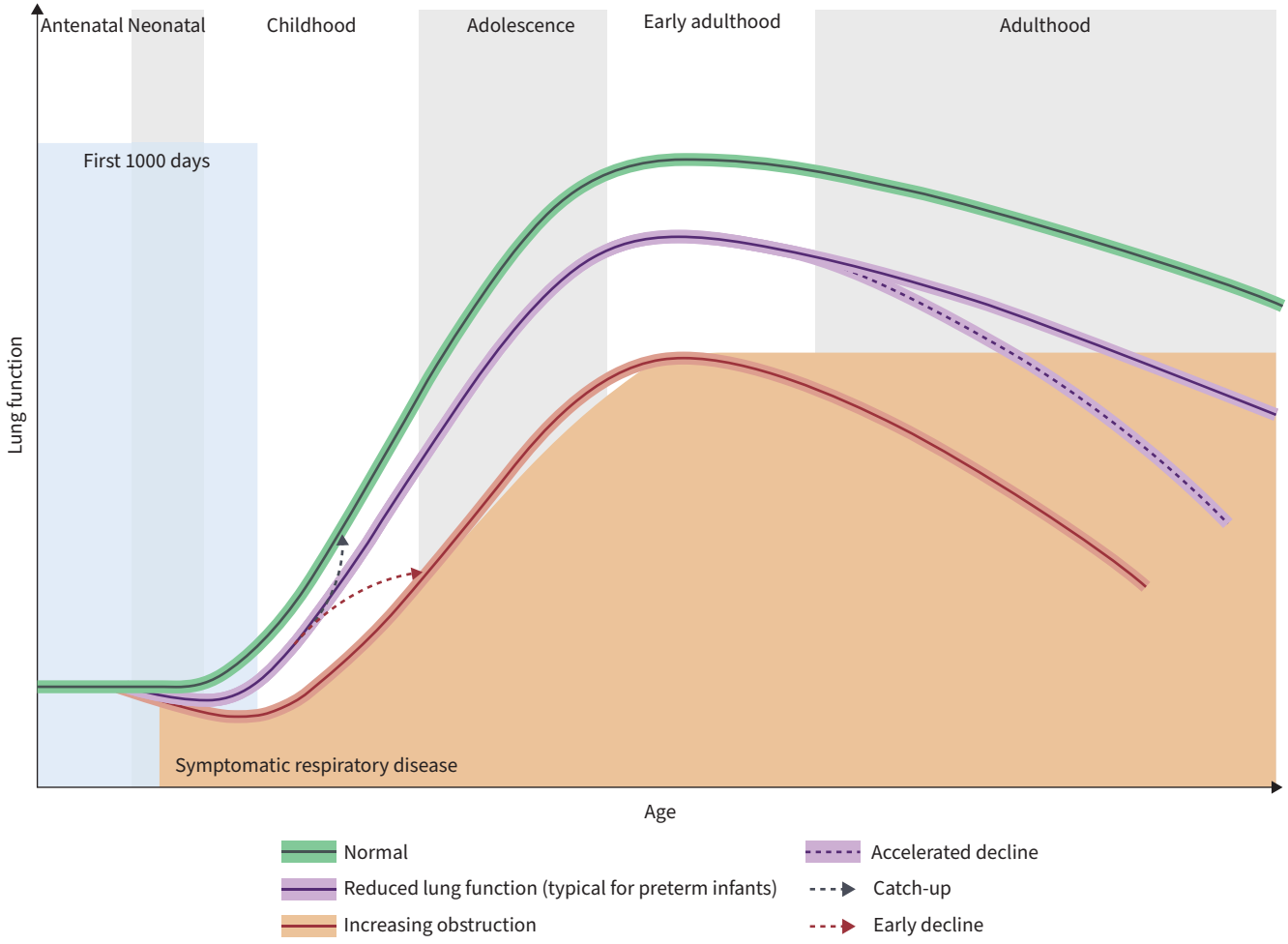

FIGURE 1 The lung function development of healthy and preterm infants based on current literature. Preterm infants do not reach peak lung function by early adulthood and are potentially experiencing accelerated decline. Literature shows that lung function development is plastic and that catch-up during childhood may be possible. Alternatively, harmful exposures could result in lung function characterised by early decline and symptomatic respiratory morbidity. The first 1000 days may be a window of opportunity to allow for interventions improving respiratory health.

It is suggested that preterm infants may experience a degree of "catch-up" in lung function as they reach adulthood. The extent and significance of this "catch-up" phenomenon are still the subject of debate [94–96]. Moreover, it remains uncertain which individuals are more likely to experience catch-up and which may face an accelerated decline in lung function over time.

In conclusion, individuals born moderate-to-late preterm do not achieve the anticipated peak lung function in early adulthood. They tend to follow a trajectory characterised by low lung function and potentially earlier decline. This increases the risk of COPD and COPD-like phenotypes. Exposures and external factors throughout life are believed to further influence the trajectory of lung function development [97].

Environmental factors affecting the risk of respiratory disease

The first 1000 days of life, often seen as the time from conception to reaching 2 years of age, is a critical period in which the foundations for physical and cognitive development and future health are established. During this period, the genome (our genetic makeup) and the exposome (our beneficial and harmful environmental exposures) interact to shape future health outcomes. Gene–environment interactions offer promising targets for health improvement. For COPD, the integration of a time dimension has recently been proposed as a critical factor alongside genetic predispositions and environmental factors [97]. The gene–environment–time (GETomics) approach is based on the concept that biological responses and clinical impacts of exposures vary by age and cumulative gene–environment interactions over time. For moderate-to-late preterm infants, this means that environmental factors may superimpose on the pre-existing risk of respiratory sequelae and impaired lung function resulting from prematurity throughout life (figure 2) [98].

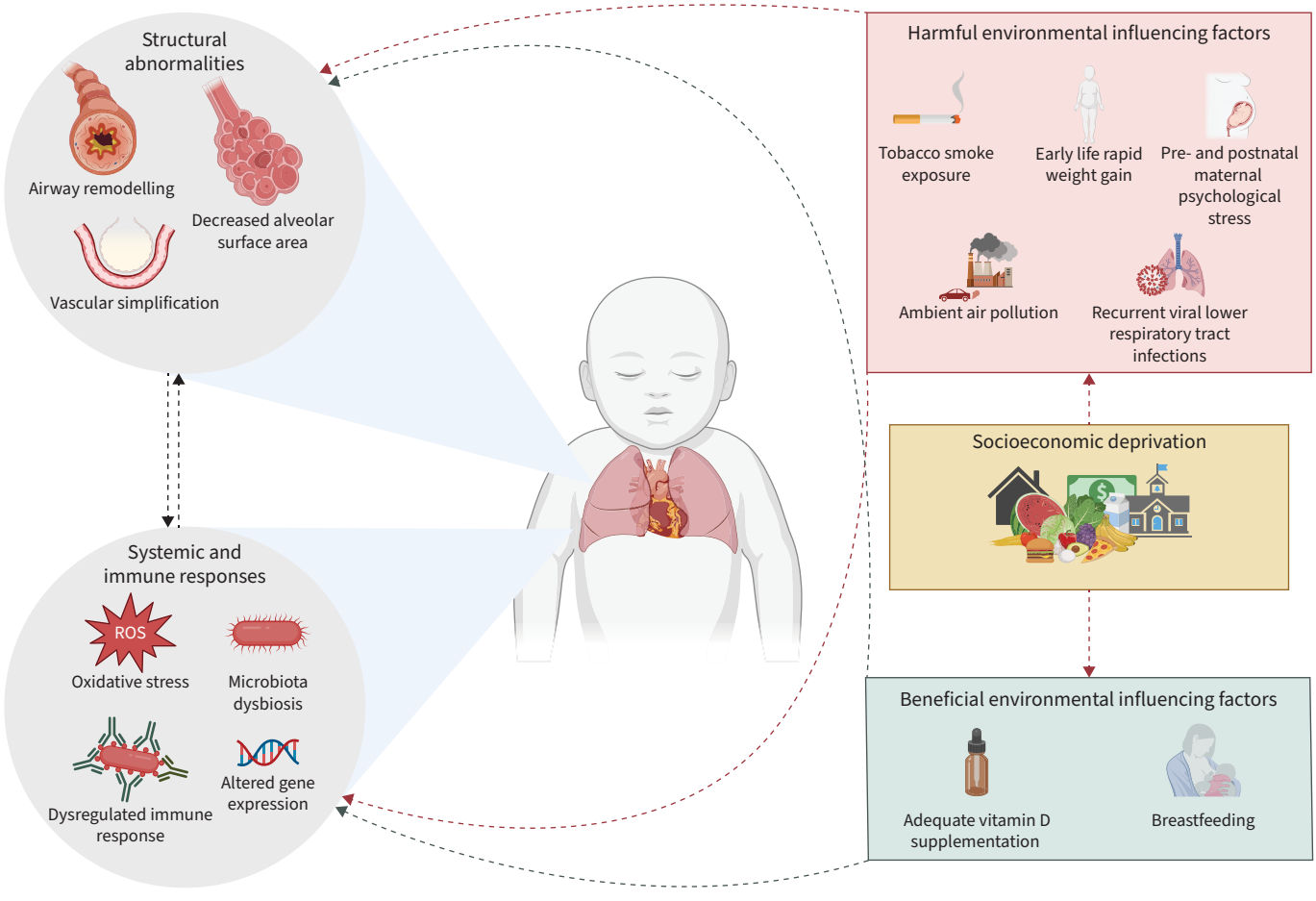

FIGURE 2 The preterm lung. This conceptual diagram summarises the current literature on the (potential) mechanisms involved in prematurity-associated lung disease and the effects of modifiable environmental factors on respiratory health in the preterm population. Socioeconomic deprivation modifies risk by increasing the likelihood of adverse exposures, which may work synergistically and therefore intensify their cumulative effects. At the same time, limited access to protective factors may result in poorer respiratory health. Figure created using BioRender. ROS: reactive oxygen species.

Understanding the impact of environmental factors on respiratory health is crucial for disease prevention and management. The first 1000 days might be a golden window of opportunity to introduce interventions, addressing modifiable factors, to optimise respiratory health. This section considers postnatal modifiable factors that influence respiratory health in individuals born moderate-to-late preterm.

Air pollution

Children are particularly vulnerable to air pollution, which can impair lung growth, increase the risk of asthma and cause long-term respiratory deficits [99, 100]. Prenatal exposure is linked to adverse birth outcomes and lung function impairments, whereas early life exposure, especially to traffic-related air pollution, can have lasting effects on respiratory health [101–105].

The BILD study aimed to determine the impact of pre- and postnatal particulate matter ⩽10 µm (PM_{10}) and nitrogen oxide (NO_2) exposure on lung function at 44 weeks of post-conceptional age in both preterm and term infants [103]. Utilising multilevel mixed-effects linear regression, the study found that exposure to low–moderate air pollution levels during the second trimester was associated with impaired lung function in both groups, with a more pronounced effect observed in moderate-to-late preterm infants. Interestingly, the study did not find a significant association between postnatal exposure to PM_{10} and NO_2 and lung function outcomes. This suggests that prenatal exposure, particularly during the second trimester, may have a more critical impact on respiratory development in preterm infants than postnatal exposure. Contrary to other studies, this study did not find a significant association between postnatal exposure to PM_{10} and NO_2 and lung function outcomes [105, 106].

A recent study in preterm infants found that increased levels of particulate matter ⩽2.5 µm and NO_2 were linked to significantly decreased FVC, with the most premature infants being the most affected [106]. In preterm infants with BPD, proximity to a major roadway resulted in increased activity limitations and was associated with more nighttime symptoms. For every 1 km increase in distance between a residence and a major roadway, the likelihood of activity limitations was decreased by 35% [107]. In this study, roadway proximity was used as a surrogate for traffic-related air pollution exposure, but no actual pollutant concentrations were measured. Other evidence has shown that individual particulate matter exposure does not relate well to stationary outdoor monitors, especially when taking indoor environments into consideration [108].

As infants and younger children spend most of their time indoors, exposure to indoor air pollution might be even more important than outdoor air pollution [109]. In a study involving 244 subjects with BPD, 75.8% reported having at least one indoor combustion source in the house. Among patients relying on respiratory support at home (oxygen, ventilator and/or tracheostomy-dependent), exposure to combustion-related indoor air pollution was linked to a higher risk of hospitalisation after initial discharge. A similar trend, although not statistically significant, was observed regarding hospitalisation in all other patients [110].

There is increasing awareness that air pollution is a preventable risk factor for a range of health problems in children. Whereas outdoor air pollution requires policy changes to reduce exposure on a population level, individuals can take steps to minimise their risks at home. Education and raising awareness are essential to optimise indoor air quality and therefore mitigate risks for preterm infants. We have listed recommendations to reduce exposure to indoor and outdoor air pollution in table 1.

Tobacco smoke exposure

Tobacco smoke exposure, both pre- and postnatally, is a major modifiable risk factor that harms lung development and increases the risk of adverse respiratory and neonatal outcomes [111–114]. During the last decade, electronic cigarettes (e-cigarettes), also commonly known as vapes, have become increasingly popular. E-cigarettes have been marketed as a safer alternative to conventional cigarettes. While some studies have found that e-cigarettes are less toxic than conventional cigarettes, the composition of e-liquids is largely unregulated, leading to a wide variety of constituents with unknown health consequences. The lack of strict regulation and control over these products raises concerns about their safety [115, 116]. In a survey carried out among 119 caregivers of individuals with BPD, 8% reported e-cigarette usage and 14% conventional cigarette usage. Importantly, households reporting conventional cigarette use were less likely to perceive e-cigarette emissions as harmful compared with nonsmoking households [117].

Despite decades of anti-smoking campaigns, up to 28% of preterm-born infants with BPD are still exposed to tobacco smoke resulting in increased hospitalisation rates and activity limitations [118, 119]. In preterm infants, exposure to tobacco smoke during pregnancy significantly increased the number of wheezing episodes [120]. Postnatal tobacco smoke exposure in moderate-to-late preterm infants is associated with

TABLE 1 Recommendations for caregivers on reducing indoor and outdoor air pollution exposure

Outdoor	Indoor
Opt for cycling or walking routes away from intersections and roads with heavy traffic.	Indoor air quality is frequently inferior to outdoor air quality. Consequently, it is advisable to ventilate continuously and to open a window and/or door for at least 15 min each day to facilitate ventilation.
Engage in physical activities earlier in the day when air quality tends to be better.	Ventilate at opportune times (avoiding rush hour) and in appropriate locations (particularly on the side not directly exposed to traffic).
Contemplate decreasing physical activity during periods of low air quality.	The detrimental effects of tobacco smoke are widely recognised. Aim for smokefree homes, as both second- and third-hand exposure are associated with adverse respiratory consequences.
When selecting a daycare centre, primary school or sports facility, consider its proximity to sources of air pollution.	Minimise emissions within one's control (*e.g.*, refrain from burning the fireplace or stove, lighting candles).
	Numerous substances are emitted during cooking, particularly when using liquefied petroleum and/or natural gas. When possible, ensure proper use of the extractor system and introduce additional ventilation during cooking.
	When showering or bathing, utilise the bathroom extractor and keep the bathroom door closed. After use, dry the bath and/or shower area. This practice helps control humidity levels in the home and reduces the growth of mould.

higher rates of bronchiolitis hospitalisation and can be seen as an important risk factor in the case of RSV infections [43, 121, 122]. It has been shown that tobacco smoke exposure or active smoking in individuals born prematurely amplifies lung function impairment during early childhood and adolescence [123, 124].

Tobacco smoke exposure can be especially harmful to infants and children with pre-existing lung disease. Smoking cessation programmes tailored towards pregnant women have been shown to be effective. A systematic review not only showed efficacy in terms of reducing the proportion of women continuing to smoke but also a significant reduction in adverse neonatal outcomes including low birthweight and preterm birth [125]. It has been shown that providing financial incentives improves smoking cessation, resulting in significantly increased abstinence rates [126, 127]. Based on the results of these studies, the National Institute for Health and Care Excellence guideline now includes incentives as part of standard practice [128].

Maternal stress

The psychological health of pregnant women has been linked to the development of wheezing episodes and/or asthma [129, 130]. It has been hypothesised that maternal stress can have a multitude of effects on the unborn child including alterations in immunologic, neuroendocrine and autonomic function as well as generating oxidative stress which all may be implicated in lung development [131–133]. Studies regarding postnatal maternal stress are broadly in line with the findings concerning prenatal stress. Two studies found that children who experienced continued maternal stress postnatally are at the highest risk of respiratory morbidity, recurrent wheezing episodes and childhood asthma [134, 135].

Childhood wheezing and asthma remain multifactorial respiratory diseases with evidence for both genetic and environmental origins of disease [136]. Although we are unaware of specific studies on maternal stress and wheezing and/or asthma in preterm infants, evidence for the role of psychosocial stress and the epigenetic mechanisms involved in wheezing episodes and/or asthma, particularly during the prenatal and early postnatal period, is currently growing [133]. It is conceivable that maternal stress during early life may serve as an additional risk factor for respiratory morbidity in preterm infants. Therefore, standardised screening and counselling for maternal stress, especially after preterm birth, (postnatal) depression or life events during and after pregnancy should be part of the follow-up care for individuals born preterm.

Breastfeeding

Numerous epidemiological studies have shown the benefits of breastfeeding to protect against a wide variety of infectious diseases during childhood and potentially to noncommunicable diseases later in life. Breastmilk contains multiple anti-inflammatory components, antimicrobial substances and agents which promote immune development, therefore enhancing the maturation of the immune system. Breastfeeding may play an important role in pulmonary development and in reducing the occurrence and severity of upper and lower respiratory infections [137, 138]. This data, however, is based on cohorts in which (moderate-to-late) preterm infants are not well represented and/or no separate risk analysis for preterm infants was carried out [139]. A notable exception is the study of Pandolfi *et al*. [140], in which almost 20% of infants with respiratory tract infections were preterm. In this case–control study, a time-dependent

protective effect of exclusive breastfeeding on the onset of viral respiratory tract infections was observed. Long-term effects of exclusive breastfeeding have also been shown in the general paediatric population. A recent systematic review concluded that a longer duration of breastfeeding was linked to a decreased risk of asthma up to 7 years of age [141]. Additionally, exclusive breastfeeding for 6 months or longer was associated with a 30% lower risk of asthma, showing significant potential benefits in asthma prevention.

In preterm infants with BPD, longer duration of breastfeeding was associated with fewer episodes of cough or chest congestion, less use of systemic steroids courses and fewer emergency department visits [142]. Therefore, like in the general paediatric population, breastfeeding should be encouraged for at least 6 months in moderate-to-late preterm infants.

Rapid weight gain

Adequate nutrition plays a key role in optimal growth and development, especially in preterm infants. Preterm infants may also experience rapid weight gain as they often experience catch-up growth, which is an increased rate of growth following low birthweight or fetal growth restriction. Preterm children more often exhibit a body composition with a higher percentage of absolute fat mass and a lower fat-free mass [143–145].

Rapid weight gain during infancy is associated with increased rates of childhood wheezing, asthma and impaired lung function [146, 147]. Moderate-to-late preterm infants exhibit a significantly higher risk of wheezing episodes compared to term infants regardless of rapid weight gain, with the strongest links between rapid weight gain and subsequent wheezing seen in preterm infants [72, 148].

Although the exact mechanisms linking rapid infant weight gain to childhood wheezing and asthma remain unclear, weight gain during infancy and obesity appear to be associated with pulmonary dysanapsis, which is a mismatch between lung tissue growth and airway size that leads to relative airflow obstruction [149]. Excess adipose tissue might also contribute to respiratory symptoms and impaired lung development by releasing adipokines, which are thought to be involved in airway remodelling, although this role is not completely understood [150]. As preterm infants face the highest risk of rapid postnatal weight gain, optimising nutrition in these infants may be crucial for supporting long-term respiratory health.

Vitamin D

Several systematic reviews and meta-analyses have shown a protective effect of vitamin D supplementation on acute respiratory tract infections during childhood [151–153]. In a study in Black preterm infants, a restricted intake of 200 IU per day resulted in a higher rate of parent-reported recurrent wheezing under the age of 12 months when compared to the daily recommended intake of 400 IU [154]. Lower levels of 25(OH) vitamin D in term-born infants with bronchiolitis are associated with increased disease severity [155, 156]. Vo *et al.* [157] found that serum total 25(OH) vitamin D levels below 20 $ng \cdot mL^{-1}$ in infants <12 months of age were significantly associated with the need for intensive care unit admissions (relative risk 1.72, 95% CI 1.12–2.64) and length of hospital stay (relative risk 1.39, 95% CI 1.17–1.65) when compared to levels of over 30 $ng \cdot mL^{-1}$.

The evidence on the potential protective effects of vitamin D supplementation on respiratory disease in moderate-to-late preterm infants is scarce. However, systematic reviews in term infants have shown the beneficial effects of vitamin D supplementation on the incidence of respiratory tract infections. Evidence has shown that low vitamin D levels are associated with a more severe course of disease in bronchiolitis. Therefore, to optimise respiratory health, vitamin D supplementation in moderate-to-late preterm infants is advised. Supplementation guidelines may exhibit regional differences based on average dietary intake.

Socioeconomic deprivation

Health outcomes during childhood, adolescence and adulthood are not equally distributed across the population. A wide range of factors, including social determinants such as education, employment status, income level, gender and ethnicity, play a critical role in shaping an individual's health. The lower one's socioeconomic position, the greater the risk of experiencing poor health. Poverty and childhood poverty as such play a critical role in child health. Pregnant women from a disadvantaged socioeconomic background are at increased risk of preterm labour [158]. Children from a disadvantaged socioeconomic background are more likely to be diagnosed with chronic illnesses, including asthma (OR 2.20, 95% CI 1.87–2.85) [159]. In the UK, research on paediatric asthma epidemiology revealed that children from deprived neighbourhoods experience higher rates of hospital admissions and longer stays compared to children from more advantaged backgrounds [160, 161]. A multicentre paediatric intensive care unit (PICU) study in England further found that these children accounted for the majority of asthma-related PICU admissions, invasive ventilation cases and asthma-related deaths [162].

Lee *et al.* [163] described a "clock/capacity/cost" model to better understand the limitations and structural problems in the case of poverty. Poverty not only increases the likelihood of harmful exposures but also amplifies their long-term effects on children's health. Children from low socioeconomic backgrounds face greater exposure to factors like air pollution, poor housing, maternal stress and second-hand smoke, all of which negatively impact lung development and respiratory health. Furthermore, these children often have limited access to healthcare services, nutritious food and safe living environments. Destigmatising poverty and addressing health effects fosters open communication, enabling healthcare professionals to provide targeted guidance and support.

Conclusion and recommendations

The respiratory burden of prematurity is significant and extends beyond individuals born extremely or very preterm with or without BPD. Individuals born moderate-to-late preterm are at risk for poor respiratory health, chronic respiratory disease and lung function impairments throughout the course of life. Recognising PALD as a spectrum of disease aids in acknowledging the potential respiratory burden of all infants born prematurely. However, the exact mechanisms underlying PALD are incompletely understood.

Additionally, there is a current lack of knowledge regarding the proportion of preterm children affected by PALD *versus* those who grow up with relatively stable lung health. Given its heterogeneity, personalised approaches may be required to improve long-term respiratory outcomes. Future research should aim to elucidate these mechanisms and identify targeted therapeutic interventions.

Traditionally, post-discharge management has focused primarily on extremely and very preterm infants with BPD, however our review underscores that moderate-to-late preterm infants and those without BPD also warrant structured follow-up. Environmental exposures, such as air pollution, tobacco smoke and respiratory infections, can further exacerbate long-term respiratory impairments. While managing treatable traits is essential, post-discharge care must also emphasise prevention of harmful exposures and early detection of individuals at risk (see table 2 for our healthcare provider recommendations).

A key component of this follow-up should include lung function monitoring. Given that lung function trajectories in preterm-born individuals are often suboptimal, routine assessments could serve as an early marker of respiratory health and risk stratification for conditions such as COPD later in life. Recent discussions in the field emphasise the importance of standardised lung function testing in clinical practice, and similar structured approaches should be applied to the moderate-to-late preterm population [164]. Although the optimal timing and frequency of lung function testing in these individuals remains uncertain,

TABLE 2 Outline of recommendations for healthcare providers regarding respiratory health in individuals born moderate-to-late preterm

Modifiable influencing factor	Recommendations
Air pollution exposure	Consider providing advice on practices that reduce both indoor and outdoor exposure to air pollution If specific sources are causing disturbance, offer health-related information and consider strategies to address or manage the issue (such as engaging in neighbourhood mediation) See table 1 for recommendations
Tobacco smoke exposure	Convince (expectant) parents of smoking cessation If parents are willing to participate in cessation programmes, opt for cessation programmes tailored to their situation
Maternal psychological stress	Consider standardised screening of maternal stress, especially after preterm birth, by using validated questionnaires and subsequent referral, if necessary
Breastfeeding	Encourage breastfeeding for at least 6 months in moderate-to-late preterm infants
Rapid weight gain	As preterm infants are at the greatest risk of rapid weight gain after birth with a negative effect on wheezing illnesses and potential other pulmonary outcomes, consider routine weighing and optimising nutrition
Vitamin D	To optimise respiratory health, vitamin D supplementation in moderate-to-late preterm infants should be provided according to regional supplementation guidelines Consider increased monitoring of vitamin D intake or determine serum levels to provide adequate vitamin D supplementation
Health inequality	Be aware of the accumulative effects of poverty on environmental exposures, limited protective measurements and limited access to medical care Destigmatise poverty and discuss financial challenges to better support families and children from disadvantaged backgrounds
Vaccination and immunisation	Vaccine hesitancy is believed to be associated with vaccine coverage Listen to the concerns of parents and address vaccine hesitancy by providing information and emphasising the benefits for individual and community health, especially in high-risk preterm infants

we propose that spirometry be incorporated into routine post-prematurity follow-up from school age onward, particularly for those with recurrent respiratory symptoms.

Beyond lung function, the role of biomarkers in PALD diagnosis and management is an emerging area of interest. While no specific biomarkers have been established at present, recent research into the urinary proteome has highlighted the heterogeneity of phenotypes and pathophysiological mechanisms in PALD. Research should focus on identifying reliable biomarkers that can aid in early detection and personalised treatment strategies.

Ultimately, we envision a structured follow-up framework for preterm infants, with increased surveillance for recurrent respiratory symptoms in early life and early lung function tracking in childhood. Standardising these approaches will allow for earlier identification of at-risk individuals, enabling timely interventions to optimise lifelong respiratory health.

Points for clinical practice

- Given the short- and long-term respiratory risks associated with prematurity, all preterm infants, regardless of gestational age or BPD history, deserve respiratory follow-up care.
- Monitoring should focus on early detection of respiratory disease and promoting preventive measures, as environmental factors may exacerbate the pre-existing risk of respiratory sequelae in these individuals.

Questions for further research

- What are the underlying mechanisms of PALD across the full spectrum of prematurity and how do they contribute to the respiratory burden in the preterm population?
- How can we address the heterogeneity of PALD to determine if personalised therapeutic options could improve respiratory health?
- What targeted interventions could reduce the risk of chronic respiratory morbidity in the moderate-to-late preterm population?

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