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# Influences of environmental exposures on preterm lung disease

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## Abstract

**Introduction:** Environmental factors play a critical role in the progression or resolution of chronic respiratory diseases. However, studies are limited on the impact of environmental risk factors on individuals born prematurely with lung disease after they leave the neonatal intensive care unit and are discharged into the home environment.

**Areas covered:** In this review, we cover current knowledge of environmental exposures that impact outcomes of preterm respiratory disease, including air pollution, infections, and disparities. The limited data do suggest that certain exposures should be avoided and there are potential preventative strategies for other exposures. There is a need for additional research outside the neonatal intensive care unit that focuses on individual and community-level factors that affect long-term outcomes.

**Expert opinion:** Preterm respiratory disease can impose a significant burden on infants, children, and young adults born prematurely, but may improve for many individuals over time. In this review, we outline the exposures that may potentially hasten, delay, or prevent resolution of lung injury in preterm children.

### Keywords

Bronchopulmonary dysplasia; environment; outpatient; smoke; electronic cigarette; air pollution; daycare; disparities; race/ethnicity; chronic lung disease

## 1. Introduction

Premature births account for over 10% of the live births worldwide, and rates of preterm births are increasing based on data from high-income and high-middle-income countries [1]. A common complication of preterm birth is post-prematurity respiratory disease (PPRD), which can encompass many respiratory phenotypes, with bronchopulmonary dysplasia

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being best known [2]. Bronchopulmonary dysplasia (BPD) was characterized in 1967 by Northway *et al.* as maldevelopment of the alveoli, airways, and pulmonary vasculature based on clinical, radiological, and pathological findings [3]. Despite advances in neonatal care, including oxygen delivery and ventilation, exogenous surfactant, surgical techniques, and nutrition, rates of BPD have remained constant for the past 2 decades, due in part to the increased survival of infants of earlier gestational ages [4,5]. Incidence rates of BPD vary worldwide based on gestational ages, birthweights, and survival rates across populations (17–75%) [6]. As many as 50,000 infants in the USA and almost 15 million infants worldwide may be affected annually [2,7].

Preterm survivors with PPRD are subject to respiratory disease that can persist into adulthood and may have life-long consequences, including adverse effects on lung function [8,9]. Thus, it is critical to identify factors that may worsen or ameliorate the course of respiratory disease in individuals born prematurely and intervene when possible. While heritability studies have demonstrated a strong genetic component for the development of BPD (53–82% of the variance in the liability for BPD) [10,11], these studies are based on phenotyping BPD at 36 weeks post-conceptual age [12]. At this particular time point, many infants may still be in a relatively stable NICU environment and not subject to environmental variation as they would be following discharge. Given that early childhood events (e.g., a history of pneumonia) in otherwise healthy individuals can have adverse effects on adult lung function [13,14], it is highly likely that early life events, including environmental exposures post NICU can also influence the course of respiratory disease in preterm individuals as they age. In this study, our goal is to provide a broad overview of the environmental factors that have been associated with respiratory outcomes in preterm individuals after NICU discharge, which is lacking in the recent PPRD literature. We do acknowledge that there are no data on the relative contributions of genes versus the environment to later phenotypes of PPRD outside the NICU, and that the relative contributions of specific environmental factors discussed to the variation seen in PPRD are unknown. Understanding the interactions between genes and the environment should be a targeted area of research to help better understand and improve long-term respiratory outcomes in preterm survivors of PPRD.

Given the paucity of the literature, we have preferentially noted studies of outpatients with preterm respiratory disease, but also commented on studies of preterm outpatients and studies for the development of BPD in inpatients where data on outpatients with BPD are lacking. It should also be noted that many studies of environmental factors are single-center studies with limited sample size, which may lead to limited detection of effects due to underpowering. The paucity of evidence also prohibits a more structured approach such as a systematic review or meta-analysis. English-language studies discussed in this review were identified through semi-systematic searches of PubMed between 12/21/2020 and 3/23/2021, through the authors' knowledge of the topic, and through citation review.

## 2. Air pollution

Ambient air pollution has a demonstrable and detrimental effect on lung function throughout the lifespan from childhood through adulthood [15]. There are likely multiple patho-

physiological mechanisms that may affect respiratory status, including oxidative stress, inflammation, endocrine disruption, and gene–environment interactions [16]. Common sources of air pollution include combustion from both indoor and outdoor sources, including secondhand exposure to environmental tobacco smoke (ETS). While maternal smoking has been linked with an increased risk (OR: 1.16–2.21) of the development of BPD in preterm infants, adverse outcomes have also been noted in outpatients with BPD [17].

### 2.1. Environmental tobacco smoke

Even full-term infants are at increased risk for decreased lung function, altered respiratory chemoreception, and rates of childhood asthma with exposure to ETS [18]. Ongoing respiratory disease at 2 years of age (hospitalizations, use of inhaled steroids, inhaled bronchodilators, and/or diuretics, asthma, reactive airway disease, etc.) has been reported in one study of 587 preterm infants to be 2.1-fold more common in those exposed to ETS [19]. Another study of 124 preterm infants observed that acute care use during the first year of life was more common (62% vs. 39%) in infants exposed to ETS [20]. Yet another study of 352 infants with BPD found a trend toward a higher frequency of inhaled steroid use (86% vs. 76%) with ETS exposure, but this was not adjusted for socioeconomic factors, and no other respiratory outcomes were found to be associated with ETS exposure [21]. Although use of inhaled corticosteroids in ETS exposed children may reflect provider treatment preference; use of inhaled corticosteroids in this population may also be a biomarker for more significant respiratory symptoms.

Additionally, the specific phenotype of wheezing may be more frequent in preterm individuals exposed to ETS. Bronchial asthma at 2 years of age was reported to be more common with exposure to ETS in a study of 98 preterm infants [22]. Cohort studies of preterm individuals report that wheezing at the later time point of 6–8 years of age can be 2.1 to 3.1-fold more common in those exposed to ETS [23,24]. This symptomatology may also be detected in lung function testing, as one study of 200 preterm children aged 4–12 yrs found a more rapid rate of decline in spirometric measures of small airway disease ($FEV_1$/FVC and $FEF_{25–75}$) in those exposed to ETS [25].

The effects of ETS may not be limited to respiratory symptoms alone. Although not conclusive, one study of 352 infants with BPD found a possible trend toward delayed weaning of home supplemental oxygen by 2 months with ETS exposure (rank sum $p = 0.13$) [21]. If there is a delay in weaning of oxygen, it may be related to physiological causes rather than socioeconomic factors (e.g., access to follow-up care) as another study in an overlapping population of 140 infants with BPD found 2.4% lower oxygen saturation nadirs and a pattern of more desaturation events in overnight polysomnography with ETS exposure [26].

However, some studies have not observed any differences in respiratory outcomes for infants with BPD exposed and not exposed to ETS [27,28], including later lung function at 8 years of age [29]. It is important to note that variation in the assessment of ETS exposure may lead to differences in outcomes between studies as different exposure questions have differing sensitivities in the BPD population perhaps related to caregiver biases [30]. Biomarker measurements of ETS exposure may be less biased than caregiver's report. For example,

higher hair nicotine levels (a biomarker of ETS exposure) have been shown to be associated with an increased risk of hospitalizations and activity limitations in infants with BPD on home respiratory support, and may be a better predictor of exposure than caregiver report [31]. In addition to caregiver reporting biases, other potential confounding factors may include socioeconomic determinants, which cannot be eliminated with the use of biomarkers [32]. Lastly, the effects of ETS may also span across generations; murine studies suggest that ETS may alter epigenetic regulation of HIF-1α through specific micro-RNAs resulting in an increased incidence of BPD in progeny mice [33].

### 2.2. Other air pollution

Although the literature surrounding ETS is most robust, other sources of ambient air pollution that have relevance to PPRD have been studied. Road traffic is a notable source of outdoor air pollution; in one study of 784 infants with BPD, the likelihood of activity limitations decreased by 35% with every 1-km increase in distance between the residence and a major roadway, but no change in acute care usage was seen [34]. In this study, infants and children who were nonwhite or had lower estimated household incomes were more likely to live closer to major highways, suggesting that environmental health disparities may influence respiratory outcomes in children at risk for pulmonary morbidities. A study from a Swedish birth cohort found that higher exposure to traffic-related air pollution during the first year of life was associated with an odds ratio of having an FVC and $FEV_1$ less than the lower limit of normal [35].

The mechanism for the effects of road traffic and other outdoor air pollution on respiratory outcomes in PPRD is not known. Of note, some common constituents of air pollution, such as carbon monoxide and hydrogen sulfide may serve as gasotransmitters as these gases have been found to have protective effects against lung injury in rodent models of BPD [36,37]. However, human data with concentrations similar to outdoor environmental exposures are lacking. Given that infants and young children spend the majority of their day in indoor settings, the effects of indoor combustion may also be problematic. One study of 224 infants with BPD found that 76% were exposed to at least one source of combustion in the home (smoking, gas stove or heat, wood stove, etc.), and this exposure was associated with 6.0-fold increased risk of hospital admission for infants/young children on home supplemental oxygen or ventilators [38]. Although studies have shown the beneficial effects of air purifiers in improving asthma symptoms in children [39]; the data are limited on whether this intervention improves respiratory symptoms in children with BPD [38].

### 2.3. Secondhand vaping exposure

Secondhand exposure to emissions from electronic cigarettes and other vaping devices is an emerging exposure. A 2017 study of 119 infants with BPD in the US found that 8% had household members reporting current electronic cigarette use, while households with conventional tobacco cigarette use were 11.3 times more likely to report electronic cigarette use as well [40]. PPRD outcome data with exposure to vaping emissions is lacking, but hypersensitivity pneumonitis in an adult non-user [41] and an increased risk of asthma exacerbations have been reported in adolescent non-users exposed to secondhand emissions [42]. Furthermore, limited data from murine models suggest that prenatal and early life

exposures to electronic cigarette emissions may impair postnatal lung growth and r *Wnt* signaling in the lung [43,44].

## 3. Disparities

The interplay between social, economic, and racial/ethnic factors in health outcomes is complex. First, the underlying disease process may be more common in certain groups. Data from the PROP study suggest that African-American infant race, male sex, and public insurance coverage are all associated with an increased risk of post-prematurity respiratory disease and increased respiratory morbidities over the first 12 months of life (corrected) [27]. Disparities related to race/ethnicity, maternal age, insurance status, immigrant status, etc. may lead to differing rates of outpatient follow-up and acute care use for preterm infants [45–47]. Structured transition-to-home programs may decrease the disparity of certain outcomes, such as emergency department visits [48]. Specific factors that have been studied in the long-term outcomes of preterm lung disease include race/ethnicity, health insurance, and household income, each of which is described in more detail below.

### 3.1. Race/ethnicity

Wheezing in former preterm individuals has been found to be more common among African-Americans. It is unclear whether a multiplicative effect between race and preterm birth exists or whether the relative rate of wheezing in preterm African-Americans compared to whites is similar to that for full-term individuals with asthma owing to genetic or environmental factors (asthma is more common in African-Americans and some Hispanic subgroups compared to whites). The TOLSURF study group reported that 69% of the relationship between persistent wheezing and maternal race was due to African-American race in a group of 420 preterm infants, whereas a diagnosis of BPD only accounted for 10% [49]. It is unclear whether the increased wheezing translates into an increase in acute therapy. A Kaiser Permanente study of 1436 infants born prior to 34 weeks found that African-Americans were 4.3 times more likely to receive oral beta-agonists, where Hispanic infants were 38% and 72% less likely to receive inhaled beta-agonists or inhaled corticosteroids, respectively [50], but a single center of 135 infants born prior to 32 weeks found that whites were 2.9 times and 2.1 times more likely to report rescue beta-agonist use in the past 7 days and systemic steroids since last clinic visit, respectively [51]. In addition, a NICHD study of 1405 preterm infants found that race was not a predictor of rehospitalization within the first 18 months of life [52]. In addition to wheezing, race/ethnicity may also be associated with obstructive sleep apnea for unclear reasons. One study of 140 infants with BPD reported that nonwhite infants and young children had a 33% higher obstructive apnea-hypopnea index compared to their white counterparts, while the white subjects had a 61% higher rate of central apneas [26]. Other factors including the presence of allergic and non-allergic rhinitis and obesity may underlie differences in frequency of OSA [53], and the presence of these conditions in children with PPRD, may be influenced by disparities in environmental and nutritional exposures.

### 3.2. Health insurance

Due to prolonged initial hospitalizations and frequent outpatient visits and readmissions after discharge, preterm infants with BPD or chronic respiratory morbidities accumulate significant healthcare costs, requiring assistance from third-party payers [54]. A 2014 survey of 183 NICU follow-up clinics estimated that in the US almost half (45%) of high-risk NICU graduates are covered by public insurance as their primary means of health-care coverage [55]. Infants with BPD have been reported to have longer initial hospitalizations if covered by public insurance compared to private insurance, but it is unclear if this is related to increased comorbidities in the population with public insurance and/or socioeconomic reasons [56]. At the time of discharge, a study of 24,151 U.S. preterm infants born prior to 36 weeks found that infants with private insurance were more likely to be discharged with home oxygen and apnea monitors, despite having no different incidences for apnea or BPD in the NICU [57]. Similar to other diseases, differences in outpatient outcomes for infants and children with preterm respiratory disease have been observed in those covered by private versus public insurance, although it is not clear whether these differences stem from differences in access to care associated with different means of health-care coverage or other disparities associated with insurance coverage (e.g., income). For preterm infants, Medicaid coverage has been associated with a higher risk of readmission in most studies [46,47,58], but not all [51]. These increased rehospitalizations could be related to a reported association between Medicaid and the development of asthma (OR: 1.8) among preterm infants [59].

### 3.3. Income

There are limited data regarding the role of household income in preterm respiratory disease, but financial burdens can be a stressor for families with preterm infants. A 1993 study of 59 infants with BPD discharged home on supplemental oxygen found that two-thirds of these families experienced increased financial stress, which, in turn, was associated with emotional stress [60]. In terms of outcomes, a single-center study of 135 infants with preterm respiratory disease suggested that lower median household income was associated with a 2.8-fold increased risk of activity limitations [51]. A study of 94 infants and children with BPD on home ventilators found that mortality was associated with lower median household income and that 93.3% of deaths occurred in subjects that resided in zip codes with income less than the median state household income [61].

### 3.4. Adherence

A limited number of studies have demonstrated that non-adherence with prescribed medical care can have adverse effects on outcomes for infants with BPD. Some factors associated with non-adherence may be related to social determinants of health and/or health disparities. In terms of follow-up, a Korean study of 3063 preterm infants found while the presence of BPD improved attendance in NICU follow-up clinics at 18–24 months of age (overall rate of follow-up: 65.4%), whereas infants with high birth weight, low NICU volume, siblings, foreign maternal nationality, and high 5 min APGAR scores were less likely to follow up [62]. A smaller U.S. study of 58 infants with severe BPD found that 26% never attended follow-up clinic with another 16% stopping attendance before discharge from clinic with nonattendance being associated with longer travel times to clinic [63].

In terms of medication adherence, a study of 33 infants with BPD found that caregivers reported medication adherence overestimated medication possession (38.8% of all chronic respiratory prescriptions) based on prescription claims data [64]. This study also reported that higher medication possession was associated with decreased odds of visiting the emergency department (OR = 0.75 for a 10% increase in actual medication possession), activity limitations (OR = 0.71), and PRN beta-agonist rescue medication use (OR = 0.84), while lower medication possession was associated with caregiver concerns about medication efficacy and side effects. In addition to medications, there may also be non-adherence with home supplemental oxygen. One study of 137 infants with BPD on home oxygen found that 32.1% of infants were weaned off by caregivers without physician supervision; factors associated with a higher odds of unsupervised weaning, included the diagnosis of pulmonary hypertension (OR = 2.61) and coverage by public insurance (OR = 2.46) [65]. Last, with regard to other preventative care, a systematic review of palivizumab compliance reported that RSV hospitalizations were reduced in compliant groups (RSV admission rates ranging 1.2–1.4% in compliant infants in reported studies) compared to non-compliant groups (RSV admission rates of 1.7–3.1%); factors that were associated with non-adherence included Medicaid coverage, minority status, caregiver perception of non-efficacy, and lack of transportation [66].

### 3.5. Care center variation

Although expert-based approaches to managing BPD have been published [67], no evidence-based guidelines have been published for the management of PPRD. In contrast, the American Heart Association and the American Thoracic Study have published guidelines for the care of children with pulmonary hypertension, including specific recommendations for pulmonary hypertension secondary to BPD [68]). The absence of widely adopted guidelines for managing children with BPD in the outpatient setting can lead to substantial variation in care. For example, a snapshot study of inpatients with severe BPD found significant variation in the use of inhaled corticosteroids, inhaled beta-agonists, and diuretics, but not systemic corticosteroids among eight U.S. tertiary care centers [69]. Similarly, a registry-based study of 162 outpatients with severe BPD from 7 tertiary care centers reported differences in percentage of those on any home respiratory support, home positive pressure ventilation, diuretics, inhaled corticosteroids, and pulmonary vasodilators between centers, but did not observe differences in acute care use [70]. Nevertheless, variation in care could potentially alter outcomes; one tertiary care center in Colorado found an increase in survival for patients with severe BPD and tracheostomy from 50% to 85% during initial hospitalization with the initiation of an interdisciplinary program for coordinated care and a non-significant reduction of readmissions by 47% [71,72].

## 4. Geographic factors

### 4.1. Altitude

The diagnosis of bronchopulmonary dysplasia is frequently made on the basis of respiratory support at a specified age [12], which in turn is influenced by the goal oxygen saturation for a patient. Geographic factors, specifically altitude, can influence oxygen saturations and thus the prevalence of BPD [73–75]. A study of 561 preterm infants born in Utah within the

Rocky Mountains found that correction for altitude reduced the rates of moderate-to-severe BPD by almost 50% [76]. However, in addition to the decreased partial pressure of oxygen found at higher altitudes, altitudes may also have physiological effects, such as delayed closure of ductus arteriosus or systemic inflammation, that could increase the rates of BPD [77,78].

### 4.2. Other geographic factors

Multiple geographic factors may also interact to alter outcomes through complex or poorly defined mechanisms. For example, one study conducted in Ontario, Canada identified colder temperatures, increased ozone levels, and lower income neighborhoods as risk factors for hospitalizations for RSV in children between the ages of 0 and 36 months [79]. Similar data for preterm infants with respiratory disease is lacking. Geography also may also play a role in the duration, and therefore risk, of certain environmental exposures. For example, the duration of the RSV season has been reported to be a prolonged 9–10 months in Taiwan [80,81]. It should also be recognized that geographic factors that impact respiratory outcomes are not static. Climate change may have an effect on host susceptibility (e.g., young children may be more vulnerable to fluctuations in ambient temperature), pathogen propagation, air pollution, etc. [82]. Additionally, it has been suggested that the spread of SARS-CoV-2 can be influenced by climatic factors, including humidity, temperature, and precipitation [83]. Studies have not addressed the relationship between temperature and humidity differences and the overall health of children with BPD or infectivity with viral pathogens.

## 5. Nutrition

Lung function on infant pulmonary function tests has been shown to be proportional to increases in height and weight [84]. Somatic growth (in particular linear growth) [67] in early life is critical, as most catch-up lung growth is thought to occur by 2 years of age [85]. Given that severe BPD in preterm infants has been associated with higher rates of growth delay compared to preterm infants with mild BPD and full-term infants through 6 months corrected age [86], it is problematic that infants who may benefit most from catch-up lung growth, are at greatest risk for growth delay. However, one study of pulmonary function tests in 6 year old patients with BPD found that lung function was not associated with growth percentiles at 2 and 6 years of age [87].

### 5.1. Human milk

Unfortunately, there are limited data regarding nutritional strategies to improve long-term respiratory outcomes in infants and children with preterm lung disease. Human milk may have effects on respiratory outcomes in BPD through alterations in the microbiome, immune modulation, or lung injury/repair through specific metabolites [88]. A meta-analysis of human milk feeding reported that both exclusive and partial human milk feeding were associated with a reduced risk for developing BPD [89]. In terms of outpatient studies, one study of 188 infants with BPD demonstrated that a longer duration of human milk consumption was associated with reduced risks of emergency department visits, systemic

steroid courses, and cough or chest congestion, and a trend toward a lower risk of rehospitalizations [90].

### 5.2. Vitamins

Vitamins are a critical part of nutrition and some studies have been published on their role in the development of BPD, but not necessarily longer-term outcomes. A meta-analysis of vitamin D levels at birth found that both vitamin D deficiency and low vitamin D levels at birth were associated with an increased risk of developing BPD [91]. The effects of vitamin A supplementation are unclear with regard to the development of BPD [92]. Similarly, most studies have reported non-significant reductions in BPD with vitamin E supplementation, but at least two studies raised concern of an increased risk of necrotizing enterocolitis [93].

## 6. Infection

The likelihood of adverse outcomes with respiratory viral infections in infancy is increased with a history of preterm lung disease [94]. Respiratory infections may alter subsequent lung function through adverse effects on immune responses, chronic pathogen colonization, or microbiome changes, and injury repair [95]. A national study from Taiwan reported that a history of BPD was associated with a 1.8–14.4-fold increased risk of hospitalization for respiratory syncytial virus (RSV) compared to gestation and age-matched controls [80]. Acute care use for respiratory viral infections is also more likely to occur in younger infants [80,96]. In addition to short-term outcomes, significant respiratory infections may have long-term consequences as well, although long-term data are limited for preterm infants with respiratory disease. The Tucson Children's Respiratory Study reported that a history of radiologically ascertained pneumonia during the first 3 years of life for healthy children was associated with persistent airway obstruction and asthma through 11 years of age and impaired lung function into early adulthood [14].

Factors that increase the risk of contracting infections may be problematic as well, presumably one of these being daycare. A study of 111 infants and young children with BPD found that attending daycare was associated with a 3.7-fold increased risk of emergency department visits, a 2.2-fold risk of systemic corticosteroid use, a 2.4-fold risk of antibiotic use, and a 2.7-fold risk of increased number of days with trouble breathing [97]. However, another study of 715 very low birth weight (≤1500 grams) infants found that BPD and daycare were not necessarily synergistic factors for developing respiratory problems [98].

Conversely, prophylaxis for viral infections may prove beneficial for some respiratory outcomes. The use of palivizumab as RSV prophylaxis can result in reduced wheezing episodes and hospitalizations during the first 2 years of life; however, it may not necessarily improve lung function in later childhood or adolescence [99,100].

## 7. Other environmental factors

There are limited studies on other modifiers of preterm lung disease. Of note, one prospective study of 124 very low birth weight infants found a 4.4-fold increased risk

for acute care use for respiratory illnesses with pest exposure requiring exterminators [20]. An autopsy study from 1988 reported a possible association between asbestos and BPD, possibly secondary to impaired lung clearance, but control data were lacking [101].

## 8. Gene–environment interactions and epigenetic changes

Associations between genetic variants and preterm respiratory disease are limited. Three genome-wide association studies of BPD have not identified any common genetic variants between them [102–104], and there are no replicated studies of any modifier gene–environment interactions. Data from the TOLSURF study suggest genetic variability in corticosteroid response may exist based on an SNP in the *CRHR1* (Corticotropin-releasing hormone receptor 1) gene [105]. Additionally, while there are at least 2 studies reporting that epigenetic profiles differ between preterm infants with and without BPD [106,107], there are no studies confirming what environmental factors may be associated with these changes.

## 9. Conclusions

Individuals born prematurely are at high risk for developing multiple phenotypes of respiratory disease, which can persist into adulthood [2]. Owing to lung disease in early life, individuals with BPD and other manifestations of preterm respiratory disease may be on lower lung function trajectories throughout their lifespans [108,109]. These trajectories may be further altered by events during infancy and childhood including environmental factors. Mitigating harmful factors and promoting preventative ones may improve long-term respiratory outcomes.

## 10. Expert opinion

Preterm birth (and its respiratory sequelae) are unfortunately common worldwide despite efforts to decrease preterm birth rates and prevent the development of respiratory disease during the initial hospitalization. This may be partly due to improved survival of preterm infants with increasing access to advancing technologies. Nevertheless, respiratory diseases associated with prematurity impose a substantial burden on individual patients, their families, and society as a whole. Ongoing studies suggest that the respiratory effects of preterm birth may persist into at least young adulthood for some individuals. Due to the small numbers of surviving extremely premature infants in decades past, the extent to which preterm birth affects outcomes in middle and old age is unknown.

In combination with the environmental studies outlined below, it is critical to also improve our phenotyping of respiratory disease of prematurity. Currently, most definitions are based on a single time point of 36 weeks corrected gestational age, and do not allow for longitudinal tracking. Furthermore, these definitions are therapy-based (on respiratory support), which is also problematic. Further standardized quantitative definitions of respiratory disease related to prematurity could include pulmonary hypertension, wheezing, etc. that could be followed over time. Large registries of outpatients of preterm individuals with respiratory disease could also help fill in our gaps in knowledge about the natural history of disease.

Most studies of factors related to respiratory disease of prematurity tend to focus on the development of bronchopulmonary dysplasia and/or factors that alter its trajectory while in the neonatal intensive care unit. There are little data on factors that alter outcomes with established disease after an initial discharge from the hospital. Part of this may be related to the common misconception that respiratory manifestations of prematurity are generally resolved by 2 years of age.

A starting point may be to examine exposures that alter outcomes in other respiratory diseases in a strategic manner. Currently, most environmental studies in this space are retrospective association-based studies with a few prospective descriptive studies. These types of studies are somewhat hampered by our ability to measure exposures. Similar to limitations of the study of other respiratory diseases, there is also a need for improved assessment of exposures, which may require home air sample monitoring, geospatial mapping, etc. Ultimately, pilot studies of interventions and randomized control trials of interventions are critically needed. One example of this could be providing in-home care options for preterm infants and young children under 2–3 years of age as opposed to center-based daycare.

Implementing interventions to improve respiratory disease of prematurity also has its challenges. Unlike diseases like cystic fibrosis, there are no national foundations to coordinate care, and respiratory care may be provided by different groups of providers depending on patient location (e.g., pulmonologists, neonatologists, and/or generalists). However, expert consensus guidelines are under consideration by at least one national respiratory society. Even if comprehensive guidelines are published, implementation may still prove difficult due to the heterogeneous nature of respiratory disease of prematurity. Ultimately, we would hope that future care includes personalized information concerning environmental exposures to improve health-care outcomes and quality of life for preterm individuals.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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## Article highlights

- Individuals who are born prematurely have a high burden of respiratory disease, which is not necessarily limited to the archetype of bronchopulmonary dysplasia.
- Although respiratory manifestations associated with premature birth generally improve with time, some can persist into adulthood.
- Although children born prematurely may have a quiescent period of symptomatology, they are at higher risk for early onset COPD; avoidance of adverse environmental exposures may mitigate this risk.
- A number of environmental factors can delay resolution, but evidence is limited. In this review, we outline factors, including air pollution, socioeconomic factors, infection risks, etc., along with strategies to mitigate them.