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REVIEW

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Long-term respiratory consequences of prematurity

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Abstract

Approximately 10% of all children worldwide are born preterm and respiratory consequences are amongst the most common sequelae of preterm birth. Except for a higher prevalence of respiratory symptoms and hospital admissions, preterm birth is associated with lower lung function that may track into adulthood. Lung function impairment is not restricted to extreme or very preterm-born subjects as also children born moderate-late preterm have lower Z-scores for lung function. Given the heterogeneity of prematurity-associated lung disease, phenotype-based, multidisciplinary management is needed to improve respiratory health in preterm-born subjects.

KEYWORDS
bronchopulmonary dysplasia (BPD), neonatal pulmonary medicine, prematurity, pulmonary function testing (PFT)

1 | INTRODUCTION

Worldwide, every year 15 million children are born preterm, and prematurity is the second leading cause of death in children under 5 years of age.

The vast majority (84%) of all preterm births takes place between 32 and 37 weeks of gestation, so-called moderate-late prematurity, while only 1%–2% occur before 28 weeks of gestation (extreme prematurity). Respiratory consequences of preterm birth are very common and although the prevalence increases with decreasing gestational age (GA), the absolute numbers of moderate-late preterm births are much higher, and therefore the highest burden of respiratory consequences is in moderate-late preterm born children.

2 | RESPIRATORY SYMPTOMS, HOSPITALIZATIONS, AND QUALITY OF LIFE

Respiratory symptoms are two to three times more common in preterm-born children compared to term-born controls, in particular during the preschool years. However, also adults born with very low birthweight experience more respiratory symptoms such as wheezing, shortness of breath, have a reduced exercise capacity and are less physically active compared to healthy controls. Impaired lung function, altered heart structure and function, and reduced physical activity may all account for this reduced exercise capacity.[1]

In addition, preterm children are more often hospitalized for respiratory tract infections. In a population-based registry study from Australia not only the risk of rehospitalization for respiratory tract infections but also "any infections" was increased with higher risk ratios at lower GA.[2] Infection-related admission rates increased by 12% for each week reduction in GA less than 39–40 weeks (RR 1.12, 95% CI 1.12–1.13). Even in children born at 38 weeks GA the risk ratio was still significantly increased (1.15, 95% CI 1.13–1.17) compared to children born between 39 and 40 weeks.

Respiratory symptoms, hospital admissions, poor sleep, acute care needs of (extreme) preterm-born patients, and additional neonatal morbidities may all negatively affect caregiver's quality of life (QOL), with the highest impact immediately post-discharge from the neonatal intensive care unit. At age 5, extreme preterm born children experience lower QOL compared to very preterm children, and, not surprisingly, children with BPD have lower QOL when compared to children without BPD.

However, these effects seem to fade away with increasing age and no significant mean difference in QOL was found in adults with BPD compared to healthy controls.

2.1 | Lung function

Prematurity has been associated with lower lung function, with children born at a lower GA and those with a BPD diagnosis being the most affected. A recent systematic review in children with BPD showed a 16% lower mean forced expiratory volume in 1 s (FEV1) compared to controls.[3] More notable, this lung function deficit further deteriorates during childhood with as much as 0.1 Z-score FEV1 per year.[4] This puts children with BPD at risk of getting a COPD diagnosis in early adulthood: indeed 30% of adults born before 32 weeks of gestation or with a birth weight <1000 g fulfill spirometry criteria for COPD.

Again, lung function impairment is not restricted to extreme preterm subjects as also children born moderate-late preterm have lower Z-scores for FEV1 (mean difference −0.22, 95% CI −0.35, −0.09), FEV1/Forced Vital Capacity and Forced Expiratory Flow at 25%–75% of FVC (FEF25-75) compared to term-born controls.[5]

As preterm-born subjects often do not reach their peak lung function and, potentially, may experience accelerated decline in lung function, this will put them at risk for poor lung function trajectories that track into adulthood. These trajectories can further negatively be influenced by genetic predisposition, pre- and postnatal exposures to tobacco smoke and/or air pollution, intercurrent respiratory tract infections, and gene-environment interactions during crucial phases of lung development.

Other lung function test that may be impaired in preterm-born children are diffusion capacity (lower) and bronchial hyperresponsiveness tests. Data on lung clearance index (LCI) are inconclusive.

Most children with prematurity-associated lung disease do have normal values of the fraction of exhaled nitric oxide (FeNO), suggesting that eosinophilic inflammation does not play a leading role.

3 | STRUCTURAL OUTCOMES

The vast majority of children born <32 weeks GA do show structural abnormalities on chest CT scans, with the more extensive abnormalities in children with a lower GA, lower birth weight Z-score and increased duration of respiratory support. The most common structural consequences of preterm birth are hypodense areas (bullae, emphysema), linear, triangular and subpleural opacities, bronchial wall thickening, and a distorted architecture. Several CT scoring systems do exist, and most do show a correlation between worse CT scores and lower FEV1, FEV1/FVC, and FEF25–75 z-scores. With MRI similar abnormalities can be visualized, and newer techniques such as Fourier Decomposition MRI allow for analysis of ventilation and perfusion defects.

Advancements in MRI, but also innovations such as photon counting CT, with higher resolution and lower radiation dose, show promise to quantify lung disease in preterm patients, define phenotypes and predict long-term outcomes. Data on longitudinal changes in structural abnormalities are largely lacking but urgently needed to understand lung development in preterm subjects.

4 | BPD PHENOTYPES

It has become more and more clear that BPD is a complex condition with different phenotypes consisting of various clinical, structural, functional, and inflammatory traits that may change during the life course.[6] Recent studies identified at least four main BPD phenotypes: (1) deficient alveolarization: characterized by simplified alveoli and low attenuation regions, (2) pulmonary vascular impairment: marked by a reduction in peripheral pulmonary arteries, leading to hypoperfusion and pulmonary hypertension, (3) central airway disease: characterized by flaccid trachea and main bronchi due to tracheobronchomalacia, and (4) chronic airways obstruction: characterized by bronchial wall thickening.

These phenotypes often overlap, necessitating precise imaging to distinguish between them and to tailor appropriate treatments. In a study by Wu and coworkers these phenotypes did show predictive value for adverse outcomes such as mortality, tracheostomy, and need of vasodilator treatment for pulmonary hypertension.[7]

5 | CONCLUSIONS

The high burden of respiratory consequences of prematurity is not limited to very or extreme preterm subjects and also not limited to childhood. BPD is only at the extreme end of spectrum and is associated with lifelong increased respiratory symptoms and reduced lung function predisposing to "COPD." Given the heterogeneity of prematurity associated lung disease, phenotype-based, multidisciplinary management is needed.

AUTHOR CONTRIBUTIONS

Mariëlle W Pijnenburg drafted the article.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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