Prematurity-related chronic respiratory disease across the life course

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Being born preterm, either extreme or late preterm, has adverse implications for respiratory health across the life course. Both child and adult respiratory physicians should raise their awareness of prematurity-related chronic respiratory disease. https://bit.ly/3IW95pW

Cite this article as: Duijts L. Prematurity-related chronic respiratory disease across the life course. *Eur Respir J* 2023; 61: 2300662 [DOI: 10.1183/13993003.00662-2023].

Received: 18 April 2023
Accepted: 27 May 2023

Background

Preterm birth and chronic respiratory diseases are both common. The global prevalence estimates for preterm birth range from 5% to 18%, and for asthma and COPD from 6.8% to 17.8% and 3.8% to 27.8%, respectively [1, 2]. The relationship between preterm birth and chronic respiratory diseases is not fully elucidated, but infants born preterm seem to have increased risks of respiratory morbidity across the life course (figure 1).

Preterm birth and respiratory morbidity in childhood

The potential adverse effects of preterm birth on respiratory morbidity start early in life. In the neonatal and infant periods, infants born preterm have high rates of infant respiratory distress syndrome and bronchopulmonary dysplasia, and even higher rates if infants are born more extremely preterm or additionally born small for their gestational age [3]. In childhood, aggregated findings of prospective studies suggest that infants born preterm (below 37 weeks of gestational age) have a 1.5-fold increased odds of asthma or wheezing disorders in childhood [4, 5]. Recent results of a meta-analysis of individual participant data of 147 000 children participating in prospective birth cohort studies were able to examine gestational age across the full range and showed consistent associations of younger gestational age at birth with higher risk of asthma in childhood [5]. The previously suggested associations of lower birth weight with asthma in childhood seemed to be largely explained by gestational age at birth. Infants born at an earlier gestational age also have lower lung function in childhood according to a meta-analysis of almost 25 000 children from 14 birth cohorts [6]. Notably, lower lung function and odds of asthma in childhood seem not only present among infants born very preterm, but across the full range of preterm gestational birth age.

Preterm birth and respiratory morbidity in adulthood

The evidence that infants born preterm have increased risks of asthma, COPD, or overlap syndromes in adulthood is scarce. In this issue of the *European Respiratory Journal*, Pulakka *et al.* [7] examined the association of the full range of gestational age at birth with asthma and COPD in early and mid-adulthood (18–29 and 30–50 years, respectively) using nationwide data of 2 376 245 participants from Finland and Norway. Results show a gradual association of gestational age at birth with the risk of having a care episode of chronic obstructive airway diseases in adulthood (p-value for trends <0.001). In Finland, infants born extremely preterm (23–27 weeks gestational age at birth) had the highest odds of asthma between age 18 and 29 years (OR 2.90, 95% CI 2.00–4.21), compared with infants born full term. In Norway, infants born extremely preterm (23–27 weeks gestational age at birth) had the highest odds of asthma and any type of COPD between age 18 and 50 years (OR 2.96, 95% CI 2.26–3.88 and 9.58, 95% CI 5.50–16.69, respectively), including emphysema, other types of COPD, and unspecified types of COPD. Also, infants born late preterm (34–36 weeks gestational age at birth) had increased odds of asthma in adulthood

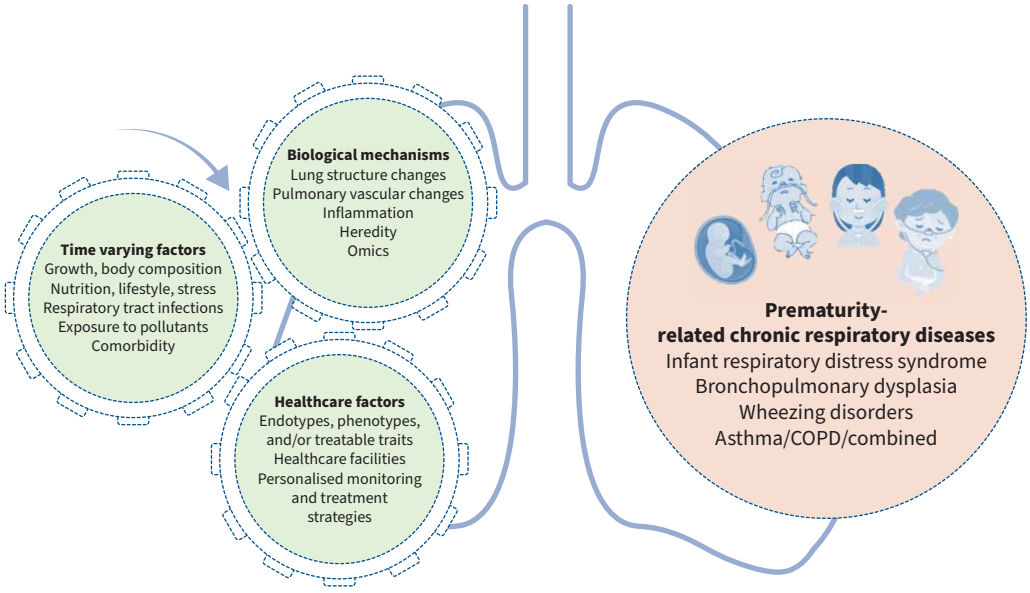

FIGURE 1 Concept of developing or mitigating the risk of prematurity-related chronic respiratory disease and its potential biological mechanisms, time varying factors, and healthcare factors across the life course.

(Finland: OR 1.17, 95% CI 1.05–1.30; Norway: OR 1.26, 95% CI 1.20–1.33), or any type of COPD (Norway: OR 1.41, 95% CI 1.22–1.63). The odds remained similar when taking important maternal diseases, lifestyle factors partly including maternal smoking, and perinatal circumstances into account, were slightly higher when analyses were restricted to care episodes from pulmonology speciality or from inpatient care, and not different between women and men, or between the first and later born infants in the family. Potential aggravating risk factors were also present [8]. Odds for respiratory morbidity in adulthood were higher for infants born preterm who, in the Finnish cohort, additionally had developed likely "new" bronchopulmonary dysplasia during the neonatal period, or those who were additionally born small, but also appropriate for gestational age at birth. Thus, their results suggest that infants born preterm have increased risks of chronic obstructive respiratory diseases in adulthood, also if they were not born extremely preterm, did not develop bronchopulmonary dysplasia, or were not small for gestational age at birth.

One of the first studies that examined the role of birth characteristics in chronic respiratory diseases in adulthood was a single retrospective cohort study of ∼6000 individuals published in the 1990s, and showed that infants born with a lower birth weight have increased risks of a lower forced expiratory volume in 1 s and death due to COPD at age 64 years [9]. Since then, aggregate data and individual participant data meta-analyses of prospective cohort studies have focused on this topic, but have been mostly limited to respiratory outcomes measured in mid- or late childhood, or early adulthood [4–6, 10]. The few previous large-scale birth cohort or registry studies, other than that of Pulakka *et al.* [7], with follow-up in mid- and later adulthood showed inconsistent findings. These studies showed that infants born before 37 weeks gestational age did not have an increased odds of asthma at age 31 years [11], that infants born between 23 and 31 weeks of gestational age had the highest odds of severe asthma up to age 34 years in a dose–response manner [12], or that infants born <32 weeks or between 33 and 36 weeks of gestational age had increased odds of asthma but only among women [13], compared with infants born at term. Studies focused on COPD showed that infants born preterm had no increased odds of COPD [13], or if born very to moderately preterm (28 to <34 weeks of gestation), but not late preterm (34 to <37 weeks), had a 2.9-fold increased odds of COPD at age 53 years [14]. For overlapping or combined chronic obstructive respiratory diseases, no associations of gestational age and adult respiratory diseases [15], or a 2.7-fold increased odds of any obstructive airways disease among women in adulthood and at old age were observed [13]. The additional value of the current study of Pulakka *et al.* [7] is the use of a large number of subjects from two Nordic countries with individual-level data and follow-up from birth to the age of 50 years, which enabled the study to examine a wide spectrum of gestational ages with the odds of diverse chronic obstructive airway diseases. Altogether, the results of these studies suggest that earlier gestational age at birth has lifelong adverse implications for respiratory health, and are therefore very important from a public health perspective.

TABLE 1 Main conclusions, gaps, and recommendations for future research on prematurity-related chronic respiratory disease across the life course

Main conclusions	• Infants born preterm have an increased risk of respiratory morbidity in infancy, childhood and adulthood, with stronger odds for those born more extremely preterm, who develop bronchopulmonary dysplasia, or are born small for gestational age • Child and adult respiratory physicians should enquire about the neonatal period in their clinical practice and raise their awareness of prematurity-related chronic respiratory disease
Main gaps in knowledge	• Acknowledgement of prematurity-related chronic respiratory disease as one separate disease entity • Unknown influencing time-varying factors, healthcare factors, biological mechanisms, and monitoring and treatment strategies across the life course
Recommendations for future research	• Formulation of, and agreement on, a definition of a prematurity-related chronic respiratory disease entity covering the life course periods and its potential endotypes, phenotypes and/or treatable traits • Life course approaches to identify adverse or beneficial time-varying and healthcare factors from preconception into adulthood, including, for example, growth and body composition, nutritional and lifestyle habits, environmental exposures, comorbidity and specialised multidisciplinary healthcare, ultimately leading to optimised prevention and intervention strategies • Observational and experimental studies to identify systemic and/or local biological mechanisms focused on inflammatory, immunological, pulmonary vascular, genetic, epigenetic, metabolomic and microbiomic processes • Therapeutic randomised clinical controlled trials or drug repositioning studies, for example the use of maintenance and reliever inhaler therapy or periodic maintenance antibiotic

Potential mechanisms

The mechanisms underlying the associations of younger gestational age at birth with chronic respiratory diseases across the life course are not known yet. The highest rate of airway and alveolar development occurs in early life. Being born preterm could lead to pulmonary developmental changes, which to date seem mainly characterised by alveolar simplification and pulmonary vascular dysregulation with functional impairment, rather than the emphysematous, fibrotic disease potentially present in infants previously born preterm and currently being middle-aged and older adults [16]. Subsequently, lung structure changes may affect lung function development and increase the odds of chronic respiratory diseases in later life. Infants born preterm might show lung structure changes on chest computed tomography scans or ventilation abnormalities on hyperpolarised ^{129}Xe MRI of the lungs across life [17, 18]. A reduced airway calibre could result in airway obstruction and limited airflow that predisposes to symptoms of chronic respiratory diseases. Previous studies have shown that infants born at an earlier gestational age may not reach their full lung function potential and, in a dose-dependent manner, have lower lung function in their childhood, adulthood and middle-aged adulthood [6, 19–21], and lower lung diffusion [22]. Additionally, their lung function decline may start earlier in life [23]. Other suggested main underlying biological pathways are genetic, pulmonary vascular, inflammatory and altered microbiome mechanisms [24–27]. Last, not preterm birth itself but underlying adverse factors during fetal life and even in the preconception period may affect embryonal and fetal lung development, consequently triggering preterm birth, and subsequently increasing the risk of chronic respiratory diseases in later life [27].

Methodological challenges

Examining the association between earlier gestational age at birth with respiratory outcomes more than 50 years later is very complex. Besides not being able to objectively verify diagnoses, registry studies such as the current study tend to lack the possibility to study detailed and time-varying influencing factors and biological mechanisms. Weight changes, or nutritional, lifestyle and stress-related factors, and genetic, epigenetic and inflammatory mechanisms across the life course, may all influence the risk of developing or mitigating chronic respiratory diseases [27]. Furthermore, prenatal and neonatal care, and healthcare systems change over time, and this should be taken into account. Future life course approaches are challenging because of the multiple open gaps, but are nevertheless urgently needed to elucidate biological, medical and other relevant related processes. Focus could be on, for example, identification of specific lung structural, inflammatory and/or pulmonary vascular processes, and potential effects of anti-inflammatory and reliever inhalers or their combination, or periodic maintenance antibiotics. These processes may be present or applicable across an individual's life course, or across generations, and influence the development or course of prematurity-related chronic respiratory disease [28]. Therefore, in future, prematurity-related chronic respiratory disease may be considered as a separate respiratory disease entity with its own endotypes, phenotypes and/or treatable traits [29].

Conclusion

The study by Pulakka *et al.* [7] has made an important contribution to the literature and supports the concept of early-life origins of chronic respiratory diseases in later life. Further detailed long-term follow-up studies are needed to support the reported findings. Furthermore, identification of the mechanisms underlying prematurity-related chronic respiratory disease throughout the life course are

urgently needed to develop appropriate personalised monitoring and treatment strategies, preferably using multidisciplinary and specialised teams (table 1) [30, 31]. It has become clear that both child and adult respiratory physicians should enquire about the neonatal period in their clinical practice and raise their awareness of prematurity-related chronic respiratory disease.

Conflicts of interest: L. Duijts has no potential conflicts of interest to disclose.

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