The PELICAN (Prematurity's Effect on the Lungs In Children and Adults Network) ERS Clinical Research Collaboration: Understanding the impact of preterm birth on lung health throughout life.

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Rationale:

An estimated 15 million babies (~11 %) are born preterm each year (before 37 weeks of gestation); the rates of which are increasing worldwide (1). Enhanced perinatal care, including antenatal corticosteroids, postnatal surfactant and improved respiratory management, have markedly improved survival outcomes since the 1990's, particularly for babies born very preterm (<32 weeks gestation) (1). However, long term pulmonary sequalae are frequent in preterm survivors and ongoing clinical management is often required. Development and severity of bronchopulmonary dysplasia (BPD), a chronic lung condition diagnosed during the neonatal period (2), is a key determinant of long-term adverse outcomes of prematurity.

The European Respiratory Society published a guideline on long term management of children with bronchopulmonary dysplasia in 2019 (3). Of the 8 questions identified as important or critical, the (conditional) recommendations were based on "low" or "very low" quality of evidence. The Task Force suggested that "Prospective, structured, standardized and multi-disciplinary follow-up of children with BPD from discharge into adulthood is needed, and may help to generate important data for future monitoring and treatment studies". An international network has evolved over time through collaborations between researchers, clinicians and consumers and we now formalise these collaborative efforts in response to this Task Force call to action.

Scientific background:

Low lung function in early life leads to a lifelong trajectory of low lung function and a failure to reach predicted peak during early adult life (4). Failure to reach predicted peak is a major risk factor for chronic obstructive pulmonary disorder (COPD), accounting for up to half of cases in adults (5). Preterm birth, and the associated lifesaving (but injurious) treatments, have a profound effect on lung growth throughout childhood. Preterm babies have additional risk factors for reduced lung growth: For example, they are over three times more likely than term-born infants to be re-hospitalised for severe respiratory tract infections in the first year of life (6) and are up to 5 times more likely to develop preschool wheezing and later childhood "asthma" than their term counterparts (7). Up to 50% of very preterm survivors report physician diagnosed asthma in mid-childhood (regardless of BPD classification) (8) and young adults born very preterm are twice as likely to have asthma medications prescribed than those born at term (9). Despite an "asthma-like" phenotype in survivors of preterm birth, there is no evidence of the typical eosinophil-mediated inflammatory airway response commonly reported in asthma.

Cross-sectional studies of lung function in children, adolescents and young adults surviving preterm birth have largely been undertaken with spirometry as the outcome. These studies clearly demonstrate airway obstruction in those born very preterm, that is further exacerbated in those with BPD (8, 10, 11). A meta-analysis reported that survivors of preterm birth with BPD (5 to 23 years old at the time of testing; born 1964 to 2000) had forced expiratory volume in one second (FEV_1) that was 19 % lower than predicted when compared with term born controls (12). Of interest, late preterm birth (32-36 weeks gestation) also impacts on subsequent FEV_1 (13). Other lung function tests have also demonstrated deficits, including altered respiratory system mechanics, gas exchange and potentially lung volumes (14-16); though contradicting findings exist. Structural lung damage is also present throughout life after preterm birth (8, 17, 18)

Longitudinal studies, though limited in number, tend to indicate increased severity of airway obstruction over time (reduction in FEV_1, FEF_{25-75} and FEV_1/FVC z-scores over time), particularly for those with bronchopulmonary dysplasia (19-22). Declining lung function trajectory over time is more severe in children and adolescents exposed to environmental tobacco smoke (21, 22), and those where bronchial wall thickening was detected on chest CT during mid-childhood; suggesting inflammatory or post-inflammatory processes may be contributing (21). Increasing airway obstruction over time and persistent symptoms suggest that many survivors of preterm birth are destined for chronic lung disease in adult life.

PELICAN (Prematurity's Effect on the Lungs In Children and Adults Network): An ERS Clinical Research Collaboration

The ERS established the Clinical Research Collaboration scheme in 2013 to promote the exchange of research ideas among clinicians and researchers, build infrastructure for prospective clinical research, secure additional funding and facilitate clinical / translational studies; particularly in areas of important clinical unmet need (23). PELICAN was launched in 2020 as the fourth CRC within the ERS Paediatric Assembly (24-26) and has additional collaboration with the GLI Network (27) and CADSET (28) through cross-over membership and complementary methodologies to address lung health trajectories across the life course.

PELICAN Aims:

The overarching objective of PELICAN is to understand the pulmonary consequences of surviving preterm birth and the natural history of lung disease across the life course, and to determine which modifiable factors are associated with the progression of lung disease within this vulnerable population. In doing so, we have identified the following aims associated with the CRC:

1. To establish an international consortium, or network, of clinicians, researchers and consumers interested in understanding and improving the long-term lung health outcomes for those born preterm.
2. To establish a harmonised global data repository that meets international data sharing, governance and management practices, to collate and integrate cross-sectional and longitudinal lung health data from cohorts of survivors of preterm birth.
3. To define and standardise outcome measures for describing prematurity's effects on lung health and publish recommendations for harmonising these elements to enable data sharing across future cross-sectional and longitudinal studies in this population.
4. To assess life-long lung function trajectories and respiratory symptom profiles for survivors of preterm birth.
5. To evaluate the impact of temporal and regional clinical practice, treatments, and lifetime exposures on lung health trajectories in this population.
6. To promote clinician and consumer education and engagement to improve lung health outcomes for the preterm community.
7. To provide an invaluable and long-lasting resource for future generations of clinicians and researchers to answer important questions regarding the lung health of survivors of preterm birth as they arise.

PELICAN data to date:

Prior to submission to the ERS CRC call, we conducted a systematic review using the PubMed and PubMed Central databases. The following search terms were used 'preterm AND lung function', 'preterm AND pulmonary function', 'bronchopulmonary dysplasia AND lung function' and 'bronchopulmonary dysplasia AND pulmonary function'. A total of 5,782 results were returned. Studies were selected from the search results based on title and abstract, with the inclusion criteria requiring the reporting of lung function data of preterm-born participants after the first year of life. Based on title and abstract, 78 unique studies were identified. A further 16 follow-up studies (based on the original studies) were additionally selected. Sub-studies of larger cohorts that had already been identified were not included. This search yielded a potential recruitment pool of 23,517 individuals: 9,029 preterm (2,867 with BPD) and 14,488 associated term born controls. The existing network met for a workshop at ERS 2018 (Madrid) and determined that we had guaranteed access to at least 8,653 individuals (via the existing collaborating data custodians): 5,167 preterm (57% of published data), including 2,174 with BPD (76% of published data in those with BPD), and 5,277 term-born controls. We look forward to identifying other recently published studies, as-yet unpublished studies and connecting with teams not currently represented within the network.

Measurements and data to be collected:

Lung function data from spirometry, single breath carbon monoxide diffusing capacity, multiple breath washout, plethysmography, oscillometry, fractional exhaled nitric oxide and bronchodilator responsiveness will be included include from cohorts as available.

Data will also be collected and harmonised for the purposes of phenotyping study participants, including:

- ***Anthropometric and respiratory health data*** including height, weight, heart rate, blood pressure etc. Current and past respiratory symptoms at rest and with exercise as well as previous and current treatment use will be obtained where possible.
- ***Perinatal information*** collected prospectively on the cohorts including (but not limited to) details of prematurity, birth anthropometrics, obstetric and delivery outcomes, surfactant use, postnatal treatments and duration and type of respiratory and oxygen support.
- ***Lifetime environmental influences and exposures*** will be collected where available such as breast-feeding duration, probiotic use, tobacco smoke exposure, respiratory infections requiring hospitalisations. Involvement in clinical trials in the NICU will be documented as available.

Additionally, we will capture information such as if lung imaging, exercise testing, biological sample collection etc. were undertaken, which would enable research teams to engage collectively in future collaborative studies.

Conclusion:

Our ambitious study will determine lung health trajectories for survivors of preterm birth over the life course, identify perinatal and lifetime exposures associated with faster progression of lung disease. We hope that our work will ultimately enable prediction of which preterm infants would benefit from appropriate follow up or early intervention, inform clinical guidelines, health practice and service planning for the long-term clinical management of survivors of very preterm birth.

Research groups interested in contributing to PELICAN in any way, including by provision of data, are encouraged to contact members of the CRC Scientific Steering Committee or the ERS through the PELICAN webpage (https://www.ersnet.org/research/pelican---prematurity-s-effects-on-the-lungs-in-children-and-adults-network).

Members of the PELICAN Executive: Shannon Simpson (chair), Jenny Hallberg (chair), Amber Bates (consumer representative), Lex Doyle / Jeanie Cheong, Graham Hall, Thomas Halvorsen, John Hurst, Sailesh Kotecha, Enrico Lombardi, Sanja Stanojevic, Petra Um Bergstrom (Early Career member).

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