# Early-life MRI biomarkers of longer-term respiratory morbidity in infants born extremely preterm (EMBLEM Study)

**Background and Importance:** Bronchopulmonary dysplasia (BPD) is a chronic lung disease of prematurity, associated with multi-system morbidity that continues into adulthood. However, clinical definitions of BPD are poor predictors of long-term respiratory morbidity. A better predictor is needed for extremely premature neonates to provide focused interventions and improve long-term outcomes. Novel high-resolution magnetic resonance imaging (MRI) methods, including phase-resolved functional lung (PREFUL) and ultra-short echo time (UTE) MRI, can measure lung structure, ventilation, and perfusion, thereby evaluating pulmonary parenchyma and vasculature, as well as their interplay.

**Goals(s)/Research Aims**: Our goal is to develop MRI biomarkers of pulmonary parenchymal and vascular abnormalities as predictors of respiratory morbidity and neurodevelopmental impairment (NDI) in infants born extremely preterm. Specifically, we will:

1. Estimate the association between lung MRI biomarkers at 36 weeks post-menstrual age (PMA) and severe respiratory morbidity up to 18 months corrected age (CA), assessed by questionnaire and chart review (***primary***);
2. Estimate the association between MRI biomarkers and NDI at 18-21 months CA (secondary); and
3. Develop a preliminary predictive model of severe respiratory morbidity at 18 months CA based on MRI biomarkers, clinically-defined BPD, lung ultrasound scores, and echocardiogram metrics of right ventricular dysfunction and pulmonary hypertension, at 36 weeks PMA (secondary).

This innovative, interdisciplinary project will deepen our understanding of prematurity-related lung disease and has a robust knowledge translation plan to improve clinical prediction of long-term respiratory outcomes.

**Methods/Approaches/Expertise:** This prospective, multi-centre cohort study will follow 319 neonates born <29 weeks gestational age from 36 weeks PMA to 18-21 months CA. At baseline (36 weeks PMA), babies will undergo PREFUL and UTE MRI, echocardiogram, and lung ultrasound. We will evaluate 4 MRI biomarkers of pulmonary parenchymal and vascular disease. We will evaluate our primary outcome, severe respiratory morbidity up to 18 months CA, through parent questionnaire every 3 months and chart review. We will assess our secondary outcome (NDI at 18-21 months CA) in-person. We will use multiple logistic regression to evaluate MRI biomarkers as predictors of respiratory morbidity and NDI, respectively. Lastly, we will construct a multiple logistic regression model to predict respiratory morbidity via MRI biomarkers, clinically-defined BPD, echocardiogram metrics, lung ultrasound score, and a priori-defined covariates.

We bring together a multidisciplinary team, from 7 institutions, of leaders in neonatology, neonatal follow-up care, respirology, cardiology, MRI physicists who have pioneered PREFUL and UTE methods, and a parent collaborator from the Canadian Premature Babies Foundation. Team members have previously collaborated on a multi-centre UTE MRI study (PI: S. Katz).

**Expected Outcomes**: These novel PREFUL and UTE MRI biomarkers will provide clinicians with a method of safely and longitudinally evaluating pulmonary parenchymal and vascular health in infants born extremely preterm. Identification of predictors of longer-term respiratory morbidity of relevance to families will enable us to target resources appropriately and identify babies who would benefit most from therapeutic intervention.

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