The Origins of Pediatric Respiratory diseases: laying groundwork for genetic, cellular and immunological analyses. (OPeRA)

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON56828

Source
ToetsingOnline

Brief title
The Origins of Pediatric Respiratory diseases: the OPeRA study

Condition

- Respiratory disorders congenital
- Bronchial disorders (excl neoplasms)

Synonym
asthma, cystic fibrosis, wheeze

Research involving
Human

Sponsors and support

Primary sponsor: KIndergeneeskunde/ Kinderlongziekten en -allergologie
Source(s) of monetary or material Support: onderzoeksbudget afdeling KInderlongziekten

Intervention

Keyword: airway organoids, bronchoscopy, pediatrics, singe-cell-sequencing

Outcome measures

Primary outcome

1. To establish epithelial organoid cell cultures for pediatric respiratory

research to enable future mechanistic and in vitro intervention studies.

2: To compare gene expression profiles of cultured bronchial and nasal

epithelial organoids (derived from brushings and BALF) with bronchial

epithelial cells directly obtained from bronchial biopsies.

3: To compare gene expression profiles of nasal and bronchial brushings in

children

4. To establish a biobank for pediatric airway samples for future research

questions that may arise

Secondary outcome

none

Study description

Background summary

Many respiratory diseases, such as asthma and cystic fibrosis, as well as low lung function, which predisposes to COPD, arise in childhood. These diseases are the outcome of the interaction of a genetically susceptible host with a permissive environment. Most lung diseases can therefore be conceived as a

developmental disease, as these arise in a child with a developing lung and immune system. Therefore, to identify the early mechanisms underlying disease development, we will need to study children instead of adults, investigate cells from the bronchial airways, and develop models that reflect bronchial epithelial cell function. However, mechanistic, invasive studies in young children with respiratory diseases are limited by ethical constraints.
In Erasmus MC - Sophia Children*s Hospital yearly 100-150 flexible bronchoscopies are performed in children for various clinical indications. In general during bronchoscopy a bronchoalveolar lavage (BAL) will be performed and BAL fluid (BALF) will be cultured (bacteria, fungi, yeast) and analysed for cells and lipid laden macrophages. Excessive BALF and/or leftover BALF after these examinations is lost. In selected cases (in particular in asthma or asthmatic symptoms) endobronchial biopsies are taken during bronchoscopy for analysis of the reticular basement membrane thickness and inflammatory cells.
The bronchial epithelial cell is a key cell orchestrating the response of the airways and the immune system, and bronchial epithelial cells express many respiratory disease genes.
We hypothesize that curative, early childhood treatment for lung disease needs to be based on detailed, mechanistic insights into the inception of disease in the bronchial epithelium rather than established disease in adults. In contrast to the bronchial epithelium, the nasal epithelium is accessible in young children. However, it is not known how well the upper airway reflects the lower airways in children with different disease conditions

Study objective

The main objective of this proposal is to establish ex-vivo models of bronchial epithelial cells from children. Use of (1) epithelial organoid cultures derived from bronchial or nasal epithelial cells; and of (2) bronchial brushings; (3) nasal brushings and (4) bronchoalveolar lavage fluid (BALF) allows us to study epithelial cell function at the genetic, cellular and immunological level.
These models will be validated by comparison of gene expression from epithelial cells of these three models to the gold standard: bronchial (single cell) gene expression in biopsies of bronchial airway wall. Furthermore, this will enable future mechanistic and intervention studies, as we will know which aspects of the bronchial epithelium will be reflected in nasal cells, and which are retained in epithelial organoid cell culture.
Another primary objective is to establish a biobank of bronchial biopsies, bronchial and nasal epithelial cells and BALF of children with different respiratory diseases.

Study design

This study will be an observational, cross-sectional cohort study that will describe characteristics of developing pulmonary disease, including asthma, severe wheeze and cystic fibrosis.

Children that will undergo a bronchoscopy based on clinical indications during office hours will be asked to participate. With an estimated inclusion of 20 children per year, the study duration will be four years. The total inclusion will be 80 children. The study will take place in Erasmus MC - Sophia Children*s Hospital from 1 October 2022 to 30 October 2026.

We will obtain the following materials:
- 4 bronchial biopsies, processed as single cell suspension for RNA-seq.
- 3 bronchial brushes (2 for epithelial organoid culture, 1 for RNA isolation)
- 3 nasal brushes (2 for epithelial organoid culture, 1 for RNA isolation)
- Excess BALF will be stored
- 1 blood sample (total amount of 10ml) for peripheral blood mononuclear cells.

Children will undergo:
- lung function assessments, if not performed < 12 weeks of bronchoscopy for clinical reasons.

Baseline data on the clinical symptoms, environmental exposures, treatment, and medical history will be retrieved from the patient files.

Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Ethical concerns are highly relevant when performing invasive research in children. We propose to perform research in (young) children, who already undergo bronchoscopy for clinical indications, where a BAL is part of the routine investigations. We aim to store excessive BALF for future research; this BALF is now lost after culturing and pathology analysis. A bronchial biopsy, bronchial and nasal brushes and 1 blood sample will be added as extra handlings for the study. This adds no extra risks to the procedure. During bronchoscopy the major risk is that of anesthetics. It has been well documented that risks related to a bronchoscopy itself are limited to the incidental need for bronchodilators, minor bleeding that always stops spontaneously, and fever. The main ethical aspect of our project therefore is obtaining (additional) primary bronchial epithelial and nasal cells for research purposes, which will prolong the planned bronchoscopy with approximately 10 minutes. The benefits of this research will relate to the validation of less or non-invasive methods to study airway epithelial cells from children, which may reduce the need for future invasive studies and will allow mechanistic studies into disease inception.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

1. age 1 year to 18 years
2. Need for a bronchoscopy based on clinical indications during office hours.

Exclusion criteria

1. All patients aged 1-18 years of age who suffer from a malignancy and also have an infectious disease, that are in need for diagnostic bronchoscopy.
2. Children that have undergone lung transplantation.
3. Children who are unstable during the procedure, where prolonging the

duration will cause increased risks, as judged by the anaesthesiologist and paediatric pulmonologist performing de bronchoscopy.
4. Children admitted at the ICU
5. Children who are in need of an emergency bronchoscopy

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-10-2024
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	18-04-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-09-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL81615.078.22