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The Swiss Cystic Fibrosis Infant Lung Development (SCILD) cohort

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Summary

The Swiss Cystic Fibrosis Infant Lung Development (SCILD) cohort is a prospective birth cohort study investigating the initiating events of cystic fibrosis lung disease during infancy, and their influence on the trajectory of disease progression throughout early childhood. Infants with cystic fibrosis are recruited throughout Switzerland after diagnosis by new-born screening. It is the first European population-based prospective cohort study of infants with cystic fibrosis taking advantage of a nationwide new-born screening programme. The study was established in 2011 and recruitment is ongoing.

The cohort study is currently divided into three study phases (phase 1: diagnosis to age 1 year; phase 2: age 1 to 3 years; and phase 3: age 3 to 6 years). Study participants have weekly telephone interviews, weekly anterior nasal swab collection and two study visits in the first year of life. They also complete follow-up study visits at 3 and 6 years of age. Data for this study are derived from questionnaires, lung function measurements, telephone interviews, nasal swab material and magnetic resonance imaging.

To date, 70 infants have been recruited into the study and 56 have completed phase 1, including a baseline study visit at 6 weeks of age, weekly surveillance and a study visit at one year of age. More than 2500 data points on respiratory health and almost 2000 nasal samples have been collected. Phases 2 and 3 will commence in 2018.

The dataset of the SCILD cohort combines lung function data, the collection of environmental and sociodemographic factors, documentation of respiratory symptoms, and microbiological analyses. The design not only allows tracking of the cystic fibrosis lung disease independent of clinical status, but also surveillance of early disease prior to severe clinical symptoms.

This cohort profile provides details on the study design and summarizes the first published results of the SCILD cohort.

Key words: *Swiss Cystic Fibrosis Infant Lung Development Cohort (SCILD), cystic fibrosis, longitudinal birth cohort, cohort profile*

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Introduction

Cystic fibrosis is the most common lethal inherited disease affecting Caucasian populations, with a prevalence of approximately 1:3300 [1]. It is a multisystem disorder that affects exocrine glands including the lung, liver, pancreas and intestine [2]. Respiratory morbidity is the leading cause of death, and despite improved survival rates the current median survival age of patients with cystic fibrosis is approximately 40 years [3].

The establishment of new-born screening for cystic fibrosis allows diagnosis before the onset of clinical signs [4, 5]. In Switzerland, new-born screening for cystic fibrosis was implemented nationwide in 2011 [6]. As not all patients with cystic fibrosis display overt symptoms during the first years of life, new-born screening allows early monitoring and treatment of preclinical disease, and a better understanding of the early disease pathogenesis. It is now well recognised that in the first months of life in individuals with cystic fibrosis, pulmonary inflammation, infection and abnormal lung function are present prior to clinically diagnosed respiratory illness [7–13]. Therefore, understanding the pathophysiology of early cystic fibrosis lung disease is essential to delay its onset and progression, implement early therapeutic interventions and further improve outcomes.

The Swiss Cystic Fibrosis Infant Lung Development Cohort (SCILD) was established in 2011 after implementation of the Swiss new-born screening for cystic fibrosis and aims to examine the initiating events of cystic fibrosis lung disease during infancy and their influence on the trajectory of disease progression throughout early childhood. The SCILD cohort was set up in a comparable way to the Bern Basel Infant Lung Development (BILD) cohort study [14], a prospective birth cohort study of unselected healthy infants, which was established in 1999. The BILD and SCILD cohort studies both aim to investigate the physiological properties of the respiratory system, and the environmental and genetic risk factors that influence lung development in individuals from infancy throughout childhood. The SCILD cohort surveillance protocol has been only slightly modified from the BILD cohort, and healthy

infants from the BILD cohort serve as controls for longitudinal measurements performed throughout the study. The following paragraphs provide details on the study design and data collection, which have not been published previously, and give a short summary of current publications from the SCILD cohort. The reader will thus gain a comprehensive and detailed overview of the study.

Overview on the study design

Study design

Infants have been recruited since 2011 following diagnosis with cystic fibrosis by new-born screening in the cystic fibrosis centres of Aarau, Basel, Bellinzona, Bern, Geneva, Lausanne, Lucerne, St Gallen and Zurich, therefore covering all of Switzerland. After diagnosis and recruitment at the treating centre, infant lung function testing is proposed to all parents of newly diagnosed infants with cystic fibrosis (Task Force for cystic fibrosis new-born screening on behalf of the Swiss Working Group for Cystic Fibrosis). The University Children's Hospital Bern is the only centre in Switzerland currently performing infant lung function measurements in infants with cystic fibrosis. Study enrolment occurs on the day of lung function testing at the age of around 10 weeks, irrespective of prior clinical symptoms. The study is performed in Bern and was approved by the Ethics Committee Bern, Switzerland. Written informed consent is obtained from the parents. Exclusion criteria include the need for respiratory support for more than 3 days after birth, severe comorbidities or known diseases other than cystic fibrosis, maternal drug abuse, other known severe maternal diseases and severe problems of communication.

The study design of the SCILD cohort is divided into three phases as shown in figure 1. Details on data assessment at each study time point are displayed in table 1.

Phase 1

The first study phase begins with recruitment after infants have been diagnosed with cystic fibrosis following new-born screening and continues throughout the first year of life. Informed written consent is collected at the baseline study visit when the infants are around 10 weeks of age. Throughout phase 1, a study nurse contacts parents weekly by telephone. Phase 1 concludes following the first follow-up visit, which is scheduled for when the child reaches 1 year of age.

Phase 2

The second study phase starts after the first follow-up visit at age one and continues until the second follow up visit at the age of 3 to 4 years for all infants born after 2014. Respiratory and environmental history during phase 2 will be assessed retrospectively at the second follow up visit.

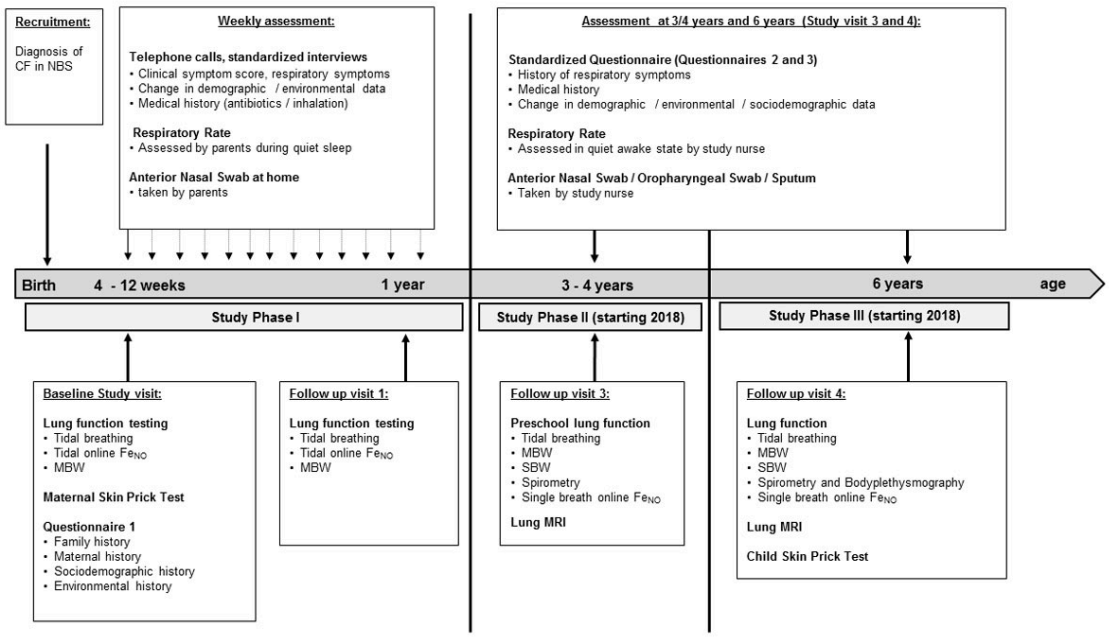
Phase 3

The third study phase starts after the second follow up at age 3 to 4 years and continues until the third follow up visit at the age of 6 years. Respiratory and environmental history during Phase 3 will be assessed retrospectively at the third follow-up visit.

Data sources and variables

Data acquisition is based on the study design of the BILD cohort [14]. Data are derived from the following sources: (1) questionnaires, (2) lung function measurements, (3) telephone interviews, (4) nasal swab samples, 5) respirato-

Figure 1: Design of the SCILD cohort study – flow chart of data collection.NBS = new-born screening; Fe_{NO} = exhaled nitric oxide; MBW = multiple breath washout, SBW = single breath washout; MRI = magnet resonance imaging



ry rate measurements, (6) skin prick tests, and (7) functional and morphological magnetic resonance imaging (MRI)

Table 1: Details of data collection from the different sources in the SCILD study.

Sources	Details of data collection
1. Standardised questionnaires [14–17]	
Questionnaire 1	• Pets and exact type of pet at home, during/after pregnancy • Type of heating, type of stove, chimney, open fire-place • Sleeping environment child (mattress, encasement, sheepskin rug use) • Damage due to damp at home, assessment of exposure to mould • Maternal active or passive smoking, ETS smoke exposure, number of cigarettes, smoking cessation and first year of life • Maternal intake of coffee/tee, caffeine containing soft drinks, vitamin supplement intake, fruit intake • Maternal treatment with antibiotics, steroid treatment during pregnancy • Respiratory infections, gastrointestinal infections, urinary tract infections, other infections during pregnancy • Paternal active smoking, number of cigarettes, smoking cessation during pregnancy and first year of life
Questionnaires 2–5	• Infections, colds (especially upper and lower respiratory tract, ear, nose, throat), number and duration • Exacerbations of disease (number, severity)* • Number, reason and course of hospitalisations† • Medication, especially antibiotics since last study visit, alternative medications and remedies used • Quality of life [17]: limits in physical activity/ ability to participate in social activities / mental health (depression, listlessness) • Atopic disease: atopic rhinitis or conjunctivitis, asthma (severity), atopic dermatitis • Behavioural problems, enuresis (primary, secondary, diurnal, nocturnal) • Level and impairment of indoor and outdoor activity, type of activity • Pets and exact type of pet at home • Farming exposure, animal type • Traffic exposure at home (trucks) • Type of heating, type of stove, chimney, open fire-place • Living condition (type of dwelling, rural/urban, number of rooms, number of people in household) • Diet (fruit, vegetables, sweets, chocolate, fast food, snacks, unpasteurized milk) • Maternal and paternal active or passive smoking, ETS exposure, number of cigarettes, smoking cessation until first major follow-up at age 3 and 6 years
2. Lung function measurements	
Infant lung function	1. Tidal breathing measurements [18, 19]: • Ultrasonic flowmeter (Spiroson®, EcoMedics AG, Duernten, Switzerland) with infant face mask • Main outcome parameters: tidal volume, minute ventilation, respiratory rate 2. Measurement of FE_{NO} [20]: • Rapid-response chemoluminescence analyser (CLD 88, EcoMedics AG, Duernten, Switzerland), with a range of 0–100 ppb, infant face mask • Breath-by-breath measurement • Main outcome parameter: mean FE_{NO} 3. Multiple breath washouts (SF_6) [21]: • Ultrasonic flowmeter (see above), infant face mask • Main outcome parameters: lung volume (FRC) and ventilation inhomogeneity (LCI)
Preschool lung function	1. Tidal breathing measurements: • Quiet tidal breathing • Ultrasonic flowmeter with mouth-piece, filter and nasal clamp • Main outcome parameters: minute ventilation (tidal volume multiplied by respiratory rate) and expiratory flow 2. Measurement of FE_{NO} [20]: • Rapid-response chemoluminescence analyser (CLD 88, EcoMedics AG, Duernten, Switzerland), with a range of 0–100 ppb • Breath-by-breath measurement and single-breath manoeuvre, with mouth-piece, no nasal clamp • Main outcome parameter: mean FE_{NO} 3. Multiple breath washouts (N_2): • Ultrasonic flowmeter (see above), mouthpiece, filter, nasal clamp • Main outcome parameters: lung volume (FRC) and ventilation inhomogeneity (LCI) 4. Single breath washouts (helium, SF_6) • Ultrasonic flowmeter (see above), mouthpiece, filter, nasal clamp • Main outcome parameters: Sacin, Scond 5. Spirometry (body plethysmography): • MasterScreen Body, Jaeger, Germany, mouthpiece, filter, nasal clamp • Main outcome parameters: lung volume (FRC, intrathoracic gas volume), forced expiratory flows and volumes
3. Telephone interviews	• Respiratory symptoms (including cough and wheeze during day and night, difficulty breathing, reduced activity) • Standardised score to group symptoms into four levels according to severity and with high sensitivity for lower respiratory tract infections • Main outcome parameter: weeks with severe respiratory symptoms (defined as total number of weeks with day/night score of ≥3 • Any changes in environment such as moving, pets, smoking habits, childcare, breastfeeding, nutrition • Medication, e.g., exact time point, kind and duration of antibiotics
3. Nasal swabs	• Microbiota analysis: microbiota assessment with PCR amplification of the 16S ribosomal RNA (rRNA) gene and 454 amplicon sequencing as described previously [22, 23] • Virological analysis: real-time (7 duplex) PCR will be used to used detect respiratory viruses as previously described [24]
4. Respiratory rate measurements	• Assessed over 60 seconds by hand on infant's chest in quiet sleep state • Assessed over 60 seconds by a study nurse in awake children at study visit 3 and 4
6. Skin prick test	• Dog dander, cat dander, *Dermatophagoides pteronyssinus*, mixed tree pollens, mixed grass pollens, *Alternaria tenuis*, positive control (histamine), negative control (NaCl) (Allergomed, Switzerland)
7. Magnetic resonance imaging	• Starting in 2018 • Matrix pencil decomposition, a new functional MRI method • Morphological MRI • Main outcome: ventilation and perfusion indices

ETS = environmental tobacco smoke; FE_{NO} = exhaled nitric oxide; FRC = functional residual capacity; LCI = lung clearance index, MRI = magnetic resonance imaging; PCR = polymerase chain-reaction * Pulmonary exacerbation is defined as any increase in respiratory symptoms from baseline that require a doctoral visit and additional treatment and/or decline in lung function measurement. † Specific reasons for hospitalisations are documented including respiratory, gastrointestinal problems or any other.

(planned for 2018). Details on the specific time points for assessments are displayed in figure 1. Further details of data collection are displayed in table 1.

Data collection

1. *Standardised questionnaires*

   Questionnaire one is administered at the baseline study visit [15, 16]. It is a validated questionnaire that has been used previously in the BILD cohort and other birth cohort studies [15, 16]. Information about health conditions, sociodemographic and environmental exposures are assessed, including pre-, peri-, and postnatal risk factors and family history. Questionnaires two to five will be used during phases 2 (at second follow up visit) and 3 (at the third follow up visit) [14]. Parent and child versions of the validated cystic fibrosis questionnaire (CFQ-R) [17, 25] are used to assess disease-specific health-related quality of life in patients with cystic fibrosis. In addition, we collect data from two previously validated questionnaires used in the BILD study to assess overall respiratory health [14]. Details on the assessed data are provided in table 1.

2. *Lung function measurements*

   Infant lung function measurements are performed at the age of 4 to 12 weeks (baseline study visit) during quiet natural sleep in the supine position, and at the age of 1 year (first follow up visit) under sedation with chloral hydrate (75–100 mg/kg bodyweight, applied rectally) according to current guidelines for infant lung function testing [26–28]. Preschool lung function measurement is performed in awake children at the second (age 3 to 4 years) and third (age 6 years) follow-up visit. Preschool lung function measurements are performed in a seated, upright position during regular breathing according to current guidelines [29, 30]. Details on the lung function tests and their outcome parameters are provided in table 1.

3. *Weekly telephone interviews*

   Throughout the first year of life study nurses conduct a standardized weekly telephone interview to track respiratory health. A standardised score (equivalent to the BILD cohort) with high sensitivity to detect lower respiratory tract infections will be calculated [31]. In addition, the questionnaire documents changes in sociodemographic and environmental exposures, medical history and antibiotic use (table 1).

4. *Nasal swab material*

   An anterior nasal swab (FLOQSwabs™, in UTM-RT™, Copan, Italy) is collected weekly during phase 1 by parents, who are instructed by study nurses about correct and standardised swab sampling. In addition, monthly nasal swabs at home and quarterly oropharyngeal swabs at clinic visits will be collected during phase 2 (throughout the year the child is 3 years of age) and phase 3 (throughout the year the child is 6 years of age). Immediately after collection, nasal swabs are sent to our study centre and frozen at −80°C until further processing. Microbiological detection and quantification of viruses and bacteria are performed in specialised laboratories specified in table 1. These analyses are for research purposes only and have no influence on the clinical treatment of the participants.

5. *Respiratory rate*

   During the first year of the infant's life, parents measure the respiratory rate every week. At the baseline study visit, parents are instructed by study nurses how to correctly measure respiratory rate in the home setting. The respiratory rate is measured for 60 seconds in quiet sleep (non-rapid eye movement), excluding periods of active sleep state, by the parents placing their hand on the child's chest. At the second and third follow-up visit respiratory rate is measured by a study nurse in awake children.

6. *Skin prick test*

   A maternal skin prick test is performed at baseline study visit and a child skin prick test at the third follow-up visit at 6 years of age. Details on tested allergens are provided in table 1.

7. *Functional and morphological chest MRI (planned for 2018)*

   We plan to establish chest MRI in the SCILD cohort at the follow-up visits at the age of three to four and six years, beginning in 2018. To overcome the need for contrast agents, a new functional MRI technique, termed matrix pencil decomposition, a derivative of the Fourier decomposition method, was developed for evaluation of regional ventilation and perfusion impairment of the lung [32–36]. This novel MRI technique provides visual and numerical information on functional deficits in perfusion and ventilation of the lung, without the need for intravenous contrast, inhaled tracers or breath-holding manoeuvres [37]. Functional MRI has the potential to detect ventilation and perfusion impairment, which may be the earliest and reversible manifestations of cystic fibrosis lung disease [37]. Morphological assessment will be based on a protocol previously described by Eichinger et al. for MRI in cystic fibrosis [38]. MRI has not been performed in the BILD cohort yet, but is also planned for the future.

We attempt to access data from each source in every participant; however, it is not mandatory to participate in all aspects of data collection, such as weekly nasal swab sampling and/or respiratory rate measurements, and infant lung function tests are also optional. The latter did not yet apply to any potential participants. In addition, they do not have to attend every study phase.

Study participants

At end of 2017, 70 infants with cystic fibrosis had been recruited in the SCILD study. Of these, 56 (80%) have completed the first year of study, and 14 (20%) have not yet reached one year of age and are still completing the first study phase.

Details on demographic data can be found in table 2. To date there have been no infants lost to follow up in phase 1 of the study and all infants completed the first year of the study. The second and third follow-up visits will begin

in 2018. Recruitment is ongoing, with approximately 9 to 13 newly diagnosed infants recruited per year (incidence of cystic fibrosis diagnosed by new-born screening approximately 25/year [1]); for details see table 3.

Summary of published studies from the SCILD cohort

Publications to date have focused primarily on longitudinal microbial and viral analyses of the nasal swab material and infant lung function measurements over the first year of life [24, 39, 40, 41]. All studies have included healthy infants from the BILD cohort as control group.

Composition of the nasal microbiota in infants with cystic fibrosis

The microbiota is known to play an important role in human health, with important influences on early adaptive immunity and innate resistance to infection [42, 43]. Recent studies suggest that diversity of the microbiota is lower in children with cystic fibrosis than in healthy children, and diversity decreases following the onset of chronic *Pseudomonas* infection [44–46]. However, little is known about the entire composition of the upper respiratory tract microbiota in infants with cystic fibrosis. We analysed the nasal microbiota longitudinally in 30 infants with cystic fibrosis (461 samples) compared with 47 healthy controls (872 samples). We identified compositional differences in the microbiota of infants with cystic fibrosis compared with healthy controls [39]. Furthermore, a disordered microbiota was found following antibiotic administration. Our data indicate that the microbiota is altered in infants with cystic fibrosis and that early antibiotic therapy influences the microbiota. These findings can be used to inform future studies on the effect of antibiotic treatment on the microbiota in infants with cystic fibrosis, and might be of importance in prevention of early disease progression [39].

Role of viral colonisation in early cystic fibrosis lung disease

Acute viral respiratory tract infections in children and adults with cystic fibrosis play a significant role in morbidity and mortality [47]. However, data about viral detection during infancy remains scarce [48]. We assessed 12 different respiratory viruses in 31 infants with cystic fibrosis (665 samples) and 32 healthy infants (712 samples) in a prospective longitudinal study during the first year of life. By weekly monitoring of respiratory symptoms, we could distinguish between asymptomatic and symptomatic viral detection. In our study, viral detection was not more frequent in cystic fibrosis infants than in healthy controls, and infants with cystic fibrosis were less symptomatic when a virus was present. We can only speculate about underlying reasons, but local epithelial properties, immunological mechanisms and even early treatment could play a role in viral detection and symptoms at the time of detection in early cystic fibrosis lung disease [24].

Lung function measurements in cystic fibrosis infants

It is unknown at what age lung function impairment may arise in children with cystic fibrosis. We assessed lung function (multiple breath washout and tidal breathing parameters) shortly after birth in 53 infants with cystic fibrosis diagnosed by new-born screening and 57 healthy controls. We reported that more than 40% of eight-week-old infants with cystic fibrosis showed abnormal lung function inde-

Table 2: Demographic details of the study population.

	Mean	Standard deviation	Total number of measurements
Gestational age (weeks)	39.2	1.5	70
Birth height (cm)	49	1.8	70
Birth weight (kg)	3.2	0.4	70
Age at infant lung function testing (weeks)	6	2.3	68*
Weekly telephone calls† (calls per infant)	38.4	13.7	2614
Weekly respiratory rate† (measurements per infant)	30.0	16.8	1915
Weekly nasal swabs† (per infant)	28.7	17.1	1955

Results are displayed as total numbers if not stated otherwise. To date, 70 infants with cystic fibrosis have been included in the study, of whom 56 have completed study phase 1. * In two infants lung function measurements were not successful, because no quiet, regular sleep episode could be obtained. † All infants are included, standard deviations are large, as some infants just started the study period and data collection is still ongoing

Table 3: Numbers of recruited participants in the SCILD cohort (2011–2017).

	Year	Total (2011–2016)						
	2011		2012	2013	2014	2015	2016	2017
Infants with CF detected by NBS*	56		19	35	20	23	n.a.‡	153
Recruited after positive NBS†	9	12	8	9	8	10	14	70
Completed study phase 1	9	12	8	9	8	10	–	56
Drop-outs during study phase 1	–	–	–	–	–	–	–	–
Phase 2 (starts in 2018)	–	–	–	–	2018/19	2019/20	2020/21	
Phase 3 (starts in 2018)	2018	2018	2019	2020	2021	2022	2023	

CF = cystic fibrosis; NBS = new-born screening * Infants that were diagnosed with CF throughout Switzerland † Infants that were recruited in the SCILD study ‡ Numbers for 2017 are not yet available

pendent of clinical symptoms and previous therapeutic approaches. Ventilation inhomogeneity or hyperinflation may serve as noninvasive markers for monitoring cystic fibrosis lung disease and specific treatment effects, and could thus be used as outcome parameters for future intervention studies in this age group [40].

Lower exhaled nitric oxide in infants with cystic fibrosis

The fractional concentration of exhaled nitric oxide (FE_{NO}) is a well-known biomarker for airway inflammation and is elevated in a number of inflammatory lung diseases [49]. However, despite chronic severe airway inflammation in patients with cystic fibrosis, FE_{NO} levels are decreased [50]. In order to understand whether reduced FE_{NO} in cystic fibrosis airways is primarily related to the loss of function of the cystic fibrosis transmembrane regulator (CFTR) or an epiphenomenon of chronic inflammation, we measured FE_{NO} in infants with cystic fibrosis and healthy controls at the age of 5 to 12 weeks prior to first respiratory infection. Airway FE_{NO} was reduced in young infants with cystic fibrosis, and the effect was more pronounced in infants with two copies of class I and/or II mutations and thus without CFTR function [41]. Hence, low FE_{NO} levels in cystic fibrosis airways shortly after birth are likely to be associated with underlying CFTR dysfunction. As reduced levels of FE_{NO} have been linked to a number of adverse effects, including effects on the defence mechanisms of the respiratory tract, this finding might open up a new chapter of research in the field of early FE_{NO} measurements in patients with cystic fibrosis.

Conclusion

Summary

The SCILD cohort includes infants with cystic fibrosis from early infancy until childhood recruited throughout Switzerland. Therefore, the course of the disease can be prospectively followed throughout early childhood. The dataset of the SCILD cohort combines lung function data, collection of environmental and sociodemographic factors, documentation of respiratory symptoms, and microbiological analyses. Lung function surveillance at several time points (after birth, at 1, 3 to 4, and 6 years of age) allows data collection during important phases of lung development. Weekly questionnaires and surveillance during the first year of life allow close monitoring during both asymptomatic and symptomatic episodes of the disease. This study design has resulted in over 2500 data points about respiratory health being collected to date and almost 2000 nasal samples being collected. This design not only allows tracking of the cystic fibrosis lung disease independent of clinical status, but also surveillance of early disease prior to severe clinical symptoms.

Strengths and limitations

The SCILD cohort is the only prospective birth cohort investigating cystic fibrosis disease in Switzerland and the third ever established in the world, in addition to the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) and the London Cystic Fibrosis Collaboration (LCFC) [51]. The latter cohort, however, recruits from centres in London only. Whereas all three cohorts focus on lung function measurements and aim to find diagnostic tools to monitor early lung impairment [52–54], novel aspects of the SCILD study are the close monitoring by weekly nasal sampling and phone calls. With the newly developed MRI imaging technique, there is no need for radiation or sedation [37, 55]. Furthermore, results are always compared with a contemporary healthy control group, the BILD cohort, for whom data are collected at the same study centre with a similar study design and setting. This comparability throughout the study period is an important feature of our study population.

The incidence of cystic fibrosis in Switzerland is approximately 1:3300 live births [1], thus the number of infants diagnosed with cystic fibrosis per year is relatively low in Switzerland (incidence approximately 25/year [1]). In previous years, logistical and disease-specific factors (e.g., prolonged hospital stay of infants due to meconium ileus, parents who are not able to travel to Bern for the measurements because of long travel distances, delayed diagnosis of cystic fibrosis after the age of 15 weeks) have led to a lower than expected number of recruited patients, which is a weakness of the study. Specific questions (e.g., stratifying by the different causative mutations) might not be possible until additional subjects are recruited, as numbers are too low for certain subgroup analyses. However, continued recruitment of newly diagnosed infants with cystic fibrosis and healthy controls throughout the planned follow-up period will ensure numbers sufficient to address the aim to investigate the physiological properties of the respiratory system and detect risk factors that influence lung development.

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Potential competing interests

PL has received personal fees from Gilead, Novartis, Polyphor, Roche, Schwabe, Vertex, Vifor and Zambon.

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