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Original Article

Lung structural and functional impairments in young children with cystic fibrosis diagnosed following newborn screening – A nationwide observational study☆

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ABSTRACT

Background: Non-invasive and sensitive clinical endpoints are needed to monitor onset and progression of early lung disease in children with cystic fibrosis (CF). We compared lung clearance index (LCI), FEV_1, functional and structural lung magnetic resonance imaging (MRI) outcomes in Swiss children with CF diagnosed following newborn screening.

Methods: Lung function (LCI, FEV_1) and unsedated functional and structural lung MRI was performed in 79 clinically stable children with CF (3 – 8 years) and 75 age-matched healthy controls. Clinical information was collected throughout childhood.

Results: LCI, ventilation and perfusion defects, and structural MRI scores were significantly higher in children with CF compared with controls, but FEV_1 was not different between groups. Lung MRI outcomes correlated significantly with LCI (morphology score ($r = 0.56$, $p < 0.001$); ventilation defects ($r = 0.43$, $p = 0.001$); perfusion defects ($r = 0.64$, $p < 0.001$), but not with FEV_1. Lung MRI outcomes were more sensitive to detect impairments in children with CF (abnormal ventilation and perfusion outcomes in 47 %, morphology score in 30 %) compared with lung function (abnormal LCI in 21 % and FEV_1 in 4.8 %). Pulmonary exacerbations, respiratory hospitalizations, and increase in patient-reported cough was associated with higher LCI and higher structural and functional MRI outcomes.

Author contributions: BF, CW, KR, and PL were responsible for the conception and design of this study. Data acquisition was conducted by BF, JC, CW, YS, EK, IK, CC, AM, JU, NR. BF, CW, EK, IK, AM, KR, and PL were responsible for data interpretation. The statistical analysis was conducted by BF and CW. BF, KR, and PL drafted the manuscript and all authors revised and approved the manuscript for intellectual content before submission.☆ Funding and support: This project was funded by the Swiss National Science Foundation, Grant Nr. 168173 (K.A. Ramsey) and 182719 (P.Latzin) and CF Switzerland (P.Latzin).

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Conclusions: The LCI and lung MRI outcomes non-invasively detect even mild early lung disease in young children with CF diagnosed following newborn screening. Pulmonary exacerbations and early respiratory symptoms were risk factors for structural and functional impairment in childhood.

1. Introduction

Cystic fibrosis (CF) is a genetic disease resulting in significant respiratory morbidity and mortality. Lung disease develops early in infants and young children with CF and progresses throughout life. The widespread adoption of newborn screening (NBS) for CF allows for diagnosis before onset of clinical signs and symptoms [1]. This provides an important window for early treatment of CF lung disease to preserve lung function, limit disease progression, and reduce morbidity [2,3].

Conventional methods to monitor lung disease in children are not optimal for routine clinical surveillance. Spirometry is difficult to perform in young children and FEV_1 remains within the normal range throughout childhood in most children with CF [4,5]. While chest computed tomography (CT) is sensitive to early CF structural lung disease, repeated scans throughout childhood causes cumulative ionizing radiation exposure [6]. Therefore, sensitive, non-invasive surveillance endpoints are needed to monitor lung disease onset and progression [1, 3,5].

Multiple breath washout (MBW) and magnetic resonance imaging (MRI) are increasingly used to monitor CF lung disease [7]. Lung clearance index (LCI) from the MBW technique is a sensitive measure of ventilation inhomogeneity associated with small airway disease [8,9]. LCI is more sensitive than spirometry to structural lung damage on chest CT [10] and to monitor disease progression in children with CF [11]. Advances in lung MRI methodology have allowed for greater spatial resolution and sensitivity to detect lung abnormalities in infants and young children with CF [3,12]. Lung MRI provides a non-invasive method to assess structural and functional defects in the lungs without the need for sedation, contrast agents, or complex breathing maneuvers [13]. The clinical utility of functional lung MRI technique and its association with lung function outcomes has not been investigated in young children with CF diagnosed following newborn-screening.

The widespread availability of disease-modifying Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulator therapies for CF will reduce disease severity, slow progression, and increase the life expectancy of patients with CF [14]. Therefore, non-invasive methods that are sensitive to assess mild early CF lung disease are needed in the care and management of adult CF lung disease in the future.

In this study, we aimed to i) compare lung function and structural and functional MRI outcomes between young children with CF diagnosed following newborn-screening and age-matched healthy controls, ii) assess structure-function and function-function associations between lung function and MRI outcomes, and iii) determine the clinical characteristics in infancy and early childhood associated with structural and functional impairment in children with CF.

2. Methods

2.1. Study population

This prospective, observational study includes children from two nationwide longitudinal cohort studies in Switzerland (study protocols [15,16] and newborn screening algorithm [17] described previously). Children with CF diagnosed following newborn-screening were recruited from all CF centres in Switzerland into the Swiss Cystic Fibrosis Infant Lung Development Cohort (SCILD) since 2011 [16]. The cohort study includes a first visit in Bern shortly after diagnosis (6 weeks) and 1 year of age. Participating children were invited to a follow-up study visit in early childhood (3–8 years). This manuscript reports on the lung function and MRI data gathered at the early childhood follow-up. Inclusion criteria for CF participants were positive newborn screening with evidence of two disease-causing mutations [17] and being clinically stable at study visit [18]. We also included aged-matched healthy children from a prospective, unselected birth cohort, the Basel-Bern Infant Lung Development Cohort (BILD) [15] with no history of respiratory disease. Written informed consent was obtained from caregivers at study entry and the study was approved by the local ethics committee in Bern.

2.2. Multiple breath washout and spirometry

Multiple breath nitrogen (N_2) washout was performed using a commercially available, validated setup (Exhalyzer D; Eco Medics AG, Duernten, Switzerland). Data were analyzed using Spiroware 3.3.1 (reloaded in this software version if collected in a previous version) and quality controlled according to international guidelines [19-21]. MBW tests with at least two acceptable trials were included in our analysis and the lung clearance index (LCI) calculated at 2.5 % exhaled N_2 concentration. Spirometry was performed after MBW according to guidelines (Jaeger MasterScreen, CareFusion, Hochberg, Germany).

2.3. Magnetic resonance imaging

Magnetic resonance imaging was performed on a 1.5 T whole-body MRI scanner (MAGNETOM Aera; Siemens, Healthineers, Erlangen, Germany) without sedation and contrast agents [22]. Matrix-Pencil (MP)-MRI was used for functional imaging, consisting of free-breathing, time-resolved multi-slice acquisitions [23]. Ventilation- and perfusion-weighted maps were determined and ventilation defect percentage (VDP) and perfusion defect percentage (QDP) endpoints calculated [24]. Structural pulse sequences consisted of respiratory triggered coronal, T2-weighted fast spin-echo with fat saturation and steady-state gradient echo sequence and 3D T1/T2-weighted ultra-fast steady state free precession [7]. Coronal and transverse T2-weighted single-shot fast spin-echo was performed as multi-breath-hold in patients older than 5 years or during free breathing in younger patients. In children older than 5 years, additional axial T1-weighted spoiled gradient pulse echo sequence was performed during a breath-hold maneuver. Structural scans were independently reviewed and scored by two experienced pediatric radiologists and the mean morphology score was used for analysis [25].

2.4. Clinical history

To determine the impact of respiratory events throughout childhood, we gathered electronic patient records from infancy onwards (respiratory symptoms, treatment, pulmonary exacerbations, hospitalizations for intravenous antibiotics or severe respiratory complications, and pathogen colonization) from routine three-monthly clinical surveillance and in-patient visits at contributing CF centres throughout Switzerland. Pathogen colonization was assessed from throat swabs (collected every three months) and colonization status over the entire study period defined as either intermittent (<50 % of samples positive for respective pathogens) or chronic (>50 % samples positive) [26]. In Switzerland, prophylactic inhalation therapy with isotonic or hypertonic saline is commonly prescribed from infancy onwards but prophylactic anti-staphylococcal antibiotics are not. Pulmonary exacerbations were classified based on modified Fuchs criteria [18]. To determine the impact of early clinical characteristics on disease outcomes in childhood, we analyzed these factors in the first year of life, during the whole

life until the study visit, and in the year prior to the study visit.

2.5. Statistical analysis

To verify that our cohort is representative of the wider CF community, we compared baseline characteristics to registry data for the entire newborn-screened CF population across Switzerland using unpaired *t*-tests (Supplemental Table 1). We then assessed whether surveillance outcomes (LCI, FEV_1, MRI morphology score, VDP, QDP) differed between our healthy and CF populations using Mann-Whitney tests. We calculated the upper limit of normal for all surveillance outcomes based on data from our healthy study participants as the mean outcome + 1.96*standard deviation (SD). We calculated the proportion of children with CF that had outcomes above the upper limit of normal and used Spearman correlation coefficients to assess associations between lung function and imaging outcomes.

Next, we assessed the impact of respiratory events throughout childhood with surveillance outcomes at study visit. We first specified unadjusted linear regression models using LCI, FEV_1, VDP, QDP as the outcome and the clinical characteristics (hospitalizations, pulmonary exacerbations, patient-reported cough, pathogen colonization) as the exposure (for further details see online supplement). Pathogen colonization was considered as individual pathogens or combined as proinflammatory pathogens (*S.aureus, Haemophilus influenzae, Pseudomonas aeruginosa or Aspergillus fumigatus*) [27]. We then specified a multivariable linear regression model to assess the impact of multiple explanatory variables on the outcome. As a sensitivity analysis, we adjusted the analysis for covariates that may influence the causal path between exposure and outcome as previously discussed in literature [11,28,29].

Robust standard errors were used to control for heteroscedasticity of the residuals. Statistical analyses were performed using Stata 16.0 (StataCorp 2019, College Station; TX).

3. Results

3.1. Study population

Compared with the Swiss CF newborn-screening registry, children enrolled in the SCILD cohort were a representative sample of the entire newborn-screened CF population across Switzerland (Supplemental Table 1).

Seventy-nine children with CF from the SCILD cohort participated in a follow-up study visit in early childhood between January 2018 and July 2021. Seventy-five healthy controls from the BILD cohort with study visits between November 2013 and May 2021 were available for comparison. Children with CF were well matched to healthy controls in terms of age and height, weight, and BMI z-scores (Table 1). Only three patients with CF were on Lumacaftor/Ivacaftor, Ivacaftor or Tezacaftor/Elexacaftor/Ivacaftor at the follow-up visit and these children were not excluded from our study population. After quality control a total 67 (84.8 %) MBW tests, 62 (78.5 %) spirometries and 58 (73.4 %) lung MRIs were available for children with CF. In the healthy controls a total of 75 (100 %) MBW tests and 35 (46.7 %) spirometries were available. Lung MRI was attempted in 16 (21.3 %) controls, with a 100 % success rate.

3.2. Surveillance endpoints elevated in children with CF

The LCI, MRI morphology score, VDP, and QDP were significantly higher in children with CF compared with healthy controls (Table 1). There were no differences in FEV_1 from spirometry or functional residual capacity from MBW between the two populations. Twenty-one percent of children with CF had an LCI above the upper limit of normal (LCI $\geq$ 7.4 TO) compared with 4.8 % who had an abnormal FEV_1 ($FEV_1 \leq -1.96$ z-score). Thirty percent of children with CF had an MRI morphology score above the upper limit of normal (1.5) and half the children with CF had signs of functional impairment on MRI, 47 % for VDP (ULN 16.6 %), and 48 % for QDP (ULN 17.9 %).

3.3. Associations between lung function and MRI outcomes

LCI was significantly associated with the total MRI morphology score ($r = 0.56, p < 0.001$), bronchial wall thickening/bronchiectasis ($r = 0.60$ $p < 0.001$), mucus plugging ($r = 0.30$ $p = 0.03$), and ventilation ($r = 0.43$, $p = 0.001$) and perfusion defects ($r = 0.64$, $p < 0.001$) on MRI (Fig. 1).

There were no associations between FEV_1 and LCI ($r = -0.15$, $p = 0.27$) or FEV_1 and the total MRI morphology score ($r = 0.16$, $p = 0.31$), bronchial wall thickening/bronchiectasis ($r = 0.15$, $p = 0.32$), mucus plugging ($r = -0.24$, $p = 0.87$), and ventilation ($r = -0.05$, $p = 0.72$) and perfusion defects ($r = -0.15$, $p = 0.33$) on MRI (Supplemental Figure 1).

The total MRI morphology score significantly correlated with both the ventilation ($r = 0.62, p < 0.001$) and perfusion defect percentages (*r*

Table 1
Demographics and study endpoints in children with CF and healthy controls.

	Cystic Fibrosis		Healthy controls		Mean difference	95 %CI		P-value	ULN	% CF > ULN
n	79		75							
Female, n(%)	39	(49)	36	(48)						
Age, years	5.7	(±1.3)	6.1	(±0.3)	0.4	[0.09 to	0.7]	**0.013**		
Weight, z-score	0.0	(±1.0)	0.1	(±0.9)	0.1	[−0.1 to	0.5]	0.53		
Height, z-score	−0.1	(±0.9)	0.3	(±1.0)	0.4	[0.07 to	0.7]	**0.03**		
BMI, z-score	0.1	(±1.0)	0.0	(±0.9)	−0.2	[−0.4 to	0.2]	0.26		
CFTR-Modulator*	3	(4 %)								
Lung function										
FEV_1, L	1.2	(±0.3)	1.2	(±0.2)	−0.01	[−0.1 to	0.1]	0.92		
FEV_1, z-score	−0.1	(±1.2)	0.1	(±0.9)	0.18	[−0.3 to	0.6]	0.44	−1.96	4.8 %
LCI, TO	6.9	(±1.0)	6.2	(±0.6)	−0.7	[−0.9 to	−0.4]	<**0.001**	7.4	21 %
FRC, L	0.8	(±0.2)	0.9	(±0.2)	0.0	[−0.03 to	0.09]	0.39		
Magnetic resonance imaging										
Structural lung disease	1.6	(±2.0)	0.4	(±0.5)	−1.2	[−2.2 to	−0.2]	**0.024**	1.5	30 %
Wall thickening / bronchiectasis	1.2	(±1.3)	0.4	(±0.4)	−0.8	[−1.5 to	−0.2]	**0.012**	1.2	33 %
Mucus plugging	0.2	(±0.6)	0.03	(±0.13)	−0.2	[−0.5 to	0.1]	0.24	0.28	18 %
VDP,%	16.7	(±5.9)	11.2	(±2.8)	−5.5	[−8.5 to	−2.5]	**0.001**	16.6	47 %
QDP,%	18.3	(±5.3)	13.7	(±2.2)	−4.5	[−7.2 to	−1.8]	**0.002**	17.9	48 %

Data presented as mean (standard deviation) or n(%). P value from *t*- test. Structural lung disease was evaluated by MRI morphological score. *One patient was on Tezacaftor/Elexacaftor/Ivacaftor for three months, one was on Ivacaftor for two years and one was on Lumacaftor/Ivacaftor for 6 months prior to the study visit. Abbreviations: ULN: upper limit of normal, CFTR: Cystic fibrosis Transmembrane Conductance Regulator, FEV_1: Forced expiratory volume in one second, LCI: Lung clearance index, FRC: Functional residual capacity, VDP: Ventilation defect percentage, QDP: Perfusion defect percentage.

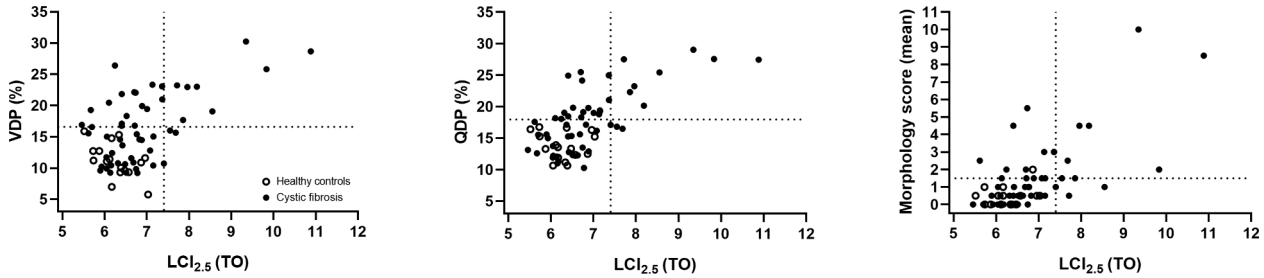

Fig. 1. Correlation between lung clearance index (LCI), and functional and structural MRI for patients with cystic fibrosis (CF) and healthy controls (HC). a) Ventilation defect percentage (VDP) (CF: $r = 0.43$, $p = 0.001$; HC: $r = 0.-0.59$, $p = 0.0159$), b) perfusion defect percentage (QDP) (CF: $r = 0.64$, $p < 0.001$; HC: $r = -0.21$, $p = 0.44$), and c) mean Morphology score (CF: $r = 0.56$, $p < 0.001$; HC: $r = 0.09$, $p = 0.75$). Estimated upper limit of normal is given as dashed lines for all modalities and was derived from the healthy controls population: LCI 7.4 lung turnovers (TO), VDP 16.6%, QDP 17.9% and Morphology score 1.5 points.

= 0.63, $p < 0.001$) (Fig. 2). Both bronchial wall thickening/bronchiectasis and mucus plugging scores correlated with both ventilation and perfusion defects (online supplement).

3.4. Impact of clinical respiratory events in infancy on surveillance outcomes

We found that pulmonary exacerbations (LCI: 0.46 unit increase (95 % confidence interval (CI) 0.05, 0.88) $p = 0.03$) and hospitalizations for intravenous antibiotics or severe respiratory complications (MRI morphology score: 0.92 (0.09, 1.76) $p = 0.03$; VDP: 3.71 % (0.67, 6.74) $p = 0.02$) in the first year of life were independently associated with impaired lung function and structural disease in childhood (Table 2). Pathogen colonization and cough in the first year of life were not associated with outcomes in childhood. In a multivariable linear regression analysis, pulmonary exacerbations in the first year of life were associated with later LCI and hospitalisations for intravenous antibiotics or severe respiratory complications were associated with later MRI morphology scores and ventilation defect percentages (Table 3).

3.5. Impact of clinical respiratory events throughout childhood on surveillance outcomes

Hospitalizations during childhood for a severe respiratory complication or exacerbations were also independently associated with increased structural and functional impairment on MRI in early childhood (MRI morphology score: 0.93 (0.02, 1.84) $p = 0.05$; VDP: 4.5 % (1.71, 7.30) $p < 0.01$; QDP: 2.66 % (0.09, 5.23) $p = 0.04$) (Table 4). Other clinical respiratory events and pathogen colonization throughout childhood were not significantly associated with lung function or MRI outcome impairment. In a multivariable linear regression analysis, hospitalisations during childhood were associated with later MRI ventilation defect percentages, but not MRI morphology scores or perfusion defects. Pulmonary exacerbations and cough were associated with later FEV1 z-scores (Table 5). We did not identify any clinical confounder (early pathogen colonization, sex, age, CFTR function) that influenced the association between respiratory events throughout childhood and surveillance outcomes (Supplemental Table 2).

3.6. Impact of recent clinical respiratory events on surveillance outcomes

Pulmonary exacerbations in the year preceding the study visit were associated with higher functional and structural impairment (Supplemental Table 3, (LCI: 0.23 unit increase (0.07, 0.39) $p < 0.01$; MRI morphology score: 0.6 (0.05, 1.14) $p = 0.03$; VDP: 1.15 % (−0.01, 2.31, $p = 0.05$, QDP: 0.97 % (0.01, 1.94) $p = 0.047$). Hospitalizations were associated with higher functional impairment on MRI (VDP: 6.92 % (0.33, 13.52) $p = 0.04$; QDP 5.77 % (0.47, 11.07) $p = 0.03$). Reporting increased cough was associated with increased functional and structural lung impairment (LCI: 0.03 unit increase (0.11, 0.49) $p < 0.01$; MRI morphology score: 0.78 (0.25, 1.31) $p < 0.01$; VDP: 1.7 % (0.52, 2.87) $p < 0.01$; QDP: 1.72 % (0.80, 2.64) $p < 0.001$). Colonization with *S. aureus* in the year before the study visit was associated with increased functional impairment on MRI (VDP: 4.55 % (1.62,7.48) $p < 0.01$; QDP: 3.77 % (1.16,6.39) $p < 0.01$). In a multivariable linear regression analysis, hospitalisations for intravenous antibiotics or increased coughing in the preceding year were associated with MRI morphology scores, increased coughing and presence of S.aureus in oropharyngel swabs also with ventilation and perfusion defect percentages (Supplemental Table 4). These associations were not influenced by potential clinical confounders (Supplemental Table 5).

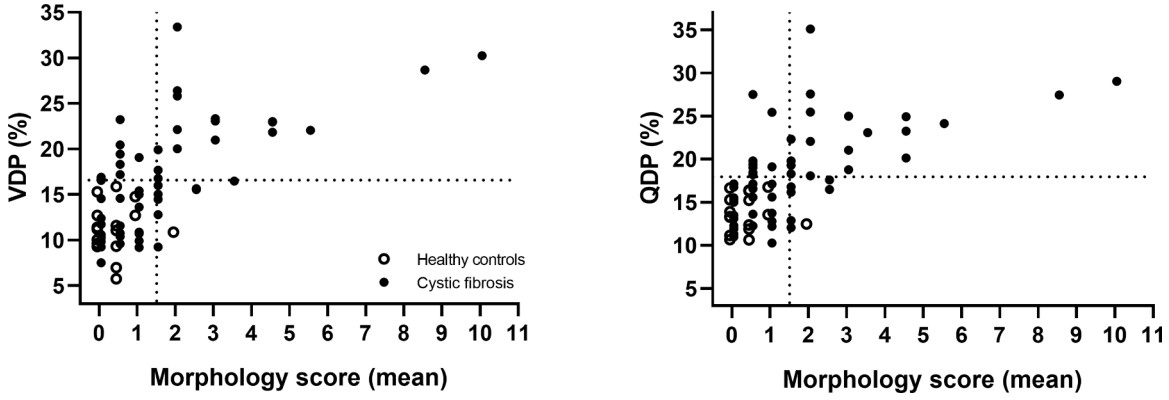

Fig. 2. Correlation between structural MRI (morphology score) and functional MRI for patients with cystic fibrosis (CF) and healthy controls. a) Ventilation defect percentage (VDP) ($r = 0.62$, $p < 0.001$), and b) perfusion defect percentage (QDP) ($r = 0.63$, $p < 0.001$). Estimated upper limit of normal is given as dashed lines for all modalities and was derived from the healthy controls population: VDP 16.6%, QDP 17.9% and mean Morphology score 1.5 points.

Table 2
Univariable regression analysis of the impact of clinical respiratory events in infancy on surveillance outcomes in individuals with cystic fibrosis.

FIRST YEAR OF LIFE	LCI	FEV_1	MRI Morphology score	MRI Ventilation defect (%)	MRI Perfusion defect (%)
Exacerbation ($n = 49$)	**0.46 (0.05, 0.88); $p = 0.03$**	0.06 (−0.62, 0.73); $p = 0.87$	0.49 (−0.32, 1.29); $p = 0.23$	1.35 (−1.71, 4.41); $p = 0.38$	2.03 (−0.07, 4.75); $p = 0.14$
Hospitalization ($n = 36$)	0.41 (−0.07, 0.89); $p = 0.09$	0.27 (−0.35, 0.90); $p = 0.38$	**0.92 (0.09, 1.76); $p = 0.03$**	**3.71 (0.67, 6.74); $p = 0.02$**	1.81 (−1.10, 4.72); $p = 0.22$
Cough ($n = 51$)	0.02 (−0.09, 0.12); $p = 0.75$	−0.06 (−0.26, 0.14); $p = 0.53$	0.12 (−0.14, 0.38); $p = 0.37$	0.08 (−0.71, 0.88); $p = 0.83$	0.06 (−0.79, 0.91); $p = 0.89$
Proinflammatory pathogens ($n = 54$)	−0.26 (−0.85, 0.34); $p = 0.39$	0.67 (−0.09, 1.43); $p = 0.08$	0.55 (−0.24, 1.34); $p = 0.16$	−0.22 (−3.25, 2.80); $p = 0.88$	0.44 (−2.56, 3.45); $p = 0.77$

Data is given as coefficient (95 % confidence interval) from univariable linear regression. Clinical respiratory events were considered if experienced at least once during the first year of life. Cough is considered if children were reported to cough more than usual. Proinflammatory pathogens were considered if any of the following bacteria were present: Staphylococcus aureus, Haemophilus influenzae, Pseudomonas aeruginosa, Aspergillus fumigatus. Abbreviations: LCI: Lung clearance index, FEV_1: Forced expiratory volume in one second. P-values < 0.05 are considered statistically significant.

Table 3
Multivariable analysis of the impact of clinical respiratory events in infancy on surveillance outcomes in individuals with cystic fibrosis.

FIRST YEAR OF LIFE	LCI	FEV_1	MRI Morphology score	MRI Ventilation defect (%)	MRI Perfusion defect (%)
Exacerbation ($n = 49$)	**0.66 (0.08,1.25); $p = 0.03$**	0.2 (−0.74,1.15); $p = 0.67$	0.84 (−0.13,1.81); $p = 0.09$	0.95 (−2.06,3.96); $p = 0.53$	2.28 (−0.48,5.04); $p = 0.10$
Hospitalization ($n = 36$)	0.47 (0.03,0.97); $p = 0.06$	0.17 (−0.47,0.80); $p = 0.60$	**0.8 (0.04,1.56); $p = 0.04$**	**4.39 (0.42,8.35); $p = 0.03$**	1.57 (−2.03,5.18); $p = 0.38$
Cough ($n = 51$)	−0.43 (1.05,0.19); $p = 0.17$	−0.38 (−1.34,0.59); $p = 0.44$	−0.82 (−1.92,0.27); $p = 0.14$	−0.61 (−3.52,2.31); $p = 0.68$	−0.82 (−3.69,2.05); $p = 0.57$
Proinflammatory pathogens ($n = 54$)	−0.5 (−1.11,0.10); $p = 0.10$	0.61 (−0.18,1.40); $p = 0.13$	0.15 (−0.53,0.84); $p = 0.66$	−2.3 (−5.68,1.07); $p = 0.18$	−0.59 (−4.12,2.94); $p = 0.74$

Data is given as coefficient (95 % confidence interval) from multivariable linear regression. Clinical respiratory events were considered if experienced at least once during the first year of life. Cough is considered if children were reported to cough more than usual. Proinflammatory pathogens were considered if any of the following bacteria were present: Staphylococcus aureus, Haemophilus influenzae, Pseudomonas aeruginosa, Aspergillus fumigatus. Abbreviations: LCI: Lung clearance index, FEV_1: Forced expiratory volume in one second. P-values < 0.05 are considered statistically significant.

Table 4
Univariable regression analysis of the impact of clinical respiratory events throughout childhood on surveillance outcomes in individuals with cystic fibrosis.

All childhood (Birth – Follow up)	LCI	FEV_1	MRI Morphology score	MRI Ventilation defect (%)	MRI Perfusion defect (%)
Age	0.01 (−0.19, 0.20); $p = 0.94$	**0.33 (0.12, 0.54); $p < 0.01$**	−0.02 (−0.62, 0.59); $p = 0.95$	1.41 (−0.18, 3.00); $p = 0.08$	0.73 (−0.81, 2.27); $p = 0.35$
Pulmonary exacerbations					
< 50 % visits ($n = 66$)					
≥ 50 % visits ($n = 13$)	0.33 (0.24,0.90): $p = 0.26$	−0.48 (−1.15,0.19): $p = 0.17$	1.58 (−0.45,3.61): $p = 0.12$	1.69 (−2.93, 6.31): $p = 0.47$	2.41 (−1.74, 6.56): $p = 0.25$
Hospitalizations					
Never ($n = 35$)					
Ever ($n = 44$)	0.38 (−0.08, 0.83); $p = 0.10$	0.29 (−0.31, 0.90); $p = 0.34$	**0.93 (0.02, 1.84); $p = 0.05$**	**4.50 (1.71, 7.30); $p < 0.01$**	**2.66 (0.09, 5.23); $p = 0.04$**
Cough					
< 50 % visits ($n = 66$)					
≥ 50 % visits ($n = 13$)	0.26 (−0.29,0.81); $p = 0.35$	−0.32 (−0.98,0.34); $p = 0.34$	1.47(−0.71, 3.64); $p = 0.18$	0.06 (−4.69, 4.80); $p = 0.98$	0.56 (−3.60, 4.72); $p = 0.79$
Proinflammatory pathogens					
Intermittent ($n = 46$)					
Chronic ($n = 33$)	0.36 (−0.14,0.86); $p = 0.15$	0.15 (−0.42,0.73); $p = 0.6$	0.99 (−0.11, 2.09); $p = 0.08$	1.62 (−1.59, 4.83); $p = 0.32$	2.09 (−0.77, 4.95); $p = 0.15$

Data is given as coefficient (95 % confidence interval) from univariable linear regression. Clinical respiratory events were either considered as present ever / never during the study period or if in less or more than 50 % of the visits present. Cough is considered if children were reported to cough more than usual. Proinflammatory pathogens were considered as intermittent (<50 % of the visits with pathogen sampled), or chronic (≥50 % of the visits with pathogen sampled) if any of the following bacteria were present: Staphylococcus aureus, Haemophilus influenzae, Pseudomonas aeruginosa, Aspergillus fumigatus. Abbreviations: LCI: Lung clearance index, FEV_1: Forced expiratory volume in one second. P-values < 0.05 are considered statistically significant.

4. Discussion

We found that lung disease in this newborn-screened prospective, nationwide CF cohort in Switzerland is generally mild, even pre CFTR-modulator exposure and without prophylactic anti-staphylococcal treatement. LCI and MRI outcomes are sensitive to identify mild lung disease. Functional and structural lung MRI was more sensitive than lung function techniques to assess lung disease in young children with CF and MBW was more sensitive than spirometry. Pulmonary exacerbations, respiratory hospitalizations, and increase in patient-reported cough were associated with structural and functional impairments in early childhood. These results support the use of LCI and MRI as

Table 5
Multivariable analysis of the impact of clinical respiratory events throughout childhood on surveillance outcomes in individuals with cystic fibrosis.

All childhood (Birth – Follow up)	LCI	FEV_1	MRI Morphology score	MRI Ventilation defect (%)	MRI Perfusion defect (%)
Pulmonary exacerbations					
< 50 % visits ($n = 66$)					
≥ 50 % visits ($n = 13$)	0.01 (−0.93,0.95); $p = 0.98$	**−1.29 (−1.95,−0.62); $p < 0.01$**	0.69 (−1.71,3.10); $p = 0.56$	2.63 (−2.46,7.73); $p = 0.30$	4.24 (−0.71,9.19); $p = 0.09$
Hospitalizations					
Never ($n = 35$)					
Ever ($n = 44$)	0.25 (−0.30,0.80); $p = 0.37$	0.37 (0.30,1.03); $p = 0.27$	0.5 (−0.25,1.26); $p = 0.18$	**4.66 (1.77,7.54); $p < 0.01$**	1.85 (−0.69,4.40); $p = 0.15$
Cough					
< 50 % visits ($n = 66$)					
≥ 50 % visits ($n = 13$)	0.14 (−0.70,0.98); $p = 0.74$	**0.72 (0.14,1.31); $p = 0.02$**	0.61 (−1.82,3.05); $p = 0.61$	−2.92 (−8.30,2.47); $p = 0.28$	−3.7 (−8.72,1.31); $p = 0.14$
Proinflammatory pathogens					
Intermittent ($n = 46$)					
Chronic ($n = 33$)	0.22 (−0.34,0.79); $p = 0.44$	0.17 (0.48,0.82); $p = 0.61$	0.41 (−0.58,1.41); $p = 0.41$	−0.8 (−4.08,2.48); $p = 0.63$	0.65 (−2.33,3.63); $p = 0.66$

Data is given as coefficient (95 % confidence interval) from multivariable linear regression. Clinical respiratory events were either considered as present ever / never during the study period or if in less or more than 50 % of the visits present. Cough is considered if children were reported to cough more than usual. Proinflammatory pathogens were considered as intermittent (<50 % of the visits with pathogen sampled), or chronic (≥50 % of the visits with pathogen sampled) if any of the following bacteria were present: Staphylococcus aureus, Haemophilus influenzae, Pseudomonas aeruginosa, Aspergillus fumigatus. Abbreviations: LCI: Lung clearance index, FEV_1: Forced expiratory volume in one second. P-values < 0.05 are considered statistically significant.

sensitive, non-invasive methods for early detection and monitoring of lung disease in children with CF.

4.1. Comparison with literature

We confirmed results from previous studies that LCI is more sensitive than FEV_1 to detect early CF lung disease [4,5,11,30]. In our study, mean LCI was higher in children with CF compared with healthy controls, but LCI was only above the upper limit of normal in 21 % of children with CF. This proportion is lower than in previous studies, which have shown that between 50 and 70 % of young children with CF have abnormal LCI values [31]. One influencing factor might be the advances in supportive therapies in the past years [32]. Our MBW data were also analyzed using the most recently updated software version for the Eco Medics device, which includes a correction for a previously unknown sensor error resulting in over-estimated LCI values [33]. We found that corrected LCI values were still more sensitive than spirometry to detect early CF lung disease. As children gain access to highly effective modulator therapies from early age and spirometry outcomes are preserved into adulthood, LCI will play a key role in clinical monitoring of the disease progression.

MRI provides a non-invasive method to visualize and quantify both structural and functional deficits in the lung [7]. We have previously shown that unsedated lung MRI is feasible in young children with CF [22]. We demonstrated that MRI outcomes were more sensitive than lung function to detect early lung disease in children with CF. Structural abnormalities were detected in 30 % and functional deficits in 50 % of children with CF, compared with 5 % abnormal spirometry and 21 % abnormal LCI values. Lung MRI outcomes were elevated in a significant proportion of children with normal LCI values. The extent of structural lung damage on morphological MRI scans was low, with a mean morphological score of 1.0, and a maximum score of 10 out of 60. This supports findings from previous studies using MRI [12] and chest CT imaging [4,34] which have shown that structural lung disease is mild in young children with CF diagnosed following newborn screening.

In addition, the MP-MRI technique allows fast acquisition of functional MRI data during regular tidal breathing without the need for sedation or the administration of intravenous or gaseous contrast agents. The technique can be applied on standard clinical MRI scanners and does not require additional hardware, hyperpolarized gases, or specialized staff, making it more appropriate for clinical application in children than dynamic contrast enhanced or hyperpolarized gas MRI [12,35]. We found that ventilation and perfusion defect outcomes were the most sensitive to differentiate between children with CF and healthy controls. Previous studies have demonstrated the sensitivity of functional and structural lung MRI to detect lung disease in clinically-diagnosed CF populations [7]. Our study provides further evidence, that structural and functional MRI is a sensitive and non-invasive method for longitudinal surveillance of lung disease in individuals with CF, particularly those with normal lung function.

We demonstrated that early pulmonary exacerbations, hospitalizations for respiratory complications and pulmonary exacerbations, and increase in patient-reported cough in infancy and throughout childhood were associated with structural and functional abnormalities in childhood. We did not find significant associations between early respiratory pathogen colonization and childhood surveillance outcomes, which is in contrast to previous studies utilizing bronchoalveolar lavage (BAL) collection to detect respiratory pathogens [36]. Throat swabs were routinely used for pathogen sampling in our cohort, which are less sensitive than BAL or sputum samples and may explain the divergent findings. In addition, prophylactic anti-staphylococcal antibiotic therapy is not routinely administered in Switzerland [37]. While there is increasing appreciation for the role of oral pathogen aspiration and viral infections in the initiation of early CF lung disease [11,12], our findings confirm that lung disease is rather mild in contemporary new-born screened cohort even without prophylactic anti-staphylococcal antibiotic therapy. We found that children presenting with respiratory symptoms and both mild and severe pulmonary exacerbations in early childhood should be considered at higher risk of developing more severe lung disease.

4.2. Strength and limitations

A strength of the present study is the prospective assessment of lung function and structural and functional lung MRI in both children with CF and healthy controls. The application of structural and functional MRI in early childhood provided novel insights into lung disease in young children with CF without the need for invasive procedures or sedation. We also had detailed information on respiratory symptoms throughout childhood available allowing us to determine the impact of early life events on later lung function outcomes. However, we did not collect chest CT or lower respiratory tract lung fluid samples, which limited our

ability to compare results directly with other studies [31,36].

4.3. Conclusion

We demonstrated that LCI and functional and structural lung MRI outcomes are sensitive and non-invasive surveillance strategies in children with CF following newborn screening and before the era of the novel CFTR modulator therapies, even without anti-staphylococcal treatment. Overall, the mild lung disease detected in our cohort can encourage patients and their families to continue early specialist CF treatment and therapies (e.g. physiotherapy, inhalation therapies) to preserve their lung function throughout childhood. With modulator therapies now available for younger patients, the need for sensitive and non-invasive outcomes to monitor early lung disease will be crucial. Further, longitudinal studies are needed to provide more insight into the evolution of structural and functional lung disease over time and whether prophylactic antibiotic therapy in early childhood is still needed.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Prof. P. Latzin reports the followind COIs:

- Grants from Vertex and OM Pharma paid to the institution
- Participation on data safety monitoring boards or advisory boards of Polyphor, Santhera DMC, Vertex, OM Pharma, Vifor, Sanofi Aventis
- Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Vertex, Vifor, OM Pharma

Jakob Usemann reports:

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2024.05.010.

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