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Respiratory symptoms do not reflect functional impairment in early CF lung disease

Insa Korten^a, Marc-Alexander Oestreich^{a,b}, Urs Frey^c, Alexander Moeller^d, Andreas Jung^d, Renate Spinas^d, Dominik Mueller-Suter^e, Daniel Trachsel^c, Isabelle Rochat^f, Ben Spycher^g, Philipp Latzin^a, Carmen Casaulta^a, Kathryn Ramsey^{a,*}, for the SCILD, and BILD, study group^{1,2}

^a Division of Paediatric Respiratory Medicine and Allergology, Department of Paediatrics, Inselspital, Bern University Hospital, University of Bern, Switzerland

^b Graduate School for Health Sciences, University of Bern, Switzerland

^c University of Basel Children's Hospital (UKBB), Basel, Switzerland

^d Division of Respiratory Medicine, University Children's Hospital Zurich, Switzerland

^e Division of Respiratory Medicine, Children's Hospital Aarau, Switzerland

^f Department of Paediatrics, Respiratory Unit, Lausanne University Hospital, Lausanne, Switzerland

^g Institute for Social and Preventive Medicine, University of Bern, Switzerland

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ABSTRACT

Background: Lung disease can develop within the first year of life in infants with cystic fibrosis (CF). However, the frequency and severity of respiratory symptoms in infancy are not known.

Methods: We assessed respiratory symptoms in 50 infants with CF and 50 healthy matched controls from two prospective birth cohort studies. Respiratory symptoms and respiratory rate were documented by standardized weekly interviews throughout the first year. Infants performed multiple breath washout in the first weeks of life.

Results: We analyzed 4552 data points (2217 in CF). Respiratory symptoms (either mild or severe) were not more frequent in infants with CF (OR:1.1;95% CI:[0.76, 1.59]; p=0.6). Higher lung clearance index and higher respiratory rate in infants with CF were not associated with respiratory symptoms.

Conclusions: We found no difference in respiratory symptoms between healthy and CF infants. These data indicate that early CF lung disease may not be captured by clinical presentation alone.

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* Corresponding author at: Paediatric Respiratory Medicine, University Children's Hospital of Bern, University of Bern, Switzerland.

E-mail address: Kathryn.ramsey@extern.insel.ch (K. Ramsey).

¹ Swiss Cystic Fibrosis Infant Lung Development (SCILD) cohort, current study group: Juerg Barben, MD, St. Gallen; Sylvain Blanchon, MD, Lausanne; Carmen Casaulta, MD, Bern; Andreas Hector, MD, Zurich; Andreas Jung, MD, Zurich; Elisabeth Kieninger, MD, PhD, Bern; Insa Korten, MD, Bern; Philipp Latzin, MD, PhD, Bern; Alexander Moeller, MD, Zurich; Anne Mornand, MD, Geneva; Dominik Mueller-Suter, MD, Aarau; Kathryn Ramsey, PhD, Bern; Nicolas Regamey, MD, Lucerne; Isabelle Rochat MD, Lausanne; Tina Schürmann, MD, Zurich; Florian Singer, MD, PhD, Bern; Renate Spinas, MD, Zurich; Daniel Trachsel, MD, Basel; Sophie Yammine, MD, PhD, Bern; Maura Zanolari, MD, Bellinzona.

² Basel Bern Infant Lung Development (BILD) cohort, current study group: Fabienne Decrue, MD, Basel; Urs Frey, MD, PhD, Basel; Oliver Fuchs, MD, PhD, Bern; Amanda Gisler, MD, Basel; Olga Gorlanova, MD, Basel; Claudia E Kuehni, MD, PhD, Bern; Johanna Kurz, Bern; Philipp Latzin, MD, PhD, Bern; Loretta Müller, PhD, Bern;

1. Introduction

The introduction of newborn screening (NBS) for cystic fibrosis (CF) has allowed for diagnosis shortly after birth and access to specialized treatment [1,2]. Neutrophil inflammation, bacterial colonization and structural damage can occur within the first year of life in children with CF [3–5], and these early events are associated with lung function decline and respiratory morbidity later in life [6,7]. While these early manifestations of lung disease can be detected in asymptomatic infants with CF, they are more likely to occur in infants with respiratory symptoms [8].

Marc-Alexander Oestreich, MD, Bern; Yasmin Salem Mahmoud, MD, Bern; Andras Soti, MD, Bern; Jakob Usemann, MD, PhD, Basel; Corin Willers, MD, Bern; Sophie Yammine, MD, PhD, Bern

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Respiratory symptoms in infants with CF have been associated with impaired lung function outcomes at preschool age [9]. However, the frequency and severity of respiratory symptoms in CF during the first year of life have not been investigated systematically. While several studies have examined respiratory symptoms and the risk factors for respiratory infections in healthy infants, there are limited data in infants with CF [10–13]. Most of our knowledge in individuals with CF is drawn from periods of pulmonary exacerbations in older children and adults [9,14]. Therefore, it is not known whether infants with CF develop more respiratory symptoms than healthy controls over the first year of life.

In the longitudinal Swiss CF Infant Lung-Development (SCILD) cohort, we have previously shown that lung function outcomes, respiratory rate, and microbiota composition differ between infants with CF and healthy infants, whereas the number of symptomatic respiratory viral infections were similar over the first year of life [15–19]. In this study we aimed to i) prospectively assess the number and severity of respiratory symptoms in the first year of life in infants with CF compared with healthy controls, ii) determine whether infant lung function outcomes are associated with subsequent respiratory symptoms in infants with CF, and iii) to identify potential risk factors for respiratory symptoms in early CF disease.

2. Methods

2.1. Study design and population

In this prospective study, we enrolled infants with CF from the Swiss CF Infant Lung-Development (SCILD) cohort [20] and healthy infants from the Basel-Bern Infant Lung Development (BILD) cohort [21] (www.scild.ch and www.bild-cohort.ch). Infants born between 2011 and 2016, who had at least 40 weeks of longitudinal surveillance were included. All infants with CF were diagnosed following NBS and thus most did not present with respiratory symptoms prior to study enrollment. Healthy controls were matched according to season of birth, sex, having siblings or not, and attendance at childcare (none of the CF infants or healthy infants in our study attended childcare). Detailed inclusion and exclusion criteria are reported in the supplementary material, characteristics of the study population are displayed in Table 1.

At the baseline study visit, at age four to thirteen weeks, we assessed pre- and perinatal information through a standardized interview with the parent and performed infant lung function testing. During the first year of life, the child's health status, antibiotic treatment, respiratory symptoms and respiratory rate were prospectively assessed by standardized weekly telephone interviews [21] (see below). The study was performed in the University Children's Hospital of Bern, University of Bern, Switzerland and approved by the Ethics committee Bern, Switzerland. Informed written consent was obtained from all parents.

2.2. Respiratory symptoms

Symptoms of lower and upper respiratory tract infections, wheeze and/or cough were recorded in standardized weekly telephone interviews conducted by a study nurse [21]. Based on reported symptoms, we calculated a symptom score with a high sensitivity for lower respiratory-tract infections (LRTIs) [22], ranging from 0 (no symptoms) to 4 (severe respiratory symptoms). The scoring system has been previously used to investigate respiratory symptoms in infants by others and us [21–23]. For details on the symptom score, see Table E1 in the supplement. Furthermore, we defined LRTIs as cough, wheeze and/or breathing difficulties in combination with upper respiratory tract symptoms or fever for more than two consecutive days. For data analysis, we classified

respiratory health in a given week as (i) free of respiratory symptoms, (ii) mild to moderate respiratory symptoms (symptom score > 0 and < 3 , but no LRTI) and (iii) severe respiratory symptoms (LRTI and/or symptom score ≥ 3).

2.3. Infant lung function and respiratory rate measurements

Infant lung function using the multiple breath washout technique was assessed in natural quiet sleep according to current guidelines [24–26]. Multiple breath washout (MBW) technique was performed using 4% sulfur hexafluoride (SF_6) as the inert tracer gas. The main outcome parameters were the functional residual capacity (FRC) and lung clearance index (LCI $_{2.5\%}$) [15]. Infant lung function and respiratory rate data in these cohorts have been published previously and therefore details on the methods are described elsewhere [15,17,25,26] and in the supplementary material. Lung function measurements were feasible in all but 15 CF patients and 6 healthy infants, which had to be excluded due to low quality of measurements. Parents measured respiratory rate weekly at home, after being instructed by a study nurse how to perform a correct measurement. We obtained data from 42 CF and 34 healthy infants, as participation in this part of study was optional.

2.4. Statistical analysis

First, we described the distribution (median (minimum – maximum)) of respiratory symptoms ((i) any (ii) mild and (iii) severe) among infants with CF and healthy infants in the first year of life. We then compared weeks with symptoms with CF status (CF/healthy) as exposure variable, fitting a multilevel logistic regression model, using a random effect to correct for correlation between multiple measurements in the same individual. In an additional model we compared the total number of weeks with symptoms in the first year of life between CF and healthy infants using Poisson regression models. To identify potential determinants for respiratory symptoms in infants with CF, we included the following potential predictors: sex; gestational age (linear in weeks), weight at birth (linear in kg); CFTR mutation (residual CFTR function yes/no); breastfeeding (yes/no); older siblings (yes/no); maternal smoking in pregnancy (yes/no), mode of delivery (vaginal or C-section), parental education (low/middle/high), maternal atopy (yes/no), LCI (linear in lung turnover), FRC (linear in ml/kg), age (younger/older 6 months) and season. We fitted univariable and multivariable (all selected variables) multilevel logistic regression models. All variables that had a p-value ≤ 0.1 (likelihood ratio test) in one or both of the multivariable models were included in the adjusted model for our primary aim (CF status as exposure of interest).

To investigate associations between respiratory rate and respiratory symptoms in CF infants, we chose respiratory rate measurement as outcome of interest and included the following possible predictors: respiratory symptoms (at week of measurement), respiratory symptoms in weeks per year (in quartiles, from no (1) to frequent weeks (4) with respiratory symptoms, siblings, season and age. Upper limit of normal (ULN) for LCI and FRC values were defined as mean $+1.64 \cdot \text{SD}$ (ULN90%) based on lung function data from the healthy infants from the BILD cohort in this study. Details of statistical analyses and power calculation can be found in the supplementary material. Statistical analyses were performed using Stata™ (Stata Statistical Software: Release 13. College Station, TX: StataCorp LP), figures were generated using GraphPad Prism 5.

Table 1
Demographics and Baseline Characteristics of Study Population.

		CF (n=50)	Healthy (n=50)
Anthropometrics	Sex (m)	26 (53)	27 (52)
	Gestational age at birth (weeks)*	39.1 (1.5)	39.5 (1.5)
	Length at birth (cm)*	48.9 (1.7)	49.2 (2.3)
	Birth weight (kg)*	3.2 (0.4)	3.3 (0.5)
CFTR mutation [‡]	No residual CFTR function (pancreatic insufficiency)	44 (88)	
	Residual CFTR function (pancreatic sufficiency)	6 (12)	
Nutrition	Breastfeeding (Bf)**	41 (82)	50 (97)
	Duration of Bf in months*	6.9 (4.1)	7.7 (3.1)
Environment	Siblings: 0	25 (50)	25 (50)
	1	17 (34)	15 (30)
	≥ 2	8 (16)	10 (20)
	Smoking in pregnancy	5 (10)	1 (4)
Parental education ^{‡‡}	Cesarean section	14 (28)	11 (22)
	Maternal atopy	11 (22)	10 (20)
	Low	19 (38)	17 (34)
	Middle	18 (36)	20 (40)
Lung function ^{††} measurements	High	13 (26)	13 (26)
	Lung Clearance Index (lung volume turnover)	7.6 (0.9)	7.5 (0.6)
	Functional Residual Capacity (ml/per kg)	25.0 (4.5)	21.8 (3.2)
Respiratory symptoms [†]	No. weeks assessed	45 (40 – 46)	45 (43–46)
	Weeks (%) with respiratory symptoms**	15 (0 – 71)	16 (0 – 44)
	Weeks (%) with mild respiratory symptoms ^{†††}	13 (0 – 56)	11 (0 – 38)
	No. of weeks (%) with severe respiratory symptoms ^{††††}	2 (0 – 20)	2 (0 – 11)
Respiratory rate	Baseline measurement at first study visit per min	41 (9.5)	35 (5.7)

Results are displayed in numbers (%) if not stated otherwise.

[†]Lung function measurements included lung clearance index (LCI) and functional residual capacity (FRC) at first study visit.

* Results are displayed as mean (SD).

[†] Results are displayed as median (range).

[‡] CF infants were grouped into (i) no residual CFTR function (pancreatic insufficient), (ii) residual CFTR function (pancreatic sufficient).

** breastfeeding referred to total amount of time and not to episode exclusively breastfed.

^{‡‡} Parental education is categorized into low (less than four years of apprenticeship), middle (at least four years of apprenticeship), and high (tertiary education).

^{||} Number of weeks in the first year of life per infant, during which respiratory symptoms were measured.

** Number of weeks in the first year of life, during which respiratory symptoms were recorded.

^{††} Number of weeks in the first year of life, during which mild to moderate respiratory symptoms were recorded (symptom score >0 and <3, no lower respiratory tract infection (LRTI)).

^{†††} Number of weeks in the first year of life, during which severe respiratory symptoms were recorded (symptom score ≥ 3 and/or LRTI).

3. Results

3.1. Study population

We included 50 infants with CF and 50 healthy infants in our study, resulting in 2217 data points in CF and in 2235 data points in healthy infants. Details on anthropometrics, environmental or nutritional status can be found in Table 1. The mean (SD) age at study inclusion was 9.0 (1.7) weeks for CF and 8.0 (0.0) weeks for healthy infants. The median (min-max) number of recorded weeks of surveillance per infant was 45 (40–46) weeks in CF and 45 (43 – 46) weeks in healthy infants. There were no significant differences in anthropometrics, environmental or nutritional status in infants with CF compared to healthy controls, except that infants with CF were slightly older when included in the study (1.8 and 2.1 months, respectively, $p < 0.001$).

3.2. Differences in respiratory symptoms between infants with CF and healthy infants

Respiratory symptoms were recorded in 7 (median; range 0 – 32) weeks in CF and 7 (0 – 20) weeks in healthy infants. Symptoms were mild to moderate in 6 (0–25) and 5 (0 – 15) weeks, and severe in 1 (0 – 9) and 1 (0 – 5) weeks in CF and healthy infants, respectively.

We compared respiratory symptoms between infants with CF and healthy infants throughout the first year of life using multi-level regression models. The number of weeks with any respiratory

symptoms (mild or severe) did not differ between CF and healthy in the univariable model (results not shown) or after adjustment for possible effect modifiers (age, season, having siblings, details in Table 2, Table E2, Fig. 1). CF infants were more likely to be treated with antibiotics during episodes with severe respiratory symptoms (43 vs. 16 weeks, OR: 4.0, 95% CI: 1.94 – 9.35, $p < 0.001$). In a sensitivity analysis, taking the total number of weeks with symptoms per infant as the outcome in a Poisson regression analysis, we found no difference between healthy and CF infants (IRR: 1.1, 95% CI: 0.93– 1.24; $p = 0.34$). In addition, duration of respiratory symptoms (counting the consecutive weeks with respiratory symptoms) was not different between CF and healthy infants (IRR: 1.12, 95% CI: 0.94 – 1.34; $p = 0.2$). Due to low numbers, we could not assess whether infants with more frequent respiratory symptoms in the first six months of life were at a higher risk for more respiratory symptoms in the subsequent six months (Fig. 2). Details on specific respiratory symptoms can be found in the supplement Table E3 and E4.

3.3. Risk factors for respiratory symptoms in infants with CF

We investigated possible predictors for respiratory symptoms for CF infants. In the univariable model, we found that those with more weeks of respiratory symptoms were older and had siblings. Infants with CF had less frequent respiratory symptoms during weeks of breastfeeding and during summer (details are provided in Table E5). The association between respiratory symptoms and breastfeeding was likely confounded by age, as no effect was seen

Table 2
Differences in respiratory symptoms between healthy and CF infants.

	Multivariable Variable*	model Category	OR	95% CI	p-value†† (LR-test)
Respiratory symptoms	CF status*	Healthy	1	[1.00,1.00]	0.6
		CF	1.1	[0.76,1.59]	
	Siblings‡	No	1	[1.00,1.00]	<0.001
		Yes	2.17	[1.50,3.14]	
	Age†	0-6 m	1	[1.00,1.00]	<0.001
		6-12 m	1.68	[1.40,2.01]	
	Season††	Summer	1	[1.00,1.00]	<0.001
		Spring	1.69	[1.30,2.21]	
Fall		2.00	[1.54,2.59]		
Winter		2.40	[1.86,3.10]		
Severe respiratory symptoms	CF status*	Healthy	1	[1.00,1.00]	0.45
		CF	1.19	[0.75,1.89]	
	Siblings‡	No	1	[1.00,1.00]	<0.001
		Yes	2.79	[1.71,4.54]	
	Age†	0-6 m	1	[1.00,1.00]	0.001
		6-12 m	1.85	[1.26,2.73]	
	Season††	Summer	1	[1.00,1.00]	<0.001
		Spring	1.90	[1.07,3.39]	
Fall		1.68	[0.93,3.03]		
Winter		3.17	[1.96,3.10]		

Logistic regression models investigating differences in respiratory symptoms and severe respiratory symptoms (outcome variables) between healthy and CF infants in a multivariable model adjusted for siblings, age and season.

OR: Odd ratio, CI: Confidence Interval

†† p-value: from likelihood ratio test.

+ all variables are included in the same model, displayed is the result for each variable (as exposure to respiratory symptoms) in the adjusted model.

* The reference category are healthy infants.

† Age displayed in two groups: the reference category is age below 6 months (m).

‡ The reference category are infants with no siblings.

†† Season is divided in the calendric seasons. The reference category is summer.

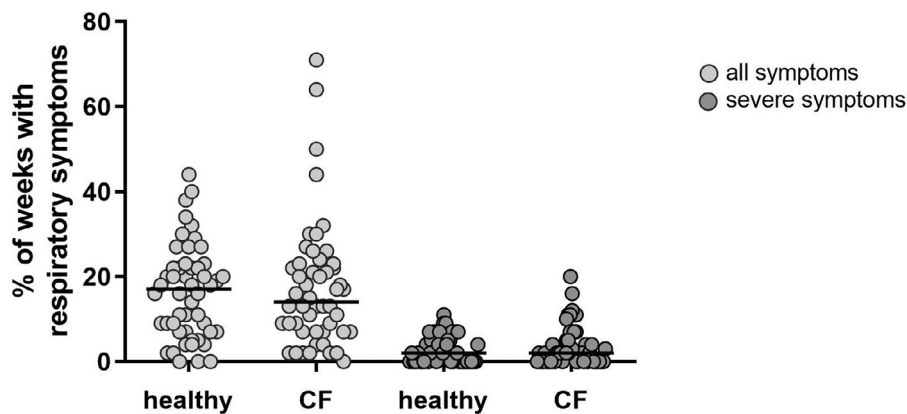


Fig. 1. a: Percentage of weeks with respiratory symptoms per infant in the first year of life. Displayed are all symptoms (light grey) and severe symptoms (dark grey) for healthy and CF infants. Fig. 1b: Number of weeks with severe respiratory symptoms in healthy and CF infants younger and older than 6 months of age. The colored symbols each represent a certain CF individual.

when age was included in the analysis (detailed results are provided in the supplement). Similar results were found when we assessed only mild or severe symptoms (results not shown) and in the multivariable analyses (adjusted for age, season and siblings) (Table 3). We found no association between respiratory symptoms and any of the other variables: sex, gestational age, weight at birth, smoking in pregnancy, mode of delivery, maternal atopy, parental education, LCI and FRC measurements (univariable analyses are displayed in Table E5 in the supplementary material).

3.4. Infant lung function measurement and respiratory symptoms

In infants with CF, no linear association was found between frequency of respiratory symptoms and LCI or FRC (Coeff: 1.06, CI:[0.72,1.55]; $p=0.8$ and 0.99 ; 95% CI: [0.92,1.07]; $p=0.9$, respec-

tively). Four infants with CF had LCI values above the ULN and eleven infants FRC values above the ULN. Values above the ULN were not associated with more severe respiratory symptoms (results not shown); however, numbers were too low for sufficient statistical analysis (Fig. 2a and b). We thus performed two additional sensitivity analyses, grouping the infants into infants with $LCI < 7.4$ and > 7.4 (below and above the 50th percentile) and into infants with $LCI < 8.0$ and ≥ 8.0 (below and above the 75th percentile). Results showed no associations between lung function outcomes and any, severe or mild symptoms in both analyses (results not shown).

We found that respiratory rate was transiently elevated during periods with severe respiratory symptoms (Coef 3.0; 95% CI: [1.50, 4.58]; $p < 0.001$) and in infants with impaired lung function shortly after birth (FRC: Coef -0.42; 95% CI: [-0.78, -0.07]; $p=0.02$,

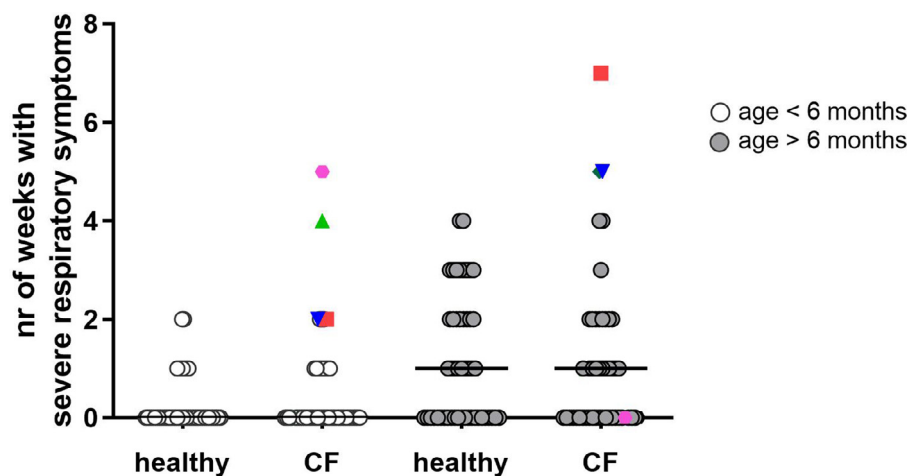


Fig. 1. Continued

Table 3
Predictors for respiratory symptoms in infants with cystic fibrosis.

	Variable	Category	OR	95% CI	p-value ^{††} (LR-test)
Respiratory symptoms	Siblings [‡]	No	1	[1.00,1.00]	0.011
		Yes	2.05	[1.18,3.55]	
	Age [§]	0-6 m	1	[1.00,1.00]	0.021
		6-12 m	1.34	[1.04,1.71]	
	Season ^{†††}	Summer	1	[1.00,1.00]	0.006
		Spring	1.45	[1.02,2.08]	
Fall		1.68	[1.19,2.37]		
Winter		1.74	[1.23,2.46]		
Severe respiratory symptoms	Siblings [‡]	No	1	[1.00,1.00]	0.013
		Yes	2.62	[1.23,5.59]	
	Age [§]	0-6 m	1	[1.00,1.00]	0.24
		6-12 m	1.35	[0.82,2.22]	
	Season ^{†††}	Summer	1	[1.00,1.00]	0.02
		Spring	1.81	[0.82,3.99]	
Fall		2.25	[1.04,4.85]		
Winter		2.93	[0.96,2.02]		
Mild to moderate respiratory symptoms	Siblings [‡]	No	1	[1.00,1.00]	0.04
		Yes	1.75	[1.03,2.95]	
	Age [§]	0-6 m	1	[1.00,1.00]	0.06
		6-12 m	1.29	[0.99,1.68]	
	Season ^{†††}	Summer	1	[1.00,1.00]	0.2
		Spring	1.34	[0.92,1.96]	
Fall		1.49	[1.03,2.14]		
Winter		1.40	[0.96,2.02]		

Possible predictors for respiratory symptoms in infants with CF and healthy infants. Displayed are only results from the multivariable model (all variables listed above in the same model).

OR.: Odds ratio, CI: Confidence Interval

[‡] The reference category are infants without siblings.

[§] Age displayed in 2 groups; the reference category is age below 6 months (m).

^{†††} season is divided in the calendric seasons. The reference category is summer.

^{††} p-value: from likelihood ratio test

for detailed results see Table E6 in the supplementary material). However, when we grouped the infants from less to more frequent respiratory symptoms in the first year (in quartiles), respiratory rate was not different between the four groups (highest quartile: Coef 0.58; 95% CI: [-4.33, 5.49]; p = 0.5), for detailed results see Table E6 in the supplementary material). Therefore, infants with more frequent respiratory symptoms did not have a higher respiratory rate over the first year of life (s. Figure E1 in the supplement)

We could not obtain acceptable lung function data and respiratory rate measurements in a small group of infants (for details see methods section). Thus, to confirm our results we compared these infants with the infants who completed all measurements. We found no differences in baseline characteristics, frequency and severity of respiratory symptoms in infants without lung function data or respiratory rate measurements.

5. Discussion

Respiratory symptoms were not more frequent in the first year of life in infants with CF compared to healthy controls in this prospective, observational study. In infants with CF, the frequency of respiratory symptoms increased with increasing age, depended on season, and symptoms were more frequent in infants with older siblings. In infants with CF, baseline LCI and FRC were not associated with subsequent respiratory symptoms, and those with more frequent respiratory symptoms in the first year of life did not have a higher respiratory rate. The lack of association between respiratory symptoms and early lung function or respiratory rate measurements indicates that early lung disease might not be captured by the clinical presentation in infants with CF.

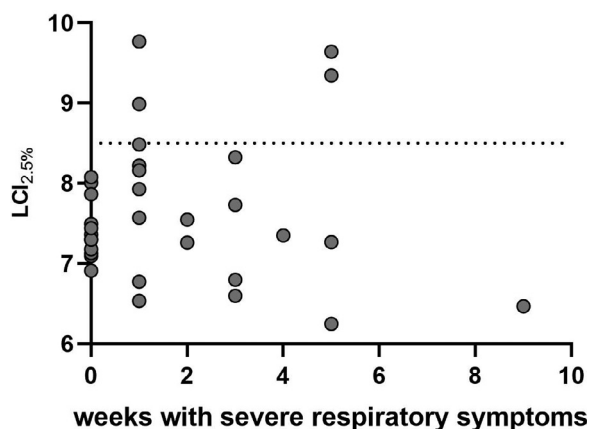


Fig. 2. a: Association of $LCI_{2.5\%}$ and consecutive weeks with severe respiratory symptoms in infants with CF within the first year of life. Each symbol represents one infant with CF. The dashed line is the ULN ($LCI_{2.5\%}$ 8.5). **Fig. 2b:** Association FRC (ml/kg) and consecutive weeks with severe respiratory symptoms in infants with CF within the first year of life. Each symbol represents one infant with CF. The dashed line is the ULN (FRC ml/kg 27.06).

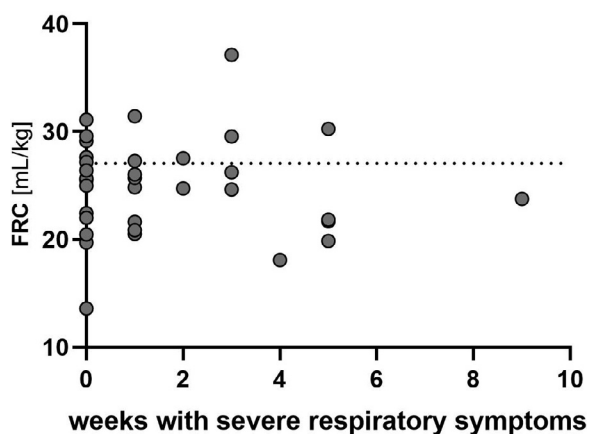


Fig. 2. Continued

5.1. Comparison with literature

This is the first study to compare weekly respiratory symptoms data between infants with CF and healthy controls in the first year of life using standardized questionnaires. We found that infants with CF have a median of 1 week with severe and 7 weeks with any respiratory symptoms in the first year of life. A study of children with CF aged 0–5 years reported a mean of 3.66 pulmonary exacerbations per person year, with higher numbers of exacerbations reported in toddlers and preschool children [9]. In the age group 0–1 year the authors reported 284 exacerbations in 168 children. Another study of young children with CF reported an average of 2.3 exacerbations per year, however the mean (SD) age of these children (2.3 (1.5) years) were older than in our study [27]. The PRECIS trial [28] reported an exacerbation rate of 1.1 (with regular hypertonic saline inhalation) and 1.2 (with regular isotonic saline inhalation) in infants with CF within the first year of life. These numbers are similar to our results. As we did not assess clinician defined exacerbations, but rather the number of weeks with parentally reported symptoms, it is not possible to directly compare these numbers.

In our study, infants with CF did not have more frequent or severe respiratory symptoms in the first year of life than healthy infants. We found no comparable studies that have examined respiratory symptoms in infants with CF and healthy controls over the

first year of life. Several studies have reported more frequent or severe respiratory symptoms in older children with CF compared to healthy controls [29]. One of these studies reported a similar frequency of acute respiratory illnesses in children with CF and healthy children, but they found longer periods of lower respiratory tract symptoms in the CF group [30].

We found that age, season, and siblings were predictors for respiratory symptoms in infants with CF. These predictors have previously been reported to be associated with respiratory symptoms in healthy infants by others and us [13,31–33]. An increased exposure to respiratory pathogens in children with older siblings (possibly attending childcare), with increasing age (increasing contact to other individuals and environment) and in winter (where respiratory viruses have their peak season) can explain these results in healthy and CF infants. As none of the infants in this study attended childcare, an important risk factor for airway infection could be excluded. The number of respiratory exacerbations has previously been shown to increase with age in children with CF [9]. Progression of lung damage and more frequent infections may result in more frequent respiratory symptoms with increasing age [34].

Lung function and respiratory rate were not associated with respiratory symptoms in our study. Lung function measurements were performed within the first weeks of life when infants were mostly asymptomatic. Infants with CF have been shown to have impaired lung function in the first year of life without overt respiratory symptoms [3,35]. Other studies have reported associations between respiratory symptoms and lung function outcomes during periods of pulmonary exacerbation in toddlers [31], school aged children, and adults with CF [36]. In toddlers and children, elevated LCI measurements, as well as ventilation and perfusion defects in magnetic resonance imaging (MRI), were reported in clinical stable patients and during exacerbations. While a strong association could be found between LCI and MRI, several patients had normal LCI values despite impaired MRI outcomes [37–39]. These data indicate that while LCI is a sensitive marker of early lung disease, it does not over-estimate the level of impairment.

We have previously shown that respiratory rate is higher in infants with CF compared with healthy infants in the first year of life and is transiently elevated during periods of severe respiratory symptoms in healthy and CF infants [17]. In the current study, we could reproduce these results with elevated respiratory rate during periods with respiratory symptoms. However, we found that elevated respiratory rate (weekly measurements investigating “individual baseline respiratory rate”) in the first year of life was not associated with a higher number of respiratory symptoms in infants with CF.

5.2. Clinical implications

Due to early diagnosis following newborn screening, all infants with CF in our cohort received medical care in a specialized CF center shortly after birth. In Switzerland, most infants with CF receive regular inhalation therapy; however, treatment can differ slightly between CF centers. We did not collect detailed information on inhalation therapy in this study. Infants with CF were more likely to receive antibiotic treatment during periods of respiratory symptoms compared to healthy controls. These precautionary measures are likely to influence respiratory outcomes in infants with CF. Only a small number (not statistically significant, but graphically visualized in Fig. 1a and b) presented as severely clinical ill at the beginning of life. The number of weeks with respiratory symptoms was not associated with early lung function measurements. This could suggest that lung function deficits are transient [40], however it could also indicate that early sub-clinical changes cannot be captured by the clinical presentation of the disease. The

latter hypothesis is supported by bronchioalveolar lavage studies which show that bacterial pathogens and markers of neutrophil inflammation were detected in the lungs of asymptomatic infants with CF [3,8,41]. Furthermore, we have previously shown that respiratory rate is consistently higher in infants with CF in the first year of life compared to healthy controls, which suggests the presence of early lung damage [17].

5.3. Strengths and limitations

A unique feature of our study is the longitudinal prospective study design with weekly follow-up throughout infancy. Respiratory symptoms were documented using a standardized symptom score. The BILD healthy infant cohort allowed us to directly compare the number of respiratory symptoms between infants with CF and contemporary healthy controls. Infant lung function and respiratory rate measurements were performed which allowed us to discriminate between clinical or subclinical changes. We evaluated parentally reported respiratory symptoms in our study but did not assess clinician-defined exacerbations. The focus of our study was to compare the frequency and duration of weekly respiratory symptoms between infants with CF and healthy infants. In order to reduce recall bias, experienced study nurses performed standardized interviews each week using a validated questionnaire. We requested information on antibiotic therapy, which can be used as a proxy for exacerbations, but did not assess any other clinical care or treatments in this multicenter study. It is likely that clinical treatment differed between centers and this may have influenced respiratory symptoms in the CF population. It is also possible that infants with CF who had higher LCI measurements received intensified treatment in some centers. These measures of precaution in CF infants might contribute to our results. A further limitation of the study is that lung function was only analyzed cross-sectionally and lung function outcomes may change throughout infancy [40]. Future studies investigating the course of lung function longitudinally in CF infants are required to determine whether early impairments is transient or track through childhood. Environmental smoking was not included as a confounder because there was a large overlap with smoking in pregnancy, the numbers were low, and there was no indoor smoking reported. Also, in this study we were not able to determine whether respiratory symptoms were caused by viral or bacterial infections or other causes. A further limitation of our study is the relatively small sample size of our study population. Sample size estimation was based on clinical considerations. If no difference in symptom frequency is detectable in groups of 50 patients, likely no clinically relevant consequences will be required. However, we cannot reject the hypothesis, that small differences in symptom patterns, further differences and/or additional risk factors are potentially detectable in very large epidemiological cohorts.

6. Conclusion

In conclusion, we found no difference in respiratory symptoms between infants with CF and healthy infants in the first year of life. The lack of association may be explained by the mild disease, early interventions (more frequent antibiotic therapy, regular inhalation therapy), and precautionary measures taken (e.g. not attending childcare) in our cohort of infants with CF diagnosed following NBS. Impaired lung function and respiratory rate outcomes in infants with CF were not associated with respiratory symptoms. The fact that CF infants do not show elevated symptoms in the first year of life indicates that early subclinical changes might not be captured by the clinical presentation of patients. Our findings support the assessment of early CF disease with sensitive measurements like MRI or MBW to capture earliest lung damage.

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Declaration of Competing Interest

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CRediT authorship contribution statement

Insa Korten: Conceptualization, Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Marc-Alexander Oestreich:** Investigation, Writing - review & editing. **Urs Frey:** Conceptualization, Writing - review & editing. **Alexander Moeller:** Data curation, Writing - review & editing. **Andreas Jung:** Data curation, Writing - review & editing. **Renate Spinass:** Data curation, Writing - review & editing. **Dominik Mueller-Suter:** Data curation, Writing - review & editing. **Daniel Trachsel:** Data curation, Writing - review & editing. **Isabelle Rochat:** Data curation, Writing - review & editing. **Ben Spycher:** Formal analysis, Writing - review & editing. **Philipp Latzin:** Conceptualization, Funding acquisition, Writing - review & editing. **Carmen Casaulta:** Conceptualization, Writing - review & editing. **Kathryn Ramsey:** Conceptualization, Funding acquisition, Writing - original draft, Writing - review & editing.

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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.2021.04.006](https://doi.org/10.1016/j.jcf.2021.04.006).

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