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Original Article

Risk factors for progression of structural lung disease in school-age children with cystic fibrosis

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ABSTRACT

Background: Computed tomography (CT) is used to monitor progression of structural lung disease (SLD) in children with cystic fibrosis (CF). Our goals were to identify the risk factors for the annual progression of SLD and the impacts of airway pathogens on SLD.

Method: Seventy-five school-aged children diagnosed with CF underwent 200 CT scans at Gothenburg CF Centre in the period 2003–2015. SLD was evaluated with a quantitative scoring system. Mixed models were used to calculate the yearly progression rates of SLD and FEV_1 and to analyse the effects of common airway pathogens in CF.

Results: The yearly mean progression (95% CI) rates for total disease (%Dis), bronchiectasis (%Be), and FEV_1 were 0.62 (0.38–0.86), 0.43 (0.28–0.58) and −0.16 (−0.18–0.13), respectively. Adjusting for airway pathogens, the yearly mean progression rates for %Dis, %Be and FEV_1 were 0.23 (−0.04–0.51), 0.12 (0.00–0.25), and −0.12 (−0.16–0.08), respectively. A single infection with *P aeruginosa* was associated with significant increase in lung damage, assessed as %Dis ($p = 0.044$) and%Be ($p = 0.0047$), but not in FEV_1 ($p = 0.96$). At age of 7 years, there was a good correlation between the extent of SLD and subsequent progression of %Dis ($r = 0.63$, $p = 0.0042$) and %Be ($r = 0.74$, $p = 0.0057$) while there was no significant correlation between the FEV_1 and the rate of decline of FEV_1 ($r = -0.22$, $p = 0.12$).

Conclusion: Intermittent respiratory infections with *P aeruginosa* were associated with significant SLD but no change in FEV_1. More SLD at the age of 7 years signals a higher progression rate of SLD subsequently.

1. Introduction

CF lung disease is monitored on a regular basis throughout life, with numerous modalities to detect and prevent progression of the disease [1]. Chest CT is the gold standard for assessing structural lung disease (SLD) [2]. The most important and well-described structural lung pathology in patients with CF is bronchiectasis, which is associated with a reduced quality of life and higher risk of pulmonary exacerbations [3,4].

Pulmonary infections play an important role in neutrophil-related inflammation in the lung, which is associated with faster progression of SLD [5,6]. It is not known to what extent intermittent and chronic infections with common CF airway pathogens causes SLD and influence the yearly SLD progression rate. Fully quantitative scoring systems to track smaller changes in SLD have primarily been used in pre-school children and have not been used in longitudinal studies in older children with CF [7]. Information gained from chest CTs has earlier been shown to identify infants and pre-school children who are at higher risk of more-rapid disease progression, although this has not been shown in school-age children with CF [4,7].

The aims of this retrospective, longitudinal study in school-age children were to: (1) describe the progression of CF lung dis-

Abbreviations: CF, Cystic fibrosis; SLD, structural lung damage; FEV_1, forced expiratory volume in one second; CT, computed tomography.

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ease in relation to different host factors; (2) describe how airway pathogens influence the degree of lung damage and SLD progression; (3) compare the abilities of chest CTs and FEV_1 values to identify individuals at risk of rapid progression of CF lung disease; (4) describe the relationships between SLD and FEV_1.

2. Methods

2.1. Study population

The study included 75 school-age children at the Gothenburg CF Centre born in the period 1990–2009 and diagnosed with cystic fibrosis"[8]. All the subjects underwent at least one chest CT during the period 2003–2015. Chest CTs were routinely performed every third year at the annual evaluation and on demand starting from 6 years of age. Spirometry were performed regularly between the ages 5–18. Demographic data for each subject were retrieved from the Swedish CF Registry. The study was approved by the local Ethics Committee (Dnr. 206-18)

2.2. CT acquisition

Chest CT's were performed with two different CT scanners: Light Speed Ultra (GE Healthcare Inc., USA); and Discovery CT750 HD (GE Healthcare Inc., USA). All scans were performed during voluntary breath hold-at-end inspiration and end expiration using a discontinuous scanning protocol. Inspiratory scans were applied at 15 mm between every 1-mm slice and generated on average 10–15 slices. On the expiratory scans, 1-mm slices were used with a distance of 30 mm between every slice, resulting on average in 3–4 slices.

2.3. CT analysis

The Perth-Rotterdam Annotated Grid Morphometric Analysis for Cystic Fibrosis (PRAGMA-CF) method was used to track changes in SLD [7]. PRAGMA-CF allows quantification of bronchiectasis (%Be), mucous, bronchial wall thickness, atelectasis, and normal lung structure on inspiratory scans, as well as trapped air (%Ta) and normal lung structure on expiratory scans. Normally, 10 equidistant axial slices are annotated on both the inspiratory and expiratory scans. However, due to the use of a sequential CT-protocol in this study, all the slices on the inspiratory scans (10–15 slices) and expiratory scans (3–4 slices) were annotated. The primary outcomes of the chest CT scans were total lung disease (%Dis), bronchiectasis (%Be), and trapped air (%Ta), expressed as the volume proportion of the respective pathology on the scan divided by the total volume of the scan.

All CT-scans were coded and randomised before being analysed. One PRAGMA-CF certified paediatric pulmonologist under training (MS) analysed all CT-scans [9]. After 1 month, 20 CT scans that were randomly selected and stratified for lung disease severity were re-scored to determine intra-observer repeatability.

2.4. Spirometry

Spirometry (Jaeger AG, Würzburg, Germany) was performed according to the ATS/ERS recommendations at the annual evaluation of the patient [10]. For FEV_1 assessment, the GLI reference equation was used, and the results are expressed as the z-score or percent-predicted [11].

2.5. Airway pathogen

Results for the period 1996–2015 from sputum cultures and cultures from laryngeal suction in non-sputum-producing individuals regarding *Pseudomonas aeruginosa* (Pa), *Mycobacterium abscessus* (Ma) *Burkholderia cepacia* complex (Bc), *Achromobacter xylosoxidans* (Ax), Aspergillus species (Asp), *Staphylococcus aureus* (Sa) and *Haemophilus influenzae* (Hi) were retrieved from the Department of Clinical Microbiology, Gothenburg. Complementary information about chronic and intermittent infections was also collected from the Swedish CF Registry. The registry summarises the yearly results of sputum cultures between annual evaluation for Pa, Ma, Bc, and Ax from diagnosis conducted at all shared health-care providers. Pa was categorised according to the Leeds criteria between every annual evaluation for each subject [12]. In order to apply Pa colonization to a longitudinal statistical model, the categories of 'never having Pa' and 'free of Pa' were pooled together. Other pathogens associated with severe lung infections in CF individuals, such as Ma, Bc, and Ax, were pooled together under the same criteria described above for Pa, due to the low numbers of patients who were infected with these pathogens [13,14]. Subjects were defined as having a temporary respiratory infection with Sa or Hi or Asp if they had a positive sputum culture for the respective organism.

2.6. Statistical analysis

For descriptive purposes, the data are presented as means and range for continuous variables and as numbers (%) for categorical variables. The intra-class correlation coefficient (ICC) was calculated to describe intra-observer variability for PRAGMA-CF.

Analysis of the longitudinal data was performed using mixed effects models with age as fixed effect, and with random intercepts and slopes for each subject. Two types of models were considered: a Gaussian linear mixed model for analysis of FEV_1; and quasi-binomial logit-linear mixed models for analysis of SLD. The latter was chosen because of the bounded, skewed and heteroscedastic nature of the SLD outcomes. After fitting the SLD models, it was judged that a simpler linear model would suffice, as the progressions were approximately linear, both at the population and subject levels. The SLD outcomes were therefore re-analysed with linear mixed models, using robust standard errors to account for heteroscedasticity.

Comparisons of sub-groups were performed by the inclusion of sub-group variables as fixed effects in the models. To assess whether disease progression differed between the sub-groups, a sub-group with age interaction was also included. We also studied the effects of a single and chronic respiratory infection by including the time-updated cumulative number of incidences and the number of years since the onset of chronic infection (only Pa, Ma, Bc or Ax) in the models.

We also evaluated the correlations between yearly progression of FEV_1 and SLD, and between progression and extent of disease at different ages. For each of FEV_1, %Dis, and %Be, correlations between progression and extent of disease were estimated from the covariance parameters of the mixed models and tested using likelihood ratio tests. Correlations between two different outcomes where calculated as Spearman's rank correlations for the estimated subject-specific parameters. In addition, concordance indices with 95% bootstrap confidence intervals were computed considering $c \geq 0.70$ providing acceptable model. Further details of the statistical analysis used are presented in the supplemental appendix.

The ICCs were computed using the SPSS ver. 23 software (IBM Corp, Armonk, NY, USA). All other statistical analyses were performed with the SAS ver. 9.4 software (SAS Institute, Cary, NC, USA).

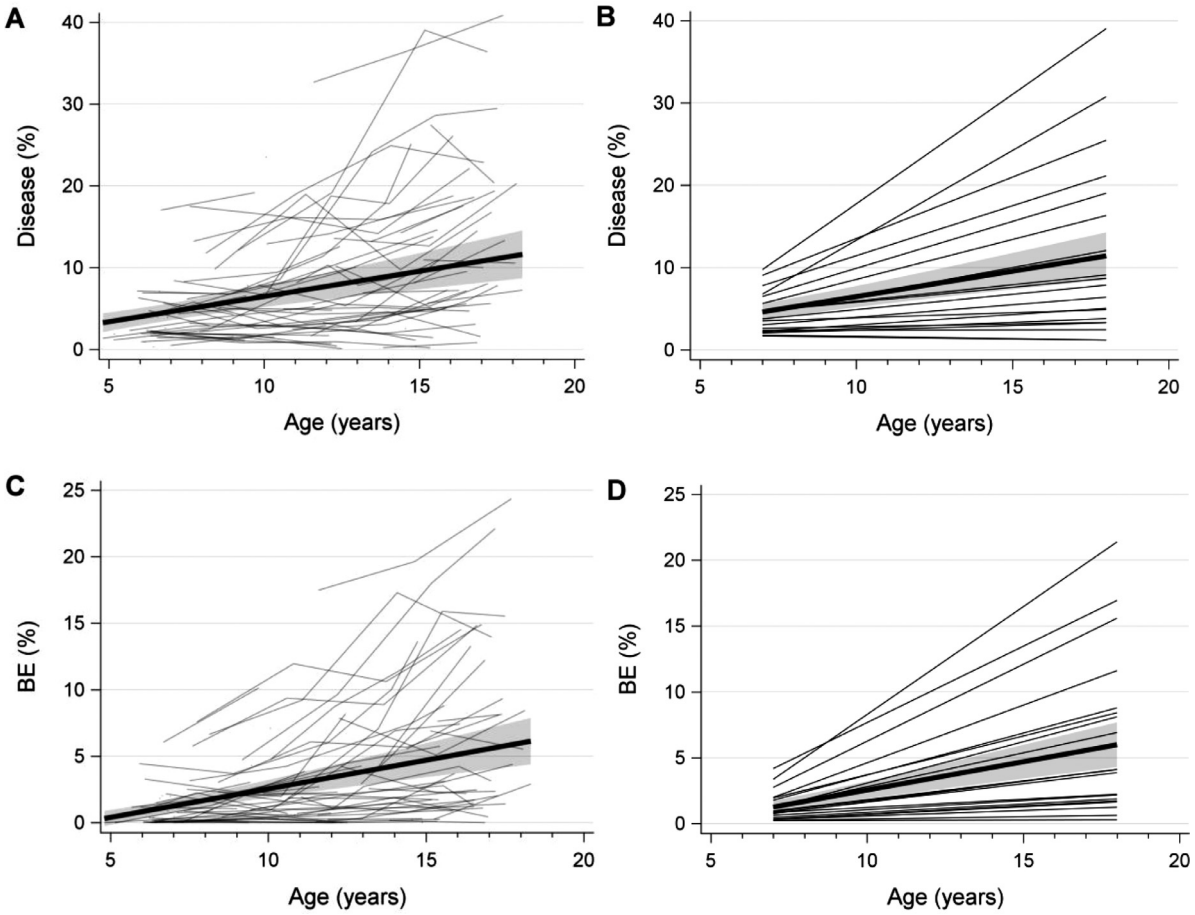

Fig. 1. Monitoring of structural lung disease (SLD) in children with CF. Panels A and C describe the observed longitudinal progression of SLD regarding %Dis and %Be for all 75 children in the cohort. Panel B and D describe the relationship between the level of SLD at age of 7 years and estimated progression of SLD, expressed as %Dis and %Be. The thick black lines and grey-shaded bands represent the mean progression with 95% CI. In the right panels, (B and D) data are presented for 20 randomly selected subjects stratified for CF disease level at age 7 to avoid over-plotting.
Abbreviations:%Dis, Total lung disease;%Be, bronchiectasis. Both of these parameters are expressed as percentage of the total lung volume.

3. Results

3.1. Extent and progression of CF lung disease

Of the 75 participants, 45 subjects had their first CT between the ages of 5 and 8 years (mean, 6.8 years). The SLD outcomes (95% CI) for this sub-group for %Dis, %Be, and %Ta were 4.67 (0.30–17.49), 1.45 (0.00–7.58) and 7.64 (0.00–31.85), respectively. Bronchiectasis was present in 78% of the subjects at the initial CT, while the mean FEV_1 (z-score) was 0.12 (−3.14–2.70). The yearly mean progression rates for the whole cohort for %Dis, %Be, and Ta% were 0.62 (95% CI, 0.38–0.86, $p < 0.0001$), 0.43 (95% CI, 0.28–0.58, $p < 0.0001$) and 1.61 (95% CI, 1.06–2.17, $p < 0.0001$) (Fig. 1). All the models showed good agreement between the observed and predicted values; at the subject level, the fraction of the total variation in %Dis, %Be and FEV_1 explained by the models were 0.94, 0.93, and 0.78, respectively. ICC calculations for intra variability for %Dis and %Be were 0.95 (95% CI, 0.85–0.98) and 0.96 (95% CI, 0.89–0.99) respectively. No further calculation of %Ta was carried out due to the diverse quality and few slices of the expiratory scans, which could affect the interpretation of further calculations.

There were no significant differences in the yearly mean progression in %Dis or %Be with regard to: gender ($p = 0.63$ and $p = 0.76$, respectively); the 1990–1999 birth cohort vs. the 2000–2009 birth cohort ($p = 0.22$ and $p = 0.24$); pancreatic insufficiency ($p = 0.99$ and $p = 0.79$); age at diagnosis ($p = 0.92$ and $p = 0.84$); and shared care ($p = 0.76$ and $p = 0.91$), (supplemental Table 2.) The mean FEV_1 (z-score) decline rate for all subjects was −0.16/year (95% CI, −0.18–0.13, $p < 0.0001$), and no significant difference was noted for the FEV_1 decline rate between the sub-groups. The age-adjusted mean difference in SLD between sub-groups was only significantly higher for %Be in subjects who had been diagnosed with CF after 1 year of age ($p = 0.016$). At the age of 7 years, the mean %Be values for subjects diagnosed before and after 1 year of age were 0.69 (95% CI, 0.22–1.16) and 1.90 (95% CI, 1.04–2.75), respectively. The entire cohort included few subjects with pancreatic sufficiency, and both groups had similar results for the progression and extent of SLD and FEV_1 measurements (Table 1). All the subjects were therefore included in further calculations.

3.2. Effects of single and chronic infections with airway pathogens on lung disease progression

When adjusting for potential damage from all the tested airway pathogens (Pa, Ma, Ax, Bc, Sa, Hi and Asp), the yearly mean progression for%Dis,%Be and decline in FEV_1 were 0.23 ($p = 0.095$), 0.12 ($p = 0.057$), and −0.12 ($p < 0.0001$), respectively (Table 2).

3.2.1. P. aeruginosa

A single respiratory infection with Pa was associated with a significant mean lung damage compared to baseline, assessed as

Table 1
Demographics of the subjects born in the period 1990–2009.

Variable	Results
Subjects	75
Study period per subject* (years)	12.0 (3.0–18.0)
Pancreatic insufficiency	67 (89%)
CF diagnosis <1 year	39 (51%)
Shared care	24 (32%)
Homozygous dF508 / heterozygous dF508 / other mutations	38 (51%) / 34(45%) / 3(4%)
Total FEV_1 measurements performed	820
FEV_1 measurements performed per subject	12.2 (2–16)
FEV_1 (z-score) at age of 7 years	0.12 (−3.14–2.70)
Total number of chest CTs performed	200
Number of CTs performed per subject	
1	17 (23%)
2	17 (23%)
3	21 (28%)
4	14 (19%)
5	6 (8%)
Weight at 7 years of age (z-score)	−0.42 (−3.01–1.75)
Height at 7 years of age (z-score)	−0.41 (−3.34–1.91)
BMI at 7 years of age (z-score)	−0.27 (−2.11–1.99)
Cultures/patient/year	4.23 (0.12–15.4)
Pa incidence/subject/year	0.24 (0.00–0.93)
Subjects with one or more Pa infection	55 (73%)
Age at first Pa infection (years)	7.4 (0.4–17.4)
Subjects with chronic Pa infection	22 (29%)
Age at onset of chronic Pa infection (years)	12.6 (3.1–18.9)
Subjects with one or more Ma, Ax or Bc infection	22 (29%)
Subjects with chronic Ma or Bc infection	7 (9%)
Age at onset of chronic Ma and Bc infection (years)	15.4 (13.2–18.5)
Sa incidence/subject/year	1.94 (0.0–7.11)
Hi incidence/subject/year	0.39 (0.00–2.36)
Asp incidence/subject/year	0.61 (0.00–5.16)

Results are presented as: n, n (%) or mean (range). * Study period for each subject is defined as the time between the first and the last airway culture retrieved from Department of Clinical Microbiology or the Swedish CF registry.
Abbreviations: Pa, *Pseudomonas aeruginosa*; Ma, *Mycobacterium abscessus*; Bc, *Burkholderia cepacia* complex; Ax, *Achromobacter xylosoxidans*; Asp, *Aspergillus* species; Sa, *Staphylococcus aureus*; Hi, *Haemophilus influenzae*.

Table 2
Estimated effects of airway pathogens on CF lung disease measured as structural lung damage (%Dis and %Be) and FEV_1. The baseline progressions for the respective outcome variables are adjusted for potential damage from the airway pathogens Pa, Ma, Bc, Ax, Sa, Hi, and Asp.

Outcome variable	Parameter	Estimate (95% CI) *p*-value	Change in progression after chronic onset (95% CI) *p*-value	Damage accrued from single infection (95% CI) *p*-value
Disease (%)	Baseline progression	0.23 (−0.04–0.51) $p=0.095$		
	Pa		0.92 (0.09–1.76) $p=0.030$	0.78 (0.02–1.53) $p=0.044$
	Ma, Bc or Ax		−0.92 (−4.79–2.94) $p=0.63$	1.10 (−0.81–3.01) $p=0.25$
	Sa			−0.01 (−0.13–0.12) $p=0.93$
	Hi			−0.07 (−0.29–0.15) $p=0.51$
	Asp			0.12 (−0.22–0.47) $p=0.47$
Be (%)	Baseline progression	0.12 (−0.00–0.25) $p=0.057$		
	Pa		0.67 (0.10–1.24) $p=0.022$	0.57 (0.18–0.95) $p=0.0047$
	Ma, Bc or Ax		1.06 (−0.99–3.12) $p=0.31$	0.75 (−0.16–1.66) $p=0.10$
	Sa			0.00 (−0.06–0.07) $p=0.93$
	Hi			−0.07 (−0.26–0.12) $p=0.47$
	Asp			0.10 (−0.09–0.28) $p=0.29$
FEV_1 z-score	Baseline progression	−0.12 (−0.16–−0.08) $p<0.0001$		
	Pa		−0.12 (−0.20–−0.03) $p=0.0068$	0.00 (−0.09–0.09) $p=0.96$
	Ma, Bc or Ax		0.16 (−0.31–0.62) $p=0.51$	−0.26 (−0.56–0.04) $p=0.11$
	Sa			−0.02 (−0.03–0.00) $p=0.058$
	Hi			0.03 (−0.05–0.11) $p=0.43$
	Asp			0.01 (−0.01–0.04) $p=0.23$

Abbreviations: %Dis, total lung disease; %Be, bronchiectasis, both parameters are expressed as a percentage of the total lung volume; Pa, *Pseudomonas aeruginosa*; Ma, *Mycobacterium abscessus*; B, *Burkholderia cepacia* complex; Ax, *Achromobacter xylosoxidans;* Asp, *Aspergillus* species; Sa, *Staphylococcus aureus*; Hi, *Haemophilus influenzae*.

increases in %Dis (0.78, $p=0.044$) and %Be (0.57, $p=0.0047$), but not in FEV_1 (−0.00, $p=0.96$). The yearly progression in %Dis, %Be and FEV_1 increased significantly after the patients became chronically infected with Pa. Compared to the airway pathogen-adjusted yearly baseline progression, the yearly progression increased by 0.92 ($p=0.030$), 0.67 ($p=0.022$), and −0.12 ($p=0.0068$) for %Dis, %Be and FEV_1, respectively (Table 2, Fig. 2).

3.2.2. M. abscessus, Burkholderia cepacia *complex* and A. xylosoxidans

The estimated mean effect of a single respiratory infection with Ma, Ax or Bc measured as %Dis, %Be and FEV_1 was 1.10 ($p=0.25$), 0.75 ($p=0.10$), and −0.26 ($p=0.11$), respectively. After chronic infection with Ma or Bc, the yearly progression rate for %Be increased by 1.06 (95% CI −0.99–3.12, $p=0.31$) compared to baseline.

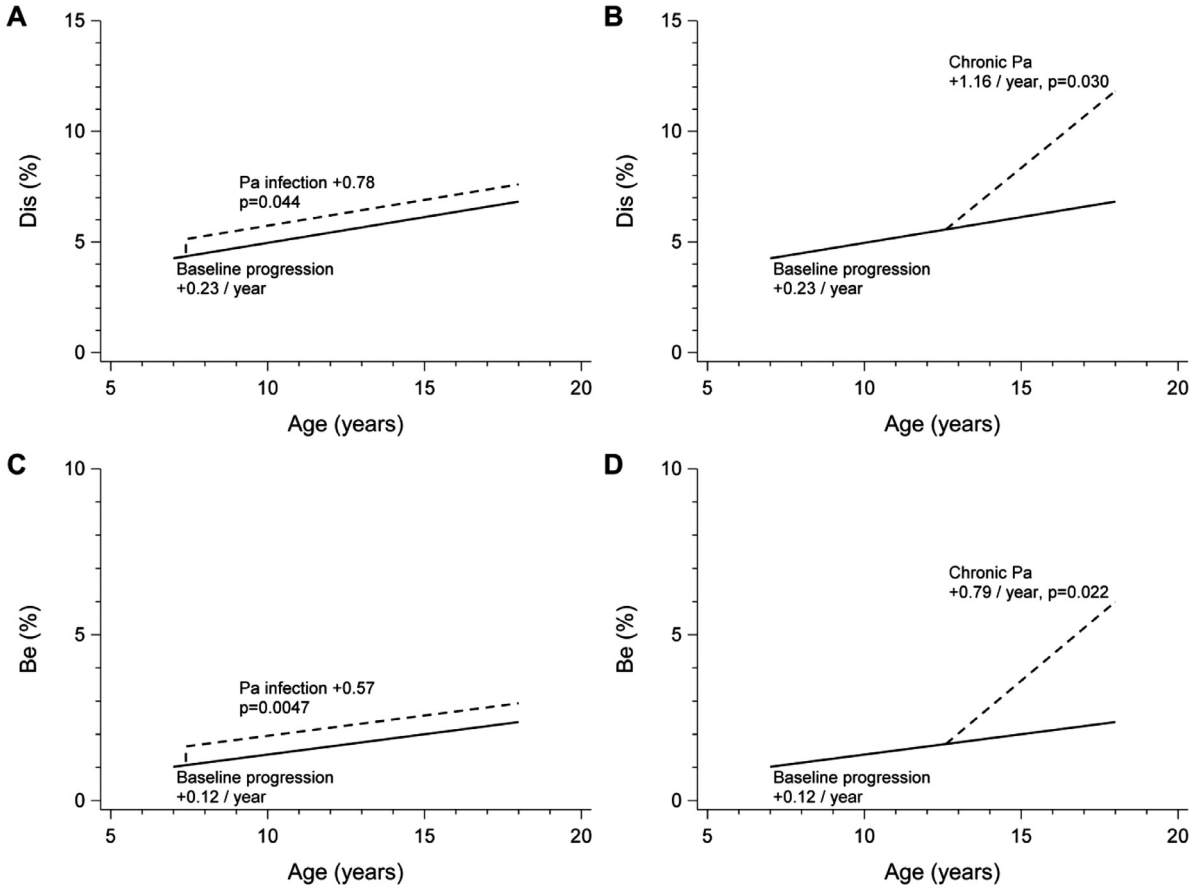

Fig. 2. Panel A and C. A single respiratory infection with *Pseudomonas aeruginosa* was associated with significant mean lung damage, expressed as increase in %Dis (0.78%, $p = 0.044$) and %Be (0.57%, $p = 0.0047$), as compared to the baselines progression rates for respective parameter. Mean age of initial Pa infection was 7.4 years. The baselines progression rates for %Dis and %Be were 0.23% per year and 0.12% per year, respectively, when adjusted for the airway pathogens Pa, Ma, Bc, Ax, Sa, Hi, Sa and Asp. Panel B and D. After chronic infected by *Pseudomonas aeruginosa (mean age 12,6)*, the mean annual rate of progression of %Be and %Dis increased significantly to 1.16% ($p = 0.030$) and 0.79% ($p = 0.022$), respectively, as compared to the baseline progression rates.
Abbreviations: %Dis, Total lung disease; %Be, bronchiectasis. Both of these parameters are expressed as percentage of the total lung volume. Pa, *Pseudomonas aeruginosa*; Ma, *Mycobacterium abscessus*; Bc, *Burkholderia cepacia* complex; Ax, *Achromobacter xylosoxidans*; Asp, *Aspergillus* spp.; Sa; *Staphylococcus aureus*; Hi, *Haemophilus influenzae.*

3.2.3. S. aureus, H. influenzae *and* Aspergillus *species*

There were no significant associations between the number of infections with Sa, Hi or Asp and %Dis, %Be, and FEV_1.

3.3. Correlations between the extent and progression of CF lung disease at different ages

There was a good correlation between the extent of SLD at 7 years of age and subsequent progression of %Dis ($r = 0.63$, $p = 0.0042$) and %Be ($r = 0.74$, $p = 0.0057$), respectively (Fig. 1 and Supplements). This also held true when adjustment was made for airway pathogens, with the correlations being 0.61 ($p = 0.012$) and 0.89 ($p = 0.010$), respectively. Lung function measured as FEV_1 at the age of 7 years showed no significant correlation with the rate of further decline in FEV_1 ($p = 0.12$). First at the age of 13 years, there was a weak but significant correlation between the level of FEV_1 and the rate of decline FEV_1 ($r = 0.31$, $p = 0.031$).

3.4. Relationships between lung function and progression of bronchiectasis

There was a weak negative correlation between the levels of FEV_1 at 7 years of age and the rates of progression of bronchiectasis: −0.28 (95% CI, −0.50–0.02, $p = 0.034$). The concordance correlation coefficient between the levels of FEV_1 and progression of bronchiectasis at age of 7 years was 0.59 (95% CI, 0.50–0.68). The correlation between the rate of decline of FEV_1 and progression rate of %Be was −0.26 (95% CI, −0.48–0.00, $p = 0.049$), and the concordance correlation coefficient was 0.59 (95% CI, 0.50–0.69) (Supplemental Table 1).

4. Discussion

This longitudinal assessment of chest CTs using the PRAGMA-CF quantitative scoring system describes the extent and yearly progression rate of SLD in school-age children with CF in relation to infection with airway pathogens. We showed that chronic respiratory infection with Pa has a strong impact on the SLD progression rate, and that intermittent Pa infections also are associated with SLD that cannot be detected by FEV_1 measurements. Our study reveals a good correlation between the extent of SLD at 7 years of age and a continuous progression rate for SLD. Neither the level of nor the decline rate of FEV_1 provided useful insights into the ongoing SLD progression rate.

For children aged 7 years, on average 4.7% of the lung volume was affected by SLD, although the extent of SLD was highly variable among the subjects (range, 0.3%–17.5%). Bronchiectasis were present in almost 80% of the subjects. Despite this, the average FEV_1 (z-score) was normal (+0.1) at the same age. Our results for SLD in young children are comparable with a cross-sectional study in children who underwent volume-controlled chest CT and were analysed with the same scoring system [15]. The extent of SLD in

children at 7 years of age showed a good correlation with the SLD yearly progression rate, and this relationship was unchanged when adjustment was made for airway pathogens. Pulmonary function testing ($FEV_{1)}$ is a poor predictor of the FEV_1 yearly decline rate and the rate of progression of SLD. In this study, we have rigorously investigated the relationships between FEV_1 and SLD progression rate and found no good evidence to support the use of FEV_1 as a surrogate for chest CT, in agreement with earlier studies [16].

Our finding also supports the results from earlier studies that chest CT needs to be performed before the age of 7 year to identify individuals with greater extent of SLD and at risk of a faster SLD progression rate [6,17,18]. The prevalence of SLD in young children and pre-schoolers is high but the extent of SLD is relatively low and the yearly progression rate of SLD is relatively slow [7]. PRAGMA-CF is not available in routine radiology so it is questionable if these small changes of SLD over time will be detected on an individual basis not using a sensitive scoring system.

Many centres monitor CF lung disease progression regularly (annually, every 2nd or 3rd year) using chest CT. As shown in this paper and earlier studies the progression rate of SLD depends on innate and dynamic risk factors, where chest CT itself provides important information about the disease progression [6,17,19]. A more personalized strategy to monitoring CF lung disease based on continues assessment of individual risk factors would be more ideal [1]. To date we don't have enough knowledge about the risk factors affecting CF lung disease to create dynamic stratified monitor protocols based on individual risk factors. Multiple Breath washout (MBW) and chest MRI are other sensitive methods to detect and track CF lung disease. Both methods have also demonstrated the ability to evaluate short term interventions and treatment responses at pulmonary exacerbations [20,21]. Lung Clearance Index (LCI) has also been shown to deteriorate faster prior to an airway infection compared to children with no pulmonary infections [22,23]. Longitudinal analysis are needed to establish whether repeated measurements of MBW or chest MRI in between routine CT scans can be used in clinical practice to create personalized monitoring protocols for CF lung disease.

The estimated SLD progression rate was strongly associated with respiratory infections (in this study defined as positive sputum culture) and the annually SLD progression rate was no longer significant after adjustment for respiratory infections. Earlier studies have identified pulmonary infections and chronic inflammation as risk factors in the development of SLD [6,7,17,24]. Aggressive treatment with antibiotics in combination with anti-inflammatory interventions might be a possible way forward to further minimize structural and physiological lung disease progression until disease modifying agents are available for all ages and CF-mutations.

Chronic colonization with *P. aeruginosa* is associated with a more aggressive decline rate in pulmonary lung function measured as FEV_1 [25,26]. Pulmonary infections with *P. aeruginosa* are also a known risk factor for accelerated SLD and faster deterioration in LCI [17,23,27–29]. Individuals chronically infected with Pa in our study had almost a 7-fold increase in the yearly progression rate regarding bronchiectasis and a 2-fold higher rate of decline of FEV_1 compared to the airway pathogen-adjusted baseline values. Only relying on spirometry test (FEV_1) as an objective modality to evaluate chronic Pa treatment strategy will probably underestimate the progression of CF lung disease. The mean age for chronic colonization with *P. aeruginosa* in our cohort occurred in early adolescence, in which chest CT also may add information in order to prevent and understand the unknown steeper decline rate in CF lung disease staring at puberty [30].We also found that even a single infection with Pa that is successfully eradicated was associated with a significant increase of bronchiectasis. Pa infections are known to be a risk factor of further development of bronchiectasis but haven't been shown to cause SLD when eradicated [6,17]. This finding further emphasizes the importance of multi-modality surveillance strategies for early detection and eradication of Pa and that chest CT can be used for evaluation of chronic treatment for Pa [31].

There were no significant changes in SLD and FEV_1 after infection or chronic colonisation with *Mycobacterium abscessus*, dominant to numbers in the group with Ax and Bc. Our results though indicate a trend towards a dramatic increase in the Be progression rate and persistent SLD after pathogen colonization. The non-significant result is most likely due to the late onset and the few subjects with Ma, Ax or Bc infection. Both chronic infection with *P. aeruginosa* and *Mycobacterium abscessus* in our study can therefore be considered as patients at high risk for faster progression of SLD and selected for frequent chest CT. Sa and Hi, did not show any significant associations with damages to the lung, although there are studies suggesting Sa may affect progression of SLD [19]. A possible explanation for this is that regular treatments with oral antibiotics covering these bacteria are given at each occurrence of mild pulmonary infection. *Aspergillus* colonisation/infection did not show any significant increase in damage to the lungs in our study. The effect of *Aspergillus* airway colonization on CF lung disease in the absence of acute bronchial pulmonary aspergillosis is not established, even though there is evidence that *Aspergillus* can cause lung damage [32,33].

This study has certain limitations. The chest CT scans were not volume-controlled, and this is known to under-estimate the amount of trapped air. Expiratory scans only included 3–4 slices and, therefore, the variable of trapped air was only used in the descriptive statistics [34,35]. No information about treatment, clinical symptoms or pulmonary exacerbations were included which might have affected the results how different pathogens are associated with SLD. The number of airway cultures regarding the pathogens Sa, Hi, Asp varied among the subjects, which could have affected the impacts that the different pathogens had on SLD. Information about yearly Pa colonization were available from diagnosis but not chest CT, which would have been valuable to strengthen the association between SLD and airway pathogens. Due to the heterogeneity of the study material with respect to the time-points for performing chest CTs, a model-based analysis strategy was used throughout. This means that any incorrect specifications in the models could have implications for the estimated effects and correlations. The main strengths of this study are that it comprises 75 individuals with an average of three chest CTs administered over a long period of time, and accompanying spirometry measurements made both at the time of the CT scanning and at all the annual reviews between the CT scans. The reliability of the data and analyses are strengthened by the high intra-observer repeatability for the PRAGMA-score and the strong agreement between the observed and fitted values.

In summary, this study describes the progression of SLD in school-age children with CF. *P. aeruginosa* infections that are successfully eradicated are associated with significant SLD but no change in FEV_1 and chronic infections with Pa are strongly associated with the yearly SLD progression rate. There is a good correlation between the extent of SLD at 7 years of age and subsequent progression of SLD but not with FEV_1 at the same age.

Author agreement

All authors have seen and approved the final version of the revised manuscript "Risk factors for progression of structural lung disease in school-age children with cystic fibrosis" They warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

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Declaration of competing interest

Dr. Tiddens has a patent licensed for the PRAGMA-CF scoring system. He is heading the Erasmus MC-Sophia Children's Hospital core laboratory Lung Analysis. FLUIDDA has developed computational fluid dynamic modeling based on chest-CTs obtained from Erasmus MC-Sophia for which royalties are received by Sophia Research BV. All financial aspects for the grants are handled by Sophia Research BV.

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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.2019.10.014.

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