
# Chest X-rays are less sensitive than multiple breath washout examinations when it comes to detecting early cystic fibrosis lung disease

Received: 16 November 2021 | Revised: 15 February 2022 | Accepted: 16 February 2022

DOI: 10.1111/apa.16302

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

ORIGINAL ARTICLE

# Chest X-rays are less sensitive than multiple breath washout examinations when it comes to detecting early cystic fibrosis lung disease

Marcus Svedberg[1,2] | Henrik Imberg[3,4] | Per Gustafsson[1,5] | Mela Brink[6] | Håkan Caisander[6] | Anders Lindblad[1,2]

[1]Department of Pediatrics, Institute of Clinical Science at The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[2]Department of Pediatrics, Queen Silvia's Children Hospital, Gothenburg, Sweden

[3]Department of Mathematical Sciences, Chalmers University of Technology and University of Gothenburg, Gothenburg, Sweden

[4]Statistiska Konsultgruppen, Gothenburg, Sweden

[5]Department of Pediatrics, Central Hospital, Skoevde, Sweden

[6]Department of Pediatric Radiology, Queen Silvia's Children Hospital, Gothenburg, Sweden

**Correspondence**
Marcus Svedberg, Department of Pediatrics, Institute of Clinical Science at The Sahlgrenska Academy, University of Gothenburg, Anders Zornsgatan 22, 412 72 Gothenburg, Sweden.
Email: marcus.svedberg@vgregion.se

**Funding information**
Queen Silvia's children hospital research foundation; Samariten foundation for paediatric research; The Swedish CF foundation; Freemasons order foundation; Erica Lederhausen foundation; Petter Silverskiolds foundation

## Abstract

**Aim:** Annual chest X-ray is recommended as routine surveillance to track cystic fibrosis (CF) lung disease. The aim of this study was to investigate the clinical utility of chest X-rays to track CF lung disease.

**Methods:** Children at Gothenburg's CF centre who underwent chest X-rays, multiple breath washouts and chest computed tomography examinations between 1996 and 2016 were included in the study. Chest X-rays were interpreted with Northern Score (NS). We compared NS to lung clearance index (LCI) and structural lung damage measured by computed tomography using a logistic regression model.

**Results:** A total of 75 children were included over a median period of 13 years (range: 3.0-18.0 years). The proportion of children with abnormal NS was significantly lower than the proportion of abnormal LCI up to the age of 4 years ($p < 0.05$). A normal NS and a normal LCI at age 6 years were associated with a median (10-90th percentile) total airway disease of 1.8% (0.4-4.7%) and bronchiectasis of 0.2% (0.0-1.5%).

**Conclusion:** Chest X-rays were less sensitive than multiple breath washout examinations to detect early CF lung disease. The combined results from both methods can be used as an indicator to perform chest computed tomography less frequently.

KEYWORDS
chest computed tomography, chest X-rays, cystic fibrosis lung disease, lung clearance index, multiple breath washout

**Abbreviations:** CF, cystic fibrosis; CT, computed tomography; CXR, chest X-ray; ICC, intra-class correlation coefficient; LCI, lung clearance index; MBW, multiple breath washout; NS, Northern Score; SLD, structural lung damage.

## 1 | INTRODUCTION

The onset and progression of clinical manifestations of lung disease in children with cystic fibrosis (CF) starts early in life and often progresses without respiratory symptoms.[1,2] Therefore, objective measurements are made on a regular basis, in order to detect and prevent the progression of the CF pulmonary disease. A chest X-ray (CXR) is quick and world-wide accessible method that is commonly performed as a routine surveillance tool in many hospitals and is still recommended by the CF guidelines.[3-5] However, computed tomography (CT) of the chest is far more sensitive than a CXR when it comes to detecting early lung disease and it is regarded as the gold standard to assess structural changes of the airways.[6] Still many challenges remain to implement chest CTs as routine surveillance in the daily care of children with CF. To obtain standardised chest CT scans, it is recommended to control the lung volume during the image acquisition and in younger children below the age of 6 years of age this procedure often requires general anaesthesia and pressured controlled protocols.[7-9] Scoring systems are available for both CXRs and chest CTs to quantify the extent and severity of structural lung damage (SLD) and to allow longitudinal follow-up in children with CF.[10,11] The levels of precision and reproducibility of the scoring systems vary, and the user needs to understand the limitations of a specific scoring system if it is to be used in clinical practice. The scoring systems for CXRs are fairly easy to learn and to perform for the radiologist compared to the scoring system available for chest CTs that requires proper training and is more time-consuming.[7,10]

Multiple breath washout (MBW) is a non-invasive test that is feasible for all age groups. The lung clearance index (LCI) is the most commonly used outcome parameter from MBW. LCI is regarded as a sensitive parameter for detecting early CF lung disease, as compared to other lung function tests.[12,13] While our understanding of how LCI can be used in clinical practice has progressed over the years, we still have insufficient data to understand the long-term development of LCI compared to other outcome measures of CF lung disease.

Currently, many CF centres use multiple modalities to detect and track CF lung disease. Chest CTs and CXR examinations measure lung structure, whereas MBW examinations measure lung function and are considered complementary markers of the CF lung disease. All examinations and procedures represent a major burden for the affected child, and some of the procedures may involve a potential risk for the child.[14] Healthcare providers must balance the benefits and risks associated with each procedure and decide whether all the methods, applied separately or in combination, add information about the CF lung disease. A question that needs to be addressed is whether annual MBW and CXR examinations, separately or a combination of both methods, can add clinical information about early CF lung disease progression on an individual level.

In this retrospective study of children with CF, we have used CXR and MBW in clinical practice over a period of 20 years. Our research questions were to describe the extent and progression lung disease measured with CXR and to describe the intra- and inter-rater variabilities for CXR. We also investigated the associations between normal or pathological CXRs and normal or pathological LCIs with SLD measured with chest CTs in school-age children.

**Key notes**

- Chest X-rays are recommended in clinical practice to track early cystic fibrosis. lung disease even though more sensitive methods are available.
- Chest x-rays are less sensitive than multiple breath washout examinations to detects early cystic fibrosis lung disease.
- The combined information from chest X-rays and multiple breath washout examinations can be useful as a surrogate marker for chest computed tomography to estimate the extent of structural lung damage.

## 2 | METHODS

### 2.1 | Study population

This retrospective study included children with CF who had performed a minimum of one CXR, MBW and chest CT examination at the Queen Silvia Children's Hospital, Gothenburg, Sweden. CXRs were collected from 1996, the year when the Northern scoring system was introduced in our clinic, until the year 2016. All tests were carried out as part of an annual review in clinically stable condition. Chest CTs were digitally available between the period 2003-2016, starting image acquisition at the age of 6 years and then every third year at the annual assessment. MBW examinations were implemented into clinical practice in 1999 and were collected annually for the period 1999-2012 and twice yearly from 2013 to 2016. The demographic data for each individual with CF were retrieved from the Swedish CF Registry. The study was approved by the local Gothenburg Ethics Committee (Dnr. 206–18).

### 2.2 | Chest X-ray and chest X-ray analyses

The radiograph system Adora (NRT, Hasselager, Denmark) was used in the study, and the chest radiograph included a posteroanterior view during inspiration and was scored using the Northern Score (NS) system.[15] NS is derived by dividing the lungs into four zones, with structural damage to the lung being interpreted in each zone and assigned a score in the range of 0-4 depending on the existing pre-defined pathology. A further 0-4 points are assigned according to the observer's perception of the severity of the structural lung damage. The final score is in the range of 0-20, with a higher score reflecting more severe SLD. A CXR with NS = 0 was defined as normal, and a NS ≥ 1 was pathological.

A total of 3 paediatric radiologists each evaluated 30 anonymised radiographs, stratified according to the original NS severity,

to determine the inter-rater variability. After 1 month, one paediatric radiologist re-analysed the same 30 radiographs in randomised order to determine the intra-rater variability.

### 2.3 | MBW acquisition and analysis

Children with CF underwent MBW examinations at the Paediatric Clinical Physiology Laboratory at Queen Silvia Children's Hospital in Gothenburg and at the Department of Paediatrics, Central Hospital, Skovde. Infants up to the age of 3 years performed MBW while sedated in a supine position using a face mask. Children 3-4 years old performed MBW while awake in a sitting position using a face mask or a mouth-piece with a nose clip. Sulphur hexafluoride (4%) was used as the inert tracer gas and washed into the lungs to equilibrium. Washout was performed during tidal breathing using room air with the mass spectrometer AMIS 2000 (Innovision A/S, Odense, Denmark) to measure the expiratory gas concentrations. Three washout trials were normally performed on each subject, and a minimum of two technically error-free MBW sessions were considered acceptable.

The MBW test was also evaluated in a 140 healthy children, using the same software, equipment and procedures as described for the subjects with CF (Table S1).

### 2.4 | Chest CT acquisition and analysis

Chest CTs were performed during voluntary breath-hold with a discontinuous scanning protocol, as previously described.[16] The Perth-Rotterdam Annotated Grid Morphometric Analysis for CF method was used to track changes in SLD.[17] The primary outcomes of the chest CT scans in this study were total airway disease and bronchiectasis, expressed as the volume proportion of the respective pathology on the scan divided by the total volume of the scan (Appendix S1).

### 2.5 | Airway pathogens

Airway pathogens were obtained through sputum cultures at clinical visits between 1996 and 2016. The incidence of *Staphylococcus aureus*, *Aspergillus species* and *Pseudomonas aeruginosa* was analysed, and a chronic infection with *Pseudomonas aeruginosa* was defined according to the Leeds criteria.[18]

### 2.6 | Statistical analysis

Descriptive data are presented as medians and ranges for continuous variables and as numbers and percentages for categorical variables. The inter- and intra-rater variability of the NS measurements was estimated by the intra-class correlation coefficient (ICC). We estimated the association between NS and LCI using the concordance and Cohen's kappa coefficient on abnormal NS and LCI, and the Pearson correlation coefficient between NS and LCI values.

The median progression of NS in the cohort was estimated from longitudinal CXR data using an ordinal logistic mixed effects regression model, with a random intercept and slope for each subject. We also estimated the unadjusted and adjusted marginal mean progression, using a linear mixed model with the same random effects structure as above, and with adjustment for infections with airway pathogens. We evaluated differences between subgroups formed by sex, pancreatic insufficiency, age at diagnosis (<1 *vs* >1 year) and birth cohort born 1990-1999 *vs* 2000-2009.

The proportion of abnormal CXR and abnormal LCI were analysed using logistic regression with age as a continuous covariate. Estimation was conducted using generalised estimating equations with an independent working correlation structure (Table S1).

Structural lung damage measured by chest CTs was evaluated in relation to normal/pathological NS and LCI in a longitudinal context using linear mixed effects models with random intercept and age slope for each subject, and with age at chest CT, pathological or normal NS at chest CT, and pathological or normal LCI at chest CT as fixed effects.

Statistical analyses were performed using the SAS version 9.4 software (SAS Institute, Cary, North Carolina, USA), and all tests were conducted at the 5% significance level. See the online supplement for more detailed information about the statistical calculations performed in this study.

## 3 | RESULTS

### 3.1 | Study population

The study included all 75 eligible subjects from Gothenburg paediatric CF centre, who all fulfilled the inclusion criteria. In total, 941 CXRs were included. All earlier acceptable MBW examinations were re-analysed, and 777 of 785 MBW examinations fulfilled consensus statements and were included in the study.[19] A total of 186 out of 200 available chest CTs had a matching CXR or MBW examination within ±4 weeks and were included in the current analysis.

The median follow-up time was 11.9 years (3.0-18.0), and none of the participants in the CF cohort were diagnosed with CF through newborn screening. The major characteristics of the study cohort are presented in Table 1, and the development of CF lung disease in the cohort is presented in Table 2.

### 3.2 | The extent and annual progression of the Northern Score

The mean yearly progression rate (95% CI) of NS in the cohort was 0.16 units (0.10-0.22, $P < 0.0001$) (Figure 1). Adjusting for airway infections, the mean progression rate decreased to 0.10 NS units (0.03-0.17, $P = 0.004$) per year. The progression rate among children

**TABLE 1** Demographics of the 75 patients with CF born 1990-2009

| Variable | n (%) / median (range) |
|---|---|
| Female sex | 24 (32%) |
| Pancreatic insufficiency | 67 (89%) |
| dF508/dF508, dF508/other, other/other | 38 (51%) / 34 (45%) / 3 (4%) |
| Children treated with CFTR modulators | 1 (1%) |
| Children with CF-related diabetes mellitus | 2 (3%) |
| Children with chronic infection of *Pseudomonas aeruginosa* | 22 (29%) |
| Age at onset of chronic *P. aeruginosa* (years) | 13.0 (3.1-18.9) |
| *P. aeruginosa* incidence/subject/year | 0.2 (0.0-0.9) |
| *Staphylococcus aureus* incidence/subject/year | 1.2 (0.0-7.1) |
| *Aspergillus species* incidence/subject/year | 0.2 (0.0-5.2) |
| Follow-up time[a] (years) | 11.9 (3.0-18.0) |
| Number of CXRs/child | 13 (4-19) |
| Number of MBWs/child | 11 (1-18) |
| Number of chest CTs/child | 2 (1-5) |

Abbreviations: CT, computed tomography; CXR, chest X-ray; MBW, multiple breath washout.
[a]Time between the first and the last CXR.

**TABLE 2** CF lung disease cross-sectionally measured with different modalities at different ages

| | 2 years (N = 27) | 5 years (N = 41) | 7 years (N = 44) | 12 years (N = 44) |
|---|---|---|---|---|
| Northern score | 0 (0 to 7) | 1 (0 to 5) | 1 (0 to 7) | 2 (0 to 9) |
| LCI (SF6) | 7.7 (6.3 to 13.8) | 7.4 (6.2 to 12.2) | 7.5 (5.7 to 12.4) | 7.9 (5.6 to 11.0) |
| ULN for LCI | 7.4 | 7.0 | 7.0 | 7.0 |
| FEV1 (*z*-score) | — | −0.1 (−2.0 to 2.1)[a] | −0.1 (−3.1 to 2.7) | −0.4 (−3.8 to 2.6) |
| Chest CT – %Dis | — | — | 3.8 (0 to 17.5)[b] | 5.4 (0.9 to 32.7)[c] |
| Chest CT – %Be | — | — | 0.8 (0 to 7.6)[b] | 2.0 (0 to 17.5)[c] |

*Note:* Results are presented as median (range).
Abbreviations: %Be, bronchiectasis; %Dis, total lung disease; LCI, Lung Clearance Index; ULN, Upper Limit of Normal.
[a]30 of 41 subjects had undergone spirometry.
[b]35 of 44 subjects had undergone chest CT between the ages of 6 and 8 years.
[c]30 of 44 subjects had undergone chest CT between the ages of 11 and 13 years.

born 2000-2009 was slower than in children born 1990-1999 when adjusted for airway pathogens, but not significant ($P = 0.12$). Diagnosis after one year of age was associated with a 1.1 (0.4-1.7) higher mean NS score ($P = 0.001$) (Table S2).

## 3.3 | Within and between variability for Northern Score

The re-evaluation of a total of 90 CXRs between raters resulted in the same NS results for 27 (30%) of the CXRs, as compared to the original NS results. The ICC between raters was 0.83, and the NS values differed up to ±3 NS units in 95% in the re-evaluated CXRs (Figure 2A). An identical score for the CXRs originally scored as NS = 0 was achieved between raters in 18 (60%) of the CXRs, while 12 (40%) of the CXRs were re-scored as having NS of 1-4. The ICC for the intra-rater analysis was 0.92. Perfect agreement was achieved for 57% of the re-evaluated CXRs, while 6% differed by more than ±2 units (Figure 2B).

## 3.4 | Abnormal CXRs and abnormal MBWs at different ages

The proportions of cases of NS ≥ 1 and abnormal LCI values at different ages during childhood are illustrated in Figure 3 and in the Table S3. The proportions of cases with abnormal LCI values were significantly higher than the proportions of cases with NS ≥ 1 until the age of 4 years ($p < 0.05$). The relationship between abnormal LCI values and NS ≥1 showed a fair agreement (concordance = 0.72, Cohen's kappa = 0.37), with a correlation coefficient of 0.56 ($p < 0.0001$) between LCI and NS values.

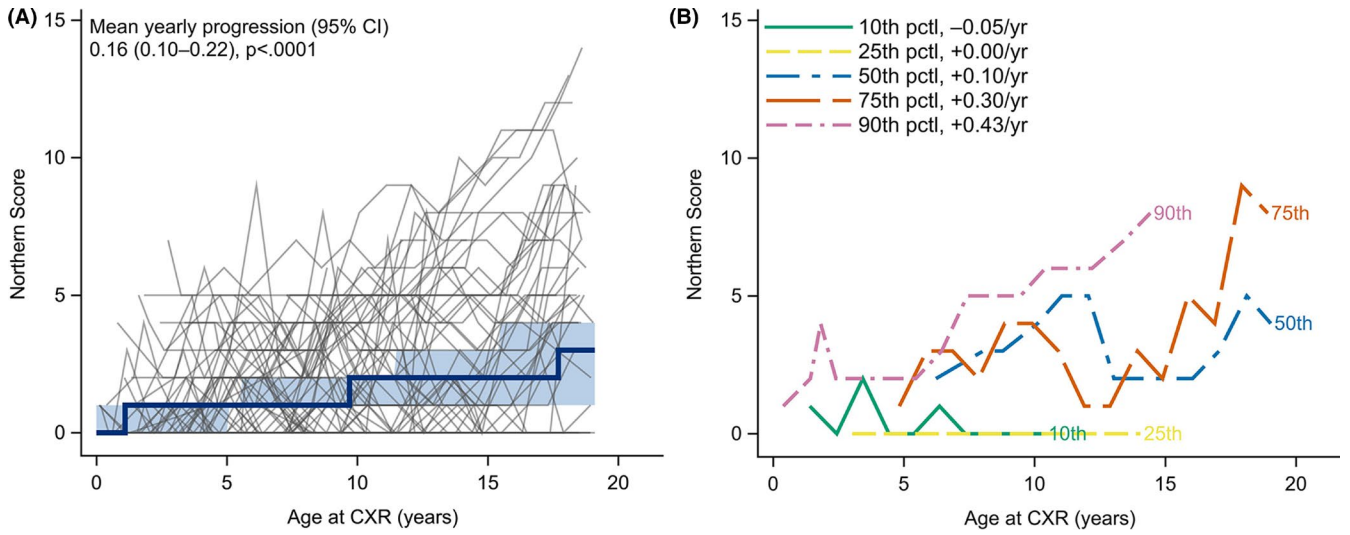


**FIGURE 1** A, Structural lung damage presented as Northern Score (NS) versus age from 941 annual chest X-rays in 75 children. Individual NS data (grey solid lines) and estimated median progression curve (blue solid line) with 95% confidence limits (shaded blue area) are shown. B, Observed NS profiles for five subjects corresponding to the 10th, 25th, 50th, 75th and 90th percentiles of NS progression, illustrating the variability within and between the subjects over time

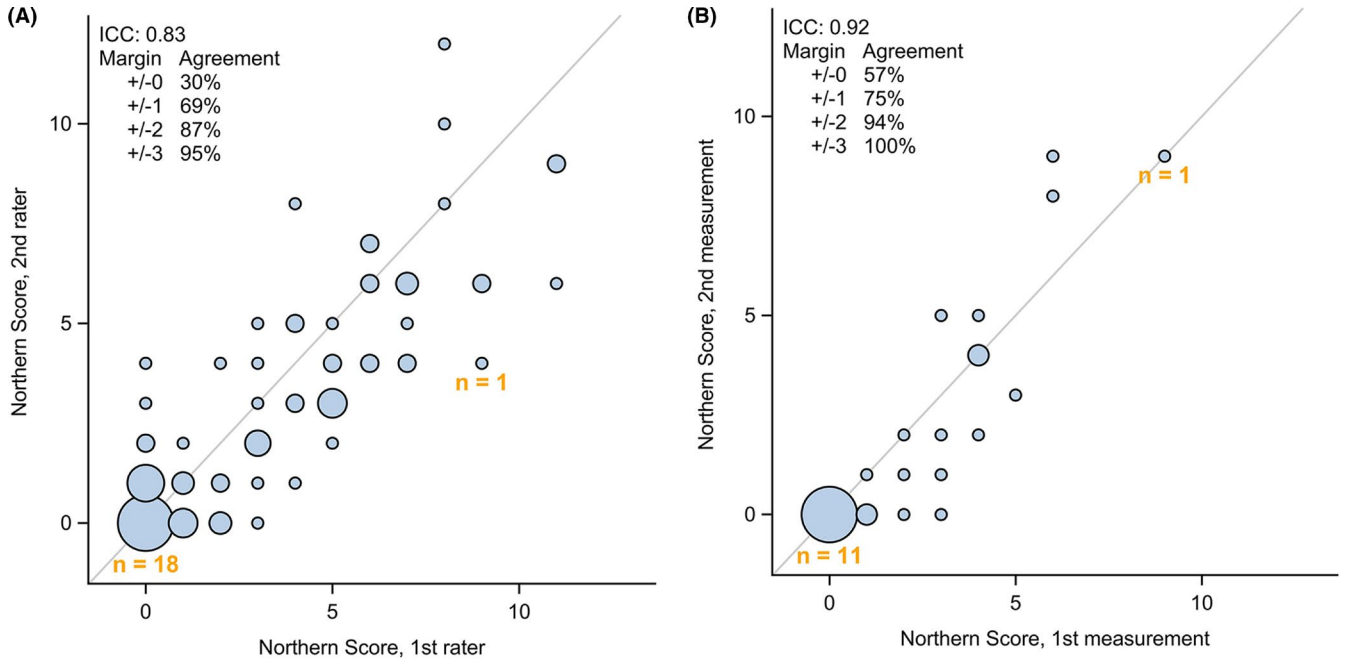


**FIGURE 2** Inter-rater variability for 90 chest X-rays (A) and intra-rater variability (B) for 30 chest X-rays using the Northern Score system. The diagonal line indicates perfect agreement between raters. The sizes of the circles are proportional to the number of evaluated chest X-rays and represent the actual similarities and differences between raters

### 3.5 | Association between NS and LCI with SLD measured with chest CT

Longitudinal analyses revealed that pathological NS and pathological LCI values were independently associated with a higher extent of SLD measured by total airway disease ($P = 0.012$ and $P < 0.001$ respectively) and bronchiectasis ($P = 0.002$ and $P = 0.001$ respectively). Both NS and LCI remained significant when further adjusted for adjusted for sex, age at diagnosis and concomitant and chronic airway infections (all $P \leq 0.01$).

A normal NS or LCI at the age of 6 was associated with median total airway disease (10-90th percentile) of 2.9% (0.8-6.9) and 2.3% (0.5%-6.0%) respectively. When both NS and LCI were normal at the age of 6 years, the median total airway disease was 1.8% (0.4%-4.7%) and bronchiectasis was 0.2% (0.0%-1.5%). A relative similar associations between NS and LCI were observed at the age of 9 (Figure 4, Table S4).

## 4 | DISCUSSION

The mean annual deterioration of SLD measured with CXR was slow in children with CF and the inter-rater and intra-rater variability observed for the scoring system NS was relatively high. The sensitivity of MBW to detect early signs of CF lung disease in infants and preschoolers was higher than that of CXR. A normal CXR and a normal LCI were both associated with low extent of structural lung damage measured by chest CT. CXR examinations alone are thus not an optimal marker of early structural lung disease but used together with a normal MBW examination the information might be a used as surrogate marker to perform chest CT less frequently in children with CF.

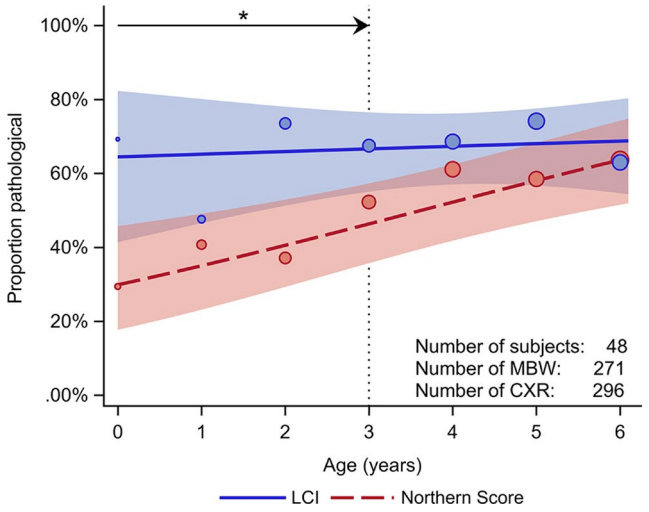


FIGURE 3 Proportion of cases with abnormal LCI and Northern Score ≥1 (abnormal chest X-ray) during infancy and pre-school ages in children with CF. The curves represent the mean trends with 95% confidence intervals for the respective measurements. The circles indicate the actual mean proportions for abnormal measurements in each year, and the sizes of the circles correspond to the number of actual measurements at a specific age. The arrow and the asterisk (*) indicate the age at which there were significant differences ($p < 0.05$) between the proportions with abnormal LCI and Northern Score ≥1

The mean structural lung damage for the cohort measured with the chest radiograph score NS during childhood was low, and the annual mean progression rate of NS was slow. The mean extent of SLD was significantly lower in the cohort with an early CF diagnosis. The reduction in the annual NS progression rate between the cohorts born 1990 and 1999 vs 2000 and 2009 is probably best explained by the continuous improvement in CF care over time.[20] This study was performed before the era of cystic fibrosis transmembrane conductance regulators modulator therapy. Cystic fibrosis transmembrane conductance regulators modulator therapy has been shown to reduce SLD progression rate and to reduce the number of infections with *Pseudomonas aeruginosa* in patients with CF.[21,22] Adjusting for common airway pathogens in our cohort the mean NS progression rate decreased by almost 40%. A more widespread introduction of cystic fibrosis transmembrane conductance regulators modulators will further decrease the already slow pulmonary disease progression rate measured with CXR and make CXR even less useful to monitor CF lung disease in children.

This variability of NS ideally reflects the effects of actual SLD changes over time, although it may also be due to the low individual reproducibility of the scoring system. For a scoring system to be useful in clinical practice, it needs to be reproducible between observers. In a previous studies, the ICC for the most common CXR scoring systems was 0.76-0.84, suggesting good-to-excellent reproducibility for the scoring systems.[11] Nonetheless, our study demonstrates substantial variation at the individual level despite high ICC values. Given the slow progression rate and large observer variability in the scoring systems, it is debatable if CXR alone is useful in clinical practice to monitor the annual progression of the CF lung disease in children. For MBW examination, the within-test repeatability

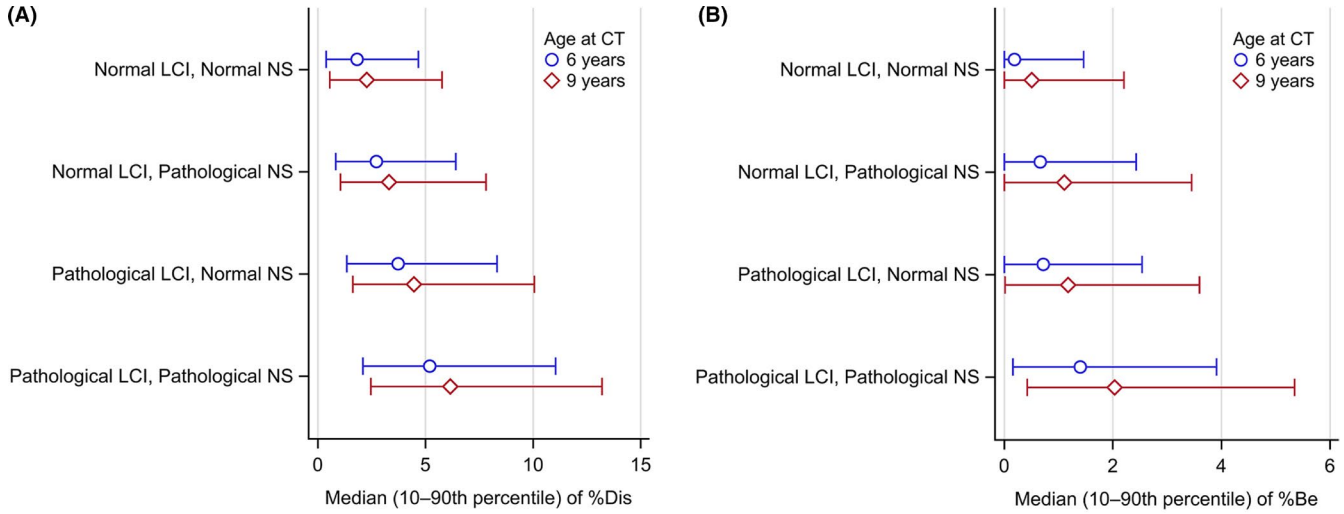


FIGURE 4 Estimated percentiles of total airway disease (A) and bronchiectasis (B) measured with chest CT at 6 and 9 years of age in relation to normal or pathological Northern Score and LCI values at chest CT

of three subsequent MBW measurements within one test occasion is considered good.[19,23] Still, it is important for the technician/clinician to study the actual parameters from the MBW examination to understand how reliable the mean LCI value is due to several challenges in both performing and interpreting an MBW examination. The inter-observer ICC for the scoring system The Perth-Rotterdam Annotated Grid Morphometric Analysis for CF, which is used in this study varies between 0.56 and 0.91 for bronchiectasis, which usually has the highest reproducibility of all different pathologies used in the scoring system.[17,24] In summary, it is important for the clinician to have knowledge about the reproducibility for each method used in clinical practise order to understand the progress of the CF lung disease.

The MBW test was the more sensitive of the two methods to detect early lung pathology in infants and pre-school children, as presented by a higher proportion of children having a pathological MBW test compared to a pathological CXR up to age 4 years. Several studies have indicated that abnormalities in the lower airways appear prior to the onset of airway symptoms, supporting intense monitoring of CF lung disease.[1,25,26] An increase in LCI may initially be reversible and respond to treatment, as the ventilation inhomogeneity may be caused by temporary mucus plugging and/or inflammation.[13,27] Currently, MBW examinations are performed every 3-6 month in some CF centres in order to capture early lung function abnormalities which enables early therapeutic interventions. A more frequent utilisation of CXRs has not been studied to our knowledge. A disadvantage of the method MBW is that the MBW examinations often are limited to tertiary care centres, due to the technical challenges to perform a MBW examination as well as to interpret the results. An MBW examination is also much more time-consuming in comparison with an CXR examination. Newborn screening for CF is not performed in Sweden. This fact might have influenced at what age CXR and MBW examinations become pathological but should not have influenced the comparison of the two methods.

This study has demonstrated the clinical advantage of combining the results from both the CXR and MBW examinations to better understand the magnitude of the SLD present in a patient with CF. The result from a normal MBW and CXR examination at the age of 6 years agreed with a very low extent of bronchiectasis and also a low extent of total airway disease. This information can be used as a surrogate to chest CT, or to perform chest CT less frequent, as children are more sensitive to radiation.[28] One problem if only performing a CXRs is if the clinician can be sure that the CXR is normal, as 40% of the normal CXRs between observers were re-scored as pathological. A combination of both MBW and CXR examinations is suggested when screening for early CF disease.

## 5 | STRENGTHS AND LIMITATIONS

This study included all individuals available for selection from a paediatric CF centre who performed MBWs and CXRs from an early age over a period of 20 years. A healthy reference cohort performed MBW examinations with the same MBW equipment and was analysed with the same software as the CF cohort. A limitation of the study was that it is an observational study using only clinical retrospective data. The patients were not allowed to have a pulmonary exacerbation at the annual examination, although a pulmonary infection close to the annual review might still have affected the outcome of both CXR and MBW examinations. The lack of chest CTs during infancy and pre-school ages is a limitation, for which the differences in detection of lung damage using LCI and NS were most pronounced. Another limitation is that the results derived from different inert gases and MBW equipment are not fully interchangeable.

## 6 | CONCLUSIONS

The low reproducibility in relation to the slow annual progression observed for the CXR scoring system NS limits the use of CXR as a sole method to track early CF lung disease. MBW was a more sensitive method than CXR to detect early CF lung disease. The combination of a MBW examination within the normal range and a CXR with no pathology, indicated a low presence of SLD measured with chest CT.

### ACKNOWLEDGEMENTS

The authors express their gratitude to the children and caregivers for participating in the study. We would also like to acknowledge the London Collaboration Group for letting us re-analyse healthy MBW examinations and many thanks to Sanna Kjellberg for letting us use her normative MBW reference material.

### CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

### ORCID

*Marcus Svedberg* https://orcid.org/0000-0002-0194-7365

### REFERENCES

1. Sly PD, Brennan S, Gangell C, et al. Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. Am J Respir Crit Care Med. 2009;180:146-152.
2. Grasemann H, Ratjen F. Early lung disease in cystic fibrosis. Lancet Respir Med. 2013;1:148-157.
3. Lahiri T, Hempstead SE, Brady C, et al. Clinical practice guidelines from the cystic fibrosis foundation for preschoolers with cystic fibrosis. Pediatrics. 2016;137:e20151784.
4. Villanueva G, Marceniuk G, Murphy MS, Walshaw M, Cosulich R, Guideline C. Diagnosis and management of cystic fibrosis: summary of NICE guidance. BMJ. 2017;359:j4574.
5. Castellani C, Duff AJA, Bell SC, et al. ECFS best practice guidelines: the 2018 revision. J Cyst Fibros. 2018;17:153-178.
6. Munro NC, Cooke JC, Currie DC, Strickland B, Cole PJ. Comparison of thin section computed tomography with bronchography for identifying bronchiectatic segments in patients with chronic sputum production. Thorax. 1990;45:135-139.

7. Szczesniak R, Turkovic L, Andrinopoulou ER, Tiddens H. Chest imaging in cystic fibrosis studies: what counts, and can be counted? J Cyst Fibros. 2017;16:175-185.
8. Thia LP, Calder A, Stocks J, et al. Is chest CT useful in newborn screened infants with cystic fibrosis at 1 year of age? Thorax. 2014;69:320-327.
9. Mott LS, Graniel KG, Park J, et al. Assessment of early bronchiectasis in young children with cystic fibrosis is dependent on lung volume. Chest. 2013;144:1193-1198.
10. Calder AD, Bush A, Brody AS, Owens CM. Scoring of chest CT in children with cystic fibrosis: state of the art. Pediatr Radiol. 2014;44:1496-1506.
11. Terheggen-Lagro SW, Arets HG, van der Laag J, van der Ent CK. Radiological and functional changes over 3 years in young children with cystic fibrosis. Eur Respir J. 2007;30:279-285.
12. Aurora P, Gustafsson P, Bush A, et al. Multiple breath inert gas washout as a measure of ventilation distribution in children with cystic fibrosis. Thorax. 2004;59:1068-1073.
13. Stahl M, Wielputz MO, Graeber SY, et al. Comparison of lung clearance index and magnetic resonance imaging for assessment of lung disease in children with cystic fibrosis. Am J Respir Crit Care Med. 2017;195:349-359.
14. Kuo W, Kemner-van de Corput MPC, Perez-Rovira A, et al. Multicentre chest computed tomography standardisation in children and adolescents with cystic fibrosis: the way forward. Eur Respir J. 2016;47:1706-1717.
15. Conway SP, Pond MN, Bowler I, et al. The chest radiograph in cystic fibrosis: a new scoring system compared with the Chrispin-Norman and Brasfield scores. Thorax. 1994;49:860-862.
16. Svedberg M, Gustafsson P, Tiddens H, Imberg H, Pivodic A, Lindblad A. Risk factors for progression of structural lung disease in school-age children with cystic fibrosis. J Cyst Fibros. 2019;19(6):910-916.
17. Rosenow T, Oudraad MCJ, Murray CP, et al. A quantitative structural lung disease computed tomography outcome in young children with cystic fibrosis. Am J Respir Crit Care Med. 2015;191:1158-1165.
18. Lee TW, Brownlee KG, Conway SP, Denton M, Littlewood JM. Evaluation of a new definition for chronic Pseudomonas aeruginosa infection in cystic fibrosis patients. J Cyst Fibros. 2003;2:29-34.
19. Robinson PD, Latzin P, Verbanck S, et al. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. Eur Respir J. 2013;41:507-522.
20. Mogayzel PJ Jr, Dunitz J, Marrow LC, Hazle LA. Improving chronic care delivery and outcomes: the impact of the cystic fibrosis Care Center Network. BMJ Qual Saf. 2014;23(Suppl 1):i3-i8.
21. Ronan NJ, Einarsson GG, Twomey M, et al. CORK study in cystic fibrosis: sustained improvements in ultra-low-dose chest CT scores after CFTR modulation with Ivacaftor. Chest. 2018;153:395-403.
22. Heltshe SL, Mayer-Hamblett N, Burns JL, et al. Pseudomonas aeruginosa in cystic fibrosis patients with G551D-CFTR treated with ivacaftor. Clin Infect Dis. 2015;60:703-712.
23. Fuchs SI, Gappa M. Lung clearance index: clinical and research applications in children. Paediatr Respir Rev. 2011;12:264-270.
24. Sandvik RM, Kongstad T, Green K, et al. Prospective longitudinal association between repeated multiple breath washout measurements and computed tomography scores in children with cystic fibrosis. J Cyst Fibros. 2021;20:632-640.
25. Stanojevic S, Davis SD, Retsch-Bogart G, et al. Progression of lung disease in preschool patients with cystic fibrosis. Am J Respir Crit Care Med. 2017;195:1216-1225.
26. Konstan MW, Hilliard KA, Norvell TM, Berger M. Bronchoalveolar lavage findings in cystic fibrosis patients with stable, clinically mild lung disease suggest ongoing infection and inflammation. Am J Respir Crit Care Med. 1994;150:448-454.
27. Rayment JH, Stanojevic S, Davis SD, Retsch-Bogart G, Ratjen F. Lung clearance index to monitor treatment response in pulmonary exacerbations in preschool children with cystic fibrosis. Thorax. 2018;73:451-458.
28. Johnson JN, Hornik CP, Li JS, et al. Cumulative radiation exposure and cancer risk estimation in children with heart disease. Circulation. 2014;130:161-167.


## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Svedberg M, Imberg H, Gustafsson P, Brink M, Caisander H, Lindblad A. Chest X-rays are less sensitive than multiple breath washout examinations when it comes to detecting early cystic fibrosis lung disease. Acta Paediatr. 2022;00:1–8. doi:10.1111/apa.16302