Prevalence and disease trajectories of pulmonary fibrosis of childhood interstitial lung disease: a register-based, multicentre observational study

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Summary

Background Pulmonary fibrosis is of critical importance in childhood interstitial lung disease (chILD), yet fibrosis prevalence, impact on clinical progression, and survival have not been systematically evaluated. Therefore, we aimed to determine the prevalence of pulmonary fibrosis and its impact on lung function as well as survival in individuals aged 0–18 years.

Methods Data were extracted from the chILD-EU register, a multicentre cohort study of children and adolescents with chILD from 23 European countries. Data collection included centralised peer review and systematic scoring of CT scans and lung biopsies. The primary outcome was the presence or absence of fibrosing lung disease. Pulmonary fibrosis was determined based on predefined criteria used in the register (fibrosis$_{register}$) or in clinical trials (fibrosis$_{trial}$). Clinical characteristics, disease categories, pulmonary function data, and survival were assessed. This study was registered with ClinicalTrials.gov (NCT02852928) and is ongoing.

Findings Data were collected prospectively between March 3, 2004 and July 23, 2025. Among the 1071 children diagnosed with chILD, 220 of 1071 fulfilled the criteria of fibrosis$_{register}$ (20·5% [95% CI 18·1–23·0]) and 62 of 534 fulfilled the criteria of fibrosis$_{trial}$ (11·6% [8·9–14·3]). Median age at inclusion was 2·4 years (IQR 0·6–9·2), 570 (53·2%) participants were male and 501 (46·8%) were female, and 882 (76·8%) were European. Pulmonary function, assessed as percent predicted forced vital capacity (ppFVC), in children with fibrosis under both fibrosis definitions was consistently 15–20% lower across all follow-up visits up to 8 years compared with individuals without fibrosing lung disease. Survival after enrolment was lower in children who fulfilled fibrosis$_{register}$ criteria than in those who did not fulfil fibrosis$_{register}$ criteria (log-rank p=0·0029; unadjusted hazard ratio (HR) for death or lung transplantation 1·64 [95% CI 1·18–2·28]). The increased hazard of fibrosis$_{register}$ remained after adjusting for sex, age category, and BMI z-score. A higher BMI z-score was protective for survival with fibrosis$_{register}$ (HR 0·80). While not statistically significant, children with fibrosis$_{trial}$ criteria had survival and HR trends in the same direction as those with fibrosis$_{register}$ criteria.

Interpretation The application of standardised criteria for diagnosing pulmonary fibrosis enables identification of affected children among patients with chILD. These children have lower pulmonary function, an increased risk of death, and could benefit from antifibrotic therapies.

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Introduction

Childhood interstitial lung disease (chILD) encompasses a diverse group of rare, diffuse parenchymal lung diseases that affect infants, children, and adolescents.[1] However, little is known about the long-term outcomes of many of these rare conditions. Mortality rates vary by age group, with prospective studies reporting rates as high as 13%.[2] Pulmonary fibrosis in adults, as a major cause of death in patients with ILD, has been a key research focus[3] resulting in international consensus statements from respiratory societies and leading to the development of antifibrotic treatments.[4] In chILD however, details about pulmonary fibrosis are scarce. A retrospective, single-centre CT-based study of 124 children with diffuse lung disease identified 19 children with fibrotic features,[5] and an international review has recently underscored its clinical relevance.[6] However, no study has yet systematically assessed the prevalence of pulmonary fibrosis in chILD, and its impact on disease trajectories and mortality.

A major barrier to advancing this field has been the lack of a standardised definition of pulmonary fibrosis in

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Research in context

Evidence before this study

Pulmonary fibrosis in childhood interstitial lung disease (chILD) is responsible for considerable morbidity and mortality, yet its disease-specific prevalence and associated outcomes in children remain poorly defined. We searched for studies of children with pulmonary fibrosis published in any language from database inception up until Oct 6, 2025, using the search terms "pulmonary interstitial fibrosis", "pulmonary fibrosis", "fibrotic lung disease", "fibrosing alveolitis", or "fibrosing interstitial lung disease". Excluding case reports or small series (<15 children), all solely based on histopathological fibrosis, we identified two relevant studies that defined childhood pulmonary fibrosis based on histological and CT radiological criteria. One retrospective, single-centre study of 124 children with diffuse lung disease included a CT-based analysis and described 19 children with fibrotic features. The other study was a randomised controlled trial enrolling 39 patients into a study of nintedanib. These investigations defined criteria to identify children with pulmonary fibrosis. However, none of these studies used a well-defined, prospectively followed cohort, systematically determined fibrosis in all available lung biopsies or CT scans, or assessed long-term pulmonary function testing and survival.

Added value of this study

To our knowledge, this study is the first comprehensive and prospective analysis of pulmonary fibrosis in chILD. Drawing from the European prospective chILD-EU register, this study includes 1071 children with CT scans and lung biopsies who were systematically scored. Children with fibrosis had a 15–20% worse percent predicted forced vital capacity during the observation period. Survival probability after enrolment for children with fibrosis according to the register definition ($fibrosis_{register}$) was lower than in children not meeting the fibrosis criteria. Male sex and a higher BMI z-score were protective. In children with fibrosis according to the trial definition ($fibrosis_{trial}$), hazard ratios for death or lung transplantation were in the same direction but not significant.

Implications of all the available evidence

The absence of standardised criteria for identifying and evaluating pulmonary fibrosis in chILD has led to uncertainty in assessing risk, outcome, and treatment planning—especially in the light of emerging antifibrotic therapies for children. This study defined imaging and histological criteria to recognise fibrotic patterns, enabling early identification of patients who could benefit from targeted interventions. The findings provide crucial estimates to inform the design of future clinical trials. Moving forwards, defining and evaluating fibrosis and its progression by clinical teams caring for chILD remains a key objective.

children. Currently two different definitions are commonly applied, a register-based definition[6] and one proposed in the first paediatric randomised trial of the antifibrotic agent nintedanib in children, published in 2023.[7] The significance of these definitions has not been assessed systematically. Both adopted the radiological criteria from the adult definition, including reticular/linear markings, traction bronchiectasis, architectural distortion, and honeycombing.[8] In children, cystic lucencies are considered as a hallmark of fibrosing lung disease in early life, particularly in genetically defined surfactant dysfunction disorders.[9] Although longitudinal data in children are scarce, cystic lesions have been shown to increase in number and size over time in disorders such as surfactant protein C deficiency and adenosine triphosphate-binding cassette subfamily A member 3 (ABCA3) deficiency.[10–12]

Notably, fibrosing processes in chILD affect lungs that are still undergoing rapid development and have a substantial regenerative potential, extending well into adolescence.[13] This plasticity offers a unique potential for possible reversibility of fibrotic processes, similar to bronchiectasis in children.[14] These developmental differences emphasise the need for paediatric specific criteria and interpretation when evaluating fibrosis in chILD.

The aim of this study was to determine the prevalence of pulmonary fibrosis and its impact on lung function as well as survival in a large, prospectively followed cohort of children aged 0–18 years, using both the trial and register fibrosis definitions. Additionally, we aimed to explore the role and clinical significance of cystic (parenchymal) changes in paediatric fibrosing interstitial lung disease.

Methods

Study design and participants

This study was based on prospectively collected data from the chILD-EU register, a multicentre European register of children and adolescents with chILD involving 23 countries. The chILD-EU register has been operating since Jan 18, 2013. It was built on a national German predecessor with the same structure. Initially, data from 69 patients enrolled between March 3, 2004, and Jan 1, 2013, were transferred to the chILD-EU database for continued follow-up. The register included centralised peer review together with systematic scoring of CT scans and lung biopsies. Participating centres adhered to all contractual, legal, and ethical standards before enrolling patients. Irrespective of ethnicity, all children with chILD were included in the cohort and due to the low number in each disease entity, no separate analyses were made. Each patient and/or caregiver provided age-appropriate verbal assent and written informed consent. The study was approved by the lead Ethics committee of the University Hospital

Munich (20-0329,22-0133) and all local committees. We followed the Declaration of Helsinki and STROBE reporting guidelines to ensure completeness and transparency.

Procedures

To be included in the register, participants were identified by their treating physicians and submitted to a web-based platform for peer review. Diagnostic categorisation was based on systematically obtained data.[15] A multidisciplinary team including clinicians, radiologists, and pathologists with expertise in chILD established the diagnosis in accordance with the guidelines of the American Thoracic Society (ATS) and the European Management Platform for Childhood Interstitial Lung Disease.[16] Diagnoses were subsequently grouped into predefined categories.[17,18] Participants were prospectively followed up at 6 and 12 months and then annually until death, lung transplantation, or transition to adult care, using standardised visit forms, pulmonary function testing (PFT) initially trained through a centralised workshop, and adhering to European Respiratory Society/ATS criteria. To minimise loss to follow-up, the register staff contacted sites via the online platform, emails, and telephone at least four times per year.[15] CT imaging was systematically reviewed by three experienced radiologists (JL-Z, BK, and IK-S) using a consensus-based approach. Each scan was evaluated for the presence or absence of reticular/linear markings, traction bronchiectasis, architectural distortion, honeycombing, or cystic lesions, as defined by the Fleischner Society.[19] Lung biopsies were evaluated for interstitial fibrosis, fibroblastic foci, or honeycombing. These scorings were routinely performed within the standardised procedures of the chILD-EU register and were extracted for secondary data analysis based on preset criteria to determine the presence of fibrosis.

Outcomes

The fibrosis definition used in the register ($fibrosis_{register}$)[6] included patients if at least one CT scan showed two of the four criteria "linear/reticular opacities", "traction bronchiectasis", "architectural distortion", and "honeycombing", or if at least one CT scan showed two of the five criteria "linear/reticular opacities", "traction bronchiectasis", "architectural distortion", "honeycombing", and "cystic lesions", or if the lung biopsy showed one of the three criteria "interstitial fibrosis", "fibroblastic foci", or "honeycombing".

The fibrosis definition used in the trial ($fibrosis_{trial}$)[7] included patients if at least two CT scans showed two of the five criteria "linear/reticular opacities", "traction bronchiectasis", "architectural distortion", "honeycombing" and "cystic lesions" or if at least one CT scan showed two of the four criteria "linear/reticular opacities", "traction bronchiectasis", "architectural distortion", and "honeycombing" and the lung biopsy showed one of the three criteria "interstitial fibrosis", "fibroblastic foci", or "honeycombing". The primary outcome was the presence or absence of fibrosing lung disease.

Clinical and sociodemographic variables were retrieved from the chILD-EU register, including PFT parameters forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and maximum mid-expiratory flow (MMEF) expressed as percent predicted (pp) using the GLI equations,[20] Fan severity score,[21] BMI z-scores, failure to thrive, and respiratory rate z-score.[22] All clinical variables were entered into an electronic case reporting system.

Statistical analysis

Demographic and clinical data were reported as counts (%) or median (IQR). Group comparisons were conducted using the Mann–Whitney U test. Longitudinal changes in ppFVC were assessed using linear mixed-effects models (appendix p 2), with fixed effects for fibrosis (yes/no), yearly visit (categorical), baseline age (age at first available PFT), and the fibrosis-by-visit interaction. Survival was analysed using time since register entry as the time scale, with follow-up from enrolment until death, lung transplantation, or last observation. Kaplan–Meier curves were constructed separately for the fibrosis register and trial definitions and compared using log-rank tests. Cox proportional hazards models were fitted on the same time scale. Multivariable survival models adjusted for sex, BMI z-score, and baseline age (categorised as <2, 2–6, 7–12, and >12 years). Statistical significance was defined as $p<0·05$. All statistical analyses were conducted in SPSS (version 26.0) and R (version 4.4.2).

Role of the funding source

The funders had no role in study design, conduct or interpretation, nor in writing or submitting the manuscript for publication.

Results

1071 children from 23 European countries (570 [53·2%] male and 501 [46·8%] female) were included in the final analysis. Data were collected between March 3, 2004 and July 23, 2025 (figure 1, appendix p 6), representing the entire spectrum of chILD conditions. At inclusion into the register, this large cohort had the characteristic features of individuals with chILD (table 1). The median age at inclusion was 2·4 years (IQR 0·6–9·2), chronic lung disease symptoms started at a median of 0·4 years (0·0–4·2), and ILD was diagnosed at 0·8 (0·3–6·3) years. Patients received care according to current recommendations with anti-inflammatory drugs.[16] 672 (63·6%) of 1057 (14 missing) had received systemic steroids at some point, 370 (35·0%) long-term macrolides, 267 (25·3%) of 1055 (16 missing) hydroxychloroquine, and less than 10% azathioprine, mycophenolate, or cyclophosphamide. Antifibrotics were used rarely:

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For the **child-EU register** see www.childeu.net

For the **BMI growth chart** see www.cdc.gov/growth-chart-training

See **Online** for appendix

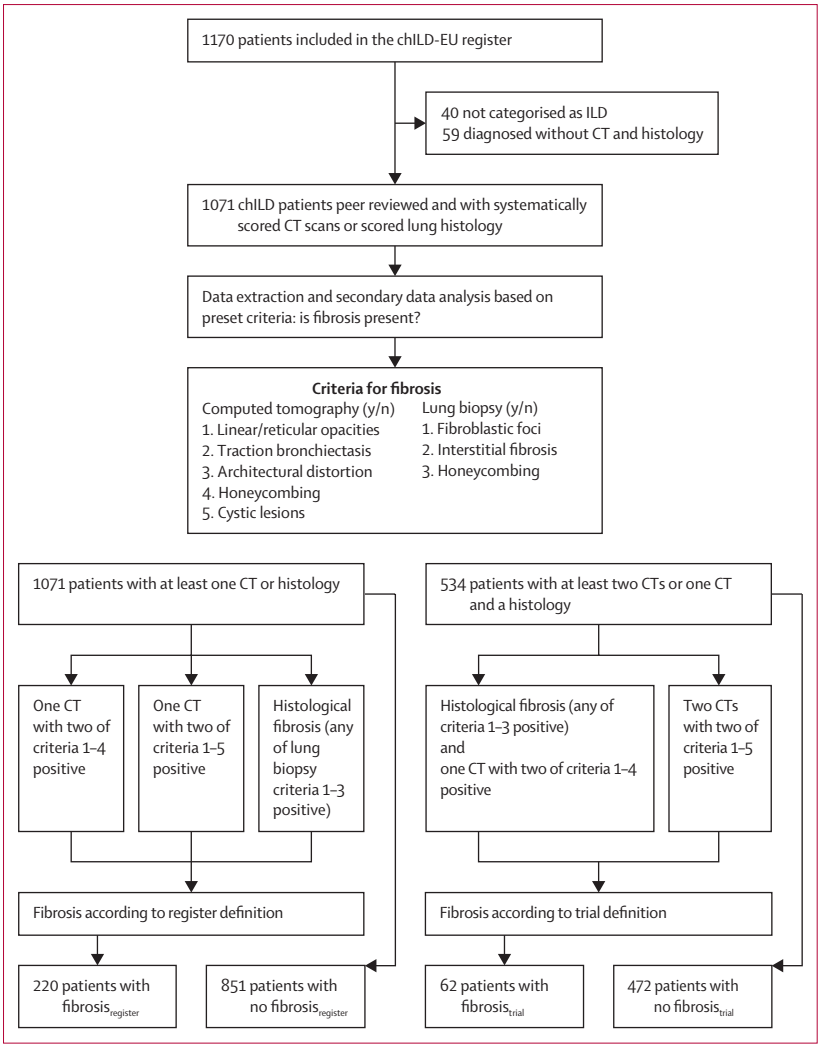

Figure 1: **Study profile**
chILD=childhood interstitial lung disease.

seven patients received pirfenidone (1 patient <3 years, all others <6 months) and three patients received nintedanib (one patient <2 years and two patients <1 year). Median follow-up duration was 2·2 (IQR 0·6–5·3) years. 143 (13·3%) of 1071 participants were lost to follow-up, and 71 (6·6%) of 1071 transitioned to adult care. PFT results (in children old enough to perform PFT), respiratory rate, and BMI were substantially decreased compared with those in patients without pulmonary fibrosis (table 2).

Of the 1071 patients with chILD who had at least one CT scan (n=1034) or lung histology (n=501), 220 (20·5% [95% CI 18·1–23·0]) had fibrosis$_{register}$ (table 1). Among the 534 participants who had at least two CT scans or one CT scan and a lung histology, 62 (11·6% [8·9–14·3]) children had pulmonary fibrosis$_{trial}$ (table 3). At inclusion into the register, patients from both fibrosis groups, when compared to the respective patients with no fibrosis, were older, had worse initial ppFVC and ppFEV$_1$, and had an older age at death.

Among the group of 220 patients with fibrosis$_{register}$, linear/reticular opacities were present in 161 (73·2%) of 220, followed by cystic lesions in 113 (51·4%), architectural distortion in 85 (38·6%), traction bronchiectasis in 63 (28·6%), and honeycombing in 21 (9·5%; table 3). Among patients who did not meet the criteria for pulmonary fibrosis, linear/reticular opacities were present in 143 (16·8%) of 851, cystic lesions in 66 (7·8%), and all other features in less than 16 (1·9%; table 3).

Of the patients meeting the diagnostic criteria for pulmonary fibrosis, 161 (73·2%) of 220 were diagnosed based on CT findings alone: ie, 113 (51·4%) based on the criteria linear/reticular opacities, honeycombing, traction bronchiectasis, and architectural distortion; an additional 48 (21·8%) were diagnosed also considering cystic CT lesions. Histology alone added the missing 59 (26·8%) of 220 fibrosis cases (table 3).

Among the 534 patients with two CT scans or one CT scan and a histology sample available, 62 patients fulfilled the trial fibrosis definition. Of these patients, 422 (79·0%) of 534 were diagnosed based on CT findings. Histological evaluation of lung tissue in combination with a CT scan accounted for the remaining 112 (21·0%) of 534 of fibrosis diagnoses (table 3). The frequency of single radiological fibrotic features in patients not meeting the necessary criteria for pulmonary fibrosis was high, ranging between 157 (33·3%) of 472 (linear/reticular opacities) and five (1·1%) of 472 (honeycombing; table 3). The stricter trial definition of fibrosis resulted in 62 (11·6%) of 534 of the patients defined as fibrotic, compared with 220 (20·5%) of 1071 when the register definition was used.

In the 49 patients fulfilling fibrosis criteria based on two CT scans, linear/reticular abnormalities were the most frequent finding (45 [91·8%] of 49), followed by architectural distortion (30 [61·2%] of 49), cystic lesions (41 [63·3%] of 49), traction bronchiectasis (23 [46·9%] of 49), and honeycombing (12 [24·5%] of 49). In only 13 patients classified as fibrotic based on histology plus one CT scan, linear/reticular abnormalities (11 [84·6%] of 13) and architectural distortion (10 [76·9%] of 13) were again the most common features, whereas cystic lesions (6 [46·2%] of 13), traction bronchiectasis (5 [38·5%] of 13), and honeycombing (1 [7·7%] of 13) were less frequent. Overall, cystic lesions appeared more frequently in patients with CT-based definitions.

Considering CT scans alone and the usage of the "cystic criterion" increased fibrosis diagnosis from 61·3% to 79·0% of included participants (+17·7%) using the trial criteria, and from 51·4% to 73·2% (+21·8%) using the register definition of pulmonary fibrosis. To assess the impact of cystic lesions on outcome, we compared lung function test results in patients with and without cystic lesions. Among all patients with lung

function data available, those with cysts (median ppFVC 65·5% [IQR 48·5–79·0]; n=108) had a worse ppFVC than those without (70·1% [52·0–91·0]; n=430; p=0·025, Wilcoxon test). Among patients with $fibrosis_{register}$ and having exactly two fibrosis criteria on their CT scans (n=58), patients with cystic lesions (n=31) had higher baseline PFT (0 years [0Y]) ppFVC values (median ppFVC 70·0% [IQR 63·0–93·5]) compared with those without cystic lesions (n=27; 52·0% [24·5–56·5]; n=27; p<0·0001, Wilcoxon test). The initial difference in ppFVC between the groups was no longer evident after 1 year and remained absent throughout the 8-year follow-up (appendix p 5).

The diagnoses investigated in this study covered almost the entire chILD spectrum of diseases (appendix pp 7–8). Those conditions with pulmonary fibrosis and represented with more than 10 patients per entity are listed in table 4. Among the conditions affecting the lungs only, ABCA3 deficiency had fibrosis rates above 30%; among conditions associated with systemic diseases, those with fibrosis rates above 30%, these were aminoacyl-tRNA synthetase deficiency, coatomer subunit α (COPA) syndrome, and a collection of other rare genetic conditions; and among the conditions related to exogenous injury, bronchopulmonary dysplasia had similarly high rates (table 4, appendix pp 7–8).

Using the register definition of fibrosis, the linear mixed-effects model estimated consistently lower ppFVC in all patients with fibrosis (figure 2). Model-based type III ANOVA showed a significant main effect of visit (p<0·0001) and a significant visit-by-fibrosis interaction (p=0·030). At baseline (0Y), ppFVC was lower for fibrosis patients (mean difference –13·4% [95% CI –18·4 to –8·5]; p<0·0001). This difference remained statistically significant at all follow-up visits, ranging from –13·3% to –22·0% over 1–8 years (all adjusted p<0·0001; appendix p 9). In the non-fibrosis group, ppFVC increased from baseline (0Y) by 3·7–8·4% during 1–4 years of follow-up (all adjusted p≤0·0082) and remained 6·9–7·5% above baseline (0Y) during 5–8 years of follow-up (all adjusted p≤0·0001; appendix pp 10–13). Counts of ppFVC measurements per visit are provided in the appendix (p 4). By contrast, the fibrosis group showed no significant within-group differences between any visits (all adjusted p>0·05; appendix pp 10–12).

Findings using the trial definition closely mirrored those under the register definition (figure 2). Model-based type III ANOVA showed a significant main effect of visit (p<0·0001), whereas the visit-by-fibrosis interaction was not significant (p=0·35). At baseline (0Y), ppFVC was lower for patients with fibrosis (mean difference –13·1% [95% CI –21·2 to –5·0]; p=0·0034). This difference remained statistically significant at all follow-up visits, ranging from –12·7% to –20·6% over 1–8 years (all adjusted p≤0·0039; appendix p 13). The

	All (N=1071)	Fibrosis according to register definition (n=220)	Fibrosis according to trial definition (n=62)
Age	2·4 (0·6–9·2)	7·2 (1·3–13·0)	9·3 (4·1–13·8)
Sex			
Female	501 (46·8%)	112 (50·9%)	34 (54·8%)
Male	570 (53·2%)	108 (49·1%)	28 (45·2%)
Consanguinity	126 (13·0%)	31 (15·0%)	10 (17·9%)
Race/ethnicity			
European			
European, no more data	794 (74·0%)	171 (75·0%)	49 (76·6%)
European, Turkish	27 (2·5%)	8 (3·5%)	3 (4·7%)
European, Roma	1 (0·1%)	0	0
African			
African, north	7 (0·7%)	0	0
African, sub-Saharan	1 (0·1%)	0	0
African, American	1 (0·1%)	1 (0·4%)	0
African, no more data	21 (2·0%)	6 (2·6%)	0
Asian			
Asian, Middle Eastern/Central Asian	5 (0·5%)	2 (0·9%)	0
Asian, northeast, including Chinese, Japanese, and Korean	9 (0·8%)	0	0
Asian, south, including Indian	6 (0·6%)	1 (0·4%)	1 (1·6%)
Asian, southeast, including Malaysian, Vietnamese, and Indonesian	18 (1·7%)	8 (3·5%)	2 (3·1%)
Others, Aboriginal, Pacific Islander, Native Hawaiian, Māori	1 (0·1%)	1 (0·4%)	1 (1·6%)
Unknown	180 (16·8%)	22 (9·6%)	6 (9·4%)
Onset of lung disease			
Insidious	463 (43·2%)	105 (47·7%)	35 (56·5%)
Sudden	262 (24·5%)	53 (24·1%)	14 (22·6%)
Sudden with respiratory tract infection	202 (18·9%)	36 (16·4%)	7 (11·3%)
Unknown	70 (6·5%)	16 (7·3%)	3 (4·8%)
Fan 5-point severity scale			
1: Asymptomatic	102 (9·5%)	18 (8·2%)	6 (9·7%)
2: Symptomatic, normal room air O_2 sat under all conditions	318 (29·7%)	70 (31·8%)	19 (30·6%)
3: Symptomatic, normal room air O_2 sat, abnormal with sleep or exercise	196 (18·3%)	32 (14·5%)	8 (12·9%)
4: Symptomatic, abnormal resting room air O_2 sat	210 (19·6%)	40 (18·2%)	15 (24·2%)
5: Symptomatic with pulmonary hypertension	165 (15·4%)	46 (20·9%)	8 (12·9%)
Cough	504 (49·2%)	114 (54·0%)	33 (56·9%)
Dyspnoea (retractions/nasal flaring)	752 (73·3%)	157 (74·1%)	42 (72·4%)
Tachypnoea	727 (70·9%)	136 (64·5%)	38 (65·5%)
Fine crackles (crepitations)	410 (40·3%)	84 (40·0%)	28 (49·1%)
Wheezing	205 (20·0%)	36 (17·1%)	9 (15·8%)
Gastro-oesophageal reflux, clinically relevant for lung disease (based on history or studies)	133 (13·0%)	40 (19·0%)	11 (19·3%)
Haemoptysis	64 (6·2%)	7 (3·3%)	4 (7·0%)
Recurrent aspirations (based on history or studies)	40 (3·9%)	10 (4·8%)	3 (5·3%)
Failure to thrive or weight loss*	451 (43·7%)	125 (58·7%)	42 (71·2%)

Data are median (IQR) or n (%). Frequencies of the two fibrosis classifications were not compared statistically, as all individuals under the fibrosis trial definition were also included under the fibrosis register definition. O_2 sat=O_2 saturation. *Defined by the treating clinician based on weight below the 5th percentile for age and sex on standardised growth charts, decline across two or more major percentile lines in weight-for-age (≤2 years) or weight-for-length (>2 years), or weight-for-length or BMI-for-age below the 5th percentile.

Table 1: **Baseline characteristics**

	All (N=1071)	Fibrosis according to register definition (n=1071)		Fibrosis according to trial definition (n=534)	
		Yes	No	Yes	No
Age at inclusion, years	2·4 (0·6–9·2); n=1070	7·2 (1·3–13·0); n=220*	1·8 (0·5–7·9); n=850	9·3 (4·1–13·8); n=62*	4·0 (0·8–10·2); n=472
Age at start of chronic lung disease symptoms, years	0·4 (0·0–4·2); n=1004	1·0 (0·0–8·1); n=211†	0·4 (0·0–3·2); n=793	1 (0·00–8·15); n=59	0·6 (0·0–6·3); n=451
Age at first interstitial lung disease detection, years	0·8 (0·3–6·3); n=1011	2·9 (0·3–9·9); n=212*	0·7 (0·3–4·7); n=799	4·4 (0·3–10·1); n=59	1·2 (0·3–7·8); n=452
Age at biopsy, years	2·1 (0·5–9·0); n=485	4·3 (0·8–10·6); n=152*	1·5 (0·4–7·5); n=333	5·8 (1·1–10·2); n=42	2·1 (0·5–9·2); n=314
Age at lung transplant, years	10·0 (3·9–13·8); n=52	7·7 (3·1–12·3); n=20	10·0 (4·3–14·5); n=32	10·5 (10·3–11·9); n=5	10·2 (4·2–13·9); n=32
Age at death, years	1·2 (0·2–7·3); n=123	8·6 (1·1–16·2); n=36*	0·6 (0·1–4·1); n=87	12·9 (8·6–18·2); n=15*	2·8 (0·5–6·6); n=54
ppFEV$_1$	65 (44–79); n=304	51 (39–70); n=89*	68 (50–85); n=215	48 (33–65); n=29‡	67 (43–84); n=170
ppFVC	68 (47–83); n=306	55 (39–73); n=91*	73 (55–87); n=215	52 (43–65); n=30*	73 (49–87); n=170
FEV$_1$/FVC	0·90 (0·80–1·00); n=304	0·89 (0·79–0·94); n=89	0·89 (0·78–0·95); n=215	0·89 (0·78–0·95); n=29	0·88 (0·78–0·95); n=170
MMEF	58 (35–90); n=241	49 (28–74); n=69	65 (42–93); n=172	59 (26–73); n=26	64 (40–92); n=130
ppDLCO	61 (42–80); n=89	42 (38–61); n=29*	69 (54–89); n=60	50 (40–60); n=8	69 (47–94); n=50
Respiratory rate z-score	2·56 (0·44–4·18); n=500	3·34 (0·90–5·09); n=104†	2·44 (0·42–4·18); n=396	3·88 (1·59–7·45); n=28	2·66 (0·52–4·95); n=206
BMI z-score	−0·90 (−2·13 to 0·28); n=970	−1·37 (−2·37 to −0·03); n=205†	−0·81 (−2·06 to 0·32); n=765	−1·31 (−2·66 to −0·10); n=55	−0·81 (−2·08 to 0·36); n=439

Data are median (IQR) and numbers of individuals. The exact age at inclusion into the register was unknown in one case. Comparisons were made using the Mann-Whitney U test and the p value was corrected for the two comparisons indicated. pp=percent predicted. FEV$_1$=forced expiratory volume in 1 s. FVC=forced vital capacity. DLCO=diffusing capacity of the lung for carbon monoxide. MMEF=maximum mid-expiratory flow. *p<0·002; †p<0·05; ‡p<0·004.

Table 2: **Age and quantitative respiratory and general data at inclusion into the register**

	Fibrosis according to register definition		Fibrosis according to trial definition	
	Patients with fibrosis (n=220; 20·5%)	Patients without fibrosis (n=851; 79·5%)	Patients with fibrosis (n=62; 11·6%)	Patients without fibrosis (n=472; 88·4%)
Imaging criteria scored				
Linear/reticular opacities	161 (73·2%)	143 (16·8%)	56 (90·3%)	157 (33·3%)
Honeycombing	21 (9·5%)	1 (0·1%)	13 (21·0%)	5 (1·1%)
Traction bronchiectasis	63 (28·6%)	13 (1·5%)	28 (45·2%)	29 (6·1%)
Architectural distortion	85 (38·6%)	15 (1·8%)	40 (64·5%)	30 (6·4%)
Cystic lesions	113 (51·4%)	66 (7·8%)	37 (59·7%)	89 (18·9%)
CT features combined				
One CT with two of criteria 1–4 positive	113 (51·4%)*	0	53 (85·5%)	24 (11·2%)
One CT with two of criteria 1–5 positive	161 (73·2%)*	0	62 (100%)	53 (11·2%)
Two CTs with two of criteria 1–4 positive	38 (17·3%)	0	38 (61·3%)	..
Two CTs with two of criteria 1–5 positive	49 (22·3%)	0	49 (79·0%)*	..
Histological features scored				
Fibroblastic foci	8 (3·6%)	0	4 (6·5%)	4 (0·8%)
Honeycombing	4 (1·8%)	0	3 (4·8%)	1 (0·2%)
Interstitial fibrosis	81 (36·8%)	0	22 (35·5%)	57 (12·1%)
Histological features combined				
Histological fibrosis (any of criteria 1–3 positive)	85 (38·6%)*	0	22 (35·5%)	59 (12·5%)
Histological and CT features combined				
Histological fibrosis and one CT with two of criteria 1–4 positive	21 (9·5%)	0	21 (33·9%)*	..
Histological fibrosis and one CT with two of criteria 1–5 positive	26 (11·8%)	0	22 (35·5%)	4 (0·8%)

Data are the frequency of fibrosis indicators expressed as the number of patients and their percentage of the respective group. Some patients were positive for more than one of the complex fibrosis criteria (figure 1), so numbers cannot be simply added to yield patients with fibrosis. *Results that led to the diagnosis of fibrosis according to the register or trial definition. Of the 1071 patients included, 1034 had at least one CT and those 37 without a CT had a lung biopsy; in total 501 had a biopsy. Of the 534 patients with fibrosis according to the trial definition, all had at least one CT and 154 with only one CT also had a biopsy; in total 368 had a lung biopsy.

Table 3: **Criteria fulfilled to diagnose fibrosing lung disease and the role of cystic lesions on CT scan**

non-fibrosis group showed increases from baseline (0Y) at several visits (2–6 years: +4·9% to +7·2%; all adjusted p≤0·0075), whereas the fibrosis group showed no significant within-group differences between any visits (appendix pp 14–16).

To evaluate whether mortality-related dropout could bias the estimated PFT trajectories, joint longitudinal-survival models were fitted as a sensitivity analysis. For both, $fibrosis_{register}$ and $fibrosis_{trial}$ association with dropout was not significant (appendix p 3).

166 children in the register definition cohort (15·5%) and 100 children in the trial definition cohort (18·7%) died or underwent lung transplantation during follow-up. Children with $fibrosis_{register}$ showed lower survival after enrolment than those without fibrosis (log-rank p=0·0029; figure 3A). In the Cox model, fibrosis was associated with an increased hazard (hazard ratio [HR] 1·64 [95% CI 1·18–2·28]; p=0·0032). In the multivariable model, adjusted for sex, BMI z-score, and age category, fibrosis remained significant (HR 1·64 [1·14–2·35]; p=0·0078). Male sex was associated with a lower hazard (HR 0·69 [0·50–0·95]; p=0·025) and a higher BMI z-score was protective (0·80 [0·71–0·90]; p=0·0018). Using the trial definition, survival did not differ significantly between children with $fibrosis_{trial}$ and those without (log-rank p=0·28; figure 3B). The unadjusted HR for fibrosis was in the same direction but not significant (HR 1·35 [95% CI 0·78–2·34]; p=0·28). The multivariable model also showed no association with $fibrosis_{trial}$ (HR 1·21 [0·65–2·23]; p=0·55). BMI z-score remained protective (HR 0·74 [0·63–0·86]; p=0·0001), while sex was not significant (0·85 [0·56–1·28]; p=0·43).

	Fibrosis according to register definition	Fibrosis according to trial definition
All	220 (20·5%) of 1071	62 (11·6%) of 534
Conditions affecting the lung only		
ABCA3 deficiency	18 (32·1%) of 56	10 (29·4%) of 34
Surfactant protein C mutations	9 (30·0%) of 30	3 (14·3%) of 21
Non-specific interstitial pneumonia	7 (22·6%) of 31	0
Persistent tachypnoea of infancy	3 (1·3%) of 237	0
Idiopathic pulmonary haemosiderosis	2 (4·3%) of 46	1 (5·0%) of 20
Pulmonary hypertension	2 (8·3%) of 24	0
Pulmonary interstitial glycogenosis	2 (9·5%) of 21	1 (6·3%) of 16
Conditions associated with systemic disease		
Aminoacyl-tRNA synthetase deficiency	9 (60·0%) of 15	4 (36·4%) of 11
COPA syndrome	8 (57·1%) of 14	1 (10·0%) of 10
ILD related to trisomy 21	7 (28%) of 25	0
Other rare genetic conditions	5 (31·3%) of 16	1 (10·0%) of 10
Stem cell transplant, oncological condition	5 (20·8%) of 24	1 (6·7%) of 15
Conditions due to exposure		
Bronchopulmonary dysplasia	15 (55·6%) of 27	4 (30·8%) of 13
Post-infectious bronchiolitis obliterans	4 (12·1%) of 33	1 (7·1%) of 14
Drug reactions	3 (11·5%) of 26	1 (9·1%) of 11
Chronic ILD from infectious or post-infectious processes	1 (5·6%) of 18	0
Conditions with no fibrosis detected*	107 (10·0%) of 1071	53 (9·9%) of 534

Data are n (%) of cohort. ILD=interstitial lung disease. *AGR2-related disease (n=1); alveolar microlithiasis (n=3); alveolar capillary dysplasia (n=18); anti-basement membrane antibody disease (n=2); anti-synthetase syndrome (n=2); aspiration syndromes (n=3); autoimmune pulmonary alveolar proteinosis (n=6); cyclin-dependent kinase 13 associated ILD (n=2); eosinophilic pneumonitis (n=5); follicular bronchitis/bronchiolitis (n=4); gestational diabetes-induced lung underdevelopment and delayed maturation (n=2); granulomatosis with polyangiitis (n=10); haemoglobinopathy (n=2); idiopathic pulmonary haemorrhage with autoimmune features (n=3); integrin α3 mutation associated kidney, lung, and skin disease (n=2); Klinefelter syndrome (n=2); lacrimo-auriculo-dental-digital syndrome 3 (n=2); haemorrhagic telangiectasia (n=4); Swyer–James–MacLeod syndrome (n=2); mixed connective tissue disease (n=3); Noonan syndrome (n=2); pulmonary alveolar proteinosis from variants in *CSF2RB* (n=1); pulmonary hypertension caused by known genes (n=3); related to chromosomal disorders other than trisomy 21 (n=5); SFTPA1-related disease (n=1); SRRM2-related disease (n=3); tuberous sclerosis complex associated lymphangioleiomyomatosis (n=2); undefined ILD in mature neonate (n=11). Details on the entire cohort are depicted in appendix pp 7–8.

Table 4: **Diagnosis and pulmonary fibrosis rates of conditions with 10 or more individuals in both the register and the trial cohort**

Discussion

To our knowledge, this is the first study to assess the prevalence, characteristics, and disease trajectories of pulmonary fibrosis in chILD. Strengths of the study lie in its systematic application of pulmonary fibrosis definitions to a large group of prospectively followed, well-defined patients representing the entire chILD spectrum.

Current definitions of fibrosing ILD in childhood largely adapt concepts developed for adult disease and therefore combine structural imaging findings with evidence of disease persistence or progression. Our data suggest that both the register-based definition, which relies on a single-timepoint assessment, and the trial-based definition, which requires longitudinal confirmation, are clinically meaningful but serve different purposes. The register definition appears well suited for epidemiological studies and early risk stratification in routine care, whereas the trial definition provides higher specificity for interventional studies but is less feasible in children due to limited availability of repeated CT imaging and concerns regarding radiation exposure and anaesthesia.

A major finding of this study is that the systematic application of a pulmonary fibrosis definition can identify individuals with decreased pulmonary function and an increased risk of death or lung transplantation during the study period. These data in children are consistent with many adult studies of non-IPF-fibrosis.[23,24] The older age at death in the fibrosis groups does not indicate longer survival after enrolment. In both non-fibrosis groups, many deaths occurred early after register inclusion, mainly during infancy. These early deaths were associated with severe developmental lung disorders or surfactant dysfunction disorders, in which mortality is likely related to impairment of gas exchange. By contrast, children with fibrosis were older at register inclusion. The association between $fibrosis_{register}$ and lower survival after enrolment persisted in the multivariable model including baseline age category.

For patients meeting $fibrosis_{trial}$ criteria, HR for death or lung transplantation were in the same direction but not significant, most likely due to reduced power. Higher

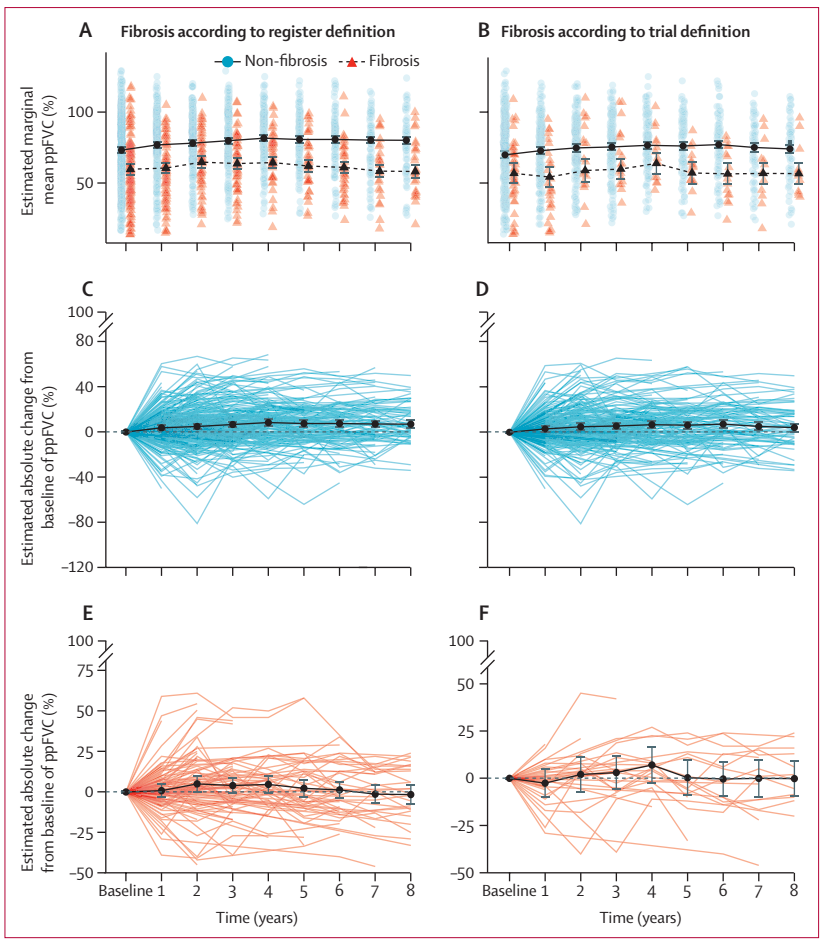

Figure 2: **Estimated marginal means of ppFVC trajectories according to fibrosis status**
(A, B) Estimated marginal mean ppFVC at each yearly visit with 95% CIs. (C, D) Estimated marginal mean change from baseline PFT (0Y) with 95% CIs. (E, F) Individual patient trajectories overlaid with group mean changes from baseline PFT (0Y). Counts of ppFVC measurements per visit are provided in the appendix (p 4). Full model-based contrast estimates are provided in the appendix (pp 9, 13). For fibrosis by register definition, at baseline PFT (0Y), the estimated marginal mean ppFVC was 73·3% (95% CI 70·8–75·7) in the non-fibrosis group and 59·8% (55·5–64·1) in the fibrosis group. For fibrosis by trial definition, at baseline PFT (0Y), the estimated marginal mean ppFVC was 69·9% (66·9–72·9) in the non-fibrosis group and 56·8% (49·2–64·4) in the fibrosis group. For the register definition (A, C, E), the linear mixed-effects model showed a significant main effect of visit ($p<0·0001$) and a significant visit-by-fibrosis interaction ($p=0·030$). ppFVC=percent predicted forced vital capacity. PFT=pulmonary function testing.

BMI z-score was independently protective, in line with adult observations,[25,26] whereas male sex was associated with lower mortality, suggesting cohort-specific risk patterns. These findings support usage of the fibrosis$_{register}$ definition as clinically meaningful for risk stratification.

The development of fibrosis can take considerable time, with the cumulative contribution of additional triggers including environmental agents or exacerbations,[27] all happening in children whose lungs are still developing. This is in agreement with our PFT results. The deterioration in patients with fibrosis likely occurs insidiously and early, as the 15–20% lower ppFVC observed throughout childhood was already established when the first PFTs were performed. This diagnostic gap when routine PFT is not yet feasible (ie, <6 years of age) highlights the potentially great importance of CT imaging at the one end of the age spectrum in young children. Beyond the necessity of limiting exposure to radiation, the requirement for general anaesthesia in young children when centres lack ultra-fast scanners to obtain appropriate quality images hinders the feasibility of repeated procedures. In older children, we need to address the unresolved challenge of defining and monitoring progressive pulmonary fibrosis during childhood and importantly the urgent need for and value of a structured transition into adult care.[27] In contrast to those children without fibrosis$_{register}$, in which ppFVC increased on average during the first years of observation, no improvement but also no deterioration was observed in children with pulmonary fibrosis$_{register}$ criteria. This result could correspond to data in adults with non-IPF fibrosis in which the clinical and lung function courses over several years can improve or are stable in 80% of patients,[24] supporting the view of pulmonary fibrosis as a continuum from childhood into adulthood.

It is expected that the development of fibrosis might also differ with the underlying aetiological entity. Previously, analysis of the chILD-EU and US-chILD registries identified 47 different entities in which fibrosis was reported, but without using a uniform definition and not able to give disease-specific frequencies.[6] In the present study, we defined the prevalence of fibrosing lung disease both at the diagnosis and within disease subcategories and identified patients across 72 entities fulfilling criteria for fibrosis. Of interest are some entities like ILD secondary to post-infectious processes such as constrictive bronchiolitis (ie, bronchiolocentric fibrosis[28]) or the undefined ILD categories. The latter warrants special attention—ie, the need for systematic molecular and genetic evaluation—as a recent study showed that these individuals had a poorer clinical course after transition to adult care.[27] This distinction has therapeutic implications, as fibrosing autoinflammatory syndromes might already be amenable to pathway-specific treatment,[29] with antifibrotic therapies potentially serving as secondary, non-specific therapy.

In this study, both the register and trial definition were applied because they serve distinct clinical as well as methodological purposes and therefore provide complementary information. The register definition identifies the full clinical phenotype of fibrotic ILD in children, whereas the trial definition was used to identify a high-specificity subset possibly relevant for interventional studies. This contrast explains some of our findings, such as those in COPA syndrome, in which fibrosis$_{register}$ prevalence is 57·1% but only 10·0% for fibrosis$_{trial}$. The main driver of this discrepancy is that patients with chILD often have only one baseline CT scan and no lung biopsy, meaning they fulfil the register definition but cannot qualify for the stricter trial requirements that mandate replicated radiological imaging or lung biopsy.

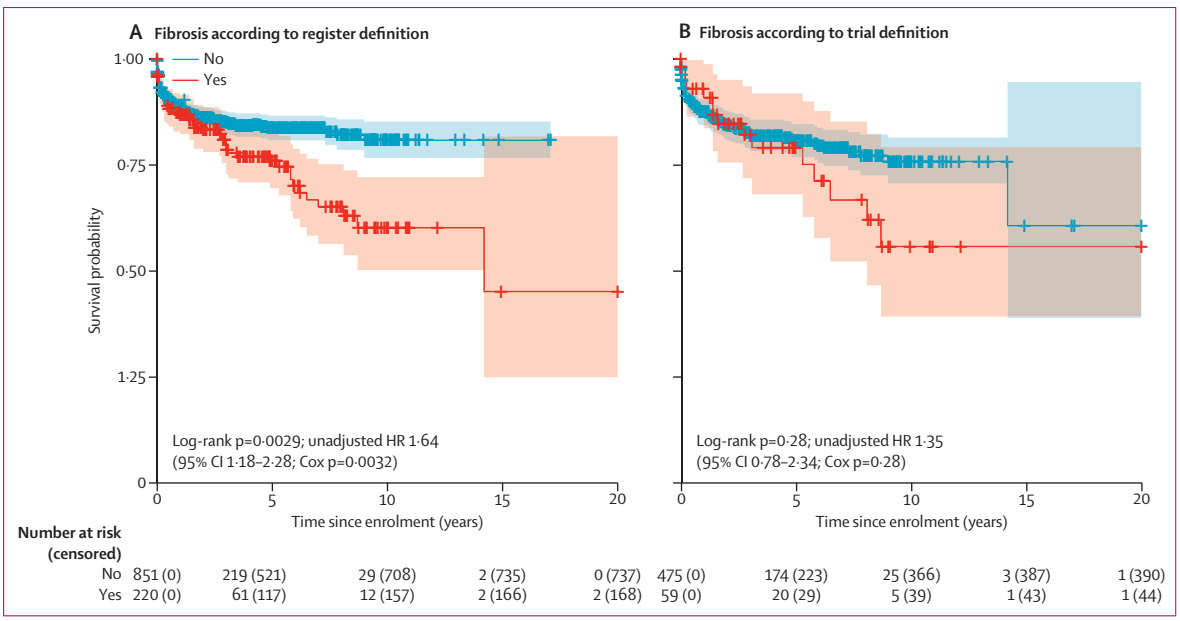

Figure 3: **Survival after enrolment according to fibrosis status**
Kaplan–Meier curves based on years since register entry, stratified by (A) fibrosis register definition and (B) fibrosis trial definition. Tick marks indicate censoring. Survival probabilities reflect the risk of death or lung transplantation after enrolment. Log-rank p-values, numbers at risk at selected timepoints, and 95% CI are shown. HR=hazard ratio.

To our knowledge, no comprehensive data currently exist for the individual criteria to define pulmonary fibrosis in children. This is particularly relevant for cystic lesions on CT imaging. Cysts are not a criterion in adult fibrotic lung disease, but they are a prominent feature of surfactant dysfunction and many other disorders in childhood, all known to result in pulmonary fibrosis.[6] In this study, we additionally assessed the impact of cystic lesions as an indicator of fibrosis. Cystic lesions were the second most frequent CT criterion noted (51–60%) and have been shown to increase with time in patients with surfactant dysfunction disorders and fibrotic lung disease.[10–12,30] Including the criterion of cystic lesions as a fibrotic criterion increased the number of fibrosis cases by about 20% (21·8% $fibrosis_{register}$ and 17·7% $fibrosis_{trial}$). At baseline PFT (0Y), fibrotic patients with a cystic lesion and one other fibrotic lesion on CT had better ppFVC than those with two non-cystic fibrotic lesions on their CT scans, but this difference disappeared over time, suggesting that progression of cystic lesions is associated with accelerated lung function decline. The main diagnostic categories included surfactant dysfunction disorders (n=19) and cystic lung diseases (n=26), including STING-associated vasculopathy or aminoacyl-tRNA synthetase deficiencies.

Several limitations of this study must be acknowledged. First, selection bias depending on national referral patterns, diagnostic pathways, access to specialised centres, and participation in the register evolving over time could have contributed to the uneven country-level representation and underrepresentation or overrepresentation of some chILD conditions (appendix p 6). Second, the entire cohort of the register was included in our study, not only those entities typically expected to develop pulmonary fibrosis. While we identified proven pulmonary fibrosis among the less-typical entities, they might represent a distinct type of pulmonary fibrosis with slower progression and a potential reversibility after removal of a noxious exposure. Third, the decision to order CT scans or biopsies was made at the discretion of the treating physician, which could influence detection rates. To overcome this shortage, our comparison group included only children who had the same diagnostic opportunity—ie, had a biopsy and one CT scan, or more CT scans. Fourth, patients were treated by their attending physicians according to current recommendations, which are largely based on expert opinion and observational data rather than evidence from randomised controlled trials, mainly with anti-inflammatory medication.[16] Proven antifibrotics were used in very few patients and only for brief treatment times, as these drugs were not available as labelled treatment for children with pulmonary fibrosis at the time of the study. Thus, the cohort could be considered as a reference for an antifibrotic-naive group of children.

In conclusion, pulmonary fibrosis manifests early in childhood with a notable prevalence. The single-timepoint register definition can be readily applied to routine care in children and identifies children with reduced survival, underscoring its clinical relevance.

Contributors

MG led project administration and planned the study, and NS and ES participated in the design of the study. SR-H (14-years board certified, 12-years specialised in paediatric lung pathology) peer-reviewed lung pathology. JL-Z (thoracic radiologist, 10-years paediatric-board certified), BK (23-years paediatric-board certified), and IK-S (12-years paediatric-board certified) performed all CT imaging evaluations, applied standardised scoring protocols, and reached consensus interpretations that formed a core element of the fibrosis definitions used in this study. JC, PM, JR, KM-S, CKR, FG, HM, JL, KK, AMR, FB, FS, PSJ, JT, MP, TS, AA, NE, NK, SH, AK, FPr, AW, AM-G, SMa, JMB, LN, MW, AM, and MK participated in the recruitment of study participants and collected their data. All the chILD-EU collaborators contributed at least one study participant and their data. JR, KM-S, N-BT, and MG performed register quality control, SMi, N-BT, and FPa performed the data analysis, MG, ES, and FB prepared the report for publication. MG, ES, N-BT, and SMi accessed and verified the underlying data. All authors had full access to the data in the study, and they had final responsibility for the decision to submit for publication.

Declaration of interests

MG reports institutional grant support from the Deutsche Forschungsgemeinschaft and Boehringer Ingelheim, and personal fees for advisory and adjudication board work from Boehringer Ingelheim, outside the submitted work. FPr reports personal fees for lectures from Sanofi/Regeneron, Allergopharma, Takeda Pharma, BioCryst, Vertex Pharmaceuticals, Nutricia-Milupa, Stallergenes Greer, and ALK-Abelló, and participation on advisory boards for Takeda Pharma and Sanofi/Regeneron. JC reports consulting fees and honoraria for lectures from Boehringer Ingelheim, and participation in an advisory board and as a sub-investigator in the InPedILD trial sponsored by Boehringer Ingelheim. JL-Z reports consulting fees from Boehringer Ingelheim and honoraria for lectures from Boehringer Ingelheim and Bayer, and an unpaid leadership role in the German Radiological Society. NS reports consulting fees, honoraria for lectures, and participation in an advisory board and as a sub-investigator in the InPedILD trial sponsored by Boehringer Ingelheim. HM and JL report non-financial interests as sub-investigators in the InPedILD trial sponsored by Boehringer Ingelheim. LN reports institutional grant support from the German Center for Lung Research. AM reports a research grant to his institution from Lunge Zürich and personal consulting fees from Vertex Pharmaceuticals. FS reports personal fees for lectures and meeting support from Vertex Pharmaceuticals, and institutional payments from Vertex Pharmaceuticals for clinical trials. AW reports honoraria for educational workshops from Westdeutsche Arbeitsgemeinschaft für Pädiatrische Pneumologie und Allergologie (WAPPA) and Gesellschaft für Pädiatrische Pneumologie (GPP), travel support from Ruhr-University Bochum, and an unpaid board membership in WAPPA. FPa reports consulting fees via his company RPACT GbR for statistical consulting services provided to Ludwig-Maximilians-Universität München, including contributions to the statistical analysis plan, data optimisation, and data analysis, with payments made to his company. AM-G reports institutional payments related to his role as local principal investigator in a paediatric nintedanib clinical trial and an unpaid role as President of the Spanish Society of Paediatric Pulmonology. All other authors declare no competing interests.

Data sharing

Anonymised aggregated data from the chILD-EU register are available upon reasonable request. Research proposals using such aggregated data can be submitted to the corresponding author (matthias.griese@med.uni-muenchen.de). The proposals will be assessed by the chILD-EU register coordination team, and aggregated data will be shared if the proposal addresses relevant research questions. Requests for anonymised individual patient data can be sent to the corresponding author, who will facilitate contact with the responsible physicians who will discuss the legal and administrative feasibility of sharing those data.

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Fibrosing interstitial lung disease in childhood: prevalence and disease trajectories

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Supplementary appendix

SUPPLEMENTAL STATISTICAL METHODS

Data were analysed using SPSS (v26.0) and R (v4.4.2). Longitudinal analyses of ppFVC were conducted using linear mixed-effects models. Repeated values within the same year were averaged and yearly means were analysed as categorical time points. The fixed part of the model included fibrosis status (Yes/No), visit, age at baseline PFT (0Y), and the interaction between fibrosis status and visit. A patient-specific random intercept was included to account for within-subject variability. Alternative residual correlation and variance structures were systematically evaluated. We compared first-order autoregressive (AR1), compound symmetry, and fully unstructured forms. Model fit was assessed using maximum likelihood estimation and information criteria (AIC and BIC). The unstructured correlation structure offered flexibility but did not converge reliably given the sparsity of later follow-ups. Compound symmetry converged but showed poorer fit. The autoregressive structure achieved stable convergence and favorable fit and was therefore used. The autoregressive structure corresponds to the assumption that correlations between repeated measures decay exponentially with the temporal lag, which is a plausible pattern for annual lung function follow-up. Residual heteroscedasticity was examined in the same way. Allowing variance to differ by visit improved model fit compared to a homoscedastic specification and was included in the final models. Final models were estimated using restricted maximum likelihood. Missing data were assumed to be missing at random. Estimated marginal means were used to describe within-group trajectories, compare fibrosis groups at each visit, and estimate change from baseline PFT (0Y). Multiple testing was controlled by Tukey adjustment for within-group comparisons across visits and Holm adjustment across visits for the between-group contrasts. Model diagnostics were inspected to check assumptions. These included residual-versus-fitted plots to assess homoscedasticity, quantile–quantile plots for residual normality and distribution of random intercepts. None of these suggested major violations. For sensitivity analyses we repeated the analyses truncating follow-up at 6 years to mitigate sparsity at later visits. Results for between-group contrasts and within-group changes were materially unchanged.

Supplemental results (sensitivity analysis with joint models)

To assess if mortality-related dropout could bias the estimated ppFVC trajectories, we fitted joint longitudinal–survival models linking individual ppFVC profiles to time-to-death. For the joint models, we parameterized follow-up time continuously (years since baseline). This parameterization was used solely for the sensitivity analysis and did not redefine the visit-specific trajectory used in the main manuscript. The models included fibrosis status, visit time (year: 0, 1, 2, …, 8), their interaction, and baseline age as fixed effects, with a patient-specific random intercept. Mortality was modeled using a Cox proportional hazards model including fibrosis status and baseline age, and the two components were linked through a shared-parameter structure in which the hazard of death depends on the underlying subject-specific ppFVC trajectory.

Models were fitted separately for the register and trial fibrosis definitions. Using the register definition, the association between the modeled ppFVC trajectory and death was small and not statistically significant (HR 1.01 per 1% ppFVC; 95% CI: 0.98–1.03; p = 0.52). Using the trial definition, the ppFVC association was also non-significant (HR 1.00 per 1% ppFVC; 95% CI: 0.97–1.03; p = 0.82). These results provide no evidence that dropout due to death was informative with respect to ppFVC.

To illustrate stability of inference within this sensitivity analysis, we report the fixed-effect estimates from the longitudinal component of the joint models in Supplementary Table Joint Analysis. These estimates indicate that mortality-related dropout did not meaningfully influence the estimated ppFVC trajectories.

Supplementary Table Joint Analysis: Fixed-effect estimates from the longitudinal component of the joint longitudinal–survival models.

	Fibrosis register		**Fibrosis trial**	
Fixed effect	**LMM Estimate (p-value)**	**Joint Model Estimate (p-value)**	**LMM Estimate (p-value)**	**Joint Model Estimate (p-value)**
Intercept	78.65 (p<0.0001)	78.66 (p<0.0001)	73.27 (p<0.0001)	73.27 (p<0.0001)
Visit time (per year)	1.06 (p<0.0001)	1.06 (p<0.0001)	0.80 (p<0.0001)	0.80 (p<0.0001)
Fibrosis (Yes vs No)	−13.36 (p<0.0001)	−13.36 (p<0.0001)	−14.50 (p=0.0001)	−14.50 (p=0.0001)
Visit × Fibrosis	−0.95 (p=0.0005)	−0.95 (p=0.0005)	−0.65 (p=0.11)	−0.64 (p=0.11)
Baseline age (per year)	−0.46 (p=0.036)	−0.47 (p=0.035)	−0.21 (p=0.46)	−0.21 (p=0.46)

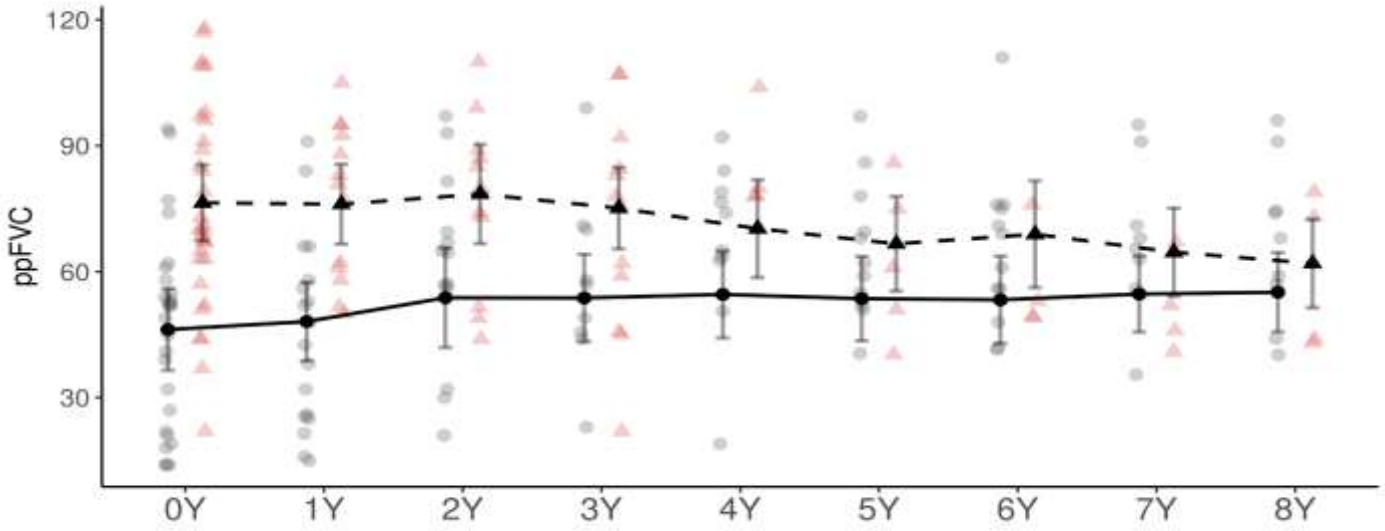
Supplemental results (counts of ppFVC measurements per visit across all follow-up years)

0Y	1Y	2Y	3Y	4Y	5Y	6Y	7Y	8Y	Fibrosis register
415	220	199	169	134	110	91	73	60	No
135	82	65	59	47	41	41	25	27	Yes

0Y	1Y	2Y	3Y	4Y	5Y	6Y	7Y	8Y	Fibrosis trial
291	170	160	141	110	93	78	59	59	No
45	29	19	18	15	16	16	12	12	Yes

SUPPLEMENTAL FIGURE

Supplemental figure 1: ppFVC over 8 years in patients with cysts and without cysts in CT scans. Estimated marginal means of ppFVC with 95% CIs, obtained from the mixed-effects model, are shown for patients with cysts in CT scans (solid circles, solid line) and without cysts in CT scans (triangles, dashed line) from baseline PFT (0Y) to 8 years of follow-up. Only patients with two fibrosis features on any CT scan were compared. Semi-transparent points represent individual observed values. The visit-by-cyst interaction was statistically significant (p = 0.0432), indicating that ppFVC trajectories differed between patients with and without cysts.



SUPPLEMENTAL TABLES

Supplemental Table 1: Country of Origin (N, % total)

Austria	17 (1.6%)
Belgium	18 (1.7%)
Czechia	5 (0.5%)
Denmark	12 (1.1%)
Germany	602 (56.2%)
Greece	11 (1%)
Hungary	12 (1.1%)
Italy	29 (2.7%)
Poland	86 (8%)
Spain	27 (2.5%)
Switzerland	32 (3%)
Turkey	109 (10.2%)
United Kingdom	94 (8.8%)
Other	17 (1.6%)
Total	1071 (100%)

Supplemental Table 2: Diagnosis of all conditions included and rates of pulmonary fibrosis

	Fibrosis register cohort N (% of all row)	Fibrosis trial cohort N (% of trial row)
All	220 (20.5%) of 1071	62 (11.6%) of 534
Conditions affecting the lung only		
ABCA3 deficiency	18 (32.1%) of 56	10 (29.4%) of 34
Surfactant protein C mutations	9 (30.0%) of 30	3 (14.3%) of 21
Nonspecific interstitial pneumonia (NSIP)	7 (22.6%) of 31	0 (0.0%) of 20
Undefined ILD in infants and children	5 (19.2%) of 26	1 of 9
Emphysema	5 of 6	5 of 5
Bronchiolitis obliterans without suspected cause	4 (25.0%) of 16	0 of 8
Lymphocytic interstitial pneumonia (LIP)	4 (40.0%) of 10	1 of 8
Interstitial lung disease with leading cystic changes	4 of 5	0 of 2
Pleuro-parenchymal fibroelastosis	4 of 4	2 of 4
Persistent tachypnea of infancy (PTI/NEHI)	3 (1.3%) of 237	0 (0.0%) of 64
Pulmonary capillary hemangiomatosis	3 (30.0%) of 10	0 of 9
Undefined ILD in almost (30-36 weeks) mature neonate	3 (30.0%) of 10	1 of 4
Surfactant protein B mutations	3 of 5	1 of 3
Idiopathic pulmonary hemosiderosis (IPH)	2 (4.3%) of 46	1 (5.0%) of 20
Pulmonary hypertension	2 (8.3%) of 24	0 (0.0%) of 14
Pulmonary interstitial glycogenosis (PIG)	2 (9.5%) of 21	1 (6.3%) of 16
Pulmonary alveolar proteinosis (CSF2RA variants)	2 (18.2%) of 11	0 of 7
Pulmonary alveolar proteinosis, juvenile	2 of 9	1 of 5
Alveolar macrophage pneumonitis (previous desquamative interstitial pneumonia (DIP))	2 of 5	0 of 4
Fibrotic on imaging, unknown etiology	2 of 4	0 of 1
Combined pulmonary fibrosis and emphysema	2 of 3	0 of 2
Diffuse alveolar damage and acute interstitial pneumonia	2 of 3	0 of 3
Lipoid pneumonia, cholesterol pneumonia	2 of 2	2 of 2
Pulmonary hypoplasia	2 of 2	1 of 1
Usual interstitial pneumonia (UIP)	2 of 2	0 of 2
Vessel diseases	1 (8.3%) of 12	1 of 5
Congenital alveolar dysplasia	1 (10.0%) of 10	0 of 5
Chronic pneumonitis of infancy (CPI)	1 of 4	0 of 2
Cryptogenic organizing pneumonia	1 of 2	0 of 2
Conditions associated with systemic disease		
Aminoacyl-tRNA synthetase deficiency	9 (60.0%) of 15	4 (36.4%) of 11
COPA syndrome	8 (57.1%) of 14	1 (10.0%) of 10
Interstitial lung disease related to trisomy 21	7 (28%) of 25	0 (0.0%) of 13
Small patella syndrome with ILD (TBX4 variants)	7 (53.8%) of 13	1 of 6
STING-associated vasculopathy, infantile-onset	7 (50.0%) of 14	1 of 7
Filamin A variants	5 (45.5%) of 11	0 of 7
Other rare genetic conditions	5 (31.3%) of 16	1 (10.0%) of 10
Stem cell transplant, oncologic condition	5 (20.8%) of 24	1 (6.7%) of 15
Antibody deficiency	4 (36.4%) of 11	1 of 6
Langerhans cell histiocytosis	3 of 4	0 of 2
Other immune-dysregulation disorders	3 of 5	1 of 2

Sarcoidosis	3 of 9	0 of 4
Syndromic immunodeficiency	3 of 8	2 of 7
Telomere-associated disease	3 of 6	0 of 4
Brain thyroid lung syndrome (NKX2.1 variants)	2 (16.7%) of 12	1 of 6
Hermandsky-Pudlak syndrome	2 of 3	2 of 3
Interstitial lung disease due to CCR2 loss of function variants	2 of 2	2 of 2
Other interferonopathies	2 of 7	0 of 5
Systemic sclerosis	2 of 3	2 of 2
Cantú Syndrome	1 of 3	1 of 1
Celiac disease with pulmonary hemorrhage (Lane-Hamilton syndrome)	1 of 3	1 of 3
Collagen vascular disorders	1 of 5	0 of 4
Congenital musculoskeletal disorder	1 of 4	0 of 2
Eosinophilic granulomatosis with polyangiitis	1 of 6	0 of 4
FINCA syndrome (NHLRC2 variants)	1 of 2	0 of 1
Interstitial lung disease from gain of function variants in STAT3	1 of 4	0 of 2
Lysinuric proteinuria (SLC7A7 variants)	1 of 4	0 of 2
Niemann-Pick disease	1 of 6	0 of 3
Systemic lupus erythematosus	1 of 3	1 of 2
Conditions due to exposure		
Bronchopulmonary dysplasia (BPD)	15 (55.6%) of 27	4 (30.8%) of 13
Postinfectious bronchiolitis obliterans (PIBO)	4 (12.1%) of 33	1 (7.1%) of 14
Drug reactions	3 (11.5%) of 26	1 (9.1%) of 11
Pulmonary hypoplasia from external compression	3 of 9	0 of 2
Bronchiolitis obliterans from toxic inhalation	1 of 2	1 of 2
Chronic ILD from infectious or post-infectious processes	1 (5.6%) of 18	0 (0.0%) of 11
Radiation lung injury	1 of 2	1 of 1
Conditions with no fibrosis detected*	107 (10.0%) of 1071	53 (9.9%) of 534

(%) values only calculated for conditions with $\geq$ 10 patients in the fibrosis register cohort.

*AGR2 related disease (1); Alveolar microlithiasis (3); Alveolar capillary dysplasia (18); Antibasement Membrane Antibody Disease (Goodpasture Syndrome) (2); Antisynthetase Syndrome (2); Aspiration syndromes (3); Autoimmune pulmonary alveolar proteinosis (aPAP) (6); Cyclin-dependent kinase 13 associated interstitial lung disease (2); Eosinophilic pneumonitis (5); Follicular bronchitis/bronchiolitis (4); Gestational diabetes induced lung underdevelopment and delayed maturation (2); Granulomatosis with polyangiitis (10); Hemoglobinopathy (2); Idiopathic pulmonary hemorrhage with autoimmune features (3); ITGA3 (Integrin α3) mutation associated kidney, lung and skin disease (2); Klinefelter Syndrome (2); Lacrimo-auriculo-dental-digital syndrome 3 (2); Hemorrhagic telangiectasia (4); Mac-Leod-Swyer-James-Syndrom (2); Mixed connective tissue disease (3); Noonan syndrome (2); Pulmonary alveolar proteinosis from variants in CSF2RB (1); Pulmonary hypertension caused by known genes (3); Related to other chromosomal disorders than trisomy 21 (5); SFTPA1 related disease (1); SRRM2 related disease (3); Tuberous sclerosis complex TSC-lymphangioleiomyomatosis (2); Undefined ILD in mature neonate (11). In brackets are the number of cases of the respective condition indicated.

Supplemental Table 3: Pairwise differences in ppFVC at all time points between groups using register fibrosis definition. Estimated marginal means for ppFVC were obtained from a linear mixed-effects model adjusted for age at baseline PFT (0Y). Pairwise comparisons between individuals with and without $fibrosis_{register}$ were conducted at each time point. P-values were adjusted for multiple testing across time points using the Holm correction. Negative values indicate that individuals with fibrosis had a lower ppFVC compared to those without fibrosis

Visit	Comparison	Difference in ppFVC (95% CI)	Adjusted p-value
0Y	Yes - No	-13.4 (-18.4, -8.5)	<0.0001
1Y	Yes - No	-16.3 (-21.1, -11.5)	<0.0001
2Y	Yes - No	-13.3 (-18.5, -8.2)	<0.0001
3Y	Yes - No	-16.1 (-21.0, -11.1)	<0.0001
4Y	Yes - No	-17.2 (-22.4, -11.9)	<0.0001
5Y	Yes - No	-18.7 (-24.0, -13.4)	<0.0001
6Y	Yes - No	-19.7 (-25.0, -14.4)	<0.0001
7Y	Yes - No	-21.9 (-27.5, -16.2)	<0.0001
8Y	Yes - No	-22.0 (-27.8, -16.2)	<0.0001

Supplemental Table 4: Estimated differences in ppFVC over time within each group ($fibrosis_{register}$ Yes/No). Estimated differences in ppFVC between follow-up visits were obtained from a linear mixed-effects model adjusted for age at baseline PFT (0Y). Pairwise comparisons across time points within each group were performed using Tukey's method to adjust for multiple comparisons. Positive values indicate an increase in ppFVC over time, while negative values indicate a decrease.

Fibrosis by register	Contrast	Difference in ppFVC (95% CI)	P-value
No	1Y - 0Y	3.7 (0.6, 6.8)	0.0082
No	2Y - 0Y	4.9 (1.4, 8.4)	0.0006
No	2Y - 1Y	1.2 (-2.0, 4.4)	0.9642
No	3Y - 0Y	6.6 (3.1, 10.2)	<0.0001
No	3Y - 1Y	2.9 (-0.3, 6.2)	0.1192
No	3Y - 2Y	1.7 (-1.4, 4.9)	0.7417
No	4Y - 0Y	8.4 (4.6, 12.2)	<0.0001
No	4Y - 1Y	4.7 (1.1, 8.3)	0.0017
No	4Y - 2Y	3.5 (-0.1, 7.1)	0.0677
No	4Y - 3Y	1.8 (-1.4, 4.9)	0.735
No	5Y - 0Y	7.5 (3.5, 11.5)	<0.0001
No	5Y - 1Y	3.8 (0.1, 7.5)	0.0436
No	5Y - 2Y	2.6 (-1.2, 6.4)	0.4585
No	5Y - 3Y	0.9 (-2.6, 4.3)	0.9977
No	5Y - 4Y	-0.9 (-4.3, 2.5)	0.996
No	6Y - 0Y	7.5 (3.5, 11.6)	<0.0001
No	6Y - 1Y	3.8 (0.0, 7.7)	0.0558
No	6Y - 2Y	2.6 (-1.3, 6.6)	0.498
No	6Y - 3Y	0.9 (-2.8, 4.6)	0.998
No	6Y - 4Y	-0.9 (-4.6, 2.8)	0.9985
No	6Y - 5Y	0.0 (-3.4, 3.5)	1
No	7Y - 0Y	7.1 (2.9, 11.3)	<0.0001
No	7Y - 1Y	3.4 (-0.6, 7.4)	0.1777
No	7Y - 2Y	2.2 (-1.9, 6.3)	0.7749
No	7Y - 3Y	0.4 (-3.4, 4.3)	1
No	7Y - 4Y	-1.3 (-5.2, 2.6)	0.9816
No	7Y - 5Y	-0.4 (-4.2, 3.4)	1

No	7Y - 6Y	-0.5 (-4.1, 3.2)	1
No	8Y - 0Y	6.9 (2.4, 11.5)	0.0001
No	8Y - 1Y	3.2 (-1.2, 7.6)	0.3507
No	8Y - 2Y	2.0 (-2.4, 6.5)	0.8936
No	8Y - 3Y	0.3 (-4.0, 4.6)	1
No	8Y - 4Y	-1.5 (-5.8, 2.9)	0.9818
No	8Y - 5Y	-0.6 (-4.8, 3.7)	1
No	8Y - 6Y	-0.6 (-4.7, 3.6)	1
No	8Y - 7Y	-0.1 (-4.1, 3.9)	1
Yes	1Y - 0Y	0.8 (-4.4, 6.0)	0.9999
Yes	2Y - 0Y	5.0 (-1.1, 11.1)	0.21
Yes	2Y - 1Y	4.2 (-1.2, 9.6)	0.2838
Yes	3Y - 0Y	4.0 (-2.0, 10.0)	0.4942
Yes	3Y - 1Y	3.2 (-2.3, 8.6)	0.6791
Yes	3Y - 2Y	-1.0 (-6.5, 4.5)	0.9997
Yes	4Y - 0Y	4.7 (-1.8, 11.1)	0.3745
Yes	4Y - 1Y	3.8 (-2.2, 9.9)	0.5551
Yes	4Y - 2Y	-0.3 (-6.6, 5.9)	1
Yes	4Y - 3Y	0.7 (-4.7, 6.1)	1
Yes	5Y - 0Y	2.3 (-4.3, 8.8)	0.9785
Yes	5Y - 1Y	1.4 (-4.7, 7.6)	0.9985
Yes	5Y - 2Y	-2.8 (-9.2, 3.7)	0.9237
Yes	5Y - 3Y	-1.7 (-7.6, 4.2)	0.9925
Yes	5Y - 4Y	-2.4 (-7.9, 3.1)	0.913
Yes	6Y - 0Y	1.3 (-5.2, 7.7)	0.9996
Yes	6Y - 1Y	0.4 (-5.6, 6.5)	1
Yes	6Y - 2Y	-3.7 (-10.1, 2.6)	0.6675
Yes	6Y - 3Y	-2.7 (-8.7, 3.2)	0.8902
Yes	6Y - 4Y	-3.4 (-9.3, 2.5)	0.6891
Yes	6Y - 5Y	-1.0 (-6.3, 4.3)	0.9997
Yes	7Y - 0Y	-1.3 (-8.5, 5.8)	0.9997
Yes	7Y - 1Y	-2.2 (-9.0, 4.6)	0.987
Yes	7Y - 2Y	-6.4 (-13.4, 0.7)	0.1211

Yes	7Y - 3Y	-5.3 (-12.0, 1.3)	0.2377
Yes	7Y - 4Y	-6.0 (-12.8, 0.7)	0.1266
Yes	7Y - 5Y	-3.6 (-10.1, 2.9)	0.7256
Yes	7Y - 6Y	-2.6 (-8.4, 3.2)	0.9
Yes	8Y - 0Y	-1.6 (-8.8, 5.6)	0.999
Yes	8Y - 1Y	-2.4 (-9.3, 4.5)	0.9755
Yes	8Y - 2Y	-6.6 (-13.7, 0.5)	0.0968
Yes	8Y - 3Y	-5.6 (-12.3, 1.1)	0.1972
Yes	8Y - 4Y	-6.3 (-13.1, 0.6)	0.1015
Yes	8Y - 5Y	-3.9 (-10.4, 2.7)	0.6655
Yes	8Y - 6Y	-2.9 (-9.2, 3.4)	0.8928
Yes	8Y - 7Y	-0.3 (-6.5, 6.0)	1

Supplemental Table 5: Pairwise differences in ppFVC at all time points between groups using the trial fibrosis definition. Estimated marginal means for ppFVC were obtained from a linear mixed-effects model adjusted for age at baseline PFT (0Y). Pairwise comparisons between individuals with and without fibrosis were conducted at each time point. P-values were adjusted for multiple testing across time points using the Holm correction. Negative values indicate that individuals with fibrosis had a lower ppFVC compared to those without fibrosis

Visit	Comparison	Difference in ppFVC (95% CI)	Adjusted p-value
0Y	Yes - No	-13.1 (-21.2, -5.0)	0.0034
1Y	Yes - No	-18.6 (-26.3, -10.8)	<0.0001
2Y	Yes - No	-15.9 (-24.8, -7.0)	0.0014
3Y	Yes - No	-15.6 (-23.8, -7.3)	0.001
4Y	Yes - No	-12.7 (-21.4, -4.1)	0.0039
5Y	Yes - No	-19.0 (-27.5, -10.5)	0.0001
6Y	Yes - No	-20.6 (-29.1, -12.2)	<0.0001
7Y	Yes - No	-18.3 (-27.1, -9.5)	0.0003
8Y	Yes - No	-17.4 (-26.0, -8.8)	0.0004

Supplemental table 6: Estimated differences in ppFVC over time within each group ($fibrosis_{trial}$ Yes/No). Estimated differences in ppFVC between follow-up visits were obtained from a linear mixed-effects model adjusted for age at baseline PFT (0Y). Pairwise comparisons across time points within each group were performed using Tukey's method to adjust for multiple comparisons. Positive values indicate an increase in ppFVC over time, while negative values indicate a decrease.

Fibrosis by trial definition	Contrast	Difference in ppFVC (95% CI)	P-value
No	1Y - 0Y	2.9 (-0.6, 6.5)	0.2095
No	2Y - 0Y	4.9 (0.8, 9.0)	0.0075
No	2Y - 1Y	1.9 (-1.8, 5.7)	0.7931
No	3Y - 0Y	5.6 (1.6, 9.5)	0.0005
No	3Y - 1Y	2.6 (-1.0, 6.3)	0.3915
No	3Y - 2Y	0.7 (-2.9, 4.3)	0.9997
No	4Y - 0Y	6.7 (2.4, 11.0)	<0.0001
No	4Y - 1Y	3.8 (-0.3, 7.8)	0.0931
No	4Y - 2Y	1.8 (-2.4, 6.0)	0.9131
No	4Y - 3Y	1.1 (-2.4, 4.7)	0.9851
No	5Y - 0Y	6.2 (1.8, 10.7)	0.0005
No	5Y - 1Y	3.3 (-0.9, 7.6)	0.2711
No	5Y - 2Y	1.4 (-3.0, 5.8)	0.9886
No	5Y - 3Y	0.7 (-3.2, 4.6)	0.9998
No	5Y - 4Y	-0.5 (-4.3, 3.4)	1
No	6Y - 0Y	7.2 (2.6, 11.8)	<0.0001
No	6Y - 1Y	4.3 (-0.1, 8.6)	0.0598
No	6Y - 2Y	2.3 (-2.2, 6.9)	0.8066
No	6Y - 3Y	1.6 (-2.5, 5.8)	0.9449
No	6Y - 4Y	0.5 (-3.6, 4.7)	1
No	6Y - 5Y	1.0 (-2.9, 4.8)	0.9976
No	7Y - 0Y	5.2 (0.4, 10.0)	0.0224
No	7Y - 1Y	2.3 (-2.3, 6.8)	0.836
No	7Y - 2Y	0.3 (-4.4, 5.1)	1
No	7Y - 3Y	-0.4 (-4.7, 4.0)	1
No	7Y - 4Y	-1.5 (-6.0, 2.9)	0.9807

No	7Y - 5Y	-1.1 (-5.4, 3.3)	0.998
No	7Y - 6Y	-2.0 (-6.2, 2.2)	0.8562
No	8Y - 0Y	4.2 (-0.6, 8.9)	0.1416
No	8Y - 1Y	1.2 (-3.3, 5.8)	0.9953
No	8Y - 2Y	-0.7 (-5.4, 4.0)	0.9999
No	8Y - 3Y	-1.4 (-5.7, 2.9)	0.9858
No	8Y - 4Y	-2.5 (-7.0, 1.9)	0.6966
No	8Y - 5Y	-2.1 (-6.5, 2.3)	0.8672
No	8Y - 6Y	-3.0 (-7.3, 1.3)	0.4114
No	8Y - 7Y	-1.0 (-5.2, 3.1)	0.9976
Yes	1Y - 0Y	-2.6 (-11.4, 6.3)	0.993
Yes	2Y - 0Y	2.0 (-9.4, 13.4)	0.9998
Yes	2Y - 1Y	4.6 (-5.6, 14.8)	0.9
Yes	3Y - 0Y	3.0 (-7.7, 13.7)	0.9939
Yes	3Y - 1Y	5.6 (-4.1, 15.3)	0.6867
Yes	3Y - 2Y	1.0 (-9.2, 11.2)	1
Yes	4Y - 0Y	7.0 (-4.3, 18.4)	0.5975
Yes	4Y - 1Y	9.6 (-0.9, 20.1)	0.1024
Yes	4Y - 2Y	5.0 (-6.6, 16.6)	0.9194
Yes	4Y - 3Y	4.0 (-5.7, 13.7)	0.9364
Yes	5Y - 0Y	0.3 (-10.8, 11.5)	1
Yes	5Y - 1Y	2.9 (-7.5, 13.3)	0.9949
Yes	5Y - 2Y	-1.7 (-13.5, 10.0)	1
Yes	5Y - 3Y	-2.7 (-12.8, 7.4)	0.9957
Yes	5Y - 4Y	-6.7 (-16.3, 2.9)	0.4247
Yes	6Y - 0Y	-0.3 (-11.3, 10.6)	1
Yes	6Y - 1Y	2.2 (-8.0, 12.5)	0.9991
Yes	6Y - 2Y	-2.4 (-14.2, 9.4)	0.9995
Yes	6Y - 3Y	-3.4 (-13.7, 6.9)	0.984
Yes	6Y - 4Y	-7.4 (-17.8, 3.1)	0.4075
Yes	6Y - 5Y	-0.7 (-9.5, 8.1)	1
Yes	7Y - 0Y	0.0 (-11.6, 11.6)	1
Yes	7Y - 1Y	2.5 (-8.5, 13.6)	0.9986

Yes	7Y - 2Y	-2.1 (-14.5, 10.4)	0.9999
Yes	7Y - 3Y	-3.1 (-14.1, 8.0)	0.9948
Yes	7Y - 4Y	-7.1 (-18.3, 4.2)	0.5819
Yes	7Y - 5Y	-0.3 (-10.7, 10.1)	1
Yes	7Y - 6Y	0.3 (-8.6, 9.2)	1
Yes	8Y - 0Y	-0.2 (-11.5, 11.1)	1
Yes	8Y - 1Y	2.4 (-8.2, 13.0)	0.9987
Yes	8Y - 2Y	-2.2 (-14.2, 9.8)	0.9997
Yes	8Y - 3Y	-3.2 (-13.7, 7.3)	0.9905
Yes	8Y - 4Y	-7.2 (-18.0, 3.6)	0.4924
Yes	8Y - 5Y	-0.5 (-10.5, 9.5)	1
Yes	8Y - 6Y	0.2 (-8.9, 9.3)	1
Yes	8Y - 7Y	-0.1 (-9.4, 9.2)	1

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