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Take home message (166/256 characters with spaces):

Lung function in children with PCD is reduced by age 6 years and further declines during the growth period. It is essential to develop strategies to improve prognosis.

Title Page

Lung function from school age to adulthood in primary ciliary dyskinesia

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Abstract

Primary ciliary dyskinesia (PCD) presents with symptoms early in life and the disease course may be progressive, but longitudinal data on lung function are scarce. This multinational cohort study describes lung function trajectories in children, adolescents, and young adults with PCD. We analysed data from 486 patients with repeated lung function measurements obtained between the age of 6 and 24 years from the international PCD Cohort (iPCD) and calculated z-scores for forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio using the Global Lung Function Initiative 2012 references. We described baseline lung function and change of lung function over time and described their associations with possible determinants in mixed-effects linear regression models. Overall, FEV_1, FVC, and FEV_1/FVC z-scores declined over time (average crude annual FEV_1 decline was -0.07 z-scores) but not at the same rate for all patients. FEV_1 z-scores improved over time in 21% of patients, remained stable in 40% and declined in 39%. Low BMI was associated with poor baseline lung function and with further decline. Results differed by country and ultrastructural defect, but we found no evidence of differences by sex, calendar year of diagnosis, age at diagnosis, diagnostic certainty, or laterality defect. Our study shows that on average lung function in PCD declines throughout the entire period of lung growth, from childhood to young adult age, even among patients treated in specialized centres. It is essential to develop strategies to reverse this tendency and improve prognosis.

Keywords: Primary Ciliary Dyskinesia; lung function; longitudinal; retrospective cohort; epidemiology; orphan diseases

Introduction

Primary ciliary dyskinesia (PCD) commonly leads to chronic upper and lower airway disease due to impaired mucociliary clearance. Clinical course is variable, but many patients present with neonatal respiratory distress, develop bronchiectasis already in preschool age , and some progress to end stage lung disease with respiratory failure and transplantation in adulthood.[1-6] In a systematic review covering the period 1980 to 2017, we identified 24 small studies on lung function in patients with PCD.[7] Twelve studies had longitudinal lung function data, mostly from adult patients. Among these, four studies reported that lung function remained stable over time and four concluded that it deteriorated. The largest study reported that FEV_1 improved over time in 10% of Danish patients, remained stable in 57%, and declined in 34%.[8] Models of lung function changes over a lifetime distinguish between lung function at birth, lung growth during childhood, a short plateau phase and the long period of lung function decline.[9, 10] The pattern of lung function growth in early years determines lung function later in life, and also life expectancy.[11, 12] Combining patients of different ages in one model does not allow to disentangle these phases and identify possible risk factors. For people with PCD, only two studies focused on lung function growth during childhood.[13, 14] One, with 137 children from specialised PCD clinics in North America, found a variable time course with ultrastructural defects highlighted as the main determinant of heterogeneity.[13] The second, with 158 children from three countries, reported variable lung function trajectories during childhood but no difference between centres.[14]

We have previously presented cross-sectional lung function data from the international PCD cohort study (iPCD) and showed that forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) were reduced compared to Global Lung Function Initiative 2012 (GLI) reference values in patients of all ages.[15] The design of that study did not permit investigation of lung function changes over time, nor did it allow to identify factors that influence lung function trajectories.

The present study describes lung function trajectories in an international cohort of children and young adults with PCD from age 6 to 24 years. We compared FEV_1, FVC, and FEV_1/FVC of study participants with the GLI reference values at baseline and investigated changes in lung function over time, i.e. whether z-scores improved, remained stable, or decreased. Second, we investigated a range of potential determinants for their association with lung function at baseline or with subsequent change of lung function over time.

Methods

Study design and study population

The iPCD Cohort is a large international dataset of patients with PCD set up during the EU FP7 project "Better Experimental Screening and Treatment for Primary Ciliary Dyskinesia" (BESTCILIA) and expanded during the COST-Action BEAT-PCD.[16, 17] The current analysis includes data from patients aged 6 to 24 years with multiple measurements on FEV_1 and FVC that were delivered by March 2019. Data came from routine follow-up in PCD clinics and were extracted from hospital records or exported from regional or national PCD registries.[17] The minimal required number of lung function measurements was one per year per patient, and for this analysis we only included patients for whom at least three lung function measurements had been recorded. When necessary, principal investigators obtained ethics approval and informed consent or assent in their countries to contribute observational pseudonymised data.

PCD diagnosis

PCD diagnosis remains challenging and has evolved over the years.[18] Guidelines recommend a combination of tests,[19] but test availability differs between countries and centres and has changed over time.[20, 21] Therefore not all iPCD patients were diagnosed according to current recommendations. We accounted for this by distinguishing three levels of diagnostic certainty: patients with definite PCD according to the ERS guidelines[19] with a hallmark ultrastructural defect identified by transmission electron microscopy (TEM) or pathogenic biallelic PCD genetic mutations; patients with probable PCD who had abnormal high-speed video microscopy findings or low nasal nitric oxide; and patients diagnosed on clinical grounds with an incomplete diagnostic algorithm. All patients had a clinical phenotype consistent with PCD, and other diagnoses had been excluded.

Lung function and microbiology

Lung function measurements were performed at each centre according to ERS/ATS guidelines. All centres provided FEV1 and FVC measurements as recorded before any use of inhaled bronchodilators. Spirometry quality assessment was performed locally at the clinics. Cleaning of data was performed after pooling data from all centres and included checking for outliers, implausible values, or missing data for which we contacted each centre to check the records. We standardized the lung function measurements by calculating FEV_1, FVC, and FEV_1/FVC z-scores adjusted for age, sex, height, and ethnicity using the GLI 2012 reference values.[22] Baseline FEV_1, FVC, FEV_1/FVC values were defined as the individuals' first available measurement, and measurements done before the age of 6 years were excluded to improve comparability. We asked local PIs to only include measurements from scheduled follow-up visits where patients were in a stable condition defined as

not having an acute infection. Sputum microbiology data was collected from the medical charts at the same time point as lung function was measured. We collected data about the five most common isolated pathogens including Haemophilus influenza, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumoniae, Moraxella catarrhalis.

Potential determinants of lung function and of lung function trajectories

We investigated associations of potential determinants on lung function by differentiating between effects on baseline lung function (the intercept) and effects on change of lung function over time (the slope). We included factors that had been described previously to affect lung function and were available from all centres: country of residence, sex, age at diagnosis of PCD, year of diagnosis, level of diagnostic certainty, organ laterality, age, body mass index (BMI) z-scores based on WHO reference values[23] at first lung function testing, and ultrastructural defect. Ultrastructural defects were grouped as in recent publications[13, 24] into: (1) Normal TEM results; (2) Outer dynein arm defect (ODA); (3) Outer and inner dynein arm defects (IDA); (4) Microtubular disorganization defects, consisting of nexin link defects combined with IDA or tubular disorganization defects combined with IDA; (5) Central complex defects, defined as central pair defects or tubular transposition defects; (6) Any other defect (i.e. isolated IDA, acilia or nexin link defects and tubular disorganization without IDA). Group 6 (any other defects) was excluded from the analysis. All determinants except age were time-independent.

Statistical analysis

In case of missing data, we contacted PIs. If the missing data could not be retrieved, the record was excluded from analysis. For laterality defects, we coded patients with missing information as "situs not reported". Ultrastructural defects and sputum microbiology had not been assessed in all patients and we therefore investigated these factors in a subgroup analysis.

We studied whether FEV_1 z-scores improved, remained stable, or decreased by computing average yearly trajectories using linear regression for each patient separately including the repeated lung function measurements and age. We classified individual FEV_1 trajectories based on the natural variability of lung function in healthy children into three groups: those that improved over time (> 0.05 z-scores/year), remained stable (≤ 0.05 & ≥ -0.05 z-scores/year), and decreased (< -0.05 z-scores/year).[25]

We compared z-scores of FEV_1, FVC, and FEV_1/FVC with the GLI reference values,[22] and investigated associations of baseline lung function and lung function trajectories with potential determinants in multivariable linear mixed effects regression models with a random intercept at the patient level. We tested for linearity of mean trajectory by including age as a linear and quadratic

term and computed the p-value for the coefficient of the quadratic term. We also included a random slope to allow for individual differences in lung function change by age. To assess whether changes in FEV_1 or FVC z-scores over time were modified by certain patient characteristics, we included interaction terms between age at lung function test and the potential determinants considered. We also tested for a possible interaction between age at diagnosis and country. We used likelihood ratio (LR) tests to calculate p-values for single variables and for interaction terms. For categorical variables, the largest group was chosen as reference category. We tested robustness of the parameter estimates across countries by running the regression model for single countries with more than 30 patients. We ran a sensitivity analysis excluding patients who were diagnosed the same year as the first lung function measurement was performed to investigate if baseline lung function and change in lung function over time could be affected by initiation of PCD-specific treatment after diagnosis. We investigated the effects of ultrastructural defects on lung function growth in a subgroup of children with available TEM results. Adjusting for the same determinants as before, we included an interaction term between type of ultrastructural defect and age to assess whether lung function changes over time differed between ultrastructural defects.

To assess the amount of variance explained by all the predictors in our model we calculated in this subgroup the marginal R^2, i.e. the proportion of variance explained by the fixed factors, and conditional R^2, .i.e. the proportion of variance explained by both the fixed and random factors, using the method by Nakagawa et al.[26] We then compared R^2 of the models with and without addition of ultrastructural defects. All analyses were performed using R 3.5.1 (www.r-project.org), linear mixed models with the R-package lme4.

Results

Population characteristics

By March 2019, 20 centres had delivered cleaned and standardised longitudinal data for 4470 lung function tests from 486 individuals (Figure S1). In 130 patients, the first lung function test stemmed from the year PCD was diagnosed, in the others it was later, often because PCD had been diagnosed at pre-school age. The largest datasets came from Germany (60 patients), Denmark (59), Turkey (49) and Israel (41) (Table 1). Half of the patients were female (49%), mean age at diagnosis was 8.6 years, 17% had been diagnosed before 1999, 38% between 1999 and 2008 and 45% after 2009. The PCD diagnosis was classified as definite in 65%, probable in 28% and clinical in 7% of patients. Half of the patients (52%) had situs solitus, 37% situs inversus, 3% heterotaxia, and 8% unknown situs. Information on ultrastructural defects was available for 366 (75%). Dynein arm defects were identified in 213 patients, a central complex defect in 40, and microtubular

disorganization in 28. Information on microbiology was available for 250 patients with 1609 samples. In 90% of the samples at least one pathogen was isolated. The most common isolated pathogen was H. Influenza found in 74% of patients and 41% of samples, followed by S. pneumoniae (35% of patients, 12% of all samples), S. aureus (33% of patients, 10% of samples), P. aeruginosa (24% of patients, 8% of samples) and M. catarrhalis (18% of patients, 7% of samples). The prevalence of isolated pathogens differed by age group (Figure S2). Mean age at the first lung function test was 11 years, mean BMI z-score -0.04 (SD =1.27).

Table 1. Demographic and baseline characteristics of patients with primary ciliary dyskinesia (PCD) (N=486)

	All included patients N = 486				Patients with information about ultrastructural defects N = 366			
Characteristic	**N**	**%**	**Measurements**	**%**	**N**	**%**	**Measurements**	**%**
Country								
Australia	16	3%	126	3%	15	4%	118	3%
Belgium	14	3%	151	3%	14	4%	151	4%
Cyprus	15	3%	145	3%	15	4%	145	4%
Czech Republic	27	5%	136	3%	27	7%	136	4%
Denmark	59	12%	1459	33%	47	13%	1063	31%
France	38	8%	340	8%	31	8%	297	9%
Germany	60	12%	664	15%	44	12%	503	15%
Greece	3	1%	16	0%	-	-		
Israel	41	8%	239	5%	33	9%	199	6%
Italy	32	7%	163	4%	32	9%	163	5%
Netherlands	38	8%	114	3%	22	6%	66	2%
Norway	13	3%	82	2%	13	4%	82	2%
Poland	21	4%	75	2%	14	4%	49	1%
Switzerland	23	5%	264	6%	20	5%	225	7%
Turkey	49	10%	329	7%	10	3%	95	3%
UK	37	8%	167	4%	29	8%	128	4%
Sex								
Male	247	51%	2192	49%	192	52%	1711	50%
Female	239	49%	2278	51%	174	48%	1709	50%
Age at diagnosis [years] (mean & SD)	8.64	6.1	-	-	8.33	6.2	-	-
Time period of diagnosis								
1978 - 1998	85	17%	1345	30%	75	21%	1139	33%
1999 - 2008	184	38%	1793	40%	150	41%	1372	40%
2009 - 2018	217	45%	1332	30%	141	38%	909	27%
Diagnostic certainty								
Definite PCD diagnosis*	318	65%	2933	66%	317	87%	2924	85%
Probable PCD diagnosis[#]	137	28%	1309	29%	40	11%	402	12%
Clinical diagnosis only	31	7%	228	5%	9	2%	94	3%
Organ laterality								
Situs solitus	254	52%	2424	54%	191	52%	1861	54%
Situs inversus	182	37%	1613	36%	139	38%	1191	35%
Heterotaxia	12	3%	99	2%	10	3%	93	3%
Situs status not reported	38	8%	334	8%	26	7%	275	8%
Ultrastructural defect								
Normal	48	10%	439	10%	48	13%	439	13%
Central complex	40	8%	452	10%	40	11%	452	13%
ODA	112	23%	1019	23%	112	31%	1019	30%
ODA/IDA	101	21%	859	19%	101	28%	859	25%
Microtubular disorganisation	28	6%	286	6%	28	7%	286	8%
Other	37	7%	365	8%	37	10%	365	11%
No information	120	25%	1050	24%	-	-	-	-

Values at 1st measure (mean, SD)								
Age at 1st measure [years]	10.94	4.35	-	-	10.52	4.28	-	-
BMI z-scores	-0.04	1.27	-	-	-0.01	1.25	-	-
FEV_1 z-scores	-1.22	1.62	-	-	-1.1	1.61	-	-
FVC z-scores	-0.74	1.71	-	-	-0.6	1.66	-	-
FEV_1/FVC z-scores	-0.91	1.44			-0.9	1.46		
Values at last measure (mean, SD)			-	-			-	-
Age at last measure [years]	16.29	4.84	-	-	16.39	5.03	-	-
BMI z-scores	0.01	1.21	-	-	0.03	1.21	-	-
FEV_1 z-scores	-1.51	1.56	-	-	-1.45	1.59	-	-
FVC z-scores	-0.71	1.58	-	-	-0.65	1.61	-	-
FEV_1/FVC z-scores	-1.43	1.31			-1.40	1.32		

Characteristics are presented as N and % of included patients and measurements; SD: standard deviation; ODA: outer dynein arm; IDA: inner dynein arm; BMI: body mass index; FEV1: Forced expiratory volume in 1 second: FVC: Forced vital capacity

* Defined as hallmark PCD ultrastructural defect identified by electron microscopy findings or biallelic PCD causing gene mutation based on the ERS PCD diagnosis guidelines [19]. # Abnormal light or high frequency video microscopy finding and/or low (≤ 77nl/min) nasal NO value.

Lung function

Median number of lung function tests per participant was 6 (IQR: 4 - 11) and median follow-up time 4.14 years (IQR: 2.3 - 7.6). Lung function was below average already at baseline, with a mean (SD) FEV_1 z-score of -1.22 (1.62), a mean (SD) FVC z-score of -0.74 (1.71), and a mean (SD) FEV_1/FVC of -0.91 (1.44) (Table 1, Figure 1 & S3). At the last test, mean (SD) FEV_1 z-score was -1.51 (1.56), mean (SD) FVC z-score -0.71 (1.58), and mean (SD) FEV_1/FVC was -1.43 (1.31). Average individual annual change in FEV_1 was -0.06 z-scores (95% CI -0.072 to -0.057), -0.03 z-scores (95% CI -0.040 to -0.023) for FVC, and -0.062 z-scores (95% CI -0.070 to -0.054) for FEV_1/FVC. Lung function slopes differed between individuals: average yearly FEV_1 improved by at least 0.05 z-scores in 21% of patients, remained stable in 40% and decreased in 39% (Table 2). Results from the regression analysis comparing FEV_1, FVC, and FEV_1/FVC z-scores with GLI reference scores showed no evidence of a non-linear trend in lung function decline (table 3, table S1 & S2).

Table 2. Characteristics of patients with primary ciliary dyskinesia (PCD) from the international PCD cohort by FEV_1 trajectories (lung function improving, stable, or decreasing over time) (N=486)

FEV_1 trajectory*	**Improving**		**Stable**		**Decreasing**	
	N	**%**	**N**	**%**	**N**	**%**
Total	99	21%	196	40%	191	39%
Country						
Australia	3	19%	5	31%	8	50%
Belgium	2	14%	6	43%	6	43%
Cyprus	3	20%	9	60%	3	20%
Czech Republic	6	22%	13	48%	8	30%
Denmark	7	12%	26	44%	26	44%
France	5	13%	9	24%	24	63%
Germany	14	23%	21	35%	25	42%
Greece	2	66%	0	0%	1	33%
Israel	6	15%	18	44%	17	41%
Italy	6	19%	14	44%	12	37%
Netherlands	5	13%	16	42%	17	45%
Norway	2	15%	5	38%	6	46%
Poland	6	29%	9	42%	6	29%
Switzerland	3	13%	11	48%	9	39%
Turkey	21	43%	16	33%	12	24%
UK	10	27%	16	43%	11	30%
Sex						
Female	49	21%	98	41%	92	38%
Male	50	20%	98	40%	99	40%
Age at diagnosis [years] (mean & SD)	9.89	5.74	8.59	6.46	8.06	5.84
Time period of diagnosis						
1978 - 1998	11	13%	33	39%	41	48%
1999 - 2008	35	19%	73	40%	76	41%
2009 - 2018	53	24%	90	41%	74	34%
Diagnostic certainty						
Definite PCD diagnosis	55	17%	137	43%	126	40%
Probable PCD diagnosis	38	28%	49	36%	50	36%
Clinical diagnosis only	6	19%	10	32%	15	48%
Organ laterality						
Situs solitus	65	26%	99	39%	90	35%
Situs inversus	26	14%	79	43%	77	42%
Heterotaxia	2	16%	5	42%	5	42%
Situs status not reported	6	16%	13	34%	19	50%
Ultrastructural defect						
Normal	10	20%	19	40%	19	40%
Central complex	10	25%	17	43%	13	32%
ODA	21	19%	50	45%	41	37%
ODA/IDA	16	16%	38	38%	47	46%
Microtubular disorganisation	3	11%	14	50%	11	39%
Other	5	14%	19	51%	13	35%
No information	34	28%	39	33%	47	39%
BMI z-scores at 1st measure (mean & SD)	-0.2	1.25	0	1.32	0	1.23
BMI z-scores at last measure (mean & SD)	0.02	1.2	0.13	1.18	-0.13	1.24
FEV_1 z-scores at 1st measure (mean & SD)	-1.96	1.47	-1.37	1.59	-0.67	1.52
FEV_1 z-scores at last measure (mean & SD)	-0.98	1.38	-1.34	1.57	-1.96	1.52
FVC z-scores at 1st measure (mean & SD)	-1.43	1.72	-0.94	1.69	-0.17	1.53
FVC z-scores at last measure (mean & SD)	-0.45	1.49	-0.58	1.59	-0.97	1.59

FEV_1/FVC z-scores at 1st measure (mean & SD)	-1.14	1.43	-0.83	1.48	-0.86	1.41
FEV_1/FVC z-scores at last measure (mean & SD)	-1.00	1.28	-1.35	1.26	-1.75	1.30

SD: standard deviation; ODA: outer dynein arm; IDA: inner dynein arm; BMI: body mass index; FEV1: Forced expiratory volume in 1 second: FVC: Forced vital capacity

Yearly lung function change, improving: > 0.05 z-scores; stable: ≤ 0.05 & ≥ -0.05 z-scores; decreasing: < -0.05 z-scores. Data is presented with row percentages.

Determinants of lung function

Lung function differed by countries (Table 3, S1 & S2, Figure 2 & figure S4). FEV_1 was reduced at the age of 6 years in most countries compared to GLI reference values, except the Netherlands. FEV_1 z-scores were lowest in Turkey (-3.02), Cyprus (-2.45) and the UK (-2.35), and highest in the Netherlands (0.37) and Denmark (-1.05). The change in FEV_1 over time was also variable; lung function deteriorated over time in most countries. Yearly decline of FEV_1 z-scores was highest in the Netherlands (-0.14), Israel (-0.05) and France (-0.05). FEV_1 z-scores increased over time in Turkey (0.11), Cyprus (0.07) and Poland (0.04). For FVC (Table S1 and Figure S4), the results were similar to FEV_1. FVC also decreased over time in most countries, except for Turkey (0.08), with the steepest decline in the Netherlands (-0.26). FEV_1/FVC was reduced at baseline in all countries and the steepest decline over time was found in German patients (table S2),

BMI was positively associated with FEV_1 and FVC but not with FEV_1/FVC. Patients with higher BMI had a better FEV_1 at baseline and improved more over time (Table 3 & S1). Baseline FEV_1 was 0.32 z-scores higher for each unit of higher BMI z-score. Yearly change of FEV_1 increased by 0.02 z-scores for each unit of z-score increase in BMI. Similarly, baseline FVC and increase of FVC over time were higher in individuals with higher BMI. BMI remained a determinant for lung function when running separate regression model for countries with at least 30 patients (table S4).

Ultrastructural defects were also associated with lung function (Table 4). Patients with microtubular disorganization defects had the worst baseline FEV_1 z-scores (-1.75), followed by patients with central complex defects (-1.38) and ODA defects (-1.27). Patients with non-diagnostic TEM (-0.91) or combined ODA & IDA defects (-0.60) had the best lung function at baseline. Yearly changes of FEV_1 also varied between groups, with the steepest decline in patients with ODA & IDA defects (-0.05), and the most favourable course in patients with central complex defects. FVC varied similarly with ultrastructural defects (Table S2), but the evidence was less strong as for FEV_1. The amount of variability explained by the model changed only marginally when we additionally included ultrastructural defects into the model: the marginal R^2 changed from 0.211 to 0.237 and the conditional R^2 from 0.817 to 0.819.

We did not find evidence that FEV_1, FVC, and FEV_1/FVC z-scores differed by sex, age at diagnosis, year of diagnosis, laterality defects, level of diagnostic certainty, or isolated pathogen (Table 3 & S1 & Table S5).

Table 3. FEV_1 of patients with primary ciliary dyskinesia (PCD) from the international PCD cohort compared to Global Lung Function Initiative 2012 reference values (linear mixed effects regression, adjusting for all covariates).

		FEV_1		
Variable	**Estimate**	**95% CI**		**p-value**[¶]
Intercept (Lung function at age 6 years for "reference patient") [+]	-1.26	-2.19	-0.3	
Age at measurement	-0.04	-0.12	0.04	
Country (Ref: Germany)				<0.01
Australia	-0.34	-1.26	0.59	
Belgium	-0.20	-1.03	0.64	
Cyprus	-1.19	-2.14	-0.23	
Czech Republic	-0.95	-1.68	-0.22	
Denmark	0.21	-0.42	0.84	
France	0.14	-0.65	0.93	
Greece	0.92	-2.35	4.19	
Israel	0.11	-0.71	0.93	
Italy	-0.28	-1.02	0.47	
Netherlands	1.63	0.84	2.43	
Norway	-0.31	-1.24	0.63	
Poland	-0.86	-1.70	-0.03	
Switzerland	0.13	-0.63	0.89	
Turkey	-1.76	-2.46	-1.06	
UK	-1.09	-1.90	-0.28	
Sex (Ref: male)				0.37
Female	-0.03	-0.33	0.27	
Age at diagnosis	-0.01	-0.05	0.02	0.21
Diagnostic period	0.02	-0.005	0.05	0.26
Diagnostic certainty (Ref: definite PCD diagnosis)				0.49
Probable PCD diagnosis	-0.04	-0.43	0.35	
Clinical diagnosis only	0.38	-0.27	1.03	
Laterality defects (Ref: situs solitus)				0.59
Situs Ambiguous	0.42	-0.53	1.36	
Situs Inversus	0.33	-0.001	0.66	
Situs Unknown	0.15	-0.54	0.85	
BMI	0.32	0.28	0.37	<0.01
Change of lung function over time[#]				
Country (Ref: Germany)				<0.01
Australia	-0.02	-0.10	0.07	
Belgium	0.02	-0.05	0.10	
Cyprus	0.07	-0.01	0.15	
Czech Republic	0.04	-0.03	0.11	
Denmark	-0.01	-0.07	0.05	
France	-0.05	-0.12	0.03	
Greece	0.01	-0.29	0.32	
Israel	-0.05	-0.13	0.03	
Italy	-0.03	-0.10	0.04	
Netherlands	-0.14	-0.24	-0.04	
Norway	-0.02	-0.12	0.09	
Poland	0.04	-0.05	0.13	
Switzerland	-0.03	-0.10	0.05	
Turkey	0.11	0.04	0.18	
UK	0.03	-0.04	0.11	
Sex (Ref: male)				0.36
Female	-0.01	-0.04	0.02	
Age at diagnosis	0.003	0.00	0.01	0.08

Diagnostic period	-0.001	-0.004	0.001	0.32
Diagnostic certainty (Ref: definite PCD diagnosis)				0.92
Probable PCD diagnosis	-0.01	-0.04	0.03	
Clinical diagnosis only	-0.001	-0.07	0.07	
Laterality defects (Ref: situs solitus)				0.52
Situs Ambiguous	-0.01	-0.11	0.08	
Situs Inversus	-0.02	-0.05	0.01	
Situs Unknown	-0.02	-0.08	0.04	
BMI	0.02	0.01	0.02	<0.01

FEV1: Forced expiratory volume in 1 second; BMI: body mass index

¶ Likelihood ratio test p-value indicating whether the characteristic explains differences in FEV_1 within the study population.

[+]The Intercept describes the FEV_1 of a reference patient at 6 years, who is male, from Germany, with a BMI z-score of 0, diagnosed at birth (age = 0) in 1978, with a definite PCD diagnosis. Categorical variables describe the change from the reference category, while continuous variables describe the change from the reference patient for each unit of increase.

* Defined as hallmark PCD ultrastructural defect identified by electron microscopy findings or biallelic PCD causing gene mutation based on the ERS PCD diagnosis guidelines [19]. # Abnormal light or high frequency video microscopy finding and/or low (≤ 77nl/min) nasal NO value.

[#]Change in lung function over time are based on interaction terms between the characteristics (e.g. country, sex) and age. Change of lung function over time thus describes the change in the trajectory of FEV_1 per year increase, based on the reference category for categorical variables and for each unit of increase for continuous variables.

Table 4. FEV_1 in patients with primary ciliary dyskinesia (PCD), by ultrastructural defect (N = 366).

		FEV_1		
Characteristic	**Estimate**	**95% CI**		**p-value[¶]**
Intercept (Lung function at age 6 years for "reference patient") [+]	-1.27	-2.41	-0.13	
Baseline FEV_1				
ODA (Reference)*				0.01
Central Complex defect	-0.11	-0.67	0.45	
ODA/IDA	0.67	0.19	1.14	
Microtubular disorganisation	-0.49	-1.15	0.17	
Non-diagnostic	0.36	-0.20	0.91	
Change of FEV_1 over time[#] ("reference patient") [†]	-0.02	-0.12	0.08	
ODA (Reference)*				0.04
Central Complex defect	0.03	-0.02	0.07	
ODA/IDA	-0.05	-0.09	-0.01	
Microtubular disorganisation	0.01	-0.05	0.08	
Non-diagnostic	-0.01	-0.06	0.05	

FEV1: Forced expiratory volume in 1 second; ODA: outer dynein arm; IDA: inner dynein arm

[¶] Likelihood ratio test p-value indicating whether the characteristic explains differences in FEV_1 within the study population.

*Data are presented as unstandardized regression coefficient representing difference from reference category.

[+]Adjusted for all variables of the full model, the full summary output is in the online supplement (Table S2)

The Intercept describes the FEV_1 of a reference patient at age 6 years, who is male, from Germany, with a BMI z-score of 0, diagnosed at birth (age = 0) in 1978, with a definite PCD diagnosis. Categorical variables describe the change from the reference category, while continuous variables describe the change from the reference patient for each unit of increase. [#]Change in lung function over time are based on interaction terms between the characteristics (e.g. country, sex) and age. The change over time thus describes the change in the trajectory of FEV_1 per year increase, based on the reference category for categorical variables and for each unit of increase for continuous variables.

FEV_1 at baseline was slightly better when we excluded patients diagnosed at the same year as first lung function measurement (FEV_1 z-score -1.10; 95% CI -2.11 to -0.09) compared to the total included population (FEV_1 z-score -1.26; 95% CI -2.19 to -0.30) (table 3 & S6). The decline over time however did not change.

Discussion

This large international study of patients with PCD found that lung function, already reduced by the age of 6 years, declined further during childhood, adolescence, and early adulthood with an overall negative trend in z-scores. There was heterogeneity between countries and individuals. Overall, FEV_1 z-scores decreased over time in 39% of children, remained stable in 40% and improved in 21%. Reduced FEV_1/FVC at baseline and follow-up supported presence of obstructive lung disease. Type of ultrastructural defect was marginally associated, and BMI more strongly associated with lung function at baseline and changes in lung function over time.

The wide variation in lung function between countries confirms previous cross-sectional data which included adults.[15] We observed that countries with poor lung function at baseline, such as Poland and Turkey, tended to have a less steep decline than countries with more favourable baseline values such as the Netherlands, Denmark, or France. Reasons for this are unclear but could include regression to the mean and differences in management of PCD. It is possible that patients who presented with a poor lung function at diagnosis were offered a strict physiotherapy and antibiotics management and were monitored more closely than patients who were better off at diagnosis. Also, length of follow-up time and frequency of lung function testing differed between countries, which could have affected the estimation of the lung function trajectories. In the Netherlands and France where the decline in lung function was steep, the mean lung function trajectory was estimated based on short individual follow-ups, while in countries with longer follow-ups, the decline in lung function was less steep such as Denmark or Belgium. We modelled mean trajectories as linear

although they may be non-linear. However, in formal testing including a quadratic term, we found no evidence for non-linearity. It is also possible that the GLI reference values might not be applicable to all countries e.g. the Netherlands. However, if that was true, we would expect regional differences in baseline lung function, but the effect on slopes should be minor. Despite the differences between countries, results from the individual country models (Table S3) highlight the robustness of our findings.

Can early diagnosis prevent disease progression? This has been suggested by previous studies,[14, 27-29] but the Danish study and ours found no association.[8] As we still lack robust evidence for the best treatments for PCD, management is based on experience from other lung diseases such as CF. Therefore, PCD diagnosis might not have led to a change in management, as patients may have been treated for chronic lung disease already before PCD was diagnosed. PCD-specific randomised controlled trials will provide more specific treatment recommendations.[30, 31] We here refer both to symptomatic treatment like antibiotics and airway clearance techniques but also to treatments under development such as gene therapy or transcript therapy. [32, 33]

When considering the different phases of lung function over a lifetime,[9, 10] what have we learnt? Our study and the North American one suggest that lung function growth during childhood is impaired.[13] The fact that lung function was already low at age six could be the result of poorer lung growth at preschool age or a reduced lung function at birth, or it could be a consequence of neonatal respiratory problems such as atelectasis or neonatal pneumonia. Studies in children with asthma have shown that impaired lung function in infancy is associated with lower lung function in childhood as well as later in life,[34, 35] which support a hypothesis that the reduced lung function in PCD could be associated with neonatal early life disease. However, this can only be investigated using infant lung function testing in children with PCD diagnosed as neonates. Studies based on mainly adult patients reported larger declines (-0.89%/year in Italy)[8, 24] suggesting that also the decline of lung function in adulthood is accelerated. The fact that FEV_1 z-scores decreased over time in all studies reflects long-term irreversible lung damage such as bronchiectasis and lung remodelling after recurrent severe infections.[36] On the positive side, the heterogeneity between patients that we followed suggests that many changes are reversible after initiation of regular physiotherapy and antibiotics, such as mucus plugging, bronchial wall thickening and temporary atelectasis.

If we compare lung function decline in patient with PCD to patients with CF, we see that lung function decline in PCD patients is comparable to that of CF patients in childhood. In young adulthood however, lung function seems to decline faster in patient with CF.[15, 37] This might indicate a worse disease course in CF than in PCD. Another explanation may be that most younger CF

patients have been diagnosed through newborn-screening and thus on average have a milder phenotype than older CF patients who have been diagnosed because they developed symptoms and lung damage has occurred. Patients with PCD in our study have all been diagnosed late, sometimes years or decades after the presentation of symptoms.[6, 38] This could explain the similar lung function for CF and PCD patients early in life despite a more severe disease course in patients with CF. In studies that assessed changes in lung function z-scores over the growth period in children with asthma, there is also evidence that some children with asthma have a reduced lung growth compared to children without asthma. In a study from France, Mahut et al. investigated trajectories of FEV1 z-scores in 295 children with asthma followed between the age of 8 to 15 years.[39] They found that in 4% of the children, FEV1 z-scores improved significantly over time, in 69% of the children FEV1 z-scores remained stable, and in 28% of the children, FEV1 z-scores decreased. McGeachie et al. studied 684 children with mild to moderate asthma aged 5-12 years at baseline and followed them for at least 11 years. They found that 51% had normal lung growth, measured by FEV1 compared to reference values from healthy children, while 49% had reduced lung growth.[40] However, as definitions and methods differed between these studies, a direct comparison with our study is not possible.

Genetic and ultrastructural differences have been offered as an explanation for variable lung function trajectories in smaller studies.[8, 13, 41] Particularly poor lung function was seen in patients with microtubular defects.[6, 13, 28, 42] A UK study in 82 adults reported an FEV_1 decline of 0.75 percent predicted in patients with microtubular defects compared to −0.51 percent predicted in patients with ODA or combined ODA and IDA defects, and −0.13 percent predicted in patients with normal or inconclusive TEM. Other studies have shown that annual change in FEV_1 percent predicted deviated from normal only in patients with central apparatus and microtubular defects (−1.11 percent predicted) and not in patients with dynein arm defects or normal TEM [13, 24]. We found microtubular defects to be associated with the worst baseline lung function, but further course did not differ. The total variability explained by the regression model (marginal R^2) increased only slightly when we included the ultrastructural defects, suggesting that ultrastructural differences explain only a small part of the heterogeneity.

Higher BMI was associated with better baseline lung function and with further change. This confirms previous cross-sectional data in people with PCD[14, 15, 43] and it is in line with what has been found in patients with CF.[44] The effect of poor nutrition on lung function is known for patients with other respiratory diseases[45-47] and dietary support should be provided when required. In contrast to our previous cross-sectional analysis where we found that FEV_1 and FVC z-

scores were lower in females than males,[15] we found no evidence of an association of lung function and sex. This is in line with what was found in the UK,[6] and studies in patients with CF.[48]

We did not find an association between any of the isolated pathogens in sputum microbiology samples and changes in lung function over time. study in 266 adults with PCD found that participants colonized with pseudomonas aeruginosa had lower baseline FEV_1 than participants without chronic Pseudomonas, however there was no difference in lung function decline between colonised and non-colonised participants.[49] In children with cystic fibrosis, in whom sputum pathogens are similar as in patients with PCD, colonisation with pseudomonas aeruginosa has been associated with a steeper decline in lung function.[50]

With 4470 lung function tests from 486 individuals this study is by far the largest showing lung function trajectories in children, adolescents, and young adults with PCD. Most other longitudinal studies combined children and older adults, not allowing to distinguish the growth period in childhood from functional decline in adulthood.[8, 24] The large study population made it possible to compare countries and ultrastructural phenotypes and test for association with possible risk factors. A limitation of the study was that the cut-off for defining whether FEV_1 z-scores improved, remained stable, or decreased was based on cut-offs defined in a study including mostly healthy children, and may therefore not fit a PCD-population. However, yet no data exist for people with PCD that describes expected normal variability of lung function. Another limitation was that some participating centres only provided one measurement per patient per year, and for these patients we therefore may not have captured all variation in lung function over time although we included only patients with at least 3 lung function measurements. These centres were instructed to select lung function measurements at random, so this should not have led to selection bias. A further limitation was that we did not have information about whether patients withheld inhaled beta agonists before lung function measurements were performed. We also lacked information about pulmonary exacerbations and could therefore not directly verify whether local centres contributed only lung function tests from patients in a steady state. However, none of the collaborating centres measures lung function in patients during or shortly after an exacerbation, and they had been instructed not to enter any such measurements into the database. Another limitation of the study was that we lacked information on other factors that can influence lung function associated with bronchiectasis from any cause such as frequency of exacerbations, colonizing organisms, and patterns of care including antibiotic treatments, airway clearance routines, and vaccinations. It would also be interesting to study if chest computed tomography scans or MRI can predict lung function decline in children and adults with PCD as it has been shown in children with cystic

fibrosis.[51] Prospective cohort studies using standardised protocols would help to clarify the relative contribution of these factors to the rate of lung function change for patients with PCD.[52]

In conclusion, this large international study found considerable heterogeneity in lung function trajectories of children, adolescents, and young adults with PCD and a wide variation between countries. Lung function was low in 6-year-olds and declined further throughout the lung growth period despite treatment. It is essential to develop PCD specific treatment strategies to improve prognosis.

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Supplementary display items:

Figure S1. Flow chart showing the patients and respective lung function measurements included for the different analyses. Npat: number of patients; Nmeas: number of measurements; EM: electron microscopy

Figure S2**:** Cross-sectional prevalence of bacteria isolated from the respiratory tract in patients with primary ciliary dyskinesia (PCD) from the international PCD cohort.

Figure S3. FVC trajectories during the lung growth period compared to Global Lung Function Initiative 2012 reference values. FVC (Forced vital capacity) is presented as z-score. A loess curve (blue line) was used to display the trajectory over time of all measurements and is plotted with a 95% confidence interval (shaded bands). Grey lines represent the individual linear trajectories of each patient included in the study. The dashed line shows the mean z-score of the normal population

Table S1. FVC of patients with primary ciliary dyskinesia (PCD) from the international PCD cohort, compared to Global Lung Function Initiative 2012 reference values (linear mixed effects regression, adjusting for all covariates).

Table S2**:** FEV_1/FVC of patients with primary ciliary dyskinesia (PCD) from the international PCD cohort, compared to Global Lung Function Initiative 2012 reference values (linear mixed effects regression, adjusting for all covariates).

Figure S4 FVC trajectories of PCD patients in different countries compared to Global Lung Function Initiative (GLI) 2012 reference values. Individual trajectories are shown as black lines, marginal effects (estimated regression line for subgroup) as blue lines, 95% confidence intervals as grey shaded areas. The dashed line shows the mean z-score of the normal population (GLI 2012). FVC: Forced vital capacity

Table S3. FEV_1 and FVC of patients with primary ciliary dyskinesia (PCD) from the international PCD cohort with available ultrastructural defect information compare to Global Lung Function Initiative 2012 reference values (N = 366).

Table S4. FEV_1 of patients with primary ciliary dyskinesia (PCD) from the international PCD cohort compared to Global Lung Function Initiative 2012 reference values (linear mixed effects regression, adjusting for all covariates) for single countries with more than 30 patients

Table S5**:** FEV_1 and FVC in patients with primary ciliary dyskinesia (PCD) from the international PCD cohort with available microbiological information compared to Global Lung Function Initiative 2012 reference values.

Table S6. Sensitivity analysis: FEV_1 of patients with primary ciliary dyskinesia (PCD) from the international PCD cohort compared to Global Lung Function Initiative 2012 reference values (linear mixed effects regression, adjusting for all covariates) excluding patients diagnosed the same year as first lung function measurement (n=356).

Author Contributions: CE Kuehni, FS Halbeisen and M Goutaki developed the concept and designed the study. FS Halbeisen cleaned and standardised the data. FS Halbeisen and E Pedersen performed the statistical analyses. All other authors participated in discussions for the development of the study and contributed data. FS Halbeisen, CE Kuehni, M Goutaki and E Pedersen drafted the manuscript. All authors commented and revised the manuscript. CE Kuehni and FS Halbeisen take final responsibility for the contents.

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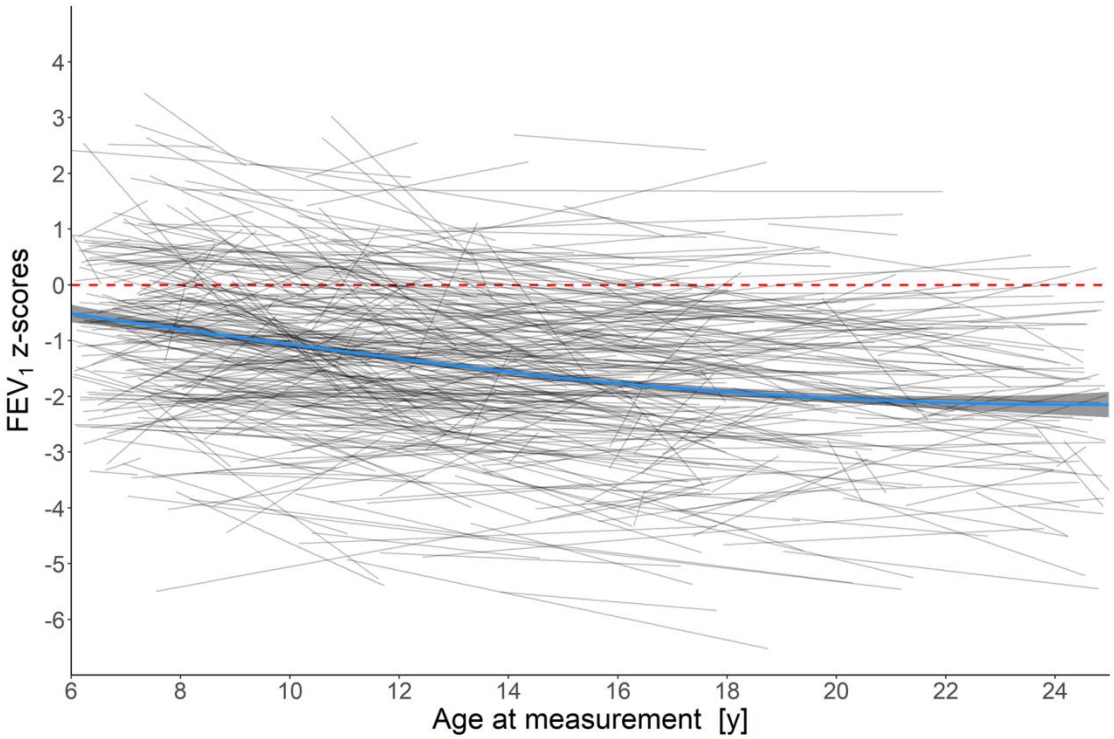


Figure 1. FEV1 trajectories during the lung growth period compared to Global Lung Function Initiative 2012 reference values.

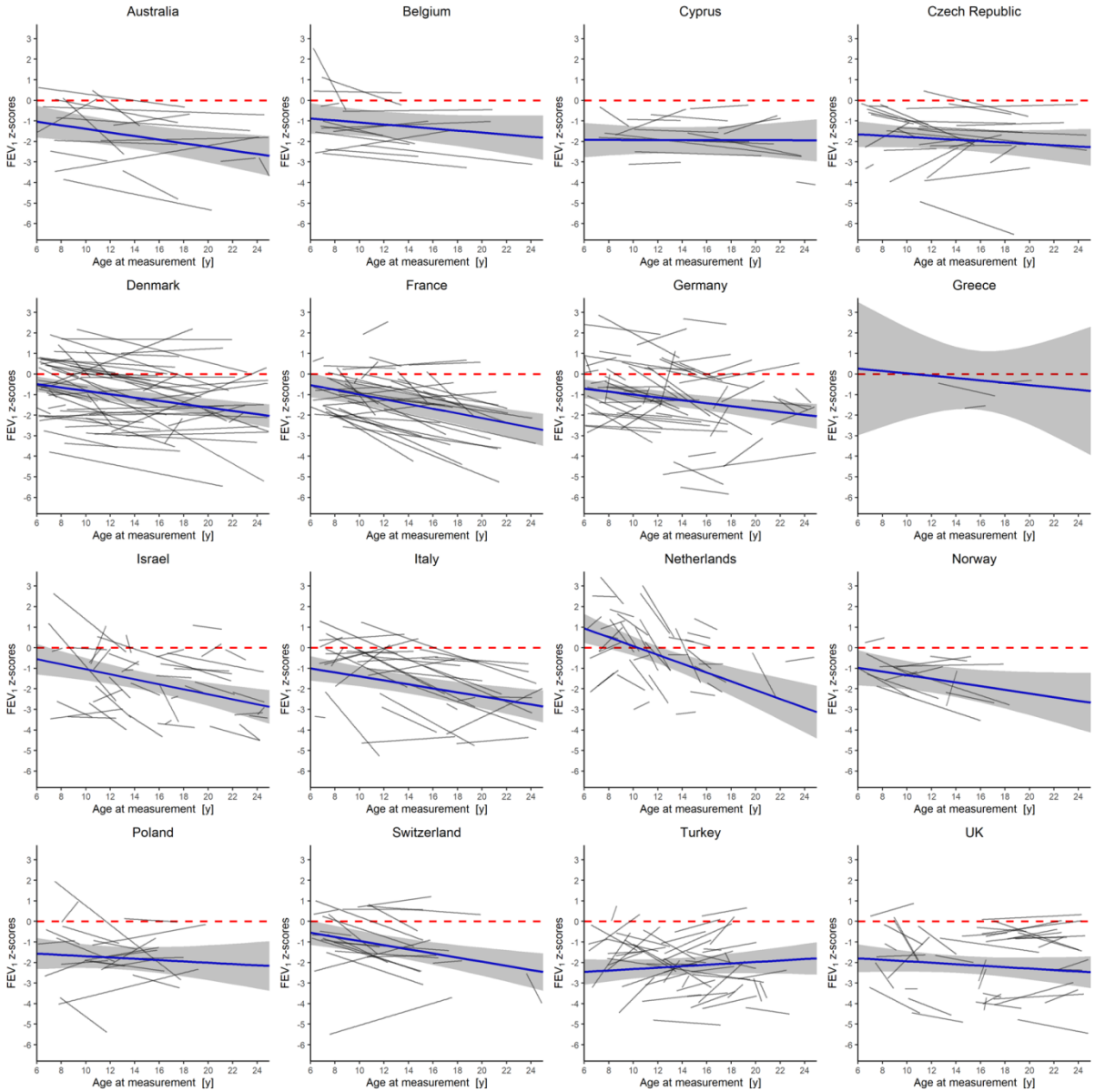


Figure 2. FEV1 trajectories of PCD patients in different countries compared to Global Lung Function Initiative (GLI) 2012 reference values.

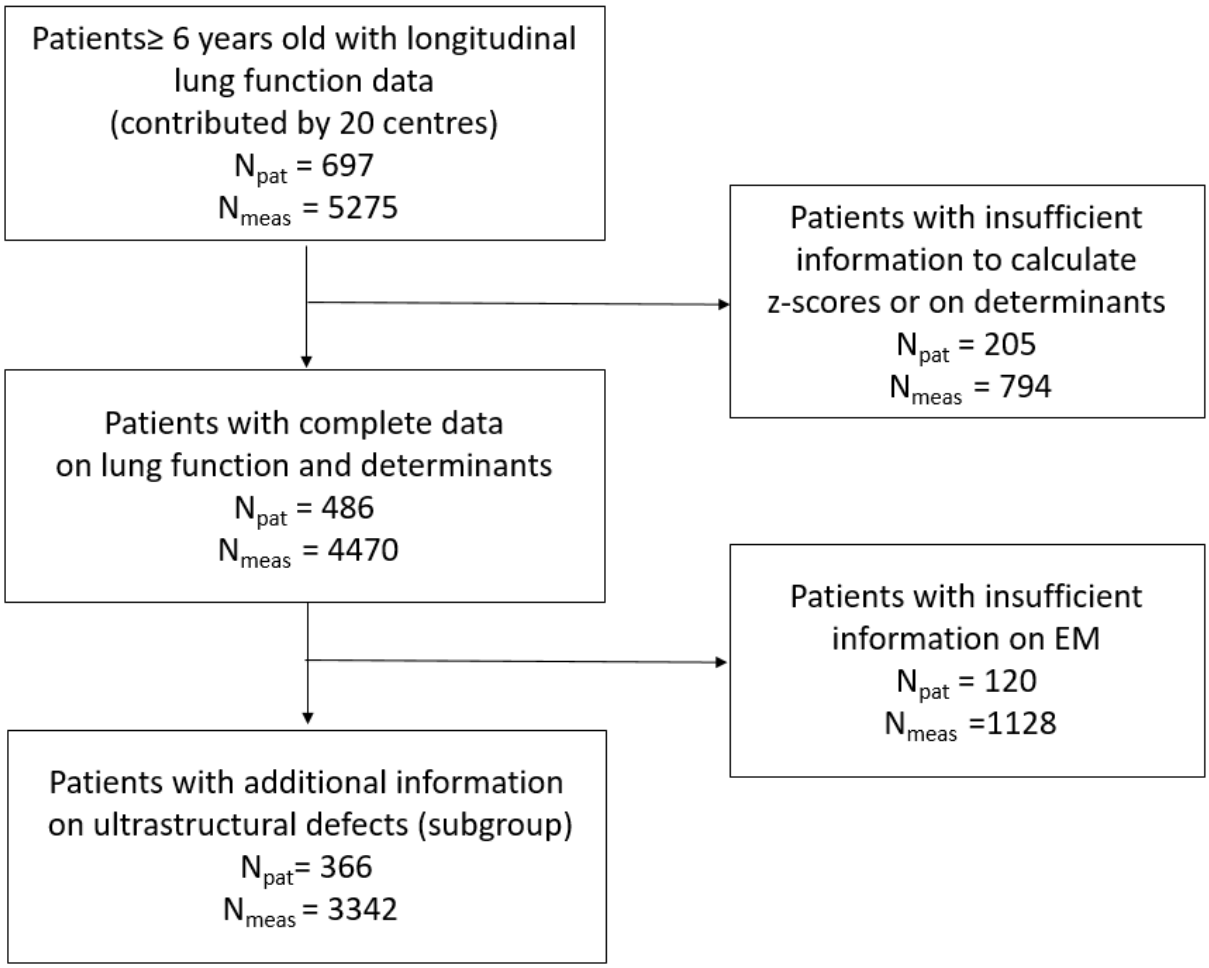
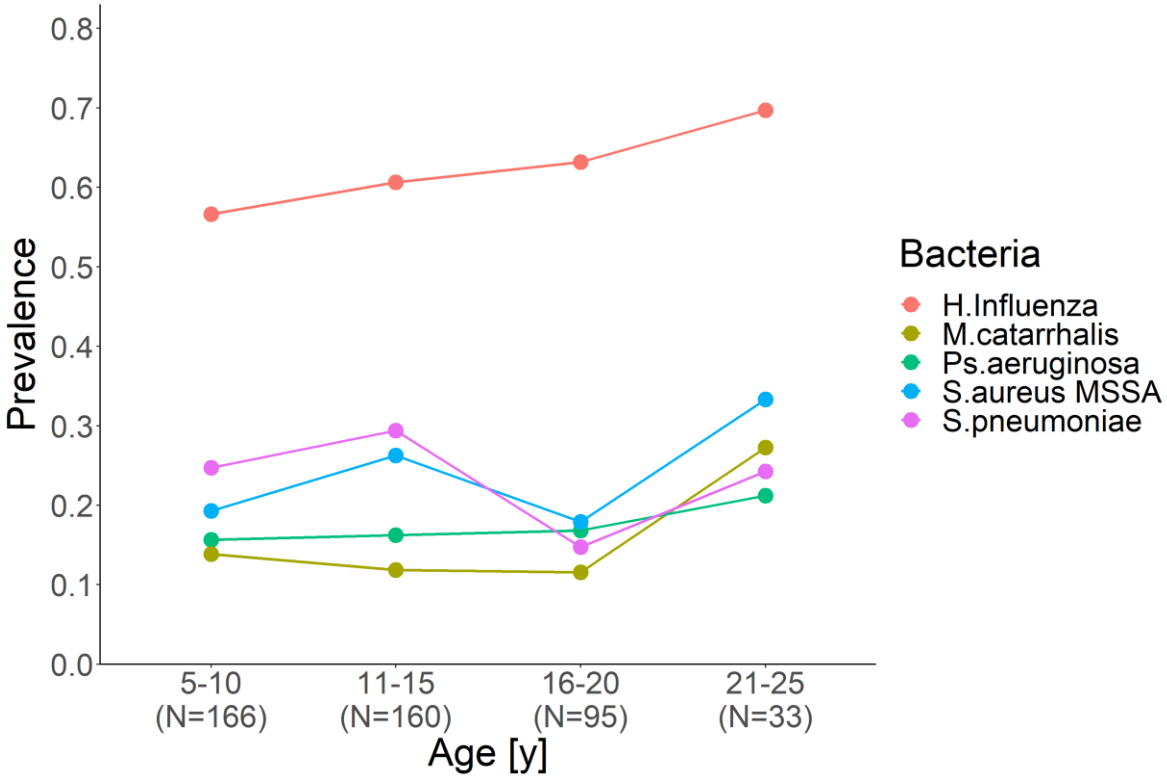


Figure S1. Flow chart showing the patients and respective lung function measurements included for the main analysis and the subgroup analysis.
Npat: number of patients; Nmeas: number of measurements; EM: electron microscopy



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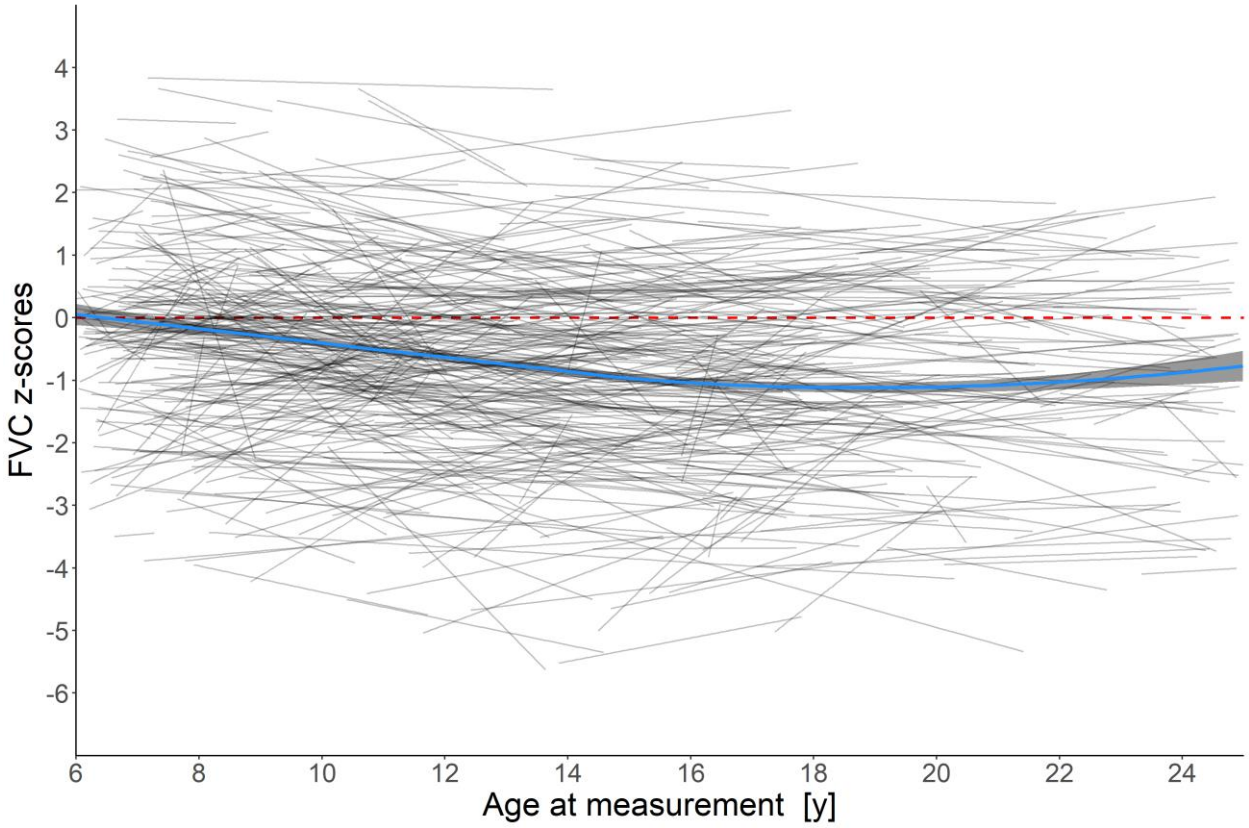

Figure S3. FVC trajectories during the lung growth period compared to Global Lung Function Initiative 2012 reference values.

FVC (Forced vital capacity) is presented as z-score. A loess curve (blue line) was used to display the trajectory over time of all measurements and is plotted with a 95% confidence interval (shaded bands). Grey lines represent the individual linear trajectories of each patient included in the study. The dashed line shows the mean z-score of the normal population

Table S1 FVC of patients with primary ciliary dyskinesia (PCD) from the international PCD cohort, compared to Global Lung Function Initiative 2012 reference values (linear mixed effects regression, adjusting for all covariates).

	FVC			
Variable	**Estimate**	**95% CI**		**p-value**[¶]
Intercept (Lung function at age 6 years for "reference patient") [+]	-1.10	-2.07	-0.13	
Age at measurement	0.02	-0.07	0.11	
Country (Ref: Germany)				<0.01
Australia	0.06	-0.90	1.02	
Belgium	0.76	-0.10	1.62	
Cyprus	-0.82	-1.81	0.17	
Czech Republic	-0.73	-1.49	0.03	
Denmark	1.09	0.43	1.73	
France	0.80	-0.02	1.63	
Greece	1.09	-2.46	4.64	
Israel	0.36	-0.49	1.22	
Italy	0.52	-0.25	1.30	
Netherlands	2.98	2.16	3.81	
Norway	0.38	-0.59	1.36	
Poland	-0.01	-0.88	0.87	
Switzerland	0.52	-0.26	1.31	
Turkey	-1.78	-2.51	-1.05	
UK	-0.20	-1.05	0.65	
Sex (Ref: male)				0.79
Female	-0.11	-0.42	0.20	
Age at diagnosis	-0.02	-0.05	0.01	0.47
Diagnostic period	0.01	-0.02	0.04	0.49
Diagnostic certainty (Ref: definite PCD diagnosis)				0.30
Probable PCD diagnosis	-0.12	-0.52	0.29	
Clinical diagnosis only	0.33	-0.35	1.01	
Laterality defects (Ref: Situs solitus)				0.40
Situs Ambiguous	0.16	-0.83	1.15	
Situs Inversus	0.30	-0.05	0.64	
Situs Unknown	0.00	-0.74	0.72	
BMI	0.40	0.35	0.45	<0.01
Change of lung function over time				
Country (Ref: Germany)				<0.01
Australia	-0.05	-0.13	0.04	
Belgium	-0.10	-0.18	-0.02	
Cyprus	-0.04	-0.12	0.05	
Czech Republic	-0.02	-0.09	0.06	
Denmark	-0.05	-0.12	0.01	
France	-0.10	-0.18	-0.03	
Greece	-0.08	-0.41	0.25	
Israel	-0.09	-0.17	-0.01	
Italy	-0.09	-0.17	-0.02	
Netherlands	-0.26	-0.37	-0.16	
Norway	-0.07	-0.18	0.04	
Poland	-0.04	-0.14	0.06	

Switzerland	-0.06	-0.14	0.02	
Turkey	0.08	0.01	0.16	
UK	-0.05	-0.13	0.04	
Sex (Ref: male)				0.61
Female	0.01	-0.02	0.04	
Age at diagnosis	0.002	-0.001	0.005	0.24
Diagnostic period	-2.12	-0.003	0.003	0.99
Diagnostic certainty (Ref: definite PCD diagnosis)				0.21
Probable PCD diagnosis	-0.01	-0.05	0.03	
Clinical diagnosis only	-0.07	-0.14	0.01	
Laterality defects (Ref: situs solitus)				0.73
Situs Ambiguous	-0.004	-0.10	0.09	
Situs Inversus	-0.01	-0.04	0.02	
Situs Unknown	-0.04	-0.10	0.03	
BMI	0.01	-0.005	0.02	0.01

FVC: Forced vital capacity; BMI: body mass index

[¶] Likelihood ratio test p-value indicating whether the characteristic explains differences in FVC within the study population.

[+]The Intercept describes the FVC of a reference patient at 6 years, who is male, from Germany, with a BMI z-score of 0, diagnosed at age 6 years in 1978, with a definite PCD diagnosis. Categorical variables describe the change from the reference category, while continuous variables describe the change from the reference patient for each unit of increase. * Defined as hallmark PCD ultrastructural defect identified by electron microscopy findings or biallelic PCD causing gene mutation based on the ERS PCD diagnosis guidelines [14]. [#] Abnormal light or high frequency video microscopy finding and/or low (≤ 77nl/min) nasal NO value. Change of lung function over time describes the change in the trajectory of FEV_1 per year increase, based on the reference category for categorical variables and for each unit of increase for continuous variables.

Table S2 FEV_1/FVC of patients with primary ciliary dyskinesia (PCD) from the international PCD cohort, compared to Global Lung Function Initiative 2012 reference values (linear mixed effects regression, adjusting for all covariates).

		FEV/FVC		
Variable	**Estimate**	**95% CI**		**p-value**[¶]
Intercept (FEV1/FVC at age 6 years for "reference patient") [+]	-0.36	-1.28	0.56	
Age at measurement	-0.09	-0.18	0.01	
Country (Ref: Germany)				<0.01
Australia	-0.70	-1-61	0.20	
Belgium	-1.75	-2.58	-0.93	
Cyprus	-0.51	-1.45	0.42	
Czech Republic	-0.40	-1.12	0.31	
Denmark	-1.25	-1.86	-0.63	
France	-1.16	-1.95	-0.38	
Greece	-0.07	-3.45	3.31	
Israel	-0.50	-1.31	0.31	
Italy	-1.32	-2.06	0.31	
Netherlands	-1.88	-2.65	-1.11	
Norway	-1.16	-2.09	-0.24	
Poland	-1.59	-2.42	-0.76	
Switzerland	-0.42	-1.16	0.33	
Turkey	-0.39	-1.09	0.30	
UK	-1.60	-2.42	-0.77	
Sex (Ref: male)				0.06
Female	-0.05	-0.35	0.24	
Age at diagnosis	-0.001	-0.01	0.03	0.01
Diagnostic period	0.02	-0.01	0.05	0.04
Diagnostic certainty (Ref: definite PCD diagnosis)				0.02
Probable PCD diagnosis	0.17	-0.22	0.56	
Clinical diagnosis only	0.21	-0.45	0.88	
Laterality defects (Ref: Situs solitus)				0.70
Situs Ambiguous	-0.19	-1.18	0.81	
Situs Inversus	0.08	-0.25	0.40	
Situs Unknown	-0.01	-0.73	0.70	
BMI	-0.04	-0.08	0.01	0.20
Change of lung function over time				
Country (Ref: Germany)				<0.01
Australia	0.04	-0.05	0.13	
Belgium	0.21	-0.12	0.26	
Cyprus	0.16	0.07	0.26	
Czech Republic	0.09	0.01	0.17	
Denmark	0.05	-0.02	0.12	
France	0.11	0.02	0.19	
Greece	0.17	-0.16	0.50	
Israel	0.08	-0.01	0.16	
Italy	0.11	0.04	0.19	
Netherlands	0.18	0.07	0.22	
Norway	0.10	-0.01	0.22	
Poland	0.16	0.06	0.26	

Switzerland	0.03	-0.05	0.11	
Turkey	0.06	-0.01	0.14	
UK	0.10	0.02	0.19	
Sex (Ref: male)				0.17
Female	-0.02	-0.05	0.01	
Age at diagnosis	0.004	0.001	0.01	0.02
Diagnostic period	-0.004	-0.01	-0.001	0.01
Diagnostic certainty (Ref: definite PCD diagnosis)				0.20
Probable PCD diagnosis	-0.001	-0.04	0.04	
Clinical diagnosis only	0.07	-0.01	0.15	
Laterality defects (Ref: situs solitus)				0.41
Situs Ambiguous	0.05	-0.06	0.15	
Situs Inversus	-0.02	-0.06	0.01	
Situs Unknown	-0.01	-0.09	0.06	
BMI	0.01	-0.01	0.02	0.17

FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; BMI: body mass index

[¶] Likelihood ratio test p-value indicating whether the characteristic explains differences in FEV_1/FVC within the study population.

[+]The Intercept describes the FEV_1/FVC of a reference patient at 6 years, who is male, from Germany, with a BMI z-score of 0, diagnosed at age 6 years in 1978, with a definite PCD diagnosis. Categorical variables describe the change from the reference category, while continuous variables describe the change from the reference patient for each unit of increase. * Defined as hallmark PCD ultrastructural defect identified by electron microscopy findings or biallelic PCD causing gene mutation based on the ERS PCD diagnosis guidelines [14]. [#] Abnormal light or high frequency video microscopy finding and/or low (≤ 77nl/min) nasal NO value.

Change of lung function over time describes the change in the trajectory of FEV_1/FVC per year increase, based on the reference category for categorical variables and for each unit of increase for continuous variables.

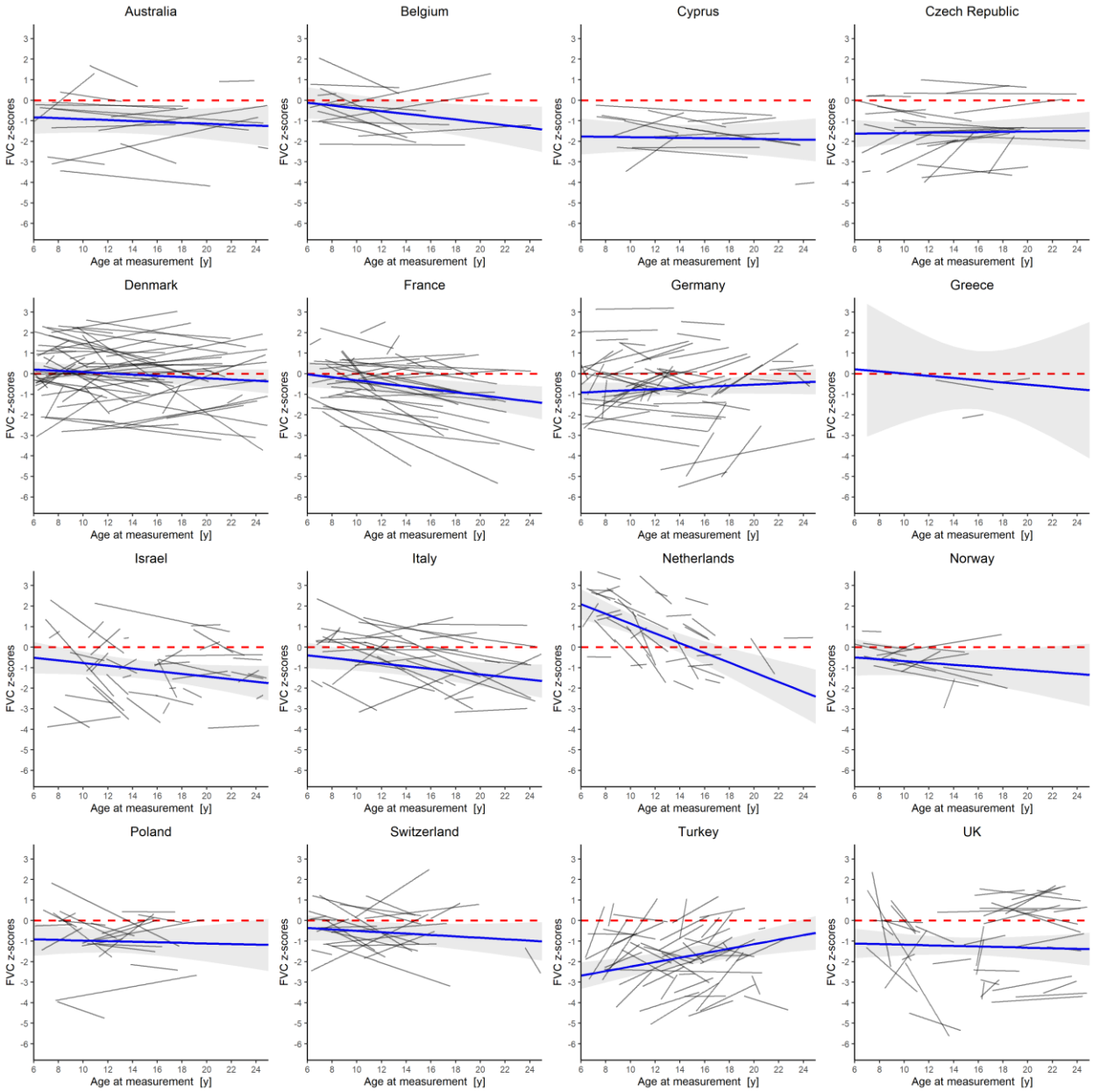

Figure S4. FVC trajectories of PCD patients in different countries compared to Global Lung Function Initiative (GLI) 2012 reference values.

Individual trajectories are shown as black lines, marginal effects (estimated regression line for subgroup) as blue lines, 95% confidence intervals as grey shaded areas. The dashed line shows the mean z-score of the normal population (GLI 2012). FVC: Forced vital capacity

Table S3. FEV_1 and FVC of patients with primary ciliary dyskinesia (PCD) from the international PCD cohort with available ultrastructural defect information compared to Global Lung Function Initiative 2012 reference values (N = 366).

	FEV_1				FVC			
Variable	**Estimate**	**95% CI**		**p-value**	**Estimate**	**95% CI**		**p-value**
Intercept (Lung function at age 6 years for "reference patient") +	-1.27	-2.41	-0.13		-0.35	-1.54	0.83	
Age at measurement	-0.02	-0.12	0.08		-0.08	-0.18	0.03	
Country (Ref: Germany)				<0.01				<0.01
Australia	-0.29	-1.30	0.71		-0.20	-1.24	0.84	
Belgium	-0.02	-0.92	0.87		0.66	-0.27	1.58	
Cyprus	-1.40	-2.36	-0.44		-1.14	-2.14	-0.14	
Czech Republic	-1.02	-1.80	-0.23		-0.90	-1.71	-0.09	
Denmark	0.53	-0.20	1.26		1.03	0.27	1.78	
France	0.74	-0.22	1.70		1.04	0.04	2.04	
Israel	0.63	-0.32	1.58		0.69	-0.29	1.68	
Italy	-0.43	-1.26	0.40		0.34	-0.52	1.21	
Netherlands	1.71	0.74	2.68		2.78	1.78	3.78	
Norway	-0.20	-1.20	0.81		0.27	-0.77	1.31	
Poland	-1.01	-2.04	0.02		-0.32	-1.40	0.75	
Switzerland	0.07	-0.79	0.93		0.07	-0.82	0.97	
Turkey	-1.04	-2.27	0.19		-1.24	-2.52	0.03	
UK	-1.02	-1.96	-0.08		-0.57	-1.55	0.40	
Sex (Ref: male)				0.08				0.30
Female	-0.05	-0.39	0.30		-0.28	-0.63	0.08	
Age at diagnosis	-0.01	-0.04	0.03	0.15	-0.004	-0.04	0.03	0.53
Diagnostic period	0.02	-0.01	0.05	0.57	-0.01	-0.04	0.03	0.33
Laterality defects (Ref: Situs solitus)				0.81				0.67
Situs Ambiguous	0.25	-0.71	1.20		0.13	-0.86	1.12	
Situs Inversus	0.14	-0.25	0.53		0.04	-0.37	0.45	
Situs Unknown	-0.41	-1.23	0.41		-0.50	-1.35	0.36	
Ultrastructural defects (Ref: ODA)				0.01				0.07
Central Complex defect	-0.11	-0.67	0.45		-0.36	-0.94	0.22	
ODA/IDA	0.67	0.19	1.14		0.41	-0.08	0.90	
Microtubular disorganisation	-0.49	-1.15	0.17		-0.47	-1.16	0.22	
Non-diagnostic	0.36	-0.20	0.91		0.10	-0.48	0.68	
BMI	0.34	0.29	0.39	<0.01	0.43	0.37	0.48	<0.01
Change of lung function over time								
Country (Ref: Germany)				<0.01				0.01
Australia	-0.03	-0.12	0.05		-0.02	-0.11	0.07	
Belgium	-0.01	-0.09	0.07		-0.07	-0.15	0.02	
Cyprus	0.05	-0.03	0.14		-0.02	-0.11	0.07	
Czech Republic	0.02	-0.05	0.10		-0.004	-0.08	0.07	
Denmark	-0.05	-0.12	0.02		-0.05	-0.12	0.02	
France	-0.10	-0.19	-0.02		-0.12	-0.21	-0.03	
Israel	-0.11	-0.20	-0.02		-0.11	-0.20	-0.01	
Italy	-0.06	-0.13	0.02		-0.08	-0.16	-0.004	

Netherlands	-0.17	-0.31	-0.03		-0.24	-0.38	-0.10	
Norway	-0.04	-0.15	0.06		-0.07	-0.19	0.04	
Poland	0.06	-0.06	0.17		-0.04	-0.16	0.09	
Switzerland	-0.02	-0.10	0.07		0.01	-0.07	0.10	
Turkey	0.01	-0.11	0.12		0.01	-0.11	0.13	
UK	0.01	-0.08	0.10		-0.01	-0.10	0.08	
Sex (ref: male)				0.11				0.20
Female	-0.03	-0.06	0.01		0.02	-0.01	0.06	
Age at diagnosis	0.003	-0.001	0.01	0.09	0.002	-0.002	0.005	0.33
Diagnostic period	-0.001	-0.004	0.002	0.50	0.002	-0.001	0.005	0.18
Laterality defects (Ref: Situs solitus)				0.99				0.87
Situs Ambiguous	0.01	-0.08	0.09		0.003	-0.09	0.09	
Situs Inversus	-0.004	-0.04	0.03		0.02	-0.02	0.05	
Situs Unknown	-0.01	-0.08	0.06		0.01	-0.07	0.08	
Ultrastructural defects (Ref: ODA)				0.04				0.18
Central Complex defect	0.03	-0.02	0.07		0.05	-0.001	0.10	
ODA/IDA	-0.05	-0.09	-0.01		-0.01	-0.05	0.04	
Microtubular disorganisation	0.01	-0.05	0.08		0.06	-0.01	0.12	
Non-diagnostic	-0.01	-0.06	0.05		-0.02	-0.08	0.04	
BMI	0.01	0.004	0.03	<0.01	0.01	0.00	0.02	0.04

[¶] Likelihood ratio test p-value indicating whether the characteristic explains differences in FEV1 or FVC within the study population. Adjusted for all variables of the full model, the full summary output is in the online supplement (Table S1).

+ The Intercept describes the FEV_1 and FVC of a reference patient 6 years, who is male, from Germany, with a BMI z-score of 0, diagnosed at birth (age = 0) in 1978, with a definite PCD diagnosis. Categorical variables describe the change from the reference category, while continuous variables describe the change from the reference patient for each unit of increase. Change of lung function over time describes the change in the trajectory of FEV_1 and FVC per year increase, based on the reference category for categorical variables and for each unit of increase for continuous variables.

FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; ODA: outer dynein arm; IDA: inner dynein arm; BMI: body mass index

Table S4. FEV_1 of patients with primary ciliary dyskinesia (PCD) from the international PCD cohort compared to Global Lung Function Initiative 2012 reference values (linear mixed effects regression, adjusting for all covariates) for single countries with more than 30 patients

N: measurements, individuals	Denmark 1459, 59				France 340, 38				Germany 664, 60				Israel 239, 41			
	Estimate	95% CI		p-val	estimate	95% CI		p-val	Estimate	95% CI		p-val	Estimate	95% CI		p-val
Intercept	0.26	-1.18	1.71		-0.98	-2.12	0.17		-6.91	-11.43	-2.39		88.5	-41.6	218	
Sex (Ref: male)				0.28				0.11				0.38				<0.01
Female	-0.28	-1.03	0.48		-0.73	-1.40	-0.06		0.56	-0.23	1.35		-0.65	-1.94	0.64	
Age at diagnosis	-0.10	-0.19	0.02	0.04	-0.01	-0.10	0.08	0.69	-0.18	-0.30	-0.06	0.02	0.23	0.02	0.44	<0.01
Diagnostic period	0.01	-0.05	0.07	0.85	0.01	-0.05	0.07	0.04	0.023	-0.07	0.39	0.02	-2.67	-6.50	1.16	0.24
Diagnostic certainty (Ref: definite)				0.23				0.70				0.46				0.02
Probable PCD	-0.08	-0.86	0.70		-	-	-		-0.49	-1.40	0.42		1.91	0.29	3.54	
Clinical diagnosis	-0.24	-2.62	2.13		0.29	-0.60	1.17		-1.47	-3.25	0.31		0.63	-0.93	2.19	
Laterality defects (Ref: situs solitus)				0.34				0.11				0.06				0.02
Situs Ambiguous	-	-	-			-	-		2.08	-0.99	5.14					
Situs Inversus	-0.80	-1.62	0.02		1.11	0.19	2.04		1.26	0.31	2.21		0.90	-0.59	2.40	
Situs Unknown	-0.09	-2.78	2.60		0.53	-0.21	1.27		-	-	-		-2.93	-5.27	-0.59	
BMI	0.48	0.38	0.57	<0.01	0.15	0.00	0.29	0.02	0.42	0.31	0.53	<0.01	0.42	0.22	0.62	<0.01
Change in FEV1 over time																
Sex (Ref: male)				0.28				0.64				0.54				0.39
Female	-0.3	-0.09	0.03		0.02	-0.07	0.11		-0.03	-0.11	0.06		-0.07	-0.21	0.08	
Age at diagnosis	0.01	0.002	0.01	0.02	-0.003	-0.01	0.01	0.56	0.02	0.002	0.03	0.04	-0.01	-0.03	0.02	0.50
Diagnostic period	-0.001	-0.01	0.004	0.57	0.01	0.001	0.02	0.04	-0.01	-0.03	0.01	0.27	0.17	-0.22	0.56	0.39
Diagnostic certainty (Ref: definite)				0.16				0.89				0.51				0.06
Probable PCD	-0.06	-0.13	0.003		-	-	-		0.06	-0.04	0.16		-0.21	-0.39	-0.03	
Clinical diagnosis	-0.08	-0.31	0.16		0.01	-0.15	0.17		0.05	-0.13	0.22		0.04	-0.17	0.25	
Laterality defects (Ref: situs solitus)				0.58				0.69				0.53				0.09
Situs Ambiguous	-	-	-		-	-	-		-0.13	-0.43	0.17					
Situs Inversus	0.02	-0.05	0.09		0.02	-0.10	0.13		-0.04	-0.13	0.06		-0.12	-0.29	0.04	
Situs Unknown	-0.08	-0.27	0.11		-0.03	-0.12	0.06		-	-	-		0.18	-0.07	0.43	
BMI	0.004	-0.02	0.03	0.72	0.03	0.001	0.06	0.05	0.03	0.002	0.05	0.05	-0.004	-0.04	0.03	0.82

Models adjusted for age at measurement as a linear term and age at measurement as quadratic term

N: measurements, individuals	Italy 163, 32				Netherlands 114, 38				Turkey 329, 49				UK 167, 37			
	Estimate	95% CI		p-val	estimate	95% CI		p-val	Estimate	95% CI		p-val	Estimate	95% CI		p-val
Intercept	0.28	-1.98	2.53		-8.26	-20.7	4.13		-6.13	-13.37	1.11		4.18	-0.52	8.88	

Sex (Ref: male)				0.58				0.04				0.60				0.81
Female	-0.30	-1.56	0.96		2.01	0.57	3.45		0.60	-0.54	1.74		-0.46	-1.94	1.01	
Age at diagnosis	-0.08	-0.20	0.04	0.15	-0.22	-0.70	0.26	0.02	-0.20	-0.41	0.02	<0.01	0.36	0.20	0.52	<0.01
Diagnostic period	-0.06	-0.15	0.02	0.23	0.28	-0.19	0.75	0.05	0.14	-0.10	0.38	0.04	-0.23	-0.38	-0.08	0.01
Diagnostic certainty (Ref: definite PCD)				<0.01				0.53				0.21				0.06
Probable PCD	0.27	-2.38	2.91		0.18	-1.46	1.83		-0.17	-1.71	1.38		0.74	-3.94	5.42	
Clinical diagnosis	-1.85	-4.78	1.09		1.55	-7.47	10.57		1.07	-0.58	2.73		7.64	2.36	12.92	
Laterality defects (Ref: situs solitus)				0.43				0.12				0.62				0.04
Situs Ambiguous	-	-	-		-0.09	-3.49	3.32		-	-	-		4.88	0.05	9.70	
Situs Inversus	0.84	-0.81	2.50		2.75	0.72	4.78		0.37	-0.67	1.41		0.68	-0.72	2.08	
Situs Unknown	-	-	-		6.78	-5.70	19.2		-	-	-		-4.34	-10.16	1.46	
BMI (continuous)	0.33	0.16	0.49	<0.01	0.32	0.01	0.64	0.05	0.28	0.12	0.44	<0.01	0.15	-0.12	0.43	<0.01
Change in FEV1 over time																
Sex (Ref: male)				0.31				0.04				0.40				0.52
Female	0.05	-0.04	0.15		-0.18	-0.34	-0.02		-0.05	-0.17	0.07		0.04	-0.07	0.14	
Age at diagnosis	0.01	0.001	0.02	0.06	0.06	-0.001	0.11	0.05	0.002	-0.03	0.03	091	-0.03	-0.05	-0.02	<0.01
Diagnostic period	0.001	-0.01	0.01	0.92	-0.06	-0.13	-0.001	0.05	-0.001	-0.03	0.03	0.99	0.02	0.01	0.04	<0.01
Diagnostic certainty (Ref: definite)				<0.01								0.12				0.03
Probable PCD	0.33	0.10	0.56		0.03	-0.20	0.25	0.97	0.09	-0.07	0.25		-0.03	-0.39	0.34	
Clinical diagnosis	0.66	0.30	1.01		0.03	-0.91	0.98		-0.10	-0.30	0.10		-0.44	-0.78	-0.09	
Laterality defects (Ref: situs solitus)				0.19				0.23				0.83				0.36
Situs Ambiguous	-	-	-		0.03	-0.38	0.44		-	-	-		-0.18	-0.48	0.11	
Situs Inversus	-0.09	-0.22	0.04		-0.23	-0.49	0.04		-0.01	-0.13	0.10		0.04	-0.07	0.14	
Situs Unknown	-	-	-		-0.86	-2.19	0.47		-	-	-		0.24	-0.26	0.74	
BMI	0.04	0.02	0.06	<0.01	0.01	-0.04	0.06	0.69	0.03	0.01	0.06	0.01	0.05	0.02	0.08	<0.01

Models adjusted for age at measurement as a linear term and age at measurement as quadratic term

Table S5 FEV_1 and FVC in patients with primary ciliary dyskinesia (PCD) from the international PCD cohort with available microbiological information compared to Global Lung Function Initiative 2012 reference values.

	FEV1				FVC			
Characteristic	**Estimate**	**95% CI**		**p-value**[¶]	**Estimate**	**95% CI**		**p-value**[¶]
Microbiology								
Any isolated pathogen	0.05	-0.26	0.36	0.07	-0.23	-0.58	0.13	0.01
Haemophilus influenzae	-0.15	-0.43	0.12	0.39	-0.28	-0.59	0.03	0.09
Moraxella catarrhalis	0.04	-0.38	0.47	0.55	0.17	-0.31	0.65	0.50
Pseudomonas aeruginosa	0.37	-0.22	0.96	0.39	0.43	-0.23	1.10	0.11
Streptococcus pneumoniae	-0.11	-0.45	0.23	0.96	-0.11	-0.50	0.28	0.67
Staphylococcus aureus	0.03	-0.37	0.42	0.28	-0.04	-0.50	0.41	0.48
Interactions with age at measurement								
Any isolated pathogen	-0.01	-0.03	0.01	0.38	0.01	-0.02	0.03	0.62
Haemophilus influenzae	0.01	-0.01	0.03	0.38	0.01	-0.01	0.04	0.19
Moraxella catarrhalis	0.0001	-0.03	0.03	1.00	-0.01	-0.04	0.03	0.62
Pseudomonas aeruginosa	-0.02	-0.06	0.02	0.29	-0.02	-0.07	0.02	0.37
Streptococcus pneumoniae	0.01	-0.02	0.03	1.00	0.01	-0.02	0.04	0.46
Staphylococcus aureus	0.003	-0.02	0.03	0.82	0.01	-0.02	0.04	0.65

[¶] Likelihood ratio test p-value indicating whether the characteristic explains differences in FEV_1 or FVC within the study population.

Table S6. Sensitivity analysis: FEV_1 of patients with primary ciliary dyskinesia (PCD) from the international PCD cohort compared to Global Lung Function Initiative 2012 reference values (linear mixed effects regression, adjusting for all covariates) excluding patients diagnosed the same year as first lung function measurement (n=356).

		FEV_1		
Variable	**Estimate**	**95% CI**		**p-value**[¶]
Intercept (Lung function at age 6 years for "reference patient") [+]	-1.10	-2.11	-0.09	
Age at measurement	-0.04	-0.13	0.05	
Country (Ref: Germany)				<0.01
Australia	-0.26	-1.30	0.77	
Belgium	-0.24	-1.09	0.61	
Cyprus	-1.05	-2.22	0.11	
Czech Republic	-1.16	-1.93	-0.40	
Denmark	0.22	-0.44	0.87	
France	-0.001	-0.84	0.84	
Greece	1.69	-1.93	5.30	
Israel	0.01	-0.87	0.89	
Italy	-0.19	-0.95	0.58	
Netherlands	1.67	0.84	2.51	
Norway	-0.40	-1.37	0.57	
Poland	-1.15	-2.04	-0.26	
Switzerland	-0.01	-0.80	0.78	
Turkey	-1.76	-2.48	-1.04	
UK	-1.24	-2.11	-0.36	
Sex (Ref: male)				0.28
Female	0.03	-0.28	0.34	
Age at diagnosis	-0.03	-0.06	0.01	0.14
Diagnostic period	0.02	-0.01	0.05	0.43
Diagnostic certainty (Ref: definite PCD diagnosis)				0.51
Probable PCD diagnosis	-0.05	-0.46	0.36	
Clinical diagnosis only	0.43	-0.24	1.10	
Laterality defects (Ref: situs solitus)				0.73
Situs Ambiguous	0.49	-0.50	1.48	
Situs Inversus	0.30	-0.06	0.66	
Situs Unknown	0.12	-0.62	0.86	
BMI	0.33	0.28	0.37	<0.01
Change of lung function over time[#]				
Country (Ref: Germany)				<0.01
Australia	-0.03	-0.12	0.06	
Belgium	0.02	-0.06	0.10	
Cyprus	0.06	-0.04	0.16	
Czech Republic	0.05	-0.02	0.13	
Denmark	-0.01	-0.07	0.05	
France	-0.03	-0.11	0.04	
Greece	-0.06	-0.39	0.28	
Israel	-0.04	-0.13	0.04	
Italy	-0.04	-0.11	0.04	
Netherlands	-0.16	-0.27	-0.05	
Norway	0.001	-0.11	0.11	
Poland	0.07	-0.03	0.17	
Switzerland	-0.01	-0.09	0.06	
Turkey	0.11	0.04	0.18	
UK	0.04	-0.05	0.12	
Sex (Ref: male)				0.20
Female	-0.02	-0.05	0.01	
Age at diagnosis	0.003	0.001	0.01	0.05

Diagnostic period	-0.001	-0.004	0.001	0.33
Diagnostic certainty (Ref: definite PCD diagnosis)				0.99
Probable PCD diagnosis	-0.002	-0.04	0.04	
Clinical diagnosis only	-0.003	-0.07	0.07	
Laterality defects (Ref: situs solitus)				0.64
Situs Ambiguous	-0.02	-0.12	0.08	
Situs Inversus	-0.02	-0.06	0.01	
Situs Unknown	-0.01	-0.08	0.06	
BMI	0.01	0.01	0.02	<0.01

FEV1: Forced expiratory volume in 1 second; BMI: body mass index ¶ Likelihood ratio test p-value indicating whether the characteristic explains differences in FEV_1 within the study population. [+]The Intercept describes the FEV_1 of a reference patient at 6 years, who is male, from Germany, with a BMI z-score of 0, diagnosed at birth (age = 0) in 1978, with a definite PCD diagnosis. Categorical variables describe the change from the reference category, while continuous variables describe the change from the reference patient for each unit of increase. * Defined as hallmark PCD ultrastructural defect identified by electron microscopy findings or biallelic PCD causing gene mutation based on the ERS PCD diagnosis guidelines [14]. # Abnormal light or high frequency video microscopy finding and/or low (≤ 77nl/min) nasal NO value. [#]Change in lung function over time are based on interaction terms between the characteristics (e.g. country, sex) and age. Change of lung function over time thus describes the change in the trajectory of FEV_1 per year increase, based on the reference category for categorical variables and for each unit of increase for continuous variables.