Online only supplementary material

METHODS

Primary ciliary dyskinesia diagnosis

The diagnostic criteria for PCD have evolved over many years [1]. Initially, diagnosis was based on the Kartagener triad [2] and transmission electron microscopy findings (EM).Then, light microscopy and, later, high frequency video microscopy (HVM) were introduced into the diagnostic algorithm. Recent recommendations include combining EM, HVM, nasal nitric oxide (nNO), and genetic testing [3], but availability of tests differs between countries [4] so not all PCD patients have been diagnosed according to current standards. Patients diagnosed years ago and patients who live in countries with limited resources are least likely to have been diagnosed according to these recommendations. The iPCD Cohort includes patients diagnosed since 1964, so we divided patients into three diagnostic subgroups based on the results of the tests available. The first subgroup included patients with definite PCD defined, based on recent guidelines of the ERS PCD Diagnostics Task Force [3], as hallmark EM findings and/or pathogenic biallelic PCD genetic mutations. The second subgroup, probable PCD, included patients with abnormal HVM findings and/or low nNO (we used a cut-off of 77nl/min [5]). The third subgroup included patients with clinical PCD diagnosis; these were patients for whom the PCD diagnostic algorithm had not yet been completed, or whose test results were negative or ambiguous. Patients in this latter group were followed up and treated as PCD at the collaborating centres based on a combination of several of the following features: situs anomalies, persistent cough, persistent rhinitis, chronic or recurrent upper or lower respiratory infections, and history of neonatal respiratory symptoms in term infants [3]. Other possible more common diseases such as cystic fibrosis and immunodeficiency were excluded.

FEV1 and FVC

We checked data quality to identify outliers and implausible values, and contacted data contributors to resolve any unclear issues. We used the Global Lung Function Initiative (GLI) reference values to calculate age, sex, ethnicity, and height-adjusted z-scores of forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) [6].

Determinants of lung function

We investigated the association of lung function with sex, age, country of residence, level of diagnostic certainty, organ laterality, BMI, and ultrastructural defect at time of lung function measurement. Despite having calculated age, height, and sex-specific z-scores, impairment of lung function might differ between male and female PCD patients. Analysis of different age groups helps to find whether PCD affects lung growth in children, or whether it accelerates lung function decline in adults. To facilitate comparison with available published cystic fibrosis (CF) data [7], we categorised patients into the same 12 age groups (6-9, 10-13, 14-17, 18-21, 22-25, 26-29, 30-33, 34-37, 38-41, 42-45, 46-49 and ≥50 years). Patients with situs inversus might have less severe disease because they are diagnosed and treated earlier, sometimes even before symptoms develop [4]. We categorised organ laterality into three groups (situs solitus totalis, situs inversus, and heterotaxia). BMI as an indicator of nutrition has been associated with lung function in many chronic respiratory diseases. We identified national growth references by contacting collaborating centres and searching the literature. For each centre, we chose one of the following methods to calculate z-scores based on national references: 1) an LMS approach using tables that contained L, M, and S parameters needed to generate exact z-scores [8]; 2) direct calculation via online national z-score or percentile growth calculators; or 3) interpolating exact z-scores from plotted percentile boundaries on growth curves. Available references for BMI were intended for use with children only. For paediatric patients aged <18 years, we calculated age- and sex-adjusted BMI z-scores based on available reference values, preferably national where they were available (the sources are listed in the online supplement, Table S1), and we defined underweight as a BMI z-score less than or equal to -1.96, and overweight as a BMI z-score ≥1.96. For patients aged ≥18 years we used the WHO international BMI classification for adults, which define underweight as BMI < 18.5 and overweight as BMI ≥ 25.0 [9]. Differences between countries could show ethnic variations, or differences in age at diagnosis or disease management. We categorised ultrastructural defects into non-diagnostic, dynein arm defects (outer and/or inner dynein arm defects), microtubular defects (central pair, tubulus disorganisation, tubular transposition and/or nexin link defect), and acilia.

Table S1. National references used for calculations of BMI z-scores

Country	Growth reference source	Year of publication
Australia	Centre for Disease Control and Prevention [10]	2000
Belgium	Flemish growth study (Roelants et al.) [11]	2009
Cyprus	Growth curves for Greek children 0-5 years (Papadimitriou et al.) [12]	2000
	Growth curves for Cypriot children 6-17 years (Savva et al.) [13]	2001
Denmark	Danish growth references (Tinggaard et al.) [14]	2014
France	French references for Height (Sempé et al.) [15]	1979
	French references for BMI (Rolland-Cachera et al.) [16]	1991
Germany	KiGGS study [17]	2006
Israel	Centre for Disease Control and Prevention [10]	2000
Italy	Centre for Disease Control and Prevention [10]	2000
Netherlands	Fifth Dutch Growth Study [18]	2009
Norway	Growth charts for Norwegian children (Júlíusson et al.) [19]	2009
Poland	Growth references (Kulaga et al.) [20]	2010
Serbia	Not available*	-
Switzerland	Swiss growth curves (Braegger et al.) [21]	2011
Turkey	Growth references for Turkish children (Neyzi et al.) [22]	2006
United Kingdom	Royal College of Paediatrics and Child Health [23,24]	1990

* No national growth references were available in Serbia, for which the WHO references are used instead. Table adapted from Goutaki et al. [25]

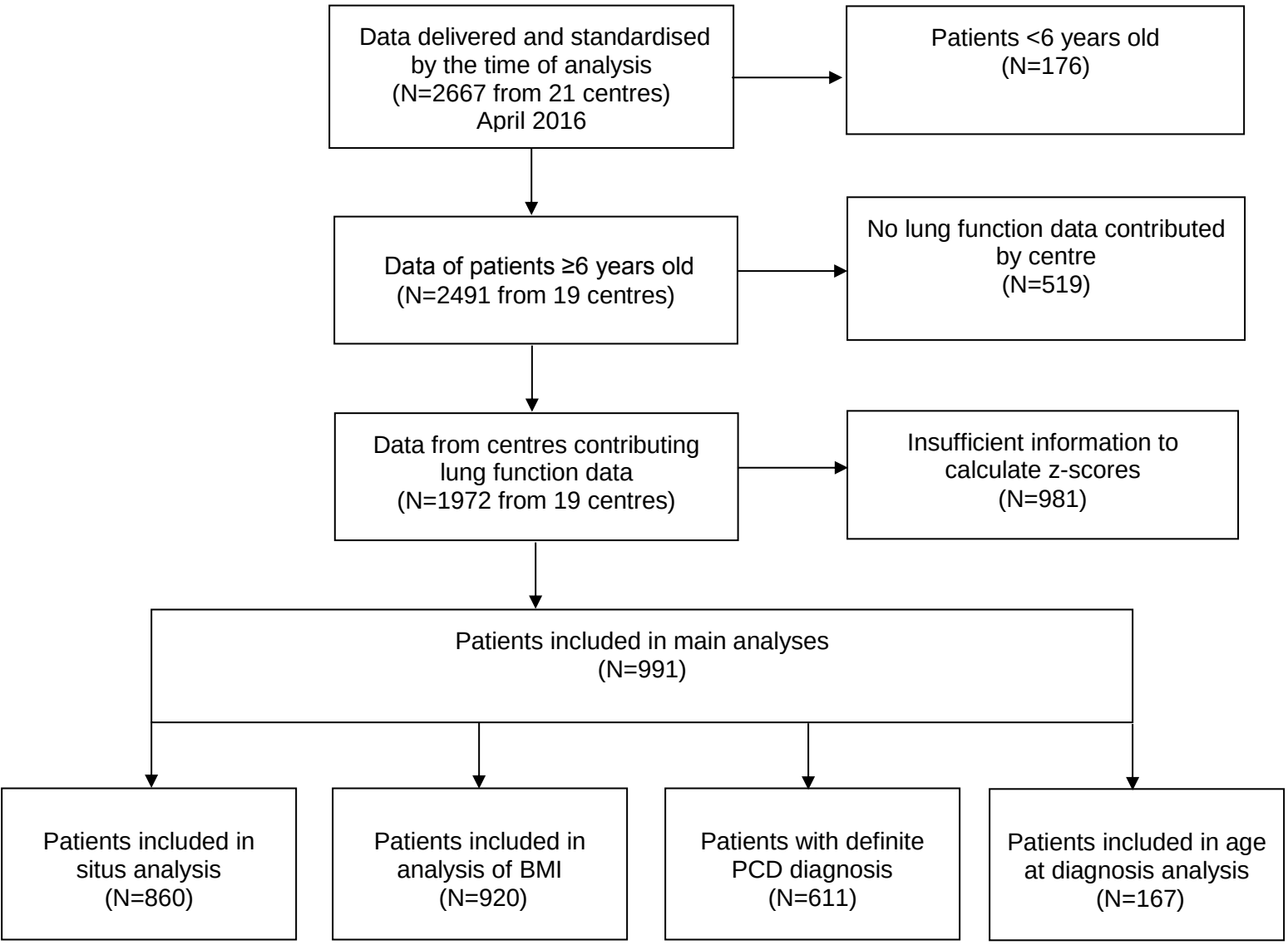

Figure S1. Flow chart showing the patients included for the different analyses performed.

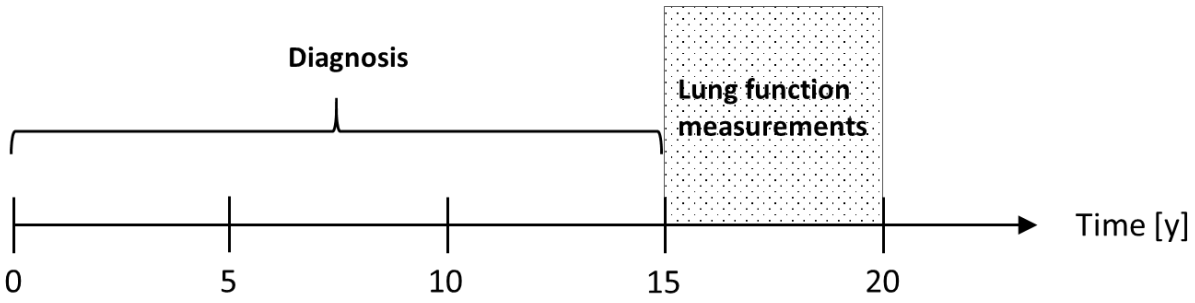

Figure S2. Study design on patient inclusion to assess the association of age at diagnosis with lung function.

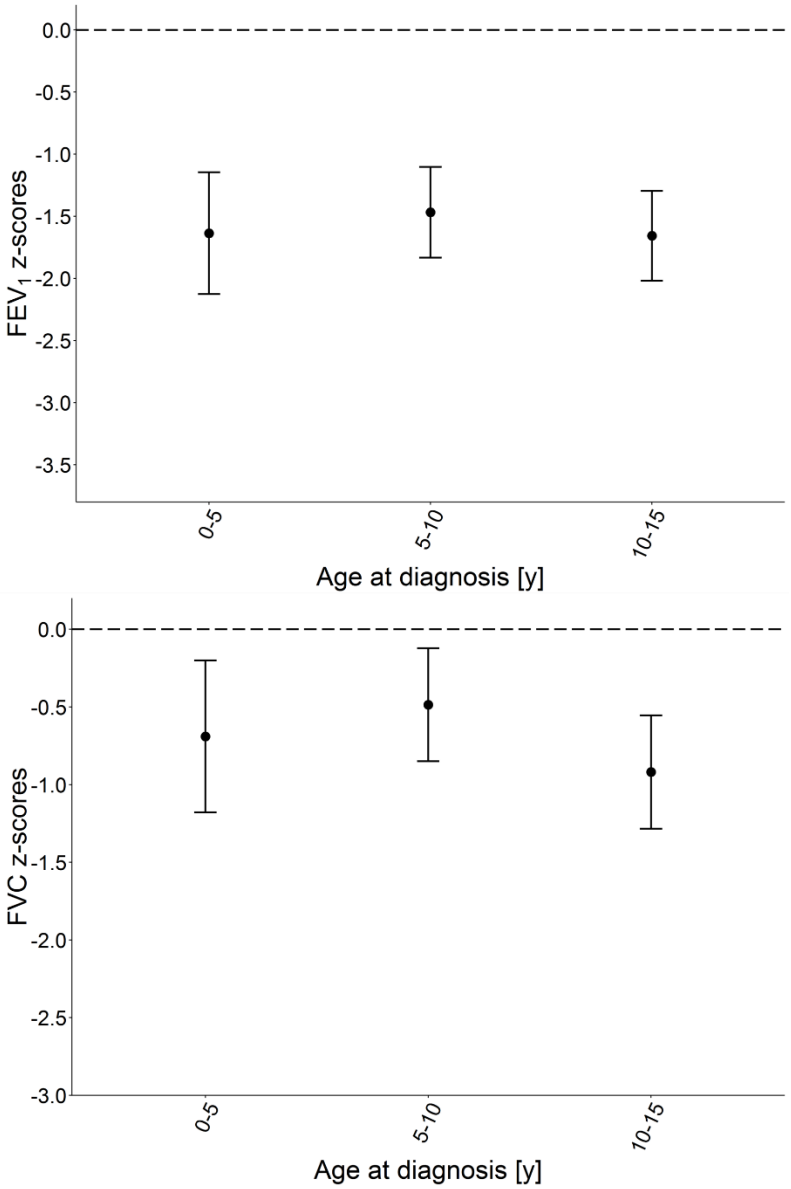

Fig S3. FEV1 and FVC in PCD patients aged 15 to 20 years by age of diagnosis compared to GLI 2012 reference values. FEV1 and FVC are presented as mean z-score (95%CI).

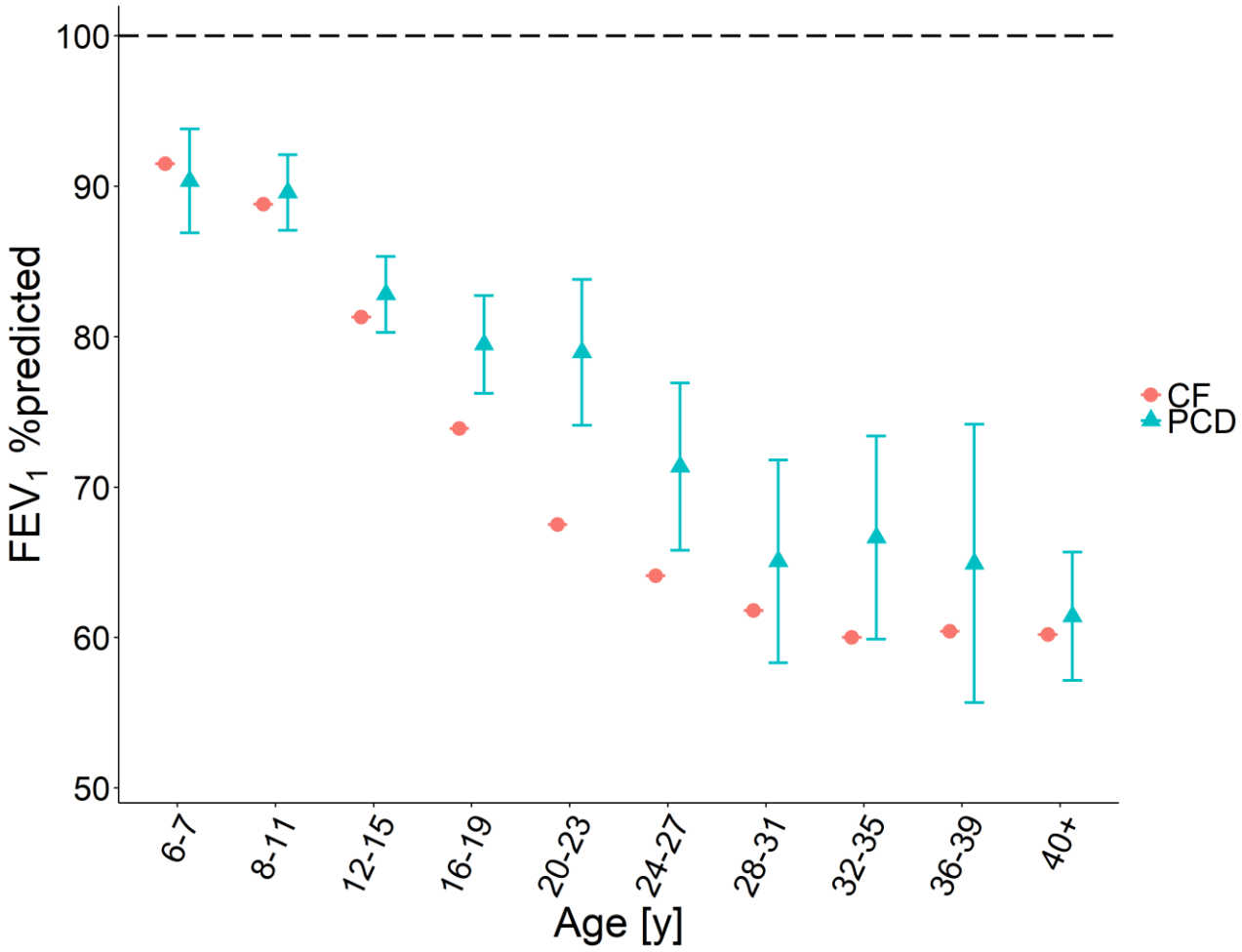

Fig S4. Association of FEV1 of PCD patients with CF patients using GLI 2012 references values. FEV1 of PCD patients are presented as mean %predicted and 95%CI, and FEV1 of CF patients are presented as mean, without adjusting for other factors. The dashed line shows the mean of the normal population.

Table S2. Characteristics of PCD patients included in this study compared to those who were excluded

Characteristic	Study Participants (n=991) n (%)	Insufficient information on lung function (n=981) n (%)	Comparison with participants p-value[¶]	No lung function data contributed (n=519) n (%)	Comparison with participants p-value[¶]
Sex			0.91		0.01
Male	487 (49)	481 (49)		290 (56)	
Female	504 (51)	491 (50)		228 (44)	
Missing	0 (0)	9 (1)		1 (0)	
Country of residence*			<0.001		<0.001
Australia	34 (3)	42 (4)		0 (0)	
Northern Europe	306 (31)	145 (15)		0 (0)	
Western Europe	392 (40)	731 (75)		0 (0)	
Eastern Europe	74 (7)	8 (1)		0 (0)	
Southern Europe	42 (4)	5 (1)		0 (0)	
Western Asia	143 (14)	50 (5)		0 (0)	
North America	0 (0)	0 (0)		418 (81)	
South America	0 (0)	0 (0)		101 (19)	
Current age[#]			<0.001		<0.001
6-9 years	15 (2)	213 (22)		44 (8)	
10-19 years	445 (45)	354 (36)		218 (42)	
20-29 years	248 (25)	146 (15)		122 (24)	
30-39 years	129 (13)	100 (10)		34 (7)	
40-49 years	64 (6)	70 (7)		43 (8)	
>50 years	90 (9)	76 (8)		57 (11)	
Missing	0 (0)	22 (2)		1 (0)	

* Based on the United Nations Statistics Division
[¶] Chi-squared tests
[#] In April 2016

Table S3. FEV_1 and FVC of PCD patients of the iPCD Cohort with available situs information compared to GLI 2012 references (N=860)

	FEV1					FVC				
Characteristic	**N**	**mean z-score**	**95% CI**		**p-value¶**	**N**	**mean z-score**	**95% CI**		**p-value¶**
Total	860	-1.52	-1.63	-1.41		853	-0.79	-0.90	-0.67	
Sex					0.10					0.51
Male	417	-1.47	-1.62	-1.32		413	-0.75	-0.90	-0.60	
Female	443	-1.56	-1.71	-1.42		440	-0.82	-0.96	-0.67	
Age group					<0.001					<0.001
6-9 years	164	-0.80	-1.04	-0.56		163	-0.29	-0.53	-0.05	
10-13 years	188	-1.05	-1.28	-0.83		187	-0.50	-0.72	-0.27	
14-17 years	184	-1.48	-1.71	-1.26		182	-0.77	-0.99	-0.54	
18-21 years	85	-1.58	-1.91	-1.25		85	-0.63	-0.96	-0.30	
22-25 years	60	-1.80	-2.19	-1.40		59	-0.89	-1.29	-0.49	
26-29 years	42	-2.29	-2.76	-1.82		41	-1.32	-1.80	-0.84	
30-33 years	27	-2.61	-3.19	-2.03		26	-1.42	-2.02	-0.83	
34-37 years	23	-2.75	-3.37	-2.12		24	-1.76	-2.38	-1.15	
38-41 years	14	-2.47	-3.28	-1.66		14	-1.25	-2.06	-0.43	
42-45 years	14	-3.24	-4.05	-2.42		14	-2.74	-3.55	-1.92	
46-49 years	20	-2.90	-3.59	-2.22		20	-1.95	-2.64	-1.26	
≥50 years	39	-2.41	-2.90	-1.92		38	-1.48	-1.97	-0.98	
Country					<0.001					<0.001
Australia	34	-1.79	-2.31	-1.27		34	-1.17	-1.69	-0.65	
Belgium	69	-1.18	-1.56	-0.81		69	-0.05	-0.42	0.33	
Cyprus	27	-1.89	-2.48	-1.30		27	-1.74	-2.34	-1.15	
Denmark	72	-1.21	-1.57	-0.86		72	-0.19	-0.55	0.16	
France	11	-1.36	-2.28	-0.45		11	-0.85	-1.78	0.07	
Germany	104	-1.21	-1.51	-0.91		99	-0.64	-0.95	-0.33	
Israel	85	-1.57	-1.89	-1.24		82	-1.09	-1.43	-0.76	
Italy	35	-1.45	-1.97	-0.93		35	-0.67	-1.20	-0.15	
Netherlands	65	-0.50	-0.88	-0.12		65	0.67	0.29	1.05	
Norway	14	-1.36	-2.17	-0.56		14	-0.79	-1.60	0.03	
Poland	74	-1.93	-2.29	-1.57		74	-0.98	-1.34	-0.61	
Serbia	7	-2.34	-3.49	-1.20		7	-2.58	-3.73	-1.42	
Switzerland	29	-1.87	-2.43	-1.31		29	-1.23	-1.79	-0.67	
Turkey	29	-1.91	-2.51	-1.31		29	-1.65	-2.25	-1.04	
UK	205	-1.85	-2.07	-1.64		206	-1.16	-1.37	-0.94	
Diagnostic certainty					0.58					0.50
Definite PCD diagnosis+	554	-1.55	-1.68	-1.42		551	-0.78	-0.91	-0.65	
Probable PCD diagnosis#	195	-1.58	-1.80	-1.35		191	-0.88	-1.11	-0.65	
Clinical diagnosis only	111	-1.27	-1.58	-0.97		111	-0.66	-0.97	-0.34	
Situs anomalies					0.67					0.35
Situs solitus totalis	499	-1.52	-1.66	-1.38		496	-0.83	-0.98	-0.69	
Situs inversus	348	-1.46	-1.63	-1.29		344	-0.77	-0.94	-0.59	
Heterotaxia	13	-1.82	-2.68	-0.96		13	-1.40	-2.29	-0.51	

Mean z-scores (95%CI) for each group after adjusting for the remaining characteristics

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

+ Defined as hallmark PCD electron microscopy findings and/or biallelic gene mutation identified based on the ERS PCD Diagnostics Task Force guidelines [26]

Abnormal light or high frequency video microscopy finding and/or low nasal NO value

Table S4. FEV_1 and FVC of PCD patients of the iPCD Cohort with available BMI information compared to GLI 2012 references (N=927)

	FEV1					FVC				
Characteristic	**N**	**mean z-score**	**95% CI**		**p-value¶**	**N**	**mean z-score**	**95% CI**		**p-value¶**
Total	927	-1.47	-1.58	-1.37		924	-0.73	-0.84	-0.62	
Sex					0.08					0.31
Male	458	-1.39	-1.52	-1.25		458	-0.68	-0.82	-0.54	
Female	469	-1.56	-1.69	-1.42		466	-0.78	-0.92	-0.65	
Age group					<0.001					<0.001
6-9 years	182	-0.76	-0.97	-0.54		181	-0.19	-0.41	0.04	
10-13 years	220	-1.03	-1.23	-0.83		217	-0.44	-0.65	-0.24	
14-17 years	207	-1.42	-1.63	-1.22		210	-0.70	-0.90	-0.49	
18-21 years	90	-1.53	-1.84	-1.22		90	-0.56	-0.88	-0.25	
22-25 years	54	-1.75	-2.16	-1.35		53	-0.85	-1.27	-0.44	
26-29 years	37	-2.21	-2.70	-1.72		36	-1.23	-1.73	-0.72	
30-33 years	25	-2.84	-3.43	-2.25		25	-1.84	-2.45	-1.24	
34-37 years	22	-2.98	-3.61	-2.36		23	-1.85	-2.48	-1.23	
38-41 years	15	-2.72	-3.48	-1.97		15	-1.53	-2.31	-0.75	
42-45 years	14	-3.43	-4.22	-2.65		15	-2.96	-3.74	-2.18	
46-49 years	20	-3.03	-3.70	-2.36		19	-2.04	-2.75	-1.34	
≥50 years	41	-2.59	-3.06	-2.11		40	-1.66	-2.15	-1.17	
Country					<0.001					<0.001
Australia	34	-1.73	-2.24	-1.23		34	-1.12	-1.63	-0.60	
Belgium	69	-1.14	-1.50	-0.78		69	-0.03	-0.40	0.34	
Cyprus	25	-1.73	-2.33	-1.13		25	-1.53	-2.14	-0.91	
Denmark	70	-1.15	-1.50	-0.80		70	-0.13	-0.49	0.23	
France	75	-1.45	-1.79	-1.10		72	-0.55	-0.91	-0.19	
Germany	123	-1.27	-1.54	-1.00		123	-0.68	-0.96	-0.41	
Israel	75	-1.57	-1.91	-1.23		74	-1.14	-1.48	-0.79	
Italy	35	-1.52	-2.02	-1.02		35	-0.72	-1.24	-0.21	
Netherlands	66	-0.52	-0.88	-0.15		66	0.58	0.21	0.95	
Norway	14	-1.30	-2.08	-0.52		14	-0.73	-1.52	0.07	
Poland	74	-1.90	-2.24	-1.55		74	-0.98	-1.34	-0.63	
Serbia	7	-2.39	-3.49	-1.29		7	-2.70	-3.83	-1.57	
Switzerland	40	-1.72	-2.18	-1.26		40	-0.97	-1.44	-0.49	
Turkey	29	-1.79	-2.35	-1.23		29	-1.56	-2.13	-0.98	
UK	191	-1.77	-1.98	-1.55		192	-1.09	-1.31	-0.87	
Diagnostic certainty					0.45					0.54
Definite PCD diagnosis[+]	574	-1.50	-1.62	-1.37		574	-0.73	-0.86	-0.60	
Probable PCD diagnosis[#]	191	-1.53	-1.74	-1.31		190	-0.82	-1.05	-0.60	
Clinical diagnosis only	162	-1.33	-1.58	-1.09		160	-0.64	-0.89	-0.38	
BMI					<0.001					<0.001
Underweight	59	-2.54	-2.92	-2.16		60	-1.94	-2.33	-1.55	
Normal	752	-1.48	-1.58	-1.37		750	-0.74	-0.85	-0.63	
Overweight	116	-0.91	-1.20	-0.62		114	-0.07	-0.37	0.23	

Mean z-scores (95%CI) for each group after adjusting for the remaining characteristics

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

[+] Defined as hallmark PCD electron microscopy findings and/or biallelic gene mutation identified based on the ERS PCD Diagnostics Task Force guidelines [26]

[#] Abnormal light or high frequency video microscopy finding and/or low nasal NO value; patients from Serbia were excluded from this analysis as there are no available national references

Table S5. FEV_1 and FVC of PCD patients of the iPCD Cohort with a definite PCD diagnosis compared to GLI 2012 references (sensitivity analysis) (N=611)

	FEV1					FVC				
Characteristic	**N**	**mean z-score**	**95% CI**		**p-value¶**	**N**	**mean z-score**	**95% CI**		**p-value¶**
Total	611	-1.54	-1.68	-1.41		606	-0.75	-0.89	-0.61	
Sex					0.07					0.17
Male	301	-1.35	-1.52	-1.17		299	-0.72	-0.90	-0.54	
Female	310	-1.58	-1.75	-1.41		309	-0.78	-0.96	-0.60	
Age group					<0.001					<0.001
6-9 years	180	-0.92	-1.16	-0.68		113	-0.25	-0.55	0.05	
10-13 years	118	-1.04	-1.31	-0.76		136	-0.45	-0.72	-0.18	
14-17 years	105	-1.48	-1.78	-1.19		130	-0.78	-1.05	-0.50	
18-21 years	51	-1.56	-1.98	-1.13		63	-0.56	-0.96	-0.17	
22-25 years	40	-1.63	-2.11	-1.14		47	-0.72	-1.19	-0.26	
26-29 years	30	-2.10	-2.65	-1.54		28	-1.13	-1.73	-0.53	
30-33 years	17	-3.07	-3.80	-2.34		17	-1.55	-2.31	-0.80	
34-37 years	14	-3.08	-3.88	-2.28		16	-2.01	-2.79	-1.23	
38-41 years	10	-2.64	-3.59	-1.68		9	-0.99	-2.04	0.05	
42-45 years	12	-3.47	-4.35	-2.60		9	-3.07	-4.12	-2.02	
46-49 years	10	-2.93	-3.89	-1.98		13	-2.43	-3.32	-1.55	
≥50 years	24	-2.18	-2.80	-1.56		27	-1.37	-1.98	-0.77	
Country					<0.001					<0.001
Australia	31	-1.86	-2.40	-1.32		31	-1.11	-1.67	-0.55	
Belgium	58	-1.21	-1.62	-0.81		58	0.00	-0.42	0.41	
Cyprus	22	-1.78	-2.42	-1.14		22	-1.64	-2.33	-0.96	
Denmark	45	-0.95	-1.41	-0.50		45	-0.21	-0.67	0.25	
France	46	-1.27	-1.72	-0.83		46	-0.50	-0.97	-0.04	
Germany	58	-1.36	-1.76	-0.97		55	-0.66	-1.08	-0.23	
Israel	50	-1.34	-1.77	-0.91		49	-0.91	-1.35	-0.46	
Italy	33	-1.25	-1.78	-0.73		33	-0.61	-1.16	-0.06	
Netherlands	35	-0.21	-0.72	0.29		35	0.90	0.38	1.43	
Norway	12	-1.44	-2.30	-0.58		12	-0.78	-1.68	0.12	
Poland	28	-2.20	-2.77	-1.63		28	-1.30	-1.89	-0.71	
Serbia	2	-1.77	-3.88	0.35		2	-2.41	-4.61	-0.21	
Switzerland	24	-1.48	-2.11	-0.86		24	-1.05	-1.69	-0.42	
Turkey	7	-2.31	-3.45	-1.18		7	-2.28	-3.45	-1.10	
UK	160	-1.86	-2.11	-1.61		161	-1.19	-1.44	-0.94	

Mean z-scores (95%CI) for each group after adjusting for the remaining characteristics

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

+ Defined as hallmark PCD electron microscopy findings and/or biallelic gene mutation identified based on the ERS PCD Diagnostics Task Force guidelines [26]

Abnormal light or high frequency video microscopy finding and/or low nasal NO value

Table S6. FEV_1 and FVC of PCD patients of the iPCD Cohort using the latest available measurement instead of the earliest compared to GLI 2012 references (sensitivity analysis) (N=991)

	FEV1					FVC				
Characteristic	**N**	**mean z-score**	**95% CI**		**p-value¶**	**N**	**mean z-score**	**95% CI**		**p-value¶**
Total	991	-1.53	-1.63	-1.42		981	-0.77	-0.88	-0.67	
Sex					0.11					0.26
Male	487	-1.45	-1.59	-1.31		483	-0.71	-0.85	-0.56	
Female	504	-1.61	-1.74	-1.47		498	-0.83	-0.97	-0.68	
Age group					<0.001					<0.001
6-9 years	185	-0.80	-1.03	-0.57		187	-0.25	-0.48	-0.01	
10-13 years	237	-1.12	-1.32	-0.92		232	-0.53	-0.74	-0.31	
14-17 years	204	-1.55	-1.77	-1.33		200	-0.80	-1.02	-0.57	
18-21 years	107	-1.54	-1.84	-1.25		107	-0.64	-0.95	-0.33	
22-25 years	59	-1.68	-2.09	-1.28		57	-0.58	-1.00	-0.15	
26-29 years	45	-2.24	-2.70	-1.77		44	-1.20	-1.69	-0.71	
30-33 years	31	-2.65	-3.21	-2.09		32	-1.68	-2.25	-1.11	
34-37 years	27	-2.82	-3.42	-2.23		26	-1.74	-2.36	-1.11	
38-41 years	15	-2.56	-3.36	-1.76		15	-1.31	-2.14	-0.49	
42-45 years	20	-3.15	-3.85	-2.46		20	-2.54	-3.26	-1.83	
46-49 years	20	-3.07	-3.77	-2.37		21	-2.24	-2.95	-1.53	
≥50 years	41	-2.39	-2.88	-1.90		40	-1.38	-1.89	-0.87	
Country					<0.001					<0.001
Australia	34	-1.83	-2.36	-1.30		34	-0.99	-1.54	-0.44	
Belgium	69	-1.18	-1.56	-0.81		69	-0.07	-0.46	0.32	
Cyprus	27	-1.67	-2.28	-1.07		27	-1.62	-2.24	-0.99	
Denmark	74	-1.29	-1.65	-0.93		74	-0.21	-0.59	0.16	
France	75	-1.44	-1.80	-1.07		72	-0.61	-1.00	-0.23	
Germany	142	-1.43	-1.69	-1.16		137	-0.82	-1.10	-0.55	
Israel	87	-1.58	-1.91	-1.25		84	-1.10	-1.45	-0.75	
Italy	35	-1.46	-1.99	-0.94		35	-0.63	-1.17	-0.08	
Netherlands	66	-0.62	-1.00	-0.24		66	0.54	0.14	0.93	
Norway	14	-1.21	-2.03	-0.39		14	-0.78	-1.63	0.07	
Poland	74	-1.89	-2.26	-1.53		74	-0.96	-1.34	-0.58	
Serbia	7	-2.08	-3.25	-0.92		7	-2.35	-3.56	-1.14	
Switzerland	40	-1.61	-2.10	-1.12		40	-0.77	-1.27	-0.26	
Turkey	29	-1.75	-2.34	-1.16		29	-1.51	-2.12	-0.89	
UK	218	-1.85	-2.06	-1.64		219	-1.13	-1.35	-0.91	
Diagnostic certainty					0.71					0.78
Definite PCD diagnosis+	611	-1.55	-1.68	-1.42		608	-0.77	-0.90	-0.63	
Probable PCD diagnosis#	207	-1.54	-1.76	-1.32		203	-0.83	-1.06	-0.60	
Clinical diagnosis only	173	-1.43	-1.68	-1.18		170	-0.70	-0.97	-0.44	

Mean z-scores (95%CI) for each group after adjusting for the remaining characteristics

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

+ Defined as hallmark PCD electron microscopy findings and/or biallelic gene mutation identified based on the ERS PCD Diagnostics Task Force guidelines [26]

Abnormal light or high frequency video microscopy finding and/or low nasal NO value

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