



## Early View

Original article

# Lung function in patients with Primary Ciliary Dyskinesia: an iPCD Cohort study

Florian S Halbeisen, Myrofora Goutaki, Ben D Spycher, Israel Amirav, Laura Behan, Mieke Boon, Claire Hogg, Carmen Casaulta, Suzanne Crowley, Eric G Haarman, Bulent Karadag, Cordula Koerner-Rettberg, Michael R Loebinger, Henryk Mazurek, Lucy Morgan, Kim G Nielsen, Heymut Omran, Francesca Santamaria, Nicolaus Schwerk, Guillaume Thouvenin, Panayiotis Yiallourous, Jane S Lucas, Philipp Latzin, Claudia E Kuehni

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# Lung function in patients with Primary Ciliary Dyskinesia: an iPCD Cohort study

Halbeisen Florian S<sup>1</sup>, Goutaki Myrofora<sup>1-2</sup>, Spycher Ben D<sup>1-2</sup>, Amirav Israel<sup>3-5</sup>, Behan Laura<sup>6-7</sup>, Boon Mieke<sup>8</sup>, Hogg Claire<sup>9</sup>, Casaulta Carmen<sup>2,10</sup>, Crowley Suzanne<sup>11</sup>, Haarman Eric G<sup>12</sup>, Karadag Bulent<sup>13</sup>, Koerner-Rettberg Cordula<sup>14</sup>, Loebinger Michael R<sup>15</sup>, Mazurek Henryk<sup>16</sup>, Morgan Lucy<sup>17</sup>, Nielsen Kim G<sup>18</sup>, Omran Heymut<sup>19</sup>, Santamaria Francesca<sup>20</sup>, Schwerk Nicolaus<sup>21</sup>, Thouvenin Guillaume<sup>22-24</sup>, Yiallourous Panayiotis<sup>25</sup>, Lucas Jane S<sup>6</sup>, Latzin Philipp<sup>2</sup>, Kuehni Claudia E<sup>1-2</sup>

## Corresponding author

Claudia Kuehni

Finkenhübelweg 11, 3012 Bern, Switzerland

+41 31 631 35 07 claudia.kuehni@ispm.unibe.ch

## Author affiliations:

1. Institute of Social and Preventive Medicine, University of Bern, Switzerland
2. Paediatric Respiratory Medicine, Children's University Hospital of Bern, University of Bern, Switzerland
3. on behalf of the PCD Israeli Consortium
4. Department of Pediatrics, Faculty of Medicine, Bar Ilan University, Israel
5. Department of Pediatrics, University of Medicine, Edmonton AB, Canada
6. Primary Ciliary Dyskinesia Centre, NIHR Respiratory Biomedical Research Centre, University of Southampton, UK
7. School of Applied Psychology, University College Cork, Ireland
8. Department of Paediatrics, University Hospital Gasthuisberg, Leuven, Belgium
9. Department of Paediatrics, Primary Ciliary Dyskinesia Centre, Royal Brompton and Harefield Foundation Trust, London, UK
10. on behalf of the Swiss PCD Group
11. Unit for Paediatric Heart, Lung, Allergic Diseases, Rikshospitalet, Oslo, Norway
12. Department of Pediatric Pulmonology, VU University Medical Center, Amsterdam, The Netherlands
13. Department of Pediatric Pulmonology, Marmara University, School of Medicine, Istanbul, Turkey
14. Department of Paediatric Pneumology, University Children's Hospital of Ruhr University Bochum, Germany
15. Host Defence Unit, Royal Brompton and Harefield NHS Foundation Trust, London, UK
16. Department of Pneumology and Cystic Fibrosis, Institute of Tuberculosis and Lung Disorders, ul.Prof.Rudnika 3b, 34-700 Rabka - Zdrój, Poland
17. Department of Respiratory Medicine, Concord Hospital Clinical School, University of Sydney, Australia
18. Danish PCD Centre Copenhagen, Paediatric Pulmonary Service, Copenhagen University Hospital, Denmark
19. Dept of General Paediatrics and Adolescent Medicine, University Hospital Muenster, Muenster, Germany
20. Department of Translational Medical Sciences, Federico II University, Napoli, Italy
21. Clinic for paediatric pulmonology, allergiology and neonatology, Hannover Medical School, Germany
22. on behalf of the French Reference Centre for Rare Lung Diseases
23. Paediatric Pulmonary Department, Trousseau Hospital APHP, Sorbonne Universities and Pierre et Marie Curie University, Paris, France
24. INSERM U938-CRSA, Paris, France
25. Medical School, University of Cyprus, Nicosia, Cyprus

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**Author Contributions:**

CE Kuehni, FS Halbeisen, M Goutaki and P Latzin developed the concept and designed the study. FS Halbeisen and M Goutaki cleaned and standardised the data. FS Halbeisen performed the statistical analyses. All other authors participated in discussions for the development of the study and contributed data. CE Kuehni, FS Halbeisen, M Goutaki drafted the manuscript. All authors contributed to iterations and approved the final version. CE Kuehni and FS Halbeisen take final responsibility for the contents.

## Abstract

Primary ciliary dyskinesia (PCD) has been considered to be relatively mild disease, especially compared to cystic fibrosis (CF), but studies on lung function in PCD patients have been few and small.

This study compared lung function from spirometry of PCD patients to normal reference values and to published data from CF. We calculated z-scores and percentage of predicted values for FEV<sub>1</sub> and FVC using the Global Lung Function Initiative 2012 for 991 patients from the international PCD (iPCD) Cohort. We then assessed associations with age, sex, country, diagnostic certainty, organ laterality, body mass index and age at diagnosis in linear regression models. Lung function in PCD patients was reduced compared to reference values in both sexes and all age groups. Children aged 6-9 years had the smallest impairment (FEV<sub>1</sub> z-score -0.84 [-1.03 to -0.65], FVC z-score -0.31 [-0.51 to -0.11]). Compared to CF patients, FEV<sub>1</sub> was similarly reduced in children (age 6-9 years PCD, 91% [88–93%]; CF, 90% [88–91%]), but less impaired in young adults (age 18-21 years PCD, 79% [76–82%]; CF, 66% [65–68%]). The results suggest that PCD affects lung function from early in life, which emphasizes the importance of early, standardised care for all patients.

**Keywords:** Primary Ciliary Dyskinesia, lung function, retrospective cohort, epidemiology, orphan diseases

## INTRODUCTION

Primary ciliary dyskinesia (PCD) is a multiorgan disease which is genetically and clinically heterogeneous [1,2]. PCD affects approximately 1:10,000 people, and it is often underdiagnosed or diagnosed late [3,4]. Due to abnormal ciliary function in PCD, mucus is not properly cleared from the airways [5], resulting in chronic lung disease. For many years, PCD was considered a relatively mild disease [6], particularly when compared to cystic fibrosis (CF).

Findings on lung function of PCD patients in previous studies are inconsistent. Children with PCD from six North American centres were found to have normal spirometric indices, with a median forced expiratory volume in the first second (FEV<sub>1</sub>) of 89% predicted [7]. In contrast, a Belgian study reported that 112 patients with PCD already had abnormal FEV<sub>1</sub> and forced vital capacity (FVC) from the age of five [8]. Recent studies, particularly in adults, have reported considerable heterogeneity among patients [9-11]. A recent systematic review of 24 studies [12] found that FEV<sub>1</sub> of patients with PCD ranged from 44 to 69% predicted. Most studies were small, with an average of 40 patients per study. While risk factors for lung function impairment have been studied in many respiratory diseases, this has not been done for PCD.

Using data from the international PCD (iPCD) Cohort [13], we assessed lung function in patients with PCD and compared it to Global Lung Function Initiative (GLI) 2012 reference values [14], and to published lung function data of patients with CF [15]. We investigated possible determinants of lung function including sex, age, situs anomalies, body mass index (BMI), country of residence, ultrastructural defect and level of diagnostic certainty. We also assessed whether age at diagnosis in paediatric patients is associated with lung function later in life.

## **METHODS**

### **Study population and study design**

The iPCD Cohort is a large, retrospective international cohort initiated during the EU FP7 project Better Experimental Screening and Treatment for Primary Ciliary Dyskinesia (BESTCILIA) and further developed through COST-Action network BEAT-PCD [16]. It includes international information on diagnostic test results, clinical symptoms, growth, lung function, and treatment for over 3200 patients [13]. For this study, we included all patients whose datasets had been delivered, cleaned, and standardised by the time of analysis (April 2016), and for whom, we had information on FEV<sub>1</sub> and FVC. Participating centres were requested to only deliver lung function data of clinical stable patients from scheduled follow-up visits. Principal investigators were responsible for obtaining ethics approval and informed consent in their countries to contribute observational, anonymised data.

### **PCD diagnosis**

PCD diagnostics remains challenging and has evolved over the years [17]. Recent guidelines recommend a combination of tests [18], but test availability differs between countries [19]. In the iPCD Cohort, we divided patients into three subgroups based on diagnostic tests. The first subgroup includes patients with definite PCD defined, according to recent guidelines of the ERS PCD Diagnostics Task Force [18], as patients with a clinical phenotype consistent with PCD and a hallmark transmission electron microscopy (TEM) finding, and/or pathogenic biallelic PCD genetic mutations. The second subgroup, probable PCD, includes patients with a clinical phenotype consistent with PCD and abnormal high-speed video microscopy findings and/or low nasal nitric oxide and a clinical phenotype consistent with PCD. The third subgroup includes patients with clinical phenotypes consistent with PCD diagnosis in whom other possible diagnoses such as CF were excluded. In most of these patients the diagnostic algorithm was not complete due to test unavailability (e.g. genetic testing was not available for most centres). The online supplement describes details of diagnosis.

### **Lung function measurements**

We calculated FEV<sub>1</sub> and FVC z-scores adjusted for age, sex, height, and ethnicity, and %predicted values using the GLI 2012 reference values [14]. We excluded data from children who were younger than 6 years to ensure better measurement quality and comparability with the published CF data [15]. We included one lung function measurement per patient in the

analysis. For patients with multiple measurements, we used the measurement recorded at the youngest age.

### **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. Details on how we categorised the selected variables and why we chose them are available in the online supplement.

### **Comparison to CF patients**

To compare with CF patients, we used recently published data of 5904 patients with CF from the United Kingdom [15], which described %predicted values for FEV<sub>1</sub> and FVC, instead of z-scores. Thus we analysed our PCD data in the same way to allow for a direct comparison. For this analysis, we stratified the data by age without further adjustment.

### **Statistical analysis**

We compared included patients with those who were excluded due to the absence of lung function measurements using chi-square tests. We compared FEV<sub>1</sub> and FVC to the GLI reference values, and investigated potential determinants of lung function including sex, age, country, and diagnostic certainty using multivariable linear regression models with z-scores as dependent variable. We tested for differences in FEV<sub>1</sub> and FVC between patient groups by performing likelihood ratio (LR) tests. We coded categorical predictor variables included in regression models using weighted effect coding. Estimated parameters for a given category thus represent mean z-score differences from the population mean [20,21]. In separate regression models including patients with available data and adjusting for the same variables, we assessed the association between BMI, organ laterality and ultrastructural defect with FEV<sub>1</sub> and FVC. In a separate model applied to our paediatric population, we assessed whether age at diagnosis influenced lung function later in life. We received date of diagnosis from the centres or calculated it from the dates of diagnostic test results. In patients without positive diagnostic test results, we defined date of clinical diagnosis as the date of the first clinical follow up. For this analysis, we only included children that had lung function measurements available after diagnosis (N=167) to ensure that they were already under PCD management at lung function measurement. We included all patients diagnosed with PCD between birth and the age of 15 years who had at least one available lung function measurement between the ages 15 and 20

years (Figure S2). We categorised age at diagnosis in 3 groups: 0-5 (N=36), 5-10 (N=65), and 10-15 (N=65) years. We performed two sensitivity analyses to test the robustness of findings, the first by including only patients with definite PCD diagnosis [18], and the second by including the latest recorded lung function measurement for patients with multiple recorded measurements, instead of the earliest. We used STATA 14.1 and R 3.1.2 for all analyses.

## **RESULTS**

### **Population characteristics**

Twenty-one centres had delivered cleaned and standardised data from 2667 patients by the time of analysis (April 2016). After exclusion of patients aged younger than 6 years and those with no lung function data or information insufficient to calculate z-scores, we included 991 patients in the main analysis (figure S1). Characteristics of the main study population are given in table 1, while table S2 compares included and excluded patients.

In total, 62% of included patients were designated as definite PCD, 21% as “probable” PCD, and 17% as having only a clinical diagnosis (Table 1). Most patients had been diagnosed during childhood. Included patients differed from those excluded because of insufficient data to calculate lung function z-scores by age and country of residence, and from those excluded due to the lack of lung function data by sex and country of residence (Table S2).

### **FEV<sub>1</sub> and FVC in patients with PCD**

Mean FEV<sub>1</sub> and mean FVC were lower than the mean reference values in all age groups. Among all patients, 46% had an FEV<sub>1</sub> z-score below the lower limit of normal (LLN) of -1.645 and 28% had an FVC z-score below the LLN. Impairment differed between age groups (table 2, figure 1). Children aged 6-9 years had the best lung function and adults the worst. Results differed between countries. PCD patients had lower FEV<sub>1</sub> z-scores than reference data in all countries and lower FVC z-scores in most countries (Table 2, Figure 2), but patients in Belgium, France, Italy, and the Netherlands had on average better FVC z-scores than rest of the study population and were comparable to the GLI reference values. Female patients had lower FEV<sub>1</sub> z-scores than male patients (Table 2, Figure 3), but their FVC was comparable. FEV<sub>1</sub> and FVC z-scores did not differ by levels of diagnostic certainty, and there was no evidence of association with organ laterality (Figure 3 and Table S3). BMI was positively associated with FEV<sub>1</sub> and FVC: patients who were underweight had worse lung function than normal and

overweight patients (Figure 3 and Table S4). FEV<sub>1</sub> z-scores differed between ultrastructural defect groups, patients with a micro tubular defect had worse lung function than patients with a non-diagnostic TEM and patients with outer or inner dynein arm defects (Table 3). Sensitivity analyses that included only patients with a definite PCD diagnosis (611 patients) had similar results for FEV<sub>1</sub> and FVC to the original models (Tables 2 and S5). When we included the latest recorded lung function measurement for patients with multiple available values instead of the earliest available, results were similar to the original models (Tables 2 and S6).

Age at diagnosis was not significantly associated with lung function in 167 patients aged 15-20 years. Among them, the children diagnosed between the age of 5-10 years had better lung function compared to those diagnosed at 10-15 years, differences however were small and not statistically significant (Figure S3).

### **Lung function in patients with PCD compared to patients with cystic fibrosis**

Both PCD and CF patients had impaired spirometric indices (Figure 4). Average FEV<sub>1</sub> and FVC values of children with PCD who were under 17 were low and similar to children with CF. During adolescence and early adulthood measurements began to diverge and older patients with PCD had better lung function than CF patients. Though differences in FEV<sub>1</sub> and FVC persisted between PCD and CF patients, after the age of 30, the differences narrowed.

## **DISCUSSION**

This multinational study found that lung function of patients with PCD was considerably lower than reference values. All age groups, including young children and patients from most countries had reduced FEV<sub>1</sub> and FVC z-scores. Female sex, underweight and type of ultrastructural defect were predictors of worse lung function. Results were consistent in all diagnostic and organ laterality subgroups. In children and adolescents, lung function of patients with PCD was similar as for CF patients. Our data therefore refute the traditionally-held assumption that PCD is a relatively mild disease.

This is the largest multi-centre study on lung function in patients with PCD. The large study population enabled us to study differences in FEV<sub>1</sub> and FVC between males and females, age groups, countries, and levels of diagnostic certainty. A potential limitation of our study is that the iPCD Cohort includes mainly patients from centres with developed diagnostic facilities.

Therefore smaller centres and some countries are underrepresented. Also, we had no data on infection status at time of measurement, such as chronic colonisation with *Pseudomonas*. In our

analysis we only included stable patients measured at scheduled follow-up visits. Only a prospective study could investigate this association, because surveillance of infections varies between countries and centres. Centres which routinely assess microbiology are more likely to detect pathogens than centres, which check patients when they are unwell. A limitation of the comparison with CF patients was that CF patients came from the UK only, and their lung function was compared using Wang-Hankison reference values; while we used GLI references for the PCD patients. However, differences between the two references are minimal [15,22]. In a sensitivity analysis we compared our PCD population to FEV<sub>1</sub> %predicted values based on GLI reference published in the 2016 annual data report of UK CF Registry and found similar results (Figure S4).

Previous studies examining lung function in patients with PCD included rather small selected patient groups from single centres and have yielded inconsistent results [12]. Our findings strongly suggest that lung function in patients with PCD is already reduced early in life. Different mechanisms could contribute, including reversible causes such as temporary atelectasis and mucus plugging [23], and irreversible damage such as lung remodelling after recurrent severe infections during the period of lung growth [24]. Our data also suggest that lung function in adulthood remains impaired. Some recent studies are in line with our findings. A study of 118 adult patients from the UK [11] and a multi-centre study including 158 children and adults from UK, Italy and Denmark [25] both reported reduced FEV<sub>1</sub> and FVC, in patients with PCD. Lung function in 168 patients from Belgium was already reduced at the age of 5 years, but there was no evidence of a difference in FEV<sub>1</sub> and FVC z-scores between age groups [8]. The wide variation between different countries, which we found, could reflect variations in genotype, in age at diagnosis [4], in management [26] or in appropriateness of the GLI reference values for the different countries.

We found that females had a poorer lung function than males (FEV<sub>1</sub> z-scores females -1.57, males -1.36). Although other studies have reported similar sex differences in PCD [9,27] and CF [28], the processes that affect lung function particularly in women are not well understood. It could reflect treatment variation, differences in therapy adherence, or anatomical, hormonal, or cultural causes. The female sex hormone progesterone is known to inhibit the function of the mucociliary apparatus and could contribute to the sex disparity [29].

We found also a strong association between lung function and BMI, thus confirming previous results from an overlapping dataset [30]. Data on BMI and lung function in PCD patients from other studies are inconsistent. The multi-centre study of 158 children found no correlation

between BMI and FEV<sub>1</sub> z-scores [25], while a study of 34 patients from Israel reported a borderline correlation between FEV<sub>1</sub> and BMI in patients with PCD [31]. It has repeatedly been shown that nutritional input can influence outcomes in chronic respiratory diseases [32]. Reduced BMI could be the result of increased energy spending because of an increased respiratory effort, or nutritional intake could lead to both lower BMI and poor lung function [33]. Lastly, purulent lung disease can negatively affect appetite and nutrition status [34]. Information on the direction of association, i.e. whether BMI influences lung function or lung function influences BMI, can only be taken from longitudinal studies with repeated measurements of both parameters. However, as intensive nutritional input from an early age has contributed to reduced mortality in CF patients in recent years [35,36] it should also be considered in PCD treatment regimens.

We found that patients with microtubular ultrastructural defects had a lower FEV<sub>1</sub> compared to the other patients. Our findings are in line with other recent studies, where patients with microtubular defects had worse lung function measured with spirometry or breath wash-out techniques, than patients with outer and inner dynein arm defects [7,11,37]. The mechanisms leading to differences in lung function based on the underlining ultrastructural defect are not understood. The findings however show a possible link between the genotype and ultrastructural phenotype with the clinical manifestations, possible due to differences in mechanics of impaired cilia movement. Adequate diagnostic evaluation could provide important information to understand severity and prognosis in PCD.

Studies have reported contradictory results about associations between age at diagnosis and lung function of PCD patients. Some studies reported that regular treatment can maintain lung function [25,38,39], and early diagnosis may prevent progression of lung disease [27]. However, other studies reported no association between age at diagnosis and decline in lung function [10,11]. We did not see evidence that early diagnosis is associated with better lung function in adolescents. An explanation, other than the relatively small subgroup sample, could be that patients with milder disease and thus with better lung function are diagnosed later in life than patients with more severe disease. Another possibility is that our studied differences in age of diagnosis might not have been large enough to have a measurable effect on spirometry. Longitudinal studies with more sensitive outcome measures will be necessary to shed further light on the importance of early diagnosis and disease management in patients with PCD.

Comparisons of lung function between PCD and CF are rare and the results have been unclear. Some studies concluded that FEV<sub>1</sub> was similar in PCD and CF patients [31,40,41], while

another one reported that it was lower in PCD children compared to pancreatic sufficient and insufficient CF children [42]. Yet another study found that children with PCD had better FVC but similar FEV<sub>1</sub> than children with CF [43]. But all these studies had low numbers and might not be representative of the average patient with PCD. Our findings from a large multinational dataset suggest that lung function in PCD patients is comparable to that of CF patients in childhood, but better in young adulthood. This may suggest that patients with CF have a worse disease course than patients with PCD because they have a more aggressive lung disease. Many of the younger CF patients might have been diagnosed via newborn screening, before they developed respiratory symptoms, while older CF patients have been diagnosed later, after initial lung damage has occurred. Patients with PCD in our study have all been diagnosed late, sometimes years or decades after the presentation of symptoms [4,11]. This could explain the similar lung function for CF and PCD patients early in life despite a more severe disease course in CF. It could also be that children with PCD are treated less effectively early in life than those with CF due to the lack of evidence-based treatment recommendations. But it also could be that patients already diagnosed with PCD in childhood have a worse disease course and thus lower lung function than patients diagnosed later in life. The decline of lung function by age was steeper in young adults with CF, and seemed to plateau in middle-aged patients in both diseases. This stabilization of impaired lung function in middle age and older patients might be an effect of mortality or lung transplantation; the surviving patients could be those with a less severe disease course. Unfortunately, there are few data on mortality in patients with PCD [24]. Longitudinal data would allow the evaluation of changes in lung function over time and the identification of predictors of poor lung function later in life. This could assist finding strategies to delay lung function impairment and disease progression.

In conclusion, although PCD has been considered a relatively mild disease, this study suggest that it affects lung function from an early age similarly to CF. This and the significant variation in PCD across countries emphasise the importance of early, multidisciplinary, standardised care and evidence-based treatments for all patients with PCD.

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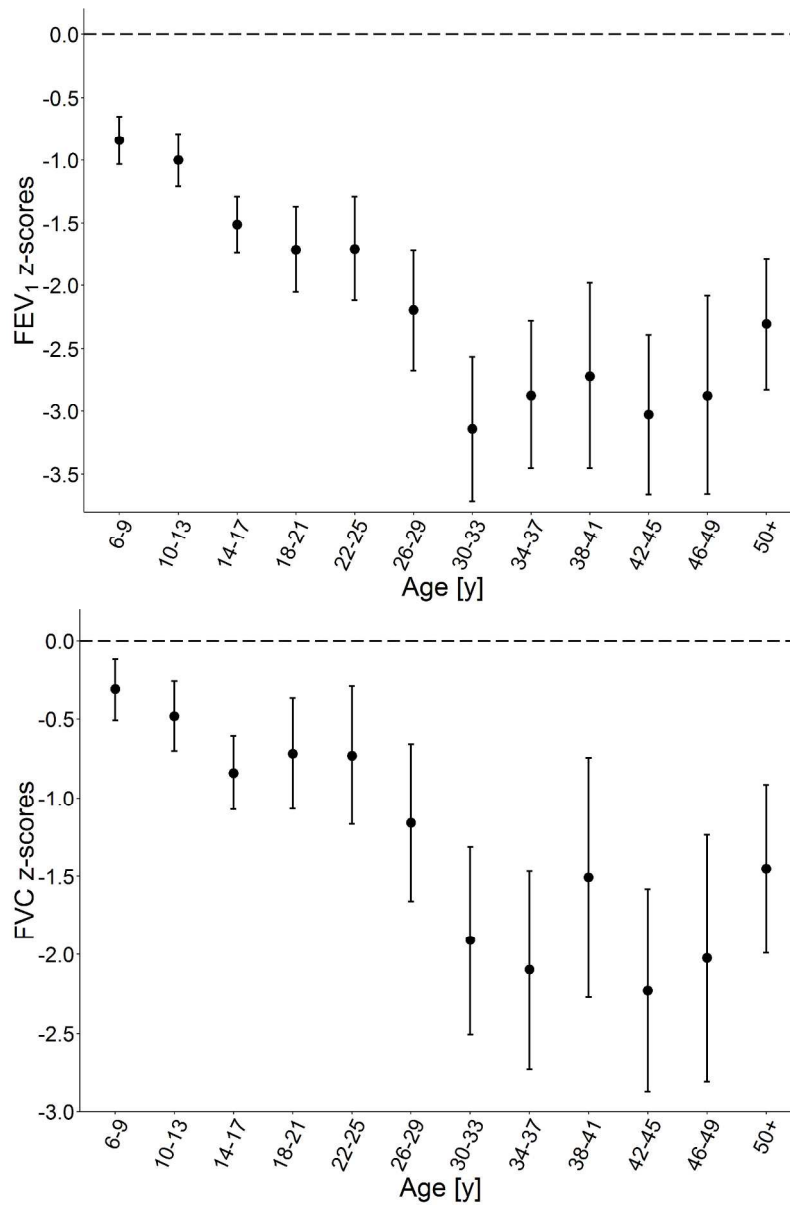
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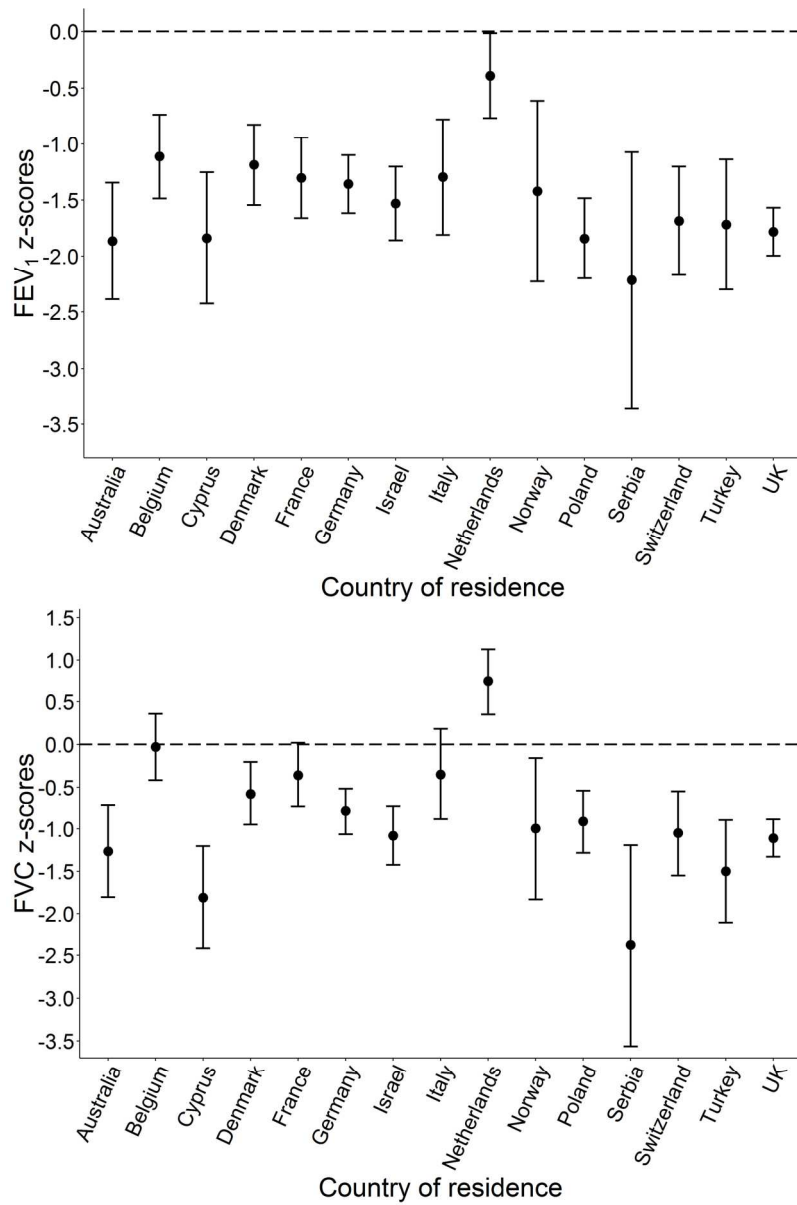
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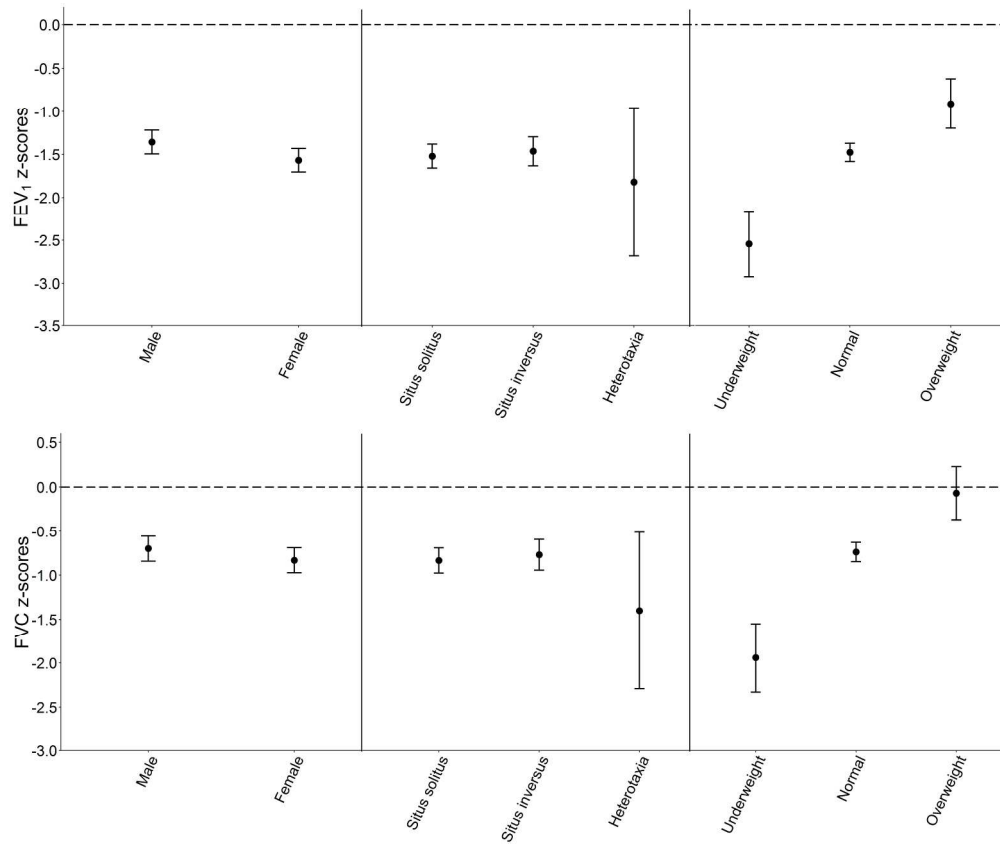
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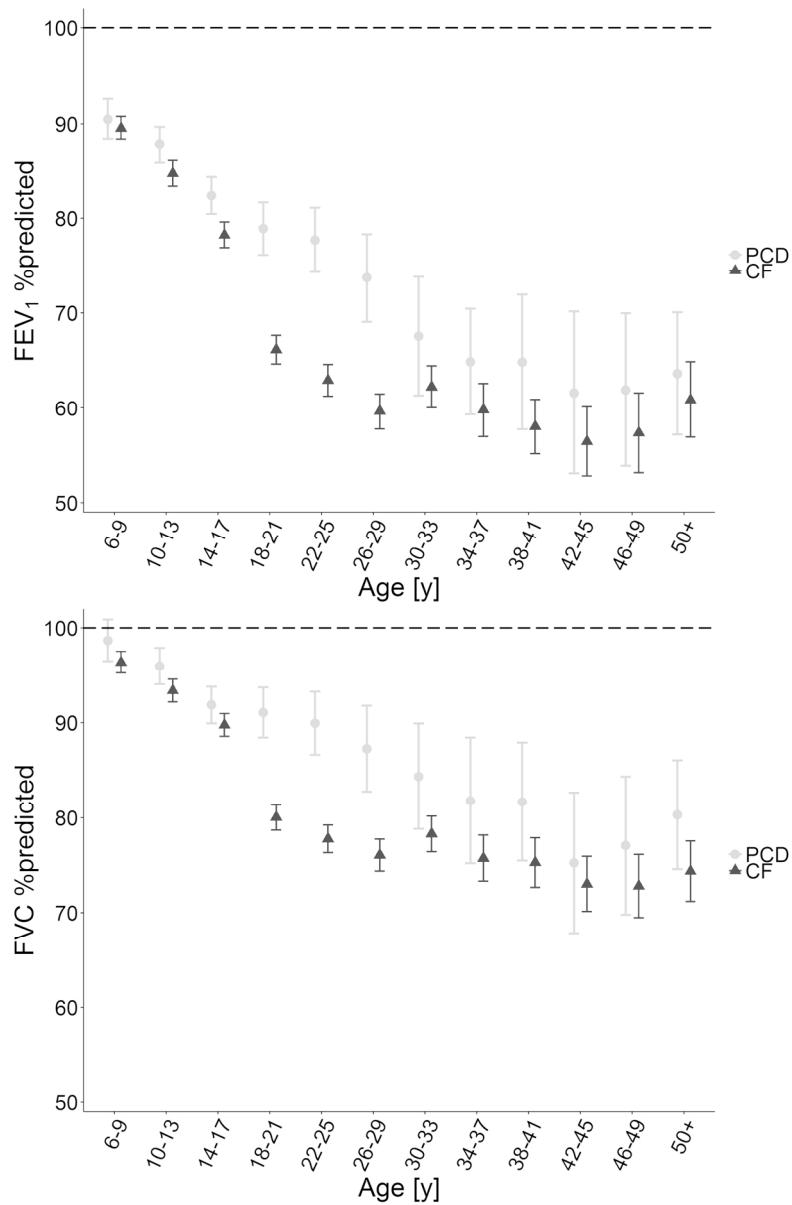
FEV<sub>1</sub> and FVC in PCD patients by age group compared to GLI 2012 reference values. FEV<sub>1</sub> and FVC are presented as mean z-score (95%CI) after adjusting for sex, country, and level of diagnostic certainty. The dashed line shows the mean z-score of the normal population.



FEV<sub>1</sub> and FVC in PCD patients by country compared to GLI 2012 reference values. FEV<sub>1</sub> and FVC are presented as mean z-score (95%CI) after adjusting for sex, age group, and level of diagnostic certainty. The dashed line shows the mean z-score of the normal population.



FEV<sub>1</sub> and FVC in PCD patients by sex, situs anomalies, and BMI compared to GLI 2012 reference values. FEV<sub>1</sub> and FVC are presented as mean z-score (95%CI) after adjusting for age, country, and level of diagnostic certainty. The dashed line shows the mean z-score of the normal population.



Association of FEV<sub>1</sub> and FVC of PCD patients with CF patients. FEV<sub>1</sub> and FVC are presented as mean %predicted (95% CI), without adjusting for other factors. The dashed line shows the mean of the normal population.

**Table 1.** Characteristics of the study population (N=991)

<b>Characteristic</b>	<b>n</b>	<b>%</b>
<b>Sex</b>		
Male	487	49
Female	504	51
<b>Country of residence*</b>		
Australia	34	3
Northern Europe	306	31
Western Europe	392	40
Eastern Europe	74	8
Southern Europe	42	4
Western Asia	143	14
<b>Organ laterality</b>		
Situs solitus	499	51
Situs inversus	348	35
Heterotaxia	13	1
Situs status not reported	131	13
<b>Time period of birth</b>		
Earlier than 1976	151	15
1977-1996	363	37
1997-2015	477	48
<b>Diagnostic information</b>		
Definite PCD diagnosis+	611	62
Probable PCD diagnosis#	207	21
Clinical diagnosis only	173	17
<b>Age at diagnosis</b>		
0-9 years	448	45
10-19 years	317	32
20-29 years	98	10
30-39 years	61	6
40-49 years	36	4
≥50 years	31	3
<b>BMI¶</b>		
Underweight	59	6
Normal	752	81
Overweight	116	13

\* Based on geographical region definitions of the United Nations Statistics Division (March 2017). Northern Europe: Denmark, Norway, United Kingdom; Western Europe: Belgium, France, Germany, Switzerland, the Netherlands; Eastern Europe: Poland; Southern Europe: Italy, Serbia; Western Asia: Cyprus, Israel, Turkey. + Defined as hallmark PCD electron microscopy findings and/or biallelic gene mutation identified based on the ERS PCD Diagnostics Guidelines [21].

# Abnormal light or high frequency video microscopy finding and/or low ( $\leq 77$ nl/min) nasal NO value.

¶ BMI z-scores  $\leq -1.96$  underweight,  $> -1.96$  &  $< 1.96$  normal,  $\geq 1.96$  overweight.

**Table 2.** FEV<sub>1</sub> and FVC in patients with primary ciliary dyskinesia from the iPCD Cohort, compared to GLI 2012 references (N=991)

Characteristic	N	FEV1				N	FVC			
		mean z-score	95% CI		p-value*		mean z-score	95% CI		p-value*
<b>Total</b>	991	-1.52	-1.62	-1.41		981	-0.77	-0.88	-0.66	
<b>Sex</b>					0.03					0.20
Male	487	-1.36	-1.49	-1.22		483	-0.70	-0.84	-0.56	
Female	504	-1.57	-1.70	-1.43		498	-0.83	-0.97	-0.69	
<b>Age group</b>					<0.001					<0.001
6-9 years	271	-0.84	-1.03	-0.65		272	-0.31	-0.51	-0.11	
10-13 years	207	-1.00	-1.21	-0.79		203	-0.48	-0.70	-0.26	
14-17 years	191	-1.51	-1.73	-1.29		186	-0.84	-1.07	-0.61	
18-21 years	81	-1.71	-2.05	-1.37		82	-0.72	-1.07	-0.37	
22-25 years	55	-1.70	-2.12	-1.29		53	-0.73	-1.17	-0.29	
26-29 years	41	-2.19	-2.67	-1.72		40	-1.16	-1.66	-0.66	
30-33 years	28	-3.14	-3.71	-2.56		28	-1.91	-2.51	-1.31	
34-37 years	27	-2.87	-3.45	-2.28		25	-2.10	-2.72	-1.47	
38-41 years	17	-2.72	-3.45	-1.98		17	-1.51	-2.27	-0.75	
42-45 years	23	-3.03	-3.66	-2.39		24	-2.23	-2.87	-1.58	
46-49 years	15	-2.87	-3.66	-2.08		16	-2.02	-2.81	-1.24	
≥50 years	35	-2.30	-2.82	-1.78		35	-1.45	-1.99	-0.91	
<b>Country</b>					<0.001					<0.001
Australia	34	-1.87	-2.39	-1.34		34	-1.26	-1.80	-0.72	
Belgium	69	-1.11	-1.49	-0.74		69	-0.03	-0.42	0.36	
Cyprus	27	-1.84	-2.43	-1.25		27	-1.81	-2.42	-1.20	
Denmark	74	-1.19	-1.55	-0.82		74	-0.58	-0.95	-0.20	
France	75	-1.30	-1.66	-0.94		72	-0.36	-0.74	0.02	
Germany	142	-1.36	-1.62	-1.10		137	-0.79	-1.06	-0.52	
Israel	87	-1.53	-1.86	-1.20		84	-1.08	-1.43	-0.74	
Italy	35	-1.29	-1.81	-0.78		35	-0.35	-0.89	0.18	
Netherlands	66	-0.39	-0.77	-0.02		66	0.74	0.35	1.13	
Norway	14	-1.42	-2.23	-0.61		14	-1.00	-1.83	-0.16	
Poland	74	-1.84	-2.20	-1.48		74	-0.91	-1.28	-0.54	
Serbia	7	-2.22	-3.36	-1.07		7	-2.38	-3.56	-1.19	
Switzerland	40	-1.69	-2.17	-1.20		40	-1.05	-1.55	-0.55	
Turkey	29	-1.72	-2.30	-1.14		29	-1.50	-2.10	-0.90	
UK	218	-1.78	-2.00	-1.57		219	-1.11	-1.33	-0.89	
<b>Diagnostic certainty</b>					0.52					0.23
Definite PCD diagnosis+	611	-1.47	-1.59	-1.34		608	-0.74	-0.87	-0.60	
Probable PCD diagnosis#	207	-1.55	-1.76	-1.33		203	-0.94	-1.16	-0.71	
Clinical diagnosis only	173	-1.36	-1.60	-1.11		170	-0.67	-0.93	-0.41	

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<sub>1</sub> within the study population. + defined as hallmark PCD electron microscopy findings and/or biallelic gene mutation identified based on the ERS PCD Diagnostics Guidelines [25].

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

**Table 3.** FEV<sub>1</sub> and FVC of PCD patients of the iPCD Cohort with available ultrastructural defect information compared to GLI 2012 references

Characteristic	N	FEV1				N	FVC			
		mean z-score	95% CI		p-value <sup>†</sup>		mean z-score	95% CI		p-value <sup>†</sup>
<b>Total</b>	689	-1.52	-1.65	-1.40	0.25	683	-0.79	-0.92	-0.66	0.52
<b>Sex</b>										
Male	344	-1.46	-1.62	-1.29		341	-0.76	-0.93	-0.58	
Female	345	-1.59	-1.75	-1.43	<0.001	342	-0.83	-1.00	-0.66	<0.001
<b>Age group</b>										
6-9 years	127	-0.77	-1.04	-0.49		126	-0.25	-0.54	0.03	
10-13 years	148	-1.19	-1.44	-0.94		147	-0.65	-0.91	-0.39	
14-17 years	152	-1.51	-1.76	-1.26		151	-0.84	-1.10	-0.58	
18-21 years	69	-1.53	-1.89	-1.17		68	-0.62	-1.00	-0.23	
22-25 years	51	-1.66	-2.09	-1.23		50	-0.61	-1.05	-0.16	
26-29 years	35	-2.14	-2.66	-1.63		34	-1.17	-1.71	-0.63	
30-33 years	23	-2.47	-3.10	-1.84		22	-1.42	-2.09	-0.76	
34-37 years	20	-2.67	-3.34	-1.99		21	-1.74	-2.43	-1.06	
38-41 years	10	-2.37	-3.33	-1.41		10	-1.00	-2.00	-0.01	
42-45 years	10	-3.24	-4.20	-2.28		11	-2.86	-3.81	-1.91	
46-49 years	17	-3.00	-3.74	-2.25		16	-2.05	-2.84	-1.25	
≥50 years	27	-2.34	-2.93	-1.75	27	-1.29	-1.90	-0.68	<0.001	
<b>Country</b>										
Australia	31	-1.82	-2.36	-1.28	31	-1.18	-1.74	-0.62		
Belgium	66	-1.20	-1.59	-0.82	66	0.03	-0.36	0.43		
Cyprus	27	-2.02	-2.62	-1.43	27	-1.79	-2.40	-1.17		
Denmark	23	-1.36	-1.99	-0.72	23	-0.60	-1.26	0.05		
France	59	-1.28	-1.68	-0.87	59	-0.45	-0.87	-0.03		
Germany	83	-1.21	-1.54	-0.87	79	-0.69	-1.05	-0.33		
Israel	67	-1.46	-1.83	-1.08	64	-0.89	-1.28	-0.49		
Italy	35	-1.46	-1.98	-0.95	35	-0.65	-1.19	-0.12		
Netherlands	30	-0.45	-1.01	0.11	30	0.66	0.08	1.24		
Norway	13	-1.43	-2.27	-0.60	13	-0.84	-1.71	0.03		
Poland	39	-1.80	-2.30	-1.30	39	-0.89	-1.41	-0.37		
Serbia	2	-1.77	-3.97	0.44	2	-2.39	-4.68	-0.11		
Switzerland	24	-1.45	-2.10	-0.81	24	-0.83	-1.50	-0.16		
Turkey	7	-2.12	-3.28	-0.96	7	-2.13	-3.33	-0.92		
UK	183	-1.90	-2.13	-1.67	184	-1.19	-1.43	-0.96		0.18
<b>Ultrastructural defect*</b>										
Non-diagnostic	123	-1.19	-1.48	-0.91	120	-0.74	-1.04	-0.44		
Dynein arm defects	425	-1.50	-1.65	-1.35	422	-0.73	-0.88	-0.57		
Microtubular defects	134	-1.91	-2.20	-1.63	134	-1.08	-1.37	-0.78		
Acilia	7	-1.44	-2.64	-0.24	7	-0.40	-1.64	0.85		

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

<sup>†</sup> Likelihood ratio test p-value indicating whether the characteristic explains differences in FEV<sub>1</sub> 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

\* Dynein arm defects: Outer and/or inner dynein arm defects, Microtubular defects: central pair, tubulus disorganisation, tubular transposition and/or nexin link defect.

## **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].

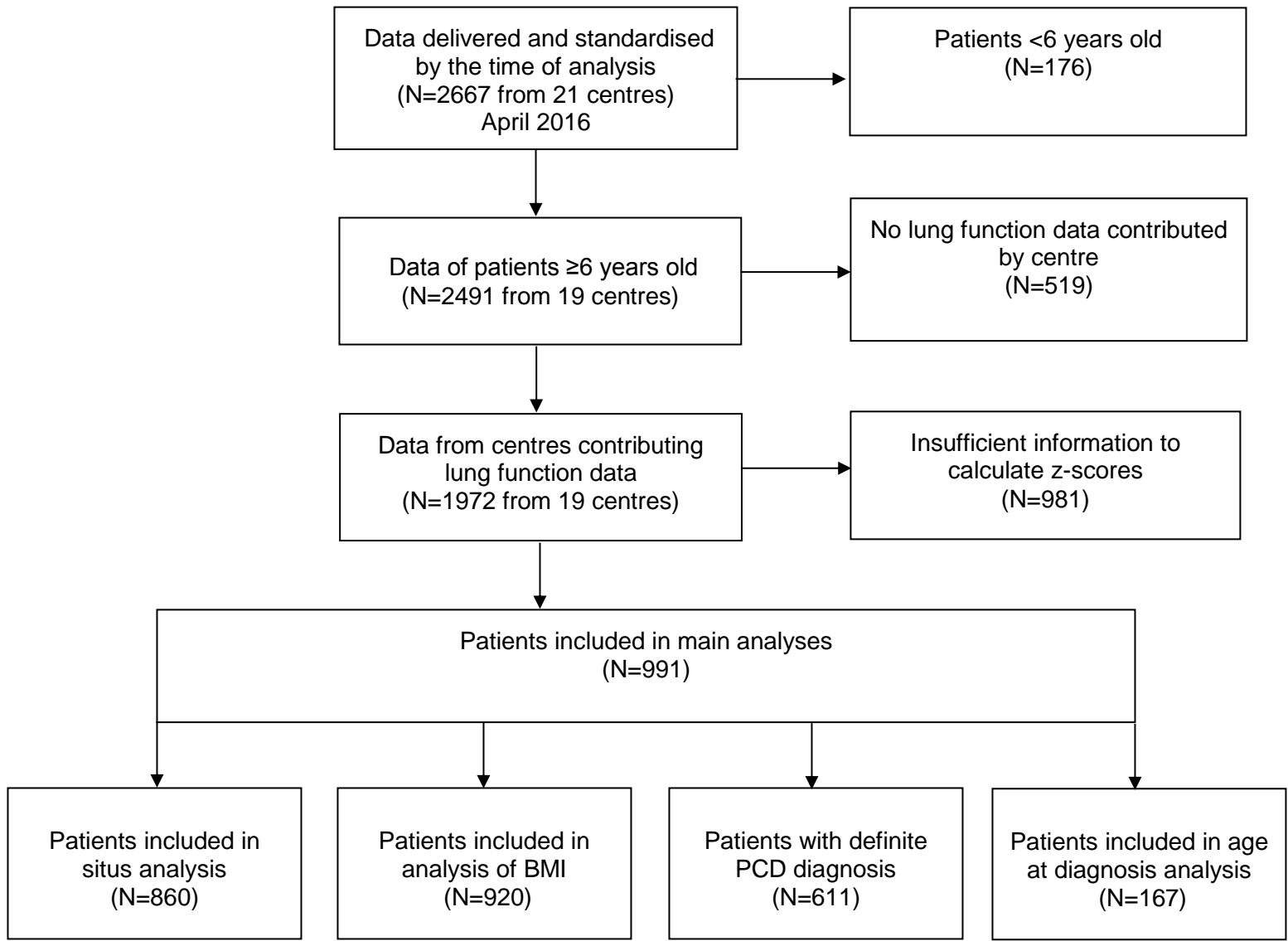
## Determinants of lung function

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  $\geq 50$  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  $\geq 1.96$ . For patients aged  $\geq 18$  years we used the WHO international BMI classification for adults, which define underweight as BMI  $< 18.5$  and overweight as BMI  $\geq 25.0$  [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.

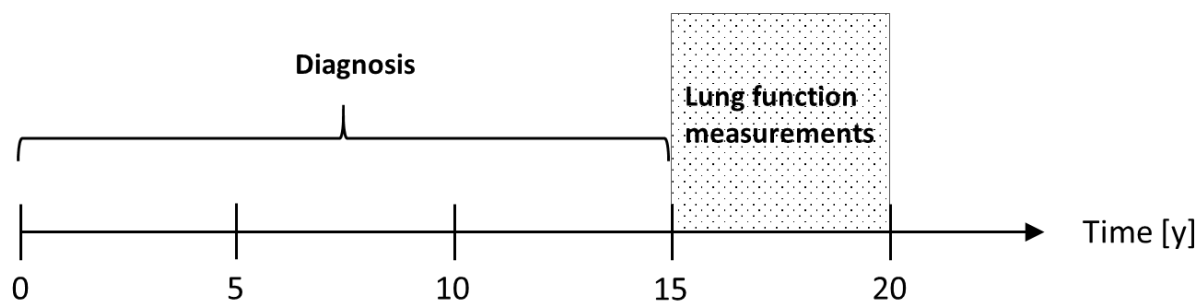
**Table S1.** National references used for calculations of BMI z-scores

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

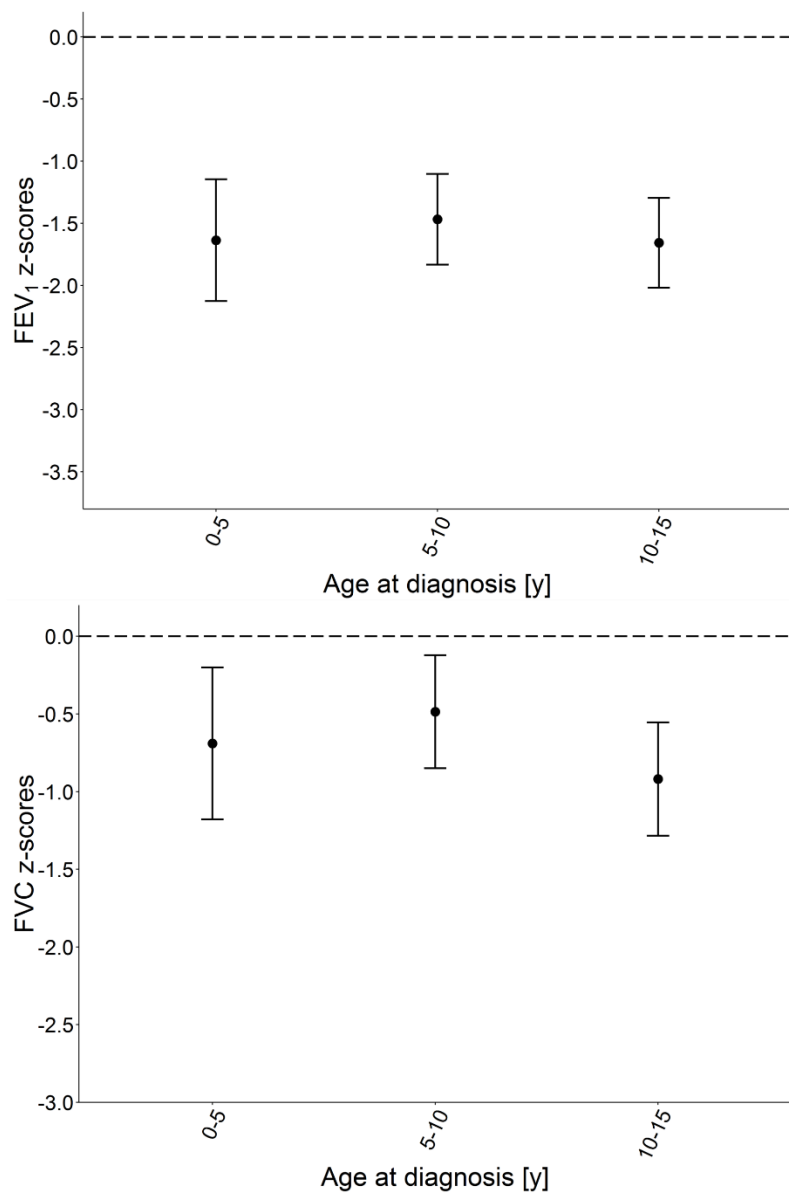
\* No national growth references were available in Serbia, for which the WHO references are used instead. Table adapted from Goutaki et al. [25]



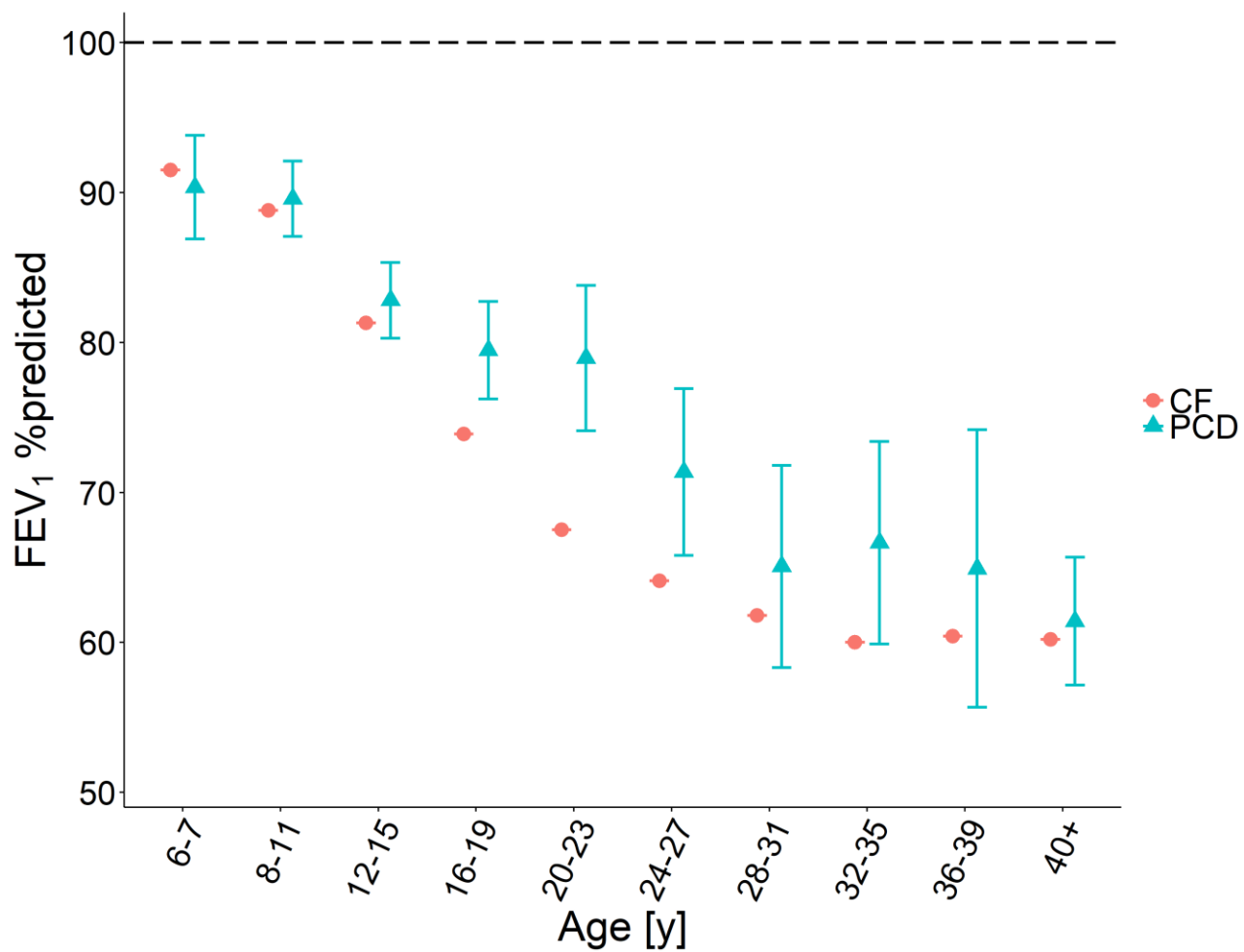
**Figure S1.** Flow chart showing the patients included for the different analyses performed.



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



**Fig S3.** FEV<sub>1</sub> and FVC in PCD patients aged 15 to 20 years by age of diagnosis compared to GLI 2012 reference values. FEV<sub>1</sub> 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 <sup>¶</sup>	No lung function data contributed (n=519) n (%)	Comparison with participants p-value <sup>¶</sup>
<b>Sex</b>			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)	
<b>Country of residence*</b>			<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)	
<b>Current age<sup>#</sup></b>			<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

<sup>¶</sup> Chi-squared tests<sup>#</sup> In April 2016

**Table S3.** FEV<sub>1</sub> and FVC of PCD patients of the iPCD Cohort with available situs information compared to GLI 2012 references (N=860)

Characteristic	N	mean z-score	FEV1		p-value <sup>†</sup>	N	mean z-score	FVC		p-value <sup>†</sup>
			95% CI					95% CI		
<b>Total</b>	860	-1.52	-1.63	-1.41		853	-0.79	-0.90	-0.67	
<b>Sex</b>					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	
<b>Age group</b>					<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	
<b>Country</b>					<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	
<b>Diagnostic certainty</b>					0.58					0.50
Definite PCD diagnosis+	554	-1.55	-1.68	-1.42		551	-0.78	-0.91	-0.65	
Probable PCD diagnosis <sup>#</sup>	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	
<b>Situs anomalies</b>					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

<sup>†</sup> Likelihood ratio test p-value indicating whether the characteristic explains differences in FEV<sub>1</sub> or FVC within the study population

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

<sup>#</sup> Abnormal light or high frequency video microscopy finding and/or low nasal NO value

**Table S4.** FEV<sub>1</sub> and FVC of PCD patients of the iPCD Cohort with available BMI information compared to GLI 2012 references (N=927)

Characteristic	N	FEV1			p-value <sup>†</sup>	N	FVC			p-value <sup>†</sup>
		mean z-score	95% CI				mean z-score	95% CI		
<b>Total</b>	927	-1.47	-1.58	-1.37		924	-0.73	-0.84	-0.62	
<b>Sex</b>					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	
<b>Age group</b>					<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	
<b>Country</b>					<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	
<b>Diagnostic certainty</b>					0.45					0.54
Definite PCD diagnosis <sup>+</sup>	574	-1.50	-1.62	-1.37		574	-0.73	-0.86	-0.60	
Probable PCD diagnosis <sup>#</sup>	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	
<b>BMI</b>					<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

<sup>†</sup> Likelihood ratio test p-value indicating whether the characteristic explains differences in FEV<sub>1</sub> or FVC within the study population

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

<sup>#</sup> 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<sub>1</sub> and FVC of PCD patients of the iPCD Cohort with a definite PCD diagnosis compared to GLI 2012 references (sensitivity analysis) (N=611)

Characteristic	N	FEV1			p-value¶	N	FVC			p-value¶
		mean z-score	95% CI				mean z-score	95% CI		
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

<sup>¶</sup> Likelihood ratio test p-value indicating whether the characteristic explains differences in FEV<sub>1</sub> or FVC within the study population

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

<sup>#</sup> Abnormal light or high frequency video microscopy finding and/or low nasal NO value

**Table S6.** FEV<sub>1</sub> 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)

Characteristic	N	FEV1				N	FVC			
		mean z-score	95% CI		p-value <sup>†</sup>		mean z-score	95% CI		p-value <sup>†</sup>
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 <sup>+</sup>	611	-1.55	-1.68	-1.42		608	-0.77	-0.90	-0.63	
Probable PCD diagnosis <sup>#</sup>	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

<sup>†</sup> Likelihood ratio test p-value indicating whether the characteristic explains differences in FEV<sub>1</sub> or FVC within the study population

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

<sup>#</sup> Abnormal light or high frequency video microscopy finding and/or low nasal NO value

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