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How well does spirometry capture the symptom range in primary ciliary dyskinesia? A cross-sectional study

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Summary

INTRODUCTION: Patients with primary ciliary dyskinesia (PCD) present a variety of respiratory symptoms. Spirometry, particularly forced expiratory volume in 1 second (FEV_1), is the most commonly used outcome measure in clinical follow-up; however, it is not known how well it captures the range of respiratory symptoms experienced by patients.

METHODS: We sent the FOLLOW-PCD questionnaire to all patients registered in the Swiss PCD Registry (to the parents of those aged <14 years) asking about upper and lower respiratory symptoms. In patients who had had a routine lung function done within a year of survey completion, we extracted data from clinical records and calculated spirometric indices z-scores based on the Global Lung Function Initiative references. We used linear regression to study associations between FEV_1, forced vital capacity (FVC), FEV_1/FVC and frequency of respiratory symptoms, adjusted for age, sex and regular physiotherapy.

RESULTS: Of 99 patients invited, 64 (67%) completed the survey; for 54 of them (median age: 24 years, IQR: 15–47; 50% females) we also had an FEV_1 measurement (mean z-score −2.29 [−3.37 to −1.03]), with 2.2 month median time between survey and lung function test. Patients reporting wheezing (76%) had lower FEV_1 and FEV_1/FVC z-scores (FEV_1 z-score for infrequent and frequent wheezing compared to no wheezing: -1.13 [95% CI: −2.13 to −0.12] and −1.11 [−2.20 to −0.20], respectively). Similarly patients reporting frequent shortness of breath (29.5%) also had lower FEV_1 and FEV_1/FVC z-scores (FEV_1 z-score for frequent shortness of breath compared to no shortness of breath: −1.27 [−2.50 to −0.04]). We found no signs of an association between reported nasal symptoms, snoring, coughing, sputum production and chest pain with FEV_1, FVC or FEV_1/FVC.

CONCLUSION: In our study, self-reported wheezing and frequent shortness of breath were associated with lower FEV_1 and FEV_1/FVC, commonly used for patient follow-up. However, we need additional outcome measures, e.g. lung clearance index, imaging outcomes or upper airway assessments, together with regular and standardised assessment of patient-reported symptoms, to capture the range of respiratory morbidity patients with PCD experience in daily life and guide management successfully.

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Introduction

Selecting the optimal assessment tools for clinical follow-up of chronic diseases is one of the main challenges healthcare professionals and researchers often face. Appropriate outcome measures are of utmost importance for research studies, especially clinical trials, but also in daily practice for the clinical follow-up of patients. Objective measures are often considered more reliable for capturing disease progression and allowing comparisons over time. Over the past decades, however, patient-reported outcomes have gained importance as they offer a different perspective relating to the patients' perception of disease severity and how it affects their daily life [1]. This is especially relevant for rare or complex diseases with large phenotypic variability, such as primary ciliary dyskinesia (PCD) [2, 3].

PCD prevalence is estimated to be 1 in 7500 and symptoms start early in life and progress over the years [4]. Most patients develop recurrent upper and lower respiratory symptoms, leading to chronic rhinosinusitis, hearing impairment and bronchiectasis [5-7]. A scoping review showed that commonly used lung health outcome measures for PCD have not been validated, and reporting is not standardised [8]. For example, the definition of chronic respiratory colonisation in PCD varies and often refers to Leeds criteria, which are derived from patients with cystic fibrosis and colonisation with *Pseudomonas aeruginosa*, while there is a lack of standardised use of CT scan scoring systems [9-12]. For the upper airways and ears, the heterogeneity in outcome definitions or measures is even more prominent [13]. Several objective measures are available to capture different aspects of lung health in PCD, but spirometry remains the most used for all patients worldwide. It is recommended for regular follow-ups, usually every 3 to 6 months [14]. Spirometry is also commonly used in research to assess lung disease progression [15-18]. Measures such as multiple breath washout or structural and functional imaging modalities have shown better sensitivity in detecting early signs of disease and monitoring lung health; however, these are not commonly available or used in routine care [18-21]. Spirometry, specifically forced expiratory volume in 1 second (FEV_1), was the only objective measure together with microbiology included in the recently published BEAT-PCD (Better Experimental Approaches to Treat Primary Ciliary Dyskinesia) consensus statement on a core outcome set for pulmonary disease interventions [22]. The core outcome set also included exacerbations and health-related quality of life as patient-reported outcomes; however, these are still not used regularly or designed specifically for use in research [23-25]. Since there is a lack of standardised and reliable clinical outcome measures that capture patient-reported symptoms, clinical decision-making often relies mainly on objective measures, in particular spirometry, and clinician-recorded symptoms extracted from records. We aimed to study associations between patient-reported respiratory symptoms and airway obstruction, assessed by spirometry, among patients with PCD living in Switzerland. We hypothesised that spirometry alone would not be able to reflect the range of symptoms patients with PCD experience.

Methods

Study design and study population

Our study is nested in the Swiss PCD registry (CH-PCD), a population-based patient registry (ClinicalTrials.gov identifier NCT03606200) that enrols Swiss residents of any age with confirmed or clinical diagnoses of PCD [26]. The CH-PCD was established in 2013 and provides data for national and international PCD monitoring and research [27-31]. After a pilot period at Bern University Hospital, it received approval nationwide from the Cantonal Ethics Committee of the Canton of Bern in 2015 (KEK-BE: 060/2015). Participants aged 14 years or over or parents of participants aged under 14 provide written informed consent that allows collection of routinely available clinical data from hospitals or practices and invitations to participate in health-related questionnaire surveys.

For our analysis, we linked data on patient-reported symptoms collected through a questionnaire survey to spirometry data from records available in the CH-PCD. We included all participants with a completed questionnaire and available lung function data from clinical follow-up within one year of completing the questionnaire. All French- or German-speaking participants registered in the CH-PCD with a valid postal address received the questionnaire. We excluded one patient who spoke only Italian and three patients with an invalid postal address. We sent the questionnaire by post to all eligible participants in June 2022. Participants who had not yet responded received two postal reminders, one three weeks after the original questionnaire mailing and a second at the end of August 2022. Our reporting complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting recommendation [32].

Questionnaire

We used the FOLLOW-PCD patient questionnaire, part of the FOLLOW-PCD standardised tool for data collection for research and clinical follow-up [33]. The questionnaire includes several questions about the frequency and characteristics of upper and lower respiratory, ear and general symptoms, questions about lifestyle and questions related to treatments, including physiotherapy alone or with a professional physiotherapist. We asked about professional physiotherapy instead of any home physiotherapy – by including any professional physiotherapy, we can be certain that at least physiotherapists ensured quality control of performed regimens. There were three age-spe-

cific versions of the questionnaire: a) a parent/caregiver version for children aged 0–13 years, b) an adolescent version for those aged 14–17 years, and c) an adult version for participants aged ≥18 years. Most questions had predefined answer categories, and we included free-text fields so participants could add any relevant comments. The FOLLOW-PCD questionnaire is available in German and French. Any additional questions were originally developed in German then translated into French by a native French speaker with knowledge of PCD.

Patient-reported symptoms

The questionnaire asked about symptoms during the past three months. For our analysis, we focused on nasal symptoms, snoring, coughing, sputum production, wheezing, shortness of breath and chest pain. Questions about symptom frequency included five possible response options: Daily / Often / Sometimes / Rarely / Never. We defined symptoms reported "Often" or "Daily" as frequent and symptoms reported "Sometimes" or "Rarely" as infrequent. When no option was chosen, we classified the symptom as "Never".

Demographic, diagnostic and spirometry information

Sex, date of birth, area of residence, spirometry results and PCD diagnostic tests were retrieved from the CH-PCD database. We calculated age based on the questionnaire completion date. The CH-PCD includes patients diagnosed on the basis of different algorithms, depending on the year they were diagnosed as diagnostic tests for PCD and their availability have evolved over the years. All participants had a strong clinical suspicion for PCD and were managed accordingly by their physicians. For most patients, the PCD diagnosis was based on a combination of tests in accordance with current recommendations; however, the diagnostic algorithm was not completed in all, and some were diagnosed based on strong clinical suspicion (e.g. Kartagener syndrome). Using the new, unified diagnostic guidelines of the European Respiratory Society and the American Thoracic Society, we defined confirmed PCD as two pathogenic or likely pathogenic variants in a known gene associated with PCD or a class I defect identified by transmission electron microscopy (TEM) [34, 35]. We defined as suspected PCD patients who had either not been tested with TEM or genetics or who had negative results for these tests and had one or more of the following: abnormal beat pattern in high-frequency video microscopy; low (≤77 nl/min) nasal nitric oxide; pathological immunofluorescence staining. Patients with a class 2 defect in TEM, a genetic test result concordant with a known genotype-phenotype association and one or more positive test results among nasal nitric oxide, high-speed video microscopy and immunofluorescence were classified as highly likely for PCD.

Lung function was measured by spirometry performed at the clinic or practice where participants were followed up, by trained personnel according to European Respiratory Society / American Thoracic Society technical standards and local standard operating practices [36]. Assessment of the quality of spirometry was performed locally and we included patients younger than 6 years if the measurement was deemed well performed by the local team of lung function technicians or clinicians. We checked the data for plausibility, and calculated z-scores for FEV_1, for forced vital capacity (FVC) and for the FEV_1/FVC ratio adjusted for age, sex, height and ethnicity, using Global Lung Function Initiative 2012 reference values [37]. For each participant, one measurement was included in the analysis. If multiple measurements were available within the timeframe of one year from questionnaire completion, we used the earliest one. If pre- and post-bronchodilator measurements were available, we used the one obtained before bronchodilator use.

Statistical analysis

We describe population characteristics and reported frequency of respiratory symptoms, overall and by age group, using median and interquartile range (IQR) for continuous variables and count and proportion for categorical variables. Missing data are reported as such. We assessed differences in basic characteristics between survey respondents and non-respondents, and between participants included and not included in the final analysis due to availability of lung function measurements using Pearson's chi-squared test. We assessed the frequency of respiratory symptoms as potential determinants of lung function, namely FEV_1 z-score, FVC z-score and FEV_1/FVC z-score, using multivariable linear regression models, separate for each symptom, adjusting each model for age, sex and regular physiotherapy with a professional physiotherapist. To allow for

graphical presentation, we ran our models again categorising age in the following categories: 0–13 years, 14–30 years, 31–50 years and >50 years. We performed all analyses using Stata version 16 (StataCorp LLC, College Station, TX, USA).

Results

Of 99 people invited to complete the questionnaire, 64 did so (a 65% response rate), 54 of whom had spirometry data available within a 1-year period from questionnaire completion (figure 1). The median age of respondents was 24 years (IQR: 15–47) with 36 adults and 18 adolescents and children participating (table 1). Most participants lived in German-speaking Swiss cantons (78%) and 27 (50%) were female. When we compared characteristics of respondents vs non-respondents and of people with vs without spirometry data available, we found no differences except one: a much higher proportion of females among the people who were excluded due to lack of spirometry data (tables S1 and S2 in the appendix).

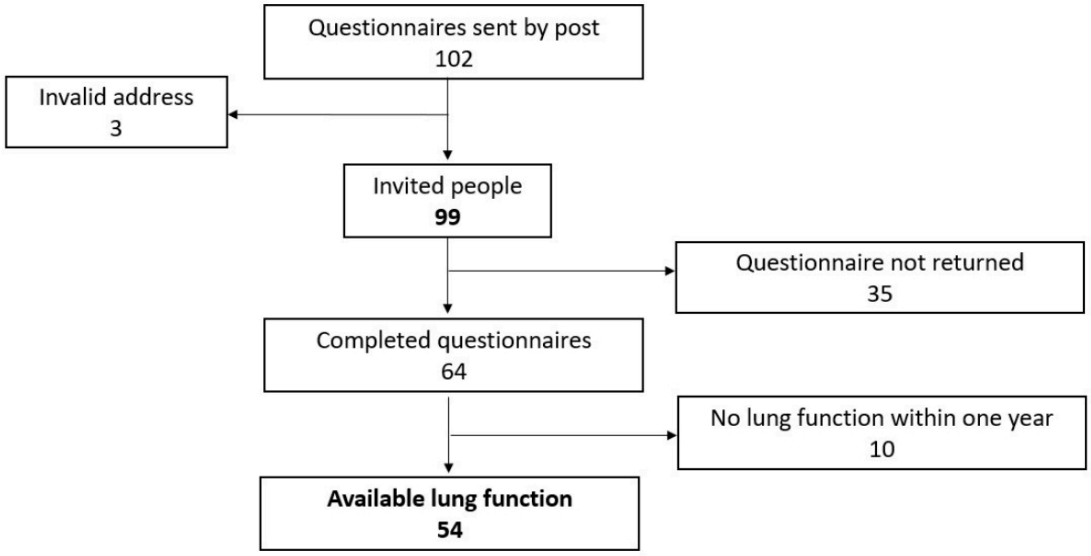


Figure 1: Flowchart of study participants with primary ciliary dyskinesia living in Switzerland (Swiss PCD registry survey 2022).

Table 1: Characteristics of study participants with primary ciliary dyskinesia living in Switzerland, overall (n = 54) and by age.

Characteristics		Total population, n (%)	Aged <18 years, n (%)	Aged ≥18 years, n (%)
Number of participants		54 (100%)	18 (100%)	36 (100%)
Age in years, median (IQR)		24 (15–47)	13 (6–15)	35 (24–55)
Sex: female		27 (50%)	7 (39%)	20 (56%)
Area of residence	German-speaking Switzerland	42 (78%)	14 (78%)	28 (78%)
	French-speaking Switzerland	12 (22%)	4 (22%)	8 (22%)
Diagnostic certainty*	Confirmed PCD	29 (54%)	12 (67%)	17 (47%)
	Highly likely PCD	2 (4%)	1 (5%)	1 (3%)
	PCD suspected	23 (42%)	5 (28%)	18 (50%)
Laterality defect	Situs inversus	13 (24%)	5 (28%)	8 (22%)
	Situs ambiguous	1 (2%)	0 (0%)	1 (3%)
	Normal situs	25 (46%)	10 (55%)	15 (42%)
	Not reported	15 (28%)	3 (17%)	12 (33%)
Congenital heart defect		2 (4%)	1 (6%)	1 (3%)
Retinitis pigmentosa		1 (2%)	0 (0%)	1 (3%)
Hydrocephalus		1 (2%)	0 (0%)	1 (3%)
Tobacco exposure	Active or ex-smoker	7 (13%)	0 (0%)	7 (20%)
	Passive smoking (in household)	5 (9%)	2 (11%)	3 (8%)
	No active or passive smoking	42 (78%)	16 (89%)	26 (72%)
Occupation/school	Student/preschool	23 (43%)	18 (100%)	5 (14%)
	81–100% employment	17 (31%)	0 (0%)	17 (47%)
	61–80% employment	2 (4%)	0 (0%)	2 (6%)
	41–60% employment	3 (5%)	0 (0%)	3 (8%)
	≤40% employment	2 (4%)	0 (0%)	2 (6%)
	Retired/disability pension	7 (13%)	0 (0%)	7 (19%)
Professional physiotherapy	Yes	21 (39%)	11 (61%)	10 (28%)
	No / not reported	33 (61%)	7 (39%)	26 (72%)

IQR: interquartile range; PCD: primary ciliary dyskinesia.

All characteristics are presented as n and column % except for age, which is presented as median and interquartile range.

* According to the European Respiratory Society / American Thoracic Society guidelines for the diagnosis of PCD: Confirmed PCD = two pathogenic or likely pathogenic variants in a known gene associated with PCD or a class I defect identified by transmission electron microscopy (TEM); Suspected PCD = patients who had either not been tested with TEM or genetics or who had negative results for these tests and had one or more of the following: abnormal beat pattern on high-frequency video microscopy; low (≤77 nL/min) nasal nitric oxide; pathological immunofluorescence finding.

PCD diagnosis and general characteristics

More than half of the participants (54%) had confirmed PCD according to the new European Respiratory Society / American Thoracic Society diagnostic guidelines [34]. Two patients had highly likely PCD based on a class 2 defect identified with TEM, a test result concordant with a known genotype-phenotype association and one or more other positive diagnostic test results (table 1). The remaining 23 (42%) participants were classified as suspected PCD. These patients had a strong clinical suspicion, usually typical Kartagener syndrome, and often one or more positive diagnostic test results; however, they had not fully completed the diagnostic algorithm, which is common in Switzerland as genetic testing for PCD was rare until recently and is still not performed routinely [38].

Twenty-five participants (46%) had normal situs and two a recorded congenital heart defect. Retinitis pigmentosa and hydrocephalus were only reported by one adult patient each.

Seven adults reported occasional or frequent tobacco smoking or past smoking, and five additional participants (9%) reported passive smoking with household exposure. Seven adults were retired or on a disability pension. Twenty-one participants (39%) reported collaboration with a professional physiotherapist for their airway clearance.

Respiratory symptoms

All participants reported chronic nasal symptoms, usually rhinorrhoea or obstruction, during the past three months, frequent for 46 (85%) of them (table 2). Snoring was less common, with only 3 participants (6%) reporting it as frequent and 26 (48%) as infrequent. Among the lower respiratory symptoms, coughing and sputum production were the most commonly reported items with 46 (85%) and 45 (83%) participants, respectively, reporting them as frequent. Fifteen participants (28%) reported frequent wheezing and almost half (48%) infrequent wheezing. Shortness of breath was quite common, reported as frequent by 16 participants (29.5%), 15 of whom were adults, while chest pain was only reported as frequent by 6 participants (11%) (table 2). Missing responses to individual symptom questions amounted to less than 5%.

Table 2: Patient-reported respiratory symptoms of study participants with primary ciliary dyskinesia living in Switzerland, overall (n = 54) and by age.

		Total population, n (%)	Aged <18 years, n (%)	Aged ≥18 years, n (%)
Number of participants		54 (100%)	18 (100%)	36 (100%)
Nasal symptoms	Frequent	46 (85%)	13 (72%)	33 (92%)
	Infrequent	8 (15%)	5 (28%)	3 (8%)
	Never	0 (0%)	0 (0%)	0 (0%)
Snoring	Frequent	3 (6%)	2 (11%)	1 (3%)
	Infrequent	26 (48%)	11 (61%)	15 (42%)
	Never	25 (46%)	5 (28%)	20 (55%)
Cough	Frequent	46 (85%)	14 (78%)	32 (89%)
	Infrequent	7 (13%)	3 (17%)	4 (11%)
	Never	1 (2%)	1 (5%)	0 (0%)
Sputum production	Frequent	45 (83%)	13 (72%)	32 (89%)
	Infrequent	6 (11%)	3 (17%)	3 (8%)
	Never	3 (6%)	2 (11%)	1 (3%)
Wheezing	Frequent	15 (28%)	5 (28%)	10 (28%)
	Infrequent	26 (48%)	7 (39%)	19 (53%)
	Never	13 (24%)	6 (33%)	7 (19%)
Shortness of breath	Frequent	16 (29.5%)	1 (6%)	15 (41.5%)
	Infrequent	22 (41%)	7 (39%)	15 (41.5%)
	Never	16 (29.5%)	10 (55%)	6 (17%)
Chest pain	Frequent	6 (11%)	1 (6%)	5 (14%)
	Infrequent	28 (52%)	5 (28%)	23 (64%)
	Never	20 (37%)	12 (66%)	8 (22%)

PCD: primary ciliary dyskinesia.

All characteristics are presented as n and column %. Frequent symptoms were those reported as "often" or "daily" by patients, while infrequent symptoms were those reported as "sometimes" or "rarely".

Lung function

The median difference between the date of questionnaire completion and the date of lung function measurement was 2.2 months (IQR: 0.5–4.9). Participants had a median FEV_1 z-score of -2.29 (-3.37 to –1.03), FVC z-score of -1.23 (-2.23 0.24) and FEV_1/FVC z-score of -1.63 (-2.70 to –0.54), with adults having lower z-scores than children (table 3).

Table 3: Spirometric indices of study participants with primary ciliary dyskinesia living in Switzerland, overall (n = 54) and by age.

	Total population, n (%)	Aged <18 years, n (%)	Aged ≥18 years, n (%)
Number of participants	54 (100%)	18 (100%)	36 (100%)
Age in years, median (IQR)	24 (15–47)	13 (6–15)	36 (24–55)
Sex: female	27 (50%)	7 (39%)	20 (56%)
FEV_1 z-score	–2.29 (–3.37 to –1.03)	–1.12 (–2.54 to 0.02)	–2.50 (–3.63 to –1.54)
FVC z-score	–1.23 (–2.23 to –0.24)	–1.03 (–1.56 to 1.12)	–1.47 (–2.78 to –0.48)
FEV_1/FVC z-score	–1.63 (–2.70 to –0.54)	–1.13 (–2.13 to –0.10)	–1.87 (–2.89 to –0.76)

IQR: interquartile range; PCD: primary ciliary dyskinesia.

Characteristics are presented as n and column % or as median and interquartile range. Age at lung function measurement.

Association of respiratory symptoms with lung function

Patients reporting any wheezing had lower spirometric indices: for frequent wheezing FEV_1 –1.11 (95% CI: –2.20 to –0.20) and FEV_1/FVC z-scores –1.00 (–1.83 to –0.18); for infrequent wheezing FEV_1 –1.13 (–2.13 to –0.12) and FEV_1/FVC –1.24 (–2.00 to –0.48) compared to those who reported no wheezing (table 4 and figure 2). Similarly, participants who reported frequent shortness of breath had lower FEV_1 (–1.27 [–2.50 to –0.04]) and FEV_1/FVC z-scores (–0.99 [–1.96 to 0.01]). We found no evidence of association between reported nasal symptoms, snoring or chest pain with FEV_1 or FEV_1/FVC. The estimated coefficients for reported coughing and sputum suggested a potential negative association with FEV_1 and FEV_1/FVC, with a magnitude of –0.75 (–3.90 to 2.37) for frequent coughing and FEV_1 z-score. Similarly, estimated coefficients for reported sputum, wheezing and shortness of breath suggested a negative association also with FVC z-score albeit of smaller magnitude (table S3 in the appendix). Increasing age was in general a predictor of lower lung function z-scores in all models (e.g. –0.02 [–0.05 to –0.01] annual FEV_1 z-score decrease accounting for reported wheezing). Patients who were supported by a professional respiratory physiotherapist appeared to have higher z-scores (e.g. 0.90 [–0.02 to 1.81] accounting for reported shortness of breath).

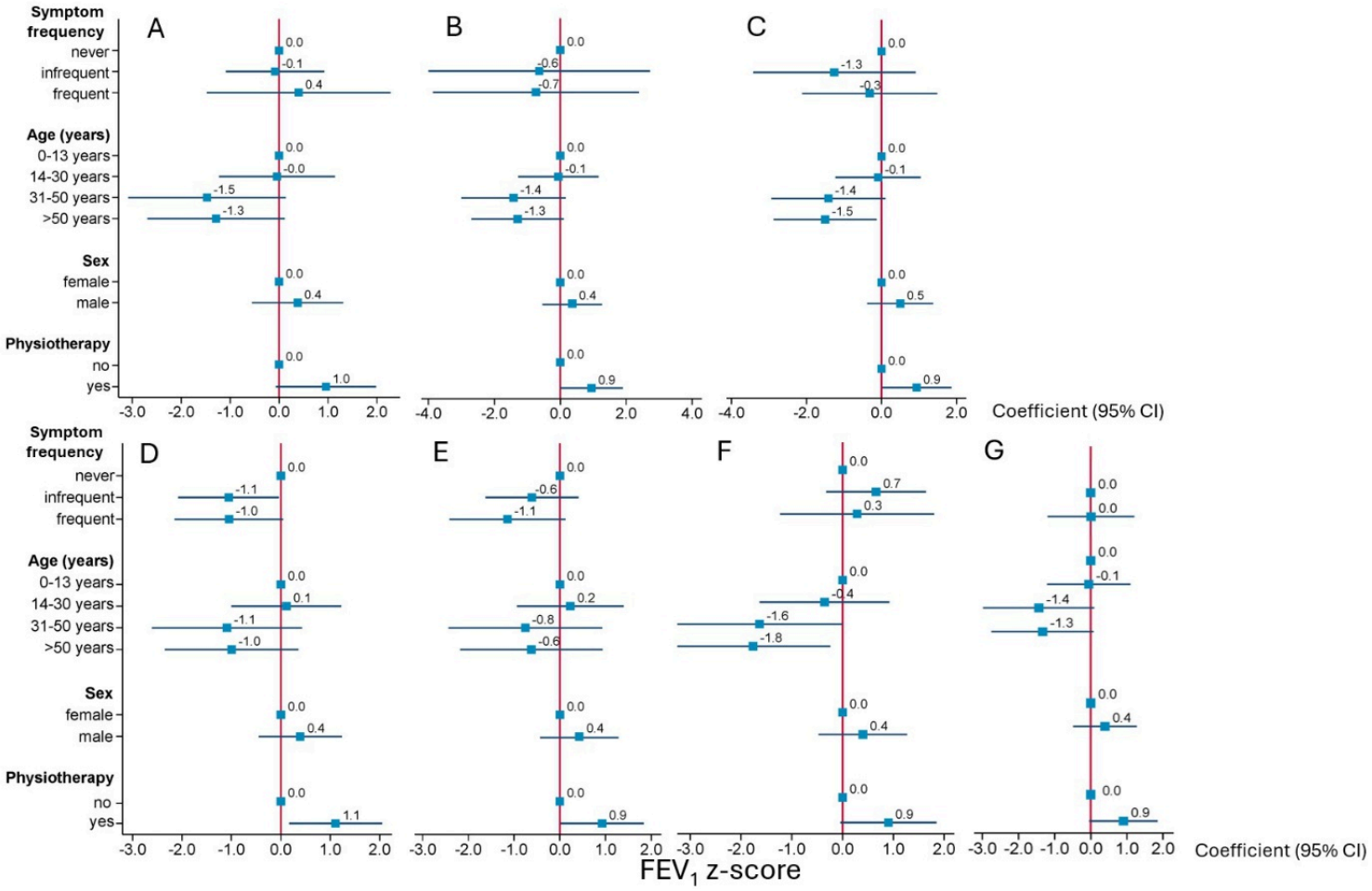


Figure 2: Determinants of FEV1 z-score among study participants with primary ciliary dyskinesia living in Switzerland. A: snoring, B: coughing, C: sputum, D: wheezing, E: shortness of breath, F: chest pain, G: nasal symptoms. z-scores are presented with 95% confidence intervals. Comparisons from baseline category, which is "never reported" for all symptoms, except for nasal symptoms where baseline is "infrequent". Frequent symptoms are those patients reported as "often" or "daily", infrequent symptoms those reported as "sometimes" or "rarely".

Table 4: Multivariable linear regression analysis of spirometric indices in study participants with primary ciliary dyskinesia living in Switzerland.

	FEV $_1$ z-score			FEV $_1$/FVC z-score		
	Coefficient	**95% CI**	**p-value #**	**Coefficient**	**95% CI**	**p-value #**
Nasal symptoms (frequent)	0.11	−1.09 to 1.31	0.853	0.17	−0.78 to 1.12	0.720
… Age	−0.03	−0.05 to −0.01	0.022	−0.02	−0.04 to −0.01	0.021
… Male sex	0.48	−0.33 to 1.30	0.240	0.56	−0.09 to 1.20	0.087
… Professional physiotherapy	0.86	−0.11 to 1.82	0.082	0.52	−0.24 to 1.29	0.176
Snoring (infrequent)	0.11	−0.86 to 1.07	0.828	0.16	−0.60 to 0.93	0.669
Snoring (frequent)	0.38	−1.48 to 2.25	0.680	0.03	−1.44 to 1.51	0.965
… Age	−0.03	−0.05 to −0.01	0.022	−0.02	−0.04 to −0.01	0.022
… Male sex	0.50	−0.32 to 1.36	0.219	0.60	−0.06 to 1.27	0.076
… Professional physiotherapy	0.84	−0.23 to 1.90	0.065	0.47	−0.37 to 1.31	0.263
Cough (infrequent)	−0.70	−3.99 to 2.60	0.673	−0.77	−3.31 to 1.77	0.544
Cough (frequent)	−0.75	−3.90 to 2.37	0.626	−1.40	−3.82 to 1.02	0.250
… Age	−0.03	−0.05 to −0.01	0.028	−0.02	−0.04 to −0.01	0.037
… Male sex	0.47	−0.36 to 1.29	0.264	0.54	−0.10 to 1.18	0.094
… Professional physiotherapy	0.92	−0.05 to 1.89	0.062	0.67	−0.07 to 1.42	0.076
Sputum (infrequent)	−1.44	−3.57 to 0.70	0.182	−0.65	−2.37 to 1.08	0.454
Sputum (frequent)	−0.41	−2.20 to 1.38	0.647	−0.36	−1.81 to 1.08	0.616
… Age	−0.03	−0.05 to −0.01	0.010	−0.02	−0.04 to −0.01	0.022
… Male sex	0.58	−0.23 to 1.38	0.155	0.61	−0.05 to 1.26	0.068
… Professional physiotherapy	0.90	−0.05 to 1.85	0.061	0.59	−0.18 to 1.35	0.129
Wheezing (infrequent)	−1.13	−2.13 to −0.12	0.029	−1.24	−2.00 to −0.48	0.002
Wheezing (frequent)	−1.11	−2.20 to −0.20	0.046	−1.00	−1.83 to −0.18	0.018
… Age	−0.02	−0.05 to −0.01	0.048	−0.02	−0.33 to −0.01	0.062
… Male sex	0.45	−0.33 to 1.22	0.250	0.53	−0.05 to 1.12	0.074
… Professional physiotherapy	1.07	0.11 to 2.02	0.028	0.81	0.10 to 1.53	0.027
Shortness of breath (infrequent)	−0.67	−1.65 to 0.31	0.174	−0.53	−1.31 to 0.24	0.174
Shortness of breath (frequent)	−1.27	−2.50 to −0.04	0.043	−0.99	−1.96 to 0.01	0.048
… Age	−0.01	−0.04 to 0.01	0.294	−0.01	−0.03 to 0.01	0.297
… Male sex	0.46	−0.33 to 1.24	0.250	0.54	−0.08 to 1.17	0.086
… Professional physiotherapy	0.90	−0.02 to 1.81	0.054	0.57	−0.15 to 1.29	0.120
Chest pain (infrequent)	0.70	−0.21 to 1.62	0.129	−0.03	−0.77 to 0.72	0.944
Chest pain (frequent)	0.25	−1.17 to 1.66	0.727	−0.04	−1.19 to 1.11	0.944
… Age	−0.03	−0.57 to −0.01	0.008	−0.21	−0.41 to 0.00	0.033
… Male sex	0.50	−0.30 to 1.31	0.216	0.57	−0.86 to 1.23	0.087
… Professional physiotherapy	0.90	−0.05 to 1.85	0.064	0.56	−0.21 to 1.33	0.152

CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

Results of multivariable regression models separate for each symptom. Age measured in years.

Comparisons from baseline category, which is "never reported" for all symptoms, except for nasal symptoms where baseline is "infrequent". Frequent symptoms are those patients reported as "often" or "daily"; infrequent symptoms are those reported as "sometimes" or "rarely".

Discussion

To our knowledge, this is the first study to assess the association of spirometry – the most commonly used outcome measure for chronic respiratory diseases – with the broad range of respiratory symptoms patients with PCD experience. Patients with PCD living in Switzerland reported a variety of symptoms, many of them experienced frequently, and had low lung function z-scores even in childhood. Among all patient-reported respiratory symptoms, wheezing and shortness of breath were associated with lower FEV_1 and FEV_1/FVC. Despite the lack of statistical significance, the coefficient's size for other lower respiratory tract symptoms such as coughing and sputum, suggested still a negative association with FEV_1 and FEV_1/FVC. Upper airway symptoms showed no evidence of association with spirometry. Our findings highlight the importance of patient-reported symptoms, which are essential for research and clinical care. Patient-reported symptoms cannot be substituted by objective measurements. The most important strength of our study was that it was nested in the CH-PCD, allowing us to invite all registered participants currently in follow-up liv-

ing in Switzerland without any selection. It also allowed us to link patient reported information on symptoms to clinical data on lung function retrieved from clinics and practices. Another strength was the use of the standardised FOLLOW-PCD patient questionnaire [33], which led to homogeneous, standardised data about symptom frequency reported directly by participants or parents of participants.

Our study presents several limitations. Not all invited participants completed the questionnaire and, among those who did, not all had lung function measurements available. Although we did not find many differences in baseline characteristics when comparing these groups, this could have potentially introduced selection bias as people with more severe symptoms might be more prone to participate. Similarly, people with less severe disease could be more prone to miss their scheduled appointment for lung function measurement. It would be relevant to distinguish between participants with an additional asthma diagnosis, but this information was not regularly recorded in clinical records. Moreover, reversible airway obstruction appears to be an independent feature of PCD, which is often misdiagnosed as asthma [39] so information on asthma diagnosis is not always accurate and we were lacking information about reversibility testing which was not commonly performed. We also lack information about exacerbation status at the follow-up visit or whether physiotherapy was performed prior to spirometry, which could have influenced respirometry results. An important limitation is that the patient-reported symptoms refer to a period of 3 months while spirometry captures lung function at one specific timepoint and it has been shown to vary naturally over time [40]. Although national, the CH-PCD still has few registered participants as PCD remains underdiagnosed. Our sample size is reasonable for a rare disease in a small country; it led, however, to limitations in considering other important factors in our analysis, such as exposure to tobacco, environmental or further clinical factors. It also did not allow us to stratify our analysis by diagnostic certainty; however, past studies with similar inclusion criteria and larger sample size showed no clinical differences between patients with confirmed and suspected diagnosis according to official guidelines [29, 41].

Our findings on patient-reported symptoms are similar to those of previous studies. In 2020, we had sent another survey to CH-PCD participants with the same questions on patient-reported symptoms as it was also based on the FOLLOW-PCD patient questionnaire. Symptom frequency was similar overall with higher prevalence of frequent wheezing (28% in 2022 vs 12% in 2020) and frequent shortness of breath (29.5% vs 20%), which could be due to the fact that participants seemed to experience fewer symptoms during the COVID pandemic, probably due to shielding and fewer infections [27]. Compared to an international study assessing the prevalence of sinonasal problems among patients with PCD, our participants more often reported frequent nasal symptoms (52% vs 85%) but less often frequent snoring (12% vs 6%) perhaps caused by different age distribution [31]. Other studies reporting on clinical symptoms use mostly nonstandard information from clinical charts and show a high variability in reported symptoms, not easy to compare with our results.

There is only one study, by our team, that compared how well patient-reported symptoms correlate with objective measures among patients with PCD, focusing on upper airway and ear manifestations [42]. In that study, which analysed international data, we found that many patients appeared to underestimate and underreport their symptoms, to which they grew accustomed over time, especially if not prompted by specific questions, and that patient-reported measures complement objective measures. The current study's findings also highlight that objective measures or unstandardised information on symptoms extracted from records cannot replace information on patient-reported symptoms, supporting the use of both for research and clinical follow-up.

Although universally accepted and commonly used, spirometry has been shown to not be sufficient on its own for monitoring respiratory morbidity in PCD. Longitudinal spirometry-derived lung function measurements from an international prospective cohort showed that changes in intra-individual FEV_1 between study visits in stable disease conditions were beyond the expected test variability [40]. Compared to spirometry, multiple breath washout has been shown to be more sensitive in identifying early lung damage, and could be used additionally to guide appropriate management especially in patients diagnosed early in life [20, 43-45]. Moreover, discordance between lung function and imaging outcomes in patients with PCD supports the use of both imaging and lung function [21]. Regular standardised assessments such as nasal endoscopy and sinus imaging are required to evaluate how upper airway disease progresses [31].

Spirometry captures some of the lower airway symptoms, but cannot capture the range of respiratory symptoms patients with PCD experience in daily life. For research and clinical follow-up, we need additional objective outcome measures e.g. assessing lung clearance index, imaging outcomes and upper airway assessments, together with regular and standardised assessment of patient-reported outcomes to successfully assess disease progression and guide management.

Data sharing statement

CH-PCD study data are not deposited in an open-access repository. Given the rarity of the disease, although data are pseudonymised, they may still include sensitive information; therefore, participants were not asked to give consent to have their data deposited publicly. Partial datasets for specific analyses including individual patient data and a data dictionary defining each included field may be made available from Dr Goutaki (myrofora.goutaki[at]unibe.ch) upon reasonable request.

Notes

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Author contributions: M Goutaki developed the concept and designed the study. M Goutaki, M Koller, YT Lam and L Schreck organised the survey, then cleaned and standardised the data. M Goutaki, YT Lam and M Koller performed the statistical analyses and drafted the manuscript. All authors commented on and revised the manuscript. M Goutaki takes final responsibility for content.

Use of AI: The authors declare that no generative artificial intelligence (AI) tools or AI-assisted technologies were used in the drafting, writing or creation of this manuscript.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix A

Table S1: Comparison of demographic characteristics of CH-PCD participants who responded to the survey to non-responders.

	Invited N (%)	Responded to survey N (%)	Non-responders N (%)	*p* -value [$]
Number of participants	102 (100) [#]	64 (100)	38 (100) [#]	
Age, median (IQR)	24 (2-75)	24 (3-75)	25 (2-71)	
Female sex	54 (53)	35 (55)	19 (50)	0.647
German speaking	80 (78)	49 (77)	31 (82)	0.551

PCD: primary ciliary dyskinesia. CH-PCD: Swiss PCD registry. All characteristics are presented as N and column % except for age in median and IQR: interquartile range. #: includes 3 participants with an invalid address $: Pearson's Chi square test

Table S2: Comparison of demographic characteristics of participants included in the analysis compared to the ones who were excluded because of no available lung function measurement within the defined period.

	Survey responders N (%)	Participants included in analysis N (%)	Participants excluded (no spirometry) N (%)	*p* -value [$]
Number of participants	64 (100)	54 (100)	10 (100)	
Age, median (IQR)	22 (3-73)	22 (3-73)	28 (3-65)	
Female sex	35 (55)	27 (50)	8 (80)	0.080
German speaking	49 (77)	40 (74)	9 (90)	0.275

PCD: primary ciliary dyskinesia. CH-PCD: Swiss PCD registry.

All characteristics are presented as N and column % except for age in median and IQR: interquartile range. $: Pearson's Chi square test

Table S3: Multivariable linear regression analysis of FVC z-score in study participants with PCD living in Switzerland.

		FVC z-score	
	Coefficient	**95% CIs**	***p* -value #**
Nasal symptoms (frequent)	–0.02	–1.12 to 1.07	0.964
… Age (in years)	–0.03	–0.05 to –0.01	0.013
… Male sex	0.07	–0.67 to 0.82	0.842
… Professional physiotherapy	0.62	–0.26 to 1.50	0.165
Snoring (infrequent)	0.05	–0.85 to 0.95	0.912
Snoring (frequent)	0.43	–1.27 to 2.13	0.616
… Age	–0.03	–0.05 to –0.01	0.012
… Male sex	0.10	–0.67 to 0.86	0.804
… Professional physiotherapy	0.60	–0.38 to 1.58	0.225
Cough (infrequent)	–0.26	–3.25 to 2.72	0.860
Cough (frequent)	0.11	–2.74 to 2.95	0.940
… Age	–0.03	–0.05 to –0.01	0.011
… Male sex	0.07	–0.69 to 0.82	0.863
… Professional physiotherapy	0.92	–0.30 to 1.47	0.189
Sputum (infrequent)	–1.48	–3.41 to 0.45	0.130
Sputum (frequent)	–0.50	–2.11 to 1.12	0.538
… Age	–0.03	–0.05 to –0.01	0.004
… Male sex	0.17	–0.57 to 0.90	0.648
… Professional physiotherapy	0.66	–0.20 to 1.51	0.131
Wheeze (infrequent)	–0.35	–1.31 to 0.61	0.466
Wheeze (frequent)	–0.56	–1.60 to 0.48	0.284
… Age	–0.03	–0.05 to –0.01	0.017
Male sex	0.51	–0.69 to 0.79	0.891
… Professional physiotherapy	0.63	–0.28 to 1.53	0.171
Shortness of breath (infrequent)	–0.43	–1.34 to 0.49	0.353
Shortness of breath (frequent)	–1.00	–2.11 to 0.17	0.093
… Age	–0.02	–0.04 to 0.01	0.148
… Male sex	0.60	–0.67 to 0.79	0.869
… Professional physiotherapy	0.69	–0.22 to 1.48	0.141
Chest pain (infrequent)	0.84	0.02 to 1.66	0.045
Chest pain (frequent)	0.28	–0.99 to 1.54	0.662
… Age	–0.03	–0.56 to – 0.01	0.002
… Male sex	0.07	–0.65 to 0.80	0.837
… Professional physiotherapy	0.63	–0.22 to 1.48	0.142

Results of multivariable regression models separate for each symptom PCD: primary ciliary dyskinesia. FVC: forced vital capacity. CI: confidence interval. #: comparisons from baseline category, which is "never reported" for all symptoms, except for nasal symptoms where baseline is infrequent. Frequent symptoms reported as often or daily. Infrequent symptoms reported as sometimes or rarely.