Association between upper and lower respiratory disease among patients with primary ciliary dyskinesia: an international study

Yin Ting Lam [1], Jean-François Papon [2,3], Mihaela Alexandru [2,3,4], Andreas Anagiotos [5], Miguel Armengot [6,7,8], Mieke Boon [9], Andrea Burgess [10], Doriane Calmes [11], Suzanne Crowley [12], Sinan Ahmed D. Dheyauldeen [13,14], Nagehan Emiralioglu [15], Ela Erdem Eralp [16], Christine van Gogh [17], Yasemin Gokdemir [16], Eric G. Haarman [18], Amanda Harris [19,20], Isolde Hayn [21], Hasnaa Ismail-Koch [10], Bülent Karadag [16], Céline Kempeneers [22], Elisabeth Kieninger [23], Sookyung Kim [2], Natalie Lorent [24,25], Ugur Ozcelik [15], Charlotte Pioch [26], Johanna Raidt [27], Ana Reula [8,28], Jobst Roehmel [26,29,30], Synne Sperstad Kennelly [12], Panayiotis Yiallouros [31,32], on behalf of the EPIC-PCD team [33] and Myrofora Goutaki [1,23]

[1]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. [2]Assistance Publique-Hôpitaux de Paris, Université Paris-Saclay, Hôpital Bicêtre, Service d'ORL, Le Kremlin-Bicêtre, France. [3]Faculté de Médecine, Université Paris-Saclay, Le Kremlin-Bicêtre, France. [4]AP-HP Département de Génétique médicale, Sorbonne Université, Inserm UMR_S933 Maladies génétiques d'expression pédiatrique, Hôpital Armand Trousseau, Paris, France. [5]Department of Otorhinolaryngology, Nicosia General Hospital, Nicosia, Cyprus. [6]Department of Otorhinolaryngology, and Primary Ciliary Dyskinesia Unit, La Fe University and Polytechnic Hospital, Valencia, Spain. [7]Medical School, Valencia University, Valencia, Spain. [8]Molecular, Cellular and Genomic Biomedicine Group, IIS La Fe, Valencia, Spain. [9]Department of Paediatrics, University Hospital Leuven, Leuven, Belgium. [10]Primary Ciliary Dyskinesia Centre, Southampton Children's Hospital, Southampton NHS Foundation Trust, Southampton, UK. [11]Department of Pneumology, University Hospital Liège, Liège, Belgium. [12]Paediatric Department of Allergy and Lung Diseases, Oslo University Hospital, Oslo, Norway. [13]Department of Otorhinolaryngology, Head and Neck Surgery, Oslo University Hospital, Oslo, Norway. [14]Faculty of Medicine, University of Oslo, Oslo, Norway. [15]Department of Pediatric Pulmonology, Hacettepe University, School of Medicine, Ankara, Turkey. [16]Department of Pediatric Pulmonology, Marmara University, School of Medicine, Istanbul, Turkey. [17]Department of Otorhinolaryngology – Head and Neck Surgery, Amsterdam UMC, Amsterdam, The Netherlands. [18]Department of Pediatric Pulmonology, Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit, Amsterdam, The Netherlands. [19]Southampton Children's Hospital, University of Southampton, Southampton, UK. [20]Primary Ciliary Dyskinesia Centre, NIHR Respiratory Biomedical Research Centre, University of Southampton, Southampton, UK. [21]Department of Otorhinolaryngology, Head and Neck Surgery, Charité-Universitätsmedizin Berlin, Berlin, Germany. [22]Division of Respirology, Department of Pediatrics, University Hospital Liège, Liège, Belgium. [23]Division of Paediatric Respiratory Medicine and Allergology, Department of Paediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland. [24]Department of Respiratory Diseases, University Hospitals Leuven, Leuven, Belgium. [25]Department Chrometa, Laboratory of Respiratory and Thoracic Diseases, KU Leuven, Leuven, Belgium. [26]Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine and Cystic Fibrosis Center, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany. [27]Department of General Pediatrics, University Hospital Muenster, Muenster, Germany. [28]Biomedical Sciences Department, CEU-Cardenal Herrera University, Castellón, Spain. [29]German Centre for Lung Research (DZL), Associated Partner Site, Berlin, Germany. [30]Berlin Institute of Health at Charité-Universitätsmedizin Berlin, Berlin, Germany. [31]Medical School, University of Cyprus, Nicosia, Cyprus. [32]Pediatric Pulmonology Unit, Hospital "Archbishop Makarios III", Nicosia, Cyprus. [33]For a list of the EPIC-PCD team see the Acknowledgements.

Corresponding author: Myrofora Goutaki (myrofora.goutaki@unibe.ch)

Shareable abstract (@ERSpublications)
Upper and lower airway disease occur interdependently in patients with PCD and need to be assessed as a common entity with appropriate clinical and patient-reported measures and managed accordingly to improve clinical outcomes https://bit.ly/48F2pXu

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Abstract

Introduction Nearly all patients with primary ciliary dyskinesia (PCD) report ear–nose–throat (ENT) symptoms. However, scarce evidence exists about how ENT symptoms relate to pulmonary disease in PCD. We explored possible associations between upper and lower respiratory disease among patients with PCD in a multicentre study.

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Methods We included patients from the ENT Prospective International Cohort (EPIC-PCD). We studied associations of several reported ENT symptoms and chronic rhinosinusitis (defined using patient-reported information and examination findings) with reported sputum production and shortness of breath, using ordinal logistic regression. In a subgroup with available lung function results, we used linear regression to study associations of chronic rhinosinusitis and forced expiratory volume in 1 s (FEV_1) accounting for relevant factors.

Results We included 457 patients (median age 15 years, interquartile range 10–24 years; 54% males). Shortness of breath associated with reported nasal symptoms and ear pain of any frequency, often or daily hearing problems, headache when bending down (OR 2.1, 95% CI 1.29–3.54) and chronic rhinosinusitis (OR 2.3, 95% CI 1.57–3.38) regardless of polyp presence. Sputum production associated with daily reported nasal (OR 2.2, 95% CI 1.20–4.09) and hearing (OR 2.0, 95% CI 1.10–3.64) problems and chronic rhinosinusitis (OR 2.1, 95% CI 1.48–3.07). We did not find any association between chronic rhinosinusitis and FEV_1.

Conclusion Reported upper airway symptoms and signs of chronic rhinosinusitis associated with reported pulmonary symptoms, but not with lung function. Our results emphasise the assessment and management of upper and lower respiratory disease as a common, interdependent entity among patients with PCD.

Introduction

Nearly all patients with primary ciliary dyskinesia (PCD) report chronic nasal problems caused by poor mucociliary clearance, leading to mucus stagnation in upper and lower airways [1–3]. Clogged airways facilitate recurrent infections, chronic microbial colonisation and airway inflammation, leading further to chronic rhinosinusitis and bronchiectasis [4, 5]. In other respiratory diseases, such as asthma and cystic fibrosis, evidence supports the theory of the "unified airway" [6, 7]. Published studies have highlighted the association of chronic rhinosinusitis with COPD [8, 9]. However, for PCD upper and lower airway manifestations are often managed independently. A common approach is usually considered when treatments for pulmonary exacerbations fail and sinuses become considered possible reservoirs for pulmonary colonisation, chronic lung infections and deterioration of lung function [10].

So far, only a few single-centre studies have attempted to connect the dots between upper and lower airways in PCD [11–13]. A study in a small cohort in Denmark presented simultaneous infections of the sinuses and lower airways with the same pathogen among patients with PCD [10]. A French study assessed associations between ear–nose–throat (ENT) symptoms and lung function among adult patients with PCD and reported otitis media with effusion associated with airway obstruction (forced expiratory volume in 1 s (FEV_1) <70%) [12]. Otherwise, scarce evidence exists about possible associations of sinonasal and otologic symptoms and signs of disease with pulmonary symptoms in PCD and whether patients with more upper airways symptoms also have more advanced lung disease. We aimed to assess what, if any, upper respiratory characteristics possibly associate with lung disease. Specifically, we studied associations 1) between patient-reported upper and lower respiratory symptoms; 2) between chronic rhinosinusitis (with or without nasal polyps) and reported lower respiratory symptoms; and 3) between chronic rhinosinusitis (with and without nasal polyps) and lung function.

Methods

Study design and population

We analysed cross-sectional data from our ENT Prospective International Cohort of Patients with PCD (EPIC-PCD), the first PCD cohort focused on upper respiratory disease [14]. EPIC-PCD started recruiting patients with PCD in February 2020, following them during regular ENT visits at participating centres. We nested examinations in regular care and collected additional questionnaires. For this study, we included eligible patients with data entered in the EPIC-PCD database by 15 May 2023 from 13 participating centres (Amsterdam, Ankara, Berlin, Bern, Nicosia, Istanbul, Leuven, Liège, Münster, Oslo, Paris, Southampton, Valencia) in 10 countries. We included participants of all ages with PCD with ENT examination and completed symptom questionnaire within a 2-week interval of the examination.

The EPIC-PCD study is hosted at the University of Bern (Bern, Switzerland; clinicaltrials.gov identifier NCT04611516). We received ethics approval from each participating centre and ethics committee for human research in accordance with local legislation. We obtained informed consent or assent from either participants or parents or caregivers of participants aged ⩽14 years as described previously [3, 15]. Our reporting conforms with the Strengthening the Reporting of Observational Studies in Epidemiology statement [16].

Patient-reported symptoms

We collected patient-reported symptoms using the disease-specific FOLLOW-PCD questionnaire (version 1.0), which is part of the standardised PCD-specific form FOLLOW-PCD developed for collecting clinical

information for research and clinical follow-up [17]. The FOLLOW-PCD questionnaire was designed with three versions for three age groups: adults, adolescents aged 14–17 years and parents or caregivers of children with PCD aged ⩽14 years. It is available in the local languages of all participating centres. Symptom-related questions asked about frequency and characteristics of symptoms during the previous 3 months. For the upper respiratory symptoms, we focused on chronic nasal symptoms, headache when bending down as proxy for sinusitis, ear pain and hearing problems. For lower respiratory symptoms we focused on shortness of breath and sputum production, which included any reported cough with expectorated or swallowed secretions. Symptom frequency options included daily, often, sometimes, rarely and never (five-point Likert scale). In addition, the questionnaire included questions about health-related behaviours, such as smoking exposure and living conditions, during the past 12 months. Depending on available response categories, we recoded missing answers as "unknown", "no" or "never."

Clinical examinations

ENT specialists performed routine examinations (sinonasal examinations by nasal endoscopy or anterior rhinoscopy if tolerated by participants, otoscopy, tympanometry and audiometry among others) at planned consultations, according to local protocols. Examination findings were recorded in a standardised way using the ENT examination module of the FOLLOW-PCD form [17]. If spirometry was performed before or after 1 month from ENT consultation, we also recorded FEV_1 values. Participating centres performed spirometry according to American Thoracic Society/European Respiratory Society (ERS) guidelines [18] during routine planned visits and not at exacerbation or during respiratory tract infection. We calculated FEV_1 z-scores based on the Global Lung Initiative 2021 reference values [19]. We calculated body mass index (BMI) using height and weight reported at ENT or spirometry visit date. For adults, we classified BMI as underweight (<18.5 $kg \cdot m^{-2}$), normal (⩾18.5 to <25 $kg \cdot m^{-2}$), pre-obesity (⩾25 to <30 $kg \cdot m^{-2}$), obesity class I (⩾30 to <35 $kg \cdot m^{-2}$), obesity class II (⩾35 to <40 $kg \cdot m^{-2}$) or obesity class III (⩾40 $kg \cdot m^{-2}$) by World Health Organization (WHO) standards [20]. For children and adolescents aged ⩽18 years, we calculated sex and age-specific BMI z-scores and categorised by thinness (<–2 z-scores), normal (−2 to 1 z-scores), overweight (1 to 2 z-scores), and obesity (>2 z-scores) based on 2007 WHO references [21].

Definition of chronic rhinosinusitis

We created a composite exposure variable chronic rhinosinusitis to study chronic rhinosinusitis associations (with and without polyps) with reported lower respiratory symptoms and lung function. The dichotomous composite variable included 1) daily or often reported nasal symptoms and 2) examination findings of nasal discharge (seromucous, mucopurulent or mixed with blood) or nasal oedema at examination.

Diagnosis and other clinical information from charts

Participants were diagnosed at participating centres following ERS guidelines [22] as described in previous publications [3, 15]. Ultrastructural defects were categorised based on the international consensus guideline for reporting transmission electron microscopy (TEM) results, which defined class 1 (hallmark, namely outer dynein arm defects, outer and inner dynein arm defects and microtubular disorganisation with inner dynein arm defects) and class 2 defects, such as central complex defects [23]. Further data collected included information on laterality defects and prescribed medication for upper and lower airways. We entered all collected data in the research electronic data capture study database based on the FOLLOW-PCD modules [17].

Statistical analysis

We described population characteristics and patient or parent-reported symptoms for the total population and separately among age groups 0–6 years, 7–14 years, 15–30 years, 31–50 years and >50 years. For continuous variables, we used median and interquartile range (IQR). For categorical variables, we used numbers and proportions, and we compared differences between age groups using Pearson's Chi-squared and the Kruskal–Wallis rank test. For aims 1 and 2, outcomes of interest were reported lower respiratory symptoms, namely frequency of shortness of breath and sputum production. We studied possible associations of reported frequency of nasal symptoms, ear pain, hearing problems and reported headache when bending down, with reported frequency of shortness of breath and sputum production using multivariable ordinal logistic regression, adjusting for age and sex. In separate multivariable ordinal logistic regression models, we assessed association of chronic rhinosinusitis (as defined earlier) with frequency of shortness of breath and sputum production, adjusting for factors possibly associated with respiratory disease such as age, sex, age at diagnosis, nasal polyp status and smoking status as either active, passive or no tobacco smoke exposure.

For a subgroup of patients with available FEV_1, we assessed the association of chronic rhinosinusitis with FEV_1 z-score as outcome, using linear regression and adjusting for age, sex, nasal polyps, smoking status

and prescribed nasal corticosteroids, prophylactic antibiotics, nasal rinsing and inhaled corticosteroids. For all models, we chose factors based on data availability and clinical importance to the study team. We noted a collinearity of age and age at diagnosis, so it was not possible to include both in our main model. Since separate models showed similar results, we only included age. Among a subgroup of participants with available TEM results, we repeated our regression models, including age and category of ciliary ultrastructural defect to study whether ciliary ultrastructural defect was a risk factor for a possible association between chronic rhinosinusitis and lower airway symptoms or FEV_1. We performed all analyses using Stata version 15 (StataCorp, TX, USA).

Results

Study population

By mid-May 2023, 504 (85%) of 596 invited patients had enrolled into the EPIC-PCD study (figure 1). Of them, 457 had data entered in the database and fulfilled eligibility criteria. We included 286 (63%) children and 171 (37%) adults; 54% male (table 1); median (IQR) age 15 (10–24) years; 162 (35%) with situs inversus totalis; and 36 (8%) having cardiovascular malformation (five with severe malformation, such as transposition of the great arteries). Height and weight were available for ∼80% of the study population; half had normal BMI (table 1). Obesity class III was more prevalent among adults aged ⩾31 years. We did not find any differences by sex for any of these characteristics. We present a summary of the test results supporting PCD diagnosis among all participants and a breakdown of the genetic mutations reported in participants with identified biallelic pathogenic variants or compound heterozygosity (n=229, 50%) in supplementary tables S1 and S2, respectively.

Association of reported upper and lower respiratory symptoms

Reported upper and lower respiratory symptoms were common for all age groups, especially nasal symptoms and sputum production (supplementary table S3). We found reported frequency of shortness of breath increased with any reported frequency of nasal symptoms (OR 4.2, 95% CI 2.18–8.16 for daily nasal symptoms compared with no nasal symptoms) and with reported headache when bending down (OR 2.1, 95% CI 1.29–3.54) (figure 2). For frequency of sputum production, we only found evidence of association with daily nasal symptoms (OR 2.1, 95% CI 1.20–4.09). Regarding reported ear symptoms, any frequency of ear pain (OR 3.7, 95% CI 1.62–8.44 for daily ear pain compared with no ear pain) and daily (OR 2.0, 95% CI 1.13–3.71) or often (OR 1.9, 95% CI 1.10–3.46) reported hearing problems compared with no hearing problems associated with frequency of shortness of breath (figure 3). Hearing problems reported daily also associated with higher frequency of sputum production (OR 2.0, 95% CI

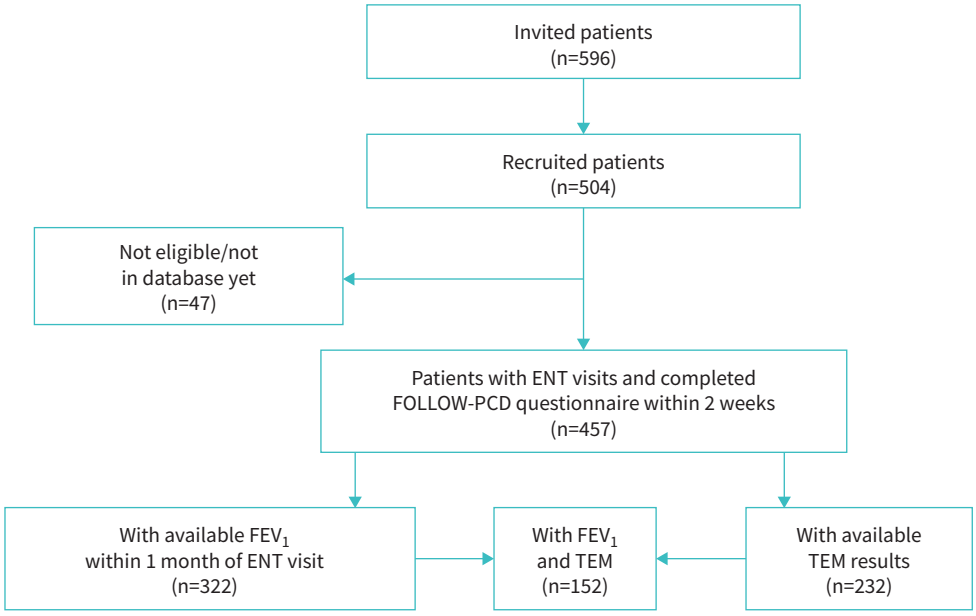

FIGURE 1 Flowchart of people who participated in the ENT (ear–nose–throat) Prospective International Cohort (EPIC)-PCD (primary ciliary dyskinesia). FEV_1: forced expiratory volume in 1 s; TEM: transmission electron microscope.

TABLE 1 Characteristics of ENT (ear–nose–throat) Prospective International Cohort (EPIC)-PCD (primary ciliary dyskinesia) participants, overall and by age group (n=457)

	Total	0–6 years	7–14 years	15–30 years	31–50 years	>50 years	p-value[#]
Participants	457 (100)	47 (100)	149 (100)	173 (100)	54 (100)	34 (100)	
Age years	15 (10–24)	2 (4–5)	10 (8–12)	18 (16–22)	38 (34–42)	57 (55–63)	
Male	246 (54)	26 (55)	82 (55)	90 (52)	30 (56)	18 (53)	0.980
Age at PCD diagnosis years	9 (4–18)	0 (0–2)	6 (1–8)	13 (9–17)	34 (29–37)	51 (44–56)	
Consanguinity							<0.001
Yes	124 (27)	7 (15)	46 (31)	56 (32)	11 (20)	4 (12)	
No	167 (37)	15 (32)	50 (33)	67 (39)	27 (50)	8 (23)	
Not reported	166 (36)	25 (53)	53 (36)	50 (29)	16 (30)	22 (65)	
Situs							0.001
Situs inversus totalis	162 (35)	26 (55)	56 (37)	64 (37)	9 (17)	7 (21)	
Situs ambiguous	5 (1)	0 (0)	2 (1)	3 (2)	0 (0)	0 (0)	
Situs solitus	278 (61)	20 (43)	88 (60)	105 (60)	40 (74)	25 (73)	
Not reported	12 (3)	1 (2)	3 (2)	1 (1)	5 (9)	2 (6)	
Cardiovascular malformation							0.003
Yes	36 (8)	7 (15)	13 (9)	14 (8)	2 (4)	0 (0)	
No	328 (72)	31 (66)	116 (78)	125 (72)	37 (68)	19 (56)	
Not reported	93 (20)	9 (19)	20 (13)	34 (20)	15 (28)	15 (44)	
Active smoking							<0.001
Yes, daily	4 (1)	NA	NA	3 (2)	0 (0)	1 (3)	
Yes, rarely	6 (1)	NA	NA	3 (2)	2 (4)	1 (3)	
Ex-smoker	17 (4)	NA	NA	2 (1)	10 (18)	5 (15)	
Never smoker	222 (49)	NA	NA	156 (90)	40 (74)	26 (76)	
Not reported	208 (45)	NA	NA	9 (5)	2 (4)	1 (3)	
Smoking in household							<0.001
Yes	83 (18)	7 (15)	29 (20)	38 (22)	5 (9)	4 (12)	
No	298 (65)	36 (77)	109 (73)	98 (56)	36 (67)	19 (56)	
Not reported	76 (17)	4 (8)	11 (7)	37 (21)	13 (24)	11 (32)	
BMI kg·m^{-2} mean (IQR)[¶]				21.1 (19.7–24.1)	23.2 (20.8–27.4)	28.1 (21.6–35.3)	<0.001[f]
BMI z-score[+]		−0.5 (−1.3–0.4)	−0.06 (−0.9–1.2)	0.1 (−0.9–1.0)			0.402[f]
BMI categories							<0.001
Thinness/underweight	26 (6)	1 (2)	7 (4)	12 (7)	5 (9)	1 (3)	
Normal weight	225 (49)	6 (13)	83 (56)	107 (62)	23 (43)	6 (17)	
Pre-obesity/overweight	66 (14)	1 (2)	22 (15)	25 (14)	13 (24)	5 (15)	
Obese/obesity class I	24 (5)	0 (0)	9 (6)	8 (5)	3 (6)	4 (12)	
Obesity class II	7 (2)	0 (0)	0 (0)	3 (2)	0 (0)	4 (12)	
Obesity class III	31 (7)	0 (0)	0 (0)	7 (4)	10 (18)	14 (41)	
Missing	78 (17)	39 (83)	28 (19)	11 (6)	0 (0)	0 (0)	
FEV_1 z-score[§]	−1.9 (−2.9–−0.6)	−0.7 (−2.0–−0.3)	−1.6 (−2.5–0.4)	−2.1 (−3.0–0.8)	−2.3 (−3.3–−0.8)	−1.7 (−3.6–−0.6)	0.008[f]

Data are presented as n (%) or median (interquartile range (IQR)), unless otherwise stated. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; NA: not assessed. [#]: Chi-squared test of independence; [¶]: BMI of 145 adults (aged ⩾18 years) based on World Health Organization (WHO) standards; [+]: BMI z-score from 208 children (aged <18 years) based on WHO standards; [§]: FEV_1 z-score available from 322 participants; [f]: Kruskal–Wallis test.

1.10–3.64). Male sex was less likely to be associated with shortness of breath (figures 2 and 3; OR for male sex in all models 0.7, 95% CI from 0.50–0.97 to 0.52–1.07). We found no differences by age.

Association of chronic rhinosinusitis with lower respiratory symptoms

We found evidence of association between chronic rhinosinusitis and reported frequency of shortness of breath (OR 2.3, 95% CI 1.53–3.32) and sputum production (OR 2.1, 95% CI 1.48–3.06) (figure 4). We did not find any differences related to the presence or absence of nasal polyps accompanying chronic rhinosinusitis, tobacco smoke exposure or by age or sex for both lower respiratory symptoms. Sinonasal examination findings used to define chronic rhinosinusitis and prescribed treatments are presented in supplementary table S4. Among 232 participants with available TEM results (supplementary table S5), we found no difference in reported shortness of breath and sputum production by ciliary ultrastructural defect class (supplementary table S6).

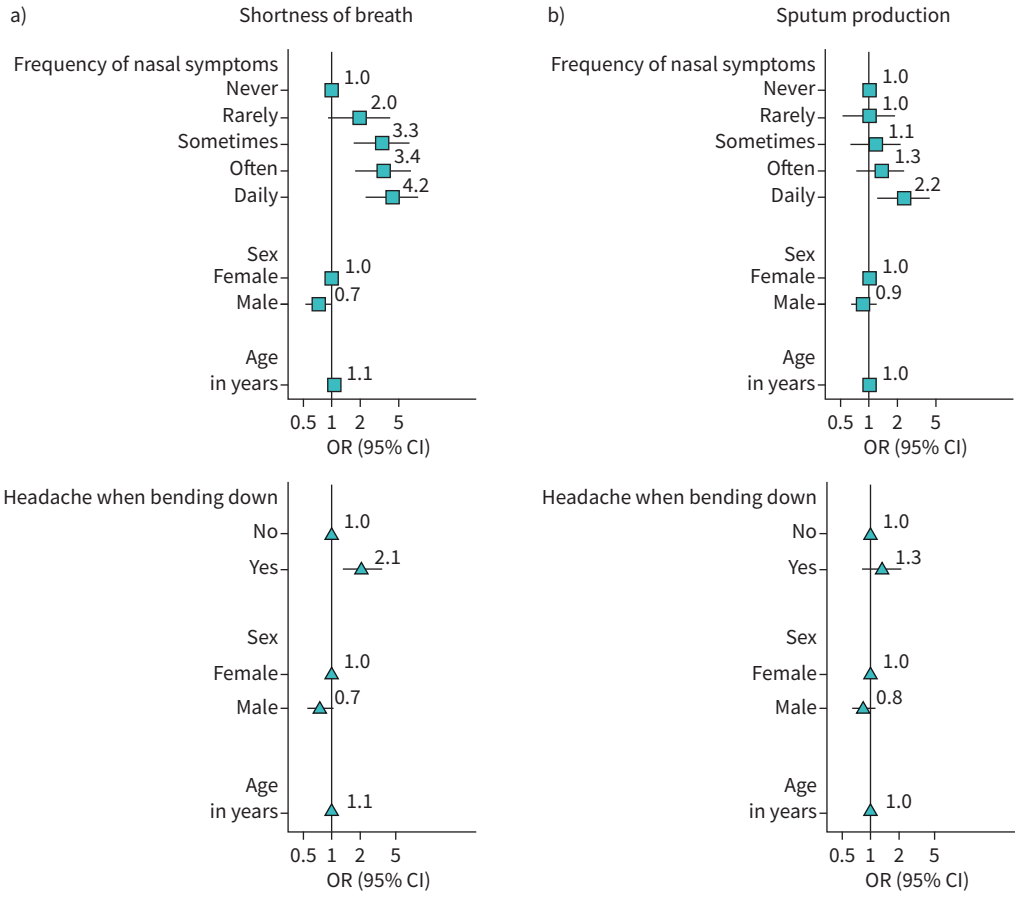

FIGURE 2 Association of patient-/parent-reported nasal symptoms or headache when bending down with a) shortness of breath and b) sputum production among ENT (ear–nose–throat) Prospective International Cohort (EPIC)-PCD (primary ciliary dyskinesia) participants (n=457).

Association of chronic rhinosinusitis with lung function

Within 1 month of ENT visit, 322 participants had available spirometry with a median FEV_1 z-score of −1.90 (IQR −2.9–−0.6) (table 1). We found no association between chronic rhinosinusitis, independently of polyps and FEV_1 z-score, adjusting for possible confounders (table 2). Participants prescribed nasal corticosteroids showed higher FEV_1 z-scores (OR 2.26, 95% CI 0.44–4.07). In addition, we found higher FEV_1 z-score among participants not prescribed inhaled corticosteroids (OR 5.54, 95% CI 2.73–8.34). In a subgroup of 152 participants with available TEM results and spirometry, we found no evidence of association of chronic rhinosinusitis with FEV_1 z-score and no differences by defect (supplementary table S7).

Discussion

Our results showed an association between upper respiratory disease and reported lower respiratory symptoms. Particularly, shortness of breath associated with reported nasal symptoms and ear pain of any frequency; often or daily hearing problems; headache when bending down and with chronic rhinosinusitis (defined using patient-reported information and examination findings), regardless of polyp presence. Sputum production associated with daily reported nasal symptoms and hearing problems, as well as chronic rhinosinusitis, again regardless of polyp presence. Contrary to symptom findings, we did not find any association between chronic rhinosinusitis and reduced lung function measured by spirometry.

Strengths and limitations

EPIC-PCD is the first prospective, international ENT cohort for PCD and, to our knowledge, the first study combining patient-reported symptoms and findings from clinical examinations of upper and lower airways and studying possible association between upper and lower respiratory disease. The cohort includes large numbers of paediatric and adult patients from several different countries. We followed participants during regular visits using FOLLOW-PCD modules, which makes collecting standardised data possible for all

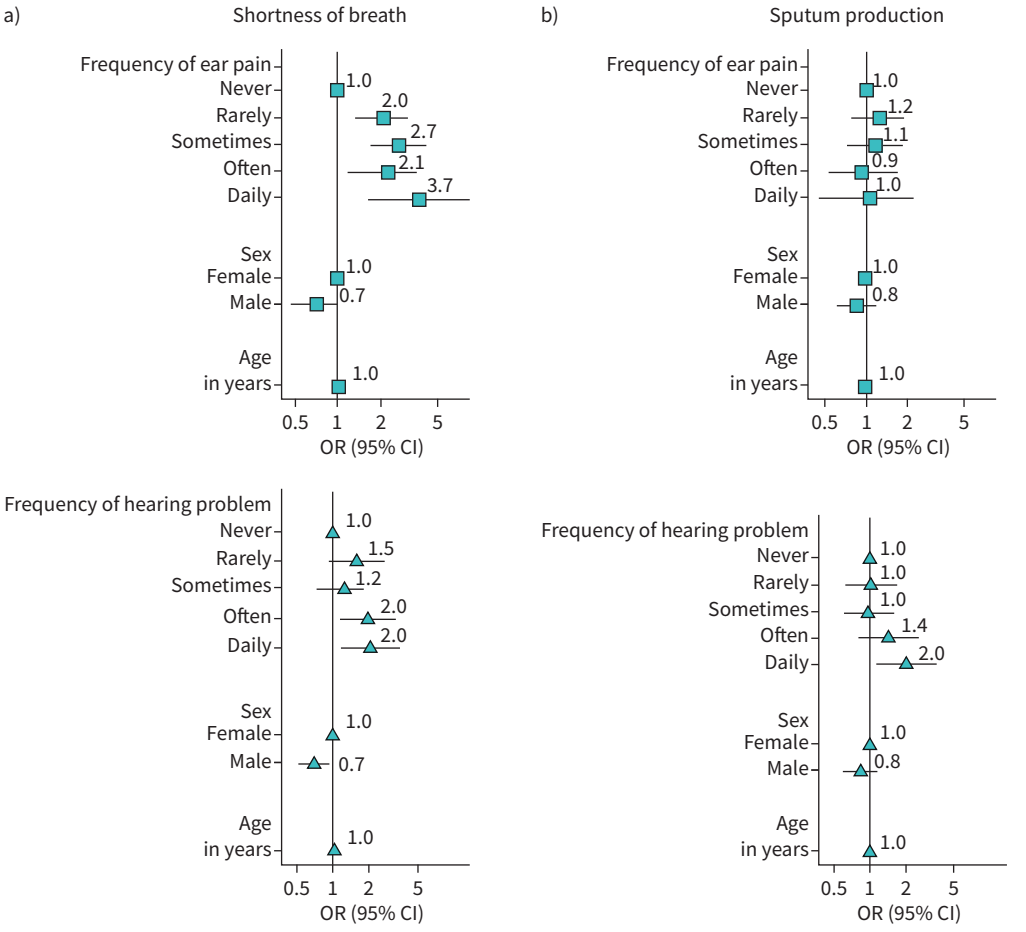

FIGURE 3 Association of patient-/parent-reported ear pain and hearing problems with a) shortness of breath and b) sputum production among ENT (ear–nose–throat) Prospective International Cohort (EPIC)-PCD (primary ciliary dyskinesia) participants (n=457).

participating centres. Since invited patients were interested and it required little effort on their part, most agreed to participate in the study. Not all participants met inclusion criteria (ENT examination and completed questionnaire). We believe exclusion was at random and mostly based on personnel resources or organisational issues at participating centres. However, it is possible that participants with fewer symptoms were less likely to complete questionnaires and fulfil inclusion criteria, introducing selection bias. Lung function measurements were unavailable for some participants within 1 month of study visit, entirely dependent on participating centres: several countries organise pulmonary and ENT visits separately. Since questions about symptoms involved the previous 3 months, we expect minimal risk of recall bias. EPIC-PCD started recruitment during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and patients with confirmed SARS-CoV-2 infection in their history were not excluded; however, infection incidence was low among people with PCD [24]. We expect possible lower reporting of symptoms, especially in the beginning of the study, probably from shielding behaviour [25]. We could not study possible associations between upper airway exacerbations and lung exacerbations, as this information was not collected consistently and using standardised definitions. Despite this being the largest study of its kind, we still lack statistical power to consider several other possible factors possibly influencing associations between upper and lower airways disease, including comorbidities such as asthma and information about management. Due to the cross-sectional nature of the analysed information, we could not study whether seasonal changes affected these associations between upper and lower respiratory disease.

Comparison with other studies

Few studies assessed associations between upper and lower respiratory disease in PCD and none used standardised information on symptoms to assess possible associations. A French study evaluating sinonasal

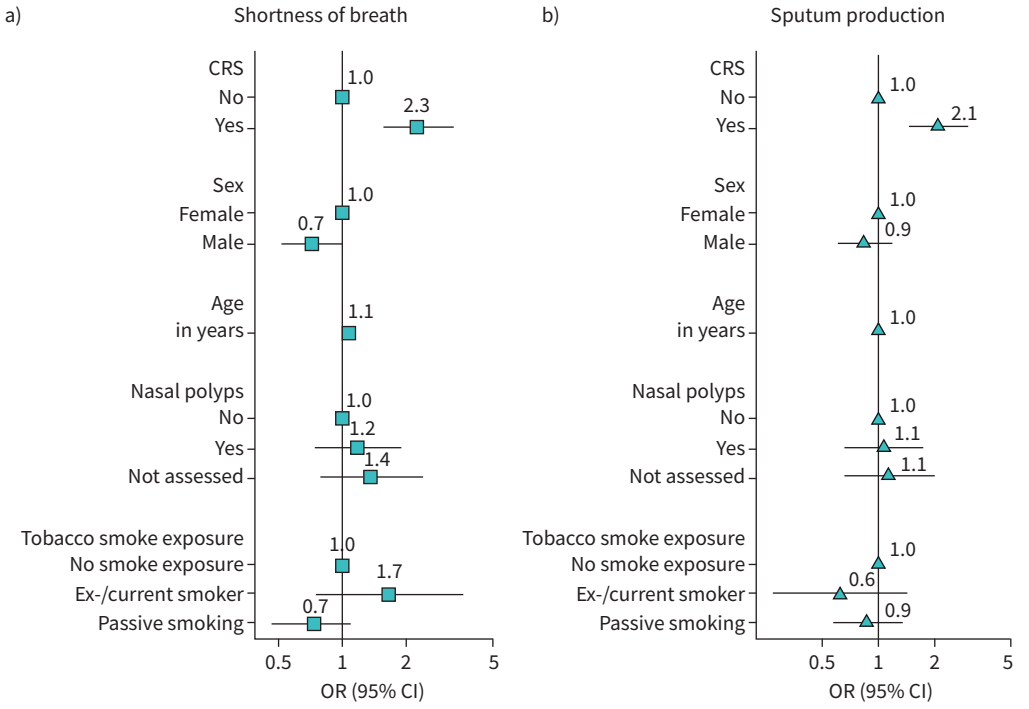

FIGURE 4 Association of chronic rhinosinusitis (CRS) with patient-/parent-reported a) shortness of breath and b) sputum production among ENT (ear–nose–throat) Prospective International Cohort (EPIC)-PCD (primary ciliary dyskinesia) participants (n=457).

TABLE 2 Association of chronic rhinosinusitis with forced expiratory volume in 1 s (FEV_1) z-score among ENT (ear–nose–throat) Prospective International Cohort (EPIC)-PCD (primary ciliary dyskinesia) participants (n=322)

	Coefficient (95% CI)	p-value
Chronic rhinosinusitis[#]	0.80 (−0.83–2.24)	0.367
Age	−0.02 (−0.09–0.04)	0.470
Male sex	0.01 (−1.37–1.39)	0.988
Nasal polyps		
Yes	0.58 (−1.43–2.60)	0.568
Not assessed	−1.13 (−3.80–1.55)	0.408
Smoking		
Ex-/current smoker	7.44 (3.27–11.62)	0.001
Passive smoking	0.08 (−1.70–1.85)	0.933
Nasal corticosteroids		
Yes	2.26 (0.44–4.07)	0.015
Not described	−1.85 (−5.00–1.31)	0.250
Nasal rinsing		
Yes	−1.50 (−3.15–0.16)	0.077
Not described	−1.92 (−4.26–0.42)	0.107
Inhaled corticosteroids		
Yes	−0.34 (−1.93–1.26)	0.667
Not described	5.54 (2.73–8.34)	<0.001
Prophylactic antibiotic		
Yes	−0.60 (−2.24–1.04)	0.473
Not described	−2.93 (−5.34–−0.53)	0.017

Results of linear regression model. [#]: composite exposure variable consisting of daily or often reported nasal symptoms and examination findings of nasal discharge (seromucous, mucopurulent or mixed with blood) or nasal oedema.

disease among 64 adults with PCD found otitis media with effusion associated with FEV_1 <70% [12]. We tested for possible association of chronic rhinosinusitis with FEV_1 and found no evidence of association. However, we found patient-reported ear pain and hearing problems associated with lower respiratory symptoms, specifically shortness of breath and sputum production. A smaller single-centre study showed simultaneous infections with the same pathogens in sinuses and lungs of patients in Denmark who underwent sinus surgery [10]. The concept of the unified airway in PCD was further supported by another Danish study showing the same *Pseudomonas aeruginosa* clone in sinuses and lungs [26]. Unfortunately, our observational study rarely included simultaneous upper and lower airway cultures, since they are routinely collected at few participating centres, so we could not use microbiology information to support our findings further.

Studies on other chronic lung diseases showed similar associations between upper and lower respiratory disease [27, 28]. A large population-based study among adults in southern Sweden found that nasal symptoms frequently coexisted with both self-reported diagnoses of asthma and chronic bronchitis/emphysema (only 33% of the total population reported nasal symptoms, compared with 40% among participants with self-reported COPD), suggesting pan-airway engagement as common for both diseases [29]. A Canadian study with 121 participants diagnosed with cystic fibrosis compared FEV_1 (% predicted) between individuals with and without chronic rhinosinusitis and found no difference (mean difference 2.0%, 95% CI −8.1–13.0%), which is similar to our study [30].

Interpretation of findings

Our findings support the concept of the unified airway in PCD, particularly the association between nasal symptoms and chronic rhinosinusitis and lower respiratory symptoms; a finding possibly explained by increased mucus production or decreased mucosal clearance along the unified airway. Since ciliary function is affected in upper and lower airways, we expect patients with PCD to report symptoms from both and account for any differences based on disease severity. Interactions with allergic rhinitis might be possible; however, lack of detailed data on most participants precluded examining such a hypothesis. We believe the interactions to be small, since we previously found no associations between sinonasal disease and any particular season, especially not pollination seasons [3]. For some patients, coexisting posterior nasal drip explained the association of daily nasal symptoms with sputum production. Recently, heterogeneity of clinical phenotypes in PCD has stimulated much discussion [31–33]. Any evidence of association we found between ear symptoms and shortness of breath could also be explained by possible underlying chronic rhinosinusitis in these patients. Ear pain and hearing problems might be symptoms of Eustachian tube dysfunction, which is prevalent among patients with chronic rhinosinusitis [34, 35]. Our study suggests that upper and lower respiratory symptoms occur dependently for most patients with PCD. Therefore, it is probable that differences in upper and lower airway disease between PCD clinical phenotypes mainly relate to disease severity and less to prevalence of specific respiratory symptoms.

We found associations of chronic rhinosinusitis with lower respiratory symptoms, yet not with FEV_1 measured by spirometry. Although spirometry is the most commonly used method for pulmonary assessment for PCD [36], it appears not sensitive enough for patients with PCD, particularly children [37]. It is prone to large intra-individual variability, which complicates assessing possible associations. Lung disease in PCD is complex and cannot be assessed only with spirometry as there is often discordance between lung function and impairment shown on imaging modalities [38]. Other tests such as multiple breath washout appear more sensitive than spirometry for detecting pulmonary disease [39–41]; we recommend studying associations using these measurements.

Conclusion

Our study shows reported upper airway symptoms and examination findings of chronic rhinosinusitis associated with reported lower respiratory symptoms; however, not with airway obstruction assessed by lung function. Upper and lower airway disease occurs interdependently; to improve clinical outcomes for patients with PCD, it needs assessing and managing as a common entity with appropriate clinical and patient-reported measures.

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EPIC-PCD team (listed in alphabetical order): Dilber Ademhan (Hacettepe University, Turkey), Mihaela Alexandru (AP-HP, France), Andreas Anagiotos (Nicosia General Hospital, Cyprus), Miguel Armengot (La Fe University and Polytechnic Hospital, Spain), Lionel Benchimol (University Hospital of Liège, Belgium), Achim G. Beule (University of Münster, Germany), Irma Bon (Vrije Universiteit, the Netherlands), Mieke Boon (University Hospital Leuven, Belgium), Marina Bullo (University of Bern, Switzerland), Andrea Burgess (University of Southampton, UK), Doriane Calmes (University Hospital of Liège, Belgium), Carmen Casaulta (University of Bern, Switzerland), Marco Caversaccio (University of Bern, Switzerland), Nathalie Caversaccio (University of Bern, Switzerland), Bruno Crestani (RESPIRARE, France), Suzanne Crowley (University of Oslo, Norway), Sinan Ahmed D. Dheyauldeen (University of Oslo, Norway), Sandra Diepenhorst (Vrije Universiteit, The Netherlands), Nagehan Emiralioglu (Hacettepe University, Turkey), Ela Erdem Eralp (Marmara University, Turkey), Pinar Ergenekon (Marmara University, Turkey), Nathalie Feyaerts (University Hospital Leuven, Belgium), Gavriel Georgiou (Nicosia General Hospital, Cyprus), Amy Glen (University of Southampton, UK), Christine van Gogh (Vrije Universiteit Amsterdam, the Netherlands), Yasemin Gokdemir (Marmara University, Turkey), Myrofora Goutaki (University of Bern, Switzerland), Onder Gunaydın (Hacettepe University, Turkey), Eric G. Haarman (Vrije Universiteit Amsterdam, The Netherlands), Amanda Harris (University of Southampton, UK), Lilia Marianne Hartung (Charité-Universitätsmedizin Berlin, Germany), Isolde Hayn (Charité-Universitätsmedizin Berlin, Germany), Simone Helms (University of Münster, Germany), Isabelle Honoré (RESPIRARE, France), Sara-Lynn Hool (University of Bern, Switzerland), Isabel Ibáñez (La Fe University and Polytechnic Hospital, Spain), Hasnaa Ismail Koch (University of Southampton, UK), Bülent Karadag (Marmara University, Turkey), Céline Kempeneers (University Hospital of Liège, Belgium), Synne Kennelly (University of Oslo, Norway), Elisabeth Kieninger (University of Bern, Switzerland), Sookyung Kim (AP-HP, France), Panayiotis Kouis (University of Cyprus, Cyprus), Yin Ting Lam (University of Bern, Switzerland), Philipp Latzin (University of Bern, Switzerland), Marie Legendre (RESPIRARE, France), Natalie Lorent (University Hospital Leuven, Belgium), Jane S. Lucas (University of Southampton, UK), Bernard Maitre (RESPIRARE, France), Alison McEvoy (University of Southampton, UK), Rana Mitri-Frangieh (RESPIRARE, France), David Montani (RESPIRARE, France), Loretta Müller (University of Bern, Switzerland), Noelia Muñoz (La Fe University and Polytechnic Hospital, Spain), Heymut Omran (University of Münster, Germany), Ugur Ozcelik (Hacettepe University, Turkey), Beste Ozsezen (Hacettepe University, Turkey), Samantha Packham (University of Southampton, UK), Jean-François Papon (AP-HP, France), Clara Pauly (University Hospital of Liège, Belgium), Charlotte Pioch (Charité-Universitätsmedizin Berlin, Germany), Anne-Lise M. L. Poirrier (University Hospital of Liège, Belgium), Johanna Raidt (University of Münster, Germany), Ana Reula (La Fe University, Spain), Rico Rinkel (Vrije Universiteit Amsterdam, the Netherlands), Jobst Roehmel (Charité-Universitätsmedizin Berlin, Germany), Andre Schramm (University of Münster, Germany), Catherine Sondag (University Hospital of Liège, Belgium), Simone Tanner (Vrije Universiteit, the Netherlands), Nicoletta Tanou (University of Cyprus, Cyprus), Guillaume Thouvenin (RESPIRARE, France), Woolf T. Walker (University of Southampton, UK), Hannah Wilkins (University of Southampton, UK), Panayiotis Yiallouros (University of Cyprus, Cyprus), Ali Cemal Yumusakhuylu (Marmara University, Turkey) and Niklas Ziegahn (Charité-Universitätsmedizin Berlin, Germany).

Author contributions: M. Goutaki developed the concept and design of the study. M. Goutaki and Y.T. Lam managed the study. Y.T. Lam cleaned, standardised the data and performed statistical analyses, supervised by M. Goutaki. Y.T. Lam and M. Goutaki drafted the manuscript. All authors commented and revised the manuscript. Y.T. Lam and M. Goutaki take final responsibility for content.

Availability of data and materials: Upon reasonable request, our datasets for the present study are available from the study principal investigator, Myrofora Goutaki (myrofora.goutaki@unibe.ch). The EPIC-PCD dataset includes individual patient data of people with a rare disease. Although data are pseudonymised, data possibly still include sensitive information which possibly lead to identifying participants; therefore, participants were not asked to consent having their data deposited or shared publicly.

Conflict of interest: J-F. Papon reports personal fees from Sanofi, GSK, Medtronic and ALK, outside the submitted work. M. Alexandru received personal fees from Sanofi and ALK outside the submitted work. M. Boon reports grants from Forton grant (King Baudouin Foundation) 2020-J1810150-217926 for cystic fibrosis research and personal fees from Vertex outside the submitted work. N. Lorent received honoraria to her institution from GSK, INSMED and AN2 Therapeutics outside the submitted work, and a travel grant from Pfizer. J. Roehmel received grants, clinical study reimbursement from Vertex, INSMED, Medical Research Council/UK, BMBF and Mukoviszidose Institut, outside the submitted work. The other authors report no competing interests.

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