Ear and upper airway clinical outcome measures for use in primary ciliary dyskinesia research: a scoping review

Mihaela Alexandru [1,2], Raphaël Veil[3], Bruna Rubbo[4,5], Myrofora Goutaki [6,7], Sookyung Kim[1], Yin Ting Lam [6], Jérôme Nevoux[1,2], Jane S. Lucas [4,5] and Jean-François Papon[1,2,8]

[1]AP-HP, Université Paris-Saclay, Hôpital Bicêtre, Service d'ORL, Le Kremlin-Bicêtre, France. [2]Faculté de Médecine, Université Paris-Saclay, Le Kremlin-Bicêtre, France. [3]AP-HP, Université Paris-Saclay, Hôpital Bicêtre, Service d'Épidémiologie et Santé Publique, Le Kremlin-Bicêtre, France. [4]Primary Ciliary Dyskinesia Centre, NIHR Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK. [5]School of Clinical and Experimental Science, Faculty of Medicine, University of Southampton, Southampton, UK. [6]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. [7]Paediatric Respiratory Medicine, Children's University Hospital of Bern, University of Bern, Bern, Switzerland. [8]Institut Mondor de Recherche Biomédicale INSERM-UPEC UMR 955, CNRS ERL7000, Créteil, France.

Corresponding author: Mihaela Alexandru (mihaela.dana.alexandru@gmail.com)

Shareable abstract (@ERSpublications)
There is a lack of data and a high heterogeneity in definitions and measures of ENT outcomes in PCD. Based on suggestions from this scoping review, future PCD research should homogenise ENT outcome definitions to improve follow-up and treatments. https://bit.ly/3ZAOOMR

Cite this article as: Alexandru M, Veil R, Rubbo B, *et al*. Ear and upper airway clinical outcome measures for use in primary ciliary dyskinesia research: a scoping review. *Eur Respir Rev* 2023; 32: 220200 [DOI: 10.1183/16000617.0200-2022].

Received: 17 Oct 2022
Accepted: 7 March 2023

Abstract

Background Primary ciliary dyskinesia (PCD) is a rare genetic disorder characterised by pulmonary, otological and sino-nasal manifestations. Well-defined clinical outcome measures are needed in such rare diseases research to improve follow-up and treatments. Pulmonary outcome measures have recently been described. The aim of this study was to identify ear and upper airway outcome measures that could be used for longitudinal follow-up of individuals with PCD.

Methods A scoping review was performed by systematically searching MEDLINE, Embase and Cochrane Database of Systematic Reviews online databases for studies published from January 1996 to March 2022 that included at least 10 adult or paediatric PCD patients and reported ear and upper airway outcomes.

Results 33 studies (1794 patients) were included. 10 ear and upper airway outcomes were reported. 17 studies reported audiometry, 16 reported otoscopic findings, and 13 reported rhinoscopic findings and sinus imaging. Health-related quality of life questionnaires were performed in seven studies. There was a high variability in definitions and measurement of outcomes between studies.

Conclusions This scoping review highlights the lack of data regarding ear and upper airway outcomes in PCD. It also reports a high heterogeneity in outcome definitions or measures. We provide well-founded specific suggestions to standardise ear and upper airway outcome definitions and reporting for future PCD research studies.

Introduction

Primary ciliary dyskinesia (PCD) is a rare genetic disorder, usually inherited in an autosomal recessive pattern. Its prevalence ranges from 1:2000 to 1:20 000 live births [1, 2]. It is characterised by functional (ciliary mobility) or ultrastructural (dynein arms, central complex) impairment of mucociliary clearance, leading to pulmonary (bronchiectasis and bronchial infections), otological and sino-nasal manifestations (chronic sinusitis and otitis media), fertility disorders, and more rarely hydrocephalus, cardiac malformations and oesophageal disorders or biliary atresia [3]. Situs inversus is present in 50% of cases [4].

The prevalence of ear–nose–throat (ENT) symptoms varies between studies, but most PCD patients present with recurrent otitis media and chronic rhinosinusitis, significantly impacting their quality of life [5–8]. Because of the limited data in the literature, for many years, management recommendations for PCD have followed those for cystic fibrosis or bronchiectasis [9–11].

Research studies on ear and upper airway outcomes of PCD are increasing. However, to date, no randomised controlled trials and only few observational studies have been performed about ENT symptoms in PCD. Well-defined and validated disease-specific outcome measures are urgently needed to perform randomised controlled trials and to assess new therapies and management options for PCD.

Recently, a scoping review reported the most commonly used pulmonary outcomes in PCD [12], highlighting significant heterogeneity in the definitions of clinical outcome measures and the use of these measures in the management of PCD.

The aim of this scoping review was to systematically describe the ear and upper airway outcomes reported in the PCD literature and to evaluate the coherence of definitions between studies and in the reporting of results.

Methods

Search strategy

We conducted a scoping review adapted from a previously published scoping review protocol for lower airway outcome measures [12]. Key terms were used to build the full search strategy, designed for use in MEDLINE and adapted to Embase. We then used Medical Subject Headings (MeSH) for the MEDLINE and Cochrane search engines, and Embase subject headings (Emtree) for the Embase search engine, along with individual terms, to develop the search strategy, with limitations applied (supplementary box S1).

The search was performed on 22 December 2021 and updated on 29 March 2022. We used the Cochrane Database of Systematic Reviews, MEDLINE and Embase databases to identify studies describing ear and upper airway clinical outcome measures in PCD. Zotero version 5.0.96.4 (www.zotero.org) was used as citation manager.

Inclusion and exclusion criteria

We included studies describing ear and upper airway outcome measures in PCD if they 1) had a study population of at least 10 PCD patients, 2) were published in English, 3) were published from January 1996 to March 2022 and 4) were conducted on humans. We did not include studies prior to 1996 because the diagnosis of PCD has changed since then, therefore older articles may contain a high proportion of patients that would no longer fulfil the current diagnostic criteria. Details of diagnostic data for each of the included studies were recorded (supplementary table S1).

We excluded studies that were not original research, conference abstracts and where full texts were irretrievable. Studies reporting on multiple disease groups (*e.g.* non-cystic fibrosis bronchiectasis) were excluded if the PCD data could not be clearly identified. Articles that reported exclusively on pulmonary symptoms were also excluded.

Definition of outcome measures and classification into subgroups

Outcome measures were defined as any ENT clinical measure used 1) to monitor patients over time or 2) as a marker of disease severity. Outcome measures were classified as 1) study outcomes, defined *a priori* as study outcome measures, or 2) study population descriptors. The latter indicates measures that were used to characterise the study population (*e.g.* otoscopic examination) and those that could potentially be used in future studies (*e.g.* sinus hypoplasia on computed tomography (CT) scan). Depending on the study, each outcome measure can be a study outcome or a population descriptor.

Statistical analysis

Results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) checklist [13]. Data were expressed as median (interquartile range (IQR)) for continuous variables and as proportions (%) for categorical variables. All analyses and graphing were carried out using R version 3.2.3 (www.r-project.org).

Results

3605 abstracts were identified, of which 2740 (76.0%) were reviewed after exclusion of 865 duplicates. 269 articles (7.5%), selected based on their title and abstract, were reviewed in full, of which 33 (0.9%) met the inclusion criteria and were therefore included (supplementary figure S1).

Study characteristics

The articles included information on 1794 patients with PCD, with a median of 54 PCD patients per article (IQR 27–70, range 15–333) (supplementary table S1). Some patients were described in several studies and were included more than once if the studies described different outcome measures.

Articles contained data collected from 14 different countries, but 26 (79%) presented single-centre data. The publication with the highest number of PCD patients was from a multicentre study [14]. Five studies included only adult patients with PCD [7, 15–18], while 12 studies had an exclusively paediatric population [5, 11, 14, 19–27], and 16 studies included children and adult patients [10, 28–41].

Reported outcome measures

33 studies reported on a total of 10 ear and upper airway outcomes (table 1, and figures 1 and 2). Five studies presented data exclusively on population descriptors, 16 presented data exclusively on study outcomes, and 12 presented both study outcomes and population descriptors (table 1 and supplementary table S2). Details on the definitions of all outcome measures reported as study outcomes or population descriptors are provided in supplementary table S2. The other study outcomes reported in combination with ear and upper airway outcomes were pulmonary outcomes (high-resolution CT and spirometry), anthropometry, nasal nitric oxide (nNO) level, microbiology, fertility status or PICADAR (PrImary CiliARy DyskinesiA Rule) score [42].

Otoscopic findings and audiometry parameters were the most frequently reported clinical outcome measures, followed by rhinoscopic findings and sinus CT scan. Microbiology and anthropometric measures were more often reported as population descriptors than as study outcomes (figure 1).

Only seven studies used ear and upper airway outcome measures to follow longitudinally the responses to PCD patient treatment: six studies used otoscopic findings and audiometry [5, 20, 23, 27, 36, 39], and one study used rhinoscopy findings, specific health-related quality of life questionnaire and microbiology to evaluate endoscopic sinus surgery in PCD [43].

Standardised definitions

Clinical ear and upper airway outcomes

Definitions of outcome measures varied considerably between studies (supplementary table S2).

ENT symptoms

In nine studies (27%), ENT symptoms definitions were not specified [10, 19, 23, 24, 27, 29, 32, 37, 39]. Of the 24 remaining studies, 12 studies (36%) provided definitions of the ENT symptoms they collected [5, 7, 11, 15, 17, 25, 26, 33–35, 38, 43]. Definitions of ENT symptoms varied considerably between studies, highlighting the lack of standardisation in definitions. No study used upper airway exacerbations as a study outcome.

Otoscopic findings

16 studies reported otoscopic findings as outcome measures (10 as study outcome and six as population descriptors) [5, 7, 11, 18, 20, 22, 23, 26–28, 30, 31, 35, 36, 40, 41]. Among them, 14 studies reported a history of ventilation tube insertion [5, 7, 18, 20, 22, 23, 26–28, 30, 35, 36, 40, 41]. Reporting of otoscopic findings included details of otoscopic examination, such as the aspect of the eardrum (perforation, retraction, calcification, middle ear effusion and cholesteatoma) and the presence of otorrhoea, for 14 studies. Only two studies did not detail the otoscopic examination [28, 31].

Rhinoscopic findings

13 studies reported rhinoscopic findings as outcome measures (nine as study outcomes and four as population descriptors) [7, 11, 15, 18–20, 24, 26, 28, 31, 35, 41, 43]. Among them, 11 studies noted the presence or absence of nasal polyps [7, 11, 15, 18, 20, 24, 26, 31, 35, 41, 43]. The other two studies did not detail the rhinoscopic physical examination [19, 28].

Other clinical ear and upper airway outcomes

Two studies used adenoid and tonsil size (both according to the Brodsky score [44]) as an outcome measure [24, 26]. They found no difference in adenoid and tonsil sizes in patients with PCD compared with a control group.

Paraclinical ear and upper airway outcomes

Audiometry

Of 17 studies reporting audiometry as an ENT study outcome, definition of normal hearing varied [5, 7, 14, 18, 21–27, 30, 35, 36, 39, 40]. Hearing was considered normal if the hearing loss was $\leqslant$20 dB for four studies [7, 14, 23, 35], following the World Health Organization's (WHO) definition of hearing loss [45],

TABLE 1 Clinical outcome measures used in studies included in this review, grouped by main outcome measure

Study	Study outcomes	Population descriptors
Otoscopic findings		
Piatti, 2017 [18]	Spirometry, rhinoscopic findings, otoscopic findings, audiometry, tympanometry, DPOAEs, vestibular investigations	None
Takeuchi, 2017 [40]	Otoscopic findings, audiometry, tympanometry	None
Prulière-Escabasse, 2010 [5]	Otoscopic findings, audiometry, history of ENT surgery	Pulmonary status, lung surgery history
El-Sayed, 1997 [36]	Audiometry, tympanometry	Otoscopic findings
Ghedia, 2018 [27]	Otoscopic findings, audiometry, tympanometry	None
Audiometry		
Andersen, 2016 [39]	Audiometry, tympanometry	None
Wolter, 2012 [20]	History of ENT surgery, otoscopic findings, rhinoscopic findings	Spirometry, pulmonary status, nNO
Majithia, 2005 [22]	Audiometry, tympanometry	Otoscopic findings
Hadfield, 1997 [23]	Otoscopic findings, audiometry, tympanometry	None
Sinus imaging		
Bhatt, 2019 [19]	Rhinoscopic findings, sinus CT scan, Lund–Mackay score, history of ENT surgery, history of ENT-related hospitalisations	None
Pifferi, 2011 [37]	Lund–Mackay score, HRCT, nNO	Sinus CT scan
Pappa, 2021 [32]	Sinus CT scan, Lund–Mackay score	None
Hervochon, 2019 [29]	Sinus CT scan	None
Rhinoscopic findings		
Rollin, 2009 [11]	Rhinoscopic findings, otoscopic findings, modified SNOT-20 questionnaire	None
Alanin, 2017 [43]	HR-QoL (SNOT-22 score), microbiology, spirometry, anthropometry (BMI)	None
Pifferi, 2018 [10]	Olfactory function, sinus CT scan, Lund–Mackay score	nNO
Questionnaires		
Behan, 2017 [17]	HR-QoL (QOL-PCD questionnaire, SF-36, shortened SGRQ-C, SNOT-20)	Microbiology, spirometry
Sommer, 2011 [38]	Non-standardised questionnaire (general, otological, paranasal sinuses)	None
Kawakami, 1996 [34]	Non-standardised questionnaire	Fertility (sperm motility)
Goutaki, 2021 [61]	Standardised non-validated PCD-specific questionnaire (upper and lower respiratory symptoms, ear symptoms questionnaire)	None
Zawawi, 2022 [26]	SNOT-22, HEAR-QL, RSI questionnaires, otoscopic findings, rhinoscopic findings, tonsil size, adenoid size, reflux finding score in laryngeal assessment, microbiology, audiometry, tympanometry	None
Sleep disorders		
Eyüboğlu, 2018 [24]	Sleep questionnaires, home sleep testing	Otoscopic findings, rhinoscopic findings, audiometry, spirometry
Non-ENT main outcome		
Frija-Masson, 2017 [16]	Sinus CT scan, Lund–Mackay score, spirometry, microbiology, HRCT, dyspnoea score, history of ENT surgery, fertility, lung surgery history, mortality	None
Jain, 2007 [21]	Chest radiography, HRCT, audiometry	Microbiology
Rubbo, 2020 [14]	Spirometry, treatment	Audiometry, anthropometry, microbiology
Mata, 2021 [31]	None	Sinus imaging (radiography or CT scan), rhinoscopic findings, otoscopic findings, fertility
No main outcome		
Chiyonobu, 2022 [41]	PICADAR score, nNO, otoscopic findings, rhinoscopic findings, sinus CT scan, Lund–Mackay score	None
Boon, 2014 [35]	None	Anthropometry, spirometry, microbiology, chest radiography and HRCT, otoscopic findings, rhinoscopic findings, audiometry
Asfuroglu, 2021 [25]	None	PICADAR score, anthropometry, audiometry, spirometry
Bequignon, 2019 [15]	Rhinoscopic findings, sinus CT scan, microbiology, treatment	None
Bequignon, 2019 [7]	Otoscopic findings, rhinoscopic findings, audiometry, sinus CT scan	Spirometry, pulmonary status, nNO

Continued

TABLE 1 Continued

Study	Study outcomes	Population descriptors
Hosie, 2015 [30]	None	History of ENT surgery, audiometry, otoscopic findings, treatment, microbiology, nNO, pulmonary status
Noone, 2004 [28]	None	Spirometry, microbiology, chest and sinus radiography, cough, ENT surgery history, otoscopic findings, rhinoscopic findings

DPOAE: distortion product otoacoustic emission; ENT: ear–nose–throat; nNO: nasal nitric oxide; CT: computed tomography; HRCT: high-resolution computed tomography; HR-QoL: health-related quality of life; SNOT-22: 22-item Sino-Nasal Outcome Test; BMI: body mass index; QOL-PCD: primary ciliary dyskinesia quality of life questionnaire; SF-36: 36-item Short-Form Health Survey; SGRQ-C: St George's Respiratory Questionnaire (COPD specific); SNOT-20: 20-item Sino-Nasal Outcome Test; PCD: primary ciliary dyskinesia; HEAR-QL: Hearing Environments and Reflection on Quality of Life; RSI: Reflux Symptom Index; PICADAR: PrImary CiliARy DyskinesiA Rule.

whereas it was considered normal if the hearing loss was ⩽25 dB for four studies [5, 18, 22, 39]. Definition of hearing loss was not reported in eight studies [21, 24–27, 30, 36, 40]. See figure 3.

Tympanometry was performed in nine out of 16 studies [7, 18, 22, 23, 26, 27, 36, 39, 40], but tympanometry was defined only in two studies [22, 39].

All studies reported hearing loss in PCD patients (25.7% [43] to 100% [40] of cases).

Sinus CT scan

Of 10 studies reporting on sinus CT as a study outcome [7, 10, 15, 16, 19, 29, 31, 32, 37, 41], seven studies qualitatively evaluated sinus volume (normal volume, hypoplasia or aplasia). Studies reported sinus hypoplasia or agenesia in 37% [7] to 93% [31] of cases. Four studies used the non-modified Lund–Mackay score [16, 19, 32, 41] to characterise sinus opacification, three used the same modified Lund–Mackay score (adapted to sinus hypoplasia or aplasia) [7, 10, 37] and the remaining three did not use any score to characterise sinus opacification [15, 29, 31]. One study reported sinus radiography [28]. See figure 4.

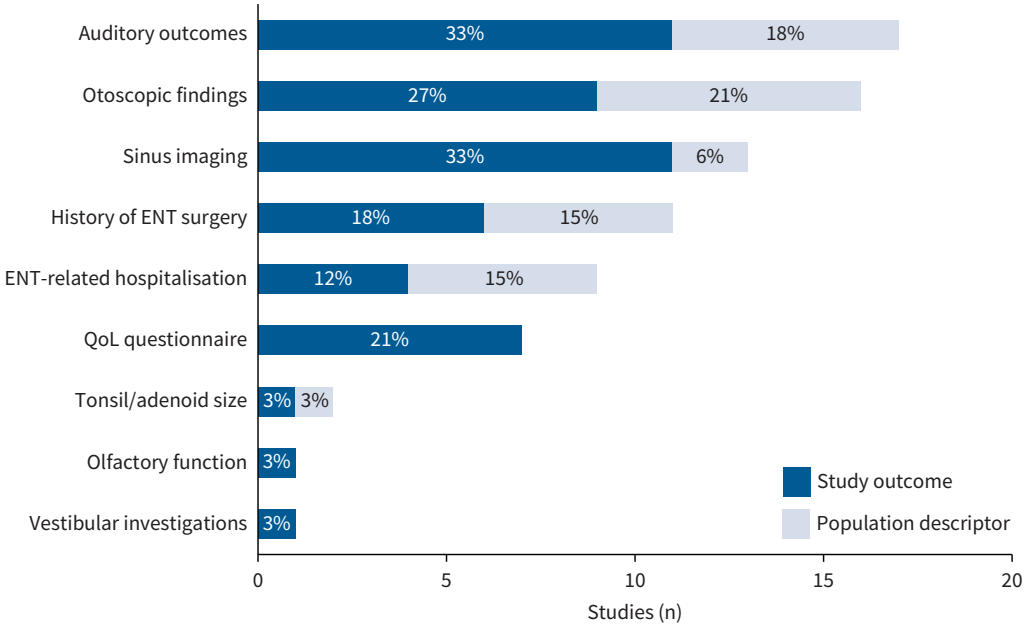

FIGURE 1 Number of studies that reported outcome measures in primary ciliary dyskinesia as either study outcome or population descriptor. Studies often reported on more than one outcome measure and might therefore be featured in more than one instance. ENT: ear–nose–throat; QoL: quality of life.

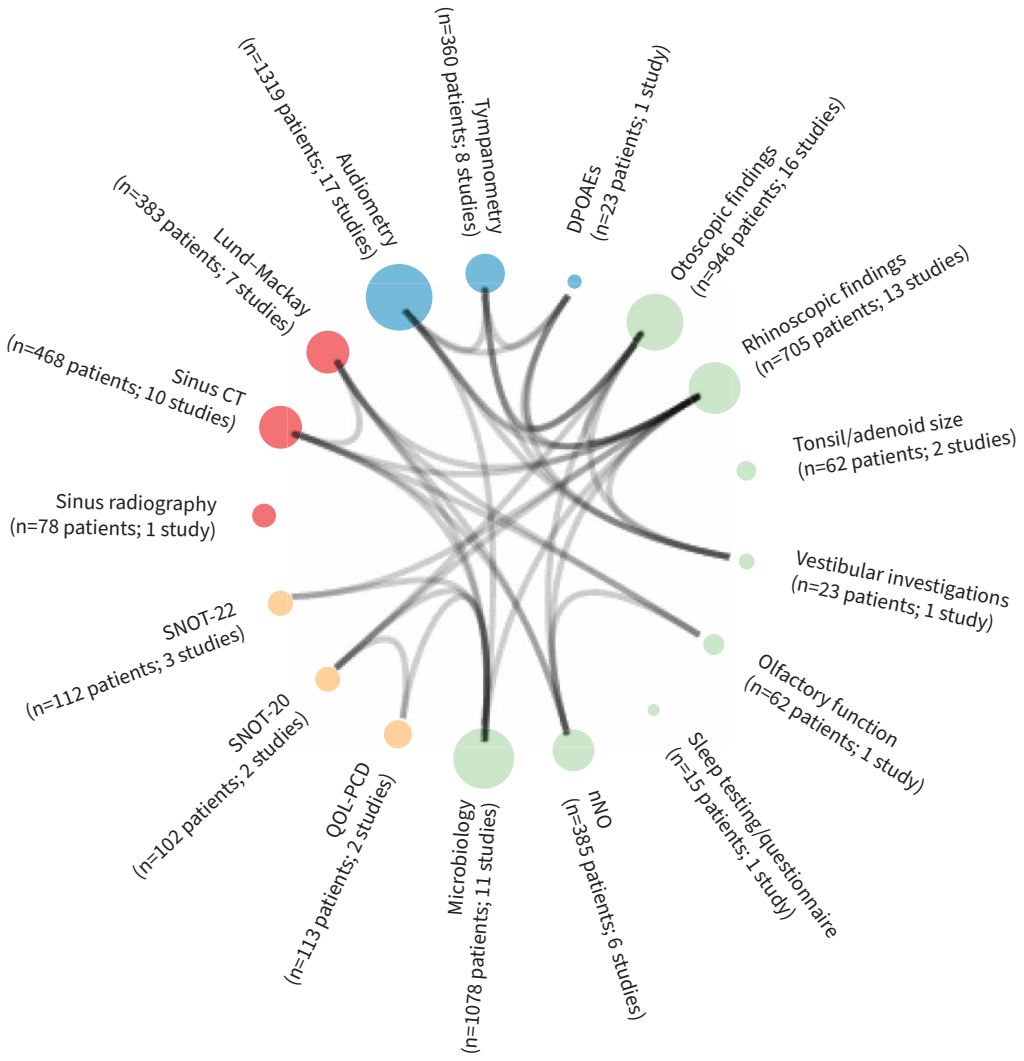

FIGURE 2 Ear–nose–throat (ENT) outcome measure associations reported in the studies included in this review. The size of the circles represents the number of patients for whom the outcome was assessed and the lines connecting the circles represent the associations between outcome measures. Two nodes connected by a line illustrate that those two outcomes have both been measured together in at least one study. Nodes with no connection represent outcomes that have not been evaluated concomitantly with others. DPOAE: distortion product otoacoustic emission; nNO: nasal nitric oxide; QOL-PCD: primary ciliary dyskinesia quality of life questionnaire; SNOT-20: 20-item Sino-Nasal Outcome Test; SNOT-22: 22-item Sino-Nasal Outcome Test; CT: computed tomography.

Microbiology

11 studies reported microbiology as a study outcome or a population descriptor, among which four studies reported sino-nasal culture results [7, 15, 26, 43]. The other seven studies only reported the results of sputum cultures [14, 16, 17, 21, 28, 30, 35]. Bequignon *et al*. [7, 15] performed aspiration of the middle meatus when there were nasal purulent secretions. They reported the presence of at least one bacterium in 84% of patients. The most frequent bacteria found were *Haemophilus influenzae* (26%), *Streptococcus pneumoniae* (19%) and *Pseudomonas aeruginosa* (19%). Alanin *et al*. [43] also reported the same bacterial colonisation in lung and sinus for 62% of patients. Zawawi *et al*. [26] reported sino-nasal cultures results in PCD children and found 61% of positive meatus cultures. The most common bacteria cultured were *Staphylococcus aureus* (23%), *S. pneumoniae* (21%) and *H. influenzae* (11%).

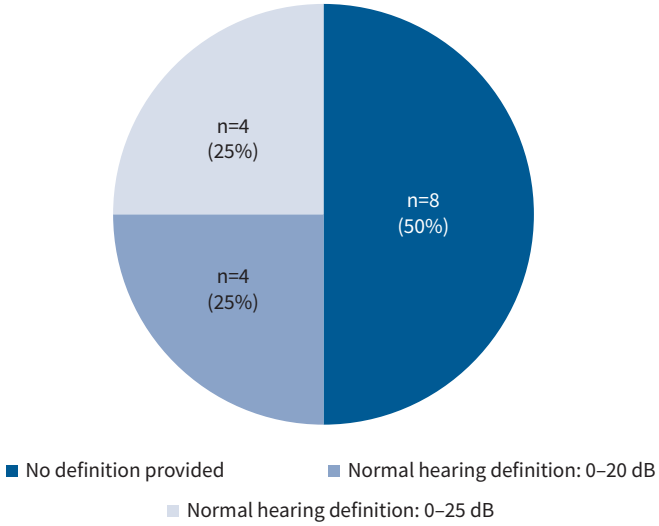

FIGURE 3 High heterogeneity in normal hearing definitions among studies reporting auditory outcomes.

Health-related quality of life questionnaires

Seven studies reported health-related quality of life questionnaires as a study outcome. Two studies used the validated PCD-specific quality of life (QOL-PCD) questionnaire, which includes ear and sino-nasal domains [15, 17]. For quality of life related to sinus symptoms, two studies used the 20-item Sino-Nasal Outcome Test (SNOT-20) [11, 17] and three studies used the more recent 22-item SNOT-22 [15, 26, 43].

Only one study evaluated a quality of life questionnaire before and after treatment. Alanin *et al.* [43] reported an improvement in SNOT-22 score results at 3, 6 and 12 months after functional endoscopic sinus surgery.

Vestibular investigations

Only one study reported vestibular investigations in PCD patients [18]. No patient reported vertigo or dizziness among the 23 included patients and all vestibular evaluations (including Head Shaking Test, Head Impulse Test or Video Head Impulse Test, caloric stimulation, and cervical and ocular vestibular evoked myogenic potentials) were normal.

Olfactory function

Only one study reported olfactory function in 62 PCD patients [10], using the Sniffin' Sticks Extended Test (Burghart Medizintechnik, Wedel, Germany). There was a significant impairment in PCD patients'

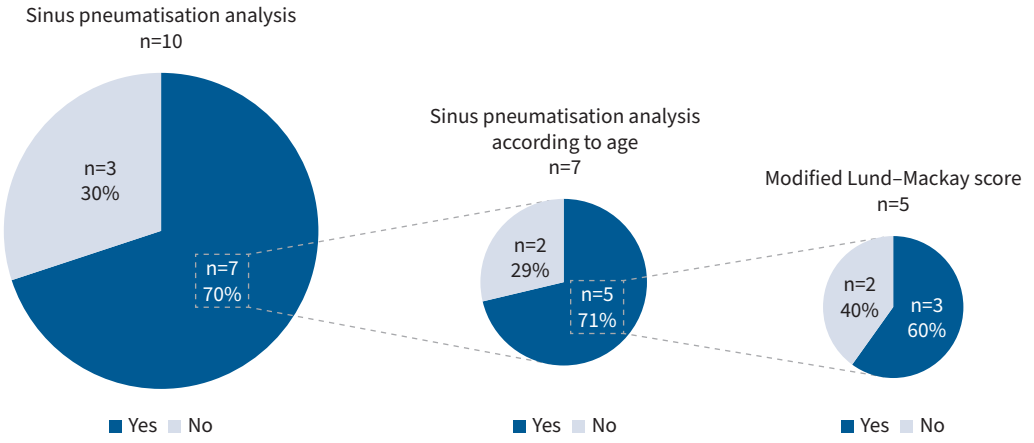

FIGURE 4 Sinus computed tomography scan analysis outcome: high heterogeneity in the literature.

olfactory functions compared with non-PCD sinusitis patients and controls. Moreover, in PCD patients, there was a significant inverse correlation between olfactory function and the modified Lund–Mackay score. There was also a significant inverted correlation between each of the following features and sinus aplasia or hypoplasia score: discrimination, threshold discrimination identification (TDI) score and TDI extended score. Finally, there was a significant positive correlation between each olfactory assessment and nNO levels.

Discussion

This scoping review reported 10 different ENT outcome measures used in PCD research studies. Although a previous review was published in 2016 [46], this is the first systematic scoping review focusing on ENT outcomes in PCD. We report a high heterogeneity in the definitions of ENT symptoms and outcome measures, similar to what was reported for lower airway clinical outcomes [12].

Our review highlighted a lack of ENT symptom standardised definitions. Thus, it would be very helpful to collect standardised data in national or international registries. The FOLLOW-PCD patient questionnaire is a standardised PCD-specific questionnaire, part of the FOLLOW-PCD form [47] that collects information on prevalence, frequency and characteristics of symptoms, including ear and upper airway symptoms, and needs to be validated by additional studies. When reported, ENT symptoms should therefore be recorded using standardised questionnaires such as FOLLOW-PCD, especially in studies where prevalence of specific symptoms is used as an outcome or population descriptor.

The most frequently reported ENT outcomes were auditory outcomes and otoscopic findings.

Normal hearing definitions varied between ⩽20 dB and ⩽25 dB among studies. Moreover, eight studies did not give any definition of normal hearing. Because >50% of PCD patients suffer from hearing loss [7, 38], a validated and reproducible definition of hearing loss should be used to evaluate PCD patients' hearing. The WHO gives the following definition for hearing loss: "a person who is not able to hear as well as someone with normal hearing – hearing thresholds of 20 dB or better in both ears – is said to have hearing loss" [45]. We suggest that each study should provide a detailed definition of hearing loss, along with the citation of where the definition was derived from (*e.g.* the WHO definition). Moreover, we suggest researchers follow the Committee on Hearing and Equilibrium recommendation of reporting raw data in scientific articles, enabling more detailed analytical studies and comparison between studies [48].

Otoscopic findings were well defined in almost all articles reporting on them. However, two studies did not look for history of ventilation tube insertion. Ventilation tube insertion is a controversial treatment of otitis media with effusion in PCD patients [20, 26]. Indeed, the superiority of ventilation tube insertion over medical treatment has not been proven regarding hearing improvement. Moreover, post-operative otorrhoea is a frequent and troublesome ventilation tube insertion side-effect, affecting ∼50% of PCD children [23]. More studies are needed to establish recommendations for the management of otitis media with effusion in PCD patients. For this reason, we suggest, when possible, to systematically report the history of ventilation tube insertion and post-operative otorrhoea in PCD patients.

Sinus imaging and rhinoscopic findings were also frequently reported in PCD studies. 85% of the studies reporting rhinoscopic findings focused on the presence or absence of nasal polyps at examination. Chronic rhinosinusitis affects 95% of adult PCD patients, significantly impairing their quality of life, and nasal polyps are found in 15–56% [16, 49]. Since the pathophysiology of nasal polyps in PCD has not been elucidated, it is important to systematically report the presence or absence of nasal polyps in this population.

Our review also reported an important heterogeneity in sinus CT scan interpretation, with only 70% of the studies reporting sinus volume (hypoplasia or aplasia) qualitative evaluation. Sinus hypoplasia or aplasia is found in almost 60% of adult PCD patients [37]. Because the volume of the sinuses increases until adolescence (especially the frontal and sphenoidal sinuses, which are the most affected by hypoplasia or aplasia), it is important to interpret sinus CT scans according to patient age. The Lund–Mackay staging score is a radiological score, often used for chronic rhinosinusitis assessment [50]. It evaluates each sinus opacification (clear, partially opaque or completely opaque) and scores from 0 (all sinuses are completely clear) to 24 (full opacification of all sinuses). Moreover, it has a very good interobserver reliability [51]. The modified Lund–Mackay score has been developed for patients who have sinus hypoplasia or aplasia. It allows to remove the hypoplastic or aplastic sinus from the score calculation and thus to give a more precise score. It is therefore very well adapted to PCD patients since hypoplasia and aplasia are commonly

TABLE 2 Expert suggestions for clinical practice[#]

Ear and upper airway symptoms	We suggest recording ENT symptoms using standardised PCD-specific questionnaires such as FOLLOW-PCD. PCD diagnosis should be considered in patients with distinct ear and upper airway symptoms but without any diagnosis yet. We suggest PCD patients complete the QOL-PCD questionnaire every year, during routine follow-up visits, and support its use in clinical trials.
ENT examination	A detailed otoscopic examination should be systematically performed, including the aspect of the eardrum (perforation, retraction, calcification, middle ear effusion and cholesteatoma) and the presence of otorrhoea. Moreover, we suggest to systematically report history of ventilation tube insertion and post-operative otorrhoea in PCD patients. A detailed rhinoscopic examination (using a nasal endoscope when possible) should also be systematically performed in PCD patients, looking for the presence or absence of nasal polyps in this population. A standardised recording of otoscopic and rhinoscopic examinations should be performed, using a PCD-specific form like the ENT module of FOLLOW-PCD.
Ear and upper airway paraclinical examinations	Each study should give a detailed definition of hearing loss with the citation to where the definition was taken from. Moreover, we suggest researchers follow the Committee on Hearing and Equilibrium recommendation of reporting raw data in scientific articles, enabling more detailed analytical studies and comparison between studies. We suggest using systematically the modified Lund–Mackay scoring system (adapted to sinus hypoplasia or aplasia) in sinus CT scan interpretation for PCD research. An annual bacteriological sampling of the middle meatus should be performed in PCD patients.

ENT: ear–nose–throat; PCD: primary ciliary dyskinesia; QOL-PCD: primary ciliary dyskinesia quality of life questionnaire; CT: computed tomography. [#]: these suggestions are the expert opinion of the authors and have not been developed through any structured methodology.

observed in these patients [10, 52]. Validation studies of this modified score for PCD patients are needed. Thus, we suggest systematically using the modified Lund–Mackay scoring system in sinus CT scan interpretation for PCD research.

Microbiology is often reported as an outcome measure in PCD studies. In our review, four studies reported microbiology results from sino-nasal cultures, the other seven studies reporting microbiology results from sputum culture. Sputum cultures have become routine in the management of PCD, unlike sino-nasal sample cultures [53]. The relations between sino-nasal and pulmonary colonisation, as well as the mechanisms of bacterial colonisation, are not yet fully understood. One hypothesis is that sinus colonisation acts as a bacterial reservoir and promotes pulmonary recolonisation [43]. Studies reported that the type of bacteria colonising the lungs varies with age in PCD [24, 54]. Zawawi *et al*. [26] did not report *P. aeruginosa* in sino-nasal cultures of PCD children. These results are in line with Noone *et al*. [28] who detected *P. aeruginosa* in 92% of sputum cultures of patients >30 years of age. It has been shown that PCD patients with *P. aeruginosa* colonisation have a poorer respiratory function than other patients [16]. Moreover, Alanin *et al*. [43] highlighted a correlation between the type of bacterial colonisation in sinuses and lung function in PCD patients. More studies are needed to fully understand these mechanisms. We therefore suggest to systematically perform annual bacteriological sampling of the middle meatus in PCD patients.

Health-related quality of life questionnaires have become routine in the management of rare diseases. SNOT-22 is a validated quality of life questionnaire focusing on sino-nasal symptoms [55], based on the previous SNOT-20 questionnaire [56]. It evaluates medical and surgical treatment effectiveness. To date, the questionnaire is validated only in adults, but more and more studies are adapting it to paediatric populations. It is available in English, Spanish, Arabic, French, Portuguese, Italian, Greek, Russian, Turkish, Moroccan, Thai, German, Estonian, Czech, Hebrew and Lithuanian.

The QOL-PCD is a validated disease-specific, health-related quality of life questionnaire. It was developed for adults and children aged ⩾6 years. It has been used since 2017 and consists of 49 items evaluating 10 scales, including physical, social functioning, upper and lower airway symptoms, and ear symptoms [17].

QOL-PCD is validated in English and translated to date in 14 languages (German/Swiss German, Danish, Dutch, Flemish, French, Spanish, Polish, Norwegian, Swedish, Portuguese (Brazilian), Czech, Greek, Turkish and Hebrew) [57]. In our review we reported that few studies used this questionnaire as most were published before 2017. Thus, with the aim to improve follow-up and to evaluate treatment efficiency, we suggest PCD patients complete the questionnaire every year, during routine follow-up visits, and support its use in clinical trials.

Some ENT outcomes have been poorly evaluated in PCD articles, such as adenoid and tonsil size, vestibular function, and olfactory function. Adenoid and tonsil size, as well as vestibular function, do not seem to be altered in the PCD population [18, 24, 26]. However, olfactory function was only evaluated in one PCD research article [10]. Pifferi *et al*. [10] reported olfactory function in PCD children compared with other chronic rhinosinusitis. They used the Sniffin' Sticks Extended Test, a very complete olfactory test composed of three subsets: olfactory thresholds, discrimination and identification [58]. This test is mainly used in Europe. The two olfactory tests most widely used worldwide are the University of Pennsylvania Smell Identification Test [59], which only includes an identification test, and the Connecticut Chemosensory Clinical Research Center test [60], which includes an olfactory threshold component and an identification component. Unfortunately, these three tests cannot be compared across studies and a consensus might be needed to select the most appropriate measure in PCD.

One limitation of this review is the small number of ENT outcome articles compared with lower airway outcome articles [12]. Indeed, this highlights the lack of data regarding ENT outcomes in PCD. However, we anticipate more data will become available because more multicentre, national or international cohort studies are being performed [14, 61].

It was not methodologically possible to conduct a meta-analysis due to the high heterogeneity in ENT outcome definitions across studies. This scoping review is therefore opportune, as it underscores the need for standardised ENT outcome measures for use in clinical research.

Finally, we suggest the use of standardised and detailed definitions for selection, measurement and reporting of ear and upper airway outcomes in PCD research studies (table 2).

Conclusions

This scoping review highlights the lack of data regarding ENT outcomes in PCD research articles. We also found a high heterogeneity in ENT outcome definitions and measures.

Because PCD is a rare disease, whose pathophysiology is not yet fully understood, more efforts are needed in research methodology to homogenise the results of studies and make well-informed evidence-based decisions in the management of this disease.

Provenance: Submitted article, peer reviewed.

Conflict of interest: No author has a conflict of interest to declare.

References

1 Bush A, Chodhari R, Collins N, *et al.* Primary ciliary dyskinesia: current state of the art. *Arch Dis Child* 2007; 92: 1136–1140.
2 O'Callaghan C, Chetcuti P, Moya E. High prevalence of primary ciliary dyskinesia in a British Asian population. *Arch Dis Child* 2010; 95: 51–52.
3 Fretzayas A, Moustaki M. Clinical spectrum of primary ciliary dyskinesia in childhood. *World J Clin Pediatr* 2016; 5: 57–62.
4 Ceccaldi P-F, Carré-Pigeon F, Youinou Y, *et al.* Syndrome de Kartagener et stérilité: observation, diagnostic et prise en charge. [Kartagener's syndrome and infertility: observation, diagnosis and treatment.] *J Gynecol Obstet Biol Reprod* 2004; 33: 192–194.
5 Prulière-Escabasse V, Coste A, Chauvin P, *et al.* Otologic features in children with primary ciliary dyskinesia. *Arch Otolaryngol Head Neck Surg* 2010; 136: 1121–1126.
6 Shapiro AJ, Zariwala MA, Ferkol T, *et al.* Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD Foundation consensus recommendations based on state of the art review. *Pediatr Pulmonol* 2016; 51: 115–132.
7 Bequignon E, Dupuy L, Zerah-Lancner F, *et al.* Critical evaluation of sinonasal disease in 64 adults with primary ciliary dyskinesia. *J Clin Med* 2019; 8: 619.
8 Goutaki M, Meier AB, Halbeisen FS, *et al.* Clinical manifestations in primary ciliary dyskinesia: systematic review and meta-analysis. *Eur Respir J* 2016; 48: 1081–1095.

9 Lucas JS, Carroll M. Primary ciliary dyskinesia and cystic fibrosis: different diseases require different treatment. *Chest* 2014; 145: 674–676.
10 Pifferi M, Bush A, Rizzo M, *et al.* Olfactory dysfunction is worse in primary ciliary dyskinesia compared with other causes of chronic sinusitis in children. *Thorax* 2018; 73: 980–982.
11 Rollin M, Seymour K, Hariri M, *et al.* Rhinosinusitis, symptomatology & absence of polyposis in children with primary ciliary dyskinesia. *Rhinology* 2009; 47: 75–78.
12 Gahleitner F, Thompson J, Jackson CL, *et al.* Lower airway clinical outcome measures for use in primary ciliary dyskinesia research: a scoping review. *ERJ Open Res* 2021; 7: 00320-2021.
13 Tricco AC, Lillie E, Zarin W, *et al.* PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med* 2018; 169: 467–473.
14 Rubbo B, Best S, Hirst RA, *et al.* Clinical features and management of children with primary ciliary dyskinesia in England. *Arch Dis Child* 2020; 105: 724–729.
15 Bequignon E, Dupuy L, Escabasse V, *et al.* Follow-up and management of chronic rhinosinusitis in adults with primary ciliary dyskinesia: review and experience of our reference centers. *J Clin Med* 2019; 8: 1495.
16 Frija-Masson J, Bassinet L, Honoré I, *et al.* Clinical characteristics, functional respiratory decline and follow-up in adult patients with primary ciliary dyskinesia. *Thorax* 2017; 72: 154–160.
17 Behan L, Leigh MW, Dell SD, *et al.* Validation of a health-related quality of life instrument for primary ciliary dyskinesia (QOL-PCD). *Thorax* 2017; 72: 832–839.
18 Piatti G, De Santi MM, Torretta S, *et al.* Cilia and ear. *Ann Otol Rhinol Laryngol* 2017; 126: 322–327.
19 Bhatt JM, Muhonen EG, Meier M, *et al.* Rhinosinusitis in pediatric primary ciliary dyskinesia: impact of disease. *Otolaryngol Head Neck Surg* 2019; 161: 877–880.
20 Wolter NE, Dell SD, James AL, *et al.* Middle ear ventilation in children with primary ciliary dyskinesia. *Int J Pediatr Otorhinolaryngol* 2012; 76: 1565–1568.
21 Jain K, Padley SPG, Goldstraw EJ, *et al.* Primary ciliary dyskinesia in the paediatric population: range and severity of radiological findings in a cohort of patients receiving tertiary care. *Clin Radiol* 2007; 62: 986–993.
22 Majithia A, Fong J, Hariri M, *et al.* Hearing outcomes in children with primary ciliary dyskinesia – a longitudinal study. *Int J Pediatr Otorhinolaryngol* 2005; 69: 1061–1064.
23 Hadfield PJ, Rowe-Jones JM, Bush A, *et al.* Treatment of otitis media with effusion in children with primary ciliary dyskinesia. *Clin Otolaryngol Allied Sci* 1997; 22: 302–306.
24 Eyüboğlu TŞ, Aslan AT, Ceylan A, *et al.* Neurocognitive disorders and sleep in children with primary ciliary dyskinesia. *Pediatr Pulmonol* 2018; 53: 1436–1441.
25 Asfuroglu P, Gursoy TR, Eyuboglu TS, *et al.* Evaluation of age at diagnosis and clinical findings of children with primary ciliary dyskinesia. *Pediatr Pulmonol* 2021; 56: 2717–2723.
26 Zawawi F, Shapiro AJ, Dell S, *et al.* Otolaryngology manifestations of primary ciliary dyskinesia: a multicenter study. *Otolaryngol Head Neck Surg* 2022; 166: 540–547.
27 Ghedia R, Ahmed J, Navaratnam A, *et al.* No evidence of cholesteatoma in untreated otitis media with effusion in children with primary ciliary dyskinesia. *Int J Pediatr Otorhinolaryngol* 2018; 105: 176–180.
28 Noone PG, Leigh MW, Sannuti A, *et al.* Primary ciliary dyskinesia: diagnostic and phenotypic features. *Am J Respir Crit Care Med* 2004; 169: 459–467.
29 Hervochon R, Teissier N, Blondeau J-R, *et al.* Computed tomography description of the uncinate process angulation in patients with cystic fibrosis and comparison with primary ciliary dyskinesia, nasal polyposis, and controls. *Ear Nose Throat J* 2019; 98: 89–93.
30 Hosie PH, Fitzgerald DA, Jaffe A, *et al.* Presentation of primary ciliary dyskinesia in children: 30 years' experience. *J Paediatr Child Health* 2015; 51: 722–726.
31 Mata M, Zurriaga J, Milian L, *et al.* IFT46 expression in the nasal mucosa of primary ciliary dyskinesia patients: preliminary study. *Allergy Rhinol* 2021; 12: 2152656721989288.
32 Pappa AK, Sullivan KM, Lopez EM, *et al.* Sinus development and pneumatization in a primary ciliary dyskinesia cohort. *Am J Rhinol Allergy* 2021; 35: 72–76.
33 Goutaki M, Hüsler L, Lam YT, *et al.* Respiratory symptoms of Swiss people with primary ciliary dyskinesia. *ERJ Open Res* 2022; 8: 00673-2021.
34 Kawakami A, Kitsukawa T, Takagi S, *et al.* Developmentally regulated expression of a cell surface protein, neuropilin, in the mouse nervous system. *J Neurobiol* 1996; 29: 1–17.
35 Boon M, Smits A, Cuppens H, *et al.* Primary ciliary dyskinesia: critical evaluation of clinical symptoms and diagnosis in patients with normal and abnormal ultrastructure. *Orphanet J Rare Dis* 2014; 9: 11.
36 El-Sayed Y, Al-Sarhani A, Al-Essa AR. Otological manifestations of primary ciliary dyskinesia. *Clin Otolaryngol Allied Sci* 1997; 22: 266–270.
37 Pifferi M, Bush A, Caramella D, *et al.* Agenesis of paranasal sinuses and nasal nitric oxide in primary ciliary dyskinesia. *Eur Respir J* 2011; 37: 566–571.
38 Sommer JU, Schäfer K, Omran H, *et al.* ENT manifestations in patients with primary ciliary dyskinesia: prevalence and significance of otorhinolaryngologic co-morbidities. *Eur Arch Otorhinolaryngol* 2011; 268: 383–388.

39 Andersen TN, Alanin MC, von Buchwald C, *et al.* A longitudinal evaluation of hearing and ventilation tube insertion in patients with primary ciliary dyskinesia. *Int J Pediatr Otorhinolaryngol* 2016; 89: 164–168.
40 Takeuchi K, Kitano M, Sakaida H, *et al.* Analysis of otologic features of patients with primary ciliary dyskinesia. *Otol Neurotol* 2017; 38: e451–e456.
41 Chiyonobu K, Xu Y, Feng G, *et al.* Analysis of the clinical features of Japanese patients with primary ciliary dyskinesia. *Auris Nasus Larynx* 2022; 49: 248–257.
42 Behan L, Dimitrov BD, Kuehni CE, *et al.* PICADAR: a diagnostic predictive tool for primary ciliary dyskinesia. *Eur Respir J* 2016; 47: 1103–1112.
43 Alanin MC, Aanaes K, Høiby N, *et al.* Sinus surgery can improve quality of life, lung infections, and lung function in patients with primary ciliary dyskinesia. *Int Forum Allergy Rhinol* 2017; 7: 240–247.
44 Brodsky L. Modern assessment of tonsils and adenoids. *Pediatr Clin North Am* 1989; 36: 1551–1569.
45 World Health Organization. Deafness and hearing loss. 2022. www.who.int/news-room/fact-sheets/detail/deafness-and-hearing-loss Last date accessed: 27 September 2022.
46 Morgan LC, Birman CS. The impact of primary ciliary dyskinesia on the upper respiratory tract. *Paediatr Respir Rev* 2016; 18: 33–38.
47 Goutaki M, Papon J-F, Boon M, *et al.* Standardised clinical data from patients with primary ciliary dyskinesia: FOLLOW-PCD. *ERJ Open Res* 2020; 6: 00237-2019.
48 Committee on Hearing and Equilibrium. Committee on Hearing and Equilibrium guidelines for the evaluation of results of treatment of conductive hearing loss. *Otolaryngol Head Neck Surg* 1995; 113: 186–187.
49 Honoré I, Burgel P-R. Primary ciliary dyskinesia in adults. *Rev Mal Respir* 2016; 33: 165–189.
50 Hopkins C, Browne JP, Slack R, *et al.* The Lund-Mackay staging system for chronic rhinosinusitis: how is it used and what does it predict? *Otolaryngol Head Neck Surg* 2007; 137: 555–561.
51 Oluwole M, Russell N, Tan L, *et al.* A comparison of computerized tomographic staging systems in chronic sinusitis. *Clin Otolaryngol Allied Sci* 1996; 21: 91–95.
52 Orlandi RR, Wiggins RH. Radiological sinonasal findings in adults with cystic fibrosis. *Am J Rhinol Allergy* 2009; 23: 307–311.
53 Lucas JS, Barbato A, Collins SA, *et al.* European Respiratory Society guidelines for the diagnosis of primary ciliary dyskinesia. *Eur Respir J* 2017; 49: 1601090.
54 Roden L, Görlich D, Omran H, *et al.* A retrospective analysis of the pathogens in the airways of patients with primary ciliary dyskinesia. *Respir Med* 2019; 156: 69–77.
55 Thamboo A, Santos RCD, Naidoo L, *et al.* Use of the SNOT-22 and UPSIT to appropriately select pediatric patients with cystic fibrosis who should be referred to an otolaryngologist: cross-sectional study. *JAMA Otolaryngol Head Neck Surg* 2014; 140: 934–939.
56 Piccirillo JF, Merritt MG, Richards ML. Psychometric and clinimetric validity of the 20-Item Sino-Nasal Outcome Test (SNOT-20). *Otolaryngol Head Neck Surg* 2002; 126: 41–47.
57 Amirav I, Shoshan NB, Behan L, *et al.* Translation of the quality of life questionnaire for primary ciliary dyskinesia (QOL-PCD) into Hebrew: the Israeli experience. *Pediatr Pulmonol* 2022; 57: 1331–1338.
58 Hummel T, Kobal G, Gudziol H, *et al.* Normative data for the 'Sniffin' Sticks' including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. *Eur Arch Otorhinolaryngol* 2007; 264: 237–243.
59 Doty RL, Shaman P, Kimmelman CP, *et al.* University of Pennsylvania Smell Identification Test: a rapid quantitative olfactory function test for the clinic. *Laryngoscope* 1984; 94: 176–178.
60 Cain WS, Gent JF, Goodspeed RB, *et al.* Evaluation of olfactory dysfunction in the Connecticut Chemosensory Clinical Research Center. *Laryngoscope* 1988; 98: 83–88.
61 Goutaki M, Lam YT, Alexandru M, *et al.* Study protocol: the ear–nose–throat (ENT) prospective international cohort of patients with primary ciliary dyskinesia (EPIC-PCD). *BMJ Open* 2021; 11: e051433.