Clinical manifestations in primary ciliary dyskinesia: systematic review and meta-analysis

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ABSTRACT Few original studies have described the prevalence and severity of clinical symptoms of primary ciliary dyskinesia (PCD). This systematic review and meta-analysis aimed to identify all published studies on clinical manifestations of PCD patients, and to describe their prevalence and severity stratified by age and sex.

We searched PubMed, Embase and Scopus for studies describing clinical symptoms of ⩾10 patients with PCD. We performed meta-analyses and meta-regression to explain heterogeneity.

We included 52 studies describing a total of 1970 patients (range 10–168 per study). We found a prevalence of 5% for congenital heart disease. For the rest of reported characteristics, we found considerable heterogeneity (I^2 range 68–93.8%) when calculating the weighted mean prevalence. Even after taking into account the explanatory factors, the largest part of the between-studies variance in symptom prevalence remained unexplained for all symptoms. Sensitivity analysis including only studies with test-proven diagnosis showed similar results in prevalence and heterogeneity.

Large differences in study design, selection of study populations and definition of symptoms could explain the heterogeneity in symptom prevalence. To better characterise the disease, we need larger, multicentre, multidisciplinary, prospective studies that include all age groups, use uniform diagnostics and report on all symptoms.

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Review of the clinical manifestations of PCD found between-study variation; large prospective studies needed http://ow.ly/Y5GC300Sw73

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Introduction

Primary ciliary dyskinesia (PCD) is a rare inherited disease which affects ciliary structure and function. As with most orphan diseases, PCD research has focused on pathology and diagnostics. PCD leads to severely impaired mucociliary clearance and a wide variety of symptoms primarily affecting the respiratory system [1]. Productive cough, rhinitis and recurrent infections of the upper and lower respiratory tract have been described as leading symptoms [2, 3]. Manifestations from other systems have also been reported and about half the patients have been described to present with situs inversus [4]. In addition, many males with PCD have immobile spermatozoa or dysfunction of cilia in the epididymal duct, leading to infertility [5]. The prevalence of the disease is estimated to be between 1:2000 and 1:40 000 [3], but it is underdiagnosed [6].

Information about clinical symptoms of PCD is derived mainly from case series and nonsystematic reviews reflecting expert opinion. There are few original studies; most include a small study population, consisting primarily of paediatric patients. Original publications describing the full spectrum of symptoms are scarce and there are few data on less common symptoms. In many diseases it is known that symptoms evolve and change with age, but few studies describe PCD patients from different age groups and show how symptoms change over time. PCD patients comprise a relatively heterogeneous group, as diagnostics and management approaches vary between centres [1, 7]. PCD diagnosis is still not uniform internationally and most recommended tests are not available in many centres and countries, so clinical manifestations continue to play an important role in the diagnosis of PCD.

In this systematic review and meta-analysis, we aimed to identify all published studies presenting clinical symptoms and signs in PCD patients and describe the reported prevalence of all clinical manifestations. This includes the prevalence of upper and lower respiratory symptoms as well as less common clinical findings. In addition, we aimed to describe differences in prevalence and severity of findings in different age groups.

Methods

We developed a protocol for the systematic review beforehand, which is described in the following sections.

Search strategy

We searched the online databases PubMed, Embase and Scopus to identify studies describing clinical manifestations in patients with PCD. In order to build a search term that would identify as many studies as possible, we first performed a pilot search. We searched for studies that were published between January 1980 and April 2015 including published abstracts. We conducted this search without any restrictions in language or study design.

The search was performed using the following terms:

PubMed: (((“kartagener syndrome”[tiab] OR “primary ciliary dyskinesia”[tiab] OR “ciliary motility disorder”[tiab] OR “immotile cilia syndrome”[tiab]) OR “ciliary motility disorders”[mh]) AND (“clinical symptoms”[All Fields] OR “clinical manifestations”[All Fields] OR “clinical presentation”[All Fields])) OR (((“kartagener syndrome”[tiab] OR “primary ciliary dyskinesia”[tiab] OR “ciliary motility disorder”[tiab] OR “immotile cilia syndrome”[tiab]) OR “ciliary motility disorders”[mh]) AND (patients[tiab] OR subjects[tiab] OR participants[tiab] OR “cases”[tiab])) AND (“1980/01/01”[PDAT] : “2015/04/30”[PDAT])

Embase: “primary ciliary dyskinesia”/syn OR “primary ciliary dyskinesia” OR “kartagener syndrome”/syn OR “kartagener syndrome” AND (“clinical symptoms”:ab OR “clinical manifestations”:ab OR “clinical presentation”:ab OR patients:ab OR subjects:ab OR cases:ab OR participants:ab) AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND [1980-2015]/py

Scopus: (((TITLE-ABS-KEY(primary ciliary dyskinesia) AND PUBYEAR > 1979) OR (TITLE-ABS-KEY (immotile cilia syndrome) AND PUBYEAR > 1979) OR (TITLE-ABS-KEY(kartagener syndrome) AND PUBYEAR > 1979)) AND (TITLE-ABS-KEY(“clinical symptoms” OR “clinical manifestations” OR “clinical presentation”) AND PUBYEAR > 1979)) OR (((TITLE-ABS-KEY(primary ciliary dyskinesia) AND PUBYEAR > 1979) OR (TITLE-ABS-KEY(immotile cilia syndrome) AND PUBYEAR > 1979) OR (TITLE-ABS-KEY(kartagener syndrome) AND PUBYEAR > 1979)) AND (TITLE-ABS-KEY(patients OR subjects OR participants OR cases) AND PUBYEAR > 1979))

After identifying all eligible studies, we checked for additional citations in their reference lists. We used the Endnote X5 (Thomson Reuters, Philadelphia, PA, USA) citation manager.

Definition of PCD patients

We defined PCD patients as all patients reported by the authors as being diagnosed with PCD. This included a wide range of inclusion criteria, ranging from patients with a clinical diagnosis to those with

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positive results from the different available diagnostic tests (electron microscopy, light or high-speed video microscopy, nasal nitric oxide (nNO) and genetics).

Study selection

We included studies containing information on clinical manifestations of patients with PCD with a study population of ⩾10 individuals. We excluded publications based on the following exclusion criteria: not original studies, studies that were not topic related or did not contain any clinical information (*e.g.* describing diagnostics or genetics) and studies describing other rare ciliary syndromes such as Joubert or Meckel–Gruber syndrome.

We decided upon inclusion initially by screening the titles and abstracts. From our pilot search we realised that many studies containing information on clinical manifestations did not explicitly articulate this in the title or abstract. For this reason, we decided to screen the full text of all studies which described an original study population of PCD patients and thus had a high probability of containing clinical information in the full text, even if it was not mentioned in the title or abstract. After reading the full text of all potentially eligible studies, the final decision on whether to include them in the review or not was made by two reviewers. During the final step of inclusion, we excluded studies that did not contain any clinical information. The two reviewers decided independently, and in case of disagreement, a consensus decision was reached after discussion.

Overlapping study population

We identified all studies which might have described the same study population, in order to avoid including the same patients multiple times in our review. We compared the author list, country of origin and department where the study took place and when we noticed a considerable overlap in the study population, we always included in the quantitative synthesis the study that was published most recently and included information on a larger number of patients and/or more clinical manifestations. When the studies were published ⩾10 years apart, we included them both, as we believe there was little chance of significant overlap. Where the possibility of an overlap was not clear, we contacted the investigators to clarify it.

Data extraction

Using the software Epidata 3.1 (www.epidata.dk), we extracted the following information from all studies, including the ones with overlapping populations: author- and publication-specific information, study characteristics and information on reported clinical manifestations of PCD patients. Specifically, we extracted publication details (*e.g.* author names, journal and year of publication and country and centre of corresponding author) and study characteristics (*e.g.* years of study performance, study design, inclusion and exclusion criteria, study population size, country where the study took place, type of clinic, age of participants and age stratification of clinical manifestations). Secondly, we extracted extensive information on all reported clinical manifestations of PCD patients, such as situs inversus, lower and upper respiratory symptoms, neonatal symptoms and other nonrespiratory findings (*e.g.* congenital heart disease or infertility). We extracted the number of affected individuals in each study and calculated the prevalence of the reported clinical manifestations. Where only percentages of affected patients were given, we calculated the number of patients affected and then the prevalence.

Meta-analysis

We used a random effects model for binomial data to perform meta-analyses on the transformed prevalence (Freeman–Tukey double arcsine transformation) of clinical manifestations [8–10] and to assess the heterogeneity (I^2) between studies [11]. Diagnosis of PCD has evolved significantly over time and could have influenced the characteristics of the patients included in the eligible studies. Therefore, we performed subgroup meta-analyses, which excluded studies where PCD diagnosis was based only on clinical manifestations or where information on diagnostics was not available.

To investigate reasons for heterogeneity we then fitted meta-regression models considering the following explanatory factors one at a time: type of clinic (general paediatrics, paediatric pulmonology, adult pulmonology, ear-nose-throat (ENT) clinic or other), age of patients (adults, children or both), publication year (published before 1994, 1995–2004 and since 2005), number of patients included (<20, 21–50, 51–100 and >100 patients), study design (retrospective or prospective) and level of diagnostic certainty (clinical diagnosis, diagnosis proven by electron microscopy or diagnosis proven by combination of electron microscopy and other tests (video microscopy, nNO or genetics)). Studies in which the inclusion criteria influenced the prevalence of some clinical manifestations were excluded from the meta-analyses and meta-regression for these characteristics. For instance, studies describing patients with Kartagener syndrome were excluded from the meta-analyses on prevalence of situs anomalies, bronchiectasis and sinusitis. We also excluded these studies from the meta-analysis on prevalence of congenital heart disease, as patients with

situs anomalies have a higher probability of having congenital heart disease than patients with situs solitus. Statistical analysis was performed using R software version 3.2 (www.r-project.org) using the meta package (version 4.2) and specifically the commands metaprop and metareg.

Results

Search

After excluding duplicates identified by more than one database (Pubmed, Embase or Scopus) our search identified 1210 articles (figure 1). First, we screened for inclusion and exclusion criteria by reading through titles and abstracts and excluded 1109 articles. It was not possible to find the abstract or the full text for 16 studies. This resulted in 101 articles. After reading the full texts, we excluded another 49 articles; 19 did not contain any clinical information and 30 had a largely overlapping study population [4, 12–40].

Three pairs of studies had partially overlapping study populations, but unique data, hence were all included in the quantitative synthesis. Studies by Pedersen and Stafanger [41] and Mygind and Pedersen [42] described different symptoms in the same population. Studies by McManus *et al.* [43] and Jain *et al.* [44] had only a small partial overlap and provided mostly unique information. Articles by Shapiro *et al.* [45] and Davis *et al.* [46] had a partial overlap in study population, but one described only situs anomalies and the other more clinical characteristics. Ultimately, we included a total of 52 studies.

Study characteristics

Table 1 lists the included studies and describes their characteristics. The 51 articles [2, 41–90] and one conference abstract [91] included described a total of 1970 patients, with a mean number of 38 patients per study (range 10–168). Nearly half of the studies originated from paediatric clinics or paediatric pulmonology departments, 11 came from ENT departments, four from adult pulmonology departments and 12 from other departments, such as diagnostic laboratories, radiology and pathology departments (table 2). Two-thirds were single-centre studies. More than half of the studies (56%) were published in the past 10 years (since 2005). Studies were relatively small, with most including <50 patients. Most studies (n=31) came from Europe, 10 from Asia, eight from North America, two from South America and one from Australia. 17 studies included only children (age <18 years), three included only adults (age ⩾18 years) and 32 studies described a study population of mixed age, consisting mainly of children with only few adults. Among those 32 studies, only 11 described the clinical data stratified by age group. Symptoms were assessed retrospectively in most studies (n=37, 71%). PCD diagnosis was established in

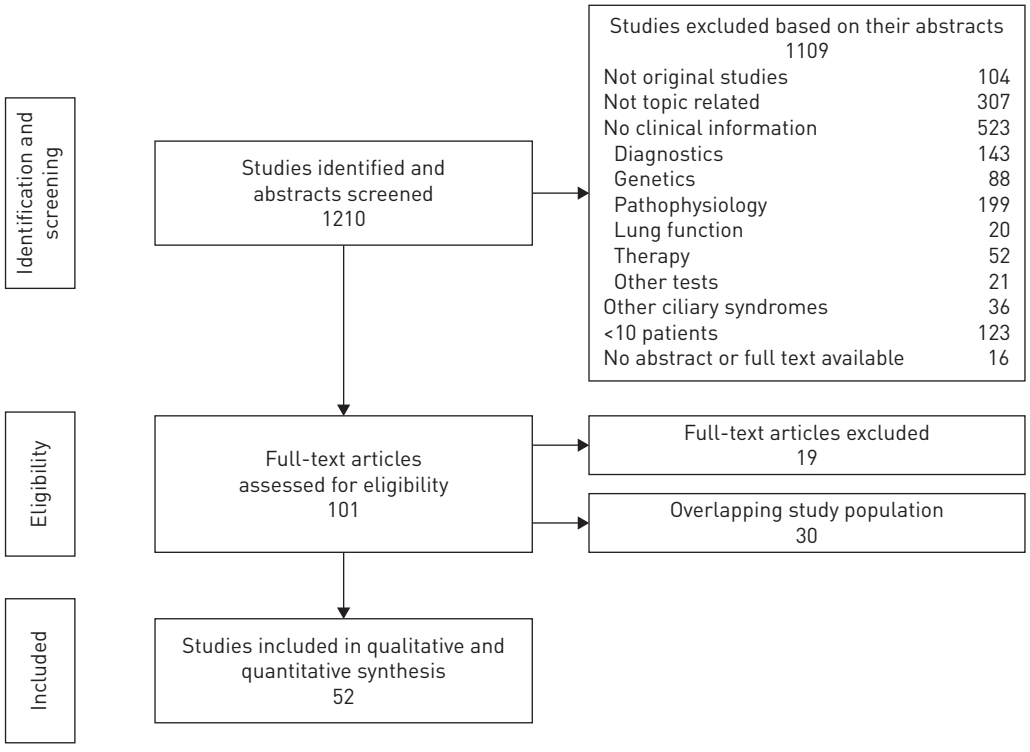

FIGURE 1 Flow chart describing the selection procedure. Data are presented as n.

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TABLE 1 Detailed characteristics of included studies describing clinical manifestations of primary ciliary dyskinesia (PCD), stratified by age group of participants

First author [ref.]	Country of publication	Year of publication	Participants n	Age years	Type of clinic	Type of study	Study design	Diagnostics	Symptoms stratified by age	Symptom severity assessed	Situs anomalies	Lower respiratory symptoms	Upper respiratory symptoms	Neonatal respiratory distress	Congenital heart disease	Infertility
Children																
Alsaadi [48]	Saudi Arabia	2013	22	11[¶]	Paediatric pulmonology	Case–control	R	EM + nNO	–	–	+	+	+	–	–	–
Barlocco [52]	Italy	1991	28	8[¶] (0–18)	Paediatric pulmonology	Case series	P	EM	–	–	+	+	+	–	–	–
Beucher [53]	France	2011	17	7[¶]	Paediatric pulmonology	Case series	R	EM + nNO	–	–	+	–	+	+	–	–
Busquets [55]	Spain	2013	35		Paediatric pulmonology	Case series	R	EM	–	–	–	+	–	–	–	–
Davis [46]	USA	2015	118	8[¶] (5–11)	Combination	Case series	P	EM + nNO + genetics	–	–	+	+	+	+	–	–
Enderby [91][#]	UK	2010	17	9[+] (4–17)	Paediatrics	Case series	R	Clinical diagnosis only	–	–	+	+	+	+	–	–
Hosie [90]	Australia	2015	84	6[+] (0–18)	Paediatrics	Cohort	R	EM + VM + nNO	–	–	+	+	+	+	+	–
Jain [44]	UK	2007	89		Paediatric pulmonology	Case series	R	EM + VM + nNO	–	–	+	+	+	+	–	–
Korppi [65]	Finland	2011	12		Paediatrics	Cohort	R	EM	–	–	+	+	–	–	–	–
Min [68]	South Korea	1995	19	10[¶] (5–15)	Paediatrics	Case series	R	EM	–	–	+	+	+	–	–	–
Mullowney [87]	Canada	2014	55	11[¶]	Paediatric pulmonology	Case–control	R	EM + nNO + genetics	–	–	+	+	–	+	+	–
O'Callaghan [70]	UK	2010	19		PCD diagnostic centre	Case series	R	EM + VM	–	–	+	+	–	+	–	–
Rachinskii [75]	Russia	1993	24		Paediatrics	Case series	R	EM	–	–	+	+	+	–	+	–
Rutishauser [76]	Switzerland	2000	30		Paediatrics	Case series	R	EM + VM	–	–	+	+	+	–	+	–
Vallet [81]	France	2013	60	0–15	Paediatric pulmonology	Case series	R	EM + VM	–	–	+	+	+	+	–	–
Wolter [84]	Canada	2012	31	7[¶] (0–17)	ENT	Case series	R	EM + nNO	–	–	+	+	+	+	–	–
Xu [85]	China	2008	26		Paediatrics	Case series	R	EM	–	–	+	+	+	–	–	–
Adults																
Afzelius [47]	Sweden	1983	29		PCD diagnostic centre	Case series	R	EM	–	–	+	–	–	–	–	+
Camner [56][#]	Sweden	1983	20	30[¶] (19–40)	Adult pulmonology	Case series	R	Clinical diagnosis only	–	–	+	+	+	–	–	–
Smit [77]	Canada	1996	21	46[¶] (24–66)	Adult pulmonology	Case series	R	EM + VM	–	–	+	+	–	–	–	–
Children and adults																
Armengot [49]	Spain	2012	25	28[¶] (1–66)	ENT	Case series	P	EM + VM	+	–	+	+	+	–	–	–
Armengot [50]	Spain	1995	14	24[¶] (5–50)	ENT	Case series	P	EM	–	–	+	+	+	–	–	–
Bai [51]	China	2014	10	35[¶] (6–56)	ENT	Case series	R	EM + nNO + genetics	+	–	+	+	+	–	–	+
Boon [39]	Belgium	2014	168	18[+]	PCD diagnostic centre	Cohort	R	EM + VM + nNO + genetics	–	–	+	+	+	+	+	–
Braun [54]	France	2005	35		ENT	Case series	R	EM + VM	–	–	+	+	–	+	+	–
Chin [89]	China	2002	73	0–48	Pathology	Case series	R	EM + nNO	–	–	–	+	+	–	–	–
de Boode [57]	The Netherlands	1989	34	23[¶] (6–55)	Paediatric	Case series	R	EM + VM	–	–	+	+	+	–	–	–
El-Sayed [58]	Saudi Arabia	1997	16	18[¶] (2–46)	ENT	Case series	P	EM	+	–	+	+	+	–	–	–
Goyal [59][#]	India	1987	11		Adult pulmonology	Case series	R	Clinical diagnosis only	+	–	+	+	+	–	–	–
Greenstone [60]	UK	1988	30	19[¶] (0–51)	Cardiothoracic	Case series	P	EM + VM	–	–	+	+	+	–	–	+
Hellinckx [61]	Belgium	1998	12	1–32	Paediatric pulmonology	Case series	R	EM + VM	–	–	–	+	–	–	–	–
Holzmann [62]	Switzerland	2000	10		ENT	Case series	R	EM + VM	–	–	+	+	+	+	–	–

Continued

TABLE 1 Continued

First author [ref.]	Country of publication	Year of publication	Participants n	Age years	Type of clinic	Type of study	Study design	Diagnostics	Symptoms stratified by age	Symptom severity assessed	Situs anomalies	Lower respiratory symptoms	Upper respiratory symptoms	Neonatal respiratory distress	Congenital heart disease	Infertility
Iñiguez [63]	Chile	2007	33		ENT	Case series	R	EM	–	–	+	+	+	–	–	–
Kawakami [64]	Japan	1996	48	38[¶] (17–72)	Paediatric pulmonology	Case series	R	EM	–	–	+	+	+	–	–	–
Lesic [66]	Austria	2009	13		Paediatrics	Case series	R	EM	–	–	+	+	+	–	–	+
Marthin [67]	Denmark	2010	74	19[+] (6–70)	PCD reference centre	Case series	R	EM + VM + nNO	–	–	+	+	+	+	+	–
McManus [43][#]	UK	2003	93	23[¶] (4–66)	Psychology	Case series	P		–	–	+	+	+	–	–	–
Montella [69]	Italy	2009	13	15[+] (10–29)	Paediatrics	Case series	P	EM + VM	+	–	+	+	–	+	–	–
Mygind [42][#]	Denmark	1983	27	24[¶] (4–56)	ENT	Case series	P	Clinical diagnosis only	+	–	+	+	+	–	–	–
Noone [2]	USA	2004	78	27[¶] (1–73)	Combination	Case series	P	EM + VM + nNO	+	–	+	+	+	+	–	–
Oktem [71]	Turkey	2013	29	10[¶] (0–24)	Paediatrics	Case–control	P	EM	–	–	–	+	+	–	–	–
Olm [72]	Brazil	2011	12	12[¶] (1–19)	Paediatric pulmonology	Case series	R	EM	+	–	+	+	–	–	+	–
Pedersen [41]	Denmark	1983	27		Paediatrics	Case series	P	EM + VM	+	–	+	+	+		+	+
Pifferi [73]	Italy	2010	78	21[¶] (2–49)	Paediatrics	Case series	P	EM + VM	–	–	+	+	+	–	+	–
Plesec [74]	USA	2008	13	15[¶] (1–49)	Pathology	Case series	R	EM	+	–	+	+	+	–	+	+
Shapiro [45]	USA	2014	35	18[¶] (2–58)	Combination	Case series	R	EM + nNO + genetics	–	–	+	+	+	+	+	–
Sommer [78][#]	Germany	2011	44	29[¶]	ENT	Case series	R		–	–	+	–	+	–	–	–
Sturgess [79]	Canada	1986	46		Paediatrics	Case series	R	EM + genetics	+	–	+	+	+	–	–	–
Tolusakow [80][#]	Russia	1981	23	3–43	Adult pulmonology	Case series	P	Clinical diagnosis only	–	–	+	+	+	–	–	–
van der Baan [82]	The Netherlands	1991	36	25[¶] (1–59)	ENT	Case series	P	EM + VM	–	–	+	–	–	–	–	–
Wang [83]	China	2009	24	29[¶] (4–63)	Radiology	Case series	R	EM	–	–	+	+	+	–	+	+
Yiallouros [86]	Cyprus	2015	30	24[¶] (1–64)	Paediatrics	Cohort	R	EM + VM + nNO	–	–	+	+	+	+	–	–

Data are presented as mean (range) or median (range) or range, unless otherwise stated. R: retrospective; EM: electron microscopy; nNO: nasal nitric oxide; P: prospective; VM: light or high-frequency video microscopy; ENT: ear, nose and throat. [#]: studies excluded from subgroup meta-analyses; [¶]: mean; [+]: median.

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TABLE 2 Characteristics of included studies reporting clinical manifestations of primary ciliary dyskinesia

Total studies	52 (100)
Type of clinic	
Paediatric department	16 (33)
Paediatric pulmonology department	9 (17)
Adult pulmonology department	4 (8)
ENT department	11 (21)
Other department	12 (21)
Number of centres	
Single centre	35 (66)
Multicentre	17 (33)
Publication period	
Prior to 1994	12 (23)
1995–2004	11 (21)
Since 2005	29 (56)
Study size (number of patients)	
⩽20	15 (29)
21–50	25 (48)
50–100	9 (14)
>100	3 (6)
Study region	
Europe	31 (60)
Asia	10 (19)
North America	8 (15)
South America	2 (4)
Australia	1 (2)
Age of participants	
Children <18 years	17 (33)
Adults ⩾18 years	3 (6)
Children and adults	32 (62)
Study design	
Retrospective	37 (71)
Prospective	15 (29)
Diagnostics performed	
Clinical diagnosis only	5 (10)
Diagnosis proven using EM	16 (31)
Diagnosis proven using EM plus other tests[#]	29 (56)
No information on diagnostics available	2 (4)
Health conditions	
Situs anomalies	48 (92)
Lower respiratory tract conditions	48 (92)
Cough	29 (56)
Sputum production	24 (46)
Lower respiratory tract infections	27 (52)
Bronchiectasis	34 (65)
Upper respiratory tract conditions	41 (79)
Rhinitis	28 (54)
Otitis media	26 (50)
Sinusitis	32 (62)
Hearing impairment	14 (27)
Grommets	12 (23)
Nasal polyps	14 (27)
Other conditions	
Neonatal respiratory distress	17 (33)
Congenital heart disease	13 (25)
Infertility	7 (14)
Hydrocephalus	3 (6)
Retinitis pigmentosa	2 (4)
Renal symptoms	0 (0)
Information for different age groups	11[¶] (34)
Information on severity	0 (0)

Data are presented as n (%). ENT: ear, nose and throat; EM: electron microscopy. [#]: one or more of the following: nasal nitric oxide, high-frequency videomicroscopy or light microscopy or genetics; [¶]: out of 32 studies including children and adults.

different ways: 16 studies assessed ciliary ultrastructure only using electron microscopy and 29 with additional diagnostic tests (one or more of the following: nNO, video microscopy and genetics). Five studies diagnosed patients only by clinical presentation; two did not describe the diagnostic evaluation of the patients. Most studies described situs anomalies (92%) and lower (92%) and upper (79%) respiratory symptoms. Other manifestations and health problems were seldom reported: 17 (33%) studies reported on neonatal respiratory distress, 13 (25%) on congenital heart disease, seven (14%) on infertility, three (6%) on hydrocephalus, two (4%) on retinitis pigmentosa and none on renal symptoms.

Prevalence of clinical manifestations

Online supplementary table S1 describes the prevalence of commonly reported clinical manifestations in the included studies, categorised by country of origin, including studies with overlapping populations. For all reported characteristics the prevalence varied widely between studies and our analysis showed considerable heterogeneity (I^2 range 68–94%). Figures 2–4 and online supplementary figures S1–S11 describe the prevalence of symptoms in the different studies. In the following text and figures we report all symptoms described in five or more studies.

Situs anomalies

41 (79%) studies explicitly reported situs inversus and seven (14%) reported only the cardiac situs of the patients or used the term situs ambiguus without any further specification. To calculate the prevalence, we summed these symptoms up under the designation of situs anomalies. After excluding studies that focused on describing patients with Kartagener syndrome, which had a high prevalence of situs anomalies (up to 100%), the prevalence of situs anomalies in the 43 eligible studies ranged from 11% to 90% (weighted mean 49% with a heterogeneity of I^2=71%; online supplementary figure S1).

Lower respiratory symptoms

Cough was reported in 29 (55.8%) studies and prevalence varied from 14% to 100% with a weighted mean of 88% (online supplementary figure S2). Sputum production was reported for 15–100% of patients (weighted mean 89%) in the 24 (46%) studies where it was described (figure 2). Lower respiratory infections, including

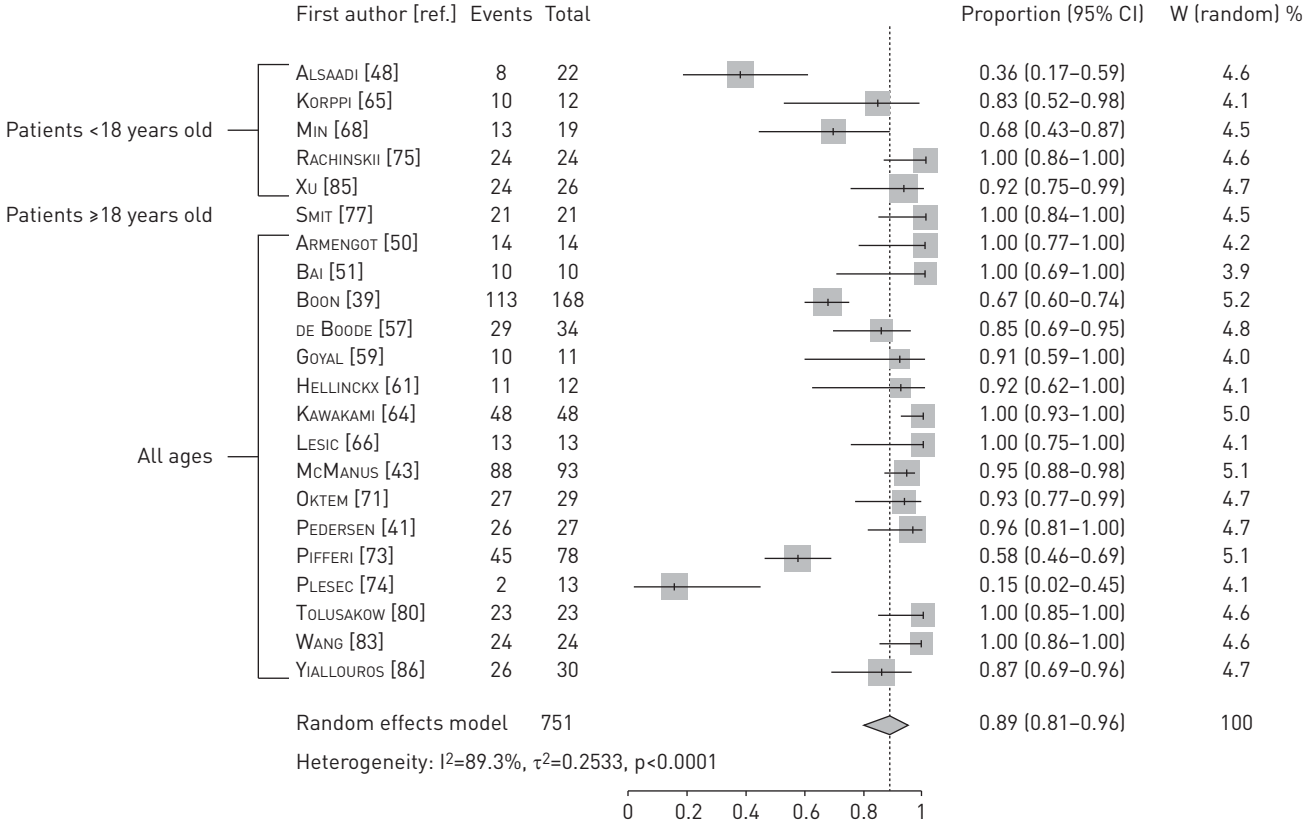

FIGURE 2 Sputum production in primary ciliary dyskinesia patients: forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

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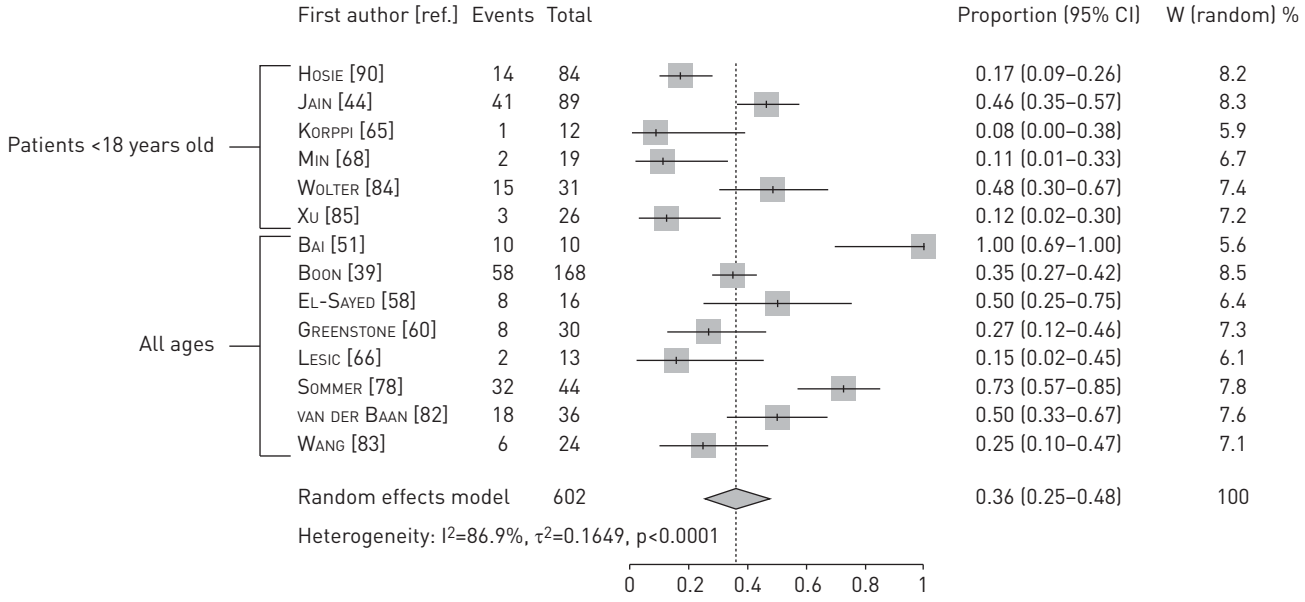

FIGURE 3 Hearing impairment in primary ciliary dyskinesia patients: forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

pneumonia, were also common, reported in 27 (52%) studies with a weighted mean prevalence of 72% (range 15–100%; online supplementary figure S3). Prevalence of bronchiectasis (reported in 29 (56%) studies after excluding studies focused on patients with Kartagener syndrome) ranged from 9% to 100%, with a weighted mean of 56% (online supplementary figure S4). The heterogeneity (I^2) in prevalence of lower respiratory symptoms ranged from 89% in sputum production to 94% in cough.

Upper respiratory symptoms

Rhinitis, rhinorrhea or nasal congestion were assessed in 28 (54%) studies and ranged in prevalence from 9% to 100% (weighted mean 75%; online supplementary figure S5). Otitis media (with or without effusion) was reported in 26 (50%) studies and its prevalence varied from 23% to 100% (weighted mean 74%; online supplementary figure S6). Sinusitis was reported in 29 studies (56%, after excluding studies focusing on Kartagener syndrome) with a weighted mean of 69% (range 10–100%; online supplementary figure S7). Hearing impairment was reported in 14 (27%) studies and prevalence ranged from 8% to 100% (weighted mean 36; figure 3). Insertion of grommets was reported in 12 (23%) studies and prevalence ranged from 5% to 92% (weighted mean 55%; online supplementary figure S8). Nasal polyps were described in 14 (27%) studies with a weighted mean of 19% (range 3–60%; online supplementary

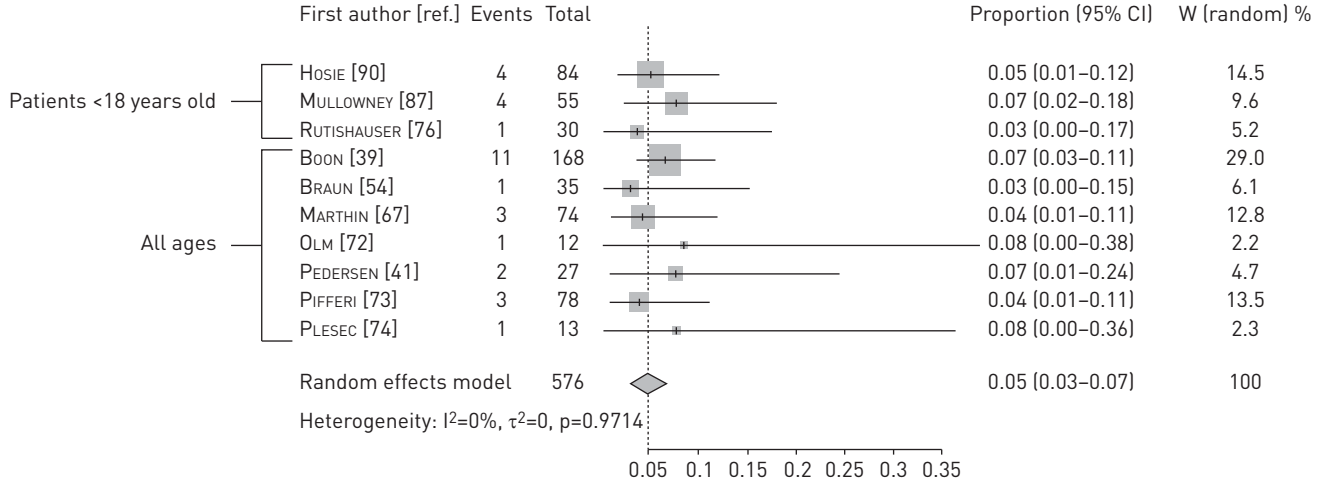

FIGURE 4 Congenital heart disease in primary ciliary dyskinesia patients: forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

figure S9). The heterogeneity in prevalence of these upper respiratory symptoms and health problems ranged from 68% for nasal polyps to 93% for rhinitis and grommet insertion.

Other symptoms

Figure 4 shows the prevalence of congenital heart disease, which was the only characteristic showing no heterogeneity (I^2=0%) with a weighted mean of 5% (ranging from 3% to 8%) and was reported in 10 studies (19%, excluding studies focusing on patients with Kartagener syndrome). 17 (33%) studies assessed neonatal respiratory distress and prevalence varied from 15% to 91% (weighted mean 55%; online supplementary figure S10) Infertility was reported in seven (13.5%) publications which had a study population of adults or adults and children, and this was assessed only in the adult patients of these studies. Prevalence ranged from 15% to 79% (weighted mean 30%; online supplementary figure S11). Of the seven studies reporting on infertility, four stratified for sex. In these four studies, 58% of females evaluated were infertile; male fertility was reported in three studies and 100% of males evaluated in these studies were infertile. The heterogeneity in prevalence ranged from 0% in congenital heart disease to 91% in neonatal respiratory distress. Other symptoms reported in a small number of studies were recurrent headaches, episodes of fever and gastroesophageal reflux. Other health conditions such as hydrocephalus and retinitis pigmentosa, which have been described as rare manifestations of PCD were only reported in three and two studies, respectively, and renal manifestations were not reported in any of the studies.

Differences in prevalence in different age groups and severity of symptoms

The clinical manifestations assessed were rarely described stratified by sex or age group. The 11 studies describing symptoms separately in adults and children included usually a small number of adults and they had no further stratification into smaller age groups. No information on symptom severity was reported.

Subgroup meta-analyses

After excluding seven studies where diagnosis was only based on clinical manifestations or where no information on diagnosis was available, subgroup meta-analyses performed in 45 studies with diagnosis proven using electron microscopy, or electron microscopy plus other tests showed similar results to the ones presented. Weighted mean prevalence, range and heterogeneity of all symptoms from the subgroup meta-analyses are presented in detail in online supplementary figs S12–S25.

Meta-regression

Meta-regression showed that the explanatory factors considered explained only a small part of the between-studies variance for all symptoms. Year of publication explained some of the heterogeneity for sputum production and sinusitis, with a higher prevalence in studies published before 2004 ($p=0.06$ and 0.005, respectively). Another factor that explained part of the heterogeneity was the type of clinic from which the study originated. Paediatric pulmonology clinics and ENT clinics in particular showed a higher prevalence of hearing impairment ($p<0.0001$) compared to general paediatric clinics. Age of patients included also explained part of the heterogeneity, as situs anomalies and bronchiectasis were more common in studies including adults, or adults and children, compared to the ones including only children ($p=0.004$ and 0.02, respectively). Bronchiectasis was also more common in prospective studies ($p=0.03$). Otitis media and hearing impairment had higher prevalence in studies where diagnosis was made using electron microscopy and other tests compared to the ones where diagnosis was only based on clinical symptoms. Detailed results of the meta-regression can be found in online supplementary table S2.

Discussion

This is the first systematic review of clinical manifestations in PCD patients. We found a prevalence of 5% of congenital heart disease and a wide range in the prevalence of all other reported clinical symptoms. This heterogeneity could not be explained by the available explanatory factors. Only 7% of the originally identified 1210 studies described clinical manifestations of the disease, and 30 reported overlapping study populations. Most studies were retrospective and small, with a mean of 38 patients per study. They often originated from specialised departments (*e.g.* pulmonary or ENT) and focused primarily on lower and upper respiratory symptoms. Fewer than half of the studies that included both children and adults reported their information stratified by age. No study described symptom severity. Year of publication, clinic of origin, age of included patients, study design and diagnostic certainty were associated with symptom prevalence.

The main strength of this study is the methodological approach: to identify eligible studies, the search was performed without language restrictions and we included conference abstracts. Because some abstracts did not mention clinical manifestations, we screened the full text of all articles with an original PCD study population, even if clinical information was not explicitly mentioned in the abstracts. This ensured that we included studies we would have missed if we had followed the custom search protocol. We identified and

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excluded studies where the population inclusion criteria introduced a clear bias in the prevalence of certain manifestations. Additionally, we proceeded to explain the heterogeneity in results by performing a meta-regression with all available explanatory factors, but we were not able to include other known possible factors such as personal interest of the authors. PCD diagnosis has changed over time and varies between countries and centres. For this reason, we performed a sensitivity analysis excluding all studies where the diagnosis had not been confirmed using recommended tests.

We restricted our search to studies published since 1980 for several reasons. First, older studies are often not available online or do not have an available abstract on the online databases. Second, since 1933 when PCD was first described by Kartagener, many things have changed in diagnosing, understanding and characterising the disease. Third, the studies that described clinical characteristics of PCD before 1980 were mostly case reports or small studies with <10 patients, which would not be eligible for our review.

The limitations of this review reflect the limitations of the included studies, namely inadequate study designs and the presence of significant selection and misclassification bias. With regards to study design, most studies were small, single-centre case series studies that collected clinical data retrospectively from patient charts. Three main sources of selection bias are apparent, as follows. 1) Diagnostic misclassification resulting from a wide variation of diagnostic criteria used in the studies, ranging from clinical diagnosis to diagnosis established using multiple available tests (electron microscopy, video microscopy, nNO and genetics). Although there is still no established diagnostic gold standard for diagnosing PCD, the recommended diagnostic algorithm has changed considerably over the years. To address this issue we performed subgroup meta-analyses excluding the studies where the diagnosis was only clinical or not described and we tested the available diagnostic information as a possible explanatory factor of the heterogeneity in our meta-regression. 2) Since most studies originated from specialised clinics, it is expected that patients with more severe manifestations were included and these study populations cannot be considered representative of all PCD patients. 3) Many studies had restrictive inclusion criteria, including, for example, only patients with situs anomalies or with reported otitis, which would increase the prevalence of manifestations related to the selection criteria (*i.e.* situs status and hearing impairment). Thus we excluded studies where the population inclusion criteria introduced a clear bias in the prevalence of certain manifestations (*e.g.* studies including only patients with Kartagener syndrome for the prevalence of situs anomalies, sinusitis and bronchiectasis). Misclassification bias is introduced when inconsistent criteria and different definitions are used to detect and define clinical manifestations. Most studies focused on symptoms from the upper and lower respiratory system. Other symptoms were rarely reported and hardly any study reported symptoms separately for different age groups. Therefore, it was not possible to describe changes in the clinical picture throughout the life course. Information on symptom severity, such as frequency of cough or volume of sputum, was not reported. Data were collected at different points of disease; some at the time of diagnosis, others at a later follow-up appointment. As most studies suffered from the same design flaws, we did not apply any quality assessment criteria to decide which studies to include in our meta-analysis.

Due to the considerable heterogeneity, the calculated mean weighted prevalence of described clinical manifestations characteristics (with the exception of congenital heart disease) should be interpreted with caution. The meta-analysis was performed to quantify the variability in prevalence and not to give valid estimates on prevalence. The possible explanatory factors tested failed to explain this heterogeneity. Still, some factors contributed to explaining differences in prevalence of some symptoms. Year of publication reflects differences in diagnosis, but also increasing awareness of PCD. Older studies included more patients with severe disease. Age is one of the most important factors in health and disease. Situs anomalies and bronchiectasis were more common in adult patients, probably because cases without situs anomalies or severe lung disease were underdiagnosed in adults, especially in the past. The type of clinic from which the study population originated can influence reported symptoms. The discovery of bronchiectasis could be highly influenced by study design; a standardised protocol for chest computed tomography (CT) imaging and the existence of two evaluators of results instead of one are among the most important factors that could explain the higher prevalence in prospective studies. Diagnostic certainty was associated with higher prevalence of upper respiratory manifestations (otitis media and hearing impairment) in studies with test-proven diagnosis. Mild hearing impairment can remain undetected unless specific tests are performed, which could be more common after test-proven diagnosis. In addition, it is possible that unspecific upper respiratory symptoms play a less important role in the differential diagnosis of PCD compared to situs anomalies and lower respiratory symptoms. The only outcome where the meta-analysis did not suggest heterogeneity (I^2=0%) was congenital heart disease, where we found a prevalence of 5%. This is perhaps not surprising, since severe heart disease is diagnosed early in childhood in most cases. Hence it is likely that severe congenital heart defects are least susceptible to measurement bias. The manifestations of bronchiectasis, hearing impairment and infertility would all be expected to have increased in frequency with time, with the uniform application of sensitive testing for

detection (*e.g.* chest CT scanning, audiograms and spermatozoa analysis, respectively). The variable "neonatal respiratory distress" is probably increasingly subject to recall bias as patients age. We were unable to detect this in our meta-regression analysis (online supplementary table S2). However, in one study [2], where uniform methods were applied to include cases prospectively, the prevalence of neonatal respiratory distress was much higher in children (87%) compared to adults (65%).

In our study, methodological variability between included studies could not explain the heterogeneity in prevalence of manifestations. We believe that heterogeneity in prevalence is caused by the large variety of inclusion criteria and the insufficient standardisation of outcomes, which cannot be tested in a meta-analysis. Another possible explanation is that patients with PCD might have several distinctive phenotypes, similar to patients with cystic fibrosis [92, 93] and childhood asthma [94, 95]; the proportion of different phenotypes might vary between centres.

Our review highlights the difficulty in describing the full clinical picture of PCD based on published studies. Future studies should conform to the following criteria: 1) report on all clinical manifestations, including the less common ones; 2) assess indicators of symptoms severity; 3) use clear, homogeneous definitions of all clinical manifestations; 4) use clear inclusion criteria for the study population; 5) collect data prospectively at specified assessment time points starting from diagnosis and continuing throughout life; and 6) stratify the analysis by the degree of diagnostic certainty of PCD of the patients.

These criteria could be fulfilled by performing prospective well-designed multicentre studies in patients with carefully assessed PCD diagnosis. Another important resource will be the international PCD registry which has been established in the framework of the European Union-funded Bestcilia project [96].

This carefully performed systematic review and meta-analysis of clinical manifestations of PCD found considerable heterogeneity between studies, not explained by methodological variations. Further prospective studies with larger and carefully selected populations and well defined outcomes will allow better characterisation of the disease, and possibly define different phenotypes of PCD.

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