

# Clinical manifestations in Primary Ciliary Dyskinesia: systematic review and meta-analysis

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None

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## Abstract

### **Introduction**

Few original studies have described 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.

### **Methods**

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

### **Results**

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.

### **Conclusion**

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, multicenter, multidisciplinary, prospective studies that include all age groups, use uniform diagnostics and report on all symptoms.

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Keywords: systematic review, meta-analysis, primary ciliary dyskinesia, clinical manifestations, rare diseases, epidemiology

## 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 of the patients have been described to present with situs inversus.[4] In addition, many men with PCD have immobile spermatozoa or dysfunction of cilia in the epididymal duct leading to infertility.[5] The prevalence of the disease is estimated between 1:2,000 and 1:40,000 [3] but the disease is underdiagnosed.[6]

Information about clinical symptoms of PCD is derived mainly from case series and non-systematic reviews reflecting expert opinion. There are few original studies which mostly 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 how symptoms have changed over time and PCD patients for different age groups. PCD patients compose 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 to 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. We also 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 with 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" OR "clinical manifestations" OR "clinical presentation")) 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 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 positive results from the different available diagnostic tests (electron microscopy (EM), light or high speed video-microscopy (VM), nasal NO (nNO) and genetics).

### *Study selection*

We included studies containing information on clinical manifestations of patients with PCD with a study population of 10 or more 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, genetics), and studies describing other rare ciliary syndromes such as Joubert or Meckel-Gruber syndrome.

We decided on the inclusion initially by screening the titles and abstracts. From our pilot search we realized that many studies containing information on clinical manifestations did not explicitly articulate this in the title or abstract. For this reason, we decided to also screen the full text of all studies which described an original study population of PCD patients and thus had a high probability to contain 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 or more 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, we extracted the following information from all studies, including the ones with overlapping population: author and publication specific information, study characteristics, information on reported clinical manifestations of PCD patients. Specifically, we extracted publication details (e.g. author names, journal and year of publication, 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 non-respiratory findings (e.g. congenital heart disease, 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 significantly evolved overtime and could have influenced the characteristics of the patients included in the eligible studies. Therefore, we performed also subgroup meta-analyses, which excluded studies where PCD diagnosis was based only on clinical manifestations or where information on diagnostics were 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  $\leq 1994$ , 1995-2004 and  $\geq 2005$ ), 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 EM, or diagnosis proven by combination of EM and other tests (VM, 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 to have congenital heart disease than patients with situs solitus. Statistical analysis was performed with R software version 3.2 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, 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. For 16 studies it was not possible to find the abstract or the full text. 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 and hence were all included in the quantitative synthesis. Studies from Pedersen et al. [41] and Mygind et al. [42] described different symptoms in the same population. Studies from McManus et al. [43] and Jain et al. [44] had only a small partial overlap and provided mostly unique information. Papers 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. In the end 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, 4 from adult pulmonology 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%) have been published in the last 10 years ( $\geq 2005$ ). Studies were relatively small, with most including less than 50 patients. Most studies (31) came from Europe, 10 from Asia, 8 from North America, 2 from South America and 1 from Australia. Seventeen studies included only children ( $<18$  years), 3 only adults ( $\geq 18$  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 groups. Symptoms were assessed retrospectively in most studies (37, 71%). PCD diagnosis was established in different ways: 16 studies assessed ciliary ultrastructure only with EM and 29 with additional diagnostic tests (one or more of the following: nNO, VM 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%), lower respiratory (92%) and upper respiratory symptoms (79%). Other manifestations and health problems were seldom reported: 17 studies (33%) reported on neonatal respiratory distress, 13 (25%) on congenital heart disease, 7 (14%) on infertility 3 (6%) on hydrocephalus, 2 (4%) on retinitis pigmentosa and none on renal symptoms.

### *Prevalence of clinical manifestations*

Table S1 (online supplement) describes the prevalence of commonly reported clinical manifestations in the included studies, categorized 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 Figures S1-S11 describe prevalence of symptoms in the different studies. In the following text and figures we report all symptoms described in at least 5 studies.

### *Situs anomalies*

Forty-one studies (79%) explicitly reported situs inversus and 7 (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  $I^2=71\%$  and can be seen in Figure S1).

### *Lower respiratory symptoms*

Cough was reported in 29 studies (55.8%) and prevalence varied from 14 to 100% with a weighted mean of 88% (Figure S2). Sputum production was reported for 15 to 100% of patients (weighted mean: 89%) in the 24 (46%) studies where it was described (Figure 2). Lower respiratory infections, including pneumonia were also common: reported in 27 studies (52%) with a weighted mean prevalence of 72% (range 15-100%, Figure S3). Prevalence of bronchiectasis (reported in 29 studies, 56%, after excluding studies focused in patients with Kartagener syndrome) ranged from 9 to 100%, with a weighted mean of 56% (Figure S4). The heterogeneity ( $I^2$ ) in prevalence of lower respiratory symptoms was ranging largely from 89% in sputum production to 94% in cough.

### *Upper respiratory symptoms*

Rhinitis, rhinorrhea or nasal congestion were assessed in 28 studies (54%) and ranged in prevalence from 9 to 100% (weighted mean: 75%, Figure S5). Otitis media (with or without effusion) was reported in 26 studies (50%) and its prevalence varied from 23 to 100% (weighted mean: 74%, 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%, 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 by 12 studies (23%) and prevalence ranged from 5 to 92% (weighted mean: 55%, Figure S8). Nasal polyps were described in 14 studies (27%) and with a weighted mean of 19% (range 3-60%, 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 grommets' 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%, after excluding studies focusing on patients with Kartagener syndrome). Seventeen studies (33%) assessed neonatal respiratory distress and prevalence varied from 15 to 91% (weighted mean: 55%, Figure S10). Infertility was reported in 7 publications (13.5%) which had a study population of adults or adults and children and it was assessed only on adult patients of these studies. Prevalence ranged from 15 to 79% (weighted mean: 30%, Figure S11). Of the 7 studies reporting on infertility, 4 stratified for sex. In these 4 studies, 58% of women evaluated were infertile; male fertility was reported in 3 studies and 100% of men 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, fever episodes 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 3 and 2 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 in smaller age groups. No information on symptom severity was reported.

### *Subgroup meta-analyses*

After excluding 7 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 by EM, or by EM 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 Figures S12 to S25.

### *Meta-regression*

Meta-regression showed that the explanatory factors considered explained only a small part of the between-studies variance for all symptoms. Publication year explained some of the heterogeneity for sputum production and sinusitis, with a higher prevalence in studies published before 2004 (p-values: 0.06 and 0.005 respectively). Another factor that explained part of the heterogeneity was the type of clinic where the study originated from. Paediatric pulmonology and especially ENT clinics showed a higher prevalence of hearing impairment ( $p < 0.0001$ ) compared to general paediatric clinics. Age of included patients 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-values: 0.004 and 0.02 respectively). Bronchiectasis were also more common in prospective studies ( $p = 0.03$ ). Otitis media and hearing impairment had higher prevalence in studies where diagnosis was made by EM 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 table S2.

### Discussion

This is the first systematic review on 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, ENT) and focused primarily on lower and upper respiratory symptoms. Less 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 done 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 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 like 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 by recommended tests.

We restricted our search to studies published since 1980 for several reasons. First, older studies were not easily available online or often do not have an available abstract on the online databases. Secondly, since 1933 when PCD was first described by Kartagener, many things have changed in diagnosing, understanding and characterising the disease. Thirdly, the studies that described clinical characteristics of PCD before 1980 were mostly case reports or small studies with less than 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 center case series studies that collected clinical data retrospectively from patient charts. Three main sources of selection bias are apparent: (1) Diagnostic misclassification resulting from a wide variation of diagnostic criteria used in the studies, ranging from clinical diagnosis to diagnosis established by multiple available tests (EM, VM, nNO and genetics). Although there is still no established diagnostic gold standard for diagnosing PCD, the recommended diagnostic algorithm has changed considerably over the last years. To address this issue we performed subgroup meta-analyses excluding the studies where the diagnosis was only clinical or not described and we also 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 for all PCD patients. (3) Many studies had restrictive inclusion criteria, including e.g. only patients with situs anomalies or with reported otitis which would increase the prevalence of manifestations related to the selection criteria (ie. 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 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 done 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 for 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, where the study population originated from, can influence reported symptoms. The discovery of bronchiectasis could be highly influenced by study design; a standardised protocol for chest 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 to 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 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 (eg. Chest CT scanning, audiograms and spermatozoa analysis respectively). The variable “neonatal respiratory distress” is probably increasingly subject to recall bias as patients get older. We were unable to detect this in our meta-regression analysis (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, such as patients with CF [92,93] and with childhood asthma [94,95]; and 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:

- report on all clinical manifestations, including the less common ones
- assess indicators of symptoms severity
- use clear, homogeneous definitions of all clinical manifestations
- use clear inclusion criteria for the study population
- collect data prospectively at specified assessment time points starting from diagnosis and continuing throughout life
- stratify the analysis by the degree of diagnostic certainty of PCD of the patients.

These criteria could be fulfilled by performing prospective well-designed multicenter 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 EU 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 characterization of the disease and possibly define different phenotypes of PCD.

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## Legends

Figure 1: Flow chart describing the selection procedure.

Figure 2: Sputum production in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

Figure 3: Hearing impairment in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

Figure 4: Congenital heart disease in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

## Supplementary Files:

TABLE S1: Prevalence of reported characteristics of PCD by country, including studies with overlapping population.

TABLE S2: Meta-regression results on prevalence of reported clinical characteristics of PCD patients.

Figure S1: Situs anomalies in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

Figure S2: Cough in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

Figure S3: Lower respiratory infections in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

Figure S4: Bronchiectasis in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

Figure S5: Rhinitis in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

Figure S6: Otitis in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

Figure S7: Sinusitis in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

Figure S8: Use of grommets in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

Figure S9: Nasal polyps in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

Figure S10: Neonatal respiratory distress in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

Figure S11: Infertility in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

Figure S12: Situs anomalies in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in publications included in subgroup meta-analysis.

Figure S13: Cough in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in publications included in subgroup meta-analysis.

Figure S14: Sputum production in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in publications included in subgroup meta-analysis.

Figure S15: Lower respiratory infections in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in publications included in subgroup meta-analysis.

Figure S16: Bronchiectasis in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in publications included in subgroup meta-analysis.

Figure S17: Rhinitis in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in publications included in subgroup meta-analysis.

Figure S18: Otitis media in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in publications included in subgroup meta-analysis.

Figure S19: Sinusitis in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in publications included in subgroup meta-analysis.

Figure S20: Hearing impairment in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in publications included in subgroup meta-analysis.

Figure S21: Insertion of grommets in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in publications included in subgroup meta-analysis.

Figure S22: Nasal polyps in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in publications included in subgroup meta-analysis.

Figure S23: Congenital heart disease in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in publications included in subgroup meta-analysis.

Figure S24: Neonatal respiratory distress in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in publications included in subgroup meta-analysis.

Figure S25: Infertility in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in publications included in subgroup meta-analysis.



Figure 1: Flow chart describing the selection procedure

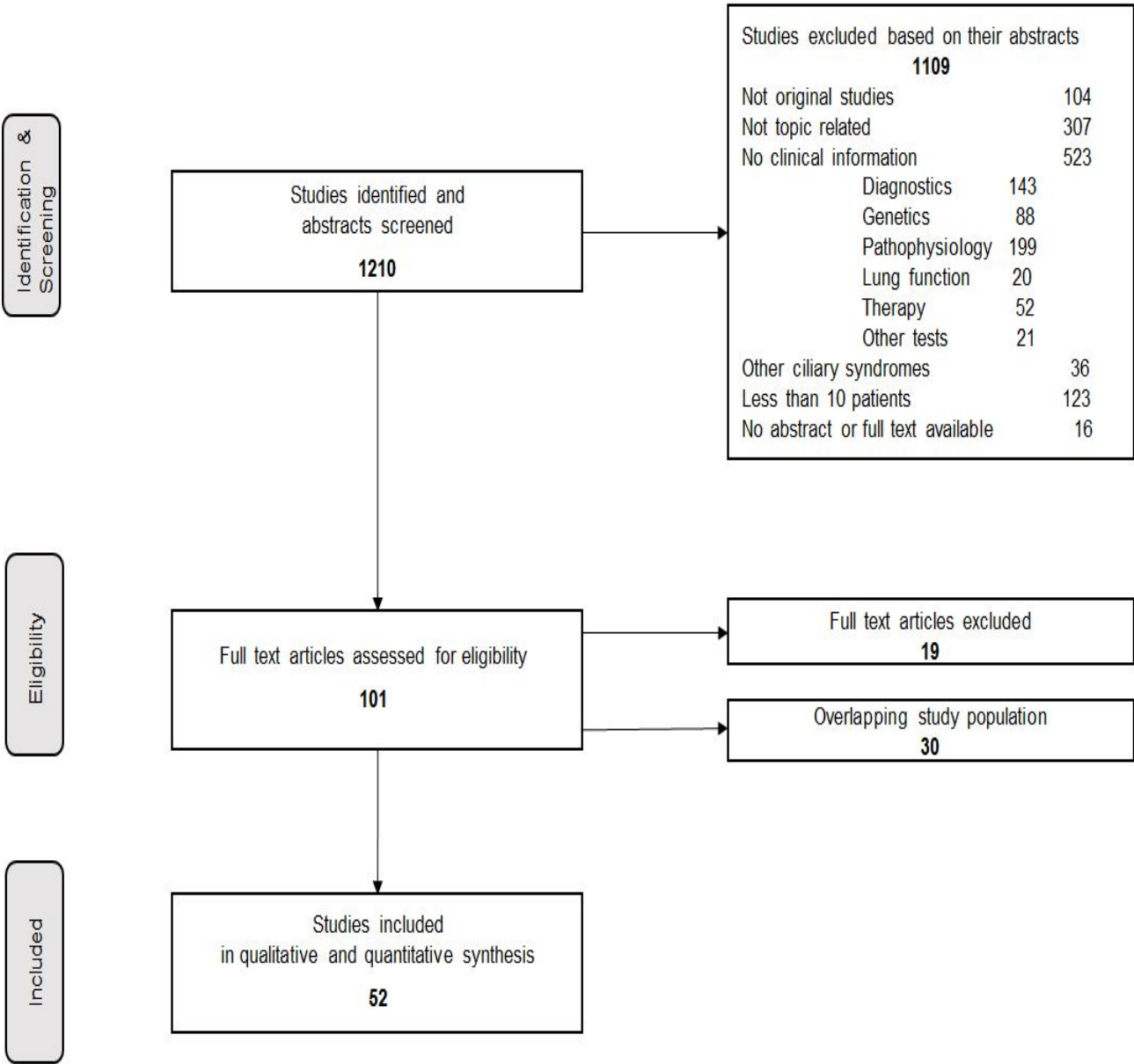


Figure 2: Sputum production in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

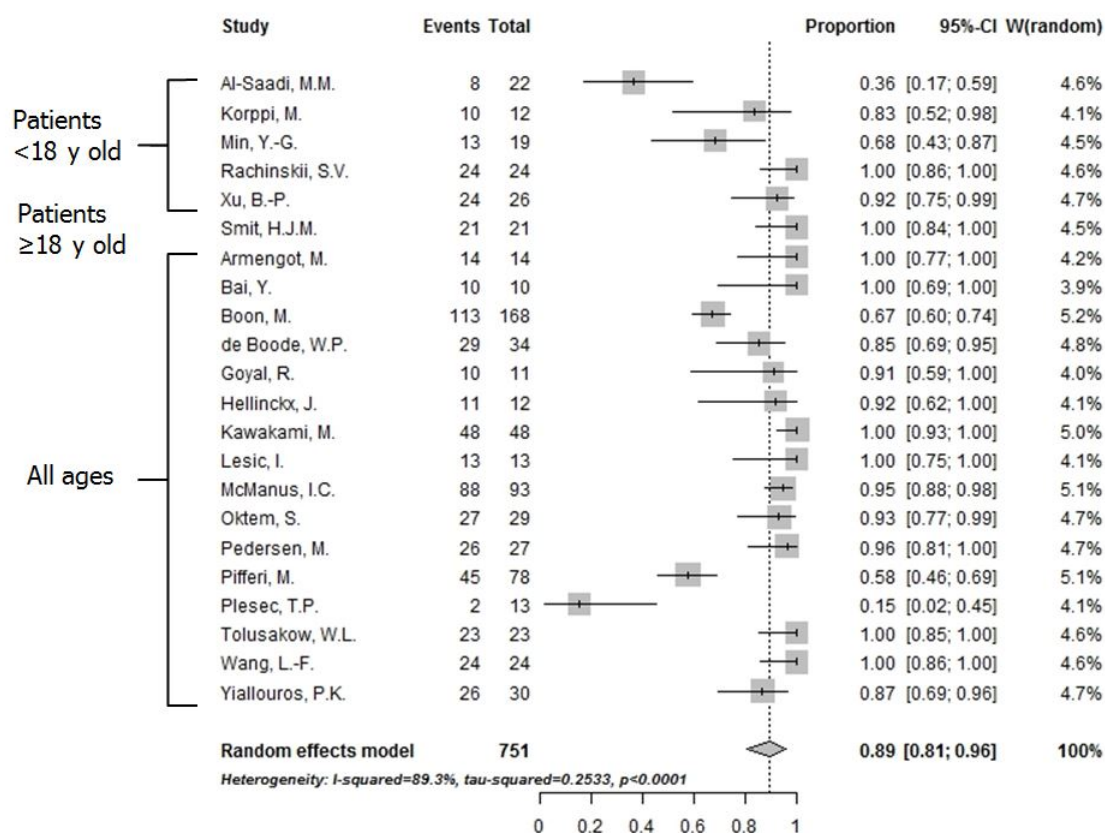


Figure 3: Hearing impairment in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

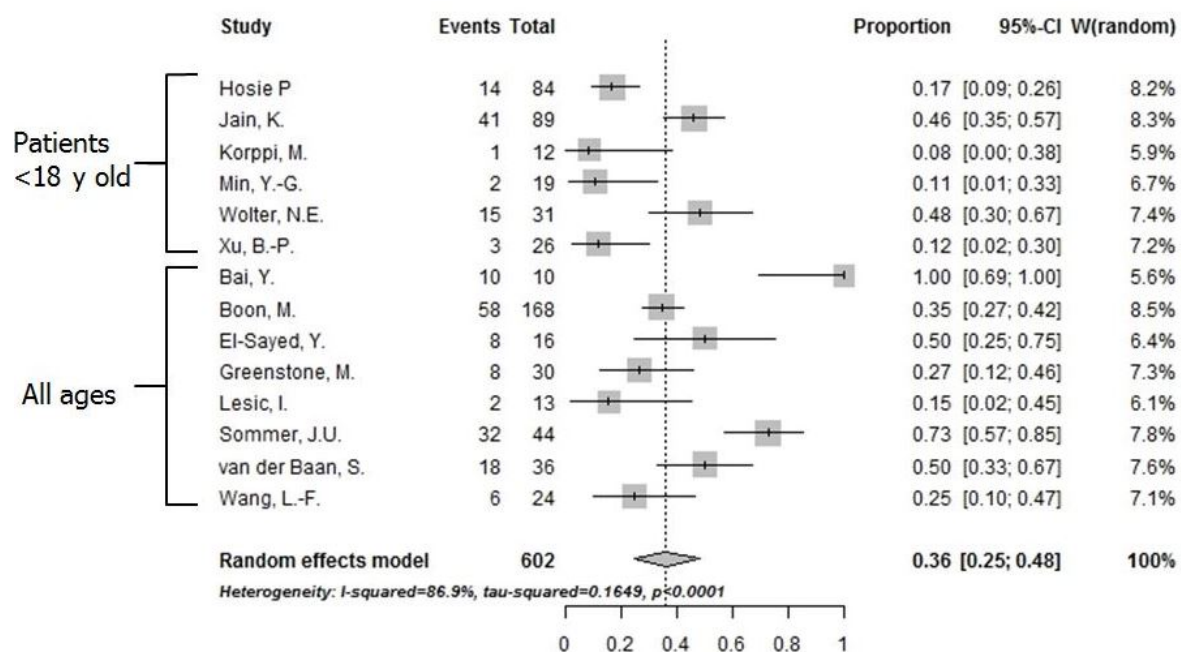
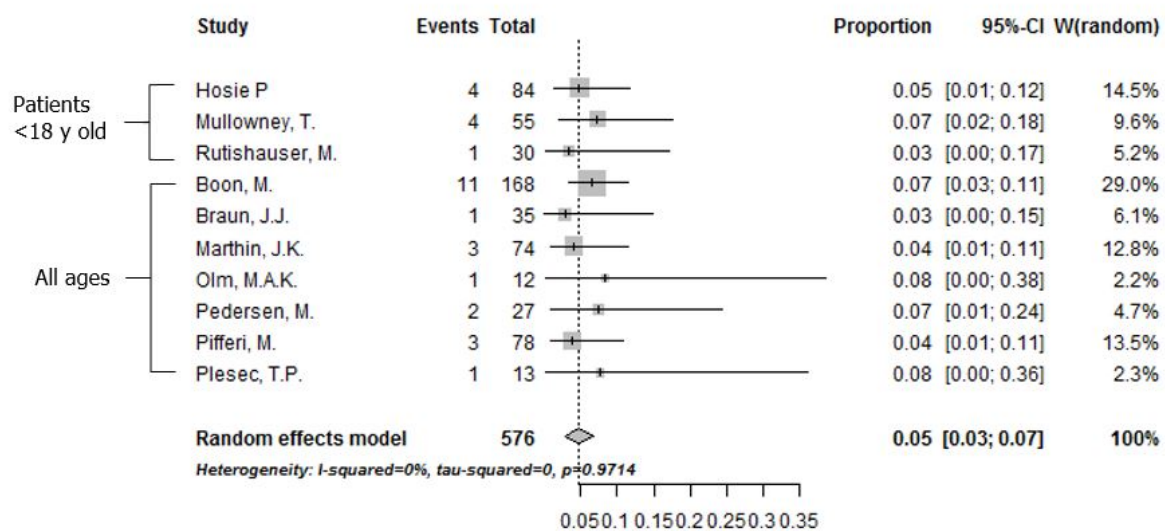


Figure 4: Congenital heart disease in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.



**TABLE 1:** Detailed characteristics of included studies describing clinical manifestations of PCD, stratified by age group of participants

Study	Publication Country	Publication Year	Participants n	Age	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
<b>Children</b>																
AL SAADI et al.	S. Arabia	2013	22	11 <sup>#</sup> (-)	paediatrics	case-control	R	EM+nNO	-	-	+	+	+	-	-	-
BARLOCCO et al.	Italy	1991	28	8 <sup>#</sup> (0-18)	paed. pulmonology	case series	P	EM	-	-	+	+	+	-	-	-
BEUCHER et al.	France	2011	17	7 <sup>#</sup> (-)	paed. pulmonology	case series	R	EM+nNO	-	-	+	-	+	+	-	-
BUSQUETS et al.	Spain	2013	35	-	paed. pulmonology	case series	R	EM	-	-	-	+	-	-	-	-
DAVIS et al.	USA	2015	118	8 <sup>#</sup> (5-11)	combination	case series	P	EM+nNO+Genetics	-	-	+	+	+	+	-	-
ENDERBY et al.*	England	2010	17	9 <sup>#</sup> (4-17)	paediatrics	case series	R	only clinical	-	-	+	+	+	+	-	-
HOSIE et al.	Australia	2015	84	6 <sup>#</sup> (0-18)	paediatrics	cohort	R	EM+VM+nNO	-	-	+	+	+	+	+	-
JAIN et al.	England	2007	89	-	paed. pulmonology	case series	R	EM+VM+nNO	-	-	+	+	+	+	-	-
KORPPI et al.	Finland	2011	12	-	paediatrics	cohort	R	EM	-	-	+	+	-	-	-	-
MIN et al.	S. Korea	1995	19	10 <sup>#</sup> (5-15)	paediatrics	case series	R	EM	-	-	+	+	+	-	-	-
MULLOWNEY et al.	Canada	2014	55	11 <sup>#</sup> (-)	paed. pulmonology	case-control	R	EM+nNO+Genetics	-	-	+	+	-	+	+	-
O'CALLAGHAN et al.	England	2010	19	-	PCD diagnostic centre	case series	R	EM+VM	-	-	+	+	-	+	-	-
RACHINSKII et al.	Russia	1993	24	-	Paediatrics	case series	R	EM	-	-	+	+	+	-	+	-
RUTISHAUSER	Switzerland	2000	30	-	Paediatrics	case series	R	EM+VM	-	-	+	+	+	-	+	-
VALLET et al.	France	2013	60	- (0-15)	paed. pulmonology	case series	R	EM+VM	-	-	+	+	+	+	-	-
WOLTER et al.	Canada	2012	31	7 <sup>#</sup> (0-17)	ENT	case series	R	EM+nNO	-	-	+	+	+	+	-	-
XU et al.	China	2008	26	-	paediatrics	case series	R	EM	-	-	+	+	+	-	-	-
<b>Adults</b>																
AFZELIUS et al.	Sweden	1983	29	-	PCD diagnostic centre	case series	R	EM	-	-	+	-	-	-	-	+
CAMNER et al.*	Sweden	1983	20	30 <sup>#</sup> (19-40)	adult pulmonology	case series	R	only clinical	-	-	+	+	+	-	-	-
SMIT et al.	Canada	1996	21	46 <sup>#</sup> (24-66)	adult pulmonology	case series	R	EM+VM	-	-	+	+	-	-	-	-

EM: electron microscopy, VM: light or high frequency video-microscopy, nNO: nasal NO, R: information on symptoms were collected retrospectively and P: prospectively, "-": information not reported in the publication

Age is reported in years as mean<sup>#</sup> (range) or median<sup>#</sup> (range) depending on the available information

\* studies excluded from subgroup meta-analyses

**TABLE 1:** Detailed characteristics of included studies describing clinical manifestations of PCD, stratified by age group of participants

Study	Publication Country	Publication Year	Participants n	Age	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
<b>Children and adults</b>																
ARMENGOT et al.	Spain	2012	25	28 <sup>#</sup> (1-66)	ENT	case series	P	EM+VM	+	-	+	+	+	-	-	-
ARMENGOT et al.	Spain	1995	14	24 <sup>#</sup> (5-50)	ENT	case series	P	EM	-	-	+	+	+	-	-	-
BAI et al.	China	2014	10	35 <sup>#</sup> (6-56)	ENT	case series	R	EM+nNO+Genetics	+	-	+	+	+	-	-	+
BOON et al.	Belgium	2014	168	18 <sup>#</sup> (-)	PCD diagnostic centre	cohort	R	EM+VM+nNO+Genetics	-	-	+	+	+	+	+	-
BRAUN et al.	France	2005	35	-	ENT	case series	R	EM+VM	-	-	+	+	-	+	+	-
CHIN et al.	China	2002	73	- (0-48)	pathology	case series	R	EM+nNO	-	-		+	+	-	-	-
DE BOODE et al.	Netherlands	1989	34	23 <sup>#</sup> (6-55)	paediatric	case series	R	EM+VM	-	-	+	+	+	-	-	-
EL-SAYED et al.	S. Arabia	1997	16	18 <sup>#</sup> (2-46)	ENT	case series	P	EM	+	-	+	+	+	-	-	-
GOYAL et al.*	India	1987	11	-	adult pulmonology	case series	R	only clinical	+	-	+	+	+	-	-	-
GREENSTONE et al.	England	1988	30	19 <sup>#</sup> (0-51)	cardiothoracic	case series	P	EM+VM	-	-	+	+	+	-	-	+
HELLINCKX et al.	Belgium	1998	12	- (1-32)	paed. pulmonology	case series	R	EM+VM	-	-	-	+	-	-	-	-
HOLZMANN et al.	Switzerland	2000	10	-	ENT	case series	R	EM+VM	-	-	+	+	+	+	-	-
INIGUEZ et al.	Chile	2007	33	-	ENT	case series	R	EM	-	-	+	+	+	-	-	-
KAWAKAMI et al.	Japan	1996	48	38 <sup>#</sup> (17-72)	paed. pulmonology	case series	R	EM	-	-	+	+	+	-	-	-
LESIC et al.	Austria	2009	13	-	paediatrics	case series	R	EM	-	-	+	+	+	-	-	+
MARTHIN et al.	Denmark	2010	74	19 <sup>#</sup> (6-70)	PCD reference centre	case series	R	EM+VM+nNO	-	-	+	+	+	+	+	-
MCMANUS et al.*	England	2003	93	23 <sup>#</sup> (4-66)	psychology	case series	P	-	-	-	+	+	+	-	-	-
MONTELLA et al.	Italy	2009	13	15 <sup>#</sup> (10-29)	paediatrics	case series	P	EM+VM	+	-	+	+	-	+	-	-
MYGIND et al.*	Denmark	1983	27	24 <sup>#</sup> (4-56)	ENT	case series	P	only clinical	+	-	+	+	+	-	-	-
NOONE et al.	USA	2004	78	27 <sup>#</sup> (1-73)	combination	case series	P	EM+VM+nNO	+	-	+	+	+	+	-	-
OKTEM et al.	Turkey	2013	29	10 <sup>#</sup> (0-24)	paediatrics	case-control	P	EM	-	-	-	+	+	-	-	-
OLM et al.	Brazil	2011	12	12 <sup>#</sup> (1-19)	paed. pulmonology	case series	R	EM	+	-	+	+	-	-	+	-
PEDERSEN et al.	Denmark	1983	27	-	paediatrics	case series	P	EM+VM	+	-	+	+	+		+	+
PIFFERI et al.	Italy	2010	78	21 <sup>#</sup> (2-49)	paediatrics	case series	P	EM+VM	-	-	+	+	+	-	+	-
PLESEC et al.	USA	2008	13	15 <sup>#</sup> (1-49)	pathology	case series	R	EM	+	-	+	+	+	-	+	+
SHAPIRO et al.	USA	2014	35	18 <sup>#</sup> (2-58)	combination	case series	R	EM+nNO+Genetics	-	-	+	+	+	+	+	-
SOMMER et al.*	Germany	2011	44	29 <sup>#</sup> (-)	ENT	case series	R	-	-	-	+	-	+	-	-	-
STURGESS et al.	Canada	1986	46	-	paediatrics	case series	R	EM+Genetics	+	-	+	+	+	-	-	-
TOLUSAKOW et al.*	Russia	1981	23	- (3-43)	adult pulmonology	case series	P	only clinical	-	-	+	+	+	-	-	-
VAN DER BAAN et al.	Netherlands	1991	36	25 <sup>#</sup> (1-59)	ENT	case series	P	EM+VM	-	-	+	-	-	-	-	-
WANG et al.	China	2009	24	29 <sup>#</sup> (4-63)	radiology	case series	R	EM	-	-	+	+	+	-	+	+
YIALLOUROS et al.	Cyprus	2015	30	24 <sup>#</sup> (1-64)	paediatrics	cohort	R	EM+VM+nNO	-	-	+	+	+	+	-	-

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Age is reported in years as mean<sup>#</sup> (range) or median<sup>#</sup> (range) depending on the available information

\* studies excluded from subgroup meta-analyses

**TABLE 2:** Characteristics of included studies reporting clinical manifestations of PCD

Characteristic	Studies (n=52)	Proportion of studies (%)
<b>Type of clinic</b>		
Paediatric department	16	33
Paediatric pulmonology department	9	17
Adult pulmonology department	4	8
ENT department	11	21
Other departement	12	21
<b>Number of centres</b>		
Singlecentre	35	66
Multicentre	17	33
<b>Publication period</b>		
≤1994	12	23
1995-2004	11	21
≥2005	29	56
<b>Study size</b>		
≤20 patients	15	29
21-50 patients	25	48
50-100 patients	9	14
>100 patients	3	6
<b>Study region</b>		
Europe	31	60
Asia	10	19
North America	8	15
South America	2	4
Australia	1	2
<b>Age of participants</b>		
Children <18 years	17	33
Adults ≥18 years	3	6
Children and adults	32	62
<b>Study design</b>		
Retrospective	37	71
Prospective	15	29

**TABLE 2:** Characteristics of included studies reporting clinical manifestations of PCD

Characteristic	Studies (n=52)	Proportion of studies (%)
<b>Diagnostics performed</b>		
Only clinical diagnosis	5	10
Diagnosis proven by EM	16	31
Diagnosis proven by EM plus other tests¶	29	56
Not available information on diagnostics	2	4
<b>Health conditions</b>		
Situs anomalies	48	92
Lower respiratory conditions	48	92
Cough	29	56
Sputum production	24	46
Lower respiratory tract infections	27	52
Bronchiectasis	34	65
Upper respiratory 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
<b>Information for different age groups</b>	11 <sup>#</sup>	34
<b>Information on severity</b>	0	0

EM: electron microscopy

¶ one or more of the following: nasal NO, high frequency videomicroscopy or light microscopy, genetics

<sup>#</sup> of 32 studies including children and adults