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

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None

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CEK had the idea of the study. CEK and MG developed the concept and designed the study. MG and ABM performed the systematic review. BDS provided statistical supervision for the analyses conducted by MG with the support of FSH. CEK, MG and ABM drafted the manuscript, all authors contributed to iterations and approved the final version. CEK and MG take final responsibility for the contents.

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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 ≥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.

199/200 Words

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 ≤1994, 1995-2004 and ≥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 peadiatric 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 (≥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 (≥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.

## References


1. Barbato A, Frischer T, Kuehni CE, Snijders D, Azevedo I, Baktai G, Bartoloni L, Eber E, Escribano A, Haarman E, Hesselmar B, Hogg C, Jorissen M, Lucas J, Nielsen KG, O'Callaghan C, Omran H, Pohunek P, Strippoli MP, Bush A. Primary ciliary dyskinesia: a consensus statement on diagnostic and treatment approaches in children. The European respiratory journal 2009;34:1264-76.
2. Noone PG, Leigh MW, Sannuti A, Minnix SL, Carson JL, Hazucha M, Zariwala MA, Knowles MR. Primary Ciliary Dyskinesia: Diagnostic and Phenotypic Features. Am J Respir Crit Care Med 2004;169:459-67.
3. Lucas JS, Walker WT, Kuehni CE, al. e. Primary Ciliary Dyskinesia. In: Courdier J-F, editor Orphan Lung diseases European Respiratory Monograph 2011:201-17.
4. Turner JA, Corkey CW, Lee JY, Levison H, Sturgess J. Clinical expressions of immotile cilia syndrome. Pediatrics 1981;67:805-10.
5. Boon M, Jorissen M, Proesmans M, De Boeck K. Primary ciliary dyskinesia, an orphan disease. Eur J Pediatr 2013;172:151-62.
6. Kuehni CE, Frischer T, Strippoli MP, Maurer E, Bush A, Nielsen KG, Escribano A, Lucas JS, Yiallouros P, Omran H, Eber E, O'Callaghan C, Snijders D, Barbato A, Children ERSTFoPCDi. Factors influencing age at diagnosis of primary ciliary dyskinesia in European children. The European respiratory journal 2010;36:1248-58.
7. Strippoli MP, Frischer T, Barbato A, Snijders D, Maurer E, Lucas JS, Eber E, Karadag B, Pohunek P, Zivkovic Z, Escribano A, O'Callaghan C, Bush A, Kuehni CE, Children ERSTFoCDi. Management of primary ciliary dyskinesia in European children: recommendations and clinical practice. The European respiratory journal 2012;39:1482-91.
8. Miller JJ. The inverse of the Freeman–Tukey double arcsine transformation. The American Statistician 1978;32:138-.
9. Freeman MF, Tukey JW. Transformations related to the angular and the square root. The Annals of Mathematical Statistics 1950:607-11.
10. Higgins J, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. Journal of the Royal Statistical Society: Series A (Statistics in Society) 2009;172:137-59.
11. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine 2002;21:1539-58.
12. Chao J, Turner JA, Sturgess JM. Genetic heterogeneity of dynein-deficiency in cilia from patients with respiratory disease. Am Rev Respir Dis 1982;126:302-5.
13. Levison HM, C. M.; Chao, J.; Turner, J. A.; Sturgess, J. M.; Stringer, D. A. Pathophysiology of the ciliary motility syndromes. Eur J Respir Dis Suppl 1983;127:102-17.
14. Nadel HR, Stringer DA, Levison H. The immotile cilia syndrome: Radiological manifestations. Radiology 1985;154:651-5.
15. Mygind NP, M.; Nielsen, M. H. Primary and secondary ciliary dyskinesia. Acta Otolaryngol 1983;95:688-94.
16. Pedersen MM, N. Rhinitis, sinusitis and otitis media in Kartagener's syndrome (primary ciliary dyskinesia). Clin Otolaryngol Allied Sci 1982;7:373-80.
17. Armengot M, Juan G, Barona R, Garin L, Basterra J. Immotile cilia syndrome: Nasal mucociliary function and nasal ciliary abnormalities. Rhinology 1994;32:109-11.
18. Carda C, Armengot M, Escribano A, Peydro A. Ultrastructural patterns of primary ciliar dyskinesia syndrome. Ultrastruct Pathol 2005;29:3-8.
19. Armengot Carceller MCB, C.; Escribano, A.; Samper, G. J. [Study of mucociliary transport and nasal ciliary ultrastructure in patients with Kartagener's syndrome]. Arch Bronconeumol 2005;41:11-5.

20. Barranco MJ, Armengot M, Carda C, Ciscar MA, Peris R, Ramon M, Juan G. The primary ciliary dyskinesia syndrome. A frequent pathology. Arch Bronconeumol 1994;30:19-22.
21. Pifferi M, Bush A, Michelucci A, Di Cicco M, Piras M, Caramella D, Mazzei F, Neri M, Pioggia G, Tartarisco G, Saggese G, Simi P, Boner AL. Mannose-binding lectin 2 gene polymorphism and lung damage in primary ciliary dyskinesia. Pediatr Pulmonol 2014.
22. Santamaria FE, M.; Montella, S.; Cantone, E.; Mollica, C.; De Stefano, S.; Mirra, V.; Carotenuto, M. Sleep disordered breathing and airway disease in primary ciliary dyskinesia. Respirology 2014;19:570-5.
23. Mirra V, Caffarelli C, Maglione M, Valentino R, Perruolo G, Mazzarella C, Di Micco LL, Montella S, Santamaria F. Hypovitaminosis D: a novel finding in primary ciliary dyskinesia. Italian journal of pediatrics 2015;41:14.
24. Gokdemir YK-S, E.; Erdem, E.; Bayindir, O.; Ersu, R.; Karadag, B.; Sekban, N.; Akyuz, G.; Karakoc, F. Comparison of conventional pulmonary rehabilitation and high-frequency chest wall oscillation in primary ciliary dyskinesia. Pediatr Pulmonol 2014;49:611-6.
25. Rollin M, Seymour K, Hariri M, Harcourt J. Rhinosinusitis, symptomatology & absence of polyposis in children with primary ciliary dyskinesia. Rhinology 2009;47:75-8.
26. Coren ME, Meeks M, Morrison I, Buchdahl RM, Bush A. Primary ciliary dyskinesia: Age at diagnosis and symptom history. Acta Paediatrica, International Journal of Paediatrics 2002;91:667-9.
27. Munro NC, Currie DC, Lindsay KS, Ryder TA, Rutman A, Dewar A, Greenstone MA, Hendry WF, Cole PJ. Fertility in men with primary ciliary dyskinesia presenting with respiratory infection. Thorax 1994;49:684-7.
28. Greenstone MS, P.; Cole, P.; Mackay, I. Upper airway manifestations of primary ciliary dyskinesia. Journal of Laryngology and Otology 1985;99:985-91.
29. Engesaeth VG, Warner JO, Bush A. New associations of primary ciliary dyskinesia syndrome. Pediatr Pulmonol 1993;16:9-12.
30. Pruliere-Escabasse V, Coste A, Chauvin P, Fauroux B, Tamalet A, Garabedian EN, Escudier E, Roger G. Otologic features in children with primary ciliary dyskinesia. Archives of Otolaryngology - Head and Neck Surgery 2010;136:1121-6.
31. Blanchon S, Legendre M, Copin B, Duquesnoy P, Montantin G, Kott E, Dastot F, Jeanson L, Cachanado M, Rousseau A, Papon JF, Beydon N, Brouard J, Crestani B, Deschildre A, Desir J, Dollfus H, Leheup B, Tamalet A, Thumerelle C, Vojtek AM, Escalier D, Coste A, de Blic J, Clement A, Escudier E, Amselem S. Delineation of CCDC39/CCDC40 mutation spectrum and associated phenotypes in primary: Ciliary dyskinesia. J Med Genet 2012;49:410-6.
32. Tamalet A, Clement A, Roudot-Thoraval F, Desmarquest P, Roger G, Boule M, Millepied MC, Baculard TA, Escudier E. Abnormal central complex is a marker of severity in the presence of partial ciliary defect. Pediatrics 2001;108:E86.
33. Pittman JER, M.; LaFave, C.; Ferkol, T.; Milla, C. E.; Sagel, S.; Dell, S.; Jones, P.; Johnson, R. C.; Leigh, M.; Knowles, M. R.; Davis, S. D. Characteristics of primary ciliary dyskinesia in children under 5 years of age. Am J Respir Crit Care Med 2011;183.
34. Ferkol TW, Puffenberger EG, Lie H, Helms C, Strauss KA, Bowcock A, Carson JL, Hazucha M, Morton DH, Patel AC, Leigh MW, Knowles MR, Zariwala MA. Primary ciliary dyskinesia-causing mutations in Amish and Mennonite communities. Journal of Pediatrics 2013;163:383-7.
35. Shapiro AJD, S. D.; Olivier, K. N.; Ferkol, T. W.; Dell, S. D.; Sagel, S. D.; Rosenfeld, M.; Milla, C. E.; Atkinson, J. J.; Knowles, M. R.; Leigh, M. W. Clinical symptoms associated with primary ciliary dyskinesia - Results of a multi-centered study. Am J Respir Crit Care Med 2010;181.
36. Shapiro AJ, Tolleson-Rinehart S, Zariwala MA, Knowles MR, Leigh MW. The prevalence of clinical features associated with primary ciliary dyskinesia in a heterotaxy population: results of a web-based survey. Cardiology in the young 2014:1-8.

37. Knowles MRO, L. E.; Leigh, M. W.; Sears, P. R.; Davis, S. D.; Wolf, W. E.; Hazucha, M. J.; Carson, J. L.; Olivier, K. N.; Sagel, S. D.; Rosenfeld, M.; Ferkol, T. W.; Dell, S. D.; Milla, C. E.; Randell, S. H.; Yin, W.; Sannuti, A.; Metjian, H. M.; Noone, P. G.; Noone, P. J.; Olson, C. A.; Patrone, M. V.; Dang, H.; Lee, H. S.; Hurd, T. W.; Gee, H. Y.; Otto, E. A.; Halbritter, J.; Kohl, S.; Kircher, M.; Krischer, J.; Bamshad, M. J.; Nickerson, D. A.; Hildebrandt, F.; Shendure, J.; Zariwala, M. A. Mutations in RSPH1 cause primary ciliary dyskinesia with a unique clinical and ciliary phenotype. Am J Respir Crit Care Med 2014;189:707-17.
38. Kim RHAHDC, E.; Knowles, M. R.; Nelligan, K. A.; Nykamp, K.; Zariwala, M. A.; Dell, S. D. The role of molecular genetic analysis in the diagnosis of primary ciliary dyskinesia. Annals of the American Thoracic Society 2014;11:351-9.
39. Boon MDB, K.; Jorissen, M.; Meyts, I. Primary ciliary dyskinesia and humoral immunodeficiency--is there a missing link? Respir Med 2014;108:931-4.
40. van der Baan SV, A. J.; Weltevreden, E. F.; Feenstra, L. Kartagener's syndrome: clinical symptoms and laboratory studies. Eur J Respir Dis Suppl 1983;127:91-5.
41. Pedersen MS, G. Bronchopulmonary symptoms in primary ciliary dyskinesia. A clinical study of 27 patients. Eur J Respir Dis Suppl 1983;127:118-28.
42. Mygind NP, M. Nose-, sinus- and ear-symptoms in 27 patients with primary ciliary dyskinesia. Eur J Respir Dis Suppl 1983;127:96-101.
43. McManus IC, Mitchison HM, Chung EM, Stubbings GF, Martin N. Primary ciliary dyskinesia (Siewert's/Kartagener's syndrome): respiratory symptoms and psycho-social impact. BMC Pulm Med 2003;3:4.
44. Jain K, Padley SP, Goldstraw EJ, Kidd SJ, Hogg C, Biggart E, Bush A. Primary ciliary dyskinesia in the paediatric population: range and severity of radiological findings in a cohort of patients receiving tertiary care. Clin Radiol 2007;62:986-93.
45. Shapiro AJ, Davis SD, Ferkol T, Dell SD, Rosenfeld M, Olivier KN, Sagel SD, Milla C, Zariwala MA, Wolf W, Carson JL, Hazucha MJ, Burns K, Robinson B, Knowles MR, Leigh MW. Laterality defects other than situs inversus totalis in primary ciliary dyskinesia: insights into situs ambiguus and heterotaxy. Chest 2014;146:1176-86.
46. Davis SD, Ferkol TW, Rosenfeld M, Lee HS, Dell SD, Sagel SD, Milla C, Zariwala MA, Pittman JE, Shapiro AJ, Carson JL, Krischer JP, Hazucha MJ, Cooper ML, Knowles MR, Leigh MW. Clinical features of childhood primary ciliary dyskinesia by genotype and ultrastructural phenotype. American journal of respiratory and critical care medicine 2015;191:316-24.
47. Afzelius BAE, R. Male and female infertility problems in the immotile-cilia syndrome. Eur J Respir Dis Suppl 1983;127:144-7.
48. Alsaadi MM, Habib SS, Al Muqhem BA, Aldrees A, Al Zamil JF, Alsadoon HA. Significance of fractional exhaled nitric oxide measurements in detecting primary ciliary dyskinesia in Saudi children. Saudi Med J 2013;34:24-8.
49. Armengot M, Bonet M, Carda C, Gomez MJ, Milara J, Mata M, Cortijo J. Development and validation of a method of cilia motility analysis for the early diagnosis of primary ciliary dyskinesia. Acta Otorrinolaringol Esp 2012;63:1-8.
50. Armengot M, Juan G, Carda C, Basterra J, Cano B. The prevalence of primary dyskinetic ciliary syndromes in patients with sinusitis and bronchiectasis. An Otorrinolaringol Ibero Am 1995;22:85-92.
51. Bai Y, Zhang J, You S, Ji L, Jia J, Wang H. [Clinical characteristics of primary ciliary dyskinesia]. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2014;49:115-20.
52. Barlocco EG, Valletta EA, Canciani M, Lungarella G, Gardi C, De Santi MM, Mastella G. Ultrastructural ciliary defects in children with recurrent infections of the lower respiratory tract. Pediatr Pulmonol 1991;10:11-7.
53. Beucher J, Chambellan A, Segalen J, Deneuville E. [Primary ciliary dyskinesia: a retrospective review of clinical and paraclinical data]. Rev Mal Respir 2011;28:856-63.

54. Braun JJD, L.; Clavert, A.; Cranz, C.; Hoffmann, L.; Gentine, A. [Primary ciliary dyskinesia. Clinical presentation and diagnosis]. Ann Otolaryngol Chir Cervicofac 2005;122:63-8.
55. Busquets RM, Caballero-Rabasco MA, Velasco M, Lloreta J, Garcia-Algar O. Primary Ciliary Dyskinesia: Clinical Criteria Indicating Ultrastructural Studies. Arch Bronconeumol 2013;49:99-104.
56. Camner PM, B.; Afzelius, B. A. Measurements of tracheobronchial clearance in patients with immotile-cilia syndrome and its value in differential diagnosis. Eur J Respir Dis Suppl 1983;127:57-63.
57. de Boode WP, Collins JM, Veerman AJ, van der Baan S. Primary ciliary dyskinesia; a questionnaire study of the clinical aspects. Ned Tijdschr Geneeskd 1989;133:2338-41.
58. El-Sayed Y, Al-Sarhani A, Al-Essa AR. Otological manifestations of primary ciliary dyskinesia. Clin Otolaryngol Allied Sci 1997;22:266-70.
59. Goyal RJ, A.; Raghu, M.; Gupta, R.; Singla, R.; Gupta, N.; Menon, M. P. Clinical profile of eleven patients of Kartagener's syndrome--certain interesting associations. Indian J Chest Dis Allied Sci 1987;29:150-9.
60. Greenstone MR, A.; Dewar, A.; Mackay, I.; Cole, P. J. Primary ciliary dyskinesia: cytological and clinical features. Q J Med 1988;67:405-23.
61. Hellinckx J, Demedts M, De Boeck K. Primary ciliary dyskinesia: Evolution of pulmonary function. Eur J Pediatr 1998;157:422-6.
62. Holzmann D, Felix H. Neonatal respiratory distress syndrome--a sign of primary ciliary dyskinesia? Eur J Pediatr 2000;159:857-60.
63. Iniguez CR, Fonseca AX, Hernandez CJ, Gonzalez BS, Sanchez DI. [Clinical and ultrastructural features of ciliary dyskinesia]. Rev Med Chil 2007;135:1147-52.
64. Kawakami M, Hattori Y, Nakamura S. Reflection of structural abnormality in the axoneme of respiratory cilia in the clinical features of immotile cilia syndrome. Intern Med 1996;35:617-23.
65. Korppi M, Dunder T, Remes S, Sjostrom PM, Holm T, Vahasarja V, Jartti T, Paakko P, Kajosaari M. [Congenital ciliary dysfunction in children]. Duodecim 2011;127:2294-302.
66. Lesic I, Maurer E, Strippoli MP, Kuehni CE, Barbato A, Frischer T, children ERSToPCDi. [Primary ciliary dyskinesia (Pcd) in Austria]. Wiener klinische Wochenschrift 2009;121:616-22.
67. Marthin JK, Petersen N, Skovgaard LT, Nielsen KG. Lung function in patients with primary ciliary dyskinesia: A cross-sectional and 3-decade longitudinal study. Am J Respir Crit Care Med 2010;181:1262-8.
68. Min YG, Shin JS, Choi SH, Chi JG, Yoon CJ. Primary ciliary dyskinesia: Ultrastructural defects and clinical features. Rhinology 1995;33:189-93.
69. Montella SS, F.; Salvatore, M.; Maglione, M.; Iacotucci, P.; De Santi, M. M.; Mollica, C. Lung disease assessment in primary ciliary dyskinesia: a comparison between chest high-field magnetic resonance imaging and high-resolution computed tomography findings. Ital J Pediatr 2009;35:24.
70. O'Callaghan C, Chetcuti P, Moya E. High prevalence of primary ciliary dyskinesia in a British Asian population. Arch Dis Child 2010;95:51-2.
71. Oktem S, Karadag B, Erdem E, Gokdemir Y, Karakoc F, Dagli E, Ersu R. Sleep disordered breathing in patients with primary ciliary dyskinesia. Pediatr Pulmonol 2013;48:897-903.
72. Olm MA, Kogler JE, Jr., Macchione M, Shoemark A, Saldiva PH, Rodrigues JC. Primary ciliary dyskinesia: evaluation using cilia beat frequency assessment via spectral analysis of digital microscopy images. J Appl Physiol (1985) 2011;111:295-302.
73. Pifferi M, Bush A, Di Cicco M, Pradal U, Ragazzo V, Macchia P, Boner AL. Health-related quality of life and unmet needs in patients with primary ciliary dyskinesia. European Respiratory Journal 2010;35:787-94.
74. Plesec TP, Ruiz A, McMahon JT, Prayson RA. Ultrastructural abnormalities of respiratory cilia: A 25-year experience. Archives of Pathology and Laboratory Medicine 2008;132:1786-91.
75. Rachinskii SV, Volkov IK, Sereda EV, Alekseevskikh Iu G, Lukina OF, Marinushkin AM. [The Zivert-Kartagener syndrome in children]. Probl Tuberk 1993:19-22.

76. Rutishauser M. Clinical features of primary ciliary dyskinesia. Schweiz Med Wochenschr 2000;130:705-10.
77. Smit HJ, Schreurs AJ, Van den Bosch JM, Westermann CJ. Is resection of bronchiectasis beneficial in patients with primary ciliary dyskinesia? Chest 1996;109:1541-4.
78. Sommer JU, Schafer K, Omran H, Olbrich H, Wallmeier J, Blum A, Hormann K, Stuck BA. ENT manifestations in patients with primary ciliary dyskinesia: Prevalence and significance of otorhinolaryngologic co-morbidities. European Archives of Oto-Rhino-Laryngology 2011;268:383-8.
79. Sturgess JM, Thompson MW, Czegledy-Nagy E, Turner JA. Genetic aspects of immotile cilia syndrome. Am J Med Genet 1986;25:149-60.
80. Tolusakow WL, Boikow GA, Lewaschow JN, Schirjaewa KF, Kartawowa WA. [Bronchiectasis in patients with situs inversus viscerum (Kartagener syndrome) (author's transl)]. Z Erkr Atmungsorgane 1981;156:167-75.
81. Vallet C, Escudier E, Roudot-Thoraval F, Blanchon S, Fauroux B, Beydon N, Boule M, Vojtek AM, Amselem S, Clement A, Tamalet A. Primary ciliary dyskinesia presentation in 60 children according to ciliary ultrastructure. Eur J Pediatr 2013;172:1053-60.
82. van der Baan S. Primary ciliary dyskinesia and the middle ear. Laryngoscope 1991;101:751-4.
83. Wang LFG, Y. B.; Gu, Y. Y.; Zeng, Q. S.; Chen, L.; Zhang, C. L.; He, J. X.; Zhong, N. S. Bronchiolitis in Kartagener syndrome: Imaging diagnosis and following up. Chinese Journal of Medical Imaging Technology 2009;25:2040-2.
84. Wolter NE, Dell SD, James AL, Campisi P. Middle ear ventilation in children with primary ciliary dyskinesia. Int J Pediatr Otorhinolaryngol 2012;76:1565-8.
85. Xu BP, Shen KL, Hu YH, Feng XL, Li HM, Lang ZQ. [Clinical characteristics of primary ciliary dyskinesia in children]. Zhonghua Er Ke Za Zhi 2008;46:618-22.
86. Yiallouros PK, Kouis P, Middleton N, Nearchou M, Adamidi T, Georgiou A, Eleftheriou A, Ioannou P, Hadjisavvas A, Kyriacou K. Clinical features of primary ciliary dyskinesia in Cyprus with emphasis on lobectomized patients. Respiratory medicine 2015;109:347-56.
87. Mullowney T, Manson D, Kim R, Stephens D, Shah V, Dell S. Primary ciliary dyskinesia and neonatal respiratory distress. Pediatrics 2014;134:1160-6.
88. Boon MS, A.; Cuppens, H.; Jaspers, M.; Proesmans, M.; Dupont, L. J.; Vermeulen, F. L.; Van Daele, S.; Malfroot, A.; Godding, V.; Jorissen, M.; De Boeck, K. Primary ciliary dyskinesia: critical evaluation of clinical symptoms and diagnosis in patients with normal and abnormal ultrastructure. Orphanet journal of rare diseases 2014;9:11.
89. Chin GY, Karas DE, Kashgarian M. Correlation of presentation and pathologic condition in primary ciliary dyskinesia. Archives of Otolaryngology - Head and Neck Surgery 2002;128:1292-4.
90. Hosie PF, D. A.; Jaffe, A.; Birman, C. S.; Morgan, L. Primary ciliary dyskinesia: Overlooked and undertreated in children. J Paediatr Child Health 2014.
91. Enderby BJD, M.; Heaver, R. A cross-sectional analysis of children treated for primary ciliary dyskinesia at birmingham children's hospital. Am J Respir Crit Care Med 2010;181.
92. Durno C, Corey M, Zielenski J, Tullis E, Tsui L-C, Durie P. Genotype and phenotype correlations in patients with cystic fibrosis and pancreatitis. Gastroenterology 2002;123:1857-64.
93. Hubert D, Bienvenu T, Desmazes-Dufeu N, Fajac I, Lacronique J, Matran R, Kaplan J, Dusser D. Genotype-phenotype relationships in a cohort of adult cystic fibrosis patients. European Respiratory Journal 1996;9:2207-14.
94. Spycher B, Silverman M, Kuehni C. Phenotypes of childhood asthma: are they real? Clinical & Experimental Allergy 2010;40:1130-41.
95. Spycher BD, Henderson J, Granell R, Evans DM, Smith GD, Timpson NJ, Sterne JA. Genome-wide prediction of childhood asthma and related phenotypes in a longitudinal birth cohort. Journal of Allergy and Clinical Immunology 2012;130:503-9. e7.

96. Werner C, Lablans M, Ataian M, Raidt J, Wallmeier J, Grosse-Onnebrink J, Kuehni CE, Haarman EG, Leigh MW, Quittner AL, Lucas JS, Hogg C, Witt M, Priftis KN, Yiallouros P, Nielsen KG, Santamaria F, Uckert F, Omran H. An international registry for primary ciliary dyskinesia. Eur Respir J 2016;47:849-59.

**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.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

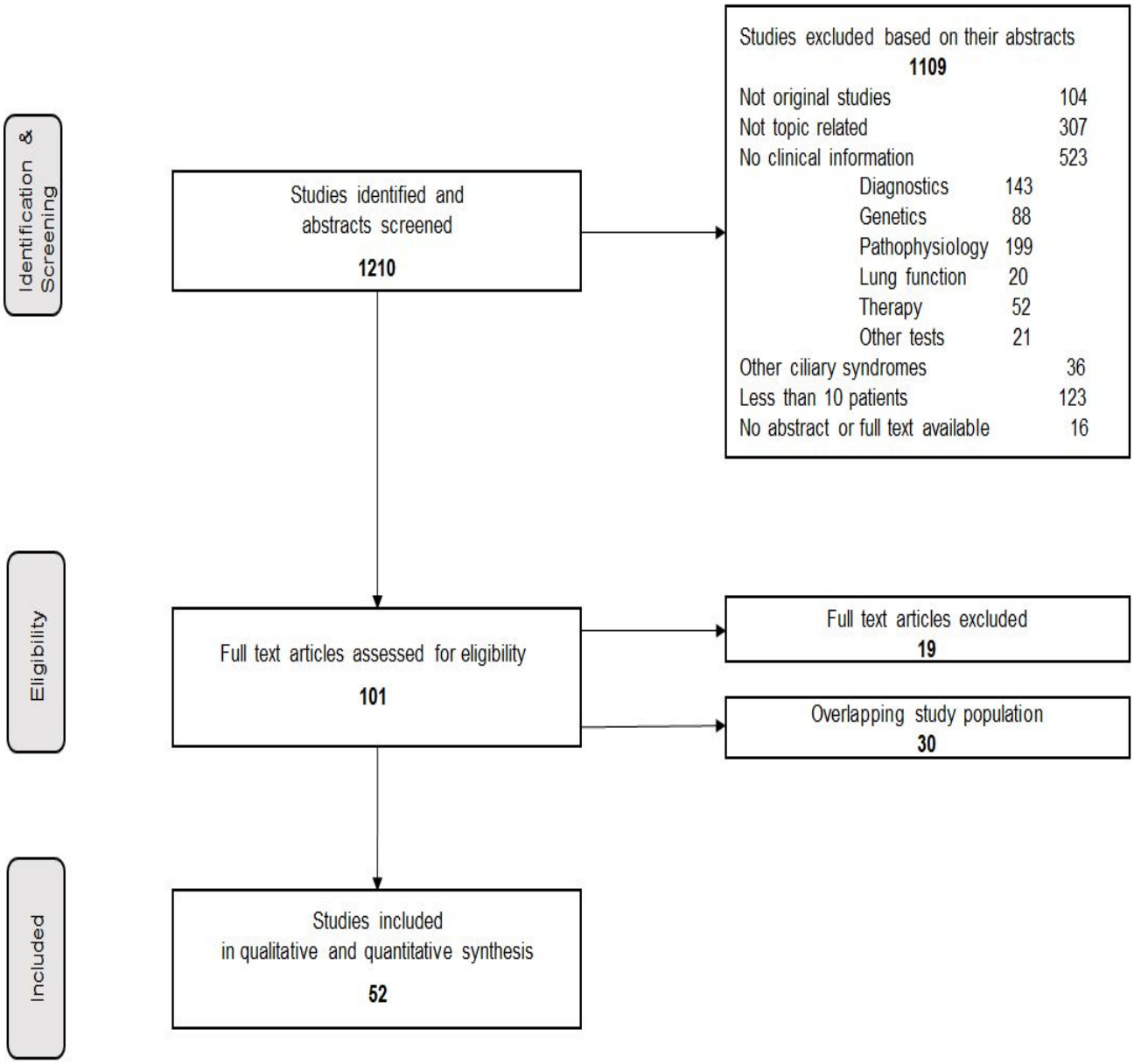

Figure 2: Sputum production in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

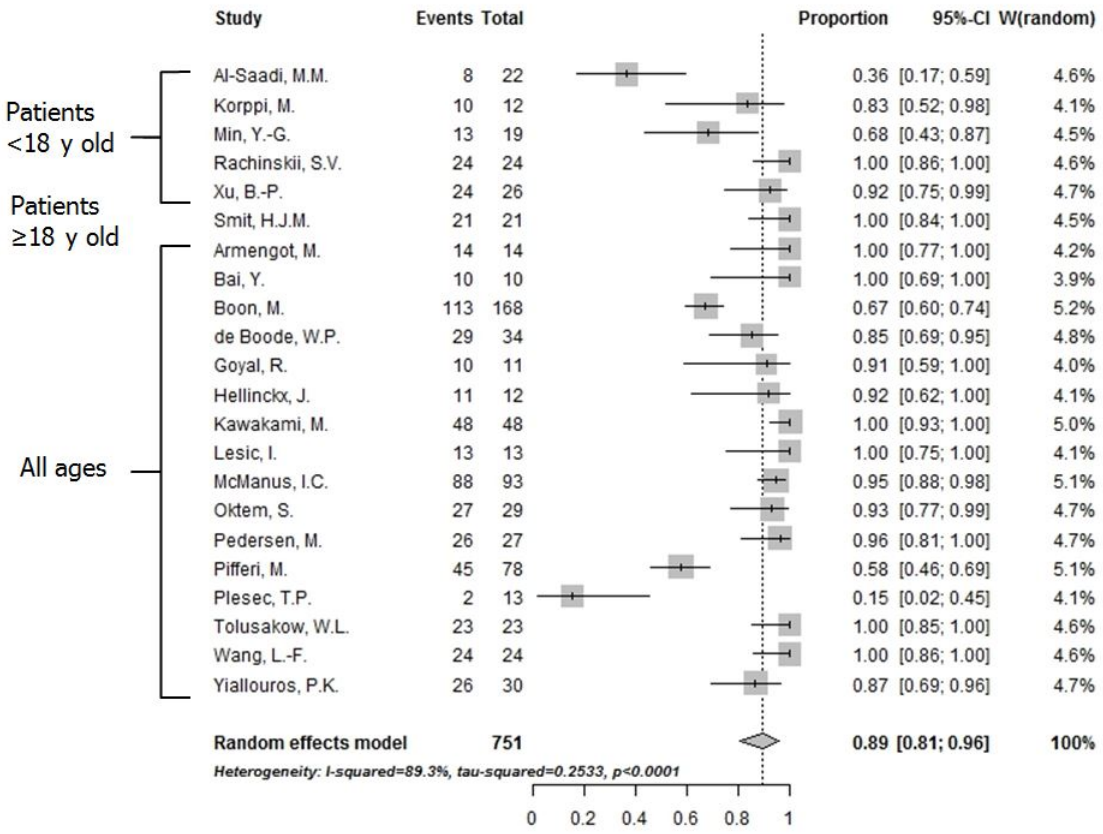

Figure 3: Hearing impairment in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

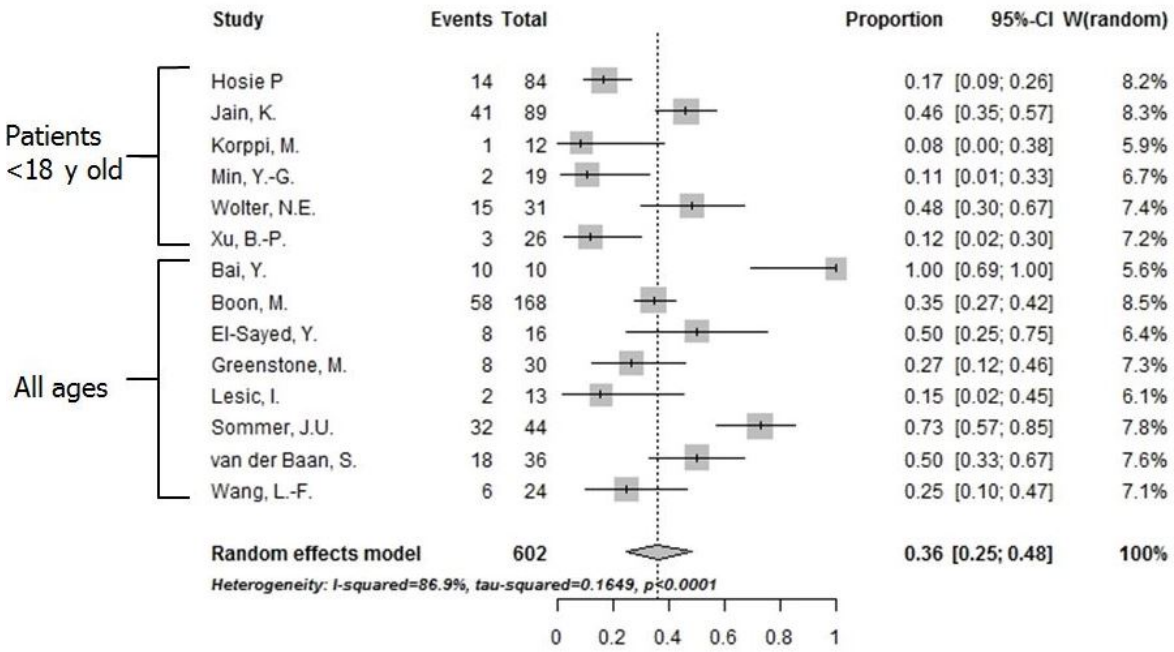

Figure 4: Congenital heart disease in PCD patients: Forest plot showing the heterogeneity and weighted mean prevalence in the included publications.

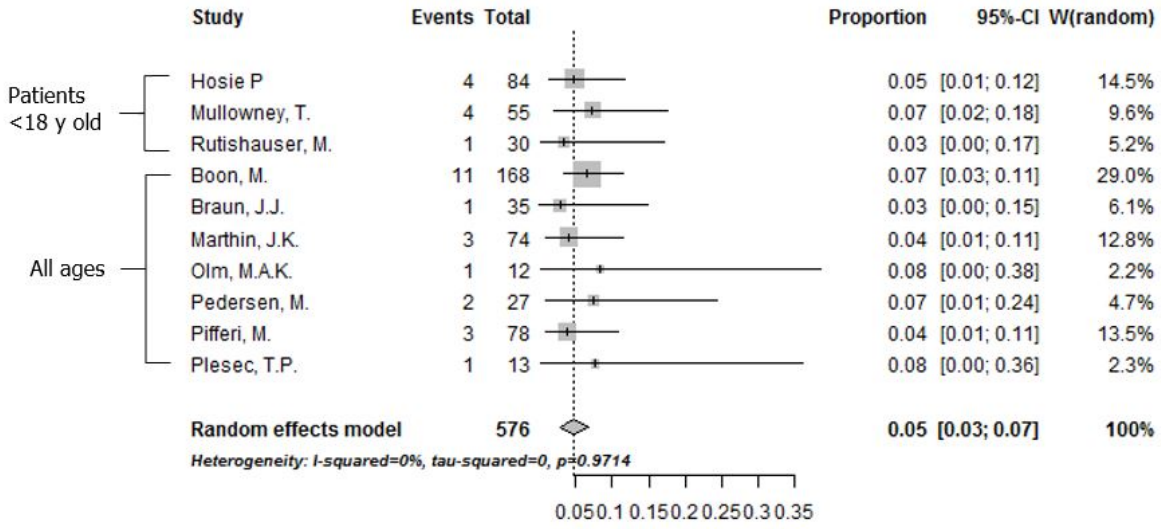

**TABLE 1:** Detailed characteristics of included studies describing clinical manifestations of PCD, stratified by age group of participants

| 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Children** | | | | | | | | | | | | | | | | |
| AL SAADI et al. | S. Arabia | 2013 | 22 | 11#(-) | paediatrics | case-control | R | EM+nNO | - | - | + | + | + | - | - | - |
| BARLOCCO et al. | Italy | 1991 | 28 | 8#(0-18) | paed. pulmonology | case series | P | EM | - | - | + | + | + | - | - | - |
| BEUCHER et al. | France | 2011 | 17 | 7#(-) | 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#(5-11) | combination | case series | P | EM+nNO+Genetics | - | - | + | + | + | + | - | - |
| ENDERBY et al.+ | England | 2010 | 17 | 9¶(4-17) | paediatrics | case series | R | only clinical | - | - | + | + | + | + | - | - |
| HOSIE et al. | Australia | 2015 | 84 | 6¶(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#(5-15) | paediatrics | case series | R | EM | - | - | + | + | + | - | - | - |
| MULLOWNEY et al. | Canada | 2014 | 55 | 11#(-) | 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#(0-17) | ENT | case series | R | EM+nNO | - | - | + | + | + | + | - | - |
| XU et al. | China | 2008 | 26 | - | paediatrics | case series | R | EM | - | - | + | + | + | - | - | - |
| **Adults** | | | | | | | | | | | | | | | | |
| AFZELIUS et al. | Sweden | 1983 | 29 | - | PCD diagnostic centre | case series | R | EM | - | - | + | - | - | - | - | + |
| CAMNER et al.+ | Sweden | 1983 | 20 | 30#(19-40) | adult pulmonology | case series | R | only clinical | - | - | + | + | + | - | - | - |
| SMIT et al. | Canada | 1996 | 21 | 46#(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# (range) or median¶ (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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Children and adults** | | | | | | | | | | | | | | | | |
| ARMENGOT et al. | Spain | 2012 | 25 | 28#(1-66) | ENT | case series | P | EM+VM | + | - | + | + | + | - | - | - |
| ARMENGOT et al. | Spain | 1995 | 14 | 24#(5-50) | ENT | case series | P | EM | - | - | + | + | + | - | - | - |
| BAI et al. | China | 2014 | 10 | 35#(6-56) | ENT | case series | R | EM+nNO+Genetics | + | - | + | + | + | - | - | + |
| BOON et al. | Belgium | 2014 | 168 | 18¶(-) | 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#(6-55) | paediatric | case series | R | EM+VM | - | - | + | + | + | - | - | - |
| EL-SAYED et al. | S. Arabia | 1997 | 16 | 18#(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#(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#(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¶(6-70) | PCD reference centre | case series | R | EM+VM+nNO | - | - | + | + | + | + | + | - |
| MCMANUS et al.+ | England | 2003 | 93 | 23#(4-66) | psychology | case series | P | - | - | - | + | + | + | - | - | - |
| MONTELLA et al. | Italy | 2009 | 13 | 15¶(10-29) | paediatrics | case series | P | EM+VM | + | - | + | + | - | + | - | - |
| MYGIND et al.+ | Denmark | 1983 | 27 | 24#(4-56) | ENT | case series | P | only clinical | + | - | + | + | + | - | - | - |
| NOONE et al. | USA | 2004 | 78 | 27#(1-73) | combination | case series | P | EM+VM+nNO | + | - | + | + | + | + | - | - |
| OKTEM et al. | Turkey | 2013 | 29 | 10#(0-24) | paediatrics | case-control | P | EM | - | - | - | + | + | - | - | - |
| OLM et al. | Brazil | 2011 | 12 | 12#(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#(2-49) | paediatrics | case series | P | EM+VM | - | - | + | + | + | - | + | - |
| PLESEC et al. | USA | 2008 | 13 | 15#(1-49) | pathology | case series | R | EM | + | - | + | + | + | - | + | + |
| SHAPIRO et al. | USA | 2014 | 35 | 18#(2-58) | combination | case series | R | EM+nNO+Genetics | - | - | + | + | + | + | + | - |
| SOMMER et al.+ | Germany | 2011 | 44 | 29#(-) | 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#(1-59) | ENT | case series | P | EM+VM | - | - | + | - | - | - | - | - |
| WANG et al. | China | 2009 | 24 | 29#(4-63) | radiology | case series | R | EM | - | - | + | + | + | - | + | + |
| YIALLOUROS et al. | Cyprus | 2015 | 30 | 24#(1-64) | paediatrics | cohort | R | EM+VM+nNO | - | - | + | + | + | + | - | - |

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Age is reported in years as mean# (range) or median¶ (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 (%)** |
|---|---|---|
| **Type of clinic** | | |
| Paediatric department | 16 | 33 |
| Paediatric pulmonology department | 9 | 17 |
| Adult pulmonology department | 4 | 8 |
| ENT department | 11 | 21 |
| Other departement | 12 | 21 |
| **Number of centres** | | |
| Singlecentre | 35 | 66 |
| Multicentre | 17 | 33 |
| **Publication period** | | |
| ≤1994 | 12 | 23 |
| 1995-2004 | 11 | 21 |
| ≥2005 | 29 | 56 |
| **Study size** | | |
| ≤20 patients | 15 | 29 |
| 21-50 patients | 25 | 48 |
| 50-100 patients | 9 | 14 |
| >100 patients | 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 |

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

| **Characteristic** | **Studies** (n=52) | **Proportion of studies (%)** |
|---|---|---|
| **Diagnostics performed** | | |
| 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 |
| **Health conditions** | | |
| 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 |
| **Information for different age groups** | 11# | 34 |
| **Information on severity** | 0 | 0 |

EM: electron microscopy

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

# of 32 studies including children and adults