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Early View

Review

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Lower airways clinical outcome measures for use in primary ciliary dyskinesia research, a scoping review

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Take home message:

Measurement and reporting of lower airways outcome measures in primary ciliary dyskinesia research are not standardised. Validated disease-specific clinical outcomes are needed to monitor disease progression in future trials and prospective cohorts.

Keywords: outcomes, standardisation, recommendations, lung function, imaging, rare diseases

Abstract

Objectives: Disease-specific, well-defined, and validated clinical outcome measures are essential in designing research studies. Poorly defined outcome measures hamper pooling of data and comparisons between studies. We aimed to identify and describe pulmonary outcome measures that could be used for follow-up of patients with primary ciliary dyskinesia (PCD).

Methods: We conducted a scoping review by systematically searching Medline, Embase and Cochrane Systematic Review online databases for studies published from 1996 to 2020 that included ≥10 PCD adult and/or paediatric patients.

Results: We included 102 studies (7289 patients). Eighty-three studies reported on spirometry, 11 on body plethysmography, 15 on multiple breath washout, 36 on high-resolution computed tomography (HRCT), 57 on microbiology, and 17 on health-related quality of life.

Measurement and reporting of outcomes varied considerably between studies (e.g. different scoring systems for chest HRCT scans). Additionally, definitions of outcome measures varied (e.g. definition of chronic colonisation by respiratory pathogen), impeding direct comparisons of results.

Conclusions: This review highlights the need for standardisation of measurements and reporting of outcome measures to enable comparisons between studies. Defining a core set of clinical outcome measures is necessary to ensure reproducibility of results and for use in future trials and prospective cohorts.

Introduction

Primary ciliary dyskinesia (PCD) is a rare genetic, multisystem disease that affects motile cilia lining the upper and lower airways, and the eustachian and fallopian tubes (1, 2). Symptoms start in early infancy, with progressive suppurative lung disease invariably leading to bronchiectasis (3, 4). Current management of patients with PCD broadly follows that used for patients with cystic fibrosis (CF) and bronchiectasis (formally non-CF bronchiectasis) (5-8). Therefore, studies have adopted similar outcome measures to monitor the natural history and disease progression in PCD even though PCD has a unique pathophysiology and disease pattern (9).

There is no minimum core set of disease-specific outcome measures in PCD research. This is particularly problematic because the choice of outcome measures informs the selection of data sources from which study information can be collected; the appropriateness, frequency, and length of follow-up measurements; and the required number of patients. Appropriate sample size relies on the expected frequency and natural variability of outcomes, and on the effect of interest (or the minimal clinically important difference) (10). The quality of the knowledge generated by research strongly relies on the selection of appropriate outcomes.

Well-defined and validated disease-specific outcome measures are the most efficient and accurate way to assess new therapies and management options. Whilst true for all diseases, this is particularly poignant for rare diseases, where the number of patients available is limited (11). An outcome measure that is valid for another disease might not be appropriate to measure the effect of interest, or sensitive enough to detect a subtle effect. Spirometry,

for example, is routinely used to monitor disease progression but is thought to be an insensitive surrogate marker for early lung disease in CF and, more recently, in PCD (12-15).

The aim of this scoping review was to systematically identify and describe the evidence in this area. We also aimed to highlight the most commonly used pulmonary and related outcomes and to examine the consistency of definitions across studies and the variations on the use and reporting of clinical outcome measures in the PCD literature.

Methodology

Search strategy

We followed the *a priori* scoping review protocol, which is available from the authors upon request. A pilot search included only terms related to the disease (Items 1-4 of search terms, Supplementary Box 1) and one reviewer (BR) scanned the first 1000 abstracts to identify key terms that could be used to build the full search strategy, designed for use in Embase and adapted to Medline. We used Embase Subject Headings (Emtree) and Medical Subject Headings (MeSH) along with individual terms to develop the search strategy, with limitations applied (Supplementary Box 1). We used EndNote (version 9.2, Thomas Reuters, Philadelphia, PA) as citation manager.

We performed the search on 2nd June 2020. We used a standardised data extraction form developed a priori in Excel, which was piloted on five randomly selected studies and then refined. Data were recorded for the following: publication details (authors, title, year of publication, country and journal), study characteristics (data collection period, study design, countries that contributed with data, inclusion criteria, clinic type, sample size, population characteristics and diagnostic data), and outcome details (outcomes reported, definitions

used, correlation between different outcome measures, equipment used and measurement details).

Two reviewers independently assessed titles and abstracts for eligibility. Full text was obtained for all studies deemed relevant by either reviewer or if there was uncertainty on eligibility. Where disagreements remained after full text review, the manuscripts were discussed with a third person. One reviewer manually searched the reference lists of all eligible studies for additional manuscripts. Three reviewers extracted data for a third of the eligible studies each. A fourth reviewer extracted data from 10% of the total manuscripts included in the study, and their extractions were compared with those extracted by the other three reviewers to ensure consistency.

Inclusion and exclusion criteria

We included studies describing clinical outcome measures in PCD if they a) had a study population of at least 10 PCD patients, b) were published in English, c) were published after 1996, and d) were conducted on humans. We did not include studies prior to 1996 because the diagnosis of PCD has changed in the last twenty years, therefore older manuscripts may contain a high proportion of patients that would no longer fulfil the current diagnostic criteria (16). Details of diagnostic data for each of the included studies were recorded (Supplementary table 1).

We excluded studies that were not original research, conference abstracts, and where full texts were irretrievable. Studies reporting on multiple disease groups were excluded if the PCD data could not be clearly identified. Manuscripts that reported exclusively on ear, nose and throat (ENT) symptoms were also excluded.

Definition of outcome measures and classification into subgroups

Outcome measures were defined as any clinical measure used a) to monitor patients over time or b) as a marker of disease severity. Outcome measures were classified as (i) study outcomes, defined *a priori* as study outcome measures; or (ii) study population descriptors. The latter indicates measures that were used to characterise the study population (e.g. baseline measures of FEV_1) and those that could potentially be used in future studies (e.g. cough frequency). The supplementary tables contain detailed information on study characteristics and definitions of outcome measures for all studies included in this review.

Statistical analysis

Critical appraisal of individual studies was not conducted because our focus was on the variety of outcomes used and how these were measured and reported, and not on disease progression, prognosis or treatment effects (17, 18). Information about scoping reviews is outlined in the supplementary files.

Descriptive and summary data were analysed in R statistical package (version 3.2.3). Continuous variables were reported as median and interquartile range. Categorical variables were reported as proportions. Results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) checklist (19). Figures were plotted in R and Tableau 2019 v4.0.

Results

Three thousand one hundred and fifty abstracts were identified, of which 2706 were reviewed after exclusion of 444 duplicates. One hundred and ninety eight manuscripts were reviewed in full, of which 102 met the inclusion criteria and were therefore included (Supplementary Supplementary Figure 1) (12, 20-120).

Study characteristics

The manuscripts included information on 7289 patients with PCD, with a median of 32 PCD patients per manuscript (IQR 20 to 62, range 10 to 1609, Supplementary Table 1). However, some patients were described in several studies and were included more than once if the studies described different outcome measures.

Manuscripts contained data collected from 23 different countries but most (89%) presented single-centre data. Publications with a higher number of PCD patients were from multi-centre studies, with the two largest studies containing data derived from a large international PCD cohort study (121).

Outcome measures reported

Ninety-three studies reported on a total of 23 main study outcomes (Table 1, Figure 1), with 19 presenting data exclusively on population descriptors. Sixty-seven presented both study outcomes and population descriptors (Table 1, Supplementary Table 2).

Spirometry-derived parameters were the most frequently reported clinical outcome measures, followed by chest high-resolution computed tomography (HRCT). Microbiology and anthropometric measures were more often reported as descriptors than as study outcomes (Figure 1).

Standardised definitions

Definitions of outcome measures varied considerably between studies (Supplementary Table 2). Of 18 studies reporting on microbiology as study outcomes, 14 provided data on chronic colonisation by potentially pathogenic bacteria (29, 31, 34, 38, 59, 65, 65, 70, 75, 82, 96, 100). The terms chronic colonisation and chronic infection were sometimes used

interchangeably, and the classification used to define them varied. Four studies used the Leeds CF criteria (or a modified version) (38, 64, 65, 70), two the European consensus for antibiotic therapy against *Pseudomonas aeruginosa* in CF (75, 104) and one the Copenhagen criteria (100). The remaining studies developed a study-specific criterion, such as pathogen cultured in at least 50% of samples from the past year (46, 47) or isolation of the same pathogen in at least 2 occasions, at least 3 months apart in a one-year period (93).

Sampling frequency of sputum and other microbiological specimens also varied between studies. Some studies did not record whether patients had a pulmonary exacerbation at the time of sampling. These differences likely biased results, particularly when reporting prevalence of different respiratory pathogens.

Details on the definitions of all clinical outcome measures reported as study outcomes or population descriptors are provided in supplementary table 2. In the next sections, we will focus on the most frequently reported outcome measures.

Lung function

Spirometry

Of the 83 studies reporting spirometry data, 42 reported adherence to ERS/ATS guidelines (122) (Supplementary Table 2). Twenty-five reported on forced expiratory volume in one second (FEV_1) z-scores, 18 as a study outcome. FEV_1 % predicted was used as an outcome as often as a descriptor (*n*=32 *vs* 31, respectively). Studies reporting on FEV_1 z-scores were published more recently (Figure 2). Fourteen studies reported calculating z-scores based on the Global Lung Function Initiative (GLI) reference equations (123), two used national references, and eight used other equations, while the remaining did not detail the equation used (Supplementary Table 2).

Five studies compared FEV_1 before and after the use of bronchodilators. Studies used inhaled salbutamol (32, 119) or albuterol (28) to assess reversibility and one study performed methacholine challenge before and after the use of salbutamol and placebo (27). One study did not report which bronchodilator was used (114).

Body plethysmography

Eleven studies reported on body plethysmography parameters as study outcomes (Table 1, Supplementary Table 2). Lung residual volume (RV) % predicted was reported by all studies, total lung capacity (TLC) % predicted in four studies and the remaining 19 parameters were rarely reported. Three of these studies additionally measured FVC and FEV_1 using plethysmography devices.

Multiple breath washouts (MBW)

Fifteen studies reported on parameters derived from the MBW test as study outcomes (Table 1, Supplementary Table 2), of which 47% were published in the last two years. Lung clearance index (LCI) was most frequently reported. Eight studies presented z-scores for LCI, and five presented values for S_{cond} and S_{acin} z-scores (representatives of ventilation inhomogeneity in small *conducting* and *acinar* airways, respectively). Studies used different inert tracer gases and equipment; nine of them used nitrogen (N_2), five used 0.2% sulfur hexafluoride (SF_6) and the other study did not report which tracer gas was used.

Chest imaging

Forty manuscripts reported on radiological findings, with 26 presenting them as study outcomes and 14 as population descriptors (Table 1, Supplementary Table 2). Of the later, five studies had spirometry measures as outcomes and provided information on presence or

absence of bronchiectasis, diagnosed through chest HRCT/CT or radiography. One study mentioned chest radiography to determine the presence of bronchiectasis; however, the main outcomes were sleep activity and attention deficit scales (85). The remaining studies did not report on specific outcomes, with data on descriptors only including spirometry, microbiology, anthropometric measurements, and fertility.

Four studies reported on both chest radiographs and HRCT and two studies on both chest HRCT and magnetic resonance imaging (MRI).

Radiography

Bronchiectasis, seen on chest radiography, was used in one study as study outcome and in six as population descriptor (Table 1, Supplementary Table 2). Similar to other imaging modalities, there are no PCD-specific radiography scoring systems, so studies used different scales to report findings. For example, Jain *et al* (54) used a modified version of the Chrispin-Norman score, which was developed for CF (124), while Kennedy *et al* (55) developed a study-specific score for bronchiectasis severity.

HRCT

Chest HRCT and/or CT was used as study outcome in 25 studies, with an additional 10 studies reporting it as population descriptor (Figure 1, Table 1, Supplementary Table 2). Studies adopted modified versions of different scoring scales as there are no PCD-specific scoring systems available. Seven studies used modifications of the Brody score (125), six used the Bhalla score (126), another four applied the Helbich score (127) and a further six used other systems. Of the latter, four used a study-specific score, one by combining the

Brody and Bhalla scores (59). Two studies did not provide any detail on the scoring system used (37, 56) and therefore were not included in Figure 5.

The use of different measurement scales resulted in inconsistent reporting of sub-scores (Figure 5). For example, extent of bronchiectasis was measured by: a) number of bronchopulmonary segments affected, b) percentages of each lobe involved, c) scores from 0-3, d) percentages of central lung and peripheral lung involvement, or e) size of largest and average bronchopulmonary segment involved. Mucus plugging was measured as size of plug (i.e. small, large), location of plug (Brody score: largest airways, small airways, peripheral lung, central lung; or Helbich score: number of segments) or a mucus classification score (Bhalla score).

As illustrated in Figure 3, not all studies using the Brody score reported on the same sub-score components, likely due to study-specific modifications. For example, one study (12) classified the location of the mucus plug as small or large airways, while five other studies used number of central and peripheral lobes involved. In another study that used a modified combination of the Brody and Bhalla scores, the partition of lungs into different segments followed a regional approach as opposed to the commonly used pulmonary segmentation approach in order to expedite the time needed for scoring each scan in routine clinical practice (59).

Unsurprisingly, all 23 studies that presented information on their scoring system reported on bronchiectasis. Studies classified bronchiectasis as mild for those with airway diameter slightly greater than diameter of adjacent blood vessel, moderate for airway lumen 2-3 times the diameter of the vessel and severe for those at least 3 times the diameter of the vessel. However, the extent of bronchiectasis varied, with some reporting the number of bronchopulmonary segments, while others reported percentage of compromised area

(Figure 3). The second most common features described were airway wall thickening and mucus plugging (*n*=19).

Two studies comparing CT scores in PCD and CF patients found no differences in the global Brody score. A third study used a study-specific system to analyse CT scans from patients with PCD and CF and then assess results against the Brody and Bhalla scores (63). They found that bronchial wall thickening, bronchiectasis, mucus plugging, atelectasis, and air trapping, features commonly seen in CF patients, were even more common in patients with PCD.

Maglione *et al* (57) reported a significantly higher sub-score for severity of collapse or consolidation in PCD compared to CF, and Cohen-Cymberknoh *et al* (82) found that the lower and middle lobes were more frequently affected in PCD compared to the typical upper lobes compromise seen in CF (34, 55, 62, 82). Tadd *et al* (63) reported a higher frequency of extensive tree-in-bud pattern of mucus plugging, bronchoceles or nodules, thickening of interlobar and intralobular septa, and atelectasis or collapse of the whole lobes in PCD; these are uncommon in CF patients.

MRI

Only five studies reported on chest MRI as study outcome (Table 1, Supplementary Table 2). Four studies applied a modified Helbich scoring system, while Smith *et al* (50) developed a study-specific scoring system for three-dimensional volumetric hyperpolarised MRI. When looking at sub-scores, Maglione *et al* (75) found no significant difference between total MRI scores and sub-scores in 20 PCD and 20 mild CF patients, aside from a higher score for severity of collapse/consolidation in PCD patients. In a smaller study of 11 PCD children, all presented with mostly small and heterogenous abnormalities on ventilation MRI (50).

Microbiology

Fifty-seven studies reported on microbiology, 18 as study outcomes and 39 as population descriptors (Table 1, Supplementary Table 2). Studies reported most commonly on *Haemophilus influenzae* and *Pseudomonas aeruginosa*, followed by *Staphylococcus aureus* (Figure 6). Some studies distinguished between mucoid and non-mucoid strains of *Pseudomonas aeruginosa*, while others simply reported on *Pseudomonas aeruginosa* infection. Similarly, *Staphylococcus aureus* subtypes were inconsistently stratified across studies, with some reporting methicillin sensitive (MSSA) and resistant (MRSA) strains separately. Not all studies stratified pathogen prevalence by age group (Supplementary Figure 2).

Other outcome measures

Health-related quality of life scores

Seventeen studies reported on HRQoL as study outcomes (Table 1). However, only two studies (74, 92) used QoL-PCD, as most were published before the disease-specific tool was validated (71, 128, 129). The most common instruments adopted were the St George's Respiratory Questionnaire (SGRQ) (eight studies) and the 36-item short form survey (SF-36) (seven studies) (Supplementary Table 2).

Pulmonary exacerbations

Nine studies reported on pulmonary exacerbations, five as study outcomes. However, none used the PCD-specific consensus, as the studies included in this review pre-date it (130). Two RCTs used pulmonary exacerbation as a primary outcome. Paff *et al* (89) defined an

exacerbation as respiratory symptoms that led to initiation of systemic antibiotic treatment irrespective of culture results, or a decline of at least 10% in FEV_1 % predicted compared to baseline at screening and randomisation (89), while Kobbernagel *et al* (92) defined it as worsening of respiratory symptoms leading to initiation of antibiotic treatment in the week prior to the clinical appointment up to the day of the appointment. Ratjen *et al* (90) studied a subset of patients that experienced an episode of exacerbation, defined as an increase in lower airway symptoms treated with oral antibiotics. Joensen *et al* (100) applied a definition developed for CF studies (61) (Supplementary Table 2). Sunther *et al* (35) only included patients with pulmonary exacerbation, defined as change in respiratory status for which intravenous antibiotics were needed.

Comparison between outcome measures

Most studies comparing outcome measures used spirometry as the reference to which the other outcomes were compared (Figure 1). Twelve studies describing imaging modalities reported on agreements or correlations with other outcome measures (12, 33, 45, 49, 53, 55, 57, 60, 93, 108, 119). The most common comparison was between spirometry-derived FEV_1 and HRCT, with studies presenting contradictory findings. Four studies (33, 53, 55, 93) found an agreement between the two outcomes, one of which used an automated CT scoring for adults with PCD (53). Three studies used a modified Bhalla system and the other a study-specific scoring system. The other four studies (45, 57, 62, 119) reported no association.

FEV_1 was compared to MBW-derived LCI in eight studies, also with contradictory results. Two studies reported no association (41, 44), while the other six (12, 35, 42, 45, 46, 49)

found correlations between some parameters. Both Boon *et al* (12) and Kobbernagel *et al* (46) found a significant negative correlation between LCI, FEV_1 and FEV_1/FVC ratio z-scores, while Irving *et al* (45) only found a correlation between LCI and FEF_{25-75} z-scores. Green *et al* (42) did not find any correlation between LCI and FEV_1 z-scores in PCD patients but reported a significant correlation between $LCI_{2.5}$ and FEV_1/FVC ratio and FEF_{25-75} z-scores.

MBW-derived LCI might be more sensitive to detect early or milder disease. Nyilas *et al* (49) found that over half of the patients with abnormal LCI values and MRI scores had normal FEV_1 z-scores. In another study, five patients (15%) had abnormal LCI but normal FEV_1 z-scores (45). LCI was also shown to be more sensitive than FEV_1 to detect lung structure abnormalities (12). Boon *et al* (12) reported that LCI z-scores were concordant with total CFCT scores (a variant of the Brody score) in 83% of the patients, while Kobbernagel *et al* (46) and Irving *et al* (45) found no correlation.

Studies comparing HRCT to indices derived from body plethysmography, chest MRI and microbiology found significant correlations. However, these were generally limited to sub-scores (e.g. bronchiectasis on HRCT and body plethysmography and collapse/consolidation on HRCT and MRI) as opposed to the global score.

Other associations between outcome measures are shown in figure 4.

Randomised controlled trials

Only five of the included studies were RCTs, of which four adopted a cross-over design (Supplementary Table 3).

The efficacy of six-months azithromycin maintenance therapy in reducing the number of respiratory exacerbations in patients with PCD was assessed in a double-blind, parallel group, placebo controlled RCT at six European PCD centres (92). Secondary outcomes included changes in spirometry, body plethysmography, N_2MBW, HRQoL, audiometry, sputum microbiology, and inflammatory markers.

The effect of hypertonic saline on HRQoL in PCD adults was investigated in a 28-week double-blind cross-over RCT with a wash-out period of 4 weeks. HRQoL was measured by the SGRQ and Quality of Life Questionnaire-Bronchiectasis (QOL-B) (89).

Gokdemir *et al* (24) assessed spirometry measurements (FEV_1, FVC, peak expiratory flow and forced expiratory flow $(FEF)_{25-75}$ % predicted) in PCD children using two different airway clearance methods. Half performed conventional pulmonary rehabilitation for 5 days in hospital followed by a 2-day wash-out period and then high frequency chest wall oscillation for another 5 days at home. However, techniques differed between the settings. Another cross-over RCT investigated differences in FEV_1 % predicted and in bronchial hyperresponsiveness after the use of salbutamol compared to placebo in PCD children at both 3 and 6 weeks compared to pre-treatment measurements (27).

Noone *et al* (106) reported on mean whole-lung clearance rates of a radionucleotide marker after inhalation of uridine-5'-triphosphate compared to placebo during a series of controlled coughs to induce mucociliary clearance in PCD adolescents and adults.

Discussion

This scoping review identified 23 clinical outcome measures used in PCD research. We found a high degree of heterogeneity in the definitions of outcome measures.

Spirometry and chest HRCT were most frequently reported as study outcomes. Spirometry is widely available, relatively easy to perform and does not require expensive equipment (122, 131); however, researchers have questioned its appropriateness as a measure to monitor disease progression in PCD (35, 49, 57). A meta-analysis found that mean FEV_1 ranged from 51% to 96% predicted, with high heterogeneity between studies that could not be explained by age or other factors (132). Studies that did not report on which reference values they used or those that did not provide information on quality control reported lower mean FEV_1 values. Clinical status at the time of measurement was rarely reported and therefore could not be included in the meta-regression. The largest study to date investigating lung disease in PCD patients found consistently low FEV_1 z-scores in patients with PCD compared to reference data, similar to those seen in CF patients (25).

To our knowledge, no study has investigated the timing of physiotherapy in relation to spirometry, which is a significant limitation as, anecdotally, airway clearance techniques can improve spirometric indices. An ongoing multicentre prospective cohort is investigating variability of lung function in stable PCD patients, adjusting for factors such as timing of inhaled medication and respiratory physiotherapy (133, 134) (https://clinicaltrials.gov/ct2/show/NCT03704896). Another potential source of variability when using spirometry-derived measurements are the adopted reference equations, as variations between the GLI and national reference equations can occur. Evidence from a longitudinal CF cohort highlighted the disparity between reference equations,

demonstrating the need for a standardised approach to interpreting spirometric measurements to facilitate appropriate comparisons both within and between centres and countries (135).

Chest HRCT has been proposed as a surrogate outcome measure in the assessment of lung disease. However, there are no validated scoring systems for PCD. All studies included in this review used CF-derived scoring systems (125-127), despite significant pathophysiological differences between the two conditions (9, 136). Additionally, studies do not report the lung volumes at which the CT scans are obtained, with no details on the standard operating procedures used to record the images.

Location, distribution, and frequency of features seen in HRCT scans of patients with PCD differ from those with CF (136). The weights applied to each feature might not be suitable for PCD as CF-derived scoring systems do not reflect the range and severity of structural changes in PCD. Studies found that extensive tree-in-bud pattern of mucus plugging, bronchoceles or nodules, thickening of interlobar and interlobular septa, and atelectasis mostly seen as collapse of whole lobes were frequently described in PCD but uncommonly in CF (52, 63, 136). Reporting only the global CT scores might be misleading as some components of the score might be more relevant to clinical outcome, particularly when using a non-disease-specific score. These findings underscore the need for disease-specific CT scoring systems. Hoang-Thi *et al* (53) highlighted the fact that visual scores such as the ones routinely used in the assessment of PCD and CF patients can be highly subjective. In response, they developed an automated CT scoring for adults with PCD, which had moderate to good correlation with FEV_1 and FVC.

MRI scans of the chest have historically been considered of limited value due to intrinsic characteristics of the pulmonary tissue, and the presence of physiological motion resulting in poor resolution and motion artefacts. Research has focused on improving techniques to obtain better quality images (137, 138).

Lack of agreement between spirometry, HRCT, MBW and MRI parameters reported by some studies might reflect variations on measurement and reporting of outcomes. Discrepancies could be explained by different scoring systems for HRCT, differences in tracer gas for MBW, variations in measurements, inability of some of the outcome measures to accurately monitor lung disease progression in PCD, or true variability between populations (e.g. underlying genetics, differences in disease severity or treatment). Interpretation of findings was limited by the retrospective nature of most studies. In some cases there was a significant time lag between measurements performed with the methods that were compared (12), or tests were applied to different sub-populations (e.g. HRCT scans conducted only in the older population with more severe lung disease (45) or conducted at different timepoints of clinical stability (57)). Contradictory results could also be attributed to variations in study design, inclusion criteria, or small sample sizes, resulting in variability due to chance.

Recent studies have focused on MBW, with almost half of them published in the last few of years. Nyilas *et al* (49) found that LCI was not able to distinguish between reversible and irreversible lung damage, despite being more sensitive than spirometry to detect changes. A limitation of LCI is the long washout time and therefore test-duration, which is particularly problematic for patients with compromised lung capacity and young children. Studies looking at shorter washout periods have shown promising results, with $LCI_{5\%}$ providing a

good alternative to the more conventional $LCI_{2.5\%}$ (39, 41, 109). However, as Nyilas et al (49) demonstrated, combining different modalities (e.g. MRI and MBW) can be necessary to accurately capture changes in the lungs of PCD patients.

In terms of microbiological outcomes, studies should present a breakdown of pathogens by age group since the prevalence of bacterial species changes with age (66, 85). Studies included in this review were also limited by the lack of a universal panel that could be applied consistently across different centres, particularly when reporting the prevalence of each pathogen isolated. Rogers *et al* (67) highlighted that some of dominant genera of bacteria found in the sputum of PCD patients were from those unlikely to be detected without specific growth conditions being present. Variations in the frequency of specimen collection and type of specimen (e.g. expectorated sputum, cough swab, bronchoalveolar lavage) will also likely affect pathogen prevalence.

Small sample sizes were a common limitation in most studies, highlighting the importance of national and international disease registries, large collaborative multicentred studies and standardised definitions that enable pooling of data (121, 139-141). Few studies included sample size calculations, hampering the interpretation of statistically insignificant results due to underpowered samples.

The number of larger multicentre studies has increased in recent years, highlighting the important role of PCD networks such as BESTCILIA, BEAT-PCD and the Genetic Disorders of Mucociliary Clearance Consortium in advancing collaborative research in the field (133, 134, 142, 143). Such collaborations were featured in two studies that used data derived from the international PCD cohort (iPCD) (121).

RCTs and prospective cohort studies with long follow-up periods are uncommon in rare diseases due to the small sample sizes available, high costs and limited commercial interest from pharmaceutical industries (5, 144, 145). As a result, the majority of PCD studies are cross-sectional, case-controls or small cohort studies with limited follow-up. Interventional studies are currently being designed but will require close international collaborations and data sharing. The success of these and of future trials will depend on the selection of appropriate outcome measures.

Our review was limited by the quality of the information provided in the studies. As our aim was to identify the evidence available and describe definitions for clinical outcome measures used in PCD research, we opted to conduct a scoping review and therefore we did not critically appraise the studies included in this review. We did not perform quantitative analysis as studies were heterogeneous, impeding a formal meta-analysis to be carried out. In fact, the aim of this review was to highlight this heterogeneity. Another limitation was the broad nature of this review impeded us from focusing on any one clinical outcome measure and therefore systematic reviews with or without meta-analysis are still needed for the more commonly used and promising outcome measures. A separate review to evaluate upper airways clinical outcome measures is underway, and therefore we deliberately excluded these studies from our scoping review. Despite our attempts not to restrict the search to specific outcomes, our review is limited to the clinical outcomes that were included as search terms.

Recommendations

We advocate that outcome measures for use in future prospective trials must fulfil the following criteria: a) be measured across different studies in a standardised manner (e.g. using the standardised PCD data collection tool FOLLOW-PCD (146)); b) be used and reported regularly by a sufficient number of studies; c) use currently recommended definitions (e.g. z-scores based on GLI recommendations) and d) be embedded within the current knowledge of PCD pathophysiology and natural history (Table 2). This will require consensus statements, which are currently being developed by a BEAT-PCD work group.

Spirometry was the outcome most frequently used for disease monitoring but there were major problems with standardisation on measuring and reporting FEV_1. Large studies are needed to investigate the suitability of spirometry-derived parameters as accurate and sensitive surrogate markers.

Chest HRCT might be a good candidate for longitudinal follow-up of lung disease progression in PCD, particularly modalities using low radiation (147, 148). However, a disease-specific scoring system must be developed. Agreement between HRCT and other outcomes were limited to sub-scores as opposed to global score, emphasising the need for PCD-specific scores that consider the distribution, frequency and patterns of lung compromise in this population, and that can be easily applied by clinicians without being unnecessarily time-consuming.

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) encourages the inclusion of patient-centred outcome measures. A systematic review on the patient's experience of PCD reported worsening of respiratory symptoms with age, which was also associated with decline in the physical and mental domains (149). QOL-PCD, a

HRQoL instrument, is the only validated disease- and age-specific cross-culture clinical outcome measure in PCD (113, 127, 128, 150-151). QOL-PCD correlated well with the Sino-Nasal Outcome Test (SNOT-20) for upper airway symptoms, SGRQ-C for lower airways symptoms and SF-36 for physical functioning, role functioning and mental health (113).

An expert consensus on the definition of pulmonary exacerbations in PCD for children and adults was recently developed (130). The importance of disease-specific definitions was highlighted by the fact that studies that used exacerbations as an outcome adopted different definitions for pulmonary exacerbations (35, 90, 92). There is now a need to validate the proposed definition and develop a separate definition for upper airway exacerbations.

Conclusions

This scoping review highlights the variety of outcomes and definitions used in PCD research. It also underscores significant differences in measurement and reporting of outcomes. Validated disease-specific clinical outcome measures are needed to monitor disease progression in PCD in future prospective cohort studies and clinical trials. Appropriate outcomes need to be chosen based on the specific patient groups and the study intervention. New studies should aim to measure and report outcomes using standardised methods to build up the body of evidence needed to meaningfully compare results. New promising outcome measures should also be used, such as MBW-derived LCI and microbiology, to assess and better understand the appropriateness of these for long-term monitoring in PCD.

Manuscript tables

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

Authors (year of publication)	**Study outcomes**	**Population descriptors**
Main study outcome: Spirometry and/or body plethysmography		
Davis *et al* (2015) (20)	Anthropometry, spirometry, CT	Microbiology
Davis *et al* (2019) (21)	Spirometry, Anthropometry, Microbiology	None
Ellerman *et al* (1997) (22)	Spirometry	Chest radiography, microbiology
Fuger et al (2018) (23)	Capillary blood test, spirometry	CT, anthropometry, microbiology
Gokdemir *et al* (2014) (24)	Spirometry, comfort and efficacy, SpO_2	Anthropometry
Halbeisen *et al* (2018) (25)	Spirometry	Anthropometry
Hellinckx *et al* (1998) (26)	Spirometry, body plethysmography	None
Koh *et al* (2000) (27)	Spirometry	None
Lopes *et al* (2015) (28)	Spirometry & body plethysmography, HRCT, dyspnoea	Anthropometry, treatment
Maglione *et al* (2014a) (29)	Anthropometry, spirometry, microbiology	None
	Spirometry	HRCT, Chest radiography

Authors (year of publication)	**Study outcomes**	**Population descriptors**
Marthin *et al* (2010) (30)		
Olveira *et al* (2017) (31)	Spirometry, microbiology, treatment, CT	Anthropometry
Phillips *et al* (1998) (32)	Spirometry	None
Pifferi *et al* (2012) (33)	Body plethysmography, HRCT	Microbiology
Shah *et al* (2016) (34)	Body plethysmography, HRCT, microbiology	None
Sunther *et al* (2016) (35)	Spirometry	Anthropometry, microbiology, treatment
Tamalet *et al* (2001) (36)	Spirometry, blood gas	CT, treatment
Vallet *et al* (2013) (37)	Spirometry, blood gas, CT	None
Videbaek *et al* (2019) (38)	Spirometry, microbiology	None
Main study outcome: MBW		
Ahmad *et al* (2015) (39)	MBW	None
Anagnostopoulou *et al* (2018) (40)	MBW	Anthropometry
Green *et al* (2012) (41)	SF_6 MBW, spirometry	Anthropometry, microbiology
Green *et al* (2016) (42)	MBW, spirometry	Anthropometry
Irving *et al* (2018) (43)	MBW	Spirometry, microbiology
Irving *et al* (2017) (44)	Spirometry, MBW	None

Authors (year of publication)	Study outcomes	Population descriptors
Irving *et al* (2013) (45)	Spirometry, MBW, HRCT	Microbiology
Kobbernagel *et al* (2019) (46)	Spirometry, MBW	Microbiology, anthropometry
Kouchy *et al* (2020) (47)	MBW, spirometry, endobronchial thickness, bronchoalveolar lavage	Anthropometry, microbiology
Nyilas *et al* (2017) (48)	MBW/SBW, body plethysmography	Microbiology, treatment
Nyilas *et al* (2018) (49)	Structural and functional MRI, MBW, spirometry	Anthropometry
Smith *et al* (2018) (50)	MRI, MBW, spirometry	Anthropometry
Main study outcome: High-resolution computed tomography		
Boon *et al* (2015) (12)	Spirometry, N_2 MBW, HRCT	Anthropometry
Cohen-Cymberknoh *et al* (2014) (51)	HRCT, spirometry, microbiology	Anthropometry
Dettmer *et al* (2018) (52)	CT	Microbiology, spirometry, anthropometry, number of exacerbations
Hoang-Thi *et al* (2018) (53)	Spirometry, CT	Anthropometry
Jain *et al* (2007) (54)	Chest radiography, HRCT	Microbiology
Kennedy *et al* (2007b) (55)	HRCT	Spirometry, microbiology, lobectomy
Li *et al* (2005) (56)	HRCT	Spirometry, microbiology

Authors (year of publication)	Study outcomes	Population descriptors
Maglione *et al* (2012) (57)	Spirometry, HRCT	None
Maglione *et al* (2017) (58)	MRI, CT	Spirometry, anthropometry, treatment, microbiology
Magnin *et al* (2012) (59)	Spirometry, arterialised capillary blood gases, CT	None
Montella *et al* (2009a) (60)	HRCT, MRI, body plethysmograghy	Microbiology
Montella *et al* (2009b) (61)	HRCT, MRI	None
Santamaria *et al* (2008) (62)	HRCT	Spirometry, microbiology
Tadd *et al* (2019) (63)	CT	None
Main study outcome: Microbiology		
Alanin *et al* (2015) (64)	Microbiology	Spirometry
Cohen-Cymberknoh *et al* (2017) (65)	Microbiology, spirometry, CT	Anthropometry
Roden *et al* (2019) (66)	Microbiology, spirometry	None
Rogers *et al* (2013) (67)	Microbiology	Spirometry
Main study outcome: Anthropometry		
Goutaki *et al* (2017) (68)	Anthropometry, spirometry	None
Svobodova *et al* (2013) (69)	Anthropometry	None
Main study outcome: Health-related quality of life		

Authors (year of publication)	**Study outcomes**	**Population descriptors**
Alanin *et al* (2017) (70)	HRQoL, microbiology, spirometry, anthropometry	None
Behan *et al* (2017) (71)	HR-QoL	Microbiology, spirometry
Carotenuto *et al* (2013) (72)	HR-QoL	Anthropometry
Ioannou *et al* (2020) (73)	HRQoL	Spirometry
Kenis Coskun *et al* (2019) (74)	HRQoL	Spirometry, anthropometry, microbiology
Maglione *et al* (2014b) (75)	HR-QoL, spirometry, exercise testing	Exacerbations, microbiology
McManus *et al* (2003) (76)	HR-QoL	Treatment
McManus *et al* (2006) (77)	HR-QoL	None
Pifferi *et al* (2010) (78)	HRQoL	Treatment
Valero-Moreno *et al* (2020) (79)	HRQoL	Spirometry
Whalley *et al* (2006) (80)	HRQoL	None
	HRQoL, sleep	None

Authors (year of publication)	Study outcomes	Population descriptors
Zengin Akkus *et al* (2019) (81)		
Main study outcome: Sleep disorder		
Cohen-Cymberknoh *et al* (2019) (82)	Sleep questionnaires, HRQoL	Spirometry
Oktem *et al* (2013) (83)	Body plethysmography, sleep questionnaire, PSQI, polysomnography, HRCT	Anthropometry
Santamaria *et al* (2014) (84)	Respiratory polysomnography, sleep questionnaire, HRCT	Spirometry, anthropometry, treatment, microbiology
Sismanlar *et al* (2018) (85)	Sleep, attention deficit	Spirometry, radiography
Main study outcome: Inflammatory markers		
Bush *et al* (2006) (86)	Inflammatory markers, sputum biophysical and transport properties	Spirometry, microbiology
Cockx *et al* (2017 a) (87)	Inflammatory markers	Spirometry, microbiology
Cockx *et al* (2017 b) (88)	Inflammatory markers	Spirometry, microbiology
Paff *et al* (2017) (89)	HRQoL, LRTI-VAS, exacerbations, inflammatory markers in blood, inflammatory markers in sputum, spirometry, adverse events, adherence	Anthropometry, MRC dyspnoea scale score, HRCT or chest radiography
Ratjen *et al* (2016) (90)	Inflammatory markers from sputum, spirometry, microbiology	None
Zihlif *et al* (2006) (91)	Inflammatory markers from exhaled breath condensate and sputum	Spirometry
Main study outcome: Exacerbations		
Kobbernagel *et al* (2020) (92)	Number of exacerbations, spirometry, body plethysmography, MBW, HRQoL, inflammatory markers, microbiology	Pulse oximetry saturation, respiratory rates, anthropometry
Piatti *et al* (2020) (93)	Number of exacerbations, CT, spirometry, microbiology	Anthropometry

Authors (year of publication)	Study outcomes	Population descriptors
Main study outcome: Exercise testing		
Loomba *et al* (2017) (94)	Spirometry, exercise testing	None
Madsen *et al* (2013) (95)	N_2 MBW, spirometry, body plethysmography, exercise testing, HR-QoL	Anthropometry, microbiology
Ring *et al* (2018) (96)	Exercise testing, spirometry	Anthropometry, microbiology
Simsek *et al* (2018) (97)	Spirometry, exercise testing, physical activity level	Anthropometry
Valerio *et al* (2012) (98)	Spirometry, exercise test, physical activity assessment	Anthropometry
Wells *et al* (2011) (99)	Exercise testing	Spirometry, anthropometry, Habitual Activity Estimation Scale questionnaire
Main study outcome: Others		
Joensen *et al* (2014) (100)	Breath profiles, microbiology, number of exacerbations	Spirometry
Kawakami *et al* (1996) (101)	Chronic sputum production, sputum and nasal scores	Fertility
Kennedy *et al* (2007a) (102)	Lythoptysis, radiographic findings	Spirometry, microbiology, lobectomy
Marino *et al* (2019) (103)	Nutrition, spirometry, anthropometry, inflammatory markers	None
Mirra *et al* (2015) (104)	Vitamin D, body plethysmography, HR-QoL, physical activity assessment, microbiology	Anthropometry, HRCT, treatment

Authors (year of publication)	Study outcomes	Population descriptors
Montuschi *et al* (2014) (105)	Breath profiles	Spirometry, microbiology, anthropometry, treatment
Noone *et al* (1999) (106)	Clearance during cough, sputum production rate	Spirometry, cough questionnaire
Paff *et al* (2013) (107)	Exhaled breath profile	Spirometry, microbiology, pulmonary exacerbations
Pifferi *et al* (2017) (108)	Spirometry, HRCT, body plethysmography, microbiology, extracellular matrix	None
Shoemark *et al* (2009) (109)	FENO	Anthropometry, spirometry, treatment, microbiology, nasal NO
Smit *et al* (1996) (110)	Lung resection, symptoms questionnaire	Spirometry, bronchiectasis, dyspnoea index
Zihlif *et al* (2005) (111)	Cough frequency, cough symptom score	Spirometry, eNO, inflammatory markers, microbiology
No main study outcome		
Abitbul *et al* (2016) (112)	None	CT, fertility, microbiology, spirometry
Boon *et al* (2014) (113)	None	Anthropometry, spirometry, microbiology, chest radiographs and CT
Eden *et al* (2019) (114)	None	Spirometry, microbiology, number of exacerbations
Emiralioglu *et al* (2020) (115)	None	Spirometry, anthropometry, microbiology, lobectomy, CT
Frija-Masson *et al* (2017) (116)	None	Spirometry, microbiology, HRCT, dyspnoea score, treatment, fertility, lobectomy, mortality
Knowles *et al* (2014) (117)	None	Spirometry, fertility

Authors (year of publication)	Study outcomes	Population descriptors
Noone *et al* (2004) (118)	None	Spirometry, microbiology, radiographs, cough
Pifferi *et al* (2015) (119)	None	Spirometry, HRCT, microbiology
Yiallouros *et al* (2015) (120)	None	CT, microbiology, spirometry, anthropometry, lobectomy

Table 2. Summary of clinical outcome measures for use in PCD research

Clinical outcome measure	Strengths	Limitations	Future directions
Spirometry	Routinely measured; Reported in 78% studies included	Unknown accuracy and sensitivity as surrogate marker for lung disease; Unstandardised reporting of indices	Investigate appropriateness of spirometry to monitor disease progression; Standardised reporting of spirometric indices (i.e. use of z-scores); Report and investigate appropriateness of other spirometric indices (e.g. FVC, FEV_1/FVC ratio) Routine performance and reporting of quality control
High-resolution computed tomography	Can assess structural lung damage; Reported in 37% studies included	Reliance on established CF scoring systems; Frequent high doses of radiation if used routinely for disease monitoring; however, low-dose radiation	Identify the most relevant features and subscores for PCD; Develop and validate PCD-specific scoring system

Clinical outcome measure	Strengths	Limitations	Future directions
		modules are being developed	
Health-related quality of life	Patient-centred outcome measure; QOL-PCD was developed and validated for use in PCD	Lack of a minimal clinically relevant difference	Adopt QOL-PCD as outcome measure in prospective longitudinal studies; Use translated and cultural validated versions, where available Calculate minimal clinically relevant difference
Pulmonary exacerbations	Developed for use in PCD	Has not been validated	Validate definition; Use in future prospective studies

Figures legend

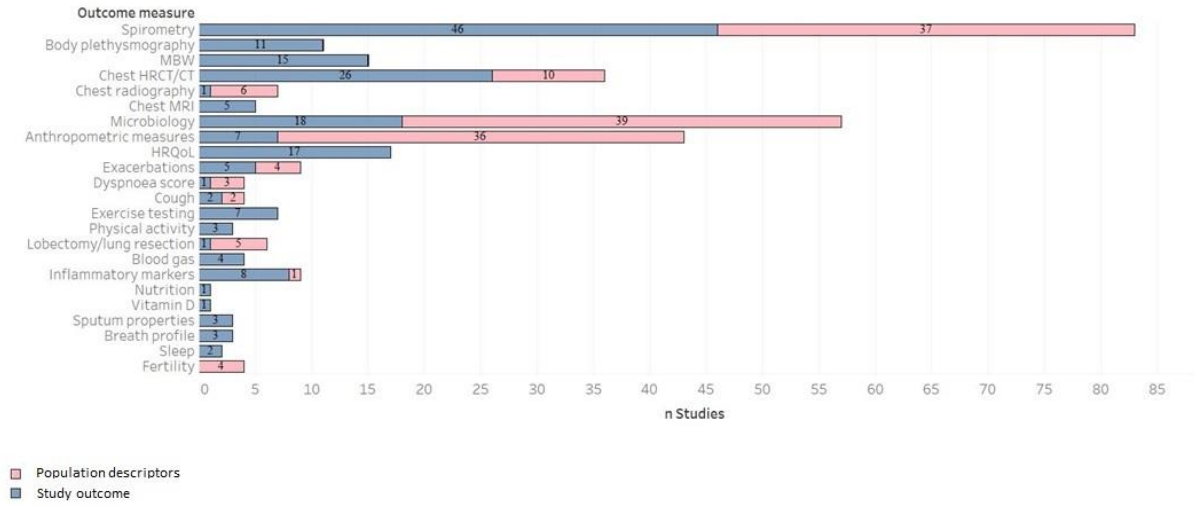


Figure 1. Number of studies that reported outcome measures in PCD as either study outcome or population descriptor. Studies often reported on more than one outcome measure and might therefore be featured in more than one instance.

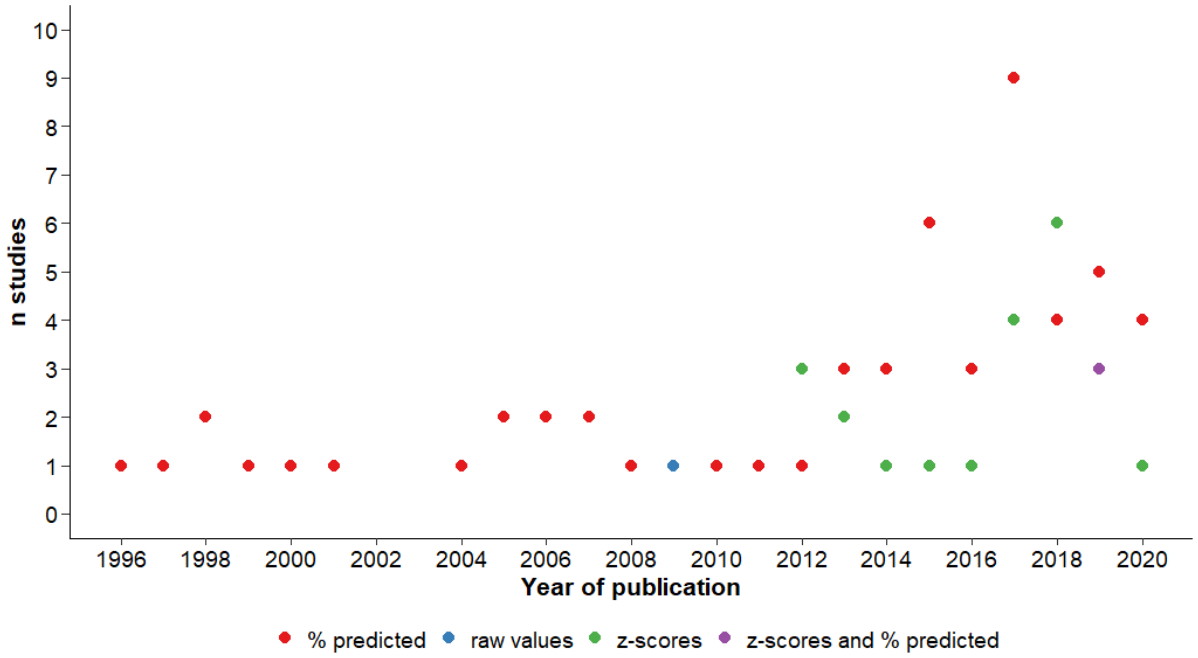


Figure 2. Number of studies that reported FEV_1 as study outcomes or population descriptors (*n*=83). Circles are coloured by the spirometric index presented in the studies.

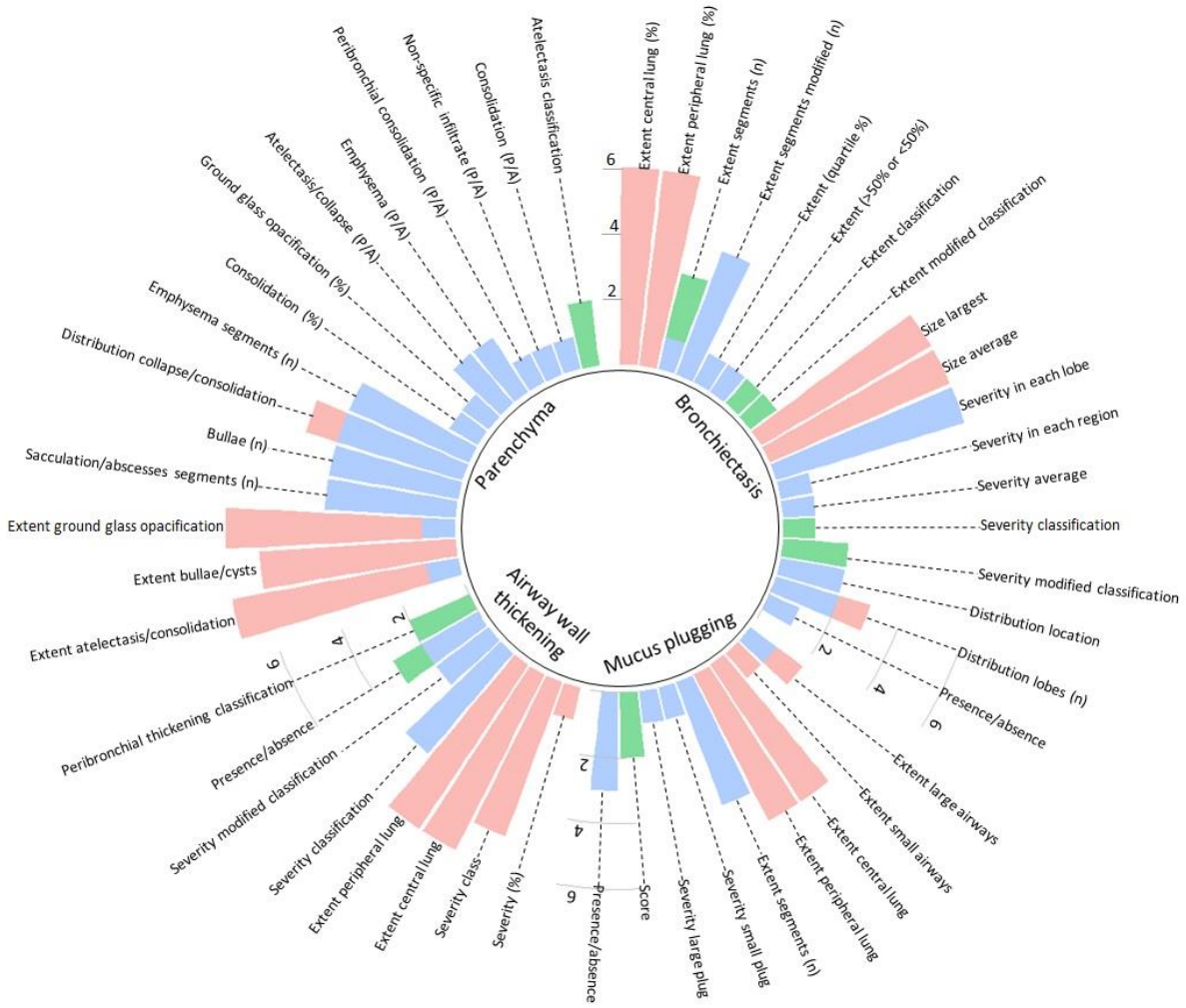


Figure 3. High-resolution computed tomography (HRCT) and computed tomography (CT) outcome measures from 23 studies that reported on HRCT/CT scans as study outcomes and had sufficient data on scoring system adopted. Stacked bars represent the number of studies that reported on each sub-score component.

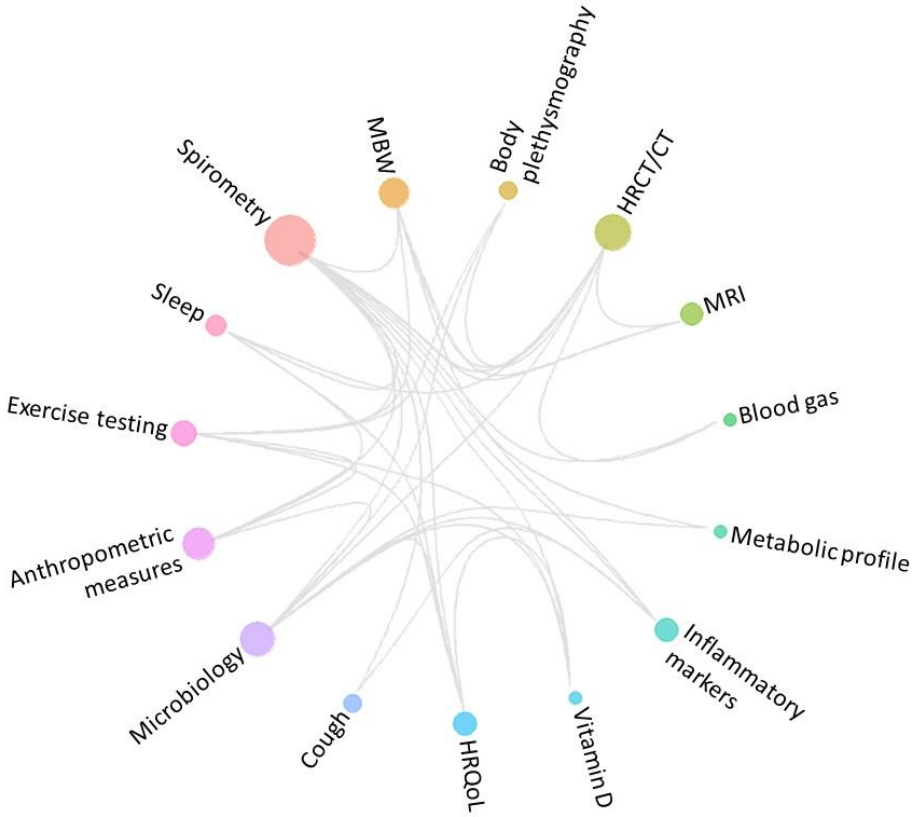
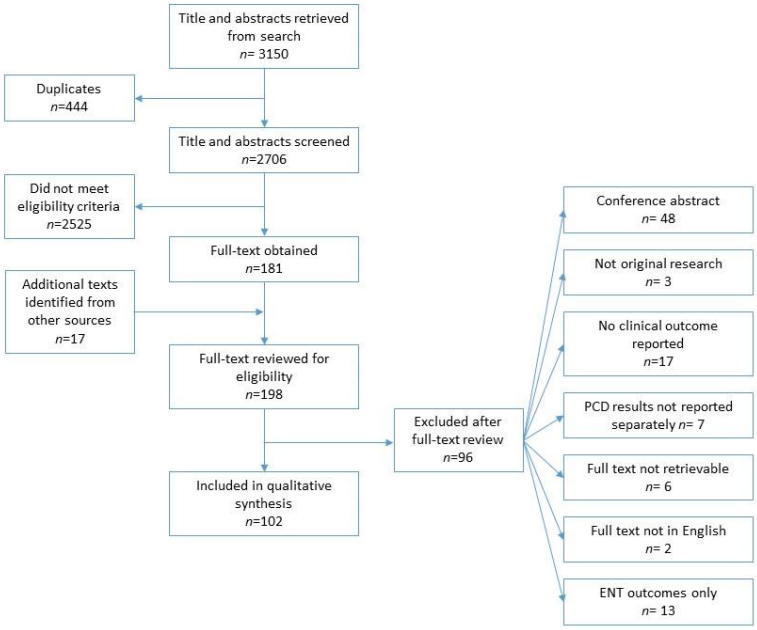


Figure 4. Correlations or associations between outcomes measures. Connections between circles depicts the correlated outcomes, with the size of each circle representing the number of studies that reported correlations or associations of that particular outcome.

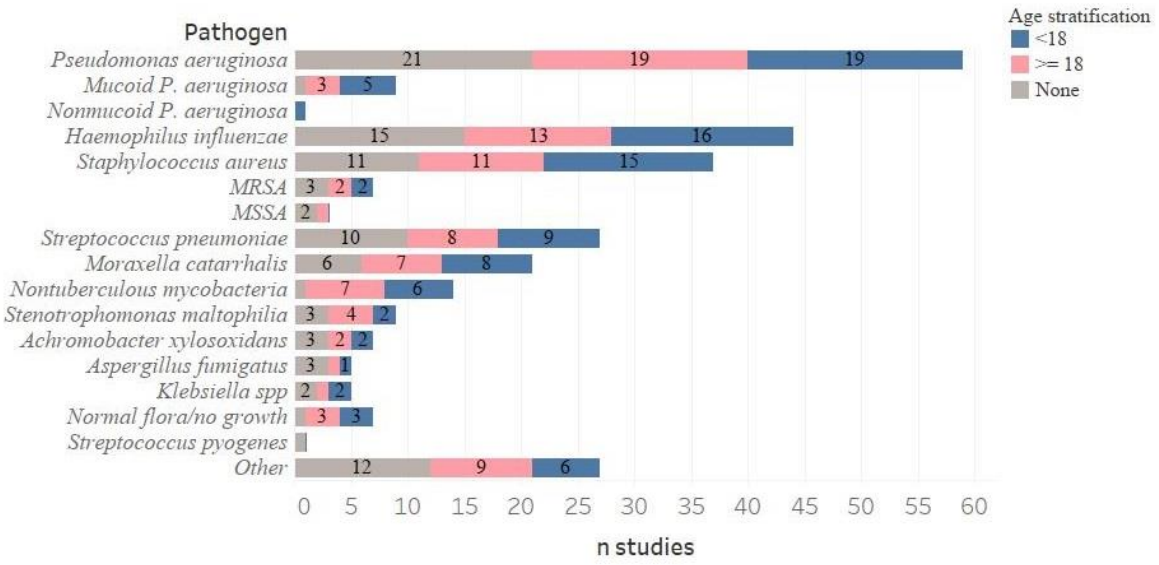
Figures footnote

Figure 1. MBW: multiple breath washout, HRCT: High-resolution computed tomography, MRI: magnetic resonance imaging, HRQoL: health-related quality of life.

Supplementary figures legend



Supplementary Figure 1. PRISMA flow diagram for the selection of studies reviewed and included in the systematic review.



Supplementary Figure 2. Number of studies that reported on each pathogen, stratified by age group (<18 and ≥18 years of age, or not differentiated). The "Other" category includes less frequently reported pathogens such as *Burkholderia cepacia, Candida albicans, Serratia marcescens, Achromobacter xylosoxidans, Aspergillus niger, Enterobacter cloacae, Escherichia coli, Proteus spp* and *Rhodococcus equi*.

Supplementary Figures footnote

Supplementary Figure 2. P. aeruginosa: *Pseudomonas aeruginosa*, MRSA: methicillin-resistant *Staphylococcus aureus*, MSSA: methicillin-sensitive *Staphylococcus aureus*

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Online supplementary files

Scoping reviews

Scoping reviews are similar to systematic reviews in terms of their structured systematic approach to synthesising the literature but differ in their aims (1-3). While systematic reviews focus on gathering evidence to address a specific question, scoping reviews map the relevant literature in the field of interest and therefore has a broader scope. Scoping reviews are useful to a) map the types of evidence that are available in a given field, particularly where this has not been comprehensively reviewed before; b) identify key concepts and definitions in the literature, highlighting inconsistencies; c) develop specific questions; and d) explore gaps in the existing literature.

We opted to perform a scoping review as it fulfilled our aims. We therefore mostly focused on reporting the clinical outcome measures that have been used in PCD research and not the findings themselves, using some of the more representative studies as examples of how these outcomes have been used and what was found throughout the manuscript.

Box 1. Key terms used in the search strategy in Embase, with results from each search term (*n* articles retrieved).

1. Exp kartagener syndrome/ (3011)
2. Exp ciliary motility disorders/ (4947)
3. primary ciliary dyskinesia.ti,ab. (3430)
4. 1 OR 2 OR 3 (6922)

5. exp respiratory function test/ or exp lung function test/ (426284)
6. exp vital capacity/ (38202)
7. exp spirometry/ (67349)
8. exp airway resistance/ (27257)
9. exp blood gas analysis/ (61158)
10. exp bronchial provocation test/ (12139)
11. capnometry/ or exp lung function test/ or patient monitoring/ (561554)
12. exp lung compliance/ (18950)
13. exp lung volume measurements/ (174399)
14. exp plethysmography, whole body/ (5794)
15. exp pulmonary gas exchange/ (33550)
16. Bronchiectasis.ti,ab. (26951)
17. exp bronchiectasis/co, di, dm, ep, et, pc, su [Complication, Diagnosis, Disease Management, Epidemiology, Etiology, Prevention, Surgery] (5957)
18. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (727603)

19. Outcome parameter$.mp. or Treatment outcome/ [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] (1823035)
20. exp hospital admission$/ or patient readmission/ or hospitalization/ (704024)
21. Hospital$.mp. (4223046)
22. mortality/ (846510)
23. morbidity/ (383659)
24. life expectancy/ (67955)
25. (Day$ antibiotic$ or antibiotic$ course$).mp. (3368)
26. Need for surgery.mp. (8952)
27. Quality of life/ (657721)
28. Disease progression (348419)
29. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (7289447)

30. Pulmonary exacerbation$.mp OR Disease exacerbation/ (278715)
31. Respiratory rate.mp (36742)
32. Monitoring, physiologic/ (57445)
33. Cough/ OR cough frequency.mp (56043)
34. Respiratory sounds/ OR respiratory frequency.mp OR breathing frequency.mp (25829)
35. Rhinomanometry/ OR exp Otorhinolaryngologic Surgical Procedures/ OR exp Otorhinolaryngologic Diseases/ (994984)
36. Sputum/ OR sputum clearance.mp OR sputum colo?r.mp (53716)
37. 30 or 31 or 32 or 33 or 34 or 35 or 36 (1467807)

38. Tomography, Emission-Computed/ or tomography.mp. (1919855)
39. Magnetic Resonance Imaging/ or MRI.mp. (1232707)
40. Radiography/ or Xray.mp. or Radiography.mp. (1057370)
41. Diagnostic Techniques, ontological/ OR Hearing tests/ OR Audiometry/ (52493)
42. Exp Otitis Media/ (63538)
43. Body mass index/ (499610)
44. Symptom score.mp OR symptom scale.mp (37036)
45. Inflammation/ or Inflammatory markers.mp or biomarkers/ (1134591)
46. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 (5276241)

47. 18 or 29 or 37 or 46 (12954712)
48. 4 AND 47 (5547)
49. limit 48 to (human and yr="1996 -Current") (2145)
50. remove duplicates from 49 (2112)

Supplementary Table 1. Characteristics of included studies

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Abitbul *et al* (2016) (112)	Israel	2012 to 2013	Multicentre prospective study	150	N/A	Mean (SD): 17.08 (11.96), median: 15.05, range: 0.15 to 60.47	At least one of the following: nNO + HSVA, TEM, IF or genetic testing	Inclusion: clinical symptoms consistent with PCD phenotype. Exclusion: acute respiratory infection 4 weeks prior to study
Ahmad *et al* (2015) (39)	UK	January 2008 to May 2014	Retrospective study	19	Healthy controls (17)	Median: 13.89	Not reported	Not reported
Alanin *et al* (2017) (64)	Denmark	November 2013 to February 2016	Prospective uncontrolled pre and post intervention cohort study	24	N/A	Median: 24, range: 10 to 65	Clinical phenotype + TEM, HSVA or genetic testing	Inclusion: definite PCD and above 6 years of age
Alanin *et al* (2015) (70)	Denmark	January 2002 to December 2012	Retrospective cohort	107	N/A	Median: 17, range 0 to 74	Clinical symptoms + (TEM, HSVA or genetic testing)	Definitive PCD diagnosis + microbiology data available

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Anagnostopoulou *et al* (2018) (40)	Switzerland, Germany	Not reported	Retrospective study	17	40	Mean: 11.8, range: 5.1–18.1	Not reported	Inclusion: free from acute respiratory disease for at least 2 weeks prior to testing. Exclusion: for healthy controls, patients with asthma or other respiratory disease, history of prematurity, and bone, neuromuscular or cardiac disease that could affect lung function were excluded.
Behan *et al* (2017) (71)	UK, USA, Canada	Between April 2014 and March 2016	Mixed cross-sectional and longitudinal study (for 10 participants that were re-assessed during an exacerbation)	72	N/A	Mean (SD): 34.8 (17.3) for UK, range 18 to 79; 31 (12.9) for USA/ Canada, range: 18 to 65	UK participants: clinical phenotype + HSVA and/or TEM. North American participants: clinical phenotype +	Adults (aged ≥18 years) with diagnosis of PCD in one of the specified diagnostic centres and ability to read and speak English fluently.

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
							TEM and/or genetic testing.	
Boon *et al* (2014) (113)	Belgium	Jan 1990 to August 2012	Retrospective study	168	N/A	Median (IQR): 17.7 (9.5 to 28.1)	(HSVA or TEM) + cell culture	Not reported
Boon *et al* (2015) (12)	Belgium	May 2011 and September 2014	Prospective observational study	38	Healthy controls (70)	Median (IQR): 16.1 (11.1 to 19.6)	HSVA + cell culture	Inclusion: chest HRCT within 1 year of the MBW measurement, and without exacerbations Exclusion: history of prematurity, asthma, allergy or recurrent respiratory symptoms
Bush *et al* (2006) (86)	UK	Not reported	Unclear	19	CF children (30)	Mean (SD): 9.5 (3)	nNO, CBF and TEM	Not reported
Carotenuto *et al* (2013) (72)	Italy	December 2011 to September 2012	Cross-sectional questionnaires	10	Healthy children and adolescents (34)	Range: 6 to 16	nNO, HSVA and TEM	Exclusion: upper and lower respiratory tract infection and asthma exacerbation, heart

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
								disease, mental retardation (IQ less than 70), epilepsy, and psychiatric disorders
Cockx *et al* (2017 a) (87)	Belgium	2012 to 2016	Case-control	36	Healthy controls (40); 21 children and 19 adults	Mean: 13, range 2 to 26	HSVA, cell culture, TEM, genetic testing	Clinically stable, defined as no change in cough or sputum, no fever, no change in therapy for a period of at least 2 weeks, change in forced expiratory volume in 1 second (FEV1) < 10% since the last measurement
Cockx *et al* (2017 b) (88)	Belgium	June 2012 to November 2016	Case-control	36	Health controls (numbers not reported)	Mean: 13, range 2 to 26	HSVA, cell culture, TEM, genetic testing	As above (see Cockx *et al* 2017 a)

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Cohen-Cymberknoh *et al* (2019) (82)	Israel	Not reported	Cross-sectional surveys	20	60 patients with CF	Mean (SD): Adults 25.8 (5.7), children 10.4 (3.5)	According to the ATS diagnostic guidelines (17)	Not reported
Cohen-Cymberknoh *et al* (2017) (65)	Israel, Belgium, Italy, Germany	January 2008 to December 2013	Retrospective study	217	N/A	Median (SD) 19.9 (13.9), range 0 to 67	According to European consensus (19)	Patients with follow-up data for at least 3 years + results from at least 2 sputum cultures
Cohen-Cymberknoh *et al* (2014) (51)	Israel	2007 to 2011	Cross-sectional study	34	CF patients (130); CF-PI (88), CF-PS (42)	Mean (SD): 15.9 (8.6)	Clinical phenotype + ((nNO + TEM), HSVA, genetic testing)	Confirmed diagnosis of PCD or CF + available spirometry, HRCT, sputum cultures and pancreatic sufficiency test
Davis *et al* (2015) (20)	USA, Canada	2006 to 2012	Cross-sectional study	118	N/A	Median (unclear): 8, range 5 to 11	TEM or genetic testing	<19 years of age and confirmed diagnosis of PCD

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Davis *et al* (2019) (21)	USA, Canada	2006 to 2011	Prospective, longitudinal, multicentre, observational study	137	N/A	Mean (SD): 7.8 (4.6)	TEM or genetic testing	<19 years at enrolment and ≥ 2 annual study visits and confirmed PCD
Dettmer *et al* (2018) (52)	Germany	2011 to 2017	Retrospective study	46	75 bronchiectasis patients	Median (range): 38 (18 to 72)	Patients with definite or probable PCD, according to Werner et al.	Exclusion: CT with insufficient quality due to a slice thickness >5mm or to severe motion artefacts
Eden *et al* (2019) (114)	USA	2008 to 2017	Longitudinal study	79	58 alpha-1 antitrypsin deficiency, 18 common variable immunodeficiency, 460 idiopathic	Mean (SD): 41.9 (14.5)	Characteristic clinical manifestations + genetic studies, mucosal biopsy, and nasal nitric oxide	Exclusion: Patients with CF

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Ellerman *et al* (1997) (22)	Denmark	Late 1970s to 1994, with minimum of 2 years follow-up	Prospective cohort	24	N/A	Median (range): 21 (2 to 56)	Clinical phenotype + HSVA + normal sweat test to exclude CF	Inclusion: confirmed diagnosis + regular spirometry. Exclusion: CF patients
Emiralioglu *et al* (2020) (115)	Turkey	January 2013 to December 2018	Cohort study	46	N/A	Median age at diagnosis (range): 8.5 (6 months to 15 years)	Clinical and radiological findings, nNO, HSVA, genetic testing, TEM	15 patients (out of the original 61) were excluded due to potential novel candidate genes
Frija-Masson *et al* (2017) (116)	France	1990 to 2010	Retrospective cohort	78	N/A	Median (IQR): 34.8 (28.6 to 47.1), range 18 to 77	Clinical phenotype or TEM or genetic testing	Not reported
Fuger *et al* (2018) (23)	France	2000 to 2015	Cross-sectional study from	42	73 CF	Median (IQR): 8.9 (6.4 to 13.5)	Typical clinical characteristics or suggestive clinical features +	Exclusion: immunodeficiencies, diseases that could alter

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
			retrospective cohort				TEM or genetic testing	PaO_2, pancreatic sufficient CF
Gokdemir *et al* (2014) (24)	Turkey	Not reported	Randomised controlled crossover study	24	N/A	Mean (SD): 12.9 (2.7), range 7 to 18	Clinical phenotype or TEM	Inclusion: clinical stability Exclusion: history of pneumothorax, massive hemoptysis or congestive heart failure
Goutaki *et al* (2017) (68)	Australia, Belgium, Cyprus, Denmark, France, Germany, Israel, Italy, Netherlands, Norway, Poland,	Up to April 2016	Cross-section of retrospective cohort	1609	N/A	Range: 0 to 19	Clinical characteristics, nNO, HSVA, TEM, genetic testing	All patients included in the international PCD cohort study

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
	Serbia, Switzerland, Turkey, UK, USA, Canada							
Green *et al* (2012) (41)	Denmark	Not reported	Cross-sectional prospective study (?)	27	N/A	Median: 11.3, range 6.3 to 18.5	Clinical phenotype + nNO, HSVA, TEM. CF and immunodeficiency were excluded	Patients <=18 years diagnosed with PCD + stable clinical condition on day of MBW measurement
Green *et al* (2016) (42)	Denmark	Not reported	Cross-sectional prospective study (?)	28	CF (61) and healthy controls (48)	Median (IQR): 12.4 (10.7 to 14.6)	According to consensus guidelines (19)	Diagnosed CF or PCD, age from 5 to 18 years; healthy controls without chronic or recurrent lung disease, fever, or symptoms of respiratory

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
								tract infection in the previous 4 weeks
Halbeisen *et al* (2018) (25)	Australia, Belgium, Cyprus, Denmark, France, Germany, Israel, Italy, Netherlands, Norway, Poland, Serbia, Switzerland, Turkey, UK	Up to April 2016	Cross-sectional retrospective study	991	N/A	Not reported	Clinical characteristics, nNO, HSVA, TEM, genetic testing	Inclusion: All patients in the international PCD cohort study that had data on FEV_1 and FVC. Exclusion: < 6 years, no lung function available, insufficient information to calculate z-scores

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Hellinckx *et al* (1998) (26)	Belgium	1996	Longitudinal study, no further details provided (?)	12	N/A	Mean (SD): 15.2 (7.0), range 6 to 32	Clinical phenotype + HSVA and TEM	Patients with PCD in regular follow-up for 3 to 20 years
Hoang-Thi *et al* (2018) (53)	France	November 2009 to July 2016	Retrospective study	62	N/A	Mean (SD): 39 (15)	According to the ESR guidelines (36)	Inclusion: CT exams performed between November 2009 and July 2016 + spirometric measurements performed within a 6-month period
Ioannou *et al* (2020) (73)	Cyprus	January 2017 to June 2019	Cross-sectional study	31	N/A	Median: 33.6	Combination of nNO, TEM, HSVA, and genetic testing	Patients with definite or highly likely diagnosis of PCD according to the ERS guidelines (36); age >18 years; and ability to speak and read Greek fluently

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Irving *et al* (2013) (45)	UK	Not reported	Case-control (?)	33	CF patients (127)	Mean: 24.66 Mean for subgroup of 21 PCD for HRCT: 31.2	According to Bush *et al* (39).	Not reported
Irving *et al* (2017) (44)	UK	2009 to 2010; 2014 to 2015	Prospective cohort	29	N/A	Median: 14, range 3 to 53	TEM or genetic testing	Not reported
Irving *et al* (2018) (43)	UK	Not reported	Cross-sectional study	69	N/A	Median (range): 13 (4 to 41)	nNO, HSVA, TEM, genetic testing	Definite or highly likely PCD according to European guidelines (36)
Jain *et al* (2007) (54)	UK	Not reported	Retrospective study	89	N/A	Median: 4, range 0 to 14.4	nNO, LM, TEM + tests to exclude CF and immunodeficiency	Not reported
Joensen *et al* (2014) (100)	Denmark	May 2013 to September 2013	Cross-sectional case-	21	CF patients (64) and healthy controls (21)	Median (IQR): 26.0	Clinical symptoms + abnormal ciliary	Exclusion for controls: active use of tobacco or a history of pulmonary

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
			control study (?)			(19.0 to 45.5)	beat pattern + TEM	disease, inflammatory disease, metabolic, or genetic disorders; fever or productive coughing 14 days prior to measurement
Kawakami *et al* (1996) (101)	Japan	Not reported	Cross-sectional questionnaires	48	N/A	Mean (SE): 38.4 (1.7), range 17 to 72	Clinical symptoms and/or TEM	Not reported
Kenis-Coskun *et al* (2019) (74)	Turkey	May 2018 to May 2019	Cross-sectional study	19	44	Mean (SD, range): 10.31 (1.73, 7 to 13)	TEM or low nNO or dextrocardia + typical clinical findings	Exclusion: acute exacerbation or hospital admittance in the last 2 weeks
Kennedy *et al* (2007a) (102)	USA	August 2003 to March 2006 for prospective study;	Mixture of prospective and retrospective study	142	N/A	Mean (SD) for *n*=7 with outcome measure: 56 (7)	TEM (only reported for *n*=7)	Not reported

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
		Prior to August 2003 for retrospective study						
Kennedy *et al* (2007b) (55)	USA	January 1995 to May 2006	Retrospective cross-sectional (?)	45	N/A	Mean (SD): 29 (3)	Clinical phenotype + TEM, nNO	Chest CT available from cohort of 140 PCD patients (46)
Knowles *et al* (2014) (117)	USA	Not reported	Cross-sectional study	90	N/A	Mean (SD): 35.3 (18.6) (RSPH1 mutations) Mean (SD): 34.2 (17.6) (75 age- and sex matched)	TEM or genetic testing	Not reported

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Kobbernagel *et al* (2019) (46)	Denmark	Not reported	Single-centre, prospective, observational, longitudinal study	42	N/A	Median (range): 15.4 (6.5 to 29.7)	HSVA, TEM, genetic testing	School-aged children and young adults (aged >5 to <30 years) with a confirmed diagnosis of PCD, and clinically stable at the baseline visit
Kobbernagel *et al* (2020) (92)	Denmark, Germany, Netherlands, Switzerland, UK	June 2014 to August 2016	Multicentre, double-blind, randomised, placebo-controlled phase 3 trial	90	N/A	Range: 7 to 50	Clinical characteristics, nNO, HSVA, TEM, IF, genetic testing	Inclusion: predicted FEV_1 >40%; received at least 30 days of antibiotics for respiratory tract infections or exacerbations within the preceding 2 years; currently received no systemic or inhaled maintenance antibiotics; and had not taken azithromycin within 1 month before screening.

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
								Exclusion: current infection (at screening) with *Achromobacter xylosoxidans* or *Burkholderia cepacia* complex, infection with non-tuberculous mycobacteria within 6 months, or chronic infection with *Pseudomonas aeruginosa* (defined as culture of *Pseudomonas aeruginosa* in 50% or more of the sputum samples within the last year, provided at least three sputum cultures were available). Other exclusions were:

Authors (year of publication)	Countries of data collection	Data collection period	Study design	*n* PCD patients	Reference group (*n*)	Age PCD patients (years)	PCD diagnostics	Inclusion/exclusion criteria
								allergic reaction to macrolide antibiotics or other ingredients of the study drug; alanine transaminase twice or more the upper limit of normal or history of portal hypertension; serum creatinine concentrations greater than 150 µmol/L or glomerular filtration rate of less than 50 mL/min; prolonged QT interval, cardiac arrhythmia, severe heart failure, or electrolyte disturbances; myasthenia gravis; treatment with medicinal

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
								products known to possibly interact with azithromycin or prolong QT interval (appendix p 1); pregnancy, breastfeeding, or fertile women using unreliable contraception; or use of home oxygen or assisted ventilation
Koh *et al* (2000) (27)	South Korea	Not reported	Randomised double-blinded, placebo-controlled, cross-over study	19	N/A	Median: 12, range 7 to 16	TEM	Children that could perform spirometry

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Koucky *et al* (2020) (47)	Czech Republic	Not reported	Cross-sectional study	11	24 CF, 15 allergic bronchial asthma, 19 control	Median (range): 7.8 (0.6 to 15.8)	TEM	Patients with confirmed PCD diagnosis
Li *et al* (2005) (56)	UK	1986 to 2002	Retrospective study	20	N/A	Not reported	Clinical phenotype, nNO (14% of cases), LM (49% of cases), TEM (70% of cases)	Inclusion: HRCT-diagnosed bronchiectasis in subjects with suggestive clinical features Exclusion: CF diagnosed by sweat test and/or analysis of genetic testing.
Loomba *et al* (2017) (94)	USA (isomerism patients and healthy	January 1998 to December 2014	Retrospective case-control study (?)	17	Healthy controls (17), patients with Fontan + isomerism (17), patients with	Mean (SD): 13.36 (3.5)	Not reported, but used the same cohort as Madsen *et al* (54)	Not reported

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
	control) and Denmark (PCD patients)				Fontan - isomerism (17)			
Lopes *et al* (2015) (28)	Brazil	Not reported	Cross-sectional study	11	Tuberculosis patients (34), non-tuberculosis infection (29), CF (21), rheumatoid arthritis (17)	Mean (SD): 56 (18.7)	Clinical phenotype + TEM	Inclusion: individuals with bronchiectasis based on HRCT findings, clinically stable, no history of smoking, and >=18 years of age. Exclusion: history or diagnosis of asthma (n= 18) or a pleural (n= 10) or cardiovascular disease; subjected to lung resection (n= 4) or used oral corticosteroids 4 weeks before the study;

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
								unknown cause of bronchiectasis (n= 35); traction bronchiectasis secondary to interstitial lung disease.
Madsen *et al* (2013) (95)	Denmark	Not reported	Case-control study	44	Healthy controls (33)	Median (IQR): 14.8 (6.5 to 29.7)	Clinical phenotype, nNO (n=42), HSVA (n=42), TEM (n=39) (19)	Inclusion: children and young adults; healthy age-, gender- and BMI-matched non-atopic subjects with normal spirometry as controls. Exclusion: unable to perform pulmonary function testing or exercises (e.g mental or physical disability or known cardiovascular disease)

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Maglione *et al* (2012) (57)	Italy	2007 to 2010	Retrospective cohort study	20	N/A	Median: 11.6, range 6.5 to 27.5	HSVA, TEM	Inclusion: availability of CT scan and spirometry at some time point during the follow-up in stable patient, and of a second CT scan plus spirometry during exacerbation. Exclusion: < 6 years of age, unable to perform spirometry, or had only one CT scan during follow-up
Maglione *et al* (2014a) (29)	UK, Italy and Denmark	UK: 1990 to 2011 Denmark: 1979 to 2011 Italy: 1994 to 2011	Cross-sectional and longitudinal study (?)	158	N/A	Median at first spirometry: 8.7, range 4.2 to 17.4	TEM	Ability to perform reliable spirometry, and availability of annual anthropometric and spirometry data over the last 3 years

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Maglione *et al* (2014b) (75)	Italy	Not reported	Prospective questionnaire	20	N/A	Median: 16.9; range 12 to 33.4	Not reported	Not reported
Maglione *et al* (2017) (58)	Italy	January 2014 to May 2015	Prospective, single-center	20	CF patients (20)	Median: 15.1, range 8.7 to 29.4	nNO, HSVA, TEM, genetic testing	Mild CF patients: selected according to the functional criteria described by Schluchter *et al* (60). PCD patients: stable lung disease, without acute dyspnea or cough, no pulmonary function changes and no requirement for intravenous antibiotics in the previous 4 weeks. Exclusion: acute respiratory infection, developmental delay, or

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
								other conditions that could compromise compliance to MRI or spirometry e.g. age < 6 years, claustrophobia.
Magnin *et al* (2012) (59)	France	1988 to 2010	Retrospective cohort study	20	N/A	Median (IQR) at first visit: 4.7 (1.7 to 7.9), range 0 to 13.8	Clinical phenotype, HSVA, TEM, computerised EM (for IDA defects, after 2002)	Inclusion: age < 15 years at the beginning of follow-up, at least 8 years of follow-up, at least 2 concurrent CT and lung function tests available in a phase of clinical stability of the lung disease without modification of the treatment regimen in the last 4 weeks.

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Marino *et al* (2019) (103)	UK	September 2016 top April 2017	Prospective study	43	N/A	Range: 0 to 16	According to the ERS guidelines (36)	Not reported
Marthin *et al* (2010) (30)	Denmark	Late 1970s onwards	Partly cross-sectional and partly designed as an uncontrolled, observational, single-group, single-centre, longitudinal and retrospective study of prospectively collected data	74	N/A	Median at first visit (1979): 9, range 4.4 to 43.7	(Clinical phenotype + HSVA), (nNO, TEM, pulmonary radioaerosol mucociliary clearance) in most patients	Inclusion: at least 1.5 years of follow-up and acceptable spirometry Exclusion: uncertain diagnosis, unable to perform reliable spirometry and nonvalid LF measurements

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
McManus *et al* (2003) (76)	UK	January 2003 to April 2013	Cross-sectional (questionnaires)	93	N/A	Median 16.5 (IQR 10.8 to 31.3)	Not reported	Patients on the mailing list of the UK's PCD Family Support Group
McManus *et al* (2006) (77)	UK	January 2003	Cross sectional (questionnaires)	71	N/A	Median (IQR): 20.1 (15.6 to 38.7)	Not reported	Patients on the mailing list of the UK's PCD Family Support Group
Mirra *et al* (2015) (104)	Italy	March to June 2012	Prospective, cross-sectional study	22	N/A	Median: 10.5, range 2 to 34	HSVA, TEM	Inclusion: stable patients with confirmed diagnosis of PCD, according to Maglione *et al* (56) Exclusion: airway infections or asthma exacerbations during the 4 weeks prior to enrolment, current smoker, long term use of oral steroids, antibiotic

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
								treatment in the last 4 weeks before enrolment, prescription of over-the-counter calcium or vitamin-D supplements prior to, or during the study period.
Montella *et al* (2009a) (60)	Italy	Not reported	Prospective, cross-sectional study	13	N/A	Median: 15.2; range 10.4 to 29.3	LM, TEM	Not reported
Montella *et al* (2009b) (61)	Italy	March 2007 to June 2008	Prospective, cross-sectional study	14	Primary immunodeficiency patients (14), recurrent pneumonia (13)	Median: 15.2, range 10.4 to 29.3	Clinical phenotype, LM, TEM	Inclusion: patients with PCD, chronic lung disorders, primary immunodeficiency, recurrent pneumonia Exclusion: acute respiratory infection and/or mental retardation or other

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
								conditions that could compromise compliance to HRCT and MRI (e.g. age <5 years, claustrophobia)
Montuschi *et al* (2014) (105)	Italy	Not reported	Cross-sectional study	45	Primary analysis: CF (21), age-matched healthy controls (21) Validation subjects: CF (25), age-matched healthy controls (25)	Mean (SD) primary Analysis: 17.4 (0.9), range 11 to 32 Mean (SD) validation subjects: 15.7 (0.6), range 11 to 31	PCD and CF were diagnosed according to published criteria (70, 71)	Not reported

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Noone *et al* (1999) (106)	USA	Not reported	Double blind, randomised, crossover study	12	N/A	Mean: 34, range 14 to 71	TEM	Exclusion: significant intercurrent infection, defined as a change in cough or sputum production or increased dyspnea within 2 weeks of screening
Noone *et al* (2004) (118)	USA	1994 to 2002	Cohort study	78	N/A	Mean: 26.8; median: 29, range 0 to 73	Clinical phenotype, nNO, HVSA, TEM	Exclusion: atypical asthma, CF, allergic bronchopulmonary aspergillosis, Young's Syndrome, and idiopathic bronchiectasis
Nyilas *et al* (2017) (48)	Germany and Switzerland	March 2013 to April 2015	Cross-sectional multicentre study	49	37	Mean (SD): 14.7 (6.6), range 11 to 18	Clinical phenotype, HSVA + (TEM, IF or genetic testing)	Not reported

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Nyilas *et al* (2018) (49)	Germany	April 2015 to February 2016	Prospective cross-sectional, single-centre, observational study	30	N/A	Median (range): 13.4 (5 to 28)	According to ERS consensus (76)	Absence of acute pulmonary exacerbation during the last 3 weeks before the study
Oktem *et al* (2013) (83)	Turkey	Not reported	Cross-sectional study	29	29	Mean (SD): 10.0 (5.9), range 0.5 to 24	Clinical phenotype, TEM	Not reported
Olveira *et al* (2017) (31)	Spain	2002 to 2011	Multicenter, nested cross-sectional study from Spanish registry	60	Other causes of bronchiectasis (n = 1987)	Mean (SD): 42.9 (18.8)	Clinical phenotype, nNO, TEM, saccharin test and labelled seroalbumin for differential diagnosis	Adult patients with bronchiectasis

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Paff *et al* (2013) (107)	The Netherlands	August to November 2011	Cross-sectional case–control study	25	CF (25), healthy controls (23)	Median (IQR): 10.7 (7.1 to 14.5)	Clinical phenotype, HSVA, TEM (19)	Exclusion: children with any pulmonary, inflammatory or metabolic disease.
Paff *et al* (2017) (89)	The Netherlands	April 2014 to May 2015	Double blind randomised controlled crossover trial over a 28-week period with 4 weeks washout	22	N/A	Median (IQR): 47.6 (26.9 to 58.1)	Not reported	Inclusion: ≥ 18 years, clinically stable, FEV_1 had to be at least 40% of the predicted value for height, age and sex and within 10% of the best value obtained during the previous six months. Exclusion: women with a current or intended pregnancy or who were breastfeeding, cigarette smokers, known quinine sulphate allergy, or in use of the following

Authors (year of publication)	Countries of data collection	Data collection period	Study design	*n* PCD patients	Reference group (*n*)	Age PCD patients (years)	PCD diagnostics	Inclusion/exclusion criteria
								medications: hypertonic saline, rhDNAse, N-acetylcysteine or non-routine antibiotics in the previous 4 weeks. Participants whose oxygen saturation fell under 90% or whose FEV_1 fell more than 15% compared to its prebronchodilator value 15 minutes after inhalation of a test solution with hypertonic saline and taste-masking agent, were not eligible to proceed in the trial.

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Phillips *et al* (1998) (32)	UK	Not reported	Cross-sectional	12	12	Median: 11, range 7 to 15	Clinical phenotype, HSVA, TEM	Inclusion for healthy controls: siblings, friends or family friends of the children with PCD with no history of chronic or recent acute respiratory problems, no use of medications, and normal physical examination and spirometry.
Piatti *et al* (2020) (93)	Italy	2007 to 2017	Single-centre, retrospective, cross-sectional study	58	N/A	Children mean (range): 11.1 (2 to 17) Adults mean (range): 39.4 (19 to 70)	Cardiac situs, nNO, HSVA, TEM, genetic testing	Clinical cases of PCD that have been diagnosed and followed-up during the last 10 years
Pifferi *et al* (2010) (78)	Italy	Dec 2007 to May 2008	Cross-sectional	78	N/A	Mean (SD): 21.4 (12.9),	HSVA + TEM	Not reported

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
			(questionnaires)			range 1.7 to 48.5		
Pifferi *et al* (2012) (33)	Italy	March 2008 to May 2010	Cross-sectional	50	N/A	Median (IQR) for children: 11 (5.25); n=26 Median (IQR) for adults: 30.5 (9.5), range 18 to 47; n=24	LM, TEM, cell culture	Not reported
Pifferi *et al* (2015) (119)	Italy	Not reported	Cross-sectional	45	53	Median (IQR): 14 (22.25)	nNO, (HSVA + TEM, n=37), (HSVA + cell culture, n=8)	Not reported
Pifferi *et al* (2017) (108)	Italy	Not reported	Cross-sectional and prospective	51	35 secondary ciliary dyskinesia, 10 controls	Median (IQR): 24.5 (22.9)	HSVA, TEM, cell culture, according to ERS	All subjects aged ≥6 years, with a diagnosis of PCD. For secondary

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
			longitudinal (subset)				consensus and guidelines (36, 76)	ciliary dyskinesia, PCD was excluded as reported in Pifferi *et al* (87).
Ratjen *et al* (2016) (90)	Canada	Not reported	Cross-sectional + prospective cohort study	35	17	Median (IQR): 11.0 (6.8 to 15.3)	Clinical phenotype, nNO, TEM, genetic testing	Inclusion: at least 6 years at enrolment; ability to perform reproducible spirometry meeting ATS standards; ability to produce sputum spontaneously; clinically stable at the time of assessment Exclusion: use of IV antibiotics or oral quinolones within previous 14 days; use of inhaled antibiotics within the previous 28 days; recent history of

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
								pneumothorax or haemoptysis; patients with *P. aeruginosa* or *Burkholderia cepacia* complex infection (for CF only)
Ring *et al* (2018) (96)	Denmark	Not reported	Prospective, observational, single-centre, cohort study	36	61 CF patients	Mean (range) at visit 1: 11.8 (6 to 18) Mean (range) at visit 2: 12.9 (7 to 18)	Clinical characteristics, nNO, HSVA, TEM	Inclusion: all patients with a definite diagnosis of PCD Exclusion: not able to perform exercise test or loss to follow between study visits
Roden *et al* (2019) (66)	Germany	2010 to March 2016	Cross-sectional and retrospective longitudinal study	106 cross-sectional; 28	N/A	Cross-sectional median (range): 13 (0 to 71)	According to ERS guidelines (36)	All patients with at least one respiratory specimen were included for cross-sectional analysis; all patients with at least 4

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
				longitudinal		Longitudinal median (range): 8 (0 to 41)		respiratory specimens for the longitudinal analysis
Rogers *et al* (2013) (67)	UK	July 2012 to February 2013	Cross-sectional	24	N/A	Median: 15, range 4 to 73	According to international diagnostic guidelines (no further details)	Not reported
Santamaria *et al* (2008) (84)	Italy and the Netherlands	Not reported	Cross-sectional, mixed retrospective and prospective study	20	CF (50) from a previously published cohort of 119 CF patients	Median: 14.3, range 4.6 to 27.5	LM, TEM	Not reported
Santamaria *et al* (2014) (84)	Italy	Not reported	Cross-sectional,	16	42	Median: 10.4, range 4.9 to 17.2	HSVA, TEM	Inclusion: lung disease stability, ability to perform reliable

Authors (year of publication)	Countries of data collection	Data collection period	Study design	*n* PCD patients	Reference group (*n*)	Age PCD patients (years)	PCD diagnostics	Inclusion/exclusion criteria
			prospective study					pulmonary function tests, availability of a chest HRCT obtained in stable conditions in the preceding 3 months Exclusion: airway infections and asthma exacerbation 4 weeks before the enrolment; symptomatic heart disease; need for chronic oxygen administration; corticosteroids or bronchodilators use during the previous 2 weeks or 24h, respectively; use of anticonvulsant or psychoactive drugs;

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
								craniofacial abnormalities, neuromuscular disorders or concomitant genetic diseases such as Trisomy 21 or Prader–Willi syndrome
Shah *et al* (2016) (34)	UK	1980 to 2014	Retrospective cohort study	151	N/A	Median (IQR) in 2014: 35 (26 to 47), range 19 to 75	Clinical phenotype, nNO, LM, TEM; 3% were diagnosed on clinical symptoms alone	Not reported
Shoemark *et al* (2009) (109)	UK	March 2005 to March 2007 and January 2006 to June 2006	Case-control	20	Non-PCD bronchiectasis (20), healthy controls (20)	40 (95%CI 32-45)	LM, TEM	Inclusion for healthy controls: no history of respiratory disease and free from bacterial or viral infections for 8 weeks before study

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
								Exclusion: Current smokers, CF patients (screened by sweat test, followed by CF genotyping), history of asthma
Simsek *et al* (2018) (97)	Turkey	December 2013 to March 2014	Unclear	31	29 healthy controls	Mean (SD): 13.3 (3.0)	According to the ERS guidelines (36)	Clinically stable with no change in medication for at least 3 weeks, and able to cooperate with the measurements
Sismanlar *et al* (2018) (85)	Turkey	Not reported	Case-control study	15	31 healthy controls	Mean (SD): 12.4 (0.88)	Clinical symptoms, nNO, HSVA, TEM	Exclusion: acute upper and/or lower airway infection, chronic oxygen supplementation, inability to perform pulmonary function tests, patients with other chronic diseases

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Smit *et al* (1996) (110)	The Netherlands	1952 to 1994	Retrospective cohort study	21	N/A	Age at present, (range): 46 (32-61) for lung resection group (n=13); 46 (24-66) for group without lung resection (n=8)	Clinical phenotype (n=8) or TEM + HSVA (n=13)	Exclusion: language barrier, psychiatric problems, and living abroad
Smith *et al* (2018) (50)	UK	Not reported	Multi-centre cross-sectional study	11	N/A	Mean: 13.3	Not reported	Free from pulmonary exacerbation on the day of testing and not undergoing any new acute treatments

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Sunther *et al* (2016) (35)	UK	January 2003 to April 2013	Retrospective cohort study	30	N/A	Median: 11.4, range 6 to 16.2	Clinical phenotype, nNO, HSVA, TEM	Inclusion: aged 6 to 16 years, able to perform spirometry, history of at least one pulmonary exacerbation Exclusion: incomplete set of spirometric assessments
Svobodova *et al* (2013) (69)	Czech Republic	Not reported	Retrospective cohort study	29	N/A	Median: 14.5, range 1.5 to 24	Clinical phenotype, HSVA, TEM, genetic testing (for ODA only)	Not reported
Tadd *et al* (2019) (63)	Australia	Not reported	Multi-centre cross-sectional study	41	N/A	Mean (range): 13 (2 to 48)	According to the ATS guidelines (17)	Undergone at least 1 CT scan when clinically stable.
Tamalet *et al* (2001) (36)	France	1989 to 1999	Prospective cohort (unclear)	43	N/A	Mean (SD): 5.8 (3.3),	CBF, TEM	Exclusion: any known pathologic conditions, such as cystic fibrosis,

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
						range 1 to 13		α1-antitrypsin deficiency or immunodeficiency
Valerio *et al* (2012) (98)	Italy	June 2007 to December 2008	Cross sectional study	10	8	Mean (SD): 13.2 (2.8)	LM, TEM	Exclusion: unable to perform spirometry or maximal cardiopulmonary exercise testing, acute upper or lower airway infections, and any concurrent medical illness at the time of the study
Valero-Moreno *et al* (2020) (79)	Spain	Not reported	Cross-sectional study	12	36 healthy controls	Mean (SD, range): 12.96 (2.71, 9 to 18)	Not reported	Not reported
Vallet *et al* (2013) (37)	France	Not reported	Retrospective study	60	N/A	Range 0 to 15	Clinical phenotype, HSVA, TEM	Not reported

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Videbaek *et al* (2019) (38)	Denmark	Not reported	Retrospective longitudinal study	85	N/A	Median (range): 8.6 (4.4 to 63.6	According to ERS guidelines and consensus (36, 76)	Known genotype and at least 2 years of lung function measurements
Wells *et al* (2011) (99)	Canada	Not reported	Observational study	10	CF (20), healthy controls (20)	Mean (SD): 13.8 (2.3)	Not reported	Inclusion: clinical stability, FEV_1 > 70% predicted, good nutritional status (BMI z score -2 ± 2) Inclusion for CF: free of a recent pulmonary exacerbation in the 3 months preceding recruitment, normal oral glucose tolerance tests near the time of the magnetic resonance spectroscopy testing

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
Whalley *et al* (2006) (80)	UK	July 2005 to January 2006	Prospective qualitative interview study (matched-pairs design)	12	N/A	Mean: 49.8, range 27 to 65	Not reported	Inclusion: living within 250 km from London Exclusion: < 18 years
Yiallouros *et al* (2015) (120)	Cyprus	1998 to 2013	Cross-sectional	30	N/A	Median: 24.3, range 0.7 to 63.7	TEM + (nNO, HSVA)	Not reported
Zengin Akkus *et al* (2019) (81)	Turkey	Not reported	Cross-sectional study	14	17 CF, 15 healthy controls	Mean (SD): 46.5 (17.5)	According to the ERS consensus (76)	Exclusion: known neurologic disease
Zihlif *et al* (2005) (111)	UK	Not reported	Cross sectional prospective study	20	10	Median (IQR): 10.8 (9 to 14)	Clinical phenotype, nNO, CBF, TEM	Inclusion: at least 7 years old, able to perform reproducible spirometry, and stable pulmonary disease Exclusion: positive

Authors (year of publication)	**Countries of data collection**	**Data collection period**	**Study design**	***n* PCD patients**	**Reference group (*n*)**	**Age PCD patients (years)**	**PCD diagnostics**	**Inclusion/exclusion criteria**
								sputum culture or baseline FEV_1 of less than 40% predicted
Zihlif *et al* (2006) (91)	UK	Not reported	Cross sectional prospective study	23	11	Median (IQR): 10.3 (9 to 14)	Clinical phenotype, nNO, CBF, TEM	Inclusion: at least 7 years old, able to perform reproducible spirometry, and stable pulmonary disease Exclusion: positive sputum culture or baseline FEV_1 of less than 40% predicted

PCD: Primary ciliary dyskinesia, N/A: not applicable, SD: standard deviation, nNO: nasal nitric oxide, HSVA: high-speed video microscopy analysis, TEM: transmission electron microscopy, IF: immunofluorescence, MBW: multiple breath washout, CF: cystic fibrosis, CBF: ciliary beat frequency, IQ: intelligence quotient, HRCT: high-resolution computed tomography, CF-PI: cystic fibrosis with pulmonary insufficiency, CF-PS: cystic fibrosis with pulmonary sufficiency, LM: light microscopy, CT: computed tomography, IDA: inner dynein arm defect, MRI: magnetic resonance imaging, ATS: American Thoracic Society, ODA: outer dynein arm defect, FEV_1: forced expiratory volume in 1 second, BMI: body mass index.

Supplementary Table 2. Definition of outcome measures, stratified by study outcome and population descriptor

Authors (year of publication)	**Study outcomes**	**Population descriptors**	**Definition of outcome measures**
Main study outcome: Spirometry and/or body plethysmography			
Davis *et al* (2015) (20)	**Anthropometry** (height, weight and BMI percentile), **spirometry** (FEV_1 and FEF_{25-75} % predicted, infant $FEV_{0.5}$, infant $_{25-75}$ z score), **CT** (n lobes with bronchiectasis, n lobes with alveolar consolidation)	**Microbiology**	Spirometry: performed according to ATS/ERS criteria and overread for quality. Spirometric measurements were expressed as percent predicted and infant lung function as z-scores. Chest CT images were scored for the presence of bronchiectasis and parenchymal disease in six lobes, including the lingula as a lobe, using the Brody score.
Davis *et al* (2019) (21)	**Spirometry** (FEV_1 % predicted)**,** **Anthropometry** (weight percentile, height percentile,	None	Reported above (see Davis *et al*, 2015)

Authors (year of publication)	**Study outcomes**	**Population descriptors**	**Definition of outcome measures**
	BMI percentile)**,** **Microbiology**		
Ellerman *et al* (1997) (22)	**Spirometry** (FEV_1 and FVC % predicted)	**Chest radiography** (presence of bronchiectasis), **microbiology**	Spirometry: the best of 3 valid attempts was used as outcome. Published reference values for children and complied Danish reference values for adults were used. Spirometry was measured 3 to 4 times per year and the annual lung function is reported as the mean of the measurements performed at the clinic during the previous years.
Fuger et al (2018) (23)	Capillary blood test (PaO2, PaCO2, PaO2/PaCO2 z-scores), spirometry (FEV1, FVC, FEF25-75 and FEV1/FVC z-scores, RV, RV/TLC, and TLC % predicted)	CT (presence of bronchiectasis), anthropometry (BMI z-scores), microbiology (presence of Pseudomonas aeruginosa in sputum)	Capillary blood test: Ear lobe capillary blood gas was performed and the mean of 2 to 4 capillary results was recorded.
Gokdemir *et al* (2014) (24)	**Spirometry** (FEV_1, FVC, PEF, FEF_{25-75} % predicted), **comfort and efficacy**	**Anthropometry** (weight and height z-scores)	Spirometry: performed according to the ERS/ATS guidelines. Measurements were taken at the same time of the day before and after 30 min period following the last treatment session of conventional pulmonary rehabilitation or high-frequency chest wall oscillation on the 1^{st} and 5^{th} day.

Authors (year of publication)	**Study outcomes**	**Population descriptors**	**Definition of outcome measures**
	(questionnaire score), **SpO_2**		SpO_2 was measured transcutaneously at rest, for 5 min immediately before, 30 min during and 30 min immediately following each session. SpO2 was measured with a fingertip pulse oximeter. Perceived efficiency and comfort level: patients completed a written questionnaire to rate comfort and efficiency of the two modalities with a 5-point scale (extremely = 4, very = 3, somewhat = 2, not very = 1, and not at all = 0).
Halbeisen *et al* (2018) (25)	**Spirometry** (FEV_1, FVC z-scores and % predicted)	**Anthropometry** (BMI)	FEV_1 and FVC z-scores adjusted for age, sex, height and ethnicity, and % predicted values using the GLI 2012 reference values. For patients with multiple measurements, the measurement recorded at the youngest age was used. Patients under the age of 6 years were excluded to ensure better measurement quality and comparability with published CF data.
Hellinckx *et al* (1998) (26)	**Spirometry** (FEV_1, FVC, change in FEV_1 and FVC % predicted), **body plethysmography** (thoracic gas volume, total lung capacity, residual volume, and airway resistance)	**None**	Spirometry: according to ERS guidelines, the best of 3 maximal expiratory flow volume manoeuvres was analysed. All measurements were expressed as % of predicted values for sex and height according to Zapletal *et al*. Body plethysmography: single breath diffusing capacity and Krogh factor were measures according to ERS guidelines (136). FEV_1, vital capacity and Raw % predicted were calculated according to Zapletal *et al*. TLC, RV, thoracic gas volume and single breath diffusing capacity % predicted were calculated according to ERS guidelines. Reference values for total respiratory system resistance and reactance were according to Duiverman *et al*.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			All tests were done before and 20 min after administration of 200 µg of salbutamol. Drug dose was chosen according to Bibi *et al*.
Koh *et al* (2000) (27)	**Spirometry** (FEV_1 % predicted, $\Delta FFEV_1$, PC_{20} (provocation concentration of metacholine producing a 20% fall in FEV_1, $M\Delta FFEV_1$)	**None**	Spirometry was performed after 3 weeks of regular use of medication. The largest value of the triplicate FEV_1 at each time point was adopted for analysis. High-dose methacholine inhalation tests were carried out by using a modification of the method described by Chai *et al*. Each subject inhaled 5 inspiratory capacity breaths of buffered saline solution and increasing concentrations of methacholine at 5-min intervals. FEV_1 was measured 60 to 90 s after inhalation of each concentration level. The procedure was terminated when FEV_1 had fallen by >40% from the post-saline value, or when a maximal response plateau had been established. This was considered to occur if 3 or more data points of the highest concentration fell within a 5% response range. An additional 5 or 10 inhalations of the 200 ug/mL solution were taken if the last three data points of less than a 40% fall did not satisfy the above criteria. The response was expressed as the % fall in FEV_1 ($\Delta FFEV_1$) from the post-saline solution value and was plotted against logged concentrations of inhaled methacholine. The dose-response curves were characterised by their position and maximal response. The position was expressed as PCD_{20}, which was calculated by log-linear interpolation between 2 adjacent data points.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			The maximal airway response plateau (MΔFFEV$_1$) was defined as the level of maximal response plateau by averaging the consecutive points on the plateau. The last data point of the dose-response curve was used if a plateau could not be achieved.
Lopes *et al* (2015) (28)	**Spirometry & body plethysmography** (FVC, FEV$_1$, FEV$_1$/FVC, PEF, FEF$_{25-75\%}$, TLC, RV and RV/TLC % predicted, DLco % predicted, % bronchodilator response), **HRCT, dyspnoea**	**Anthropometry** (BMI), **treatment** (use of inhaled medication (bronchodilator, corticosteroids, antibiotics, DNase))	Dyspnoea: modified Medical Research Council (MRC) scale. Spirometry/body plethysmography: All tests followed the standards formulated by the ATS (114). Bronchodilator response was identified based on the presence of a variation of 12% and 200 mL in FEV$_1$ or FVC after the use of 400ug of inhaled salbutamol. Pereira's and Neder's equations were used in the interpretation of the functional parameters. Airflow obstruction was defined by an FEV$_1$/FVC value <70% predicted. A restrictive pattern was defined as the presence of a TLC <80% of predicted; this cut off point was also used to define abnormality in DLco. HRCT: extent of bronchiectasis was established by the modified scale described by Bhalla *et al* (150), which ranges from 0 to 18. Each lung lobe (considering the lingual and middle lobes as independent) was scores as follows: 0 = no bronchiectasis; 1= one or partial bronchopulmonary segment involved; 2 = two or more bronchopulmonary segments involved; and 3 = generalized cystic bronchiectasis.

Authors (year of publication)	**Study outcomes**	**Population descriptors**	**Definition of outcome measures**
Maglione *et al* (2014a) (29)	**Anthropometry** (height, weight and BMI z-scores), **spirometry** (FEV_1, FVC and FEF_{25-75} % predicted and z-scores), **microbiology**	**None**	Spirometry: according to published criteria. FEV_1 z score <-1.96 was considered abnormal. Anthropometry: BMI z-scores were calculated according to Cole *et al*. Microbiology: chronic pseudomonal airway infection: presence of *Pseudomonas aeruginosa* for at least 6 months, with at least 3 positive cultures.
Marthin *et al* (2010) (30)	**Spirometry** (FEV_1 and FVC % predicted)	**HRCT** (bronchiectasis), **Chest radiography** (chronic abnormalities)	Spirometry: for each child every flow–volume curve was evaluated and excluded if technique was insufficient. FEV_1 and FVC measurements were as per ATS standards. Longitudinal lung function measurements in each subject following diagnosis were analysed using linear regression on time since diagnosis, for each subject separately, yielding subject-specific estimates of slope. From these slopes, each patient was grouped according to whether the course of lung function increased overall ≥10% points, stabilised (change within 10% points), or decreased ≥10% points in predicted values.
Olveira *et al* (2017) (31)	**Spirometry** (FEV_1, FVC, FEV_1/FVC, FEV_1>80%, FEV_1 50%–80% and FEV_1<50% predicted),	**Anthropometry** (BMI)	Microbiology: chronic bronchial infection (CBI) was defined as 3 or more positive cultures for a microorganism in a 6-month period. Spirometry: patients were classified according to their FEV_1 into 3 groups: FEV_1 >80%, between 50%–80% and <50%. Bronchiectasis can be diagnosed from clinical and radiological criteria,

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	microbiology (chronic bronchial infection by any pathogen, by *Pseudomonas aeruginosa*, by *Haemophilus influenzae*), **treatment** (inhaled antibiotics), **CT**		bronchography or computed tomography (CT) according to the criteria of Naidich *et al*. Bronchiectasis was classified as localized, bilateral, or diffuse (≥ 4 lobes). Patients diagnosed according to clinical-radiological criteria only were excluded.
Phillips *et al* (1998) (32)	**Spirometry** (changes in % in FEV_1 and PEFR in response to exercise and to bronchodilator, baseline measurements FEV_1, FVC, FEF_{25-75} and PEFR % predicted)	**None**	Spirometry: baseline pulmonary function was recorded as the best of three flow volume loops. Significant change was 11% for FEV_1, 9% for FVC and 17% for PEFR. Treadmill exercise test: performed according to standardised protocol. Bronchodilator response was assessed by giving 200 µg salbutamol via a metered-dose inhaler and spacer device under supervision. PEFR and the best of three flow volume loops were recorded before and 15 min after administration of the bronchodilator.

Authors (year of publication)	**Study outcomes**	**Population descriptors**	**Definition of outcome measures**
Pifferi *et al* (2012) (33)	**Body plethysmography** (FEV_1, FVC, FEF_{25-75}, FRCpleth, RV, TLC, RV/TLC, airway resistance (Raw), specific airway resistance (sRaw) and effective specific resistance (sReff) % predicted and z-scores), **HRCT**	**Microbiology** (infection with *Pseudomonas aeruginosa*)	Body plethysmography: to be accepted, single inspiratory manoeuvres needed to yield superimposable X-Y plots and values of FRCpleth had to be within 5% of each other. HRCT: Modified Bhalla system, which includes severity of bronchiectasis (score 0-3) and extent of bronchiectasis (score 0-3), mucous plugging (score 0-3), peribronchial thickening (score 0-3), parenchymal abnormalities such as atelectasis (score 0-3) and focal air-trapping (score 0-3). Bronchiectasis was identified according to standard criteria. A severity class (from 1 to 3) for total lung impairment was obtained (class of severity 1 for total score of 0-6, class 2 for total score of 7-12, class 3 for total score 13-18).
Shah *et al* (2016) (34)	**Body plethysmography** (FEV_1, FEV_1/FVC, TLC, RV/TLC, TLCO and KCO % predicted, estimated change in FEV_1 % predicted per year), **HRCT,**	**None**	Body plethysmography: lung function at time of diagnosis or transition to adult care was used to determine baseline. Longitudinal lung function data were obtained from patients with at least two lung function records when clinically stable with a minimum of three forced expiratory manoeuvres within the same lung function laboratory in the absence of bronchodilator. Lung function decline was expressed as FEV_1 % predicted and estimated using Global Lung Function Initiative reference equations. Microbiology: chronic colonisation was defined as the isolation of potentially

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	microbiology (*P aeruginosa* colonisation, non-tuberculosis mycobacteria infection, allergic bronchopulmonary aspergillosis, other pathogens, cumulative sputum analysis)		pathogenic bacteria or fungi in the sputum on two or more occasions at least 3 months apart in a 1-year period with >50% positive cultures during the year. All patients had three or more sputum cultures over the duration of follow-up. Sputum microbiology for patients was presented as cumulative colonisation over the duration of the follow-up period. Nontuberculous mycobacteria infection was defined according to the ATS guidelines and allergic bronchopulmonary aspergillosis according to the British Thoracic Society guidelines. Body plethysmography: European Community for Steel and Coal reference equations were used for measurement of transfer factor of the lung for carbon monoxide (TLCO). HRCT: extent of bronchiectasis, severity of bronchial dilatation, bronchial wall thickness, mucus plugging in large and small airways, mosaicism and emphysema were scored for each lung lobe (the lingula was considered as a different lobe, making a total of 6 lobes), according to a modified Bhalla system (150). The scoring system was as follows: 1) extent of bronchiectasis (0 = none, 1 = one or partial bronchopulmonary segment involved, 2 = two or more bronchopulmonary segments involved, 3 = generalized cystic bronchiectasis); 2) severity of bronchial dilatation (0 = normal, 1 = less than twice the diameter of the adjacent pulmonary artery, 2 = more than twice the diameter of adjacent pulmonary artery); 3) severity of bronchial wall thickening (0 = normal, 1 = <0.5 × the diameter of the adjacent

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			pulmonary artery, 2 = 0.5 - 1.0 × the diameter of the adjacent pulmonary artery, 3 = ≥ 1.0 × the diameter of the adjacent pulmonary artery); 4) presence of mucous plugging in large airways (0 = none, 1 = minimal, 2 = extensive 5) presence of mucous plugging in small airways (0 = none, 1 = minimal, 2 = extensive); 6) extent of mosaicism (to nearest 5%) and 7) extent of emphysema (to nearest 5%). Patients with previous lobectomies had scores adjusted to represent the maximum score available. Scores for extent of bronchiectasis, severity of bronchial dilatation and thickening and mucus plugging in small and large airways are expressed as percentages of maximum possible score.
Sunther *et al* (2016) (35)	**Spirometry** (FEV_1 % predicted, baseline FEV_1 < 40%, mean baseline and admission FEV_1 % predicted)	**Anthropometry** (BMI), **microbiology** (persistent infection with pathogens), **treatment** (*n* treated with intravenous antibiotics, *n* oral prophylactic antibiotics, *n* in use of hypertonic saline or rhDNase)	Pulmonary exacerbation: defined as change in respiratory status for which intravenous antibiotics were prescribed. Spirometry: FEV_1 % predicted values were calculated using the Global Lung Initiatives (GLI) equations. Baseline FEV_1 was defined as the best FEV_1 in the 12 months before the pulmonary exacerbation. Recovery to baseline was defined as any FEV_1 within 3 months after treatment that was greater than or equal to 90% of the baseline FEV_1. Microbiology: persistent infection was defined as at least two positive growths of the same microorganisms on cough swab or sputum culture in the 12 months before the pulmonary exacerbation.

Authors (year of publication)	**Study outcomes**	**Population descriptors**	**Definition of outcome measures**
Tamalet *et al* (2001) (36)	**Spirometry** (FEV_1 % predicted), **blood gas** (mean arterial PO_2)	**CT** (bronchiectasis, radiologic deterioration, lobectomy), **treatment** (antibiotic use)	Respiratory tract infections: defined as persistent cough with bronchial rhonchi, with or without fever. Frequency of infections: classified as less than or more than 6 infections per year since birth. CT: presence of bronchiectasis (internal diameter of bronchus larger than that of an adjacent artery) was assessed, and its topography was scored as absent, unilateral, or bilateral. The course of bronchiectasis was evaluated by CT scan performed every 2 years and classified as stable or progressive. Radiologic deterioration corresponded to bronchiectasis extension. Blood gas: arterialized capillary blood. Spirometry: results were expressed as a percentage of the expected value for age and considered as normal when > 80% of the expected value. Pulmonary function tests were performed at least twice in 35 of 41 children, at a mean interval of 6 years. Treatment: frequency of antibiotic use prescribed over the entire follow-up period for their lower or upper respiratory tract infections was evaluated and scored (no antibiotics, intermittent or continuous).
Vallet *et al* (2013) (36)	**Spirometry** (FEV_1, FVC and FRC % predicted, *n*	**None**	Spirometry: at least 3 curves reproducible for FEV_1 were recorded and the best curve was retained for analysis. Flows were considered normal when > 80% of the expected value.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	abnormal FRC and FEV_1), **blood gas** (PaO_2, *n* hypoxemic patients), **CT** (bronchiectasis, progressive bronchiectasis)		Blood gas: arterialised capillary blood gases for hypoxemia, which was defined as a value of PaO2 below the lower limit of normality (2 standard deviations below predicted measures in age-matched healthy children). CT: bronchiectasis was classified as stable or progressive (increasing diameter and/or extension to a new segment). Radiological deterioration was defined as the extension of bronchiectasis.
Videbaek *et al* (2019) (38)	**Spirometry** (FEV_1, FVC, FEV_1/FVC % predicted and z-scores), **microbiology** (presence of *Pseudomonas aeruginosa*)	None	Spirometry: performed according to ATS/ERS guidelines. GLI reference equation was used to normalise spirometry parameters. Microbiology: patients were classified according to *Pseudomonas aeruginosa* infection status in 4 groups according to sputum culture results and level of precipitating antibodies (precipitins) against *Pseudomonas* using microbiology data from the latest 2 years of observation: chronic infection, intermittent infection, not-positive and not-classifiable. Chronic infection with Pseudomonas was defined as >4 samples per year with >50% positive sputum cultures and/or positive precipitins (≥ 2). Intermittent infection was defined as >4 samples per year with <50% but at least 1 positive sputum culture and negative precipitins (value 0 or 1). Patients not positive for *Pseudomonas* was defined as >4 samples per year with no positive sputum cultures and negative precipitins. Patients were deemed not classifiable if they had <4 samples per year and negative precipitins.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
Main study outcome: MBW			
Ahmad *et al* (2015) (39)	**MBW** (correctly categorised %, mean time saved in seconds, mean time saved %, coefficient of variance)	None	MBW: conducted according to published standardised protocol. Correctly categorised was defined as % of correctly predicted values using the upper limit of normal, calculated from healthy controls. Reference was 'LCI standard', to which $LCI_{0.75}$, $LCI_{0.5}$ and $LCI_{0.25}$ were compared. Coefficient of variance: calculated from the mean of the coefficient of variance of the intra-test FRC and LCI (SD/mean). Time saved in each of the shortened MBWs is to their respective end-points.
Anagnostopoulou *et al* (2018) (40)	**MBW** ($LCI_{standard}$, functional residual capacity (FRC), cumulative expiratory volume (CEV))	**Anthropometry** (weight z-score, height z-score)	MBW: Each child performed 3 to 4 N_2MBW according to the current consensus statement. $LCI_{standard}$ was calculated according to current recommendations, *i.e.* end-tidal nitrogen concentration (Cet) defined as the average value between 95% and 98% of expired volume and LCI as the ratio of CEV to FRC (CEV/FRC) at the first of three consecutive breaths below the cut-off of 2.5% (1/40th). Anthropometry: z-scores were calculated according to Centers for Disease Control and Prevention growth charts.
Green *et al* (2012) (41)	**SF_6 MBW** (LCI absolute values and z-scores, LCI within-session variability	**Anthropometry, microbiology**	MBW: LCI was calculated as the number of lung volume turnovers (the cumulative expired volume divided by the functional residual capacity) needed to lower the end-tidal tracer gas concentration to less than $1/40^{th}$ of the starting concentration. The mean LCI result from 3 MBW measurements in each patient was used for

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	(CV)%, S_{acin}, S_{cond}, FRC_{SF6}), **spirometry** (FEV_1, FVC, FEF_{25-75}, FEV_1/FVC ratio z-scores)		analysis. Spirometry: performed according to ATS/ERS standards. Abnormal lung function was defined as z-scores < -1.96. The upper limit of normal was defined as the predicted mean plus 1.96 SD for MBW variables and the lower limit of normal as predicted minus 1.96 SD for spirometry variables. Spirometry parameters were calculated using the British growth reference charts. MBW z-scores calculated using Swedish normative data.
Green *et al* (2016) (42)	**MBW** ($LCI_{2.5}$, $LCI_{3.0}$, $LCI_{4.0}$, $LCI_{5.0}$, $LCI_{7.0}$, $LCI_{9.0}$), **spirometry** (FEV_1, FVC, FEV_1/FVC ratio and $MMEF_{25-75}$ z-scores)	**Anthropometry** (weight, height, BMI z-scores)	Spirometry was performed according to ATS/ERS guidelines. GLI reference equation was used to obtain z-scores and a z score < -1.64 was considered an abnormal spirometric value.
Irving *et al* (2018) (43)	**MBW** (LCI)	**Spirometry** (FEV_1, FEF_{25-75} z-scores)**, microbiology** (presence of *Pseudomonas aeruginosa*)	Spirometry: FEV1 and FEF25–75 z-scores were calculated using the GLI. MBW: minimum of 2 runs of acceptable quality were required, in accordance with ERS/ATS guidelines. Abnormal LCI was defined as > 7.4.

Authors (year of publication)	**Study outcomes**	**Population descriptors**	**Definition of outcome measures**
Irving *et al* (2017) (44)	**Spirometry** (FEV_1 z-score), **MBW** (LCI)	**None**	MBW: LCI was calculated as the mean of at least 2 acceptable tests. Spirometry: performed according to ATS/ERS guidelines.
Irving *et al* (2013) (45)	**Spirometry** (FEV_1, FVC and MEF_{25-75} z-scores), **MBW** (LCI and functional residual capacity), **HRCT**	**Microbiology** (infection with *Pseudomonas aeruginosa*)	Spirometry: performed according to ATS/ERS recommendations. Subjects completed a minimum of 3 forced expiratory manoeuvres, and FEV_1 (L) and FVC (L) were expressed as z-scores. MBW: LCI was defined as the number of volume turnovers of the lungs required to reduce an inert gas to $1/40^{th}$ of its starting concentration. Minimum of 2 of the 3 tests had to meet the acceptability criteria to be included in the analyses. HRCT: presence and severity of specific CT features was recorded for each lobe (individual scoring system), including extent of bronchiectasis, severity of bronchiectasis, bronchial wall thickness, small and large mucus plugs, and air trapping. Used a study-specific score that was then compared to the Brody score. Chronic infection with *Pseudomonas aeruginosa* was defined as at least 2 positive cultures on cough swab or sputum culture over the last 5 years.
Kobbernagel *et al* (2019) (46)	**Spirometry** (FEV_1, FCV, FEV_1/FVC z-scores and % predicted)**, MBW** (LCI, M_1/M_0, M_2/M_0, $S_{cond}*V_T$, $S_{acin}*V_T$)	**Microbiology, anthropometry** (BMI)	Respiratory exacerbation was defined as worsening respiratory symptoms at test occasion leading to the start of systemic antibiotic treatment within 1 week before or at the visit. Chronic infection by Pseudomonas aeruginosa: pathogen was cultured in ≥50% of the mucus samples from the past year, provided at least 4 annual samples were provided.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			N_2 MBW: performed according to the ERS/ATS consensus statement. Spirometry: measured according to ERS/ATS standards. % predicted values and z-scores were calculated using all-ages prediction equations for spirometry from the GLI. Microbiology: mucus samples were included in the data analysis if they originated within 1 week before or after the test occasion, and the mucus samples were considered positive for bacteria if the culture was positive, regardless of the microscopy results.
Kouchy *et al* (2020) (47)	**MBW** ($LCI_{2.5}$, Sacin*Vt and Scond*Vt, functional residual capacity)**,** **spirometry** (FEV_1, FVC and $MMEF_{25-75}$ % predicted)**,** **endobronchial thickness** (reticular basement membrane width)**,** **bronchoalveolar**	**Anthropometry** (weight, height and BMI z-scores), **microbiology**	MBW: N2-MBW adhering to relevant recommendations. Spirometry: In children aged ≥ 4 years, forced spirometry was performed according to ERS/ATS recommendations. FVC, FEV_1, and maximal mid-expiratory flow were measured and compared to the GLI 2012 reference values. Endobronchial thickness: measured using computer image analysis software according to previously validated criteria. Microbiology: *Burkholderia cepacia* complex ever positive in respiratory cultures; chronic Haemophilus influenzae, Pseudomonas aeruginosa and Staphylococcus aureus infections were defined as positive in > 50% of respiratory cultures in the last year.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	lavage (fluid cytology)		
Nyilas *et al* (2017) (48)	**MBW/SBW** ($LCI_{2.5\%}$, $LCI_{5\%}$, S_{acin}, S_{cond}, S_{acin}*, S_{cond}*, M1/M0, M2/M0, SIII-DTG z-scores), **body plethysmography** (FEV_1 and FEF_{25-75} z-scores)	**Microbiology** (chronic colonisation), **treatment** (use of antibiotic long-term therapy)	N2-MBW: $LCI_{2.5\%}$ was calculated as the lung volume turnovers required to reach $1/40^{th}$ of the starting N2 concentration. All subjects performed 2 different tidal gas washout measurements, triplicate N2-MBW and DTG-SBWm according to consensus (166). S_{cond} was calculated from the phase III slope (SIII) of washout breaths between the 1.5th and 6th lung turnover. S_{acin} was derived from the first nitrogen SIII and reflects regional acinar ventilation inhomogeneity. LCI5%, S_{cond}(*) and S_{acin}(*) were calculated from abbreviated protocols requiring washout until 1/20th instead of $1/40^{th}$ of the initial nitrogen concentration, and the (*) indices were calculated even earlier. DTG-SBW: SIII was calculated between 65% and 95% of the expired tidal volume and adjusted for tidal volume, as recommended.
Nyilas *et al* (2018) (49)	**Structural and functional MRI** (Eichinger score)**, MBW** (LCI, Scond and Sacin z-scores)**, spirometry** (FEV_1 and FVC z-scores)	**Anthropometry** (weight, height)	MRI: Eichinger MRI morphological score was used to assess the presence and extent of structural lung disease: 0 (not present); 1 (present and affecting 50% or less of the lobe); or 2 (present and affecting greater than 50% of the lobe). The lobe scores for each component were summed to produce a score out of 12. The total morphology score is composed of five sub-scores each with a maximum score of 12 (maximum score = 60). Functional MRI imaging, MP decomposition method was applied to generate maps of regional fractional ventilation. The distribution of

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			ventilation and perfusion was assessed, and a threshold was applied to determine the degree of impairment. The relative fractional ventilation (RFV) and relative perfusion (RQ) impairment were calculated and expressed as a percentage of lung volume for each study participant. To estimate the degree of functional abnormalities in patients with PCD we relied on historical normal values for MRI. Spirometry according to current guidelines. N_2-MBW: performed in accordance with current consensus guidelines. Spirometry: a calculated z-scores from recommended reference equations for spirometry. To assess the prevalence and concordance of structural and functional outcomes abnormality was defined at ±1.64 z-scores for spirometry and MBW outcomes, structural MRI sub-scores of 2 points or greater (indicates >15% structural impairment), and functional MRI outcomes, RFV of 24.2% or greater and RQ of 19.3% or greater, according to healthy reference data.
Smith *et al* (2018) (50)	**MRI, MBW** (LCI, Scond, Sacin, ventilation defect %, coefficient of variance of ventilated image signal	**Anthropometry** (height, weight)	MRI: Three-dimensional volumetric hyperpolarized helium-3 ventilation MRI and 1H anatomical images were acquired during the same breath-hold. From these images two indices were calculated: 1) ventilation defect percentage (VDP), which quantifies the percentage of the lung volume that is not ventilated; and 2) the mean coefficient of variance of ventilated image signal intensity (CV), a metric of regional ventilation heterogeneity. 1H steady-state free precession magnetic

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	intensity)**, spirometry** (FEV_1, FEV_1/FVC z-scores)		resonance images were separately acquired for assessment of lung morphology and mucus. MBW was performed as previously described, and the parameters LCI, ventilation heterogeneity in the convection-dependent airways (Scond), and ventilation heterogeneity in diffusion–convection-dependent airways (Sacin) were calculated. The upper limit of normal for LCI was defined as >7.4 (119).
Main study outcome: High-resolution computed tomography			
Boon *et al* (2015) (12)	**Spirometry** (FEV_1, FVC, FEV_1/FVC and $FEF_{25–75}$ z-scores), **N_2 MBW** (LCI), **HRCT**	**Anthropometry** (weight, height and BMI z-scores)	MBW: LCI was calculated by dividing the cumulative expired volume by the functional residual volume. At least two technically acceptable measurements per patient were performed. S_{cond} and S_{acin} were both multiplied by tidal volume to normalise for age, as proposed in the MBW consensus guidelines. The mean LCI of at least two technically acceptable measurements was used. Spirometry was performed according to the ATS/ERS guidelines. FEV_1, FVC, FEV_1/FVC and $FEF_{25–75}$ were expressed as z-scores according to the reference equations from the GLI. A z score below −1.96 was defined as abnormal. Spirometry was performed on the same day as MBW. HRCT: A cystic fibrosis computed tomography (CFCT) score, a variant of the modified Brody Score, was used to quantify specific abnormalities on chest CT: severity and extent of bronchiectasis, severity and extent of airway wall thickening, mucus plugging in central and peripheral airways, parenchymal abnormalities

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			(consolidation, atelectasis, cysts and ground glass opacities) and air trapping. The lingula was considered as a separate lobe. Scores were expressed as percentage of the maximum score of 207 and a total CFCT score >5% was defined as abnormal. Anthropometry: height, weight and BMI were expressed as z-scores according to Flemish reference equations.
Cohen-Cymberknoh *et al* (2014) (51)	**HRCT, spirometry** (FEV_1 % predicted), **microbiology**	**Anthropometry** (BMI percentile)	Pancreatic insufficiency was defined as stool elastase <100µg/g stool or coefficient of fat absorption < 93%. Spirometry: pulmonary function tests were performed according to ATS/ERS guidelines. FEV_1 was presented as % predicted, according to Wang *et al* for children and Hankinson *et al* for adults. HRCT: each lung lobe, including the lingula, was counted as a separate lobe. The Brody score was calculated with a slight modification: hyperaeration of the lungs was evaluated instead of air trapping, as expiratory images were not obtained in all patients. Sub-scores for the presence and severity of bronchiectasis, mucous plugging, bronchial wall thickening, parenchyma, and focal hyperaeration in each lobe were calculated. Parenchymal findings of ground glass, consolidation, and cysts or bullae were all considered in determining a single parenchyma sub-score. The sum of sub-scores constituted lung total Brody scores for each patient. Microbiology: chronic infection was defined when patients had at least three positive sputum cultures within 1 year.

Authors (year of publication)	**Study outcomes**	**Population descriptors**	**Definition of outcome measures**
Dettmer *et al* (2018) (52)	**CT** (Reiff score, lobar distribution, type of bronchiectasis, collateral findings)	**Microbiology, spirometry** (FEV_1 and FVC %predicted)**, anthropometry** (BMI)**, number of exacerbations**	CT: Bronchiectasis was diagnosed according to the criteria described by Naidich. The Reiff-score was used to evaluate bronchiectasis. Each lobe (with the lingula considered as a separate lobe) was scored for the extent of involvement (0 = none, 1 = one or partial segment, 2 = two or more segments); severity of bronchial dilatation (0 = normal, 1 = less than twice the diameter, 2 = 2–3 times the diameter, and 3 = more than 3x the diameter of the adjacent pulmonary artery); severity of the bronchial wall thickening (0 = normal, 1 = half the diameter, 2 = 0.5 to 1x diameter, and 3 = more than 1x the diameter of the adjacent pulmonary artery); type of bronchiectasis (1 = cylindrical, 2 = varicose, or 3 = cystic). The lobar distribution of bronchiectasis (0 = widespread, 1 = predominantly upper lobe, 2 = predominantly middle lobe, 3 = predominantly lower lobe, 4 = middle and lower lobes equally involved, or 5 = unclassifiable) was registered. In case of situs inversus or heterotaxy, right-sided changes were assigned to the left site according to the architecture of the lobes. collateral findings were registered. Therefore, mucous plugging, tree in bud, peripheral and central consolidations, peripheral and central ground glass opacities, interlobular septal thickening and intralobular lines were scored (0 = none, 1 = 1–3 bronchopulmonary segments involved, 2 = >3 bronchopulmonary segments involved) for the whole lung. Mosaic attenuation, atelectasis, emphysema and situs inversus / heterotaxy were classified as present / absent. It was subsequently indicated if bronchiectasis was predominant in the

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			middle and lower lobes and if both mucous plugging and tree in bud were present in more than three segments. All terms were used according to the definition of the Fleischner Society. Subtotal or total atelectasis or a condition after resection of a lower or middle lobe or lingula was registered.
Hoang-Thi *et al* (2018) (53)	**Spirometry** (FEV_1, FVC % predicted)**, CT** (Bhalla score)	**Anthropometry** (BMI)	CT: lung structural changes were assessed by visual scoring, histogram analysis and thresholding of high attenuating lung structures. Images were scored by one thoracic radiologist using the Bhalla score. Twenty randomly selected examinations were also independently scored by a second radiologist to assess interobserver repeatability. For automated CT scoring, histogram characteristics were analysed: mean lung density (MLD), mode (the most highly represented attenuation value), standard deviation, kurtosis (sharpness of the density distribution), and skewness (asymmetry of the density distribution). CT-density scores (one for each tested threshold value) were expressed as the proportion of lung showing attenuation values above the selected threshold. Spirometry: performed as recommended by the ATS/ERS guidelines, predicted values were calculated using the European Community for Steel and Coal reference values.
Jain *et al* (2007) (54)	**Chest radiography** (dextrocardia, hyperinflation,	**Microbiology**	Chest radiography: modified Chrispin-Norman score (no need for lateral film). Lungs were divided into 4 zones on the frontal film: right upper, left upper, right lower, left lower; the following were scored for each zone: bronchial wall

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	bronchial wall thickening and dilation, mottled shadows, consolidation or collapse), **HRCT**		thickening, ring shadows, mottled shadows, and large soft-tissue shadows; scores of 0 (not present), 1 (present but not marked), and 2 (marked) were given for each of these 4 parenchymal lung features. Radiographs were also assessed for over-inflation, with a possible maximum score of 6. HRCT: Brody score used to evaluate 5 features independently in each lobe (bronchiectasis, mucus plugging, peribronchial thickening, parenchymal changes of consolidation and ground-glass density, and focal air-trapping).
Kennedy *et al* (2007b) (55)	**HRCT** (study-specific score)	**Spirometry** (FEV_1 % predicted), **microbiology, lobectomy**	High-resolution CT images were assessed for severity of bronchiectasis in each lobe. A score of 0 indicated no bronchiectasis; 1, mild bronchiectasis (bronchial dilatation 2 times the diameter of the accompanying blood vessel); 2, moderate bronchiectasis (bronchial dilatation 2 to 3 times vessel diameter); 3, severe bronchiectasis (bronchial dilatation more than 3 times vessels diameter). An overall bronchiectasis severity score for all 6 lobes was calculated (score range 0-18). The distribution of bronchiectasis was classified in each lobe as central (proximal 50% of lung parenchyma), or diffuse. If lobectomy was performed, a severity score of 3 was assigned to the missing lobe by arbitrary definition, and distribution was presumed diffuse. The presence or absence of peribronchial thickening and mucous plugging for each lobe was recorded. Other radiographic findings included: mucous plugging, peribronchial consolidation, lobar collapse and atelectasis, pleural effusion, nonspecific infiltrate, emphysema, calcium deposition, pectus excavatum)

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
Li *et al* (2005) (56)	**HRCT** (distribution of bronchiectasis)	**Spirometry** (FEV_1 and FVC % predicted), **microbiology**	HRCT: presence or absence of bronchiectasis was recorded in each lobe, with the lingula being considered as a separate lobe. Widespread disease was defined as bronchiectasis involvement of 5 or more lobes. Spirometry: performed according to the ATS guidelines. Three technically acceptable manoeuvres were performed each time, and the highest value of FEV_1 and its corresponding FVC were recorded. Bronchiectasis was defined as idiopathic if extensive investigations failed to reveal an underlying aetiology. The commonest organism isolated for each aetiology were reported.
Maglione *et al* (2012) (57)	**Spirometry** (FEV_1, FVC, FEV_1/FVC and FEF_{25-75} z-scores, change in FEV_1 z-score), **HRCT**	**None**	Definition of stability: partly modified definition of stability previously suggested in CF. Stable patients were those with no recent change (preceding 4 weeks) in chest physical examination, sputum volume or colour, dyspnoea, cough frequency, malaise, fatigue, or weight. Definition of unstable lung disease: febrile, illness indicating substantial infectious insult, and/or worsening symptoms suggesting progression of bronchiectasis, that were unresponsive to prolonged oral and/or IV Abx and daily physiotherapy with nebulized saline. In the absence of any generally agreed protocol or evidence, the decision to perform a second CT scan was also made on an individual basis after discussion with the patient and his family. HRCT scan scoring: modified Brody scoring system. Bronchiectasis score range 0-12,

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			mucus plugging score (range 0 to 6), peribronchial thickening score (0 to 9), parenchyma score (0 to 9), mosaic perfusion score (0 to 4.5). A score was calculated for each abnormalities and these scores were summed to provide a total score for each lobe. The scores from the 6 lobes were then summed to provide a total HRCT scan score, with a theoretical range from 0 (normal) to 243 (maximal score in all lobes). In practice the maximal score could not exceed 207, since a lobe cannot have more than 2/3 involvement from all abnormalities at the same time. All scores were normalized to a scale of 0-100, representing a percentage of a maximum possible score, and a total score of >5% was abnormal. Spirometry: measured according to published criteria. The best of 3 valid attempts was used in the analysis. FEV_1 z-score <-1.96 was defined as abnormal. Acceptability was checked by an independent blind reviewer inspecting the spirometry loops. The changes in the scores between the 2 evaluations were calculated. A positive value for CT score changes indicated that lung structure abnormalities worsened, while a positive value for change in spirometry indicated an improvement in LF. Spirometry remained stable if the change in FEV_1 % predicted between the 2 evaluations was of no more than +/-10%.
Maglione *et al* (2017) (58)	**MRI, CT**	**Spirometry** (FEV_1, FVC, FEV_1/FVC and $FEF_{25–75}$ z-scores),	Pancreatic insufficiency: stool elastase <100 µg/g. Spirometry: FEV_1 z score < −1.64 was considered abnormal. Chronic airway infection: same pathogen was detected, after adequate antibiotic

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
		anthropometry (height, weight and BMI z-scores), **treatment** (courses of antibiotics, hospital admissions), **microbiology** (sputum)	therapy, in at least three consecutive cultures within 6 months. HRCT and MRI: morphologic scoring system, originally developed for CF by Helbich *et al*, later modified by Puderbach *et al*. Maximum achievable total score was 25, indicating the most severe lung changes. For the purpose of quantifying the severity of PCD or CF lung structure deterioration, the total MR score into mild (scores 0-9); moderate (scores 10-18); and severe (scores 19-25). For the categories "severity of bronchiectasis" and "severity of peribronchial wall thickening", the most prevalent degree of severity was recorded. If mucous plugging was seen within the periphery of a lung segment, bronchiectasis was scored also in that segment. Six lobes were examined, the lingula being scored as a separate lobe. In patients with situs viscerum inversus, the right lung was the lung in which the middle lobar bronchus and the corresponding middle lobe were identified at scans.
Magnin *et al* (2012) (59)	**Spirometry** (FEV_1, FVC, FEV_1/FVC and FEF_{25-75} z-scores), **arterialised capillary blood gases** (oxygen (PaO_2) and carbon dioxide ($PaCO_2$) tensions), **CT**	**None**	Stability: applied definition accepted in CF (no weight loss or fever, no subjective change in cough frequency, sputum volume and/or colour, and no worsening of dyspnoea). Arterialised capillary blood gases were obtained using a technique described in Gaultier *et al*. Spirometry: the best curve out of 2 reproducible expiratory curves were recorded. Beta-agonists were withheld for 12 hours before lung function test, as recommended.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			Chest CT: protocols varied over time. Chest CT examination protocols have been standardised in accordance with the national recommendations from the French Society of Pediatric Radiology (SFIPP) (i.e. parameters and doses) since 2003. To describe the structural impairment of the lung, items from Bhalla's and Brody's CT scoring systems were used and slightly modified to obtain a score easy to use in routine practice. The score described five items (bronchiectasis, mucous plugging, peribronchial thickening, parenchymal abnormalities, and pulmonary hyperinflation), in six pulmonary regions, each lung divided into three regions: (i) the upper region was described from the apex to the tracheal carina, (ii) the middle region from the carina to the lower pulmonary veins, (iii) the lower region from the lower pulmonary veins to the bases. In each region, 0 point was given for absence and 1 point for presence of the following items: mucous plugging, peribronchial thickening, parenchymal abnormalities (condensation and collapse), and pulmonary hyperinflation. Likewise, bronchiectasis were absent (0 point), or present with different degrees of severity assessed by the comparison with the adjacent pulmonary arteria (APA), as proposed in Bhalla's and Brody's CT scoring systems: 1 point for mild bronchiectasis (1–2 times larger than the APA), 2 points for moderate bronchiectasis (2–3 times larger than the APA), and 3 points for severe bronchiectasis (up to 3 times larger than the APA). Additional points were assessed on a CT each time the patient had history of lung surgery: 5 points for lobectomy

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			and 2 points for partial lobectomy. The score ranged from 0 to 42 points without the points assessed for surgery.
Montella *et al* (2009a) (60)	**HRCT, MRI, body plethysmograghy** (FEV_1 and FVC % predicted)	**Microbiology**	MRI and HRCT scores: modified version of Helbich *et al*. The severity of mosaic perfusion was excluded as it could not be assessed by morphological MRI. The maximum score was 25 points (instead of the original 27). For the categories "severity of bronchiectasis" and "severity of peribronchial wall thickening", the most prevelant degree of severity was recorded. It was not possible to assess peribronchial wall thickening in the presence of mucous plugging. Hyperintensity on HASTE images had to be present for an MRI diagnosis of mucous plugging. If mucous plugging was seen within the periphery of a lung segment, bronchiectasis was scored also in that segment. Sacculations and abscesses were defined as circular structures with a minimum diameter of 1.5 cm that were air-filled or showed an air-fluid level. A size of 2 cm was required for a diagnosis of collapse and consolidation. Emphysema was defined as an area of decreased signal (compared with the surrounding lung parenchyma) due to a reduction of vessel and parenchymal density. In case of lobectomy or segmentectomy, the maximum scores for "severity of bronchiectasis" and "severity of collapse/consolidation" were arbitrarily assigned to the missing lobe/segments. The assessment of "extent of bronchiectasis" considered the number of missing segments. Six lobes were examined; the lingula was scored separately. In patients with situs viscerum

Authors (year of publication)	**Study outcomes**	**Population descriptors**	**Definition of outcome measures**
			inversus, the right lung was the lung in which the middle lobar bronchus and the corresponding middle lobe were identified at scans. Body plethysmography: performed according to ATS criteria. FEV_1 > 85% predicted was considered normal.
Montella *et al* (2009b) (61)	**HRCT, MRI**	**None**	Same as above for HRCT and MRI.
Santamaria *et al* (2008) (62)	**HRCT**	**Spirometry** (FEV_1 and FVC % predicted), **microbiology**	HRCT: Brody score modified to assess the hyperinflation by mosaic perfusion pattern since only the findings of inspiratory CT scans were available for the study. Observations were made on six lobes, with the lingula being regarded separately. In patients with situs viscerum inversus, the lung in which the middle lobar bronchus and the corresponding middle lobe was considered as the right lung. A score was calculated for each abnormality, and these scores were summed to provide a total score for each lobe. The scores for the six lobes were then summed to provide a total HRCT scan score, with a theoretical range from 0 (normal) to 243 (maximal score in all lobes). Sub-scores were also calculated for each abnormality by limiting the score to the finding of that abnormality. All scores were normalized to a scale of 0 to 100, representing a percentage of the maximum possible score. A total score of > 5% was abnormal, as in a recent CF study. Spirometry: FEV_1 of > 85% predicted was considered normal. Microbiology: deep throat or sputum cultures were obtained.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
Tadd *et al* (2019) (63)	**CT** (Brody and Bhalla scores)	None	CT: Patients were assessed for the presence and extent bronchiectasis, bronchial wall thickening, atelectasis, mucous plugging, and air trapping, using the Brody and Bhalla scoring systems. If present, each abnormality was designated as mild-moderate if the extent was <50% of the lobe, and moderate-severe ≥50% of the lobe. The relative frequencies and lobar distributions of the changes were described. CT changes were annotated for all five lobes of the lung, with the lingula classified as an additional sixth lobe. Bronchiectasis was identified when the outer edge bronchus-artery cross-sectional area ratio was greater than 1, or the bronchus was non-tapering as it approached the pleura, assessed subjectively. Bronchial wall thickening was identified when airway walls were thicker than healthy airways, assessed subjectively. Mucous plugging was identified when there was a high-density occlusion seen in an airway, or tree-in-bud appearance in small airways. Trapped air was identified on expiratory images only as an area of reduced signal intensity compared to healthy lung.
Main study outcome: Microbiology			
Alanin *et al* (2015) (64)	**Microbiology** (period prevalence rate (PePR), period prevalence rate for	**Spirometry** (FEV_1 and FVC % predicted)	Microbiology: PePR was defined as the percentage of patients who grew the pathogen during a calendar year and PePRchr the percentage of patients who could be classified as chronically infected during a calendar year according to the study criteria detailed below. Criteria and definitions were based on the modified 'CF Leeds criteria'. Lung

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	chronic infection (PePRchr))		infection status was based on at least 4 samples from the lower airways collected during a period of 1 year and was defined as: a) Chronic infection, when >50% of the preceding 12 months' cultures were positive for the specific pathogen; b) Intermittent colonization, when 50% or less of the preceding 12 months' cultures were positive for the specific pathogen; c) Free of colonization and infection, when no growth has occurred in the lungs in the previous 12 months. However, patients with 2 or 3 positive bacteriological samples in combination with abnormal precipitins were classified as chronically infected.
Cohen-Cymberknoh *et al* (2017) (65)	**Microbiology** (colonized vs non-colonized with Pseudomonas aeruginosa (PA)), **spirometry** (FEV_1% predicted), **CT**	**Anthropometry** (BMI percentile for ≤20 years and BMI for >20 years)	Microbiology: Several definitions of colonized and non-colonized with PA were used. Only a few patients in the study could meet the Leeds criteria, which is the most rigorous criteria and used in CF. Therefore, patients were classified as non-colonized if they had never been cultured with PA or cultured only once whereas colonized patients were defined as having had least two positive sputum cultures for PA during the study period. Colonized groups were defined as having a) at least 4 positive cultures during the study period (n = 41), b) at least 6 positive cultures during the study period (n = 28) or c) two or more consecutive positive cultures or two consecutive years with at least one positive PA culture each year (n = 54). Spirometry: Decline of FEV_1% predicted throughout the study period was calculated

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			numerically by subtracting the first best FEV_1 from the last one in the study, divided by the number of years each participant took part in the study. CT: Brody scores were calculated with a slight modification (hyperaeration of the lungs was assessed instead of air trapping).
Roden *et al* (2019) (66)	**Microbiology** (mean daily alteration, yearly rate)**, spirometry** (FEV_1 and FVC % predicted)	None	Microbiology: Microbiological cultures were performed in line with recommendations for the work-up for CF specimens. The mean daily rate of alteration (MDRA) was calculated based on number of follow-up visits of patients (without baseline), and number of changed species (loss or gain) at each visit compared to the previous visit of patient , and time in days between each visit and previous visit. The yearly rate (MRA) describes the fluctuation and persistence of species in the individual patient. Spirometry: Parameters were expressed as FEV_1 % predicted and FVC % predicted estimated using the Global Lung Function Initiative reference equations (126).
Rogers *et al* (2013) (67)	**Microbiology** (bacterial loads, dominant genus relative abundance)	**Spirometry** (FEV_1 % predicted)	Exacerbations: defined as a change in respiratory symptoms that the PCD specialist considered to be caused by a lower respiratory tract infection requiring antibiotic therapy.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
Main study outcome: Anthropometry			
Goutaki *et al* (2017) (68)	**Anthropometry** (height, BMI z-scores)**, spirometry** (FEV_1, FVC z-scores)	None	Anthropometry: age- and sex-adjusted height and BMI z-scores, based on international reference values from the WHO and national reference values. For patients aged <20 years, height and BMI z-scores were calculated based on the exact age-specific references. For patients aged ≥20 years, height z-scores were calculated based on the reference values for 19-year-olds; these describe final adult height. BMI z-scores were also calculated for adults, based on the reference values for 19-year-olds, because no BMI z-score references presently exist for adults. Short stature was defined as a height z-score ≤-2; underweight, as a BMI z-score ≤-2; and overweight, as a BMI z-score ≥2, according to the definitions used by WHO. Spirometry: GLI reference values were used to calculate age, sex, ethnicity, and height-adjusted z-scores for FEV_1 and FVC values. All lung function measurements were checked for quality, and since 2005, they have been performed according to ERS/ATS guidelines.
Svobodova *et al* (2013) (69)	**Anthropometry** (height SD, weight, BMI)	None	Anthropometry: data were converted into a standard deviation score (SDS) of body height, according to the latest available normative data of the background population
Main study outcome: Health-related quality of life			

Authors (year of publication)	**Study outcomes**	**Population descriptors**	**Definition of outcome measures**
Alanin *et al* (2017) (70)	**HRQoL** (SNOT-22 score)**, microbiology** (lung infection status, bronchoalveolar lavage culture, sputum culture, precipitins against Pseudomonas)**,** **spirometry** (FEV_1 and FVC % predicted), **anthropometry** (BMI)	None	HRQoL: SNOT-22 contains 22 questions which evaluate the effect of CRS on HRQoL. The maximum score is 110. The questionnaire has been validated to evaluate the outcome after ESS in CRS patients. Microbiology: Bronchoalveolar lavage was performed in conjunction with ESS as described. Adjuvant therapy included 2 weeks of systemic antibiotic therapy according to susceptibility testing of the bacteria cultured from the bronchoalveolar lavage and/or sinuses, 2x daily nasal irrigations with saline, and topical nasal steroids for at least 3 months. Lung bacteriology was based on sputum samples or bronchoalveolar lavage fluid. Lung infection status was assessed by modified CF Leeds criteria. The % bacteriologically positive lung samples with the dominant pathogen 12 months before surgery was compared to % positive samples during follow-up. Normal values of precipitins are 0 or 1, while 2 precipitins are considered abnormal. Chronic infection was defined as abnormal precipitins with a positive sample for Pseudomonas from the lower airways. Spirometry: ATS standards.
Behan *et al* (2017) (71)	**HR-QoL** (QOL-PCD questionnaire, SF-36, shortened SGRQ-C, SNOT-20)	**Microbiology** (infection with *Pseudomonas aeruginosa*),	The analyses assessed the extent to which items correlated with their hypothesised versus competing scales; item-to-scale correlations should be ≥0.40 with the intended scale and lower correlations with competing scales. Correlations between 0.50 and 1.00 were interpreted as strong, correlations between 0.30 and 0.50 as moderate, correlations between 0.10 and 0.30 as small

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
		spirometry (FEV_1 % predicted)	and correlations <0.1 as weak, following Cohen's guidelines. 1. The QOL-PCD questionnaire was developed specifically for PCD and consists of 49 items, with most responses captured using a 4-point Likert scale. 2. SF-36 was derived from an observational study that began in 1986 on subjects with cardiac impairment. It is a 36-item self-administered questionnaire that includes eight scales, four of which relate to physical health: physical functioning, physical role limitation, bodily pain and general health perception. The remaining four scales are related to mental health: emotional role limitation, mental health, social functioning and vitality. Each scale is scored from 0-100. These eight scales provide two component summary scores: mental component summary and physical component summary in which normal score is 50±10. 3. The SNOT-20 is a validated disease-specific HR-QoL measure for rhinosinusitis that consists of 20 items. Each item is measured on an ordinal Likert scale from 0 to 5, with higher scores indicating worse symptoms. The first 12 items pertain to specific physical sinonasal symptoms including nasal symptoms and ear symptoms. The final 10 items address more systemic and psychological symptoms. 4. SGRQ-C is a disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease. The shorter 40-item version of the SGRQ does not specify a recall period and has been validated specifically for COPD patients.

Authors (year of publication)	**Study outcomes**	**Population descriptors**	**Definition of outcome measures**
Carotenuto *et al* (2013) (72)	**HR-QoL** (Wechsler Intelligence Scale for Children-III edition (WISC-III), Child Behavior CheckList (CBCL) questionnaire, Parental stress index-short form (PSI/SF))	**Anthropometry** (BMI)	Intelligence assessment: WISC-III is composed of 13 distinct subtests with 6 verbal scales including language-based items, whereas the 7 performance scales consist of visual-motor items that are less dependent on language. 5 of the subsets in each scale produce scale-specific IQs as verbal IQ and performance IQ and the 10 subtest scores produce a total scale IQ. Behavioural assessment from CBCL: mothers were instructed to answer questions about their child's behaviour during the past 6 months. Items are scored as 0=not true, 1=somewhat true or sometimes true, or 2=very true or often true. The questionnaire yields 8 factors: withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention-hyperactive, rule-breaking behaviour, and aggressive behaviour; as well as 3 global scores for externalizing and internalizing behaviours and total behaviour score. PSI/SF: yields scores of maternal stress across 4 domains: parental distress, parent-child dysfunctional interaction, difficult child, and total stress. Each item was graded on a 5-point Likert scale, with higher scores indicated higher perceived stress in the parents. A score at, or above, the 85^{th} percentile indicates high stress level.
Ioannou *et al* (2020) (73)	**HRQoL** (QOL-PCD questionnaire, SF-36)	**Spirometry** (FEV_1, FVC z-scores)	HRQoL: The Greek version of the adult QOL-PCD questionnaire included 40 questions that compose 10 sub-scales: physical functioning (n = 5), vitality (n = 3), emotional functioning (n = 5), health perception (n = 4), treatment burden (n = 4),

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			upper respiratory symptoms (n = 4), lower respiratory symptoms (n = 6), role (n = 4) social functioning (n = 3), hearing symptoms (n = 2). Higher scores in each subscale represent increased HRQoL.
Kenis Coskun *et al* (2019) (74)	**HRQoL** (PCD-QOL, Zerit caregiver burden scale)	**Spirometry** (FEV_1, FVC, PEF % predicted)**, anthropometry** (BMI z-score), **microbiology** (presence of *Pseudomonas aeruginosa*)	Zerit caregiver burden scale: has been widely used in investigating the caregiver burden of various chronic childhood diseases and genetic conditions. It contains 22 questions which are scored with a 5-point Likert scale. Higher scores indicate a higher burden, and the maximum score is 88.
Maglione *et al* (2014b) (75)	**HR-QoL** (SGRQ, Leicester Cough Questionnaire, SF-36), **spirometry** (FEV_1, FVC and FEF_{25-75} % predicted), **exercise testing** (6-min walk test)	**Exacerbations** (number of respiratory exacerbations, courses of antibiotics), **microbiology** (% positive sputum cultures)	Respiratory exacerbation: required systemic antibiotics.
McManus *et al* (2003) (76)	**HR-QoL** (SGRQ scores on symptoms,	**Treatment** (use of antibiotics)	Respiratory symptoms were assessed by SGRQ, which provides 3 separate scales (symptoms, activity and impact). The scores are scales in the range 0 to 100, where

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	activity and impact, SF-36 measures of Health Status physical and mental component scores)		a score of 100 indicates optimal functioning within the context of respiratory illness. Health Status overall was assessed by version 2 of the SF-36 questionnaire, which is a widely used generic instrument for assessing mental and physical functioning, for which UK population norms are also available. The questionnaire has 8 sub-scales which can be divided into 2 broad groups: physical functioning, role physical, bodily pain and general health, which are primarily physical, and energy/vitality, social functioning, role emotional and mental health, which are primarily mental. The 8 sub-scales are each scored in the range 0 to 100, where a score of 100 indicates optimal functioning. The physical and the mental component scores have well-described population norms. Respondents indicated the extent to which the symptoms had affected them over the past 4 weeks, using 5 categories: 'not at all' (scored 0), 'one day or so' (scored 1), 'a few days a month' (scored 2), 'several days a week' (scored 3), 'almost every day' (scored 4).
McManus *et al* (2006) (77)	**HR-QoL** (SGRQ: symptoms, activity, impacts; SF-36 questionnaire: PCS, MCS; General Health	**None**	Same as above for SGRQ and SF-36. Stress levels were assessed using the 12-item version of the General Health Questionnaire (GHQ). Each item is on a 4-point scale and the 4 levels on each question are given scores of 0, 1, 2 or 3, with 3 being the most serious. This scale has a range of 0 to 36, and is approximately normally distributed in the population.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	Questionnaire; 'Big Five' personality dimensions, stigma questionnaire)		The 'Big Five' personality dimensions of the Five-Factor Theory were assessed using a modified adjective checklist. Stigma questionnaire: study-specific measure. Used the stigma sub-scale of the PDQ-39, which is used to assess quality of life in Parkinson's disease, as a model on which to base and develop study-specific questions.
Pifferi *et al* (2010) (78)	**HRQoL** (SGRQ and SF-36)	**Treatment** (daily physiotherapy, regular antibiotics, regular bronchodilators, intermittent bronchodilators, mucolytics, surgical procedures)	HRQoL: SGRQ contains 50 items and 76 weighted responses divided into three components: symptoms, activity and impacts. The symptoms component comprises of eight items concerning the level of symptoms, including frequency of cough, sputum production, wheeze, breathlessness, and the duration and frequency of breathlessness or wheeze. The activity component (16 items) is concerned with physical activities that either cause or are limited by breathlessness. The impacts component (26 items) covers a range of aspects concerning social functioning and psychological disturbances resulting from airways disease. Scores ranging from 0 to 100 are calculated for each component, as well as a total score which summarises the responses to all items. A zero score indicates no impairment of quality of life. The SF-36 questionnaire contains 36 items which provide eight scales, four of which relate to physical health: physical functioning, role physical, bodily pain and general health. The remaining four scales are related to mental health: vitality, social functioning, role emotional and mental health. Each scale is scored from 0 to 100. A score of 100 in physical functioning, role physical, bodily pain, social functioning

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			and role emotional indicates absence of limitations or disability, while in general health, mental health and vitality the best health corresponds to a score of 50. These eight scales provide two summary scores: Physical Component Summary and Mental Component Summary, in which a normal score is 50±10. The normal value is 50 and diminishing scores indicate worsening conditions. A study-specific questionnaire on PCD/Kartagener Syndrome was used comprising of 15 questions relating to diagnosis, clinical features, follow-up, therapy and the presence of other PCD patients within the family. Questions on quality of life improvement after diagnosis were scores from 1=greatly worsened to 5=greatly improved.
Valero-Moreno *et al* (2020) (79)	**HRQoL** (Psychological Well-Being Scale for Adolescents (BIEPS-J), Rosenberg Self-Esteem Scale (RSE), Hospital Anxiety and Depression Scale (HADS))	**Spirometry** (FVC, FEV_1, FEV_1/FVC % predicted)	HRQoL: Psychological Well-Being Scale for Adolescents (BIEPS-J) measures psychological well-being on 4 subscales (situation control, psychosocial bonds, self-acceptance and projects). It consists of 13 items, with 3 answer options: "agree", "neither agree nor disagree" and "disagree". It has an overall emotional well-being score, which is the total of all the scores. Rosenberg Self-Esteem Scale (RSE) focused on feelings of respect for and acceptance of oneself. It consists of 10 items (a Likert format, ranging from 1 -Strongly disagree, to 4—Strongly agree), focused on feelings of respect for and acceptance of oneself. The total score ranges from 10 to 40 points, distinguishing between low (scores less than or equal to 29) and high (equal to or greater than 30) self-esteem. Hospital Anxiety and Depression Scale (HADS) evaluate cognitive clinical anxiety and depression, as opposed to the

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			somatic clinical profile. It is divided into two dimensions: the anxiety subscale (HADS-A) and the depression subscale (HADS-D). Adding the scales of anxiety and depression provides an overall score for emotional distress. Scores between 0–6 represent 'no anxiety', 7–9 'anxiety possible', over 10 'anxiety probable'. In depression, 0–5.4 represent no depression, 5.5–7.5 depression possible, over 7.5 depression probable and for emotional distress, below 15.5 no emotional distress, and over 15.5 emotional distress probable.
Whalley *et al* (2006) (80)	**HRQoL** (Stigma score, SGRQ scores on symptoms, activity and impact, SF-36 component scores on physical and mental, questionnaire on mental and physical health status)	**None**	Stigma rating: each participant was rated on a four-point scale for perceived stigma (1 = no perceived stigma to 4 = high perceived stigma). These rating were based upon an informal subject analysis of psycho-social themes within the qualitative data, including self-reported symptom concealment, trust in medicine, and current and past social support.
Zengin Akkus *et al* (2019) (81)	**HRQoL** (Ages and Stages Questionnaire for Turkish children (ASQ-TR), Ages and	None	HRQoL: Ages and Stages Questionnaire (ASQ) was administered via parent interviews in conjunction with the literature. ASQ has 19 age-specific sub-questionnaires assessing the development of children in terms of communication, gross motor skills, fine motor skills, problem solving, and personal-social skills. Ages

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	Stages Questionnaire: Social-Emotional (ASQ:SE), Child Behavior Checklist for ages 1.5 to 5 years (CBCL/1.5–5)), **sleep** (Pediatric Sleep Questionnaire (PSQ))		and Stages Questionnaire : Social-Emotional (ASQ:SE) is a screening tool designed to be completed by parents to assess their children's social-emotional behaviours in terms of self-regulation, compliance, communication, adaptive behaviours, autonomy, affect, and interactions with people. Child Behavior Checklist for ages 1.5 to 5 years (CBCL/1.5–5), which is the extended form of the checklist for the children between the ages 2 and 3, is designed to be completed by parents to score their own child's behaviours. CBCL/1.5–5 has seven syndrome scores: (i) emotionally reactive, (ii) anxious/depressed, (iii) somatic complaints, (iv) withdrawn, (v) sleep problems, (vi) attention problems, and (vii) aggressive. The combination of emotionally reactive, anxious/depressed, somatic complaints, and withdrawn scores constitute the "internalising problems score" and the combination of attention problems and aggressive scores constitute the "externalising problems score". Sleep: Pediatric Sleep Questionnaire (PSQ) is a tool to evaluate sleep-related breathing disorders in children. PSQ is composed of 22 items evaluating frequency and severity of snoring, apnoea at night sleep, breathing difficulty during sleep, daytime sleepiness, attention deficit, hyperactivity, and other paediatric obstructive sleep apnoea symptoms. Parents of children with PCD completed the validated Turkish version of Pediatric Sleep Questionnaire for the assessment of sleep related breathing disorders.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
Main study outcome: Sleep disorder			
Cohen-Cymberknoh *et al* (2019) (82)	**Sleep questionnaires** (Sleep disturbance scale for children (SDSC), Pittsburg Sleep Quality Index (PSQI), Epsworth Sleepiness Scale (ESS))**, HRQoL** (Pediatric Quality of Like Inventory (PedsQL), QOL-B)	**Spirometry** (FEV_1 % predicted)	PedsQL yields information on the physical, emotional, social and school functioning of the child during the previous 4 weeks. Abnormal scores are defined as those lower than the standard error of measurement. SDSC instrument categorises sleep disorders in children over the past 6 months in 6 subdomains to the score (disorders of initiating and maintaining sleep, sleep breathing disorders, disorders of arousal, sleep-wake transition disorders, disorders of excessive somnolence, and sleep hyperhidrosis). The average global score in the general paediatric population is 35. QOL-B contains several different scales, including symptoms, physical, social and emotional functioning. PSQI questionnaire assesses sleep quality and disturbances over a 1-month time interval that has been previously used in CF patients. There are 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. A value of >5 is regarded as evidence of poor sleep quality. ESS respondents are asked to rate their usual chances of dozing off or falling asleep while engaged in eight different activities. Values of >10 are considered as an indication of excessive daytime sleepiness, and values between 5 and 10 indicate increased normal range daytime sleepiness. In children, parents completed the ChildHood Adenotonsillectomy Trial modified ESS.

Authors (year of publication)	**Study outcomes**	**Population descriptors**	**Definition of outcome measures**
Oktem *et al* (2013) (83)	**Body plethysmography** (FVC, FEV_1 and FEV_1/FVC % predicted), **sleep questionnaire**, **PSQI** (score, poor sleepers, good sleepers), **polysomnography, HRCT**	**Anthropometry** (weight and height z-scores)	Severity of symptoms score: cough, sputum production, sputum colour, amount of sputum, wheezing, and breathlessness within the previous month was scores from 0 = none to 3 = severe. Habitual snoring was defined as snoring more than 3 days a week. HRCT: modified Brody score, with the total score derived by adding scores for each abnormality, and ranged from 0 to 37. Pittsburgh Sleep Quality Index (PSQI): "poor sleeper" was defined as those with a score of ≥ 5. Polysomnography: an apnoea hypopnea index of > 1/hr signified a positive polysomnography result and was diagnosed with obstructive sleep apnoea syndrome. Mixed apnoeic events were counted as obstructive. The following parameters were reported: total sleep time in minutes, sleep efficiency (%), Arousal index (n/hr), stage 1 (%TST), stage 2 (%TST), slow wave sleep (%TST), rapid eye movement sleep (%TST), mean saturation (%), mean lowest saturation, obstructive apnoea (n/hr), mixed apnoea (n/hr), hypopnea (n/hr), apnoea–hypopnea index. Sleep questionnaire: habitual snoring, witnessed sleep apnoea, excessive daytime sleepiness, difficulty breathing during sleep, increased parental anxiety about child's sleep, restless sweating, blue colour during sleep, parental shaking for apnoea).

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
Santamaria *et al* (2014) (84)	**Respiratory polysomnography** (obstructive apnoea index, central apnoea index, hypopnoea index, apnoea–hypopnoea index, oxygen desaturation index, mean oxygen desaturation %, mean and nadir oxygen saturation %), **sleep questionnaire** (Sleep Disturbances Scale for Children), **HRCT**	**Spirometry** (FEV_1, FVC and FEF_{25-75} % predicted), **anthropometry** (BMI), **treatment** (n antibiotic courses in the last year), **microbiology** (positive sputum cultures in the last year)	Respiratory polysomnography: Apnoea–hypopnoea index and oxygen desaturation index (ODI) ≤ 1 per hour were considered normal. Obstructive sleep apnoea syndrome was defined mild, moderate or severe if apnoea–hypopnoea index was >1 to <5, ≥5 to <10, and ≥10, respectively. Sleep questionnaire: Sleep disturbances scale used for school-aged children made of 26 items subdivided into six disorder subscales, i.e. disorders in initiating and maintaining sleep, sleep disordered breathing, disorders of arousal, sleep–wake transition disorders, disorders of excessive somnolence and sleep hyperhidrosis. The total score ranges between 26 and 130, and higher scores indicate more severe disturbances. HCRT: modified Helbich score.
Sismanlar *et al* (2018) (85)	**Sleep** (Pediatric Sleep Questionnaire, home sleep testing)**, attention deficit**	**Spirometry** (FEV_1, FVC, FEV_1/FVC, FEF_{25-75} % predicted), **radiography** (presence	Sleep: Turkish validated Pediatric Sleep Questionnaire (PSQ) was completed by the parents for assessing sleep habits and quality (187). Home sleep testing (HST) is a simple, portable and easy accessible test for evaluating sleep, and it could be used safely in children.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	(Stroop test, Conner's parents and teachers rating score)	of bronchiectasis, peribronchial wall thickening, atelectasis)	Attention deficit: Stroop test was performed, which is commonly used for evaluating selective attention, cognitive flexibility, and inhibitory control (190). Turkish validated Conner's parents (CPRS) and teacher (CTRS) rating score were used. In CPRS, there were 48 questions for evaluating children's attitude and behaviour at home. In CTRS, there were 28 questions for children's assessment of behaviours in the school. There were subscales for: inattention, hyperactivity, oppositional defiant disorder, and conduct disorder according to scales. Performance was assessed in five stages as the time (in seconds). Scoring was based on how the child completed each reading as well as reading time, correction or errors made. Turkish validated Conner's parents (CPRS) and teacher (CTRS) rating score were used. In CPRS, there were 48 questions for evaluating children's attitude and behaviour at home. In CTRS, there were 28 questions for children's assessment of behaviours in the school. There were subscales for: inattention, hyperactivity, oppositional defiant disorder, and conduct disorder according to scales.
Main study outcome: Inflammatory markers			
Bush *et al* (2006) (86)	**Inflammatory markers** (IL-8 concentration), **sputum biophysical and transport**	**Spirometry** (FEV_1 and FVC % predicted), **microbiology** (chronic infection with	Spirometry: performed according to ATS guidelines. Three reproducibility flow-volume curves with <10% variability in FEV_1 were recorded. Sputum properties: viscosity was defined as the loss of energy from a rheologic probe (stress) and thus the resistance to flow. Elasticity referred to the recoil energy transmitted back to the probe. Cohesivity was defined as interfacial tension

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	properties (dynamic viscoelasticity, wettability, cohesivity, interfacial tension, solids composition, DNA, IL-8 concentration, cough transportability)	*Pseudomonas aeruginosa*)	multiplied by the new area as after a test substance is subjected to non-shearing stress. Interfacial tension measured the interfacial tension at the sputum/air interface. Sputum was collected during exacerbation, which was defined only by the centre physician's decision to begin antibiotic therapy at clinic visit.
Cockx *et al* (2017 a) (87)	**Inflammatory markers** (Chemotactic response of PCD neutrophils to 4 chemoattractant: C5a, LTB4, chemokine CXCL5 and chemokine CXCL8)	**Spirometry** (FEV_1 and FVC % predicted), **microbiology**	Migration of the PCD polymorphonuclear neutrophils was expressed relative to migration of the reference adult control.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
Cockx *et al* (2017 b) (88)	**Inflammatory markers** (monocytes, CCR1, CCR2, CCR5, BLT1 and FPR1, CL2, fMLP, C5a, LTB4, CD14, CD16, IL-1β, TNF-α, CCL3, CCL5, CCL18 and CCL22)	**Spirometry** (FEV_1 and FVC % predicted), **microbiology** (sputum)	Inflammatory markers: The induced cytokines and chemokines present in the supernatants after 24 h of stimulation were measured by ELISA. Analysed non-classic monocytes by flow cytometry to determine whether a shift between those monocyte subgroups can be observed in PCD patients. Phagocytic capacity of monocytes was tested with fluorescent beads coated with S. aureus.
Paff *et al* (2017) (89)	**HRQoL** (change in SGRQ total score, SGRQ subscores and QoL-B scales), **LRTI-VAS** (modified score for chest pain), **exacerbations** (number of pulmonary exacerbations), **inflammatory markers in blood** (C-	**Anthropometry** (BMI), **MRC dyspnoea scale score** (0-2, ≥3), **HRCT or chest radiography** (bronchiectasis severity index score: mild, moderate, severe)	HRQoL: change in SGRQ total score (0–100, with 100 being worst QoL) after 12 weeks of treatment was the primary outcome. A 4-point reduction in SGRQ total score has previously been used as the minimal clinically important difference (MCID). Secondary outcomes included sub-scores of the SGRQ and the QoL-B (0–100, with 0 being worst QoL). SGRQ has 50 items with 76 weighted responses divided into 3 categories (symptoms, activity, impact). The categories are scored separately and can be added to provide a total score ranging from 0 to 100, with 0 indicating no impairment of health-related quality of life. The QoL-B is the first disease-specific HRQoL measure for non-CF bronchiectasis patients and includes 37 items on 8 scales (respiratory symptoms, physical, role, emotional and social functioning, vitality, health perception and treatment burden). The scores range from 0-100, with 0 indicating maximum impairment of HRQoL. Minimal clinically

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	reactive protein, erythrocyte sedimentation rate, white blood cell count, neutrophils, eosinophils, basophils, lymphocytes, monocytes), **inflammatory markers in sputum** (% sputum cell differentiation, IL-1B, IL-6, IL-8, IL-10, TNF-α, neutrophil elastase, myeloperoxidase, IFN-α, INF-β), **spirometry** (FEV_1, FVC, FEF_{25-75} %		important differences range from 7-10 for the different domains. Inflammatory markers: serum C-reactive protein, erythrocyte sedimentation rate, white blood cell count and cell differentiation, microbiological evaluation, sputum cell differentiation, sputum neutrophil elastase, interleukin-1β, -6, -8 and -10, tumour necrosis factor-α, myeloperoxidase, IFN-α and -β. Adherence was determined by the investigator count of all ampoules. LRTI-VAS: Symptoms were measured using a modified lower respiratory tract infection visual analogue scale (LRTI-VAS). Four of five symptom domains were scored similar to the LRTI-VAS: dyspnoea, fatigue, cough, chest pain, with sputum colour replaced by ease of sputum expectoration. Pulmonary exacerbation: defined as an acute and significant change in one or more of the common symptoms of bronchiectasis (increase in sputum volume or purulence, worsening dyspnoea, increased cough, declining lung function, increased fatigue/malaise) or the appearance of new symptoms (fever, pleurisy, haemoptysis, requirement for antibiotic treatment), as described by the British Thoracic Society Guideline for non-CF bronchiectasis.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	predicted), **adverse events, adherence**		
Ratjen *et al* (2016) (90)	**Inflammatory markers from sputum** (IL-8, neutrophil elastase activity, total cell count, % neutrophils, absolute neutrophils, bacterial density), **spirometry** (FEV_1, FVC and $FEF_{25–75}$ % predicted, change in FEV_1 and FVC from baseline in %, pulmonary exacerbation score), **microbiology** (presence of the	None	Pulmonary exacerbation: defined as an increase in respiratory symptoms treated with oral antibiotics. CF Akron pulmonary exacerbation score was used to measure exacerbation severity in patients with PCD and CF. Inflammatory markers and microbiology: obtained from spontaneously expectorated sputum.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	pathogens in sputum)		
Zihlif *et al* (2006) (91)	**Inflammatory markers from exhaled breath condensate and sputum** (IL-8, LTB4 and 8-isoprostane, sputum neutrophil count)	**Spirometry** (FEV_1 % predicted)	Stable pulmonary disease: defined clinically as no hospitalisation or changes in antibiotic regimen within 2 weeks prior to being in the study and FEV_1 within 10% of best recorded value in the last year. The volume loop with the highest FEV_1 was selected as opposed to the more conventional sum of FEV_1 and FVC as PCD patients often terminated their expiratory effort by coughing before their residual volume was reached. Sputum: neutrophil cell count was expressed as a percentage of total cell count.
Main study outcome: Exacerbations			
Kobbernagel *et al* (2020) (92)	**Number of exacerbations, spirometry** (FEV_1, FVC, FEF_{25-75} % predicted), **body plethysmography** (RV, RV/total lung capacity, airway residence %	**Pulse oximetry saturation** (%)**, respiratory rates** (breaths per minute)**, anthropometry** (BMI)	Respiratory exacerbation was defined as any respiratory tract symptoms leading to initiation of systemic antibiotics, irrespective of the results of bacterial culture, or decline in percent of predicted FEV_1 of ≥10% points relative to the average of %predicted FEV_1 at screening and randomisation, whether antibiotics were prescribed or not. HRQoL: Three domains of the QOL-PCD questionnaire were measured: respiratory symptoms, sinus symptoms, and ear and hearing symptoms.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	predicted), **MBW** (LCI, S_{cond}*V_T, S_{acin}*V_T), **HRQoL** (QOL-PCD), **inflammatory markers** (white blood cells, C-reactive protein, interleukin 1β, 8 and 10, granulocyte-colony stimulating factor, tumour necrosis factor α, growth-regulated oncogene α, monocyte chemoattractant protein-1), **microbiology**		

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
Piatti *et al* (2020) (93)	**Number of exacerbations, CT** (modified Bhalla score, % bronchiectasis, severity of bronchiectasis, BSI, FACED, eFACED)**, spirometry** (FEV_1, FVC % predicted)**, microbiology** (colonisation by *Pseudomonas aeruginosa*)	**Anthropometry** (BMI)	Exacerbation: defined as indicated by expert consensus. Since the median of exacerbations was 2 per year prior to the analysis in the study, patients were divided into two groups: Low-EXAC < 2/year and High-EXAC ≥2/year. CT: scores were classified according to modified Bhalla scoring system, BSI, FACED and e-FACED scores. Lingula was considered as separate lobe. If lobectomy had been performed a severity score of 3 was assigned to the missing lobe by arbitrary definition and distribution was presumed diffuse. The mean score for all lobes for each abnormality was calculated and lobar predominance was assessed. The CT scores ranged between 0 and 48. BSI identifies patients at risk of future mortality, hospital admissions and exacerbations; FACED classifies the severity of bronchiectasis according to 5-years prognosis; e-FACED detects patients with more frequent exacerbations. Classification of severity was stratified into mild, moderate, and severe according to the original Authors designations. Diagnosis of bronchiectasis was based on criteria by Naidich *et al*. Microbiology: Chronic bronchial infection was defined as the isolation of the same pathogen in sputum culture on 2 or more occasions, at least 3 months apart in a 1-year period. Patients were classified as non-colonized by *Pseudomonas aeruginosa* colonization if the pathogen had never been cultured or had been cultured only once, and as colonized if they showed at least 2 positive sputum cultures for *Pseudomonas* in 1 year (3 months apart).

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			Spirometry: according to the ATS/ERS guidelines. Volumes and flows were considered as normal when >80% of the expected value. The most recent spirometry was considered.
Main study outcome: Exercise testing			
Loomba *et al* (2017) (94)	**Spirometry** (FEV_1, FVC, FEV_1/FVC and FEF_{25-75} % predicted), **exercise testing** (peak VO_2 absolute values and % predicted, peak $EtCO_2$, exercise time, resting O_2 saturation, % increase in blood pressure, arrythmia during exercise test)	**None**	Exercise testing: modified Bruce protocol. Those undergoing cardiopulmonary exercise testing using a cycle ergometer, there was a warm-up period followed by a progressive exercise test with a modified Godfrey protocol. Ventilatory data were obtained every 15 seconds.
Madsen *et al* (2013) (95)	**N_2 MBW** (LCI, S_{cond}, S_{acin}, FRC_{N2}), **spirometry** (FEV_1, FVC, FEV_1/FVC, FEF_{25-}	**Anthropometry** (BMI z-scores), **microbiology**	VO_{2peak}: a valid peak was defined by continuous objective signs of exhaustion during verbal encouragement from the test leader, combined with at least one of the following criteria: respiratory exchange ratio >1 at test termination, or maximal heart rate > 85% of age-based predicted maximum. The VR reflecting ventilatory

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	$_{75}$ and TLC z-scores), **body plethysmography** (sRaw, FRC, RV, TLC, VC, RV/TLC z-score, Dlco and Dlco/V_A), **exercise testing** (VO_{2peak} absolute value, % predicted and z-score, maximal heart rate, test duration, oxygen pulse, maximum workload corrected for body weight, FR, VT, RER, VR, VE, $V_E/VCO_{2,\ anaerobic\ threshold\ \%\ predcited}$), **HR-QoL** (study-specific questionnaire)		capacity was calculated, as was the ventilatory equivalent of CO_2 (V_E/VCO_2) reflecting efficacy of ventilation. VR< 15% or V_E/VCO_2>40 was considered abnormal and to be positive signs of ventilatory limitation during the test. Reference values of VO_{2peak} were derived from comparable assessment in 937 healthy Danish children and young adults and this reference material was evaluated and compared with the group of matched healthy controls. Spirometry & body plethysmography: all-ages reference equations were used (115). For children, the reference equations of Koopman *et al* were used for DLco and Zapetal *et al* for whole-body plethysmography, except sRaw for which the reference equation of Kirby *et al* was used. For adults (>18 years), reference equation of Cotes *et al* and Quanjer *et al* for DLCO and whole-body plethysmography were used, respectively. N_2 MBW: Calculated LCI and the normalized phase III slope indices S_{cond} and S_{acin} using pre-reviewed normative data as reference material. HR-QoL: selected and combined validated questions from the SGRQ, CF Questionnaire (CFQ-R), SNOT-22 and SF-36, to extract simple questions about physical activity and limitations that were useful for the study. All, including healthy control subjects, answered questions on the following subjects: physical limitations in activities of every-day-life due to symptoms, subjective judgement of the difficulty performing vigorous activities, and weekly hours spent on physical

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			activities, such as running, cycling and sports. Abnormal lung function and VO_{2peak} was defined as z-score <-1.96, whereas abnormal LCI was defined as z-score >1.96. Chronic PSA: chronic infection with P aeruginosa, defined as more than 50% of positive airway cultures the previous year. Intermittent *P aeruginosa*: intermittent infection with *P aeruginosa*, defined as least one positive culture in the last year. Chronic XA: chronic infection with *Achromobacter xylosoxidans*, defined as more than 50% of positive airway cultures the previous year.
Ring *et al* (2018) (96)	**Exercise testing** (Peak oxygen uptake (VO_{2peak}) in mL/kg/min, z-score and %abnormal, single-breath diffusing capacity for carbon monoxide (DL_{CO}))**, spirometry** (FEV_1, FVC and FEF_{25-75} z-scores)	**Anthropometry** (height, BMI z-score), **microbiology**	Exercise peak: Testing was performed using an ergometer bike with step increments determined according to the modified Godfrey protocol. A national reference material of VO_{2peak} data from 937 healthy Danish children and young adults was used. DL_{CO} test was performed as a safety precaution and to exclude an obvious oxygen uptake limitation before the exercise test. The reference equation by Koopman *et al* was applied. Spirometry: "all-ages" reference equations were used for FVC, FEV_1, and $FEF_{25–75}$. All pulmonary function tests were performed according to ATS and ERS recommendations.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
Simsek *et al* (2018) (97)	**Spirometry** (FEV_1, FVC, FEV1/FVC, FEF_{25-75} % predicted), **exercise testing** (aerobic performance (modified shuttle walk test, resting heart rate, resting SpO_2%), anaerobic performance (muscle power sprint test, hand grip strength, quadriceps muscle strength, mean anaerobic power)), **physical activity level** (mean kcal per day)	**Anthropometry** (weight, height and BMI z-scores)	Spirometry: performed in sitting position, and the best of at least three technically acceptable manoeuvres were recorded. An FEV1 >85% predicted was considered normal. Physical activity level: determined using Bouchard 3-Day Physical Activity record. In the activity record, a day was divided into 15-min intervals, and energy expenditure was qualified on a scale from 1 to 9. Approximate median energy cost for each of the 9 categories in kcal/kg/15 min was used to compute the daily energy expenditure for each. The mean value from 3 days was considered for the analysis. Anaerobic performance: muscle power sprint test (MPST) was used, with subjects performing 15-m sprints 6 times at maximum pace with 10 seconds of recovery. Hand grip strength (HGS) and quadriceps muscle strength (QMS) in sitting while elbow in flexion and QMS was evaluated in sitting while knee in extension. Each muscle group was tested bilaterally, and each muscle's test was repeated for three times. Average value of three reproducible attempts was recorded in Newton. The mean value of right and left sides was calculated. Both were presented as % predicted values. Aerobic performance: 15-level modified shuttle walk test (MSWT) was considered completed when subjects were unable to maintain the required speed, fail to achieve a shuttle in the time allowed, to have a SpO2 of < 75%, and to attain maximal heart rate. The distance completed was recorded in meters.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
Valerio *et al* (2012) (98)	**Spirometry** (FEV_1, FVC and FEV_1/FVC % predicted), **exercise test** (VO_{2peak}, VE/VCO_2 slope, O_2 pulse, heart rate peak), **physical activity assessment** (total time spent in physical activity, vigorous physical activity)	**Anthropometry** (BMI and BMI SDS)	Spirometry: according to standard spirometric techniques. FEV_1 > 85% predicted was considered normal. Physical activity assessment: modified version of the long International Physical Activity Questionnaire for adolescents. The questionnaire focuses on 4 domains: school-related physical activity, including activity during physical education classes and breaks, transportation, housework and leisure time. For each of the 4 domains, the number of days per week and the number of physical activity periods per day (> 10 min of walking, moderate activity or vigorous activity) were recorded. Outcome measures were average minutes per day of walking, moderate or vigorous activities, with the sum of these variables computed to obtain minutes per day of total physical activity. Cardiopulmonary exercise test: peak oxygen consumption (VO_2peak) was recorded as the mean value of VO_2 during the last 20 seconds of the test and was expressed in millilitres per kilogram per minute. VO_{2peak} was compared with maximal predicted VO_2 by use of a sex-, age-, height- and weight-adjusted and protocol-specific formula.
Wells *et al* (2011) (99)	**Exercise testing** (maximal aerobic capacity, maximal oxygen uptake,	**Spirometry** (FEV_1 and FVC % predicted), a**nthropometry** (height, mass, lean	Spirometry: according to standard spirometric techniques and expressed as % predicted value for height and gender. Habitual Activity Estimation Scale questionnaire: was used as an estimation of activity levels as previously described and validated in this population.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	change in pH after exercise, Pi/PCr ratio (ADP ratio), halftime of PCr recovery in seconds, work during exercise trial in Watts)	body mass), **Habitual Activity Estimation Scale questionnaire**	Change in pH after exercise (rest pH - end-exercise pH) - Intracellular pH was calculated for each spectrum based on the chemical shift difference between PCr and Pi. The cytosolic [Mg2] was calculated from the chemical shift of ATP measured from the resonance of PCr, and this information was used to correct calculated pH for changes in [Mg2] Halftime of PCr recovery (seconds): The time constant of the recovery rate of PCr was calculated during recovery after each exercise bout using an exponential curve fit Work during exercise trial (Watts): Watts and repetitions per minute (rpm) of the ergometer were recorded every 5 seconds during exercise
Main study outcome: Others			
Joensen *et al* (2014) (100)	**Breath profiles** (volatile organic compounds), **microbiology** (chronic infection), **number of exacerbations**	**Spirometry** (FEV_1 and FVC % predicted)	Microbiology: chronic infection was defined by the Copenhagen criteria (persistent presence of pathogen in microbiological culture samples for at least 6 consecutive months, or less when combined with the presence of 2 or more *Pseudomonas aeruginosa* precipitins). Samples were obtained by expectoration sputum, endo-laryngeal suctioning and bronchoalveolar lavage. Pulmonary exacerbation was defined as need to start additional antibiotic therapy and presence of at least 2 of the following criteria: change in sputum volume and/or colour, increased coughing, increased lethargy, feeling unwell, or increased need for sleep, decreased appetite or weight loss, decrease in lung function ≥10%,

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			increased shortness of breath or new acquired radiological changes. Spirometry: performed according to the ATS/ERS guidelines. Exhaled breath sampling: 2 measurements per patient were performed with an interval of 5 minutes between them.
Kawakami *et al* (1996) (101)	**Chronic sputum production** (duration throughout the year, daily amount, colour), **sputum and nasal scores**	**Fertility** (sperm motility)	Sputum and nasal scores were calculated to estimate the severity of the symptoms using the answer from the patients in the following manner. Most severe symptoms for each question were valued at 30. Scores were obtained by summing the points from the five questions concerning chronic sputum production and from the six questions concerning chronic nasal symptoms, respectively. The maximum possible scores for the sputum and the nose were 150 and 180 respectively and 0 indicated that they had no symptoms. Chronic sputum production: obtained from questionnaires sent to patients. Questions included duration of sputum production throughout the year, daily amount of sputum and colour of mucus.
Kennedy *et al* (2007a) (102)	**Lythoptysis** (symptoms), **radiographic findings** (calcium deposition)	**Spirometry** (FEV_1 % predicted), **microbiology, lobectomy**	Spirometry: FEV_1 used was the best +/- 1 year of when the CT scan was performed. Symptoms of lythoptysis: spitting up a hard concretion, a firm stone-like structure in the sputum or a gritty sensation in the sputum. Radiographic findings: evidence of calcification.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
Marino *et al* (2019) (103)	**Nutrition** (vitamin D, selenium, zinc, copper, ferritin, folate, vitamin B12, vitamin B6, iron, transferrin, transferrin iron saturation, haemoglobin, albumin, calcium, phosphate, magnesium, low energy intake), **spirometry** (FEV_1 and FVC % predicted and z-scores)**,** **anthropometry** (weight, height and BMI z-scores, fat free mass index,	None	Spirometry: performed according to ERS/ATS guidance. GLI equations were used to estimate z-scores for FEV_1 and FVC; ethnicity specific equations were used where available. Anthropometry: performed and recorded in accordance with WHO guidelines. Moderate malnutrition was defined as a height-for-age, weight for height, BMI or FFMI of ≤ -2 z-scores below the mean of the WHO child growth standards. Reference nutrient intake (RNI) for protein and estimated average requirements (EARs) for energy. As recommended by the Scientific Advisory Committee on Nutrition in the United Kingdom (SACN), insufficient protein was defined as an intake <100% of the lower reference nutrient intake (LRNI—meeting nutrient requirements for 2.5% of population), sufficient intake was between the LRNI 100% and ≤200% of the RNI and excessive intake ≥200% of the RNI.

Authors (year of publication)	**Study outcomes**	**Population descriptors**	**Definition of outcome measures**
	bioelectrical impedance spectroscopy)**, inflammatory markers** (c-reactive protein, alkaline phosphatase, pro-inflammatory cytokines (IL-1B, IL-2, IL-6, IL-8 & TNF-α))		
Mirra *et al* (2015) (104)	**Vitamin D** (total 25(OH)D), **body plethysmography** (FVC, FEV_1, FEF_{25-75}, FRC, RV and FEV_1/FVC % predicted), **HR-QoL** (SGRQ), **physical activity assessment**	**Anthropometry** (BMI), **HRCT** (bronchiectasis), **treatment** (number of courses of antibiotics)	Vitamin D levels: categorized as being sufficient when >30 ng/ml (>75 nmol/L), insufficient between 20 and 30 ng/ml (50 and 75 nmol/L), and deficient when <20 ng/ml (<50 nmol/L) Self-reported physical activity: assessed using a previously published questionnaire by Madsen *et al*. Microbiology: chronic bacterial colonization was defined as persistence of specific bacteria for at least 6 months, with at least 3 positive cultures.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	(questionnaire), **microbiology**		
Montuschi *et al* (2014) (105)	**Breath profiles** (ethanol, methanol, saturated fatty acids, formate, lactate, acetate, leucine/isoleucine, isobutyrate, glutamine/glutamic acide)	**Spirometry** (FEV_1 and FVC % predicted), **microbiology** (sputum culture), **anthropometry** (BMI), **treatment** (inhaled medication)	Not reported – correspondence, therefore limited information available.
Noone *et al* (1999) (106)	**Clearance during cough** (mean clearance rates (%/min)), **sputum production rate** (sputum rheology and ion content (Avg Log G, cough-clearance index,	**Spirometry** (FEV_1 % predicted), **cough questionnaire** (cough severity and type, amount, ease of expectoration, and nature of sputum, chest tightness, and wheezing)	Studied clearance during a series of controlled coughs from t = 20 to 60 min (t = 0 to 20 min represents the period of delivery of solution). The total number of coughs (spontaneous plus controlled) was limited to 90 during the 60-min period by having each subject cough under the direction of the investigators into a spirometer. Sputum was obtained during the cough manoeuvres as soon as possible after aerosol delivery was completed. Sputum production rate: if a subject produced X grams of sputum Y minutes after the commencement of the study, the sputum production rate was calculated as X/Y grams per minute for that individual.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	mucociliary-clearance index, Na+ content, Cl- content))		Questionnaire: Before and after aerosol dosing, patients were asked to score, on a questionnaire sheet, the severity and type of their cough, amount, ease of expectoration, and nature of sputum, chest tightness, and wheezing, on a scale of 0 to 10. They were also asked to record comments about any symptoms or feelings in the chest after inhalation.
Paff *et al* (2013) (107)	**Exhaled breath profile** (volatile organic compounds)	**Spirometry** (best FEV_1 and FVC in past year % predicted), **microbiology** (positive bacterial cultures by pathogens), **pulmonary exacerbations** (number of episodes)	Pulmonary exacerbation: defined as the need to start additional antibiotic treatment as a consequence of a recent change in at least 2 of the following: change in sputum volume or colour, increased cough, increased shortness of breath, increased malaise, fatigue or lethargy, temperature over 38^{o} Celsius, anorexia or weight loss, change in sinus discharge, change in physical findings on examination, decrease in pulmonary function by 10% or more and radiographic changes, according to CBO guidelines based on internationally accepted criteria. Exhaled breath profile: collected with reverse valve system allowing tidal inspiration through a face mask and inspiratory VOC filter and tidal expiration into the spacer. The VOC filter minimizes the influence of environmental VOCs on the breath profile as a potential source of bias. The spacer was connected to the electronic nose during sampling for direct sample analysis during tidal breathing.
Pifferi *et al* (2017) (108)	**Spirometry** (FEV_1, FVC, FEF_{25-75} and FEV_1/FVC z-scores)**,**	None	HRCT: The modified Bhalla score includes severity of bronchiectasis (score 0-3) and extent of bronchiectasis (score 0-3), mucous plugging (score 0-3), peribronchial thickening (score 0-3), parenchymal abnormalities, such as atelectasis (score 0-3) and

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
	HRCT (modified Bhalla)**, body plethysmography** (Raw, sRaw, sReff, FRC, RV, TLC and RV/TLC z-scores) **microbiology, extracellular matrix** (metalloproteinase-8 and -9, metalloproteinase tissue inhibitors)		focal air-trapping (score 0-3). Bronchiectasis was identified according to standard criteria. Severity class for total lung impairment (from 1 to 3) was calculated: class of severity 1 for total score of 0-6, class 2 for total score of 7-12, class 3 for total score of 13-18. Spirometry and body plethysmography: performed according to ATS guidelines. At least three reproducible manoeuvres were obtained for each patient. To be accepted, single inspiratory manoeuvres needed to have yielded virtually superimposable XY plots, and values of FRCpleth had to be within 5% of each other.
Shoemark *et al* (2009) (109)	**FENO** (FENO50, FENO100, FENO200, J'awNO, CalvNO)	**Anthropometry** (height, weight), **spirometry** (FEV_1 raw), **treatment** (requirement for antibiotics, inhaled corticosteroids), **microbiology**	Fraction of exhaled nitric oxide (FENO): J'awNO is total NO flux in the airways and CalvNO is steady-state NO concentration in alveolar air. The mean of 2 FENO measurements at each flow rate measured (50, 100 and 200 ml/s) was used to calculate J'awNO and CalvNO, according to ATS standards. Nasal NO: measured according to ATS/ERS standards using the breath-hold technique for velum closure.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
		(pathogens in sputum samples), **nasal NO** (ppb)	
Smit *et al* (1996) (110)	**Lung resection** (location and extent), **symptoms questionnaire**	**Spirometry** (FEV_1 and FVC % predicted), **bronchiectasis** (n and % bilateral), **dyspnoea index** (0+1, 2, 3+4), hospitalisations	Symptoms questionnaire: present complain about daily cough, phlegm, haemoptysis, respiratory infections, dyspnoea, fitness for work, and the influence of resection on pulmonary complaints.
Zihlif *et al* (2005) (111)	**Cough frequency** (n cough episodes), **cough symptom score**	**Spirometry** (FEV_1 % predicted), **eNO, inflammatory markers** (sputum neutrophil count), **microbiology** (presence of pathogens)	Exhaled Nitric Oxide (eNO): the mean value out of three correctly executed exhalations was recorded. Spirometry: at least 2 manoeuvres were required to have an FEV_1 within 10% of each other. Baseline FEV_1 was recorded as the best of three manoeuvres. Values were expressed as percent of predicted normal values. Cough frequency: cough was identified by 2 signals: the electromyography signals from the muscles of active expiration, and a filtered audio signal. Visual inspection confirmed that all cough epochs identified automatically were in fact genuine. Coughing events were counted both as individual spokes and as clusters. Each cluster (cough epoch) was arbitrarily defined as a close succession of cough spikes (<2 seconds between individual coughs) recorded by each trigger of the recorder.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
			Cough data were expressed as total numbers of cough episodes (individual spikes + cough cluster) per recording time. Cough symptom score: questionnaires handed to parents, with scores ranging from 0 = no cough to 5 = distressing cough
No main study outcome			
Abitbul *et al* (2016) (112)	None	**CT** (bronchiectasis), **fertility, microbiology** (sputum cultures), **spirometry** (FEV_1 % predicted)	Not described
Boon *et al* (2014) (113)	None	**Anthropometry** (weight, height and BMI z-scores), **spirometry** (FEV_1 and FVC z score), **microbiology** (life-time prevalence), **chest radiographs and CT**	Chest radiographs or CT scans: presence or absence of pulmonary infiltrates, lobar consolidation/atelectasis and bronchiectasis. Microbiology: Sputum, bronchoalveolar lavage or cough swabs available since diagnosis were evaluated for the presence of respiratory pathogens, and lifetime prevalence was reported as 'has ever had infection with'. Chronic colonisation by pathogen was defined as persistence of the same bacteria in at least 3 sputum samples over a period of at least 6 months. Anthropometry: weight, height and BMI were reported as z-scores, according to Flemish growth curves. Spirometry: z-scores reported according to Quanjer equations.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
Eden *et al* (2019) (114)	None	**Spirometry** (FEV_1, FVC, FEV_1/FVC % predicted), **microbiology, number of exacerbations** (past 2 years)	Exacerbations were recorded as historical information and based on the answer to the BRR baseline question: "Has the patient experienced an exacerbation of bronchiectasis within the past 2 years?" Investigators at each centre had available the definition of an exacerbation as given by O'Donnell *et al* as a guideline for the response to the question.
Emiralioglu *et al* (2020) (115)	None	**Spirometry** (FEV_1, FVC, FEF_{25-75} % predicted and z-scores)**, anthropometry** (BMI z-scores)**, microbiology, lobectomy** (history), **CT** (bronchiectasis)	Anthropometry: BMI was calculated by dividing weight in kilograms by the square of height in meters. The z-score for BMI-for-age was obtained from the WHO AnthroPlus packet programme. Spirometry: performed in accordance with the American Thoracic Society standards.
Frija-Masson *et al* (2017) (116)	None	**Spirometry** (FEV_1 % predicted, FEV_1, FVC, FVC, TLC, TLC, FEV_1/FVC % predicted),	Spirometry: performed according to the ERS/ATS guidelines. Postbronchodilator FEV_1 was used and FEV_1 decline was calculated if there were 3 or more values of FEV_1 and a follow-up of at least 2 years. Annual decline was calculated according to the European Coal and Steel Community (ECSC)/ERS 1993 reference equation. Microbiology: chronic infection was defined as those with a positive pathogen in at

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
		microbiology (with and without chronic *Pseudomonas aeruginosa* infection), **HRCT** (modified Bhalla score), **dyspnoea score** (Modified Medical Research Council scale), **treatment** (number of courses of antibiotics (IV, oral, inhaled)), **fertility, lobectomy** (long-term oxygen use, lung transplant), **mortality**	least 3 sputum samples in less than 6 months. CT scoring system: modified Bhalla score for chest bronchiectasis. In patients with situs inversus, the lung in which the middle lobe was identified was considered as the right lung. The scores from the 6 lobes were summed to provide a total score ranging from 0 (normal) to 48 (maximal score).
Knowles *et al* (2014) (117)	**None**	**Spirometry** (FEV_1 % predicted), **fertility** (status)	Spirometry: FEV_1 % predicted was calculated using ERS Task Force multi-ethnic reference values. The latest available FEV_1 was used for the *RSPH1* individuals and the value recorded at the research visit for the classic PCD cases.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
Noone *et al* (2004) (118)	**None**	**Spirometry** (FEV_1 % predicted), **microbiology** (sputum), **radiographs** (presence of bronchiectasis), **cough** (number)	Bronchiectasis was primarily diagnosed clinically based on history of chronic excess mucopurulent sputum production associated with finger clubbing, and, where available, computed tomographic scans of the thorax or with clear abnormalities on chest radiographs were also used to support the diagnosis.
Pifferi *et al* (2015) (119)	**None**	**Spirometry** (FEV_1, FVC and FEF_{25-75} % predicted, changes in FEV_1 and FEF_{25-75} % predicted after bronchodilator), **HRCT** (bronchiectasis (%), class total lung impairment, class extent of bronchiectasis, class severity of bronchiectasis),	Spirometry: best of three flow volume loops was recorded (15 minutes after administration of bronchodilator, when applicable). The % change in FVC. FEV_1 and FEF_{25-75} was calculated to assess bronchodilator response. HRCT: same as above. Secondary ciliary dyskinesia: defined as abnormal ciliary movement or abnormal TEM results that are not PCD-specific or that disappear upon cellular regrowth in culture.

Authors (year of publication)	Study outcomes	Population descriptors	Definition of outcome measures
		microbiology (infection with *P aeruginosa*)	
Yiallouros *et al* (2015) (120)	**None**	**CT** (presence of bronchiectasis), **microbiology** (presence of pathogens in sputum culture), **spirometry** (FEV_1 and FVC z-scores, % with low FEV_1 and % with low FVC), **anthropometry** (BMI z score), **lobectomy** (location of resected lobe)	Spirometry: z-scores < -1.96 were considered abnormal. Anthropometry: BMI was expressed as age- and gender-specific z-scores based on the US Centers for Disease Control 2000 growth charts.

HRCT: High-resolution computed tomography, CT: computed tomography, FEV_1: forced expiratory volume in one second, MBW: multiple-breath washout, SBW: single-breath washout, FRC: functional residual capacity, SD: standard deviation, FVC: forced vital capacity, HRQoL: health-related quality of life, QOL-PCD: Quality of life-primary ciliary dyskinesia, SF-36: Short-Form 36 Health Survey, SGRQ: St George Respiratory Questionnaire, SNOT-20: Sino-Nasal Outcome Test 20, COPD: chronic obstructive pulmonary disease, BMI: body mass index, FEF_{25-75}: forced expiratory flow at 25-75%, LCI: lung clearance index, ATS: American Thoracic Society, ERS: European Respiratory Society, IL: interleukin, IQ: intelligence quotient, LT; leukotriene, CXCL: chemokine ligand, TLC: total lung capacity, IV: intravenous, SPO_2: peripheral capillary oxygen saturation, VO_2: oxygen consumption measured during incremental exercise, $EtCO_2$: end-tidal carbon dioxide, RV: residual volume, DL_{CO}: diffusing capacity of the lungs for carbon monoxide, VR: ventilatory reserve, Abx: antibiotics, DTG: double-tracer gas, VOC: volatile organic compounds, TNF: tumor necrosis factor, IFN: interferon, PEFR: peak expiratory flow rate, FRCpleth: functional residual capacity made by plethysmography, Pi: inorganic phosphate, PCr: phosphocreatine, ADP: adenosine di-phosphate, ATP: adenosine-5'-triphosphate

Supplementary E-table 3. Summary of study characteristics of cross-over randomised controlled trials included in this systematic review.

Authors (year of publication)	***n* PCD patients**	**Intervention**	**Reference group**	**Limitations**
Kobbernagel *et al* (2020) (92)	90	Azithromycin maintenance therapy	Placebo	Did not reach the estimated sample size of 125 patients
Paff *et al* (2017) (89)	22	Hypertonic saline	Isotonic saline	Small sample size Non-disease-specific outcomes Isotonic saline might have beneficial effect
Gokdemir *et al* (2014) (24)	24	High frequency chest wall oscillation	Conventional pulmonary rehabilitation	Small sample size Short follow-up and wash-out periods No *a priori* definition of clinically significant effect
Koh *et al* (1999) (27)	19	Salbutamol	Placebo	Small sample size Over 80% had bronchiectasis (disease severity) Unclear if all had PCD (only 42% had hallmark TEM) Lack of definition for clinical stability

Authors (year of publication)	***n* PCD patients**	**Intervention**	**Reference group**	**Limitations**
Noone *et al* (1999) (106)	12	Aerosolised uridine-5'-triphosphate	Placebo (0.12% saline)	Small sample size All had bronchiectasis (disease severity) Unclear clinical significance as differences were only temporary