Estimates of primary ciliary dyskinesia prevalence: a scoping review

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This scoping review systematically examined the primary ciliary dyskinesia literature to determine the best global prevalence estimate, and highlights the key considerations of disease frequency studies and the methodologies implemented https://bit.ly/3TQJbIY

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Abstract

Background Primary ciliary dyskinesia (PCD) is a rare multisystem genetic disease caused by dysfunctional motile cilia. Despite PCD being the second most common inherited airway disease after cystic fibrosis, PCD continues to be under-recognised globally owing to nonspecific clinical features and the lack of a gold standard diagnostic test. Commonly repeated prevalence estimates range from one in 10 000 to one in 20 000, based on regional epidemiological studies with known limitations. The purpose of this scoping review was to appraise the PCD literature, to determine the best available global PCD prevalence estimate and to inform the reader about the potential unmet health service needs in PCD. The primary objective of the present study was to systematically review the literature about PCD prevalence estimates.

Methods A scoping review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) methodology. Included studies estimated PCD prevalence and used cohort, clinical or genomic data. Case reports, conference abstracts, review articles, animal studies or non-English articles were excluded.

Results A literature review identified 3484 unique abstracts; 34 underwent full-text review and eight met the inclusion/exclusion criteria. Seven articles were based on epidemiological studies of specific geographical regions and provided prevalence estimates that ranged from approximately one to 44.1 in 100 000. Only one study estimated global prevalence, using two large genomic databases, and calculated it to be ~13.2 in 100 000 (based on pathogenic variants in 29 disease-causing genes).

Conclusions A population-based genomic approach for estimating global prevalence has found that PCD is much more prevalent than previously cited in the literature. This highlights the potential unmet health service needs of people living with PCD.

Introduction

Primary ciliary dyskinesia (PCD) is a rare genetic multisystem disease involving dysfunctional motile cilia [1], which can affect mucociliary clearance, fertility and organogenesis. Clinical manifestations vary by age (table 1). *In utero*, patients with PCD may demonstrate laterality defects on fetal ultrasound (which occur in about 50% of patients). Shortly after birth, they can present with neonatal respiratory distress, hypoxaemia and abnormalities on chest X-ray that may require prolonged hospitalisation during the neonatal period [2, 3]. Later on, usually before 6 months of age, patients with PCD generally develop a chronic wet cough, nasal congestion and recurrent respiratory tract/otological infections. By adulthood, most patients will develop bronchiectasis and experience subfertility [4].

TABLE 1 Select primary ciliary dyskinesia clinical manifestations by age

Age	Common clinical manifestations based on age
Fetus	Laterality defects (~50%)
Infancy	Laterality defects, neonatal respiratory distress, wet cough, nasal congestion, chest infection, atelectasis
Childhood	Laterality defects, chronic wet cough, chronic nasal congestion, otitis media, conductive hearing loss, rhinosinusitis, chest infection, atelectasis, bronchiectasis
Adulthood	Laterality defects, chronic wet cough, chronic nasal congestion, otological dysfunction, rhinosinusitis, chest infection, atelectasis, bronchiectasis, infertility

The heterogeneous, and often nonspecific, PCD clinical manifestations combined with the lack of a diagnostic gold standard test can lead to diagnostic delays. The reported median age of diagnosis in European children was 5.3 years in 2009 [5], and for England it was 2.6 years in 2015 [6]. PCD experts have developed disease prediction tools to aid in the identification of potential PCD patients and to increase the positive predictive value of diagnostic testing [7, 8]. In North America, the diagnostic tests for PCD [9] typically include nasal nitric oxide (nNO) measurement [10], transmission electron microscopy (TEM) analysis assessing for causative ciliary ultrastructural defects [11] and genetic panel testing for variants in a portion of the 51 PCD-associated genes [9, 12]. In Europe, high-speed video microscopy (VM) analysis is also used as part of the diagnostic workup [13]. Unfortunately, these confirmatory diagnostic tests still miss up to 30% of PCD cases and are generally limited to specialised centres [9]. These limitations have made estimating the disease frequency of PCD challenging, despite it being the second most common inherited airways disease after cystic fibrosis (CF) [14].

Until recently, the commonly reported and repeated PCD prevalence estimates ranged from approximately one in 10 000 to one in 20 000 [15–17]. For comparison, the estimated incidence of CF, in live births of European descent, is one in 3000 to one in 6000 [18, 19]. CF disease frequency is typically reported as incidence, as opposed to prevalence, owing to several diagnostic advancements in the field. Previously, CF disease frequency was reported as a prevalence, based on epidemiological cross-sectional studies, which underestimated the disease frequency due to missed diagnoses, underreporting of cases and the variability in the geographical distributions and time periods of the studies [20]. However, with the implementation of newborn genetic screening and the complete registration of cases detected at birth, CF incidence became the more reliable estimate of disease frequency [20].

However, unlike CF, there is a lack of a diagnostic gold standard for PCD and the limitations of epidemiological studies have made estimating disease frequency difficult. Nonetheless, it is important to know PCD disease frequency to understand the global burden of disease and improve resource allocation in the diagnosis and management of PCD patients.

Therefore, the purpose of this scoping review was to systematically identify and appraise articles that estimate the prevalence of PCD, for readers to gain a greater understanding of the strengths and limitations of these studies, to determine the best available global prevalence estimate for PCD and to inform on the potential unmet health service needs of this patient population.

Methodology

Inclusion and exclusion criteria

Articles were included if they aimed to estimate the prevalence of PCD. Articles were excluded if they were case reports, conference abstracts, review articles, animal studies or non-English articles.

Search strategy

An *a priori* scoping review protocol following the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) methodology was conducted [21]. The initial pilot search included terms related to the disease (supplementary table S1). One reviewer (WBW) scanned the first 100 articles (from 1950 onwards) to identify key terms to build the full search strategy. The full search strategy was conducted in MEDLINE, Embase, Cochrane Central Registry of Controlled Trials, Web of Science and Scopus. The citation managers used include EndNote (version 7.8; Thomas Reuters, Philadelphia, PA, USA) and Covidence (Veritas Health Innovation, Melbourne, Australia).

The full search strategy was performed on 15 February 2024. Three reviewers (WBW, DG, ES) independently assessed the titles and abstracts for eligibility. Full texts were obtained for all studies

TABLE 2 Search results

Database[#]	Results
Ovid MEDLINE	793
Embase Classic+Embase	693
Cochrane Central Registry of Controlled Trials	35
Web of Science	2678
Scopus	721
Total (not deduplicated)	4920
Total (deduplicated)	3484

[#]: searches run 15 February 2024.

deemed relevant by all reviewers, and abstracts were eliminated by consensus. If there were any uncertainties with eligibility a fourth reviewer (SDD) reviewed the abstract. Additional abstracts were identified using the references of included articles and reviewed by WBW. Full-text reviews were completed by reviewer WBW and if there were any reservations, then the full text was reviewed by the senior reviewer, SDD.

Data extraction was performed by reviewer WBW using a standardised data extraction form based on a template from Covidence (supplementary table S2). This form included the publication details (*i.e.* authors, title, year of publication, country), journal study characteristics (*i.e.* data collection period, study design, countries, sample size, database characteristics) and outcome details (prevalence estimates).

Results

The original literature search identified 4920 abstracts with 1437 duplicates (table 2). One additional abstract was found from other sources (*i.e.* article references). After deduplication, 3484 unique abstracts were reviewed and 34 were identified for full-text review. Of those, eight met the inclusion and exclusion criteria and were included in the scoping review (figure 1) [5, 15, 22–27].

Study characteristics

The included articles were primarily epidemiological studies that used data from patient cohorts and registries that spanned at least 22 countries and from the 1940s to the present. The largest combined patient

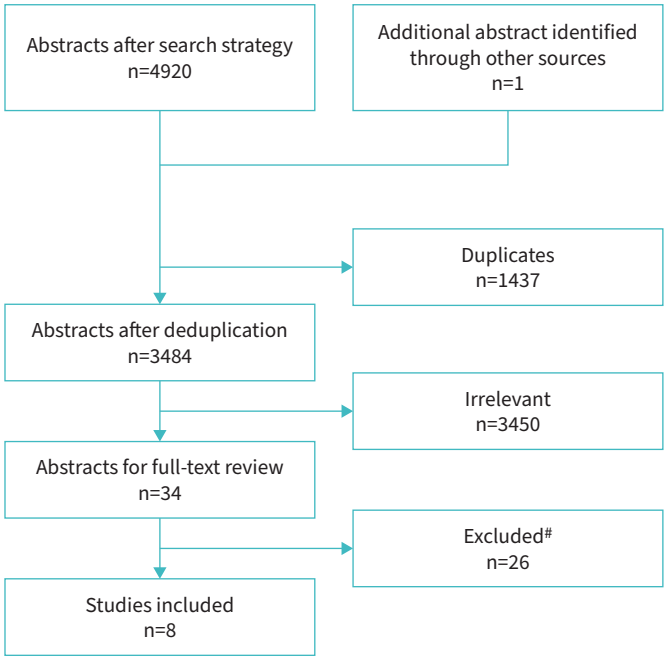

FIGURE 1 Literature flow diagram. [#]: full-text articles were excluded if they were case reports, conference abstracts, review articles, animal studies or non-English articles.

registry had 3824 patients. One article [22] used aggregate genomic data from Invitae and GnomAD databases (https://data.mendeley.com/datasets/nc3zm6v6cg/1), which had a total of 182 681 records.

Case definition

The case definitions used in the studies were highly variable (table 3). Among the registry studies, the most rigorous PCD case definitions were based on diagnostic algorithms (*e.g.* nNO, high-speed VM, TEM, immunofluorescence and genetics). Studies conducted in the last decade were more likely to use this rigorous PCD case definition. Other older registry studies were less precise, including a Japanese study that inferred a PCD diagnosis based on the clinical manifestations of situs inversus totalis (SIT) and bronchiectasis [23]. Another study only reported their TEM and VM results when diagnosing PCD [27]. Three other studies [5, 15, 24] did not provide sufficient details or discussions about the case definitions. A genomic study [22] used a PCD case definition based on pathogenic variants in 29 PCD disease-causing genes.

Study population

Most studies used study populations that were restricted to geographical regions such as Japan [23], Sweden [24], Bradford (UK) [27], Israel [25] and Switzerland [26]. One registry study used data from 22 countries, listed in table 3. Some studies identified a high rate of consanguinity in their study populations, including the British Asian population in Bradford, UK, and the non-Jewish (*i.e.* Druze and Arab Muslim) population in Israel [25, 27]. The genomic study used all data that were available in the Invitae and GnomAD genetic databases and assumed these databases were representative of the global population, although the genes were primarily identified in North American and European centres [22].

Estimated prevalence

There was a wide range of prevalence estimates reported in the manuscripts (table 3): Japanese: one in 16 400 [23]; Swedish: one in 10 000 [24]; South Asian (Pakistani and Bangladeshi) in Bradford, UK: one in 2265 [27]; Israeli (Jewish and non-Jewish): one in 54 000 [25]; and Swiss: one in 63 000 [26]. A European estimate based on the combined national PCD registries (*i.e.* Cyprus, Norway, Denmark, Switzerland) was three to seven in 100 000 (for children age 0–19 years) and 0.2 to six in 100 000 (for adults) [15]. Another European prevalence estimate, based on countries that had a >60% response rate from surveyed institutions, was ∼14.8 in 1 000 000 (for children age 5–14 years) [5]. The study using the Invitae and GnomAD genetic databases estimated the global prevalence to be one in 7554 [22].

Discussion

The initial pilot search was conducted in PubMed and consisted of ("primary ciliary dyskinesia" OR "PCD" OR "ciliopathy" OR "Kartagener's syndrome" OR "immotile cilia syndrome") AND ("prevalence" OR "incidence" OR "frequency"). This search strategy found numerous articles, with the majority referencing other papers, and most notably no scoping or systematic reviews were found. The most recently published manuscript estimating PCD global prevalence suggested that the core PCD prevalence studies could be distilled down to four articles, and noted the limitations of these articles [22]. In our scoping review, we found an additional four articles that provided prevalence estimates when using a more comprehensive search strategy (supplemental table S3) and one additional article based on the references of the included articles. We excluded the two articles by Torgersen [28, 29] because they were not estimating the prevalence of PCD but rather the prevalence of laterality defects. This highlights the value of conducting a well-designed scoping review that systematically searches all available medical literature databases.

Seven of the eight articles were epidemiological studies that provided prevalence estimates for a specific geographical region (*e.g.* city, country or continent). The regional prevalence estimates were from Bradford (a district in the UK), Sweden, Japan, Israel, Switzerland, and combinations of European countries. The estimates were one in 2265 (Bradford, UK), one in 10 000 (Sweden), one in 16 400 (Japan), one in 54 000 (Israel), one in 63 000 (Switzerland), 14.8 in 1 000 000 (European children 5–14 years old), three to seven in 100 000 (European children 0–19 years old) and 0.2 to six in 100 000 (European adults) [5, 15, 23–27]. The large variation in the prevalence estimates may be, in part, due to differences in the geographical regions and time periods when the studies were conducted, given that this would impact the study population and case definitions. For example, the estimated prevalence may be higher [30] in geographical regions that have isolated communities, founder mutations or higher rates of consanguinity [25, 27] (*e.g.* *RSPH4A* in Puerto Rico [31, 32], *CCDC114* in Volendam, the Netherlands [33] or *DNAH5* variant in Amish communities [34]). Additionally, over time the case definition for PCD has evolved from a syndrome (*e.g.* Kartagener's syndrome) to confirmatory diagnostic testing. Conceivably, earlier studies may not have included individuals with PCD, particularly those with subclinical or uncommon clinical manifestations. But there are also other limitations to the study designs.

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TABLE 3 Database characteristics and prevalence definitions used by the included studies

Study	Source	Case ascertainment	Case definition	Study population	Estimated prevalence
Katsuhara *et al.* 1972 [23]	Atomic Bomb Casualty Commission and Adult Health Study	8 cases identified by radiological screening of study population	SIT SIT and bronchiectasis	Population living in geographic region affected by the Atomic Bomb in Hiroshima and Nagasaki, Japan	SIT: 1 in 4100 SIT and bronchiectasis: 1 in 16 400
Afzelius and Stenram 2006 [24]	Swedish database	239 PCD patients identified by physician	Immotile ciliary syndrome	Swedish children	1 in 10 000
O'Callaghan*et al.* 2010 [27]	Bradford, UK	19 PCD patients identified by physician	PCD diagnosed based on VM and TEM	South Asian (Pakistani and Bangladeshi) population in Bradford, UK	1 in 2265
Kuehni *et al.* 2010 [5]	Questionnaire survey (26 European countries) Surveys returned: 223 Response rate: 51.8%	1192 PCD patients identified by physician	Clinician-diagnosed PCD Unknown if based on diagnostic testing or clinical diagnosis	Children (aged 0–19 and 5–14 years) in European countries Limited to paediatricians and institutions that were considered likely to be treating paediatric PCD patients in Europe	In countries that had >60% response rate, the estimated prevalence per million of inhabitants aged 5–14 years old: 3.0 (the Netherlands) 3.3 (Slovakia) 4.9 (Finland) 5.1 (Portugal) 6.9 (Belgium) 8.7 (France) 14.7 (Greece) 17.3 (Hungary) 20.5 (Spain) 24.1 (Austria) 24.6 (Israel) 45.7 (Denmark) 47.4 (Switzerland) 111.0 (Cyprus) 14.8 (total of above countries)
Abitbul *et al.* 2016 [25]	National multicentre (2012–2013) 14 paediatric centres 51 paediatric pulmonologists	150 PCD patients identified by physician: Jewish, n=44 Arab, n=91 Druze, n=13 Unknown, n=2	PCD diagnosed using nNO, VM, TEM, IF and genetics	Israeli population	1 in 54 000 general population 1 in 25 000 children (age 5–14 years) 1 in 30 000 children (age 0–19 years) 1 in 100 000 adult (age >19 years) 1 in 16 500 (non-Jewish) 1 in 139 000 (Jewish)
Goutaki *et al.* 2019 [26]	Swiss Primary Ciliary Dyskinesia Registry	134 PCD patients identified by physician (566 physicians)	PCD diagnosis stratified by diagnostic certainty because not all diagnostic tests were up to standard Diagnostic tests that were assessed included nNO, TEM, genetics and VM	Swiss population	1 in 63 000
Ardura-Garcia *et al.* 2020 [15]	National registries: Danish PCD Registry Cyprus PCD Registry	Cases identified by physician 136 PCD patients 44 PCD patients	Patients referred to the Danish national PCD centre for diagnostic workup Patients referred to the Cyprus national PCD centre for diagnostic workup	Danish population Cypriot population	European estimates based on the Danish, Cyprus, Swiss and Norwegian PCD Registries: 3–7 in 100 000

Continued

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TABLE 3 Continued

Study	Source	Case ascertainment	Case definition	Study population	Estimated prevalence
	Swiss PCD Registry	139 PCD patients	Patients identified by contacting specialists and patient organisations	Swiss population	(age 0–19 years) 0.2–6 in 100 000 (adults)
	Norwegian PCD Registry	91 PCD patients	Combination of patients referred for workup and actively contacting specialists	Norwegian population	
	English Paediatric PCD Management Service	396 PCD patients	National diagnostic service	English, 0–17 years old	2.7 in 100 000 (paediatric)
	French RaDiCo-PCD Cohort	185 PCD patients	Patients identified by contacting specialists and patient organisations	French population	0.6 in 100 000 (age <20 years) 0.4 in 100 000 (age 20–39 years) 0.1 in 100 000 (age ⩾40 years)
	iPCD (22 countries)[#]	3824 PCD patients			
	The International PCD Registry (16 countries)[¶]	920 PCD patients			
Hannah *et al.* 2022 [22]	Genomic databases: Invitae GnomAD	Case ascertainment completed by genomic analysis 14 512 variants analysed in 29 genes: 2133 likely pathogenic variants, 7842 VUS	Allele frequency of pathogenic and VUS genes with autosomal recessive inheritance in 29 PCD disease-causing genes Used Hardy–Weinberg equilibrium equation to estimate disease frequency	Population of diverse ethnicities referred for genetic testing (Invitae) Population of unrelated individuals of diverse ancestries (GnomAD) 182 681 individuals with genomic data Invitae: n=41 225 GnomAD: n=141 456	**Excluding VUS** 1 in 7554 (Global) 1 in 9906 (African or African American) 1 in 10 388 (non-Finnish European) 1 in 14 606 (East Asian) 1 in 16 216 (South Asian) 1 in 16 309 (Latino) 1 in 19 466 (Ashkenazi Jewish) 1 in 55 712 (Finnish) 1 in 7295 (other ethnicities) **Including VUS:** 1 in 127 (Global) 1 in 106 (African or African American) 1 in 178 (non-Finnish European) 1 in 188 (East Asian) 1 in 293 (South Asian) 1 in 196 (Latino) 1 in 2409 (Ashkenazi Jewish) 1 in 2247 (Finnish) 1 in 178 (other ethnicities)

SIT: situs inversus totalis; PCD: primary ciliary dyskinesia; VM: video microscopy; TEM: transmission electron microscopy; nNO: nasal nitric oxide; IF: immunofluorescence; iPCD: International PCD Cohort; VUS: variant of unknown significance. [#]: Argentina, Australia, Belgium, Canada, Colombia, Cyprus, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Netherlands, Norway, Poland, Serbia, Spain, Switzerland, Turkey, UK, USA; [¶]: Austria, Belgium, Canada, Cyprus, Denmark, France, Greece, Germany, Italy, Netherlands, Slovakia, Spain, Switzerland, Turkey, UK, USA.

The earliest study, by Katsuhara *et al.* in 1972 [23], was based on a Japanese population. They used clinical records of 16 566 individuals from the Adult Health Study and Atomic Bomb Casualty Commission registries in Hiroshima and Nagasaki, Japan. They assumed that this fixed study population was a representative sample of the Japanese population, used a limited case definition (Kartagener's syndrome, which represents a subset of PCD patients) and estimated the prevalence based on the presence of SIT and chest X-ray evidence of bronchiectasis. There was no confirmatory diagnostic testing (specifically no nNO, TEM or genetic testing) available at the time. This study is likely to have severely underestimated the prevalence for several reasons. First, the presence of SIT in PCD occurs in ∼50% of PCD patients [35]. Second, the gold standard for diagnosing bronchiectasis is chest computed tomography, because chest X-ray is known to be insensitive to early or mild cases of bronchiectasis [36, 37]. Third, the case definition for PCD is limited and incomplete, and without any confirmatory diagnostic testing. Finally, there are likely systematic differences between the study population, who were survivors of the atomic bomb, compared to the rest of Japan.

The next study, chronologically, was by Afzelius and Stenram in 2006 [24] using a Swedish registry. The prevalence estimates were based on the national cohort registry of known PCD patients. They calculated prevalence using the number of new PCD patients diagnosed in a given time period. For example, they reported a prevalence of one in 22 000 for 1976–1990 *versus* one in 11 000 based on the number of cases identified in three specific years (*i.e.* 1976, 1979 and 1982), where they saw increased numbers of children diagnosed with PCD. The authors recognised that these prevalence calculations were likely conservative and suggested that the true prevalence was around one in 10 000 [24]. Similar to the first study, there were notable limitations: 1) lacking a case definition for PCD, 2) no details about confirmatory diagnostic testing, 3) using the misnomer "immotile ciliary syndrome", 4) unorthodox use of time periods and 5) no central referral PCD centre or network.

In 2010, O'Callaghan *et al.* [27] investigated the British Asian population in Bradford, UK, and identified 19 children with PCD, 18 of Pakistani descent and one of Bangladeshi descent. These individuals were identified based on clinical manifestations and positive confirmatory diagnostic testing (*i.e.* ciliary beat pattern, ciliary beat frequency and electron microscopy). The authors then estimated the PCD prevalence in this study population to be one in 2265. It is important to remember that this prevalence estimate is high due to the highly consanguineous study population of Bradford, UK, and the study does not attempt to estimate the global PCD prevalence [30]. Of note, a strength of this study was its affiliation with the Leicester Royal Infirmary, which is a national centre for PCD with standardised PCD diagnostic testing. A limitation of this study was the lack of details about the diagnostic algorithm used, and if only a portion of the algorithm were used, this may have led to false negatives [13, 38].

In 2010, Kuehni *et al.* [5] conducted a European cross-sectional questionnaire survey of all institutions considered likely to be treating paediatric PCD patients, with the primary aim of determining the age of diagnosis and the risk factors that led to diagnostic delays. Given the widespread inclusion of many European institutions that treated PCD patients, they also attempted to estimate the prevalence. They estimated that for children (aged 5–14 years old) the prevalence of PCD was about one in 68 000 but with several caveats. First, the national response rates to the surveys were highly variable (ranging from 18% to 100%) and the prevalence estimate was, therefore, based on countries who had a response rate of >60% of surveyed institutions. Second, the national population census data were based on the US Census Bureau International Database for 2007 (table 3). Third, the PCD diagnostic criteria at each institution were not validated or standardised. Last, the authors selected institutions to survey based on whether they were likely to be treating paediatric PCD patients and it is unclear what the referral patterns were like at each of these institutions. Overall, these are limitations that likely contributed to an underestimation of the prevalence.

The studies by Abitbul *et al.* [25] in 2016 and Goutaki *et al.* [26] in 2019 assessed the Israeli and Swiss populations, respectively. They used similar approaches of creating a national PCD patient registry consisting of either patients with confirmed PCD or patients with a high clinical suspicion for PCD. The reported prevalence in Israel was one in 54 000 for the general population (Non-Jewish: one in 16 500, Jewish: one in 139 000), and in Sweden was one in 63 000. The significant limitations of these studies were the heavy reliance on clinicians to voluntarily take part in these studies and to accurately identify possible PCD patients. Moreover, it is unclear whether surveyed physicians had access to specialised PCD referral centres and what the referral patterns were. All of these factors have impacts on the estimated prevalence in their respective studies and potentially lead to conservative estimates.

In 2020, Ardura *et al.* [15] published an article that examined different PCD patient cohorts that included national and international registries. Based on the national registries of Cyprus, Denmark, Norway and

Switzerland, the authors estimated the European PCD prevalence to be three to seven in 100 000 for children (ages 0 to 19 years) and 0.2 to six in 100 000 for adults. No attempt was made to estimate the PCD prevalence based on the larger international registries (*i.e.* the International PCD Cohort [39] and the international PCD Registry [40]). The authors identified potential limitations of these registries, including how PCD patients were accrued, the reliance on clinician engagement (for participating, inputting and accurately identifying PCD patients for the registries) and the poor representation of countries outside of Europe and North American, such as those in Asia and Africa. Similar to the other studies, the referral patterns to specialised PCD centres are also lacking.

Hannah *et al.* [22] used a genomic approach for estimating the global PCD prevalence. They analysed the allele frequencies of pathogenic variants in 29 PCD disease-causing genes (estimated to represent ~65% of all PCD cases) from clinical testing data aggregated from Invitae (a Clinical Laboratory Improvement

TABLE 4 Notable study limitations

Study	Limitation(s)	Description	Anticipated effect on prevalence estimate in study population
Katsuhara *et al.* 1972 [23]	Case definition	Case definition for PCD is outdated and based on the presence of SIT and bronchiectasis.	Underestimate
Afzelius and Stenram 2006 [24]	Case definition	Case definition of "immotile ciliary syndrome" is outdated; no other details about how patients were diagnosed.	Underestimate
	Study population	Study population required clinician engagement to enrol participants.	Underestimate
	Time period	Time periods used to estimate prevalence were non-standard. The high prevalence estimate was based on three specific years with the highest number of PCD cases (as a proportion of the number of children born that year). Unclear if there were changes to the diagnostic algorithms over time.	Unknown
O'Callaghan *et al.* 2009 [27]	Case definition	Case definition included diagnostic tests of VM, TEM and ciliary function. No description on whether other diagnostic tests (*i.e.* nNO, genetics) were completed.	Underestimate
	Study population	Patients were identified by clinicians based on clinical manifestation and confirmed by TEM and ciliary function. Not all children in Bradford, UK, underwent PCD diagnostic testing, thus likely underestimating the prevalence.	Underestimate
Kuehni *et al.* 2010 [5]	Case definition	Case definitions for the different centres were not standardised.	Underestimate
	Study population	Study population based on surveys that were only sent to paediatricians and institutions "considered likely to be treating paediatric PCD patients". Surveys had variable response rates.	Underestimate
Abitbul *et al.* 2016 [25]	Study population	Study population required clinician engagement to enrol participants, and may not be representative of poorly serviced populations.	Underestimate
Goutaki *et al.* 2019 [26]	Case definition	Case definition based on diagnostic algorithms; however, there is uncertainty about the reliability of the testing.	Unknown
	Study population	Study population required clinician engagement to enrol participants.	Underestimate
Ardura-Garcia *et al.* 2020 [15]	Case definition	Variable methods for identifying PCD patients in the different registries.	Underestimate
	Study population	Study population required clinician engagement to enrol participants.	Underestimate
Hannah *et al.* 2022 [22]	Case definition	Genomic analysis was limited to 29 PCD disease-causing genes. Did not include certain common genes like *DNAH11* and *HYDIN*, nor AD or XL mutations. Lack of functional data to investigate VUS pathogenicity.	Underestimate
	Study population	Limited based on patient and ethnic data in the genetic testing. Majority of the genetic data was based on individuals from North America and Europe. Hardy–Weinberg conditions needed to be satisfied.	Underestimate

PCD: primary ciliary dyskinesia; SIT: situs inversus totalis; VM: video microscopy; TEM: transmission electron microscopy; nNO: nasal nitric oxide; AD: autosomal dominant; XL: X-linked; VUS: variant of unknown significance.

Amendments (CLIA)-approved clinical genetic laboratory, San Francisco, CA, USA) and GnomAD databases [41]. Using the Hardy–Weinberg equilibrium, they estimated the global PCD prevalence to be one in 7554 when variants of unknown significance (VUS) were excluded. Further subgroup analyses of different ethnic populations found a range of prevalences: one in 9906 (African or African American), one in 10 388 (non-Finnish European), one in 14 606 (East Asian), one in 16 216 (South Asian), one in 16 309 (Latino), one in 19 466 (Ashkenazi Jewish), one in 55 712 (Finnish) and one in 7295 (other ethnicities). The global and ethnic PCD prevalence estimates were significantly higher when VUS were included (table 3). Interestingly, the prevalence estimate in HANNAH *et al.* [22] of non-Finnish Europeans is similar to the estimate by AFZELIUS and STENRAM [24] in the Swedish population of approximately one in 10 000.

The main strengths of the genomic approach include the use of large patient databases (*e.g.* Invitae with 41 225 patient records and GnomAD with 141 456 individuals) and the reduced reliance on clinician engagement. The main limitations of this study are the inclusion of only 29 PCD disease-causing genes, limited genetic data for individuals outside of North America and Europe, lack of functional data to investigate VUS pathogenicity, and the assumption that the Hardy–Weinberg conditions were satisfied: 1) no new allele mutations were introduced into the study population, 2) there was random mating, 3) there was an infinite population size and 4) there was no preferential selection of genes and no gene flow (*i.e.* no new individuals or genes entered the study population).

This scoping review is the first to critically appraise the PCD literature to determine the best estimate for the PCD global prevalence. With any scoping review, a potential limitation is missing relevant studies, especially those published in languages other than English. However, we believe that our comprehensive review covered the majority of known literature on this topic, having used large, well-known research databases, applied broad search terms and reviewed the references of all included full-text articles.

Based on our scoping review, we found that the best estimate for PCD global prevalence is one in 7554. This estimate was calculated by HANNAH *et al.* [22] using a genomic approach. While it is conservative, it is higher than the typically quoted one in 10 000 to one in 20 000 and may be attributable to limitations of the earlier studies and the use of patient registries. First, these earlier studies were not intended to provide estimates of PCD global prevalence, because they were based on study populations for specific geographical regions. Second, these studies had known methodological limitations that would impact patient enrolment including 1) the reliance on clinician and patient engagement, 2) the ongoing evolution of the PCD case definitions over time (*e.g.* Kartagener's syndrome, North American *versus* European criteria), 3) the differential access and referral patterns of healthcare centres to specialised PCD centres and 5) the ongoing advancement of the diagnostic algorithms (table 4). Third, certain races are underrepresented in the patient registries, including the African and African American populations [42].

This difference in the traditionally accepted prevalence estimates and that of HANNAH *et al.* [22] has important clinical implications, specifically that current patient registries are not fully capturing the PCD population and ongoing work is needed to bridge this gap. Areas of ongoing advancement include the need for 1) a gold standard diagnostic test (such as newborn genetic screening) with complete patient registration at birth, similar to what has been accomplished in CF; 2) improvements in the delivery of PCD care to underrepresented and marginalised populations; and 3) strategies to increase patient enrolment in PCD clinical registries. In an effort to tackle these challenges, different patient advocacy organisations and international research groups have been established over the past two decades, including the PCD Foundation, Genetic Disorders of Mucociliary Clearance Consortium, International PCD Cohort, European Reference Network-LUNG PCD Core, and the Better Experimental Approaches to Treat PCD (BEAT-PCD) networks. However, there remains an urgent need for more healthcare policies to accelerate improvements in PCD care and to expand services to underserved populations, especially with the recognition that PCD is more prevalent than previously thought.

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