Original Research Article

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Epidemiology of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: identification of the most accurate estimates from a systematic literature review

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Abstract

This systematic review of literature and online reports critically appraised incidence and prevalence estimates of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension to identify the most accurate estimates. Medline® and Embase® databases were searched for articles published between 1 January 2003 and 31 August 2020. Studies were grouped according to whether they were registries (population-based estimates), clinical databases (hospital-based estimates) or claims/administrative databases. Registries were classified into systematic and non-systematic registries, according to whether every national centre participated. Of 7309 publications identified, 5414 were screened after removal of duplicates and 33 were included. Inclusion was based on study type, availability of a clear numerator (diagnosed population) and a population- or hospital-based denominator, or all primary data required to calculate estimates. Only the most recent publication from a database was included. Most studies were based on European data and very few included children. In adults, the range of estimates per million was approximately 20-fold for pulmonary arterial hypertension incidence (1.5–32) and prevalence (12.4–268) and of similar magnitude for chronic thromboembolic pulmonary hypertension incidence (0.9–39) and prevalence (14.5–144). Recent ($\leq$5 years) national systematic registry data from centralised healthcare systems provided the following ranges in adult estimates per million: approximately 5.8 for pulmonary arterial hypertension incidence, 47.6–54.7 for pulmonary arterial hypertension prevalence, 3.1–6.0 for chronic thromboembolic pulmonary hypertension incidence and 25.8–38.4 for chronic thromboembolic pulmonary hypertension prevalence. These estimates were considered the most reliable and consistent for the scientific community to plan for resource allocation and improve detection rates.

Keywords
pulmonary hypertension, pulmonary arterial hypertension, epidemiology, registries

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Introduction

Pulmonary hypertension (PH) is a progressive disease characterised by increased pulmonary vascular resistance that ultimately leads to right heart failure and death. Patients usually present with non-specific symptoms, such as shortness of breath, fatigue, angina and syncope.[1] Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are two groups of PH (Groups 1 and 4, respectively).[2,3] As per the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines, PH should be diagnosed by right heart catheterisation (RHC) and imaging techniques are required to differentiate CTEPH from PAH, with ventilation/perfusion (V/Q) scintigraphy being the recommended diagnostic tool for CTEPH.[2,3]

PAH and CTEPH are rare diseases with low but also wide ranges of published incidence and prevalence estimates.[2,3] The variety of design, data sources and observation period used in studies can create discrepancies in the reported epidemiology of the diseases.

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While awareness, diagnosis and clinical management of PAH and CTEPH have greatly improved over the past few decades,[4–6] there is still a lack of consensus in the scientific community on which estimates could reflect the true incidence and prevalence of PAH and CTEPH.[7–9] Identifying the most generalisable estimates would help clinicians and scientists to assess the likelihood of PAH and CTEPH being under-diagnosed in certain countries and subsequently support realistic goal-setting for improving disease detection. This systematic review aimed to first, identify PAH and CTEPH incidence and prevalence estimates available in the literature and online reports and, second, to critically appraise these estimates, in order to better understand their quality, validity and relevance in research and clinical practice.

Materials and methods

The design of this systematic literature review was based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[10] The search of literature and online reports, screening and data extraction was conducted by the first author (L.L.).

Search strategy

Medline® and Embase® databases were searched using OvidSP® for articles published between 1 January 2003 and 31 August 2020. The start of this search period coincides with a major modification made to the clinical classification of PH at the 2003 World Symposium on PH in Venice, where the term 'primary pulmonary hypertension' was replaced by 'idiopathic pulmonary arterial hypertension'.[11] The definition of the term 'primary pulmonary hypertension' has changed considerably since its first use in 1950 and previously encompassed both PAH and CTEPH, hence the rationale for excluding articles prior to 2003 that may use outdated and ambiguous terminology.[12] The following search string was used to identify articles on the population and outcome of interest: pulmonary hypertension [Title/Abstract] OR pulmonary arterial hypertension [Title/Abstract] AND prevalence [Title/Abstract] OR incidence [Title/Abstract]. The searches were filtered for human studies, written in the English language and with abstract available. Duplicate records were removed. Details of this search strategy are available in Appendix 1.

In addition, ClinicalTrials.gov and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance websites were screened using the keywords 'pulmonary hypertension' and 'registry' to identify potentially relevant data sources. Publicly available reports of PH registries were extracted from websites of identified registries.

Eligibility criteria

Eligible articles were (i) studying patients diagnosed with PAH or CTEPH, and included a description of the diagnostic or identification method(s), and (ii) reporting primary data on the incidence and/or prevalence of PAH and/or CTEPH. The primary data had to clearly state the numerator of the diagnosed population and include a population or hospital-based denominator that is not specific to a disease associated with PH (e.g. PAH in systemic sclerosis population) or report all primary data and information from which to calculate estimates that satisfy these criteria. In instances where estimates for PAH or CTEPH were available in several publications from the same database, only the most recent publication was selected. Review articles, letters to the editor, case reports, case studies, clinical trials, in vitro or animal studies were excluded, as were original research articles in which the main disease under investigation was not the disease of interest (PH Groups 2, 3 or 5, subgroups of PAH/CTEPH or not PH). Conference abstracts were included.

Article selection

First, the titles and abstracts were manually screened for eligibility. If the article remained potentially relevant, or its eligibility was not clear from the title and abstract, the full text article was screened. The bibliographies of identified articles were then manually searched for other articles potentially of interest to this literature review.

Data extraction

Data extraction was performed using Microsoft Excel. To the best of the authors' knowledge, there is no data extraction form validated for PH. However, the data extraction form used was very similar to the validated Joanna Briggs Institute data extraction form for prevalence studies.[13] Data extracted included details of the publication (first author, year of publication), the study (design, observation period, location), the patient population (age, diagnosis, size of population), the outcomes of interest (denominator, incidence and prevalence estimates) and any relevant information that would contribute to appraisal or interpretation of epidemiology estimates. For publications that did not have estimates directly available, the country's population at the time of study was taken from the US Census[14] or Eurostat[15] as appropriate, and was used to derive incidence and prevalence.

Critical appraisal

A narrative synthesis of the evidence is presented herein. Results are grouped according to the following study designs: (i) national systematic registries, defined as those in which all national referral PH expert centres participate and all patients with a confirmed PAH or CTEPH diagnosis

are invited to enrol, (ii) non-systematic registries, including national registries, in which the majority but not all PH-treating centres are included, as well as multi-centre registries, (iii) claims/administrative databases, where estimates are based on prescriptive or diagnostic codes, and (iv) clinical (hospital) databases, in which diagnoses are clinically confirmed. Clinical databases and registries are differentiated by whether they present hospital-based estimates (clinical database) or population-based estimates (registries).

The appraisal of PAH and CTEPH incidence and prevalence estimates was based on assessment of: database type, number of centres included, country and healthcare system, observation period, age criteria, diagnosis or identification methods, PH classification used, sample size and finally the numerator and denominator of the estimates. These factors were selected and evaluated by the authors; further details of this process are presented in the discussion. The latest PH guideline recommendations[2,3] were followed to assess the validity of the disease diagnosis and classification.

Results

The literature search returned a total of 7309 publications. Following the removal of duplicates, 5414 publications were screened, and 33 were found to meet the eligibility criteria, as summarized by the PRISMA flow diagram in Fig. 1. The selected publications comprised 30 manuscripts, one conference abstract and two online registry reports (the UK PH Audit (2019)[16] and the Swedish Pulmonary Arterial Hypertension Registry (SPAHR)),[17] from 13 European, 3 Asian, 2 North American countries and 1 South American country. Fifteen publications were on PAH, 7 on CTEPH and 11 included both diseases. PAH and CTEPH epidemiology estimates were mostly reported for adult populations only ($n = 12$ for PAH, $n = 7$ for CTEPH and $n = 7$ for publications studying both diseases).

All studies were open cohort studies (patients were continually added at diagnosis) and used the 2003 PH classification (Venice) or a later version.[11] When the study observation period was partly prior to 2003, the latest classification available at end of the study was systematically used (i.e. 2003 classification or a later version), avoiding misclassification bias by the use of out-dated and ambiguous PH terminology. The included publications are summarised in Tables 1–4 and Supplementary Tables 1–2.

All but one[18] incidence estimates were incidence proportions (incidence based on person at risk) rather than incidence rate (incidence based on person-time at risk). Studies calculated incidence using the last year of observation ($n = 19$), an average of each annual incidence of the period ($n = 4$) and an average over the whole observation period ($n = 4$). Point prevalence using the last year of observation was reported in 12 studies. Period prevalence using the last year of observation was reported in 11 studies, and two used the whole observation period. For simplicity, the terminology 'incidence' and 'prevalence' are used consistently in this review. Supplementary Table 3 contains full details on how incidence and prevalence were calculated and reported. Estimates for incidence are presented in patient per million (ppm) per year and estimates for prevalence are presented in ppm at a given time.

Incidence and prevalence of PAH in adults

The published estimates of PAH epidemiology in adults are summarised in Table 1. The publications include five national systematic registries, eight non-systematic registries, five claims/administrative databases and three clinical

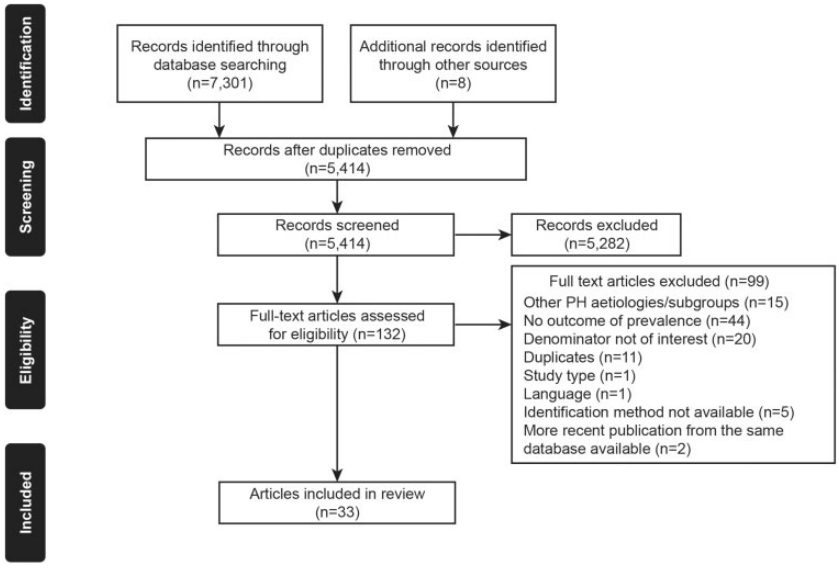

Fig. 1. PRISMA flow diagram.
PH: pulmonary hypertension.

Table 1. Study details and epidemiology estimates from identified studies investigating PAH epidemiology in adults.

Study classification	Study description	Country	Time period range	Number of participants	Publication (study acronym)	Annual incidence (ppm)	Prevalence (ppm)
National systematic registry	National systematic registry	UK	2018–2019	NR	NHS Digital, 2019[16,a]	–	54.7[b]
		Sweden	2008–2019	1034	Kjellström et al., 2020 (SPAHR)[17,a]	5.8[b]	47.6[b]
		UK (Scotland)	1997–2006	NR	Peacock et al., 2007[25,a]	7.6	26
		Czech Republic	2000–2007	191	Jansa et al., 2014[41,a]	10.7	22.4
		Latvia	2007–2016	130	Skride et al., 2018[20,a]	13.7	45.7
Non-systematic	National, non-systematic	Portugal	2008–2010	46	Baptista et al., 2013[44,a]	1.5	–
		South Korea	2008–2011	297	Chung et al., 2015 (KORPAH)[26]	1.9	–
		France	2002–2003	674	Humbert et al., 2006[22,a]	2.4	15
		Switzerland	1999–2004	152	Tueller et al., 2008[23]	3.5	15.5
		Spain	2007–2008	866	Escribano-Subias et al., 2012 (REHAP)[33,a]	3.7	16
		Germany	2007–2014	1752	Hoeper et al., 2016 (COMPERA)[21,a]	3.9	25.9
		Poland	2018	970	Kopeć et al., 2020 (BNP-PL)[19,a]	5.2	30.8
	Non-national (multi-centre)	USA	2006–2007	2967	Frost et al., 2011 (REVEAL)[5,a,c]	2.3	12.4
Claims/administrative databases	Claims (Medicare)	USA	1999–2007	215	Kirson et al., 2011[28]	–	30.4[b]
	Claims (PHIC)	Colombia	2015	18	Miranda-Machado et al., 2019[47,a]	–	28
	Claims (HIRA)	South Korea	2008–2016	1307	Song et al., 2018[27]	4.8	20.2
	National hospitalization database (SMR)	UK (Scotland)	1986–2001	374	Peacock et al., 2007[25]	7.1	52
	Administrative database (ICES)	Canada	1993–2012	6705	Wijeratne et al., 2018[24]	32	268
Clinical databases	Single-centre study	UK	2001–2010	598	Hurdman et al., 2012 (ASPIRE)[48,a]	6.1	–
	Single-centre study	Israel	1998–2005	84	Fruchter and Yigla, 2008[49]	7.1[b]	–
	Single-centre study	USA	2016	154	Dubroff et al., 2020[50,a]	14	93

Notes: Studies are ordered by study design and then in ascending order of incidence estimate. Estimates are rounded to one decimal place, except where only integers were published.

[a]PAH definition included mPAP >/≥ 25 mmHg at rest (± or >30 mmHg on exercise) and PAWP </≤ 15 mmHg, as assessed by RHC.

[b]Estimates are derived from the publication using the method outlined in Table 5.

[c]REVEAL registry included an expanded criterion for patients with PAWP ≤18 mmHg.

ASPIRE: Assessing the spectrum of pulmonary hypertension identified at a REferral centre; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; HIRA: Health Insurance Review and Assessment Service; ICES: Institute for Clinical Evaluative Sciences; KORPAH: Korean Registry of Pulmonary Arterial Hypertension; NHS: National Health Service; NR: not reported; PAWP: pulmonary arterial wedge pressure; ppm: patients per million; REHAP: Spanish Registry of Pulmonary Arterial Hypertension; REVEAL: The Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; RHC: right heart catheterisation; SMR: Scottish Morbidity Record scheme; SPAHR: Swedish Pulmonary Arterial Hypertension Registry; BNP-PL: Polish Registry of Pulmonary Hypertension.

databases (Table 1). One publication used two different study designs and is therefore counted twice, resulting in a total of 21 studies. For six of the 13 registries, the observation period was prior to 2010, and the most recent registries include the SPAHR (2019 data cut-off),[17] the UK National Health Service (NHS) Audit (2019),[16] Polish Registry of Pulmonary Hypertension (BNP-PL, 2018),[19] Latvian registry (2016)[20] and the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA, 2014).[21] Mean age ranged between 43 and 67 years, and female gender predominated in all data sources (55–81%, Supplementary Table 1). The French and Swiss registries included information on the number of patients who withdrew: none of the 121 incident cases included in the French registry were lost to follow-up,[22] 24 patients were lost to follow-up in the Swiss registry and these withdrawals occurred uniformly throughout the follow-up period.[23]

The ranges of estimates for PAH incidence and prevalence were 1.5–32 and 12.4–268 ppm, respectively. National systematic registries reported PAH adult incidence to be between 5.8 and 13.7 ppm (four studies), while estimates

Table 2. Study details and epidemiology estimates from identified studies investigating PAH epidemiology in children.

Study classification	Study description	Country	Time period	Number of participants	Publication (study acronym)	Annual incidence (ppm)	Prevalence (ppm)
National, non-systematic registry	National, non-systematic registry	France	2005–2006	50	Fraisse et al., 2010[51]	–	3.7
		Poland	2018	80	Kwiatkowska et al., 2020 (BNP-PL)[52]	2.4	11.6
		Spain	2009–2012	142	Del Cerro Marin et al., 2014 (REHIPED)[53]	2.6	14
		Netherlands	1991–2005	154	Van Loon et al., 2011[54]	3	20
Claims/ administrative database	Claims (MarketScan)	USA	2010–2013	695	Li et al., 2017[18]	4.8	28.2
	Administrative database	Turkey	2009–2013	2079	Pektas et al., 2016[34]	16.7[a]	–
	Administrative database (ICES)	Canada	1993–2012	1198	Wijeratne et al., 2018[24]	12[a]	397

Notes: Studies are ordered by study design and then in ascending order of incidence estimate. Estimates are rounded to one decimal place, except where only integers were published.

[a]Estimates are derived from the publication using the method outlined in Table 5.

ICES: Institute for Clinical Evaluative Sciences; ppm: patients per million; REHIPED: The Spanish Registry for Paediatric Pulmonary Hypertension; BNP-PL: Polish Registry of Pulmonary Hypertension.

Table 3. Study details and epidemiology estimates from identified studies investigating CTEPH epidemiology in adults.

Study classification	Study description	Country	Time period	Number of participants	Publication (study acronym)	Annual incidence (ppm)	Prevalence (ppm)
National systematic registry	National systematic registry	Sweden	2008–2019	417	Kjellström et al., 2020 (SPAHR)[17]	3.1[a]	25.8[a]
		Latvia	2007–2016	44	Skride et al., 2018 [20]	5.1	15.7
		UK	2018–2019	2492	NHS Digital, 2019[16]	6.0[a]	38.4[a]
Non-systematic registry	National, non-systematic	Slovakia	1998–2014	81	Bohacekova et al., 2016[55]	–	18
		Portugal	2008–2010	33	Baptista et al., 2013[44]	1.1	–
		Spain	2007–2018	1019	Martínez-Santos et al., 2019 (REHAP)[56]	1.7	22.5
		Germany	2016	392	Kramm et al., 2018 (COMPERA)[57]	5.7	–
Claims/administrative database	Claims	USA	1999–2007	431	Kirson et al., 2011[28]	–	39.4[a]
	Administrative database (PMSI)	France	2009-2015	3138	Cottin et al., 2019[58]	–	47
	Administrative database (ICES)	Canada	1993–2012	4360	Wijeratne et al., 2018[24]	39[a]	144
Clinical database	Multi-centre	Spain	1998–2017	42	Llanos-González et al., 2019[59]	0.9	14.5
	Single-centre study	Israel	1998–2005	16	Fruchter et al., 2008[49]	1.3	–
	Single centre study	UK	2001–2006	105	Condliffe et al., 2008[60]	1.8	–
	Single-centre study	UK	2001–2010	242	Hurdman et al., 2012 (ASPIRE)[48]	3.7	–
	Single-centre study	Thailand	2012–2016	20	Puengpapat and Pirompanich, 2018[61]	37.8	–

Notes: Studies are ordered by study design and then in ascending order of incidence estimate. Estimates are rounded to one decimal place, except where only integers were published.

[a]Estimates are derived from the publication using the method outlined in Table 5.

ASPIRE: assessing the spectrum of pulmonary hypertension identified at a REferral centre; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; ICES: Institute for Clinical Evaluative Sciences; NHS: National Health Service; PMSI: French exhaustive hospital discharge database; ppm: patients per million; REHAP: Spanish Registry of Pulmonary Arterial Hypertension; SPAHR: Swedish Pulmonary Arterial Hypertension Registry.

Table 4. Study details and epidemiology estimates from identified studies investigating CTEPH epidemiology in children.

Study classification	Study description	Country	Time period	Number of participants	Publication (study acronym)	Annual incidence (ppm)	Prevalence (ppm)
Non-systematic registry	National, non-systematic	Spain	2009–2012	2	Del Cerro Marin et al., 2014 (REHIPED)[53]	0.076	0.22
		Netherlands	1991–2005	5	Van Loon et al., 2011[54]	0.1[a]	–
Claims/administrative database	Administrative database	Turkey	2009–2013	22	Pektas et al., 2016[34]	0.2	–
	Administrative database (ICES)	Canada	1993–2012	65	Wijeratne et al., 2018[24]	2[a]	19

Notes: Studies are ordered by study design and then in ascending order of incidence estimate.
[a]Estimates are derived from the publication using the method outlined in Table 5.
ICES: Institute for Clinical Evaluative Sciences; ppm: patients per million; REHIPED: The Spanish Registry for Paediatric Pulmonary Hypertension.

from all non-systematic registries except one (BNP-PL; 5.2 ppm) were below 4 ppm (1.5–3.9 ppm; seven studies). A similar trend was observed for PAH prevalence, with estimates from national systematic registries being generally higher than those from non-systematic registries (Table 1).

The estimates from claims/administrative databases overlapped with those from registries, with the exception of a Canadian (Ontario) administrative database study reporting an incidence of 32 ppm and a prevalence of 268 ppm.[24] PAH estimates from all databases other than the Canadian study, including clinical databases, ranged from 4.8 to 14 ppm for incidence and from 20.2 to 93 ppm for prevalence.

In Scotland, the USA and South Korea, estimates were available from registries as well as claims/administrative databases. For Scotland, the registry-based estimate was similar to that reported in a claims/administrative database study for PAH incidence, with estimates of 7.6 and 7.1 ppm, respectively, while prevalence estimates differed more substantially (26 and 52 ppm, respectively).[25] The registry-based estimate used RHC-confirmed diagnoses, whilst the administrative database included patients with an International Classification of Diseases, ninth revision (ICD-9) or ICD-10 code for a discharge diagnosis of primary PH/PAH (ICD-9 code 416.0; ICD-10 code I27.0).[25] For the USA and South Korea, national estimates from claims/administrative databases were more than double compared with the respective multi-centre registries (Table 1).[5,26–28]

Incidence and prevalence of PAH in children

Paediatric epidemiology was reported among four national non-systematic registries and three claims/administrative database studies (Table 2). PAH incidence and prevalence ranged from 2.4 to 16.7 ppm and 3.7 to 397 ppm, respectively. Considering only registry-based estimates, incidence was approximately 2–3 ppm and prevalence ranged from 3.7 to 20 ppm, while estimates from claims/administrative databases were higher (Table 2).

Incidence and prevalence of CTEPH in adults

The systematic review identified 15 publications (Table 3). Mean age ranged between 58 and 73 years, and female gender represented 37–70% of CTEPH patients (Supplementary Table 2). The ranges of CTEPH incidence and prevalence in adults were 0.9–39 ppm and 14.5–144 ppm, respectively (Table 3).

According to national systematic registries (three studies), the incidence of CTEPH was between 3.1 and 6.0 ppm and prevalence ranged from 15.7 to 38.4 ppm. Estimates from non-systematic registries (four studies) were similar or lower than those from systematic registries.

Estimates were also reported in three claims/administrative databases, including the Canadian administrative database study reporting high incidence (39 ppm) and prevalence (144 ppm),[24] and five clinical databases.

Incidence and prevalence of CTEPH in children

CTEPH epidemiology among children was identified in two non-systematic registries and two claims/administrative database studies. The Canadian administrative database study reported an incidence of 2 ppm and a prevalence of 19 ppm,[24] while the others estimated the incidence and prevalence to be lower than 1 ppm (Table 4).

Discussion

This systematic literature review reports a wide variation in the published estimates of PAH and CTEPH epidemiology. In adults, the range of estimates was approximately 20-fold for PAH incidence and prevalence (1.5–32 and 12.4–268 ppm, respectively) and a similarly large range was observed for CTEPH incidence and prevalence (0.9–39 and 14.5–144 ppm, respectively). The critical appraisal of the most robust estimates, outlined in this discussion, focuses on the adult population, since so few paediatric studies were identified.

Table 5. Method of deriving estimates from articles not stating the incidence/prevalence of PAH/CTEPH per million individuals.

Estimate(s)	Publication	Method of derivation
PAH and CTEPH prevalence	Kirson et al., 2011[28]	Numerator derived by summing the numerators for patients aged <65 years (based on administrative claims data for a privately-insured population) and those aged ≥65 years (based on administrative claims data for a random sample of the Medicare population). US population in 2007 according to US census used as denominator: Overall population: 301,231,297. <65 years: 263,405,496. ≥65 years: 37,825,711. RHC-confirmed PAH prevalence was: <65 years: 25 ppm, ≥65 years: 68 ppm. Total calculated by: $(263{,}405{,}496 \times 25) + (37{,}825{,}711 \times 68)/301{,}231{,}297 =$ **30.4 ppm (derived)** RHC-confirmed CTEPH prevalence was: <65 years: 16 ≥65 years: 202 Total calculated by : $(263{,}405{,}496 \times 16) + (37{,}825{,}711 \times 202)/301{,}231{,}297 =$ **39.4 ppm (derived)**
PAH and CTEPH incidence	Wijeratne et al., 2018[24]	Estimates at 2012 approximated from graphs PAH: 12 for children CTEPH: 39 for adults, 2 for children
PAH prevalence, CTEPH incidence and prevalence	NHS Digital, 2019[16]	Numerators (number of active PAH patients on 31 March 2019: 3551, number of patients newly diagnosed with CTEPH in 2018–2019: 387 and number of CTEPH patients alive on 31 March 2019 in Great Britain: 2492) taken directly from publication. Great Britain population in June 2019 according to Office for National Statistics (64,903,100).
PAH and CTEPH incidence and prevalence	Kjellström et al., 2020[17]	Numerators for PAH estimates (number of PAH patients alive in 2019: 487 and number of PAH patients newly diagnosed in 2019: 59) calculated as 59% and 56% of respectively 825 PH patients alive in 2019 and 106 PH patients newly diagnosed in 2019. Numerators for CTEPH estimates (number of CTEPH patients alive in 2019: 264, and number of CTEPH patients newly diagnosed in 2019: 32) calculated as 32% and 30% of number of PH patients alive in 2019 and number of PH patients newly diagnosed in 2019, respectively. Swedish population in 2019 according to Eurostat used as denominator (10,230,185).
PAH incidence	Fruchter and Yigla, 2008[49]	Estimate (7.09) derived by summing incidence of idiopathic PH (1.92), and PH associated with (i) collagen vascular disease (3.08), (ii) haematological disease (1.17) and (iii) liver disease (0.92).
CTEPH incidence	Van Loon et al., 2011[54]	CTEPH patients comprised 0.15% of the total PH study population. Therefore, estimate (0.1) was calculated as 0.15% of PH incidence (63.7).
PAH incidence	Pektas et al., 2016[34]	Estimate (16.7) derived by summing the incidence of iPAH (11.7), PAH-CHD (4.5) and CTD-PAH (0.5).

CTD-PAH: connective tissue disease-associated pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; iPAH: idiopathic pulmonary arterial hypertension; NHS: National Health Service; PAH: pulmonary arterial hypertension; PAH-CHD: pulmonary arterial hypertension associated with congenital heart disease; PH: pulmonary hypertension; ppm: patients per million; RHC: right heart catheterisation.

The variation in estimates across the included studies could be indicative of geographic differences in PAH and CTEPH populations. Recent publications have suggested racial and ethnic differences in prevalence, presentation and outcomes of PH sub-groups.[29–31] However, most estimates identified in this research originated from Western European countries with comparable ethnicity and socioeconomic status. No major differences were noted for demographic distribution of the populations observed in the selected studies.

The geographic variation of disease estimates may be the consequence of differences in healthcare systems and patient tracking. In the UK, PH care is centralised: patients must be referred to one of the eight designated PH centres to receive diagnosis and disease-targeted treatment. These centres are governed by NHS England and are audited annually,[32] making the PH audit an authoritative data source for PH epidemiology in the UK. Similarly, in Sweden, the seven nationally designated specialist centres automatically invite every patient with a confirmed PAH or CTEPH diagnosis to enrol into the SPAHR registry.[17] As a result, 88% of the national PH population and 91% of the national PAH population, registered by the National Board of Health and Welfare, were estimated to be covered by the Swedish registry in 2017.[17] Interestingly, the most recent nationwide estimates from the Swedish and UK registries are similar for PAH prevalence (47.6 and 54.7 ppm) and are in the same range for CTEPH prevalence (25.8 and 38.4 ppm).[16,17] In countries where these referral pathways and/or registry upkeep are not mandatory, national registries may not be representative and their estimates are likely an underestimate. Indeed, in the present review, estimates from non-systematic national registries and/or countries with decentralised healthcare systems, such as the national registries from Switzerland, France or Spain, were lower than those from the UK and Sweden (PAH prevalence from 15 to 16 ppm).[22,23,33] Despite using non-systematic patient registration, in which centres were invited – rather than mandated – to participate, the Polish registry reported a higher PAH prevalence estimate (30.8 ppm). This likely reflects the fact that all expert PH centres in the country agreed to participate.[19]

Routine clinical practice also differs between countries and may also influence the reported estimates. Confirmation of PH/PAH diagnosis by RHC is the gold standard as per the current ESC/ERS guidelines.[2,3] While being routinely carried out in France, the UK and Sweden, only 40% and 72% of registrants in the South Korean and Swiss registries underwent RHC.[23,26] In countries where RHC or V/Q scanning are either unavailable or not systematically used, estimates of epidemiology can be less accurate due to misdiagnosis.

The type of data source used to derive incidence or prevalence estimates could also cause variability in the epidemiology estimates. Large claims/administrative databases were used by several authors, despite the limitation of unconfirmed PAH or CTEPH diagnosis with this study type.[18,24,27,28,34] PH ICD codes can be assigned to patients with suspected PH to ensure reimbursement for the diagnostic procedure, regardless of the final diagnosis. These coding practices likely contribute to an overestimation of patient numbers in claims/administrative databases. The coding status of PAH and CTEPH is also problematic. Although the ICD-10 codes released in October 2017 allow the identification of idiopathic or hereditable PAH (primary PH; I27.0), PAH associated with other conditions (secondary PAH; I27.21) and CTEPH (I27.24),[35] no study identified in this systematic literature review included the five digit ICD-10 code implemented in 2017 and thus, may have misclassified patients. The highest PAH and CTEPH estimates were reported from the Canadian (Ontario) administrative database study, in which only 40.9% of the incidence cohort had a record of RHC. Furthermore, the study algorithm allowed all PH patients, except those in Group 1, to belong to multiple PH Groups and, as a result, 35.4% of patients were assigned to more than one PH diagnosis. This study may therefore be overestimating the true epidemiology of the diseases in Ontario.[24]

Several studies using claim/administrative databases implemented algorithms combining ICD codes with medication and procedure codes to improve the specificity of patient identification. There is no standardisation across studies and only a few code-based algorithms have been evaluated against clinical data, albeit with a limited success.[36] The risk of including false-positive patients (those who were not diagnosed with the disease of interest) remains a limitation of this data source and may partly explain the higher PAH estimates reported in the US and South Korean claims/administrative databases compared with the respective country's national registries.[5,26–28]

Registries have the advantage of being designed with the purpose of supporting scientific research for a specific disease and, as such, only patients with a confirmed diagnosis should be included. The same advantage is true for clinical databases (i.e. hospital-based estimates as per the definitions used in this systematic review); however, their national coverage is less clear and, therefore, their estimates cannot be extrapolated to the whole country's population.

Another key factor in assessing the validity of epidemiology estimates is the observation period for data collection. The number of PAH-targeted treatments available has increased since the first treatment – epoprostenol – was licensed in 1995[37]: more than 10 drugs and formulations are currently available.[38–40] In the Czech Republic registry, the increase in PAH-specific therapy options after 2006 is thought to explain why the number of incident cases in 2006 sharply increased ($n = 91$) given that only 100 prevalent cases were identified in the previous six-year period.[41] Moreover, when the aetiology is multifactorial or unclear,

there may be an incentive to classify patients as PH Group 1 or 4, which have procedures and drugs available. Given the burden of RHC, in the absence of treatment options, performing this diagnostic procedure to reach a definitive PAH or CTEPH diagnostic may be perceived as unethical, thus it may have been used less frequently in the past.

The observation period is also important to consider when interpreting CTEPH estimates. In Latvia, for example, routine use of V/Q scanning to differentiate CTEPH from PAH was not available across the total observation period (2007–2016) of the national registry and, as a result, the number of CTEPH cases may have been underestimated.[20] Treatment options for CTEPH are also evolving rapidly[8,40,42,43] and it is therefore important to identify studies using data collected during a recent time period. The most recent publications from the Swedish and UK systematic registries may therefore be the most accurate, as their observation periods are within the previous five years and diagnosis was based on the latest PH guideline's recommendations.[16,17]

The length of observation period also determines the extent to which the study's estimate represents the true epidemiology. For example, epidemiology data provided by the French and US registries were derived from enrolled consecutive PAH patients over a time period of one year,[5,22] with the assumption that patients have an annual clinic visit as a minimum. In cases where this assumption does not reflect the reality, patients with less frequent visits captured in the database will be missed, resulting in underestimation of prevalence. Of note, six of the 12 registries reporting PAH incidence estimates had an observation period of $\leq$4 years, and all but the BNP-PL registry reported incidence to be below 4 ppm.[5,19,22,26,33,44] The remaining six registries had an observation period of $\geq$5 years and incidence for all but the two non-systematic registries conducted in countries with de-centralised healthcare (Germany and Switzerland) was higher.[21,23]

The present study represents the authors' recommendation for which estimates are considered most valid, based on objective criteria. The incidence/prevalence estimates were critically appraised according to the criteria outlined herein. The following factors were considered, shown in order of importance, as key for selecting the most valid estimates: (i) study design, with national systematic registries being the most likely to yield accurate estimates, (ii) structure of the healthcare system, with centralised systems in countries with access to the latest treatments and procedures being selected, and (iii) the recency of the observation period (ideally from the previous five years). As such, the estimates from the Swedish registry SPAHR and the UK PH Audit are considered to be the most generalisable.

Critically appraising epidemiology estimates is important for several reasons. These estimates could be used as a guide or threshold level to assess if a country is likely to be underdiagnosing PAH and CTEPH. This would help to set detection rate goals and guide allocation of research grants and healthcare resources by decision-makers. Furthermore, by providing an assessment of the published incidence and prevalence estimates, the authors hope to guide readers in their own critical appraisal of such upcoming data. This is particularly important given that the highest estimates identified in this systematic review create confusion on whether PAH and CTEPH are rare diseases. The critical appraisal presented herein highlighted the possible reasons for overestimation by these studies and is in agreement with the classification of PAH and CTEPH as rare diseases.

This study has several potential limitations. There was the potential for reviewer bias, however, given the sparsity of PH literature, the authors' specialisation in PH and as the systematic screening of bibliographies of the identified articles was conducted to capture any additional eligible publications, a single reviewer was believed to be sufficient. It remains possible that non-indexed publications may have been missed, particularly publications in non-English language.

The methods used to calculate incidence and prevalence were not consistent across the publications, thus hindering comparison of their estimates.[45] While incidence rate is a more accurate estimate of the rate at which the outcome develops, its denominator is more challenging to calculate in open populations that are, per definition, dynamic rather than fixed in time. Incidence rate can only be calculated if periodic follow-up information is available for each patient, including if they developed the disease and when they developed it. Checking every citizen at the beginning and end of the year, to calculate the incidence of PAH or CTEPH in a country over a calendar year is not feasible. However, the population at risk, i.e. the general population of the country, is so large compared with the number of new patients with the disease, that the impact of these patients on the size of the population at risk is negligible. As incidence rate is similar to annual incidence proportion for a rare disease, the only incidence rate identified[18] was interpreted in the same way as for incidence proportions in this review. Point prevalence refers to prevalence measured at a particular point in time, while period prevalence refers to prevalence measured over an interval of time. As PAH and CTEPH prevalence estimates have increased over the past few decades, period prevalence calculated over a long period would not be representative of the contemporaneous epidemiological status of the diseases. Thus, this critical appraisal only selected estimates from recent observation periods.

Populations from Asia, Africa and South America were under-represented in the literature. Data from these regions will be required to establish whether generalising estimates from European and North American countries to other regions is appropriate.

This literature review identified few studies in paediatric populations: seven studies reported epidemiology estimates

for paediatric cases while the remaining 26 studies only included adult estimates. Due to their pathophysiology, PAH and CTEPH are predominantly diagnosed in older patients, with mean age at diagnosis often being between 50 and 65 years old.[2,17] Paediatric PAH and CTEPH are rare forms of rare conditions and the relative lack of research into paediatric cases of rare diseases is still being addressed.[46] It is then unsurprising that this systematic literature review highlights the scarcity of paediatric epidemiology studies in PAH and CTEPH, and the need for further study.

In conclusion, the appraisal of available evidence identified through a systematic literature review suggests that the following adult estimates are the most reliable for the scientific community to use as a guide for resource allocation and improvement of detection rates: approximately 5.8 ppm for PAH incidence, 47.6–54.7 ppm for PAH prevalence, 3.1–6.0 ppm for CTEPH incidence and 25.8–38.4 ppm for CTEPH prevalence.

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Author contributions

All authors contributed to the conception and design of the study, analysis and interpretation of the data, and critical revision of the manuscript.

Conflict of interest

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Guarantor

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Supplemental material

Supplemental material for this article is available online.

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