Study Report

P3-C3-011

DARWIN EU® - Incidence, period prevalence, and characterisation of individuals with paediatric pulmonary arterial hypertension

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Version 4.0

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Public

CONTENTS

Study title	DARWIN EU® - Incidence, period prevalence, and characterisation of individuals with paediatric pulmonary arterial hypertension
Study report version	3.0
Date	13/01/2026
EU PAS number	EUPAS1000000716
Active substance	Bosentan, ambrisentan, macitentan, sildenafil, tadalafil, riociguat, treprostinil, epoprostenol, iloprost, selexipag, and ralinepag
Medicinal product	All medicinal products with the ingredients listed within the classes: endothelin receptor antagonists (ERAs: bosentan, ambrisentan, macitentan), phosphodiesterase type 5 inhibitors (PDE-5 inhibitors: sildenafil, tadalafil), soluble guanylate cyclase stimulators (sGC: riociguat), and prostacyclin receptor antagonists (PRAs: treprostinil, epoprostenol, iloprost, selexipag, ralinepag)
Research question and objectives	1. Estimate the yearly incidence and period prevalence of pulmonary arterial hypertension (PAH) in the paediatric population, stratified by age group (0 to 1 year, 1 to 2-years, 2 to 5-years, 5 to 12-years, and 12 to 18-years) 2. Characterise paediatric patients newly diagnosed with PAH (index date = first PAH diagnosis): a) Describe the number and proportions of individuals by sex and age at index date b) Within 180-days prior to index date and then within the first five years after index date, within sequential 90-day periods describe the distribution of comorbidities (right heart failure, ascites, arrhythmia, haemoptysis, lung-heart transplant, atrial septostomy or Potts shunt, syncope), and within any time prior to index date, describe the distribution of potential aetiology indicating diagnoses (congenital heart disease, bronchopulmonary dysplasia [180 days prior only], congenital diaphragmatic hernia, persistent pulmonary hypertension of the newborn) c) Within the first five-years after index date, within sequential 90-day periods, describe the number and proportion of individuals treated with monotherapy of the following treatment classes, ERA, PDE-5 inhibitors, sGCs, or PRA or with combination therapy of these classes, including ERAs + PDE-5 inhibitor, ERAs + sGC, PDE-5 inhibitor + PRAs, and ERA + PDE-5 inhibitor + PRAs d) Describe the number and proportion of individuals treated with monotherapy of the following treatment classes, ERAs, PDE-5, sGC, , PRAs, or combination therapy of these classes, including ERAs + PDE-5 inhibitor, ERAs + sGC, PDE-5 inhibitor + Prostacyclin receptor agonists, and ERA + PDE-5 inhibitor + PRAs by age group (0 to 1 year, 1 to 2-years, 2 to 5-years, 5 to 12-years, and 12 to 18-years) at time of prescription/dispensing e) Within 180-days prior to index date and then within the first five-years after index date, within sequential 90-day periods, describe the number and proportion of individuals with at least one record for each of the following measures: 6-minute walk distance (6MWD) test, echocardiography, NT-proBNP, WHO functional class, right heart catheterisation, and cardiovascular MRI (Magnetic resonance imaging) f) Within the first five-years after index date in sequential 90-day periods, describe the number of and proportion of individuals who were admitted to the hospital or died
Countries of study	Denmark, Finland, France, Germany, Norway, Sweden
Authors	Nicholas Hunt, n.hunt@darwin-eu.org Katia Verhamme, k.verhamme@darwin-eu.org

1. TITLE

DARWIN EU® - Incidence, period prevalence, and characterisation of individuals with paediatric pulmonary arterial hypertension

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Nicholas Hunt Katia Verhamme	Erasmus MC
Data Scientist	Ioanna Nika Cesar Barboza	Erasmus MC
Study Manager	Natasha Yefimenko	Erasmus MC
Data Partner*	**Names**	**Organisation**
CDW Bordeaux	Guillaume Verdy Romain Griffer	Bordeaux University Hospital
DK-DHR	Claus Møldrup Elvira Bräuner Susanne Bruun	Danish Medicines Agency
FinOMOP-THL	Tiina Wahlfors Gustav Klingstedt Toni Lehtonen	Finnish Institute for Health and Welfare
HI-SPEED	Fredrik Nyberg Huiqi Li	University of Gothenburg
InGef RDB	Josephine Jacob Raeleesha Norris Alexander Harms Annika Vivirito	InGef - Institute for Applied Health Research Berlin GmbH
NLHR	Saeed Hayati Nhung Trinh Hedvig Nordeng Maren Mackenzie Olson	University of Oslo

*Data partners do not have an investigator role. Data partners execute code at their data source, review, and approve their results.

3. DATA SOURCES

Country	Name of data source	Health Care setting	Type of Data	Number of active subjects	Calendar period covered by each data source
France	CDW Bordeaux	Hospital care	EHR	246k	01/01/2014–31/12/2024
Denmark	DK-DHR	Primary ((all prescription retrievals as a proxy of primary care) and secondary care (hospital in-and outpatient records and emergency department)	Registry	5.9m	01/01/2014–07/11/2024
Finland	FinOMOP-THL	Primary and secondary care	Registry	5.7m	01/01/2015–09/10/2024
Sweden	HI-SPEED	Secondary care with linkage to primary care (primary care available for 40% of population)	Registry	10.6m	01/01/2016–30/08/2024
Germany	InGef RDB	Primary and secondary care (in-and outpatient for objective 1 and characterisation on objective 2), secondary care (inpatient only objective 2 index date)	Claims	7.7m	01/01/2015–31/12/2024
Norway	NLHR	Primary and secondary care	Registry	6.9m	01/01/2014–31/12/2023

4. ABSTRACT

Title

DARWIN EU® - Incidence, period prevalence, and characterisation of individuals with paediatric pulmonary arterial hypertension

Rationale and background

The main objective of the study was to investigate the occurrence of pulmonary arterial hypertension (PAH) in paediatric patients by age group, and to understand the size of this population in various EU countries. Additionally, the study aimed to characterise the disease and treatments use in the paediatric PAH population in a real-world setting. This study can therefore be used in any future paediatric PAH related regulatory procedures.

Research objectives

1. Estimate the yearly incidence and period prevalence of pulmonary arterial hypertension (PAH) in the paediatric population, stratified by age group (0 to 1 year, 1 to 2-years, 2 to 5-years, 5 to 12-years, and 12 to 18-years)
2. Characterise paediatric patients newly diagnosed with PAH (index date = first PAH diagnosis):
   a) Describe the number and proportions of individuals by sex and age at index date
   b) Within 180-days prior to index date and then within the first five years after index date, within sequential 90-day periods describe the distribution of comorbidities (right heart failure, ascites, arrhythmia, haemoptysis, lung-heart transplant, atrial septostomy or Potts shunt, syncope), and within any time prior to index date, describe the distribution of potential aetiologies (congenital heart disease, bronchopulmonary dysplasia [180 days prior only], congenital diaphragmatic hernia, persistent pulmonary hypertension of the newborn)
   c) Within the first five-years after index date, within sequential 90-day periods, describe the number and proportion of individuals treated with monotherapy of the following treatment classes, ERA, PDE-5 inhibitors, sGCs, or PRA or with combination therapy of these classes ERAs + PDE-5 inhibitor, ERAs + sGC, PDE-5 inhibitor + PRAs, and ERA + PDE-5 inhibitor + PRAs
   d) Describe the number and proportion of individuals treated with monotherapy of the following treatment classes ERA, PDE-5 inhibitors, sGCs, or PRA or combination therapy of these classes: ERAs + PDE-5 inhibitor, ERAs + sGC, PDE-5 inhibitor + PRAs, and ERA + PDE-5 inhibitor + PRAs by age group (0 to 1 year, 1 to 2-years, 2 to 5-years, 5 to 12-years, and 12 to 18-years) at time of prescription
   e) Within 180-days prior to index date and then within the first five-years after index date, within sequential 90-day periods, describe the number and proportion of individuals with at least one record for each of the following measures: 6-minute walk distance (6MWD) test, echocardiography, NT-proBNP, WHO functional class, right heart catheterisation, and cardiovascular MRI (Magnetic resonance imaging).
   f) Within the first five-years after index date in sequential 90-day periods, describe the number of and proportion of individuals who were admitted to hospital or died

Study design

Retrospective cohort study of population-level descriptive disease epidemiology and characterisation.

Study period

The study period was from 01/01/2014 to 31/12/2024.

Population

For objective 1, all individuals (<18 years) were included from the first day in each calendar year when all eligibly criteria are met. For the incidence calculation, individuals should have had no prior PAH diagnosis upon study entry, and for period prevalence this did not apply.

For objective 2, the index date was the date of first identified diagnosis of PAH (if this fell within the study period) and individuals should have had no prior PAH diagnosis upon study entry.

For both objectives, individuals with less than 365 days continuous observation prior to the index date were excluded (not applicable to individuals aged less than one year old, or those followed in CDW Bordeaux).

Variables

The outcome for objective 1 was PAH diagnosis.

For objective 2, various covariates were used to characterise the included individuals with PAH: demographic factors included sex, age and age group; conditions included right heart failure, ascites, arrhythmia, haemoptysis, syncope, congenital heart disease, bronchopulmonary dysplasia, congenital diaphragmatic hernia, persistent pulmonary hypertension of the newborn; procedures or measurements including lung-heart transplant, atrial septostomy or Pott shunt, 6 minute walking test, echocardiography, NT-proBNP test, WHO functional class, right heart catheterisation, cardiovascular MRI; and drug treatments, including mono- and combination therapies of endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, soluble guanylate cyclase stimulators, and PRAs.

Data sources

1. Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux), France
2. Danish Health Registries (DK-DHR), Denmark
3. Consortium of the Finnish OMOP data partners (FinOMOP-THL), Finland
4. Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED), Sweden
5. InGef - Institute for Applied Health Research Berlin GmbH (InGef RDB), Germany
6. Norwegian Linked Health Registry data (NLHR), Norway

Statistical analysis

The calculation of PAH incidence rates (with 95% confidence intervals) per data source was stratified by calendar year and age group (0 to 1 year, 1 to 2-years, 2 to 5-years, 5 to 12-years, and 12 to 18-years). Period prevalence was reported as the number per 1000 persons with new or ongoing PAH of the total population at risk in each data source, stratified by calendar year and age group.

We characterised individuals with PAH in terms of demographics at index date, as well as the number and proportion of records of comorbidities, procedures, treatments, hospitalisation in sequential 90-day windows after index date, and within 180 days before or at index date for procedures, measurements, and acute conditions. Chronic conditions for characterisation by aetiology were measured at index date and any time prior. Characterisation by number and proportion of treatment records was also stratified by age group at time of prescribing

Results

The overall incidence of paediatric PAH was 0.52–2.78 per 100,000 person-years across five data sources in Denmark, Finland, Sweden, Germany, and Norway across the study period 2014-2024. The incidence rate of PAH was greatest in the 0 to 1 year age group, with an IR between 6.36–28.56 per 100,000 person-years. The period prevalence of PAH across the study period was 0.06–0.19 per 1000 persons.

In the data sources which had sufficient counts of the conditions (i.e., >5 records per window and data source), 21.5%–57.0% of individuals with PAH had a record of congenital heart disease, 3.7%–22.5% had a record of persistent pulmonary hypertension of the newborn, and 3.5%–12.2% had a record of congenital diaphragmatic hernia any time prior to index date, and within 180-days prior to index date, bronchopulmonary dysplasia was present in 4.2%–13.9% of individuals. Prior right-sided heart failure was present in 3.7% (HI-SPEED) and 28.8% (NLHR) of individuals. Ascites was recorded in 4.7% (InGef RDB) and 5.6% (CDW Bordeaux), and cardiac arrythmia in 8.6%–21.1% of individuals in the period -180 to 0 days prior to the index date.

In the five-year follow-up [1 to 1800 days], 14.6%–38.9% of individuals with PAH in NLHR were prescribed PDE-5 inhibitor monotherapy for at least 30-days, and in FinOMOP-THL, HI-SPEED, and InGef RDB, 3.8–10.7% were prescribed ERA monotherapy. PRA or sGC monotherapy was prescribed in <5 or 0 individuals across all data sources. PDE-5i-ERA combination therapy was observed in 4.8–12.5% of individuals in FinOMOP-THL, HI-SPEED, and InGef RDB. ERA-sGC or PDE-5i-PRA combination therapy was prescribed in <5 or 0 individuals across all data sources. ERA-PDE-5i-PRA combination therapy was observed in HI-SPEED (2.4%), and <5 or 0 individuals in other data sources. 60–79% did not receive one of the targeted PAH treatment regimens across five data sources, and in CDW Bordeaux it was 97%.

Conclusion

Overall, the incidence rate of paediatric PAH was 0.52–2.78 per 100,000 person-years across five data sources in Denmark, Finland, Sweden, Germany, and Norway in the study period 2014–2024. The incidence rate was highest in children younger than 1-year old, and in many cases, the children with a PAH diagnosis were also diagnosed with congenital heart disease. The majority of individuals with newly diagnosed PAH remained untreated by targeted PAH therapy (under the condition of at least 30-days of treatment) in the 5-year period following index date. PDE-5 inhibitors were the most extensively used targeted PAH therapy, followed by dual PDE-5 inhibitor and ERA therapy.

5. LIST OF ABBREVIATIONS

Acronyms/terms	Description
CC	Coordination centre
CCBs	Calcium channel blockers
CDM	Common Data Model
CDW Bordeaux	Clinical Data Warehouse of Bordeaux University Hospital
CHD	Coronary heart disease
DARWIN EU®	Data Analysis and Real World Interrogation Network
DK-DHR	Danish Data Health Registries
DRE	Digital Research Environment
DQD	Data Quality Dashboard
ED	Emergency department
EHR	Electronic health records
EMA	European Medicines Agency
ERA	Endothelin receptor antagonist
FinOMOP - THL	Consortium of the Finnish OMOP data partners - Finnish Institute for Health and Welfare
GDPR	General Data Protection Regulation
GP	General practitioner
HI-SPEED	Health Impact - Swedish Population Evidence Enabling Data-linkage
InGef RDB	InGef - Institute for Applied Health Research Berlin GmbH research database
IP	Inpatient
IR	Incidence rate
MRI	Magnetic resonance imaging
NLHR	Norwegian Linked Health Registry
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
PAH	Pulmonary arterial hypertension
PDCO	Paediatric Committee
PDE-5i	Phosphodiesterase type 5 inhibitor
PIP	Paediatric Investigation Plan
PPHN	Persistent pulmonary hypertension of the newborn
PRA	Prostacyclin receptor antagonist
SMPA-GU	Swedish Medical Products Agency – Gothenburg University
sGC	Soluble guanylate cyclase
WHO	World Health Organisation

6. AMENDMENTS AND UPDATES

None.

7. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Draft Study Protocol	9th May 2025	9th May 2025
Final Study Protocol	19th August 2025	19th August 2025
Creation of Analytical code	5th June 2025	5th June 2025
Execution of Analytical Code on the data	25th August 2025	12th September 2025
Draft Study Report	30th September 2025	31st October 2025
Final Study Report	11th December 2025	9th January 2026

8. RATIONALE AND BACKGROUND

This study was triggered by discussions in the paediatric committee (PDCO) about the Paediatric Investigation Plan (PIP) for the endothelin receptor blocker Ambrisentan. The scope of the study was extended beyond describing the use of Ambrisentan, aiming to investigate the occurrence of pulmonary arterial hypertension (PAH) in paediatric patients and to characterise the disease and treatment use in a real-world setting. This study can therefore be used in any future PAH related regulatory procedures.

The course of PAH will lead to hypertrophy and remodelling of the right ventricle, and, if untreated, may lead to death.[1] Pulmonary hypertension (PH) is divided into 5 groups.[2] Group 1 is PAH, and in this group, there are different subgroups. The most prevalent groups in the paediatric population are idiopathic PAH, PAH associated with congenital heart disease (CHD), and persistent pulmonary hypertension of the newborn (PPHN). Group 2 includes pulmonary hypertension due to left-sided heart disease, group 3 includes pulmonary hypertension due to lung diseases and/or hypoxia, group 4 includes chronic thromboembolic pulmonary hypertension, and group 5 includes pulmonary hypertension with unclear, multifactorial, or other uncommon causes. Two common causes of pulmonary hypertension in children are bronchopulmonary dysplasia and congenital diaphragmatic hernia, these two are included in group 3.

In the general adult population, as estimated in French hospital data sources, there was an annual incidence of PAH of two to five cases per million.[3] However, PAH in children is rare and it is therefore difficult to enrol this specific population in clinical trials. Treatment patterns and disease course in the paediatric population remains understudied. The use of real-world data from across the DARWIN EU® network will be leveraged to cover wider populations across diverse data source to better understand the incidence, prevalence, and characterisation including treatment course for the European population. This study builds on evidence from a previous DARWIN EU® study, that specifically investigated co-prescribing the endothelin receptor antagonists (ERAs) and phosphodiesterate-5 inhibitors (PDE-5is) in individuals with PAH.[4]

9. RESEARCH QUESTION AND OBJECTIVES

1. Estimate the yearly incidence and period prevalence of pulmonary arterial hypertension (PAH) in the paediatric population, stratified by age group (0 to 1 year, 1 to 2-years, 2 to 5-years, 5 to 12-years, and 12 to 18-years)
2. Characterise paediatric patients newly diagnosed with PAH (index date = first PAH diagnosis):
   a) Describe the number and proportions of individuals by sex and age at index date
   b) Within 180-days prior to index date and then within the first five years after index date, within sequential 90-day periods describe the distribution of comorbidities (right heart failure, ascites, arrhythmia, haemoptysis, lung-heart transplant, atrial septostomy or Potts shunt, syncope), and within any time prior to index date, describe the distribution of potential aetiologies (congenital heart disease, bronchopulmonary dysplasia [180 days prior only], congenital diaphragmatic hernia, persistent pulmonary hypertension of the newborn)
   c) Within the first five-years after index date, within sequential 90-day periods, describe the number and proportion of individuals treated with monotherapy of the following treatment classes, ERA, PDE-5 inhibitors, sGCs, or PRA or with combination therapy of these classes ERAs + PDE-5 inhibitor, ERAs + sGC, PDE-5 inhibitor + PRAs, and ERA + PDE-5 inhibitor + PRAs
   d) Describe the number and proportion of individuals treated with monotherapy of the following treatment classes ERA, PDE-5 inhibitors, sGCs, or PRA or combination therapy of these classes: ERAs + PDE-5 inhibitor, ERAs + sGC, PDE-5 inhibitor + PRAs, and ERA + PDE-5 inhibitor + PRAs by age group (0 to 1 year, 1 to 2-years, 2 to 5-years, 5 to 12-years, and 12 to 18-years) at time of prescription
   e) Within 180-days prior to index date and then within the first five-years after index date, within sequential 90-day periods, describe the number and proportion of individuals with at least one record for each of the following measures: 6-minute walk distance (6MWD) test, echocardiography, NT-proBNP, WHO functional class, right heart catheterisation, and cardiovascular MRI (Magnetic resonance imaging).
   f) Within the first five-years after index date in sequential 90-day periods, describe the number of and proportion of individuals who were admitted to hospital or died

10. RESEARCH METHODS

10.1. Study type and study design

For the first objective, we performed a disease epidemiology study to estimate the incidence and period prevalence of PAH.

For the second objective, we performed a characterisation study to describe the demographic, conditions, procedures, hospital admissions, and treatments for paediatric individuals newly diagnosed with PAH. We also described the number and proportion of individuals with a record of PAH drug treatment by age group.

An overview of the study design for objective 1 can be seen in **Figure 1** and for objective 2 in **Figure 2**.

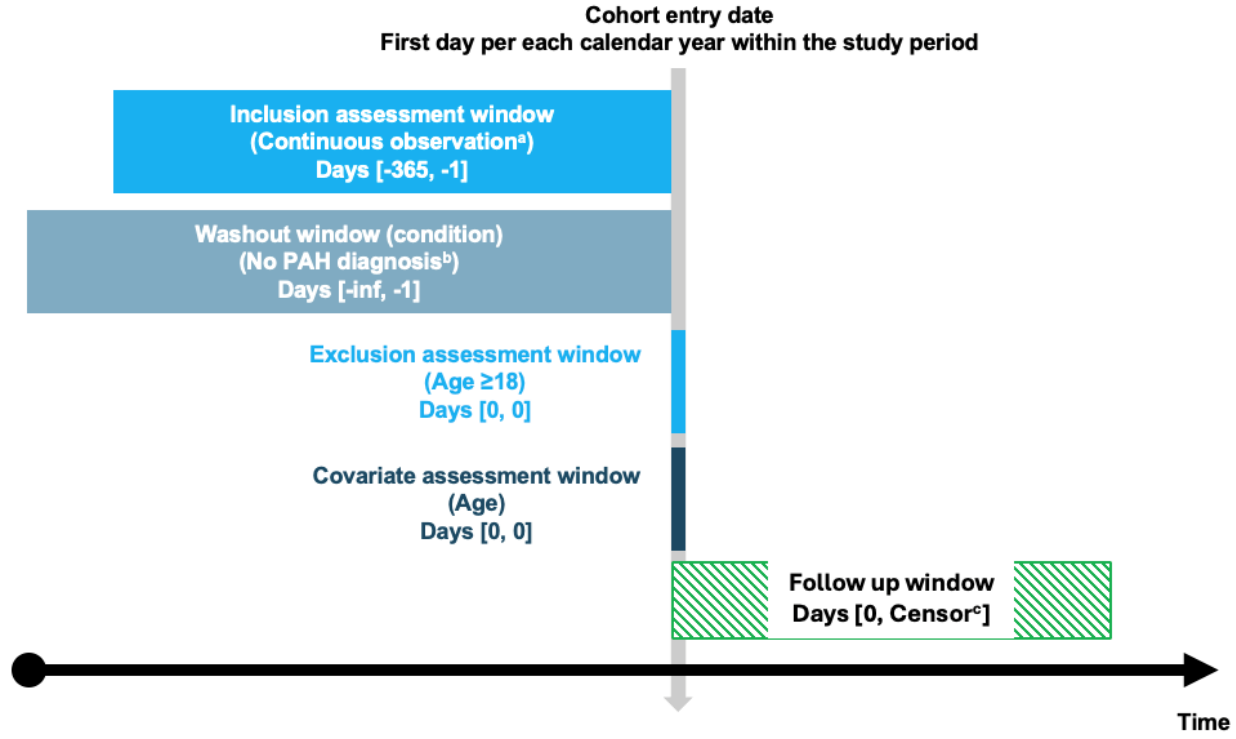

Figure 1. A graphical depiction of the study design for objective 1.

a. Applies to individuals older than one year
b. Applies for incidence estimation only
c. First of death, disenrollment, end of data source availability, occurrence of PAH (incidence estimation only), end of each calendar year (i.e., 31st December), or end of the study period (31/12/2024)

PAH = pulmonary arterial hypertension

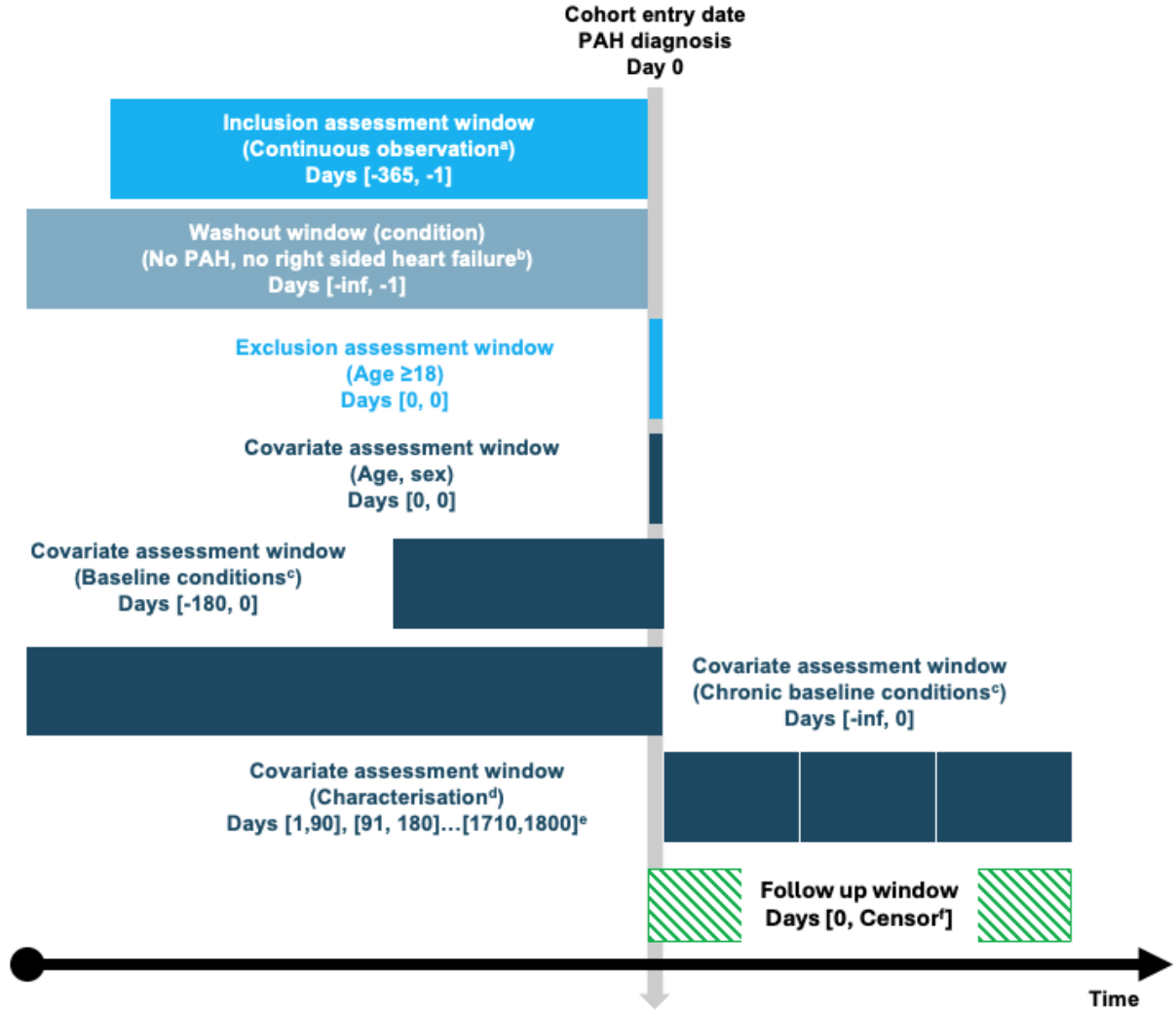

Figure 2. A graphical depiction of the study design for objective 2.

a. Applies to individuals older than one-year and those in CDW Bordeaux
b. "No right sided heart failure" only applies in the characterisation of individuals in terms of right sided heart failure incidence
c. Comorbidities
d. Comorbidities, drugs, tests, occurrence of death, occurrence of hospitalisation or emergency department visit
e. Assessed within sequential 90-day intervals until five years (twenty 90-day intervals)
f. First of death, disenrollment, end of data source availability, five years, or end of the study period (31/12/2024)

PAH = pulmonary arterial hypertension

10.2. Study setting and data sources

This study was conducted using routinely collected data from six data sources in six European countries, five of which are EU countries. All data were a priori mapped to the OMOP CDM. The data sources include:

1. Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux), France
2. Danish Health Registries (DK-DHR), Denmark
3. Consortium of the Finnish OMOP data partners (FinOMOP-THL), Finland
4. Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED), Sweden
5. InGef - Institute for Applied Health Research Berlin GmbH (InGef RDB), Germany
6. Norwegian Linked Health Registry data (NLHR), Norway

In general, the selection process was based on the number of individuals with the diagnosis of interest, geographical spread, and the experience gained from data sources that participated in other similar DARWIN EU® studies. For this specific study, the selection process also extended to ensure that some of the included data sources had coverage of both the inpatient and outpatient settings, as individuals with PAH are often treated over both healthcare settings. Based on the feasibility assessment performed, the suggested data sources were considered fit for purpose for at least part of the objectives.

When it comes to assessing the reliability of data sources, the data partners are asked to describe their internal data quality assurance process on the source data as part of the DARWIN EU® onboarding procedure. To further ensure data quality, we utilise the Achilles tool, which systematically characterises the data and generates data characteristics such as age distribution, condition prevalence per year, data density, measurement value distribution which can be compared against expectations for the data. Additionally, the data quality dashboard (DQD) provides more objective checks on plausibility consistently across the data sources. In terms of relevance, more general-purpose diagnostic tools, *CohortDiagnostics* and *DrugExposureDiagnostics*, were developed. The *CohortDiagnostics* package provides additional insights into cohort characteristics, record counts, and index event misclassification. The *DrugExposureDiagnostics* package assesses ingredient specific diagnostics for drug exposure records. Furthermore, data is maintained up to date by extracting the release dates for each dataset in the network and monitoring when data is out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it is important to have a clear understanding of the time period covered by each released data source, as this can vary across different domains. To facilitate this, the CDMOnboarding (and Achilles) packages contain a 'data density' plot. This plot displays the number of records per OMOP domain on a monthly basis. This allows getting insights when data collection started, when new sources of data were added, and until when data was included.

CDW Bordeaux does not have continuous follow-up of individuals contained within the data source. As such, this data source was not used to calculate incidence or period prevalence (objective 1) but only characterisation (objective 2). In addition, for CDW Bordeaux, there was no requirement of 365 days observation prior to the index date to be included.

Information on data sources used can be seen in **Annex I** with an overview and a justification for their choice in terms of ability to capture the relevant data described in **Table 1**.

Table 1. Description of the selected data sources.

Country	Name of Data source	Justification for Inclusion	Objectives	Health Care setting	Type of Data	Number of active subjects (total subjects)	Feasibility count of disease (PAH)	Data lock for the last update
France	CDW Bordeaux	Adequate number of individuals with the disease of interest (PAH) Contributes to the geographical diversity of data sources included Adequate coverage of PAH treatments	2	Hospital care	EHR	246k (2.3m)	4,000	01/09/2024
Denmark	DK-DHR	Adequate number of individuals with the disease of interest (PAH) Coverage of in- and outpatient prescribing data Nationwide denominator Contributes to the geographical diversity of data sources included Adequate coverage of PAH treatments	1, 2	Primary (all prescription retrievals as a proxy of primary care) and secondary care (hospital in-and outpatient records and emergency department)	Registry	5.9m (8.6m)	16,100	18/01/2025
Finland	FinOMOP-THL	Adequate number of individuals with the disease of interest (PAH) Contributes to the geographical diversity of data sources included Adequate coverage of PAH treatments	1, 2	Primary and secondary care	Registry	5.7m (6.6m)	1,500	01/10/2024
Sweden	HI-SPEED	Adequate number of individuals with the disease of interest (PAH) Nationwide denominator. Contributes to the geographical diversity of data sources included Adequate coverage of PAH treatments	1, 2	Secondary care with linkage to primary care (primary care available for 40% of population)	Registry	10.6m (11.7m)	9,700	01/08/2024

Country	Name of Data source	Justification for Inclusion	Objectives	Health Care setting	Type of Data	Number of active subjects (total subjects)	Feasibility count of disease (PAH)	Data lock for the last update
Germany	InGef RDB	Adequate number of individuals with the disease of interest (PAH) Nation representative denominator Contributes to the geographical diversity of data sources included Adequate coverage of PAH treatments	1, 2	Primary and secondary care (in-and outpatient for objective 1 and characterisation on objective 2), secondary care (inpatient only objective 2 index date)	Claims	7.7m (10.5m)	9,500	18/04/2025
Norway	NLHR	Adequate number of individuals with the disease of interest (PAH) Nationwide denominator. Contributes to the geographical diversity of data sources included Adequate coverage of PAH treatments	1, 2	Primary and secondary care	Registry	6.9m (7.3m)	1,300	01/12/2024

PAH = pulmonary arterial hypertension, EHR = electronic health records, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Consortium of the Finnish OMOP data partners - Finnish Institute for Health and Welfare, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef - Institute for Applied Health Research Berlin GmbH research database, NLHR = Norwegian Linked Health Registry

10.3. Study period

The study period was from 1st January 2014 to 31st December 2024. In HI-SPEED and InGef RDB the study period began on 1st January 2016 due to data availability.

10.4. Follow-up

For objective 1, the index date was the first day of each year within the study period on which an individual included in the study satisfied the eligibility criteria. For objective 2, the index date was the date of first diagnosis of PAH in the study period, with no prior diagnosis of PAH. For InGef RDB, only the inpatient data source was used for the study population objective 2 (characterisation) due to potential misclassification of index date with the outpatient data source.

For objective 1, individuals were followed up until the first of: death, end of observation in data, end date of each sequential year within the study period, or end of the study period (31/12/2024). For objective 1 incidence estimation, follow-up was additionally stopped at the date of first PAH diagnosis. For estimating period prevalence, all records of PAH within the study period were used. For objective 2, individuals were followed up until death, end of the study period (31/12/2024), end of observation in data, or the administrative end of follow-up at 5 years (1800 days).

The operational definitions of the index dates are described in **Table 2** and the concept set definitions of PAH are listed in **Annex II (Table 14)**.

Table 2. Operational definition of time 0 (index date) and other primary time anchors.

Study population names	Time Anchor Description	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type	Diagnosis position	Incident with respect to…
Incidence estimation	Time 0 (index date)	Multiple (one per calendar year until the first PAH diagnosis or end of observation)	n/a	[-inf,-1]	IP, OP	SNOMED	n/a	Pulmonary arterial hypertension
Prevalence estimation (PAH)	Time 0 (index date)	Multiple	n/a	none	IP, OP	n/a	n/a	n/a
Patient characterisation	Time 0 (index date)	Single	Incident	[-inf,-1]	IP, OP[2]	SNOMED	any	Pulmonary arterial hypertension

[1] IP = inpatient, OP = outpatient, n/a = not applicable, PAH = pulmonary arterial hypertension.
[2]Not for InGef RDB

10.5. Study population with in and exclusion criteria

For objective 1 (incidence of individuals with PAH):

Inclusion criteria

- Aged <18 years at index date
- Observation in the data source of 365 days prior to the index date (except for those aged less than one year old and individuals in hospital settings, CDW Bordeaux)

Exclusion criteria

- Occurrence of PAH prior to index date

For objective 1 (period prevalence of individuals with PAH):

Inclusion criteria

- Aged <18 years at index date
- Observation in the data source of 365 days prior to the index date (except for those aged less than one year old and individuals in hospital settings, CDW Bordeaux)

For objective 2 (characterisation of individuals with PAH)

Inclusion criteria

- Recorded diagnosis of PAH
- Aged <18 years at index date
- Observation in the data source of 365 days prior to the index date (except for those aged less than one year old and individuals in hospital settings, CDW Bordeaux)

Exclusion criteria

- Occurrence of PAH prior to index date
- Occurrence of right sided heart failure any time prior to index date (for characterisation of individuals in terms of right sided heart failure incidence)

The operational definitions of the inclusion and exclusion criteria are presented by means of **Table 3** and **Table 4**, respectively.

Table 3. Operational definitions of inclusion criteria.

Criterion	Details	Assessment window	Care Settings	Code Type	Applied to study populations:
PAH diagnosis	Pulmonary arterial hypertension diagnosis	[0,0]	IP[1], OP[2]	SNOMED	Objective 2
Paediatric	Aged <18 years at index date	[0,0]	n/a	n/a	Objective 1 and 2
365 days observation	Data source start date >365 days prior to index date in individuals older than one-year and not in CDW Bordeaux	[-365,-1]	n/a	n/a	Objective 1 and 2 (except CDW Bordeaux)

[1]All included data sources used information obtained from the inpatient setting to identify incident PAH
[2]All included data sources used information obtained from the outpatient setting to identify incident PAH except for InGef RDB
PAH = pulmonary arterial hypertension, IP = inpatient, OP = outpatient, n/a = not applicable, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital.

Table 4. Operational definitions of exclusion criteria.

Criterion	Details	Assessment window	Care Settings[1]	Code Type	Applied to study populations:
PAH diagnosis prior to index date	Prior diagnosis record of PAH	[-inf,-1]	IP, OP	SNOMED	Objective 1 (when estimating incidence) and objective 2
Right-sided heart failure diagnosis prior to index date	Prior diagnosis record of right sided heart failure	[-inf,-1]	IP, OP	SNOMED	Objective 2 (for characterisation of individuals by right sided heart failure only)

[1] IP = inpatient, OP = outpatient, PAH = pulmonary arterial hypertension

10.6. Variables

10.6.1. Exposures

Characterisation of treatment of PAH is described under other covariates.

10.6.2. Outcomes

The outcome was a record of a PAH diagnosis (for objective 1). The operational definition of this outcome is presented in **Table 5**. For InGef, we used diagnoses from both the in- and outpatient data sources for this outcome.

Table 5. Operational definitions of outcome.

Outcome name	Details	Type of outcome	Washout window	Care Settings[1]	Code Type	Applied to study populations
Pulmonary arterial hypertension	Diagnosis record of pulmonary arterial hypertension occurring during follow-up	Binary	Yes	IP, OP, ED	SNOMED	Objective 1

[1] IP = inpatient, OP = outpatient, ED = emergency department,
[2] Specify whether a diagnosis code was required to be in the primary position (main reason for encounter)

10.6.3. Other covariates, including confounders, effect modifiers, and other variables

Age and sex were measured at index date [0,0]. Individuals were categorised at index date into age groups (0 to 1 year, 1 to 2-years, 2 to 5-years, 5 to 12-years, and 12 to 18-years).

Occurrence of hospitalisation and death were assessed within sequential 90-day periods after index date until five-years post index date (e.g., from day one until day 90, from day 91 to day 180… day 1,710 to day 1800), or end of follow-up (**Table 6**).

Conditions including right heart failure, ascites, arrhythmia, haemoptysis, syncope, and bronchopulmonary dysplasia were measured between index date and 180 days prior [-180,0] and within sequential 90-day periods after index date until five-years post index date (except bronchopulmonary dysplasia), or end of follow-up (**Table 6**). There are several conditions, including congenital heart disease, congenital diaphragmatic hernia, and persistent pulmonary hypertension of the newborn, which were measured for at any time prior to the index date and index date itself [-inf,0]. For ascites, cardiac arrhythmia, haemoptysis, and syncope, we applied a washout window of 90-days after each diagnosis record to account for any

potential repeated diagnosis records of the same condition. For right heart failure only the first diagnosis record in follow-up was considered.

Potential aetiology of the incident PAH diagnosis was assessed through the characterisation of individuals in terms of a prior record of bronchopulmonary dysplasia, congenital heart disease, congenital diaphragmatic hernia, or persistent pulmonary hypertension of the newborn before index date. The aetiology could not be discerned from of the index PAH diagnosis code itself due to a lack of granularity in the data.

Cardiac arrhythmia was assessed as an overall category and further categorised (if counts allowed) into type of cardiac arrhythmia, namely atrial flutter, atrial fibrillation, SVT (supraventricular tachycardia), VT (ventricular tachycardia), VF (ventricular fibrillation), sick sinus syndrome, and AV block.[5]

Procedures including lung-heart transplant, atrial septostomy or Pott shunt, 6 minute walking test, echocardiography, NT-proBNP test, WHO functional class, right heart catheterisation, cardiovascular MRI were measured at index date minus 180 days [-180,0] and within sequential 90-day periods after index date until five-years post index date, or end of follow-up (**Table 6**). For lung-heart transplant and atrial septostomy or Potts shunt, only the first procedure record in follow-up was considered.

Drug prescription/dispensing records of monotherapy and combination therapy of endothelin receptor antagonists (ERAs, *bosentan, ambrisentan, macitentan*), phosphodiesterase type 5 inhibitors (PDE-5 inhibitors, *sildenafil, tadalafil*), soluble guanylate cyclase stimulators (*riociguat*), PRAs (*treprostinil, epoprostenol, iloprost, selexipag, ralinepag*) were assessed within sequential 90-day periods after index date until five-years post index date for objective 2c, or end of follow-up (**Table 6**). For objective 2d, drug prescription/dispensing records were assessed until day 1800.

The operational definition of the covariates is described in the **Table 6** and the associated concept set definitions are listed in **Annex II (Table 13)**.

Table 6. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment windows	Care Settings [1]	Code Type	Diagnosis Position[2]	Applied to study populations
Sex	-	Binary	[0,0]	n/a	n/a	n/a	Objective 2
Age	Age at index date	Continuous	[0,0]	n/a	n/a	n/a	Objective 2
Age group	Age group at index date: 0 to 1 year, 1 to 2-years, 2 to 5-years, 5 to 12-years, and 12 to 18-years	Categorical	[0,0]	n/a	n/a	n/a	Objective 1 and 2
Hospitalisation	Record of hospitalisation or emergency department visit	Binary	90-day sequential intervals[3]	IP, ED	n/a	n/a	Objective 2
Death	Death record	Binary	90-day sequential intervals[3]	IP, ED	n/a	n/a	Objective 2
Right sided heart failure	Condition record of right sided heart failure	Binary	[-inf,0], 90-day sequential intervals[3], [1,1800]	IP, OP, ED	SNOMED	Any	Objective 2

Characteristic	Details	Type of variable	Assessment windows	Care Settings [1]	Code Type	Diagnosis Position[2]	Applied to study populations
Ascites	Condition record of ascites	Binary	[-180,0], 90-day sequential intervals[3], [1,1800]	IP, OP, ED	SNOMED	Any	Objective 2
Cardiac Arrhythmia*	Condition record of Cardiac arrhythmia (for cardiac arrhythmia overall) and by type of cardiac arrhythmia*	Binary	[-180,0], 90-day sequential intervals[3], [1,1800]	IP, OP, ED	SNOMED	Any	Objective 2
Haemoptysis	Condition record of haemoptysis	Binary	[-180,0], 90-day sequential intervals[3], [1,1800]	IP, OP, ED	SNOMED	Any	Objective 2
Syncope	Condition record of syncope	Binary	[-180,0], 90-day sequential intervals[3], [1,1800]	IP, OP, ED	SNOMED	Any	Objective 2
Congenital heart disease	Condition record of congenital heart disease	Binary	[-inf,0]	IP, OP, ED	SNOMED	Any	Objective 2
Bronchopulmonary dysplasia	Condition record of bronchopulmonary dysplasia	Binary	[-180,0]	IP, OP, ED	SNOMED	Any	Objective 2
Congenital diaphragmatic hernia	Condition record of congenital diaphragmatic hernia	Binary	[-inf,0]	IP, OP, ED	SNOMED	Any	Objective 2
Persistent pulmonary hypertension of the newborn	Condition record of persistent pulmonary hypertension of the newborn	Binary	[-Inf, 0]	IP, OP, ED	SNOMED	Any	Objective 2
Endothelin receptor antagonists	Monotherapy of either bosentan, ambrisentan, or macitentan	Binary	90-day sequential intervals[3], [1,1800]	IP, OP, ED	RxNorm	n/a	Objective 2
Phosphodiesterase type 5 inhibitors	Monotherapy of either sildenafil or tadalafil	Binary	90-day sequential intervals[3], [1,1800]	IP, OP, ED	RxNorm	n/a	Objective 2
Soluble guanylate cyclase stimulators	Monotherapy of riociguat	Binary	90-day sequential intervals[3], [1,1800]	IP, OP, ED	RxNorm	n/a	Objective 2

Characteristic	Details	Type of variable	Assessment windows	Care Settings [1]	Code Type	Diagnosis Position[2]	Applied to study populations
Prostacyclin receptor agonists	Monotherapy of either treprostinil, epoprostenol, iloprost, selexipag, or ralinepag	Binary	90-day sequential intervals[3], [1,1800]	IP, OP, ED	RxNorm	n/a	Objective 2
Endothelin receptor antagonists and phosphodiesterase type 5 inhibitors	Combination therapy of ERAs + PDE-5 inhibitor	Binary	90-day sequential intervals[3], [1,1800]	IP, OP, ED	RxNorm	n/a	Objective 2
Endothelin receptor antagonists and soluble guanylate cyclase stimulators	Combination therapy of ERAs + sGC	Binary	90-day sequential intervals[3], [1,1800]	IP, OP, ED	RxNorm	n/a	Objective 2
Phosphodiesterase type 5 inhibitors and PRAs	Combination therapy of PDE-5 inhibitor + PRAs	Binary	90-day sequential intervals[3], [1,1800]	IP, OP, ED	RxNorm	n/a	Objective 2
Endothelin receptor antagonists and phosphodiesterase type 5 inhibitors and PRAs	Combination therapy of ERA + PDE-5 inhibitor + PRAs	Binary	90-day sequential intervals[3], [1,1800]	IP, OP, ED	RxNorm	n/a	Objective 2
No PAH treatment	No treatment of one of the PAH drug classes (ERAs, PDE-5 inhibitors, PRAs, or sGCs)	Binary	90-day sequential intervals[3], [1,1800]	IP, OP, ED	RxNorm	n/a	Objective 2
6 minute walking test	Measurement or procedure record of 6 minute walking test	Binary	[-180,0], 90-day sequential intervals[3], [1,1800]	IP, OP, ED	SNOMED, LOINC	n/a	Objective 2
echocardiography	Measurement or procedure record of echocardiography	Binary	[-180,0], 90-day sequential intervals[3], [1,1800]	IP, OP, ED	SNOMED, LOINC	n/a	Objective 2
NT-proBNP	Measurement record of NT-proBNP test	Binary	[-180,0], 90-day sequential intervals[3], [1,1800]	IP, OP, ED	LOINC	n/a	Objective 2

Characteristic	Details	Type of variable	Assessment windows	Care Settings [1]	Code Type	Diagnosis Position[2]	Applied to study populations
WHO functional class	Measurement record of WHO functional class	Binary	[-180,0], 90-day sequential intervals[3], [1,1800]	IP, OP, ED	LOINC	n/a	Objective 2
Right heart catheterisation	Procedure record of right heart catheterisation	Binary	[-180,0], 90-day sequential intervals[3], [1,1800]	IP, OP, ED	SNOMED	n/a	Objective 2
Cardiovascular MRI	Procedure record of cardiovascular MRI	Binary	[-180,0], 90-day sequential intervals[3], [1,1800]	IP, OP, ED	SNOMED	n/a	Objective 2
Lung-heart transplant	Procedure record of lung-heart transplant	Binary	[-180,0], 90-day sequential intervals[3], [1,1800]	IP, OP, ED	SNOMED	n/a	Objective 2
Atrial septostomy	Procedure record of atrial septostomy	Binary	[-180,0], 90-day sequential intervals[3], [1,1800]	IP, OP, ED	SNOMED	n/a	Objective 2
Potts shunt	Procedure record of Potts shunt	Binary	[-180,0], 90-day sequential intervals[3], [1,1800]	IP, OP, ED	SNOMED	n/a	Objective 2

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Specify whether a diagnosis code was required to be in the primary position (main reason for encounter)
[3] Sequential 90-day assessment windows from one day after the index date (e.g., from day one until day 90) until five-years after index date
*Cardiac arrhythmia was classified as “cardiac arrhythmia overall” and further categorized into atrial flutter, atrial fibrillation, SVT (supraventricular tachycardia), VT (ventricular tachycardia), VF (ventricular fibrillation), sick sinus syndrome, and AV block

10.7. Study size

No sample size was calculated for this study, as it was an exploratory descriptive disease epidemiology study in which the entire available data from each source was used. A feasibility assessment has been undertaken.

10.8. Data transformation

Analyses were conducted separately for each data source. Before study initiation, test runs of the analyses were performed on a subset of the data sources and quality control checks were performed. Once all the tests passed (Annex II), the final study codes package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP CDM in R Studio and reviewed and approved the, by default, aggregated results.

The study results of all data sources were checked after which they were made available to the team, and the dissemination phase started. All results were locked and timestamped for reproducibility and transparency

10.9. Statistical methods

10.9.1. Main summary measures

For objective 1, the measures to summarise the data are incidence rates (and 95% confidence intervals) and for period prevalence, percentage (and 95% confidence intervals). For objective 2, the measures to summarise the data are number and percentage, except in the case of age which is presented as median (and IQR) in addition percentage within age groups.

10.9.2. Main statistical methods

R packages

The analysis was conducted on data mapped OMOP CDM using the standardised R packages developed for DARWIN EU® which are described per objective:

Objective 1: Incidence and prevalence of pulmonary arterial hypertension

Calculation of population-based incidence rates and prevalence proportions is part of DARWIN EU® pipelines for population-level descriptive epidemiology. This analysis was performed using the *IncidencePrevalence* R package and provided incidence rates, stratified by age and for all age groups combined.[6] To ensure the reliable estimation of incidence rate using an appropriate denominator population, this objective was investigated only within the data sources with continuous observation: DK-DHR, FinOMOP-THL, HI-SPEED, NLHR, and InGef RDB.

Objective 2: Characterisation of individuals diagnosed with pulmonary arterial hypertension

Characterisation of patient demographics, potential aetiologies, comorbidities, and treatments before and after diagnosis was conducted using the *CohortCharacteristics* R packages.[7] Characterisation by the proportion of individuals with PAH treatment within age groups of treatment was conducted using the *IncidencePrevalence* R package.[6] To construct combination treatment cohorts, the *CohortConstructor* R package was utilised.[8] To estimate the number of untreated (by one of the four drug classes), the *DrugUtilisation* R package was used.[9]

10.9.3. Methods to obtain point estimates with confidence intervals of measure of occurrence

Objective 1: Incidence and period prevalence of pulmonary arterial hypertension

Incidence

Annual incidence rates of PAH were calculated as the number of newly diagnosed PAH per 100,000 person-years of the population at risk of the condition during the study period for each calendar year. Individuals entered the denominator population at the start of each calendar year or when they first fulfilled the eligibility criteria within the respective calendar year. Those study participants who entered the denominator population then contributed time at risk up until their first diagnosis. If they did not have the condition of interest, they contributed time at risk until the end of the calendar year. Time-at-risk of subjects who died or were diagnosed with PAH were censored at the time of death or diagnosis date, respectively. Similarly, time at risk of subjects who were lost to follow-up were censored at the time of loss to follow-up (last contact). Subjects with data until the end of the calendar period without a record of the condition were administratively censored at the end of each calendar period. Incidence rates are given together with 95% Poisson confidence intervals. **Figure 3** represents an example of incidence rate estimation.

Prevalence

Period prevalence was calculated by counting the number of individuals with a PAH diagnosis per calendar year, as well as ongoing disease from prior to each period (**Figure 4**). Each individual with PAH were considered as ongoing disease since the first diagnosis of PAH recorded. These counts were divided by the denominator (the number of persons at risk in the period) to calculate a proportion. Period prevalence is reported as per 1000 persons with 95% confidence intervals, as estimated by the Wilson Score method.

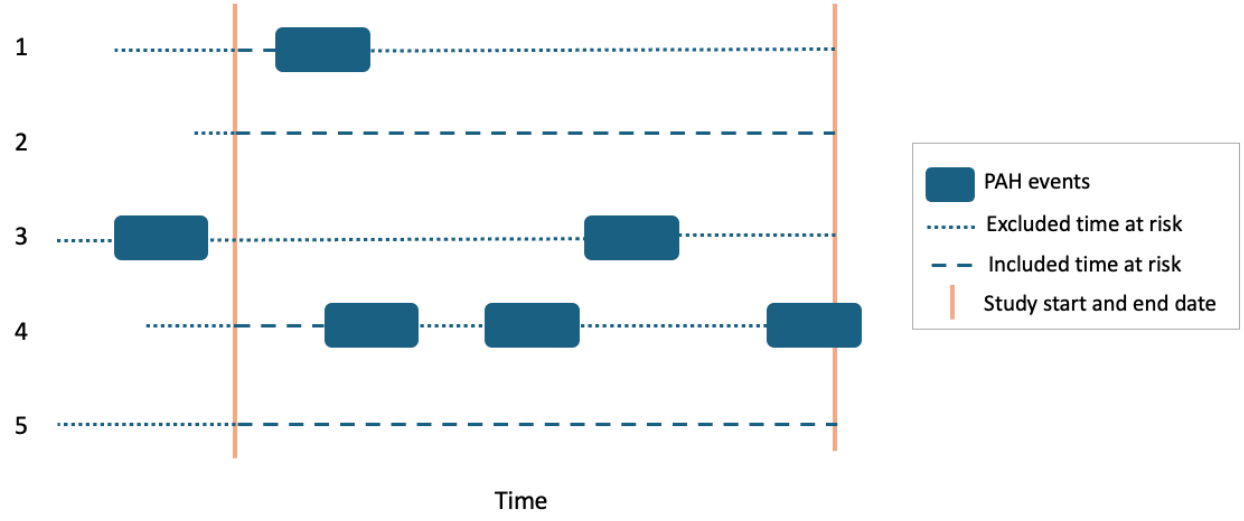

Figure 3. Example of incidence rate estimation.

Patient IDs 1 and 4 contribute time at risk between the study start until they have an incident outcome of interest. Patient IDs 2 and 5 contribute time at risk between the study start and end date, as no outcome of interest is observed between this period nor before the study start date. Infinite wash out was applied because only the first outcome after follow-up was included.

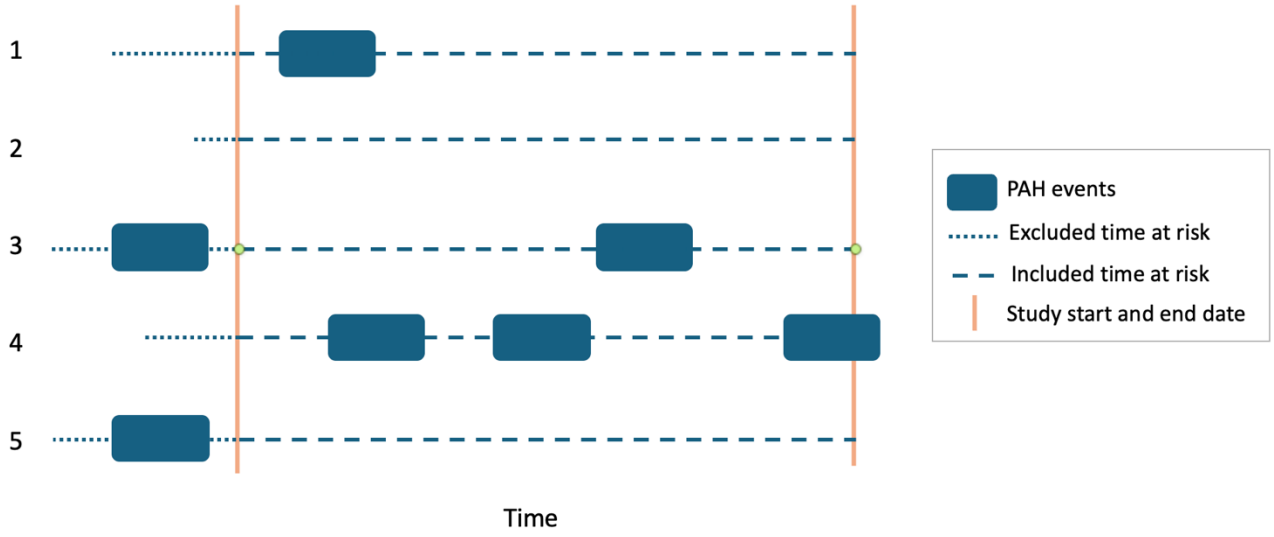

Figure 4. Example of period prevalence estimation.

Patients 1, 3 , 4, and 5 contribute to the numerator population, therefore the prevalence would be 80%.

Objective 2: Characterisation of individuals diagnosed with pulmonary arterial hypertension

For each patient characteristic (as defined using a list of concepts seen in **Annex III**) the number and proportion of individuals with a record within each specified time window is presented. Sex and median age were measured at index date (i.e., date of diagnosis of incident PAH). For the characterisation of individuals in terms of comorbidities, only the first occurrence of chronic conditions (e.g., right-sided heart failure) was considered. For acute conditions (cardiac arrhythmia, ascites, haemoptysis, syncope), we applied a 90-day washout window prior to each diagnosis to ensure there was no overestimation of conditions' occurrence due to repeated records of the same event. Any repeated records of the same diagnosis within 90-days prior were disregarded. With the exception of the 90-day window, acute conditions were measured repeatedly over the course of follow-up. We excluded individuals who had a prior occurrence of right heart failure at any time prior to index date to ensure it was the incident diagnosis. With one-time procedures (lung-heart transplant and atrial septostomy or Potts shunt), we only considered the first event during follow-up.

In objective 2c, the number and proportion of individuals prescribed or dispensed PAH drug treatments, including ERAs, PDE-5 inhibitors, sGCs, or PRAs, were calculated over follow-up, which was divided into 90-day windows from the index date until five-years after index date. Drug eras were constructed with a maximum gap between two sequential prescriptions of the same drug class (i.e., the end date of one to the start date of the next) of 30 days, adding seven days to the end of last prescription to account for surplus supply.

Combination therapy included the following: ERAs + PDE-5 inhibitor, ERAs + sGC, PDE-5 inhibitor + PRAs, and ERA + PDE-5 inhibitor + PRAs. Using drug eras of each individual drug class (ERAs, PDE-5 inhibitors, sGCs, or PRAs), drug combinations were identified as overlaps in individual drug eras. When one of the components of a combination therapy ends (i.e., end of that individual drug era), the combination ends, and the individual enters monotherapy or another combination therapy (e.g., switching from triple to dual therapy). See **Figure 5** for a graphical depiction of a treatment assignment example.

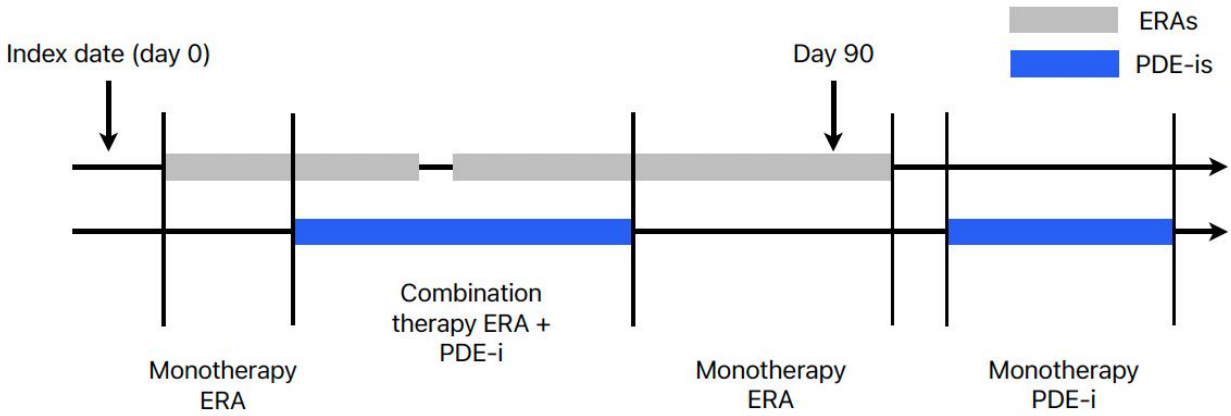

Figure 5. An example of an individual treatment trajectory.

The individual was considered to be treated with monotherapy ERA and combination therapy ERA +PDE-I in the day 1 to 90 window. In the 91 to 180 window, the individual considered to be treated with monotherapy ERAs and monotherapy PDE-is.

Combination therapy was assigned in a hierarchal manner due to the likely event that an individual could fall into multiple predefined groups at one time. The full algorithm can be seen in **Annex IV**. In short, the algorithm first selects the time during triple overlap combination therapy (ERA + PDE-5

inhibitor + PRAs) and excludes it from the time of dual or monotherapy that are subsets of the drugs included in the triple combination. Likewise, this hierarchy applies for the time on the dual therapies (ERAs + PDE-5 inhibitor, ERAs + sGC, PDE-5 inhibitor + PRAs) over the monotherapies. Overlapping treatment eras may result in data artifacts which should not be considered as combination therapy, as for example in the case that an individual switches from one monotherapy to another monotherapy. The way that drug prescription duration is estimated will mean that there may be a period which is considered to be a combination therapy when this was not true in practice. To ensure these instances were not taken into account for the characterisation, we applied a minimum length of treatment of 30-days for all monotherapies and combination therapies. This minimum length requirement was applied after the assignment of the monotherapy and combination therapy time, during the process of the algorithm.

In objective 2d, the number and proportion of individuals using PAH monotherapies or combination therapies was estimated within each age group (0 to 1 year, 1 to 2-years, 2 to 5-years, 5 to 12-years, and 12 to 18-years). The follow-up time after the index date until day 1800 for each individual was divided into these age groups. When a drug cohort (monotherapy or combination therapy) intersects with the age group period in the follow-up, that drug class was counted and included as a numerator.

A minimum cell counts of 5 was used when reporting results, with any smaller counts reported as "<5" for privacy protection reasons.

10.9.4. Missing values

For the disease epidemiology studies, we assume that the absence of a diagnosis record means that the person did not receive the diagnosis.

10.9.5. Sensitivity analysis

We have implemented two post-hoc sensitivity analyses: the first aimed to describe the number of individuals with PAH by prescriptions of targeted PAH treatment and calcium channel blockers (CCBs) in the five-years after index date (i.e., from day 1 to day 1800). This analysis estimated the proportion of individuals with at least one prescription of either PDE-5-I, ERAs, PRAs, sGCs, or CCBs, irrespective of the treatment course of mono- or combination therapy. The output was percentage and counts. This sensitivity analysis was performed to check whether the treatment characterisation algorithm developed for objective 2c underestimated the proportion of individuals prescribed targeted PAH therapies. The second sensitivity analysis aimed to identify the number of individuals who had none of the pre-specified aetiologies (congenital heart disease, congenital diaphragmatic hernia, bronchopulmonary dysplasia, or persistent pulmonary hypertension of the newborn) recorded in the period prior to index date. The percentage of individuals without prior conditions were estimated by defining cohorts of individuals with incident PAH and excluding those with prior conditions any time before and including the index date (except bronchopulmonary dysplasia, where the period was then -180 days to index date).

11. RESULTS

The full results can be explored on the shiny app: EUPAS1000000716

For objective 1 (incidence) within the study period 01/01/2014 to 31/12/2024 (except HI-SPEED and InGef RDB which was 01/01/2016 to 31/12/2024), the study population consisted of 1,925,633 individuals in DK-DHR, 1,712,212 in FinOMOP-THL, 3,111,132 in HI-SPEED, 2,244,739 in InGef RDB, and 1,761,534 in NLHR (**Tables S1–5**).

For objective 1 (prevalence) within the study period 01/01/2014 to 31/12/2024 (except HI-SPEED and InGef RDB which was 01/01/2016 to 31/12/2024), the study population consisted of 1,925,714 individuals in DK-

DHR, 1,712,249 in FinOMOP-THL, 3,111,180 in HI-SPEED, 2,244,847 in InGef RDB, and 1,761,590 in NLHR (**Tables S6–10**).

For objective 2 within the study period 01/01/2014 to 31/12/2024 (except HI-SPEED and InGef RDB which was 01/01/2016 to 31/12/2024), in DK-DHR, 6,192 individuals had a record of PAH, 144 were aged <18 years, 123 had no previous PAH diagnosis, and 118 had a prior observation of at least 365 days (for those aged older than 1-year); in FinOMOP-THL, 1,062 individuals had a record of PAH, 70 were aged <18 years, 61 had no previous PAH diagnosis, and 58 had a prior observation of at least 365 days; in HI-SPEED, 8,980 individuals had a record of PAH, 244 were aged <18 years, 220 had no previous PAH diagnosis, and 214 had a prior observation of at least 365 days; in InGef RDB, 6,026 individuals had a record of PAH, 241 were aged <18 years, 220 had no previous PAH diagnosis, and 213 had a prior observation of at least 365 days; in NLHR 1,006 individuals had a record of PAH, 125 were aged <18 years, 111 had no previous PAH diagnosis, and 108 had a prior observation of at least 365 days; and in CDW Bordeaux, 3,348 individuals had a record of a PAH, 171 were aged <18 years, and 168 had no previous PAH diagnosis.

11.1. PAH incidence and prevalence

11.1.1. Incidence

The overall incidence rate of PAH across the study period was 0.52 (0.39–0.67) per 100,000 person-years i FinOMOP-THL, 0.95 (0.78–1.14) in DK-DHR, 1.00 (0.82–1.21) in NLHR, 1.17 (1.02–1.34) in HI-SPEED, and 2.78 (2.48–3.10) in InGef RDB. The incidence rate was the lowest in FinOMOP-THL, where some calendar years miss incidence rates due to censoring of events <5, however in 2014 their incidence rate is highest at 0.91 (0.44–1.68) per 100,000 person-years. The incidence rate of PAH remains highest in InGef RDB, where it ranges from 1.82 (1.16–2.74) to 4.14 (3.09–5.42) per 100,000 person-years. HI-SPEED has a decreasing incidence rate over the study period: the incidence rate in 2016 was 2.33 (1.71–3.09) per 100,000 person-years, while in 2023 the incidence rate was 0.60 (0.32–1.03) per 100,000 person-years. Full results are graphically depicted per calendar year in **Figure 6**, and the values per year and overall can be found in **Table S1**.

There are no discernible differences in the incidence rates between the sexes (**Figure S1, Table S2**, and **Table S3**).

Regarding age-group stratification, the incidence rate of PAH was greatest across all data sources in the 0 to 1 year age group. In DK-DHR the incidence rate was 6.36 (4.43–8.85) per 100,000 person-years in FinOMOP-THL, 8.13 (6.09–10.63), 11.54 (8.88–14.73) in NLHR, 14.47 (12.14–17.12) in HI-SPEED, and 28.56 (24.18–33.49) in InGef RDB (**Table S4** and **Table S5**). In the older age groups (2 to 5, 5 to 12, and 12 to 18), the incidence rates for all data sources except InGef RDB were below 1.00 per 100,000 person-years. Incidence per age-group and by calendar year is graphically depicted in **Figure 7**.

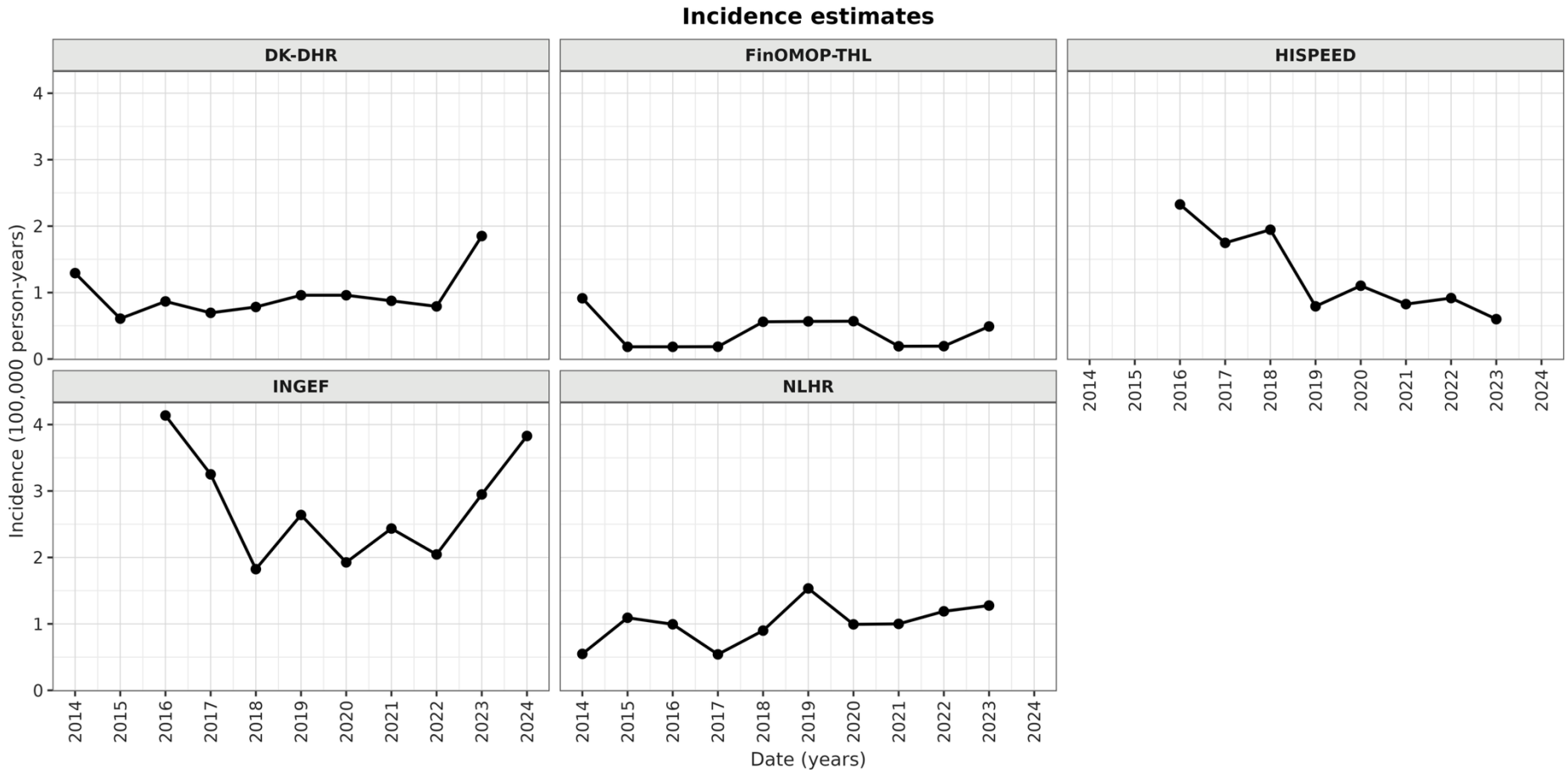

Figure 6. Incidence rates of PAH in paediatric individuals per calendar year.

Abbreviations: DK-DHR = Danish Data Health Registries, FinOMOP-THL = Consortium of the Finnish OMOP data partners - Finnish Institute for Health and Welfare, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef - Institute for Applied Health Research Berlin GmbH research database, NLHR = Norwegian Linked Health Registry

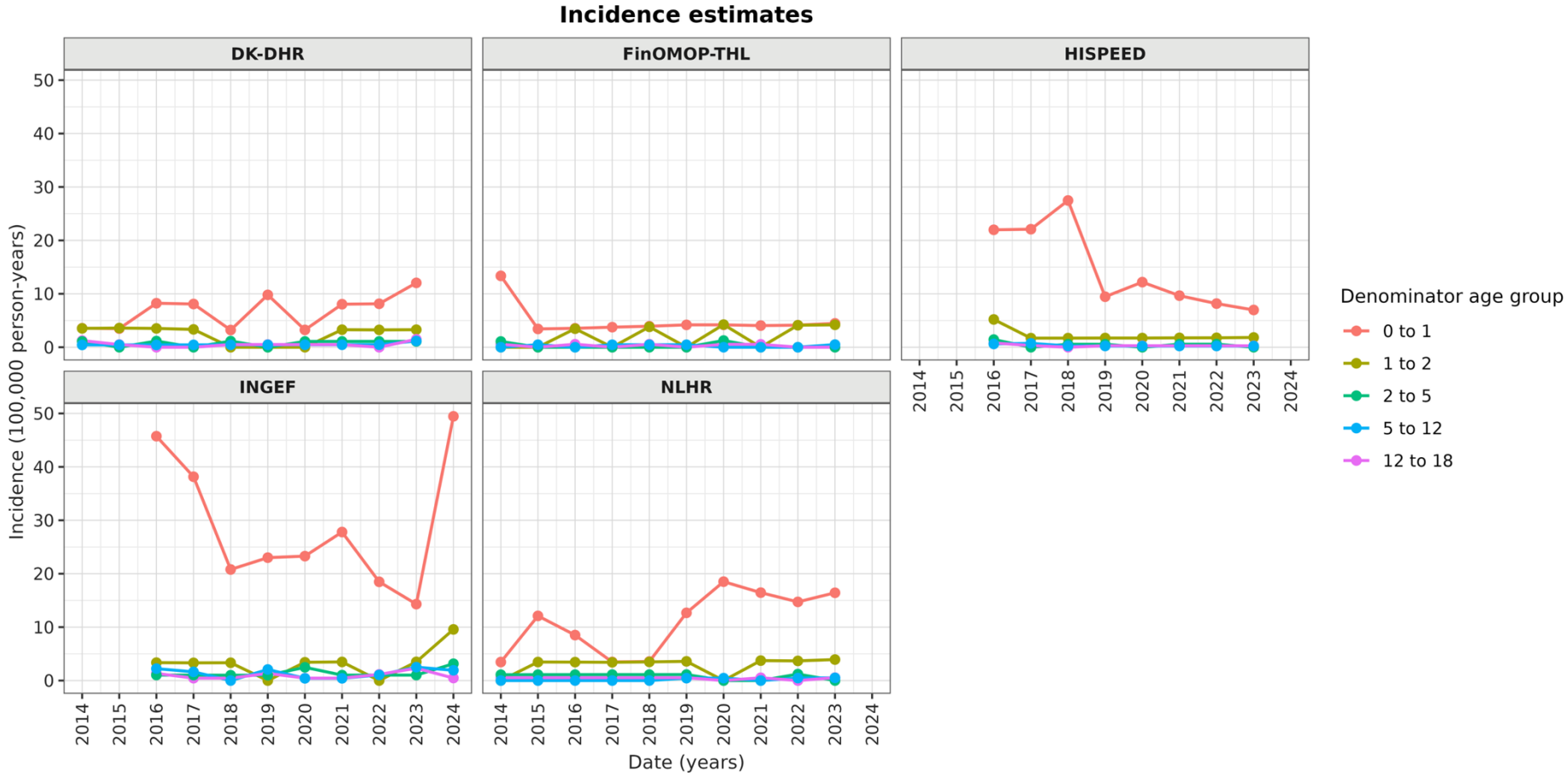

Figure 7. Incidence rates of PAH in paediatric individuals per year, stratified by age group.

Abbreviations: DK-DHR = Danish Data Health Registries, FinOMOP-THL = Consortium of the Finnish OMOP data partners - Finnish Institute for Health and Welfare, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef - Institute for Applied Health Research Berlin GmbH research database, NLHR = Norwegian Linked Health Registry

11.1.2. Prevalence

The overall period prevalence of PAH across the study period was 0.10 (0.09–0.12) per 1000 persons in DK-DHR, 0.06 (0.05–0.07) in FinOMOP-THL, 0.08 (0.08–0.10) in HI-SPEED, 0.19 (0.17–0.21) in InGef RDB, and 0.09 (0.08–0.011) per 1000 persons in NLHR. In all data sources, the period prevalence per year increased over the study period, from 0.08 (0.06–0.09) per 1000 persons in 2014 to 0.11 (0.09–0.13) in 2023 in DK-DHR, from 0.04 (0.03–0.05) per 1000 persons in 2014 to 0.06 (0.04–0.07) in 2023 in FinOMOP-THL, from 0.04 (0.03–0.05) per 1000 persons in 2016 to 0.09 (0.08–0.10) in 2023 in HI-SPEED, from 0.11 (0.09–0.13) per 1000 persons in 2016 to 0.24 (0.22–0.27) in 2024 in InGef RDB, and from 0.05 (0.04–0.07) per 1000 persons in 2014 to 0.12 (0.10–0.14) per 1,000 persons in 2023 in NLHR. Full results are graphically depicted per calendar year in **Figure 8**, and the values per year and overall can be found in **Table S6**. There are no discernible differences in the period prevalence between the sexes (**Figure S2, Table S7**, and **Table S8**). There were no clear trends across all data sources for period prevalence for each of the age groups **Table S9** and **Table S10**). Period prevalence by calendar year is graphically depicted in **Figure 9**.

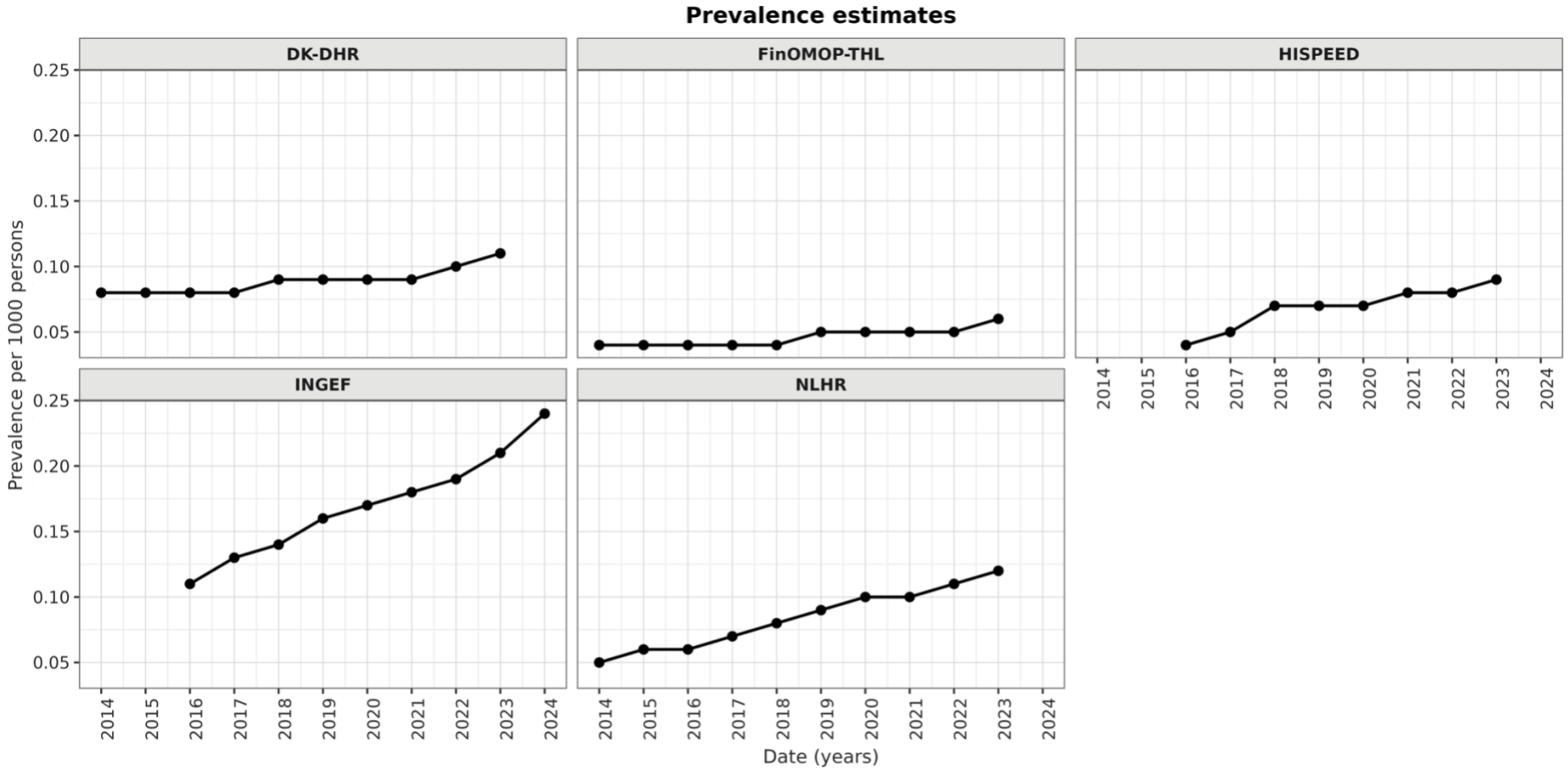

Figure 8. Period prevalence of PAH in paediatric individuals per calendar year.

Abbreviations: DK-DHR = Danish Data Health Registries, FinOMOP-THL = Consortium of the Finnish OMOP data partners - Finnish Institute for Health and Welfare, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef - Institute for Applied Health Research Berlin GmbH research database, NLHR = Norwegian Linked Health Registry

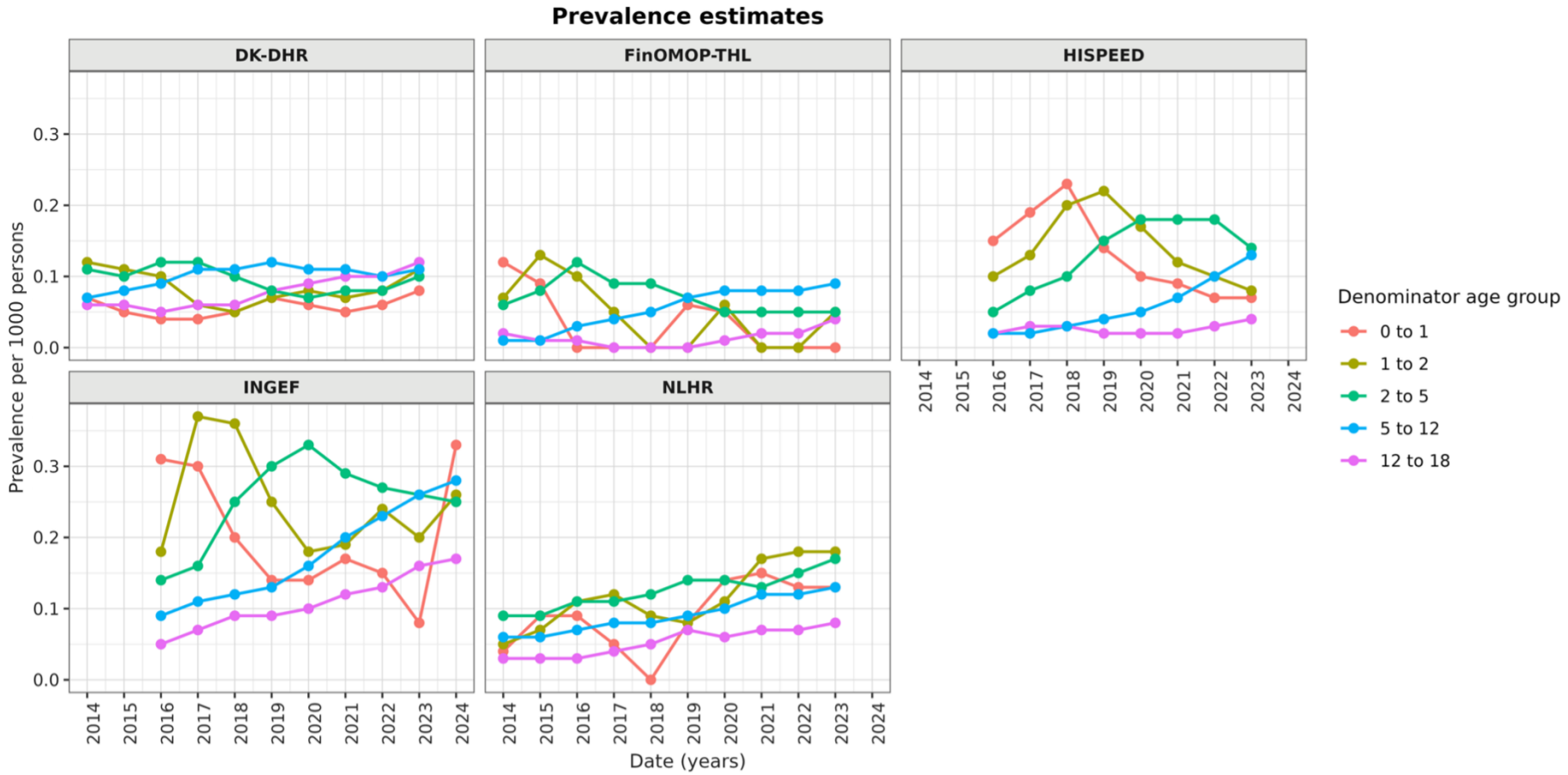

Figure 9. Period prevalence of PAH in paediatric individuals per calendar year, stratified by age group.

Abbreviations: DK-DHR = Danish Data Health Registries, FinOMOP-THL = Consortium of the Finnish OMOP data partners - Finnish Institute for Health and Welfare, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef - Institute for Applied Health Research Berlin GmbH research database, NLHR = Norwegian Linked Health Registry

11.2. Participants with PAH

A total of 853 individuals with incident PAH within the study period from six data sources (**Table 7**) were included. The median age of incident diagnosis was 0 to 1 years old, with between 44.9% (DK-DHR) and 79.6% (CDW Bordeaux) of individuals diagnosed before their first birthday. The range of ages at diagnosis was from 0 to 18 years old across the data sources. The proportion of females ranged from 43.0% (CDW Bordeaux) to 56.9% female (FinOMOP-THL).

Table 7. Cohort characteristics of individuals with incident pulmonary arterial hypertension.

			CDW Bordeaux	DK-DHR	FinOMOP-THL	HI-SPEED	InGef RDB	NLHR
Number subjects*	-	N	142	118	58	214	213	108
Age at diagnosis	-	Median [Q25–Q75]	0 [0–0]	1 [0–9]	0 [0–5]	0 [0–2]	1 [0–8]	0 [0–2]
		Mean (SD)	1.75 (4.23)	4.50 (5.94)	3.05 (4.97)	2.38 (4.48)	4.04 (5.25)	2.59 (4.86)
		Range	0 to 18	0 to 18	0 to 15	0 to 18	0 to 18	0 to 18
Age group	0 to 1	N (%)	113 (79.58%)	53 (44.92%)	35 (60.34%)	136 (63.55%)	98 (46.01%)	64 (59.26%)
	1 to 2	N (%)	<5	12 (10.17%)	5 (8.62%)	24 (11.21%)	18 (8.45%)	13 (12.04%)
	2 to 5	N (%)	9 (6.34%)	12 (10.17%)	<5	11 (5.14%)	25 (11.74%)	12 (11.11%)
	5 to 12	N (%)	7 (4.93%)	18 (15.25%)	9 (15.52%)	25 (11.68%)	41 (19.25%)	5 (4.63%)
	12 to 18	N (%)	12 (8.45%)	23 (19.49%)	7 (12.07%)	18 (8.41%)	31 (14.55%)	14 (12.96%)
Sex	Female	N (%)	61 (42.96%)	62 (52.54%)	33 (56.90%)	101 (47.20%)	108 (50.70%)	50 (46.30%)
	Male	N (%)	81 (57.04%)	56 (47.46%)	25 (43.10%)	113 (52.80%)	105 (49.30%)	58 (53.70%)

*Not all individuals with PAH were included in all objectives due to use of different data sources (e.g., use of outpatient data in objective 1, but not for defining the study population in objective 2 for InGef RDB), and data sources (e.g., CDW Bordeaux were not used in objective 1)
Abbreviations: CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Consortium of the Finnish OMOP data partners - Finnish Institute for Health and Welfare, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef - Institute for Applied Health Research Berlin GmbH research database, NLHR = Norwegian Linked Health Registry

11.3. Descriptive analysis of incident PAH patients

11.3.1. Aetiology

In terms of potential aetiology (**Table 8**), measured any time prior to index date, congenital heart disease was identified in 57.0% (CDW Bordeaux), 22.9% (DK-DHR), 51.7% (FinOMOP-THL), 21.5% (HI-SPEED), 38.5% (InGef RDB), and 53.7% (NLHR) of individuals.

Persistent pulmonary hypertension of the newborn was identified in 10.6% (CDW Bordeaux), 13.6% (DK-DHR), 20.7% (FinOMOP-THL), 3.7% (HI-SPEED), 22.5% (InGef), and 6.5% (NLHR) of individuals.

Congenital diaphragmatic hernia was identified in 3.5% (CDW Bordeaux), 12.2% (HI-SPEED), and 9.9% (InGef RDB) of individuals. DK-DHR and NLHR had <5 records of congenital diaphragmatic hernia, and FinOMOP-THL had zero records.

Between 180-days prior to index date and index date itself, bronchopulmonary dysplasia was present in 4.2% (CDW Bordeaux), 13.6% (DK-DHR), 7.5% (HI-SPEED), 8.9% (InGef RDB), and 13.9% (NLHR) of individuals. There were <5 records in FinOMOP-THL.

In paediatric individuals diagnosed with PAH, 42.3% (CDW Bordeaux), 45.5% (DK-DHR), 36.1% (FinOMOP-THL), 45.0% (HI-SPEED), 37.3% (InGef RDB), and 36.0% (NLHR) had none of the prior prespecified aetiologies in the period prior to and including the index date.

Table 8. Characterisation of individuals diagnosed with PAH in terms of potential aetiology.

Variables	Look back Window	CDW Bordeaux	DK-DHR	FinOMOP-THL	HI-SPEED	InGef RDB	NLHR
Congenital heart disease	-180 to 0	67 (47.18%)	9 (7.63%)	17 (29.31%)	27 (12.62%)	38 (17.84%)	32 (29.63%)
	-inf to 0	81 (57.04%)	27 (22.88%)	30 (51.72%)	46 (21.50%)	82 (38.50%)	58 (53.70%)
Bronchopulmonary dysplasia	-180 to 0	6 (4.23%)	16 (13.56%)	<5	16 (7.48%)	19 (8.92%)	15 (13.89%)
	-inf to 0	8 (5.63%)	26 (22.03%)	6 (10.34%)	32 (14.95%)	34 (15.96%)	19 (17.59%)
Persistent PH of the newborn	-180 to 0	11 (7.75%)	12 (10.17%)	10 (17.24%)	6 (2.80%)	35 (16.43%)	5 (4.63%)
	-inf to 0	15 (10.56%)	16 (13.56%)	12 (20.69%)	8 (3.74%)	48 (22.54%)	7 (6.48%)
Congenital diaphragmatic hernia	-180 to 0	<5	<5	0 (0.00%)	22 (10.28%)	13 (6.10%)	<5
	-inf to 0	5 (3.52%)	<5	0 (0.00%)	26 (12.15%)	21 (9.86%)	<5
No prior aetiology	-inf to 0[1], -180 to 0[2]	71 (42.26%)	56 (45.52%)	22 (36.07%)	99 (45.00%)	82 (37.27%)	40 (36.04%)

[1]Congenital heart disease, persistent PH of the newborn, and congenital diaphragmatic hernia, [2]Bronchopulmonary dysplasia
Abbreviations: CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Consortium of the Finnish OMOP data partners - Finnish Institute for Health and Welfare, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef - Institute for Applied Health Research Berlin GmbH research database, NLHR = Norwegian Linked Health Registry

11.3.2. Procedures

Full results can be seen in **Table S11** and graphically depicted in **Figure 10.**

NT-proBNP Test:

In the 180 days prior to the index date, 18.6% of individuals in the DK-DHR dataset received an NT-proBNP test. In the first 90-day period after index date, up to 23.1% of individuals had a record of this test in DK-DHR. This test was not reported in the other data sources.

Echocardiography:

Echocardiography was the most frequently recorded procedure of those pre-specified. During the 180-day period before the index date, an echocardiography was performed in 9.4% of individuals in the InGef RDB dataset, 62.1% in FinOMOP-THL, 73.4% in HI-SPEED, and 83.8% in CDW Bordeaux. In the first 90 days following index date, an echocardiography was performed in 82.4% (CDW Bordeaux), 73.2% (FinOMOP-THL), 58.1% (HI-SPEED), and 5.2% (InGef RDB) of individuals. In the second 90-day period following index date, an echocardiography was performed in 42.7% (CDW Bordeaux), 51.1% (FinOMOP-THL), 40.3% (HI-SPEED), and 2.6% (InGef RDB) of individuals.

Cardiovascular MRI:

Only the InGef RDB dataset reported cardiovascular MRI usage, with 3.8% of individuals receiving the scan within 180 days prior to the index date.

Right Heart Catheterisation:

This procedure was recorded in the 180 days before and on the index date in 7.6% of individuals in DK-DHR and 17.4% in InGef RDB. In the 90 days following the index date, right heart catheterisation was performed in 15.4% of DK-DHR cases and 4.2% in InGef RDB. Between days 91 and 180 after the index date, the procedure was recorded in 5.5% of DK-DHR and 3.7% of InGef RDB cases.

Walking Six-Minute Test & WHO Pulmonary Hypertension Functional Class Assessment:

No records of either the walking six-minute test or the WHO pulmonary hypertension functional class assessment were found in any of the data sources.

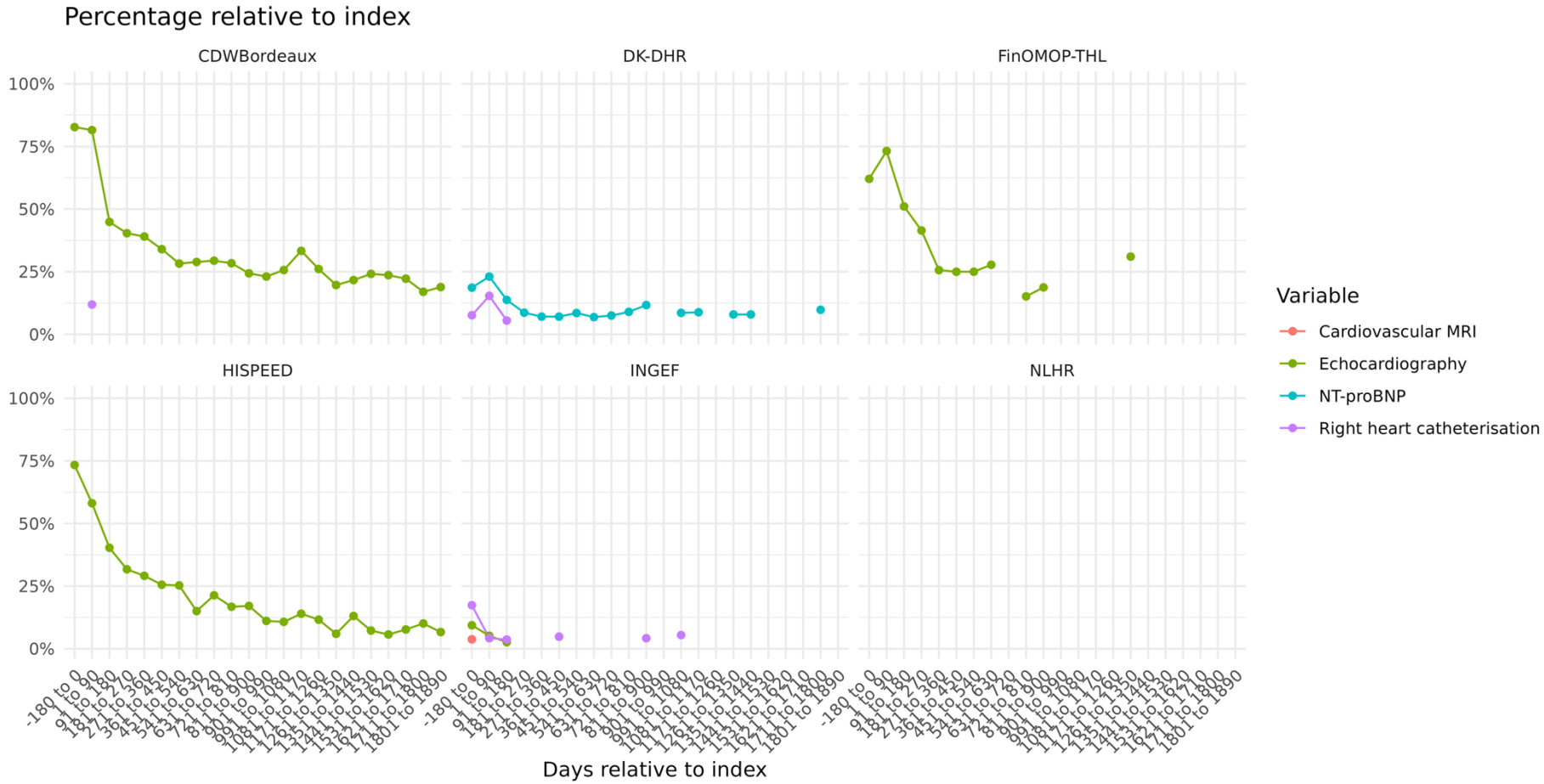

Figure 10. PAH-related procedure occurrences after index date per 90-day interval.

Note: Figure does not display 6-minute walking test, WHO functional class status, atrial septostomy, or heart-lung transplant due to low counts.
Abbreviations: PAH = pulmonary arterial hypertension, NT-proBNP = N-terminal prohormone of brain natriuretic peptide, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Consortium of the Finnish OMOP data partners - Finnish Institute for Health and Welfare, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef - Institute for Applied Health Research Berlin GmbH research database, NLHR = Norwegian Linked Health Registry

11.3.3. Conditions

Full results of the characterisation by comorbidity can be found in **Table S12** and the characterisation by comorbidity is graphically depicted in **Figure 11.**

Right-sided heart failure:

In the period any time prior to index date to index date itself, right-sided heart failure was present in 3.6% (HI-SPEED) and 28.8% (NLHR) of individuals. No or very few records of right-sided heart failure were recorded for InGef RDB and FinOMOP-THL, CDW Bordeaux or DK-DHR.

There were few records of right sided heart failure in the periods after the index date, except in the 1 to 90-day period for which 6.5% (DK-DHR), 6.9% (HI-SPEED), 2.5% (InGef RDB), and 9.6% (NLHR) of individuals.

Haemoptysis:

No or very few records of haemoptysis were observed both before and after index date in all data sources.

Ascites:

Ascites was recorded in 4.7% (InGef RDB) and 5.6% (CDW Bordeaux) of individuals in the period of 180-days prior to and including index date. It was not recorded in the other data sources. Throughout follow-up there were mostly zero records in each window, except InGef RDB with <5 records in each window in the first year.

Syncope:

No or very few records of syncope were observed both before and after index date in all data sources.

Cardiac arrythmia:

In the period 180-days prior to index date and index date, between 8.6% (FinOMOP-THL) and 21.1% (CDW Bordeaux) of individuals had a record of cardiac arrythmia. This excludes DK-DHR and NLHR which both had <5 records each in this period. Within the first 90-days after index date, there are between 2.4% (InGef RDB), 2.9% (HI-SPEED) and 5.6% (CDW Bordeaux) of individuals with a record of cardiac arrythmia. There are individuals with records of cardiac arrythmia through the five-year follow-up, albeit less with <5 occurrences in most windows in all data sources except DK-DHR. Supraventricular tachycardia was recorded in 7.9% (CDW Bordeaux) and 5.2% (InGef RDB) of individuals in the -180 to 0 window, the other data sources had <5 records in this window. All other subtypes of cardiac arrythmia including AV block, ventricular tachycardia, ventricular fibrillation, sick sinus, atrial fibrillation, and atrial flutter were seldom recorded both before and after index date.

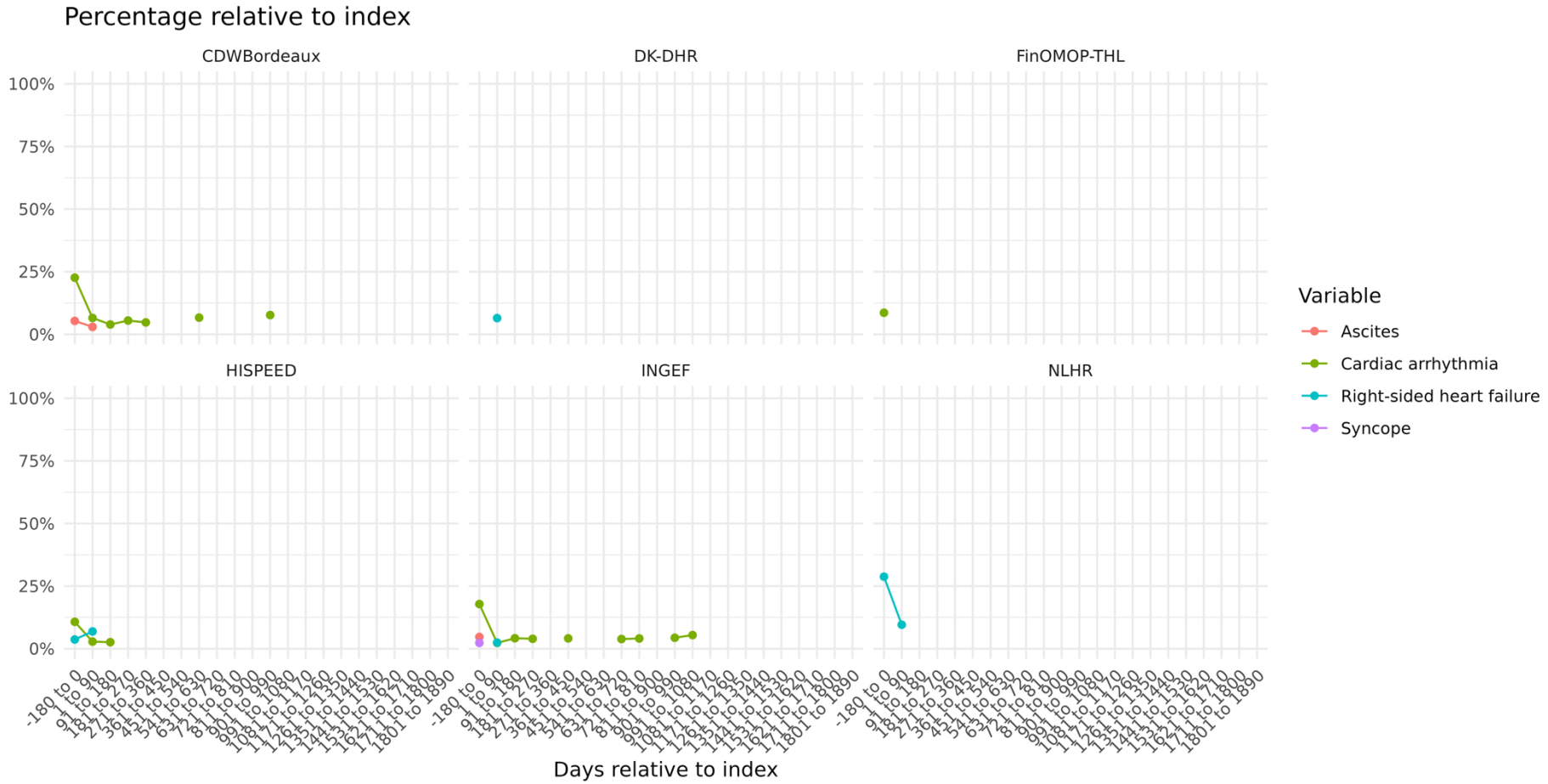

Figure 11. Comorbidity diagnoses after index date per 90-day interval.

Note: Figure does not display haemoptysis, supraventricular tachycardia, atrial fibrillation, atrial flutter, sick sinus, ventricular fibrillation, or ventricular tachycardia due to low counts.
Abbreviations: AV =atrioventricular, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Consortium of the Finnish OMOP data partners - Finnish Institute for Health and Welfare, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef - Institute for Applied Health Research Berlin GmbH research database, NLHR = Norwegian Linked Health Registry

11.3.4. Treatments

Proportion of individuals prescribed monotherapy:

During the entire five-year follow-up, the most commonly prescribed classes were: PDE-5 inhibitor monotherapy and ERA monotherapy: 35.0% (DK-DHR), 21.4% (FinOMOP-THL), 22.9% (HI-SPEED), 14.6% (InGef RDB), and 32.9% (NLHR) of individuals with PAH were prescribed **PDE-5 inhibitor monotherapy** for at least 30-days. **ERA monotherapy** was prescribed in 10.7% (FinOMOP-THL), 3.8% (HI-SPEED), and 8.5% (InGef RDB) of individuals with PAH, over the entire 5-year follow-up, despite most characterisation windows for FinOMOP-THL having <5 records. There were no prescriptions of ERAs in CDW Bordeaux or DK-DHR. **PRA monotherapy** was prescribed in <5 individuals in FinOMOP-THL, HI-SPEED, InGef RDB, and NLHR in the entire 5-year follow-up. There are no records of PRA monotherapy in the 5-years after index date in CDW Bordeaux or DK-DHR. There were <5 records of **sGC monotherapy** prescription in the 5-years following index date in InGef RDB. There were zero records in all other data sources for sGC monotherapies.

Proportion of individuals prescribed combination therapy:

Combination therapy of targeted PAH drugs were only seen in the use of PDE-5i-ERA combination therapy. **PDE-5i-ERA combination therapy** was observed in 12.5% (FinOMOP-THL), 4.8% (HI-SPEED), and 9.4% (InGef RDB) in the 5-years following index date. **ERA-sGC combination therapy** was only observed in InGef RDB with <5 events in the 5-year follow-up [1 to 1800]. **PDE-5i-PRA combination therapy** was only observed in HI-SPEED and NLHR in the 5-year follow-up [1 to 1800], each with <5 events. **ERA-PDE-5i-PRA combination therapy** was observed in HI-SPEED (2.4%), as well as FinOMOP-THL (<5 events) and NLHR (<5 events) in the entire 5-year follow-up In HI-SPEED <5 individuals were prescribed this triple combination therapy for the majority of 90-day windows over the 5-years, and in NLHR <5 individuals were prescribed this therapy regimen from window 811 to 900 onwards.

Proportion of individuals not treated with any of the prespecified PAH therapies:

The proportion of individuals not receiving any treatment of interest (for minimum 30 consecutive days) during the entire follow up was high: 65% (DK-DHR), 77% (FinOMOP-THL), 74% (HI-SPEED), 79% (InGef RDB), and 60% (NLHR).

In addition to the values reported in **Table S13, Figure 12** graphically depicts the proportion of PAH targeted treatment within each data source.

Proportion of individuals prescribed monotherapy by age at first prescription:

When exploring prescribing in function of age, the age group 0 to 1 (less than 1-year old) the prevalence of **PDE-5i monotherapy** prescribing was 23% (DK-DHR), 15% (HI-SPEED), 8% (InGef RDB), and 31% (NLHR). In the age group 1 to 2, the prevalence was 15% (HI-SPEED), 12% (InGef RDB), and 29% (NLHR). In the 2–4 year age group, the prevalence was 10% (DK-DHR), 15% (HI-SPEED), 9% (InGef RDB), and 20% (NLHR). In the 5–11 year age group, the prevalence was 22% (DK-DHR), 10% (HI-SPEED), 13% (InGef RDB), and 17% (NLHR). In the 12-18 year age group, the prevalence was 38% (DK-DHR), 50% (FinOMOP-THL), 14% (HI-SPEED), and 17% (InGef RDB). Those prevalences that are not reported are due to <5 or zero events present in that respective data source. The prevalence of **ERA monotherapy** was zero or <5 occurrences in age groups 0 to 1, 1 to 2, and 2 to 5 age groups. In the 5 to 12 age group the prevalence was 8% in InGef RDB. In the 12 to 18 age group the prevalence was 11% in InGef RDB.

Proportion of individuals prescribed combination therapy by age at first prescription:

The prevalence of **ERA-PDE-5i combination therapy** was zero or <5 occurrences in age groups 0 to 1, 1 to 2, and 2 to 5 age groups. In the 5 to 12 age group the prevalence was 6% (HI-SPEED) and 8% (InGef RDB). In the 12 to 18 age group the prevalence was 14% (HI-SPEED) and 13% (InGef RDB). The prevalence of all other targeted therapy (mono- or combination) was either <5 occurrences or zero in all data sources when stratified by age at first prescription. **Table S14** reports the prescribing of PAH targeted treatment reported per age at date of prescribing.

Sensitivity analysis:

We additionally carried out a post-hoc sensitivity analysis which estimated the number of paediatric individuals with PAH who had a prescription of one of the targeted PAH drugs or calcium channel blockers any time in the 5-year period following index date (**Table 9**). PDE-5i are prescribed in between 18.8% (InGef RDB) and 47.2% (NLHR) of individuals with PAH. ERAs are prescribed in between 6.5% (NLHR) and 14.3% (FinOMOP-THL) of individuals with PAH, excluding DK-DHR, which had zero counts of ERA prescriptions. Calcium channel blockers (CCBs) are prescribed in 3.8% (HI-SPEED) to 6.1% (InGef RDB) of individuals with PAH, excluding FinOMOP-THL, which had zero counts. PRAs were prescribed in 4.3% of individuals with PAH in HI-SPEED.

Table 9. Sensitivity analysis of prescriptions of targeted PAH drugs and CCBs during the entire 5-year period after index date.

PAH medication	DK-DHR	FinOMOP-THL	HI-SPEED	InGef RDB	NLHR	CDW Bordeaux
CCB	7 (5.98%)	0 (0.00%)	8 (3.81%)	13 (6.10%)	5 (4.63%)	7 (4.17%)
PDE-5i	46 (39.32%)	14 (25.00%)	55 (26.19%)	40 (18.78%)	51 (47.22%)	31 (18.45%)
PRA	<5	<5	9 (4.29%)	<5	<5	<5
ERA	0 (0.00%)	8 (14.29%)	15 (7.14%)	26 (12.21%)	7 (6.48%)	12 (7.14%)
sGC	0 (0.00%)	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)	0 (0.00%)

Abbreviations: CCB = calcium channel blockers, ERA = endothelin receptor antagonists, PDE-5i = phosphodiesterase type 5 inhibitor, PRA = prostacyclin receptor antagonists, sGC = soluble guanylate cyclase stimulator, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Consortium of the Finnish OMOP data partners - Finnish Institute for Health and Welfare, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef - Institute for Applied Health Research Berlin GmbH research database, NLHR = Norwegian Linked Health Registry

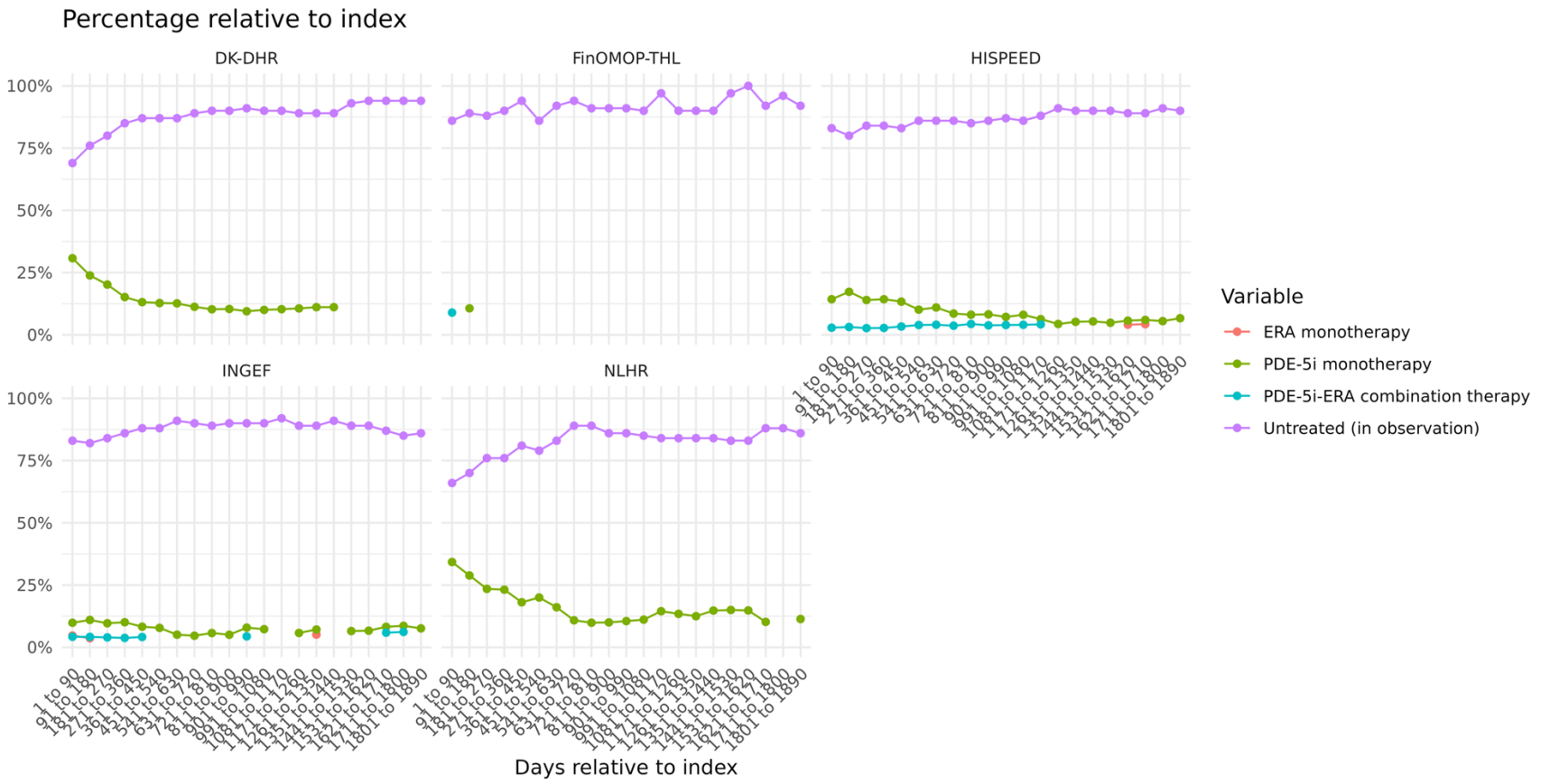

Figure 12. PAH targeted treatment assignment after index date per 90-day interval.

Note: Figure does not display sGC monotherapy, PRA monotherapy, ERA-sGC combination therapy, PDE-5i-PRA combination therapy, or ERA-PDE-5 i-PRA combination therapy due to low counts. Does not include CDW Bordeaux because only inpatient drug dispensing was captured. Combined values do not sum to 100% due to censored results in the event counts are <5 events. Abbreviations: ERA = endothelin receptor antagonists, PDE-5i = phosphodiesterase type 5 inhibitor, PRA = prostacyclin receptor antagonists, sGC = soluble guanylate cyclase stimulator, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Consortium of the Finnish OMOP data partners - Finnish Institute for Health and Welfare, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef - Institute for Applied Health Research Berlin GmbH research database, NLHR = Norwegian Linked Health Registry

11.3.5. Hospitalisation and death

Full results can be seen in **Table S15** and graphically depicted in **Figure 13**.

Hospitalisation:

In the first 90-days following index date between 29.6% (InGef RDB) and 60.7% (DK-DHR) of individuals with PAH were admitted to hospital. In the next period 90 days period, 19.2% (NLHR) to 40.4% (DK-DHR) were hospitalised. A downward trend of hospitalisation is observed over time, in all data sources.

Death:

Death was most frequently recorded in the first 90-days after index date with 14.8% (CDW Bordeaux), 6.0% (DK-DHR), 14.3% (FinOMOP-THL), 9.1% (HI-SPEED), and 2.4% (InGef RDB) of individuals diagnosed with PAH. There were no deaths recorded in NLHR in this period. More generally, most deaths occurred in the first year of follow up, decreasing afterwards,

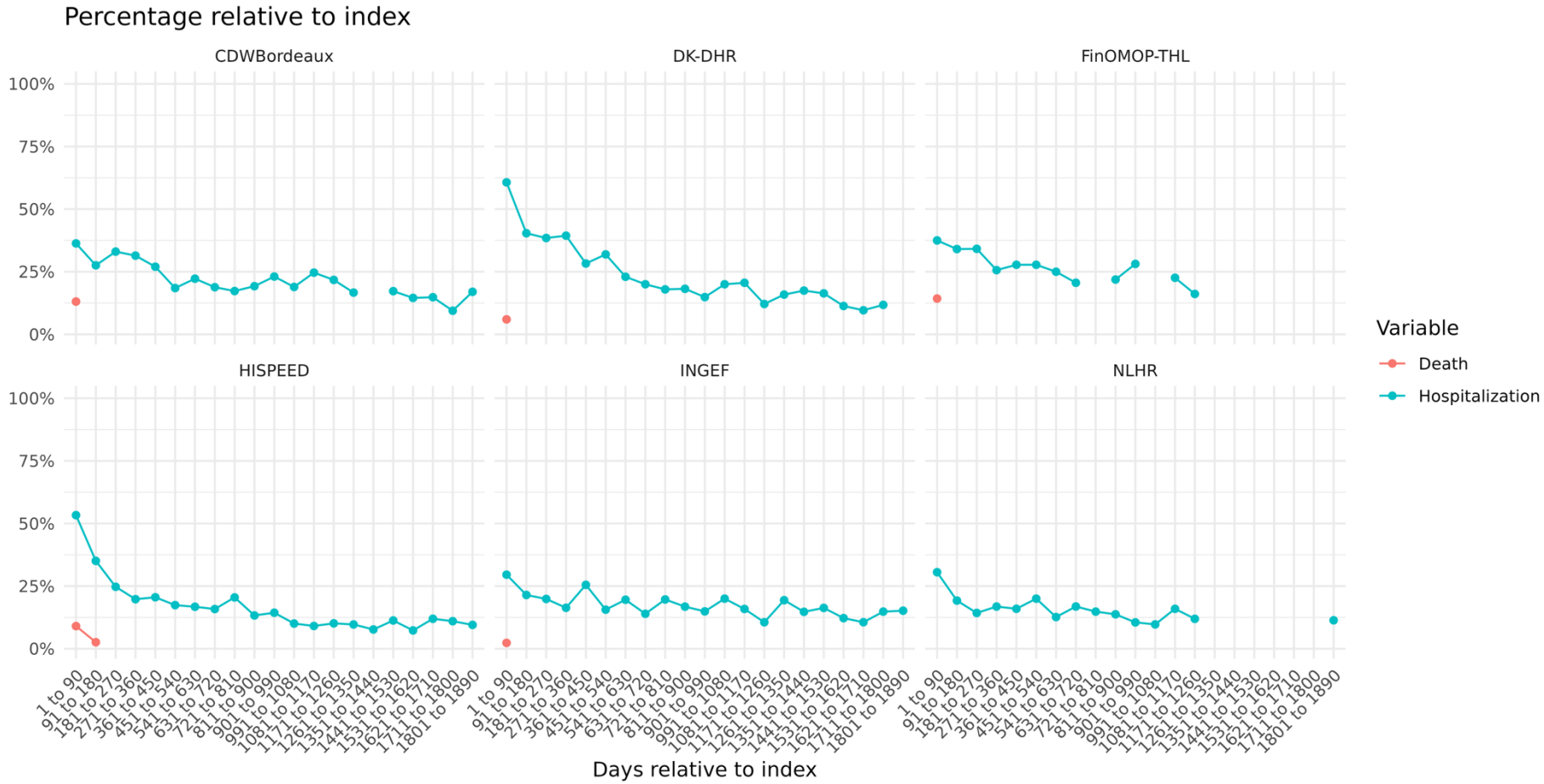

Figure 13. Proportion of death and hospitalisation after index date per 90-day interval.

Abbreviations: PAH = pulmonary arterial hypertension, CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Consortium of the Finnish OMOP data partners - Finnish Institute for Health and Welfare, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef - Institute for Applied Health Research Berlin GmbH research database, NLHR = Norwegian Linked Health Registry

11.4. Other analysis

No other analyses were performed as part of this study.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions will not be collected or analysed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfil the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).

Only in case of prospective data collection, there is a need to describe the procedures for the collection, management, and reporting of individual cases of adverse events/adverse reactions.

13. DISCUSSION

13.1. Key results

Objective 1: Estimate the yearly incidence and period prevalence of PAH in the paediatric population, stratified by age group

The overall incidence rate of PAH across the study period was 0.95 (0.78–1.14) per 100,000 person-years in DK-DHR, 0.52 (0.39–0.67) in FinOMOP-THL, 1.17 (1.02–1.34) in HI-SPEED, 2.78 (2.48–3.10) in InGef RDB, and 1.00 (0.82–1.21) in NLHR. The incidence rate of PAH was greatest across all data sources in the 0 to 1 years age group, between 6.36 (4.43–8.85) in FinOMOP-THL and 28.56 (24.18–33.49) per 100,000 person-years in InGef RDB.

The overall period prevalence of PAH across the study period was 0.010 (0.09–0.12) in DK-DHR, 0.06 (0.05–0.07) in FinOMOP-THL, 0.08 (0.08–0.10) in HI-SPEED, 0.19 (0.17–0.21) in InGef RDB, and 0.09 (0.08–0.11) per 1000 persons in NLHR.

Objective 2: Characterise paediatric patients newly diagnosed with PAH

In terms of assessing potential aetiology, a history of congenital heart disease was identified in between 21.5% (HI-SPEED) and 57.0% (CDW Bordeaux) of individuals. Persistent pulmonary hypertension of the newborn was identified in between 3.7% (HI-SPEED) and 22.5% (InGef RDB) of individuals. Congenital diaphragmatic hernia was identified in 3.5% (CDW Bordeaux), 12.2% (HI-SPEED), and 9.9% (InGef RDB) of individuals. Within 180-days prior to the index date and index date itself, bronchopulmonary dysplasia was present in 4.2% (CDW Bordeaux) to 13.9% (NLHR) of individuals. Between 36.0% (NLHR) and 45.0% (HI-SPEED) of individuals had none of the prior prespecified aetiologies in the period prior to and including the index date.

Procedures related to PAH were not well captured except for echocardiography within 6 months prior to diagnosis where 9.4% to 83.8% (CDW Bordeaux) of individuals received an echocardiography test.

In the period any time prior to index date and index date itself, a diagnosis of right sided heart failure was present in 3.7% (HI-SPEED) and 28.8% (NLHR) of individuals. Ascites was recorded in 4.7% (InGef RDB) and 5.6% (CDW Bordeaux) of individuals in the period of 180-days prior to and including

index date. In the same time period, between 8.6% (FinOMOP-THL) and 21.1% (CDW Bordeaux) of individuals had a record of cardiac arrhythmia. Within the first 90-days after index date, there were between 2.4% (InGef RDB), 2.9% (HI-SPEED) and 5.6% (CDW Bordeaux) of individuals with a record of cardiac arrhythmia.

In the entire five-year follow-up 14.6% (InGef RDB) to 38.9% (NLHR) of individuals with PAH were prescribed PDE-5 inhibitor monotherapy for at least 30-days. ERA monotherapy was prescribed in 10.7% (FinOMOP-THL), 3.8% (HI-SPEED), 8.5% (InGef RDB). PRA monotherapy was prescribed in <5 individuals in FinOMOP-THL, HI-SPEED, InGef RDB, and zero records in DK-DHR. There were <5 individuals with sGC prescriptions in InGef RDB, and zero records in all other data sources. The most prescribed combination therapy was PDE-5i-ERA combination therapy which was observed in 12.5% (FinOMOP-THL), 4.8% (HI-SPEED), and 9.4% (InGef RDB) in the 5-years following index date. Use of the other combination therapies (ERA-sGC, PDE-5i-PRA, and ERA-PDE-5i-PRA) were seldom recorded in all data sources. In the 5-year period following index date, 60% (NLHR) to 79% (InGef RDB) did not receive treatment with any of the pre-specified targeted PAH treatments.

In the first 90-days after the index date but not index date itself, between 29.6% (InGef RDB) and 60.7% (DK-DHR) of individuals with PAH were (re-)admitted to hospital for any reason. Death was most frequently recorded in the first 90-days after index date with occurrences in 2.4% (InGef RDB) to 14.8% (CDW Bordeaux) of individuals diagnosed with PAH.

13.2. Limitations of the research methods

The study was informed by routinely collected health care data and so data quality issues must be considered. In particular, a recording of a prescription does not mean that the patient actually took the drug. In addition, the recording of events used for patient characterisation may vary across data sources and may be incomplete. Coverage of data on drug treatments and procedures is likely incomplete leading to underestimation in the treatment characterisation. This is the case in the data sources HI-SPEED, NLHR, and InGef RDB, which do not cover inpatient hospital treatments. Inpatient dispensing or prescribing often has a different mechanism of duration estimation (i.e., duration of 1-day), which this study did not take into account and therefore we would underestimate prescribing in the inpatient setting. Additionally, FinOMOP-THL has an incomplete mapping of drugs and so lower counts are observed. CDW Bordeaux does not cover drug treatments prescribed outside of hospital and so is only included in the sensitivity analysis.

PAH has several aetiologies which would have been of interest to measure including: pulmonary hypertension due to left heart disease, pulmonary hypertension due to lung diseases or hypoxia, pulmonary hypertension due to pulmonary artery obstructions, and pulmonary hypertension with unclear and/or multifactorial mechanisms.[2] However, given the lack of granularity of the data source vocabularies, the aetiologies could not be investigated directly by use of aetiology-specific concepts. Misclassification can occur between PAH and PH due to lung disease/hypoxia if lung diseases such as bronchopulmonary dyspepsia or congenital diaphragmatic hernia are incorrectly labelled as PAH. To counteract this, we characterised study participants in terms of diagnosis records of lung-related conditions prior to first PAH diagnosis (index date).

We did not apply the inclusion criteria of a minimum of 365 days observation prior to the index date in the included hospital data source (CDW Bordeaux). This may have resulted in misclassification of the index date (first PAH diagnosis), as the individuals may have had a diagnosis of PAH before being admitted to hospital. In addition, duration of treatment was not available in CDW Bordeaux because each prescription duration is set to 1-day in the inpatient setting. Therefore, it was excluded from the main analysis of targeted PAH drug use in which treatment duration of at least 30 days was a

condition for a treatment to be counted (see below and in the methods section). Treatment data from CDW Bordeaux was included in the sensitivity analysis, which did not account for duration.

The InGef RDB outpatient component of the data source has the date of each diagnosis set to the end of each quarterly period (three-months) in which the diagnosis takes place. This means that the date of condition diagnoses recorded in the outpatient setting are likely misclassified. To avoid this, for objective 2, PAH was therefore only be identified from the inpatient setting in InGef. This under-reported the number of individuals included in the characterisation of PAH (can be observed in that the population on incident PAH patients identified in objective 1 is higher than the one used for objective 2).

Individuals were characterised in terms of use of PAH drugs by drug eras constructed by estimation of the end date of the treatment episode of sequential prescriptions. Prescription end date is not recorded and it is therefore imputed by each data source. This imputation can differ in terms of how accurately it represents the actual prescription length, depending on medicinal product, indication, and data source. Descriptions of overall prescribing trends through the use of multiple sequential assessment windows gave an understanding of general treatment course. In this study, the bespoke algorithm developed relied on the assumption that prescriptions of least 30-days should be identified in the data. We assumed drug era overlaps of less than 30-days, or monotherapy eras of duration less than 30-days to not be treated. This could mean that there is underestimation of treatment characterisation. However, the sensitivity analysis showed that while underestimation was present, the drug utilization algorithm did not constitute the main reason for the lower than expected observed targeted treatment use.

13.3. Interpretation

The overall incidence rates in this study over the entire study period 2014 to 2025 are somewhat higher than those published elsewhere. Indeed, we estimated the IR of PAH to between 0.52–2.78 per 100,000 person-years across five European countries. del Cerro Marín et al used patient data from the Spanish Registry for Paediatric Pulmonary Hypertension, estimated the IR of PAH to be 0.246 per 100,000 person-years.[10] van Loon et al used data from the Netherlands paediatric cardiology and national hospitalisation registries and estimated the IR of PAH at 0.30 per 100,000 person-years.[11], in US claims data, Li et al estimated the IR of PAH at 0.48-0.81 per 100,000 person-years.[12] Constantine and colleagues estimated the IR of PAH was 0.98 per 100,000 person-years in the UK National Paediatric Pulmonary Hypertension Service database.[13] Kwiatkowska et al estimated the IR of PAH at 0.24 per 100,000 person-years in the Polish Registry of Pulmonary Hypertension.[14]

All similar studies referred to had a higher median age at diagnosis: 2.2 years in the study of van Loon et al, while in our study the median age was less than or around 1 year.[11] Our higher IR was largely driven by the 0–1 year age group, where rates reached between 6.36–28.56 per 100,000 person-years across five data sources.

No information about the aetiology of PAH could be obtained from the index diagnosis, including the indication of idiopathic disease. Therefore, we estimated the proportion of individuals with PAH who had a prior diagnosis suggesting a possible aetiology. We estimated that 21.5–57.0% of individuals with PAH had a record of CHD, lower than in comparable studies, (61–75%).[10-12, 14, 15] Advances in the treatment of congenital heart disease in recent years means such individuals reach older ages before any subsequent diagnosis of PAH. In addition, our paediatric PAH population potentially includes misclassified individuals with PPHN and PH associated with lung disease, reducing the proportion of individuals with CHD-PAH.

We estimated that 36.0%–45.0% of individuals had none of the prior prespecified aetiologies in the period prior to the index date, which likely represent idiopathic PAH. Previous studies on the other hand showed smaller proportions of idiopathic or heritable PAH: 37.7% of the individuals with PAH in the study of Qian et al, 23.7% in the study of van Loon et al, and 31.3% in the study of Kwiatkowska et al. Despite excluding PPHN from the index diagnosis, a proportion of the population had a prior recorded PPHN diagnosis (3.7–22.5%), despite this being excluded from the definition of the index PAH diagnosis. A prior record of congenital diaphragmatic hernia was identified in 3.5–12.2%, and bronchopulmonary dysplasia was present in 4.2–13.9% of individuals, which are both part of WHO group 3 pulmonary hypertension.[17] In these individuals the diagnosis of primary PAH taken at index date may have been misclassified. This could also have contributed to the raised incidence rate of PAH we find compared to other studies. Transient PH, such as persistent pulmonary hypertension of the newborn, could explain the relatively high incidence rate of PAH in the youngest 0 to 1 year age group. This misclassification likely reduced the proportion of patients receiving targeted PAH therapy over the course of follow-up.

We estimated a large proportion of untreated paediatric individuals with PAH, with around 60–79% untreated across five data sources, and 97% untreated in CDW Bordeaux. This may partly be explained by the inclusion of individuals with PAH with different aetiologies that do not require PAH-specific therapy or require it only for a limited duration. Of the treated patients, most were prescribed PDE-5 inhibitor monotherapy with 14.6–35.0% treated for at least 30 days in the 5-year follow-up after index date). In US claims data, PDE-5 inhibitor monotherapy were estimated to be prescribed in 68.5% of individuals, as well as, ERA monotherapy in 1.4%, and PRA monotherapy in 1.7% of individuals.[12]. Constantine and colleagues estimated initial targeted monotherapy use at 50.3% of individuals with PAH, including 36.5% PDE-5 inhibitor monotherapy, 10.2% ERA, and 0.4% PRA use.[13] The same study estimated combination therapy at initiation to be 17.0%, and triple at 6.4% of individuals. While in the study of Li et al, PDE-5 inhibitor and ERA combination therapy were estimated at 7.5% of individuals with persistent PAH. In our study this combination was estimated at 4.8–12.5% , and triple combination therapy was observed in 2.4% . The treatment guidelines for paediatric patients largely follow those of adults, and this is based on expert opinion rather than evidence based. There are similarities between the course of PAH in adults and children, for example there has been proposed treatment algorithms to handle the potentially more complex comorbidities that arise in paediatric individuals.[16, 18, 19] Targeted PAH therapies such as sildenafil are indicated for individuals older than 1-year, and for tadalafil older than 2-years old.[20, 21] This study did not characterise the use of CCBs, except for their inclusion in the sensitivity analysis. Although CCBs can be used for those who respond to acute vasodilator testing, the clinical preference is often to begin treatment with targeted PAH therapy.

Echocardiography is used often in the diagnosis of PAH, as shown by the proportion of records within 180 days prior to index date: 62.1% (FinOMOP-THL), 73.4% (HI-SPEED), and 83.8% (CDW Bordeaux) of individuals received an echocardiography test. In Germany this was seen less often with only 9.4% (InGef RDB). In other studies, in the US this was estimated at 58.4%, and in the Netherlands at 29%.[11, 12]

13.4. Generalisability

This study uses data from six data sources across six countries, including data sources which draw information from different types of data. For example, the use of hospital data will have a greater capture of events occurring in hospitalisation, while the use of primary care data and nationwide registries means a wider selection of data from a broader selection of society is also included. Data sources include large registries in northern Europe (Sweden, Denmark, Finland, and Norway), as well

as claims data in Germany and Hospital data from France. Northern Europe is well represented, thus our data is most generalisable to this region than to the wider Europe.

13.5. Other information

There is no further information to disclose.

14. CONCLUSION

The incidence of paediatric PAH was 0.52–2.78 per 100,000 person-years across five data sources in Denmark, Finland, Sweden, Germany, and Norway across the study period 2014–2024. This incidence of PAH was largely driven by children younger than 1-year old, and in many cases, a possible cause of the PAH was congenital heart disease (identified as diagnosis before PAH debut). The majority of individuals with newly diagnosed PAH remained untreated with pre-specified targeted PAH therapy in the 5-year period following index date. PDE-5 inhibitors were the most extensively used targeted PAH therapy, followed by dual PDE-5 inhibitor and ERA therapy.

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16. ANNEXES

Annex I. Descriptions of data sources

Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux), France

#	Section	Description
1	Database Identification and country	CDW Bordeaux (Clinical Data Warehouse of Bordeaux University Hospital) Nouvelle-Aquitaine, France
2	Data partner information section	CHU DE BORDEAUX - DIRECTION GENERALE Gironde / Nouvelle-Aquitaine
3	Coverage and timespan	Data collection since: 2005 Extent: Regional. It covers the population of Bordeaux metropolitan area, and possibly beyond, as the health care centre for referrals and expertise for the Nouvelle Aquitaine region. The database contains data from 2005 onwards.
4	Healthcare setting / type of data	Secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care, and claims data. The database currently captures information about patient demographics, visit details, conditions, procedures, drugs, measurements, and mortality.
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Inpatient hospital billing systems, and Biobank. The integrated data is extracted from the hospital production information system via a real-time research database. The data is then processed and quality controlled by a team dedicated to maintaining the database. Internal evaluations were carried out to ensure consistency between the research database and the patient bedside software.
6	General representativeness	This is the 6th largest metropolitan area in France, and CHUBX is the largest hospital in the region. More than 75% of the patients administered to Bordeaux university hospital reside in the Gironde departments, with almost 50% coming directly from the Bordeaux metropolitan area. The hospital also captures additional cases from Nouvelle-Aquitaine region.
7	Data content /source coding	Diagnosis source data is coded in ICD-10 terminology. Procedures are coded in CCAM (French terminology). Laboratory measurements are coded in local terminology and partially mapped to LOINC. Drugs are coded through a local terminology and then mapped to UCD (French terminology), as well as ATC codes.
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. We use the hospital's unique identifier to generate the patient identifier in OMOP. If two identities are merged at the hospital, the merge is taken into account in the CDW. An automatic (hourly) detection of suspected duplicated identities has been implemented at the hospital since 2020, with merging of duplicated identities by a specialized team. Identities since 2015 were processed retrospectively. Thus, the rate of identity duplication in the database is low, especially since 2015.
9	Quality control (database specific)	- The integrated data comes from the hospital production information system through a real-time replicated database. Consistency evaluations between the replicated database and the production system are performed by the technical team in charge of maintaining the replicated database. - In the same way, consistency checks are performed between the replicated database and the data integrated into the i2b2 CDW. In addition, dashboards enable monitoring the data integrated into the i2B2 CDW, in particular by controlling the amount of data available over time, and its evolution, according to the various data sources. - An internal evaluation was carried out to ensure the consistency between the data integrated into i2b2 and the data available in the software used at the patient's bedside. In

#	Section	Description
		addition, many use cases were performed on the i2b2 CDW, with return to the patient chart and comparison of the data integrated into i2b2 and the data available in the care file.
10	Linkage	Death certificates (without the cause of death).
11	Vital status	The database is linked to the French death registry.
12	Limitations	CDW Bordeaux is limited to events captured in the hospital setting, and thus does not include patient events not treated by the hospital (e.g. rare cancers). Patient events that are not included in CDW Bordeaux are rare disease treatments or specialist events that occur outside of CHUBX.
13	Main references	Cossin S, Diouf S,Griffier R,Le Barrois d'Orgeval P,Diallo G,Jouhet V "Linkage of Hospital Records and Death Certificates by a Search Engine and Machine Learning." JAMIA open (2021): 33709061
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111112 Website: https://www.chu-bordeaux.fr/

Danish Health Registries (DK-DHR), Denmark

#	Section	Description
1	Database Identification and country	DK-DHR (Danish Data Health Registries) Denmark
2	Data partner information section	Danish Medicines Agency (DKMA) Data Analytics Centre (DAC)
3	Coverage and timespan	Data collection since: 1995 Extent: Nation-wide. The data is representative of the entire Danish population.
4	Healthcare setting / type of data	Community pharmacists, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. The following data elements are collected: diagnosis (including rare diseases and pregnancy data), hospital admissions, discharge and ICU data, Cause of death, Drug prescriptions, dispensing, vaccination and contraception, Procedures, Devices, and Sociodemographic information.
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries, and Other. All causes of deaths, all retrieved drug prescriptions, all records of vaccinations, all hospital inpatient and outpatients contacts including disease diagnoses and hospital surgical and non-surgical procedures, cancers, laboratory test results for the entire Danish population from 1/1/1995 onwards.
6	General representativeness	The data is representative of the entire Danish population. Healthcare is free in Denmark, so we do not expect any bias in data collection based on socio-economic status.
7	Data content /source coding	Diagnoses and causes of death are collected using the ICD-10 vocabulary. ATC and RxNorm are used for Drugs. SNOMED codes are used for Procedures.
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. No.
9	Quality control (database specific)	The data we have received relating to nationwide Danish Health Data registries offer an opportunity for large-scale, population-based studies with several advantages 1) Their large size improves the precision of estimates and enables the study of rare exposures and outcomes with

#	Section	Description
		long-term latency, 2) Inclusion of nearly all individuals in the target population ensures that the data reflect routine clinical care and all clinical segments of the source population, 3) Data are collected independently of each research study, thus minimising certain types of bias, e.g., non-response, and the influence from attention to the research question on the diagnostic process. Before the source data is sent to us, the Danish Health Data Authority runs and does comprehensive checks of the registry table data validity of the variables, breaks in data, changes in variable coding, missingness, etc. We perform checks of missingness/completeness in relation to requested variables. In essence, we are receiving a dump of a mirror of the data that is controlled by the SDS. The documentation performed by SDS is available online, in Danish primarily https://www.esundhed.dk/Dokumentation (all variables), but also in English https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/national_health_registers
10	Linkage	There is no linkage in this data source.
11	Vital status	The Cause of Death registry (DAR) is used, the cause of death is collected using ICD-10 codes.
12	Limitations	No database-specific limitations documented. General limitations for the data type applicable.
13	Main references	Schmidt M, Schmidt SAJ,Adelborg K,Sundbøll J,Laugesen K,Ehrenstein V,Sørensen HT "The Danish health care system and epidemiological research: from health care contacts to database records." Clinical epidemiology (2019): 31372058
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111217 Website: https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/healthdatadenmark

Consortium of the Finnish OMOP data partners (FinOMOP-THL), Finland

#	Section	Description
1	Database Identification and country	FinOMOP-THL (Finnish Care Register for Health Care) Finland
2	Data partner information section	Finnish Institute for Health and Welfare (THL) Department of Knowledge Brokers
3	Coverage and timespan	Data collection since: 1998 Extent: Nation-wide. The current CDM population comprises all persons having been alive and residing in Finland since the beginning of 2011.
4	Healthcare setting / type of data	Primary care – gps, and primary care specialists (e.g. paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. The THL database covers both public and private, primary, and specialised inpatient and outpatient health care encounters in Finland, starting from 2011. The entire public sector and private inpatient encounters have been included since 2011, while private outpatient encounters, including occupational care, are included since 2020. Since 1998, the register has covered both public outpatient and inpatient specialized care and private inpatient care (TerveysHilmo). Since 2009, the Finnish National Vaccination Register is covered (complete since 2020). The vaccination register covers all vaccinations from the public sector and from a large part of private vaccination providers, with the data coverage from both sections being very good from 2020 onwards. Since 2011, the register has covered public primary care (AvoHilmo). Since 2020, the register has covered private outpatient care and occupational care. In addition, the CDM also contains positive COVID-19 test results from the Finnish National Infectious Diseases Register, which is maintained by THL.

#	Section	Description
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries. Data is entered by clinicians upon healthcare contact and processed by THL.
6	General representativeness	The THL data has national coverage and is therefore well representative of the Finnish population. Using the complete population as a basis for the person table also serves to facilitate calculations on a population level, e.g. incidence rates.
7	Data content /source coding	The following coding systems have been OMOP-mapped, typically to a good level of completeness: ICD10fi Finnish Extension, ATC, Toimenpideluokitus (procedure classification adapted from the Nordic Classification of Surgical Procedures (NCSP)), Terveydenhuollon erikoisalat (Hilmo specific provider speciality), Rokotustapa (AR/YDIN National classification for vaccine administration), Tupakointistatus (AR/YDIN National classification for smoking status). Vaccinations are identified on product level based on batch number, trade name, vaccine title, and ATC-code. This is mapped on brand and type in the OMOP CDM.
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Each patient in THL has a unique identifier.
9	Quality control (database specific)	The source data collection undergoes a structural and semantic validation before entry into the source database. Additionally, some coded variables undergo quality assessment against the respective code systems post entry into the database. The source registers are also assessed for completeness and coverage, with the aim of improving future collection in the areas where data is lacking.
10	Linkage	THL is already a linkage of multiple Finnish registries (see above).
11	Vital status	The National Population registry data forms the basis for forming the patient population. This ensures an up-to-date location (municipality of residence) of patients, as well as complete death occurrences (although not the cause of death).
12	Limitations	No database-specific limitations documented. General limitations for the data type applicable.
13	Main references	Häkkinen, Pirjo; Mölläri, Kaisa; Saukkonen, Sanna-Mari; Väyrynen, Riikka; Mielikäinen, Lasse; Järvelin, Jutta "Hilmo - Sosiaali- ja terveydenhuollon hoitoilmoitus 2020 : Määrittelyt ja ohjeistus : Voimassa 1.1.2020 alkaen" Terveyden ja hyvinvoinnin laitos (2019):
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111187 Website: https://thl.fi/fi/tilastot-ja-data/ohjeet-tietojen-toimittamiseen/hoitoilmoitusjarjestelma-hilmo

Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED), Sweden

#	Section	Description
1	Database Identification and country	HI-SPEED (Health Impact - Swedish Population Evidence Enabling Data-linkage) Sweden
2	Data partner information section	SMPA-GU, Läkemedelsverket, Box 26 Pharmacoepidemiology and Analysis Department (FeA)
3	Coverage and timespan	Data collection since: 2020 Extent: Nation-wide. The catchment area includes the whole of Sweden, covering the full population of approximately 10 million.
4	Healthcare setting / type of data	Primary care – gps, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. The following data elements are collected: Socio-demographics, drug use and prescriptions,

#	Section	Description
		diagnoses, cause of death, primary care procedures and visits, as well as secondary care and inpatient visits or clinical events.
5	Data collection process	Registries. The data is acquired from the Swedish nation and regional registries, only once all legislative, GDPR and ethical approvals have been granted. Therefore, only relevant data is passed on, which will then be entered and processed by the
6	General representativeness	The coverage includes all patients of all sociodemographic characteristics. Therefore, it should mirror the source population to a very good extent.
7	Data content /source coding	Medicines are coded with ATC, ICD10 is used for diagnoses, and the Swedish procedure coding system (KVA) is used for clincal procedures.
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. No.
9	Quality control (database specific)	The source data is obtained from the Swedish National and Regional Registers. The registers perform some regular quality controls on their data. After receiving the data, we perform additional checks and cleaning. We also run regular quality checks on the data we manage.
10	Linkage	Data on specialist care is acquired from the National Patient Register; mortality information is provided by the Cause-Of-Death Registry. Drug data is provided by the Patient Drug Register.
11	Vital status	Data on death and cause-of-death are extracted from the Cause-of-Death registry.
12	Limitations	No database-specific limitations documented. General limitations for the data type applicable.
13	Main references	No main reference provided.
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: Website:

InGef - Institute for Applied Health Research Berlin GmbH (InGef RDB), Germany

#	Section	Description
1	Database Identification and country	InGef RDB (InGef Research Database) Germany
2	Data partner information section	Institut für angewandte Gesundheitsforschung Berlin GmbH
3	Coverage and timespan	Data collection since: 2014 Extent: Nation-wide. The data source contains information from the statutory health insurances (SHI), which insure a total of about 89% (~73 million individuals) of the German population. Since the InGef RDC currently includes about ten million individuals, it covers about 13% of the total population insured in one of the German SHIs. The data in the database depicts all health care use which has been reimbursed by the SHI.
4	Healthcare setting / type of data	Primary care – gps, and community pharmacists, and primary care specialists (e.g. paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care, and claims data. The following data elements are collected: pregnancy data, hospital admission and/or discharge also with ICU admission. Prescription, dispensing drugs and Advanced therapy medicinal products. Contraception, medical devices, vaccinations, procedures, diagnoses and demographic information.

#	Section	Description
5	Data collection process	Insurance/administrative claims. The data in the database depicts all health care use which has been reimbursed by the SHI (statutory health insurances).
6	General representativeness	The data source contains information from the statutory health insurances (SHI), which insure a total of about 89% (~73 million individuals) of the German population. Since the InGef RDC currently includes about ten million individuals, it covers about 13% of the total population insured in one of the German SHIs.
7	Data content /source coding	The ATC and OPS (Operationen- und Prozedurenschlüssel) are used for prescription and dispensing drugs. For Procedures the EBM (Einheitlicher Bewertungsmaßstab - doctor's fee scale) and for ambulatory procedures; OPS (Operationen- und Prozedurenschlüssel) for operations conducted at the hospital are used. Medical events are coded in ICD-10-GM and another vocabulary used is PZN (Pharmazentralzummer -pharmaceutical reference number).
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. No. In the German statutory health system, a person can only be enrolled in one health insurance at a time. However, if a person changes from one contributing insurer to another, a new ID number will be generated.
9	Quality control (database specific)	Before entering the InGef database, the data elements are checked with respect to data format, completeness, and plausibility. After each data update, data are compared with the previous data update in regard to number of records, number of data providers, etc. Due to the anonymized nature of the database, no direct validation of the data (e.g. using medical charts as the gold standard) is possible. Data delivery by health care providers is generally based upon standardized data requirements and formats provided by the National Association of Statutory Health Insurance Funds (compare: https://www.gkv-datenaustausch.de/leistungserbringer/leistungserbringer.jsp)
10	Linkage	No
11	Vital status	The Cause of Death is not captured; the date of death is captured.
12	Limitations	Ambulatory diagnosis are received from the source on a quarterly basis. These diagnoses are mapped to the observation table with the concept_id History of event within 3 months (1340222), with the actual diagnosis concept_id recorded in the field value_as_concept_id, and the date as the last day of the respective quarter (i.e. 30/31st of Mar/Jun/Sept/Dec). Ambulatory prescriptions are available with exact dates. The cause of death is not captured and there is no linkage with other data sources. Approx. 10.5 Million insurees are included in the database, 7.8 Million of these actively insured in 2024. This corresponds to 7% of the total German population. Data are longitudinally linked over a period of currently ten years.
13	Main references	Andersohn F, Walker J "Characteristics and external validity of the German Health Risk Institute (HRI) Database." Pharmacoepidemiology and drug safety (2016): 26530279
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111207 Website: https://www.ingef.de/en/

Norwegian Linked Health Registry data (NLHR), Norway

#	Section	Description
1	Database Identification and country	NLHR (Norwegian Linked Health Registry data) Norway
2	Data partner information section	University of Oslo Faculty of Mathematics and Natural Science – Department of Pharmacy
3	Coverage and timespan	Data collection since: 2008 Extent: Nation-wide. Norway has a universal public health care system, consisting of primary and specialist health care services covering a population of approximately 5.4 million inhabitants.
4	Healthcare setting / type of data	Primary care – gps, and primary care specialists (e.g. paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. The following registries are included: the Medical Birth Registry of Norway (MBRN), the Norwegian Prescription Registry (NorPD), the Norwegian Patient Registry (NPR), Norway Control and Payment of Health Reimbursement (KUHR), the Norwegian Surveillance System for Communicable Diseases (MSIS), the Norwegian Immunisation Registry (SYSVAK), the National Death Registry, and the National Registry (NR).
5	Data collection process	Registries. Many population-based health registries were established in the 1960s, with use of unique personal identifiers facilitating linkage between registries. Data in these health registries are used for health analysis, health statistics, improving the quality of healthcare, research, administration, and emergency preparedness.
6	General representativeness	The NLHR data covers the full Norwegian population.
7	Data content /source coding	NPR: ICD-10 for diagnosis, ATC and some special codes for drug use, Norwegian codes for clinical procedures (surgery (NCSP), medicine (NCMP) and diagnostic imaging, image-guided intervention, and nuclear medicine (NCRP)). KUHR: ICD-10 and ICPC-2 and ICPC-2B for diagnosis/procedure. NorPD: ATC. SYSVAK and MSIS: national classifications. MBRN: custom classifications by questionnaires (incl. check box variables in Maternity health care card)
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Linkage between the registries was facilitated using project-specific person IDs generated from unique personal identification assigned at birth or immigration for all legal residents in Norway.
9	Quality control (database specific)	In-house data quality checks of rates of common conditions, drug exposures, and outcomes. We compare obtained rates with official national statistics (e.g., birth statistics, yearly rates of drug dispensing, and diagnosis by age and gender). We also review missing data and outliers and inform registry holders of any unusual patterns.
10	Linkage	The NLHR is, by definition, a linkage of datasets. Helsedata.no is one central portal to apply for 11 national health registries, including all the registries that have been mapped to the OMOP CDM.
11	Vital status	The national death registry is linked.
12	Limitations	No database-specific limitations documented. General limitations for the data type applicable.
13	Main references	Mitter VR, Lupattelli A,Bjørk MH,Nordeng HME "Identification and characterization of migraine in pregnancy: A Norwegian registry-based cohort study." Cephalalgia : an international journal of headache (2024): 38663979
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1000000409 Website: https://www.mn.uio.no/farmasi/english/research/groups/pharma-safe/

Annex II. Operational and reporting considerations

DATA MANAGEMENT

Data management

All data sources have previously mapped their data to the OMOP common data model. This enabled the use of standardised analytics and using DARWIN EU® tools across the network since the structure of the data and the terminology system was harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

The analytic code for this study was written in R and used standardized analytics wherever possible. Each data partner executed the study code against their data source containing individual data and then returned the results (csv files) which only contained aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

Data storage and protection

For this study, personal data from individuals in various EU member states were processed, using information collected from national/regional electronic health record data sources. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All data sources used in this study were already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control were adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generate non-identifiable aggregate summary results.

QUALITY CONTROL

Data source quality control

When defining drug cohorts, non-systemic products will be excluded from the list of included codes summarised on the ingredient level.

When defining cohorts for indications, a systematic search of possible codes for inclusion will be identified using the *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This package allows the user to define a search strategy and will use this to query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the *CohortDiagnostics* (https://github.com/OHDSI/CohortDiagnostics) and *DrugExposureDiagnostics* (https://cran.r-project.org/web/packages/DrugExposureDiagnostics/index.html) R packages will be run, if needed, to assess the use of different codes across the data sources contributing to the study and identify any codes potentially omitted in error. The *DrugExposureDiagnostics* package evaluates ingredient-specific attributes and patterns in drug exposure records.

The study code will be based on DARWIN EU® R packages: *IncidencePrevalence* to estimate Incidence and Prevalence, and *CohortCharacteristics* to characterise the cohort by indication. These packages will include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

Annex III: Concept sets

Table 10. List of pulmonary arterial hypertension concept IDs.

Concept	Concept IDs	Ontology
Pulmonary arterial hypertension	4013643,4119611,4124831,40482858,44782560,44782562,44783618,44783619,44783620,44783621,44783622,44783623,44783624,44783625,44783626	SNOMED

Table 11. List of covariate concept IDs.

Concept	Concept IDs	Ontology
Right heart failure	312927,317000,608954,4014159,4030258,4079296,4193236,4195785,4195892,4215446,4233424,4242669,4273632,4284562,4307356,35615055,37163135,37163261,37163264,37163266,37163268,37167218,37309625,44782713	SNOMED
Ascites	200528	SNOMED
Cardiac Arrhythmia	313209,313217,313224,313780,313791,313792,314059,314379,314664,314665,314749,315069,315643,316135,316429,316432,316998,316999,317100,317302,317893,318448,320425,320744,321042,321315,321587,321590,433225,437579,437892,437894,441872,443522,443523,506573,506574,506575,506576,506577,507776,605092,606035,606036,606049,606053,606054,606055,606056,606057,606060,606064,606067,606069,606073,606078,606079,606083,606084,606087,606090,606091,606092,606093,606094,606095,606096,606097,606139,607219,607220,608077,609068,724616,724617,724618,724619,724620,724621,724622,724623,724624,724643,724644,724645,724681,724682,724683,761738,764719,766249,911827,954119,954120,954121,1073865,1073964,1075855,1126208,1126209,1126210,1126211,1242809,1242814,1244511,1245080,1245123,1340258,2000048,2000050,2000051,2001571,2001572,2001576,2001578,2001581,2001972,2001973,2001980,2006614,2006615,2006616,2006617,2006618,2106984,2106985,2106986,2106987,2106988,2106990,2106991,2107002,2107003,2107005,2107006,2107007,2107008,2107010,2107023,2107024,2107025,2107027,2107028,2107029,2107030,2107031,2107042,2107043,2107046,2107049,2107050,2107051,2313846,2313847,2313848,2313853,2313855,2313860,2313861,2313862,2313863,2313864,2313865,2313866,2313926,2313928,2313929,2313930,2313931,2313932,2313933,2313934,2313938,2313948,2725709,2725711,2726059,2726070,2726081,2726087,2726167,2726169,2726174,2726176,2726181,2726183,2726188,2726190,2726195,2726197,2726202,2726204,2726209,2726211,2726216,2726218,2726232,2726234,2726239,2726241,2726246,2726248,2726253,2726255,2726260,2726262,2726267,2726269,2726272,2726274,2726277,2726279,2726282,2726284,2727195,2727206,2727217,2727228,2755317,2755330,2755343,2788031,2788033,3172795,3175422,3176607,3182147,3183100,3188998,3190461,3655803,3655806,3655970,3656145,3656226,4006208,4008580,4018711,4018843,4018844,4019139,4019140,4019141,4020231,4020233,4020234,4020668,4023336,4028322,4029303,4029763,4030583,4032785,4034164,4035447,4036236,4038688,4041343,4043871,4044395,4046707,4048694,4049219,4049398,4049399,4049400,4049402,4049403,4049986,4049987,4049990,4049991,4049992,4050568,4050570,4050573,4050574,4050575,4050710,4051472,4051934,4051938,4051939,4051940,4055567,4057008,4068155,4068740,4069188,4070936,4077018,4078058,4078453,4081675,4085558,4086313,4087076,4087901,4088210,4088332,4088336,4088337,4088338,4088347,4088348,4088349,4088350,4088351,4088352,4088496,4088501,4088502,4088503,4088504,4088505,4088506,4088507,4088982,4088983,4088984,4088985,4088986,4088987,4089460,4089461,4089462,4089463,4089464,4089511,4091446,4091899,4091900,4091901,4091902,4091903,4091904,4092011,4098133,4099402,4099484,4099778,4101624,4101854,4102252,4103295,4106274,4106715,4108241,4108828,4108830,4109365,4110550,4111543,4111546,4111552,4111570,4111698,4111700,4115173,4117045,4117046,4117112,4119598,4119599,4119600,4119601,4119602,4119603,4119604,4119605,4119917,4120084,4120085,4120086,4120087,4120088,4121479,4121480,4121481,4121482,4121483,4121584,4121613,4121615,4122762,4124696,4124697,4124698,4124699,4124700,4124701,4124702,4124703,4124704,4125933,4128968,4135823,4136517,4137382,4137871,4138545,4138973,4139206,4140976,4140992,4141360,4142917,4143042,4144860,4144921,4145787,4146580,4148028,4149327,4150419,4152132,4153404,415429	SNOMED

Concept	Concept IDs	Ontology
	0,4155152,4155153,4161527,4161597,4161821,4164083,4164309,4166380,4166844,4169261,4171193,4171269,4171683,4171887,4172822,4172863,4173170,4173446,4173792,4174419,4174878,4175473,4175656,4176112,4179363,4180293,4180298,4183537,4184950,4185572,4187537,4190306,4191222,4198013,4198540,4199501,4201023,4201134,4202955,4203562,4204395,4205137,4205990,4205991,4206128,4209904,4210313,4215909,4216345,4216773,4217221,4217860,4218242,4218739,4221549,4222125,4223369,4224848,4225150,4226342,4226399,4228448,4228672,4228836,4229766,4232614,4232691,4232697,4233619,4234169,4235124,4235141,4236004,4236489,4237586,4238833,4238843,4239324,4241102,4242529,4243143,4243151,4243335,4244395,4244693,4244893,4246210,4247537,4248028,4249027,4250169,4250607,4253363,4254116,4256374,4258998,4261842,4262389,4263207,4267892,4268046,4269927,4270363,4271464,4275423,4275747,4277903,4280348,4280489,4280816,4281670,4286047,4287115,4290930,4293626,4294868,4295336,4296729,4296792,4298806,4299518,4300181,4300434,4301015,4302802,4303238,4303256,4303408,4304095,4304839,4305210,4305862,4306984,4307238,4308117,4308455,4309332,4310280,4315013,4320474,4322483,4323629,4325850,4327066,4328649,4329105,4329391,4331102,4331222,4333083,35608001,35608087,35622031,35624231,36674897,36675005,36676642,36712986,36714539,36714606,36714994,36715042,36715370,36717434,37016896,37017187,37108582,37109912,37109917,37110729,37110775,37116420,37117768,37151415,37153707,37155430,37157743,37157799,37157813,37160789,37160790,37160982,37161418,37162087,37162755,37162997,37163002,37163034,37163037,37163070,37163094,37163279,37163281,37163282,37163284,37163286,37163287,37163297,37163299,37163313,37163323,37163325,37163819,37163851,37164344,37164794,37164796,37164955,37164956,37169385,37169854,37170582,37171038,37172212,37172244,37174277,37203868,37203869,37312140,37312595,37395821,37395937,37396235,37397458,37398927,37398951,37399476,40217340,40479221,40479232,40479264,40479379,40479415,40479833,40479859,40480216,40480274,40481055,40481058,40481494,40481890,40481891,40481942,40482387,40482781,40483201,40483213,40483283,40483670,40484036,40484152,40485437,40487117,40487514,40488431,40488929,40490499,40491027,40492022,40622721,40756830,40756840,40756942,40756943,40756983,40757045,42534858,42536724,42536725,42536726,42537346,42537348,42538755,42539038,42539346,42539500,42593919,42593955,42593956,42599769,42599777,42742522,42742523,42742524,42742525,42742528,42742529,42742530,42872818,42872827,42872828,42872924,42894719,42894720,42894721,42894722,42894723,42894724,42894725,42894726,42894727,42894728,42894729,42894730,42894731,42894753,42894754,42894758,42894759,42894763,43020494,43020495,43020929,43020930,43021222,43021509,43021733,43022053,43528005,43528006,43530960,44511202,44511203,44511207,44511210,44511211,44511216,44514185,44782442,44782643,44782661,44782707,44782789,44783080,44783089,44783090,44783199,44783658,44784217,44784218,44784219,44784220,44784234,44784235,44784236,44784368,44790271,44790298,44790432,44790501,44790530,44790597,44790598,44791688,44791697,44806668,44807913,44807914,44809477,44809600,44809601,44810457,44811732,44816473,44816475,45757098,45765997,45766074,45766861,45768480,45769228,45771051,46269694,46269805,46269812,46270961,46272503,46272748,46274066,46284985	
Atrial Flutter	314665,4137382,4146580,36712986,36714994,37395937	
Atrial Fibrillation	313217,605092,1340258,4020234,4117112,4119601,4119602,4141360,4154290,4199501,4232691,4232697,37170582,37171038,37172212,37172244,37395821,42539346,42709991,44782442,45768480	
Supraventricular Tachycardia	314665,317893,606035,606036,606049,606055,606057,606067,606069,606087,609068,954120,954121,4108830,4120085,4124696,4137382,4137871,4146580,4190306,4253363,4275423,4303256,36712986,36714994,37170582,37171038,37172212,37172244,37312595,37395937,42536724,42536725,43021733,43022053,44782789	
Ventricular Tachycardia	433225,437579,606060,606064,606073,4088348,4088349,4088501,4088982,4091899,4091900,4103295,4111700,4119598,4119599,4119600,4120086,4121482,4121483,4124701,4124703,4135823,4139206,4233619,4303238,4305862,37110729,37160789,37160790,37163002,37163034,37163037,37163070,37163313,37164955,37164956,37397458,40480274,40622721,42539346,42599769,44782707,45771051,46272503	

Concept	Concept IDs	Ontology
Ventricular Fibrillation	437894,4111700,4119604,4138468,4208907,4325850,37109917	
Sick Sinus Syndrome	608077,4119603,4254116,4261842	
AV block	313780,314379,316135,318448,320744,4068740,4069188,4088332,4111570,4119605,4205137,4298806,37116420,42593955,42593956,43020494,43020495,43020929,46269694	
Haemoptysis	261687,4048152	SNOMED
Lung-heart transplant	725037,725038,725039,2101017,2106871,2106882,2106884,2106885,2106886,2107477,2107480,4017743,4019926,4020370,4137127,4138959,4178637,4187247,4228489,4269789,4335479,4336751,4337138,4337309,4337611,4337612,4339619,44509427,44511390	CPT4, SNOMED
Atrial septostomy or Potts shunt	2313809,4151906,4195096,4312891,4336893,44511471	CPT4, OPCS4, SNOMED
Syncope	135360,140586,1340472,1450403,4053712,4119784,4120935,4120936,4121812,4121813,4125000,4125001,4152074,4154638,4162208,4162976,4206148,4229670,4234105,4240219,4302523,36716914,37312020,40484193,42574152	SNOMED
Congenital heart disease	76798,259123,312723,312728,313005,313006,313007,313011,313867,314457,316226,318537,319921,320206,320835,321107,321109,432431,433010,434146,434467,435912,440207,441108,441385,441409,441950,442277,605954,618819,619141,619237,619246,764796,1075369,1075865,1076119,1076866,3172110,3183233,3654641,3654922,3654940,3654947,3654949,3654955,3654965,3655649,3656057,3656059,3656061,3656063,3656072,3656075,3656077,3656078,3656079,3656080,3656081,3656082,3656083,3656084,3656085,3656086,3656087,3656088,3656089,3656090,3656093,3656095,3656097,3656099,3656101,3656102,3656104,3656105,3656110,3656116,3656118,3656120,3656121,3656123,3656125,3656127,3656128,3656130,3656131,3656132,3656138,3656140,3656143,4000084,4006983,4007735,4012483,4016142,4027245,4027246,4028349,4028376,4029361,4029362,4029827,4029833,4030224,4030427,4030676,4031264,4031265,4032476,4032995,4033445,4033446,4033447,4033449,4033905,4035467,4040838,4046113,4046114,4046115,4048042,4049296,4066746,4068741,4068742,4068743,4068833,4069090,4069096,4069177,4069180,4069182,4069184,4069185,4069186,4069190,4069191,4070297,4070298,4070299,4070789,4070795,4070798,4070914,4070916,4078058,4093290,4094649,4099993,4099994,4099995,4099996,4099998,4099999,4100000,4100001,4100003,4100005,4100121,4100122,4100128,4100129,4100130,4100131,4100134,4100138,4100139,4100143,4100146,4100149,4100150,4100151,4100152,4100153,4100254,4100255,4100256,4100258,4100259,4100260,4100270,4100271,4100272,4100273,4100274,4100275,4100276,4100277,4100279,4100392,4100393,4100394,4100396,4100397,4100398,4100401,4100402,4100403,4100404,4100732,4100733,4100734,4100735,4100736,4100815,4100863,4100865,4100866,4100867,4100868,4100869,4100870,4100871,4100875,4100877,4100879,4101005,4101006,4101007,4101008,4101009,4101011,4101012,4101013,4101014,4101020,4101021,4101028,4101032,4101033,4101035,4101036,4101160,4101162,4101164,4101165,4101166,4101167,4101169,4101170,4101171,4101173,4101174,4101175,4101176,4101177,4101183,4101184,4101187,4101313,4101314,4101315,4101316,4101318,4101319,4101320,4101321,4101322,4101324,4101325,4101327,4101329,4101330,4101331,4101481,4101484,4101485,4101486,4101487,4101490,4101491,4101492,4101493,4101494,4101605,4101606,4101607,4101608,4101609,4101611,4101612,4101613,4101614,4101615,4101616,4101618,4101619,4101620,4101622,4101628,4101629,4101630,4101631,4101632,4101633,4101634,4102708,4102709,4102710,4102711,4102712,4102833,4102834,4102835,4102836,4102838,4102846,4102847,4102857,4102862,4102863,4102865,4102988,4102989,4102990,4102991,4102993,4102996,4102997,4102998,4103006,4103008,4103009,4103010,4103012,4103013,4103014,4103015,4103129,4103130,4103131,4103132,4103133,4103135,4103138,4103139,4103140,4103143,4104799,4107391,4108587,4108723,4108725,4108726,4108727,4108728,4108730,4108731,4108736,4108872,4108873,4108874,4108876,4109200,4109201,4109202,4109333,4109336,4109337,4109338,4109339,4109341,4109467,4109483,4109484,4109485,4109486,4109487,4109491,4	SNOMED

Concept	Concept IDs	Ontology
	109642,4109644,4109647,4109649,4112080,4112081,4112082,4112084,4112091,4112092, 4112093,4112096,4113297,4113298,4113299,4113300,4113301,4113303,4118403,4119463 ,4121799,4123286,4126122,4129018,4130892,4131334,4132742,4133527,4136255,413625 9,4141179,4141309,4145158,4149568,4152843,4154303,4161005,4161304,4161597,41632 92,4165564,4170062,4171835,4172085,4173466,4174077,4178750,4182602,4183030,4184 499,4187043,4188636,4197259,4203920,4206334,4207052,4213824,4214375,4216144,421 6863,4218450,4219995,4223063,4224751,4225420,4228527,4231324,4235784,4236884,42 39569,4242177,4242188,4242604,4244027,4244029,4244173,4244184,4244935,4244966,4 245104,4245227,4245321,4245347,4245348,4245443,4245543,4245618,4245646,4245692, 4245803,4245810,4245811,4245920,4245933,4246484,4246492,4246514,4251327,4252111 ,4253217,4261813,4262976,4263510,4263915,4268609,4269199,4289152,4289542,429347 7,4294530,4298429,4300540,4300644,4301767,4301771,4302306,4305961,4312035,43142 03,4314504,4315819,4322316,4326746,4328498,4328721,4329430,4337282,4353743,4354 052,35615056,35621810,35621978,35622329,35622345,35622374,35622375,35622647,356 22773,35624311,35625532,36674400,36674713,36674714,36674716,36676316,36683267,3 6683354,36713473,36713499,36713568,36713638,36713761,36714239,36714252,3671425 7,36714291,36715086,36715118,36715122,36715123,36715141,36715217,36715308,36715 369,36715370,36715371,36715372,36715405,36716111,36716113,36716138,36716258,367 16451,36717199,36717401,36717434,36717662,36717720,37109595,37109597,37109669,3 7110040,37110775,37111359,37111410,37111650,37118888,37160624,37160755,3716208 5,37162245,37162277,37163003,37163356,37163928,37163930,37164181,37164405,37164 423,37164818,37164933,37165081,37165651,37166821,37204188,37204189,37204370,372 04437,37204832,37204854,37205075,37311139,37312323,37396245,37396391,37396800,3 7397481,37397487,37397525,37398927,37399403,37399551,40280309,40403695,4040400 7,40456182,40481128,40481432,40481579,40481625,40482888,40482892,40482894,40482 925,40482926,40483289,40483294,40483337,40483747,40484273,40484305,40486033,404 86037,40486038,40486039,40486041,40486042,40486044,40486045,40486046,40486055,4 0486057,40486063,40486065,40486071,40486072,40486073,40486135,40486136,4048617 9,40486225,40486554,40486559,40486560,40486608,40486610,40486611,40486615,40486 616,40486625,40486626,40486633,40486663,40486664,40486705,40486706,40486733,404 86737,40486738,40486740,40486743,40487013,40487037,40487038,40487039,40487081,4 0487083,40487087,40487102,40487103,40487107,40487108,40487118,40487152,4048715 3,40487161,40487165,40487167,40487168,40487182,40487183,40487184,40487185,40487 186,40487383,40487476,40487499,40487527,40487538,40487539,40487547,40487550,404 87571,40487573,40487587,40487600,40487602,40487637,40487647,40487649,40487652,4 0487653,40487654,40487967,40487968,40487969,40487971,40487978,40487979,4048798 0,40487981,40487986,40487988,40487992,40488003,40488013,40488024,40488032,40488 058,40488065,40488066,40488067,40488068,40488071,40488072,40488396,40488397,404 88398,40488437,40488444,40488445,40488466,40488467,40488468,40488469,40488827,4 0488829,40488838,40488841,40488967,40488968,40488970,40489394,40489410,4048942 3,40489450,40489451,40489903,40489905,40489971,40489973,40489974,40489995,40490 310,40490318,40490417,40490481,40490482,40490515,40490932,40490939,40490945,404 90946,40490947,40490956,40491008,40491462,40491482,40491515,40491519,40491525,4 0491529,40491892,40491893,40491894,40491895,40491898,40491938,40491939,4049195 6,40491967,40491971,40491976,40491986,40491993,40491994,40491995,40492030,40492 189,40492434,40492470,40492471,40492475,40492500,40492501,40492522,40492532,404 92953,40492956,40492960,40492963,40492964,40492965,40492982,40492983,40492988,4 0492991,40493209,40493243,40493417,40493418,40493430,40493431,40493444,4049345 9,40493460,40493470,40493472,40493476,40493477,40493497,40493519,42537639,42538 529,42538530,42538531,42538671,42538695,42539142,42573200,42599730,42599731,425 99733,42599734,42599735,42599736,42599737,42599747,42599797,42873050,42873051,4 2873052,43020504,43020561,43020569,43020570,43020571,43020572,43020573,4302057 4,43020575,43020576,43020579,43020580,43020689,43020880,43020914,43020915,43020 916,43020917,43020919,43020920,43020921,43020922,43020939,43021193,43021294,430 21301,43021302,43021303,43021304,43021305,43021306,43021307,43021308,43021309,4 3021310,43021311,43021312,43021313,43021314,43021336,43021432,43021434,4302143 5,43021436,43021437,43021470,43021472,43021474,43021475,43021476,43021570,43021 572,43021574,43021578,43021579,43021580,43021581,43021582,43021615,43021627,430 21628,43021630,43021631,43021749,43021795,43021796,43021885,43021886,43021888,4	

Concept	Concept IDs	Ontology
	3021923,43021936,43021937,43021973,43022025,43022026,43022037,43022045,44782956,44792297,44803294,44803295,44803309,44803310,44803448,44803449,44803450,44803451,44803452,44803453,44803454,44803455,44804745,44804750,44804759,44804760,44804761,44804762,44804766,44804767,44804768,44804776,44804777,44804848,44804855,44813205,44813207,44813666	
Bronchopulmonary dysplasia	1245453,1245454,1245455,4283942	SNOMED
Congenital diaphragmatic hernia	194403,198246,200143,201061,765110,1243182,1448894,1448895,2003467,2003468,2003484,2003485,4012461,4027751,4055004,4066010,4069166,4099622,4103218,4103231,4117680,4117984,4136887,4140878,4147525,4147560,4147561,4148481,4148482,4148483,4159156,4169418,4197409,4202994,4217665,4224004,4230527,4231663,4234293,4244809,4247417,4249303,4277355,4283224,4302032,4340516,4340517,4340518,4340519,4342897,4344629,36674343,36687117,36715421,36717796,36717797,37110042,37160988,37162906,37163587,37170126,40486607,40756891,40756938,40757001,40757002,40757015,40757063,40757103,42593431,44509689,45773368,45881158,46270686	SNOMED, LOINC
Persistent pulmonary hypertension of the newborn	4121462	SNOMED
Endothelin receptor antagonists	792985,792986,792987,792988,792989,792990,792991,792992,995033,1235149,1235150,1236353,1321636,1321637,1321641,1337068,1337069,1337070,1337102,1337103,1337104,1830508,1830509,1830720,1830721,1830722,1970973,1970974,1971082,1971083,1971084,1971085,2062459,2062460,2062461,2062462,2062463,2062464,2062465,2063987,2063988,2063989,2063990,2063991,2063992,2063993,2063994,2063995,2063996,2925167,2925168,2925169,2925170,2925171,2925172,2925173,2925174,2925175,2925176,2925177,2925178,2925179,2925180,2925181,2925889,2925944,2926072,2926073,2926074,2926075,2926076,2926077,2926078,2926079,2926080,2926081,2926082,2926083,2926084,2926085,2926086,2926087,2926088,2926089,2926090,2926091,2926092,2926093,2926094,2926095,2926096,2926097,2926098,2926099,2926100,2926101,2926102,2926104,2926105,2926106,2926107,2926108,2926109,2926110,2926111,2926112,2926113,2926114,2926115,2926116,2926117,2926118,2926119,2926120,2926121,2926122,2926123,2926124,2926125,2926126,2926127,2926128,2926129,2926130,2926131,2926132,2926133,2926134,2926135,2926136,2926137,2926138,2926139,2926140,2926141,2926142,2926143,2926144,2926145,2926146,2926147,2926148,2926149,2926150,2926151,2926152,2926153,2926154,2926155,2926156,2926157,2926158,2926159,2926160,2926161,2926162,2926163,2926164,2926165,2926166,2926167,2926168,2926169,2926170,2927520,2927521,2927522,2927523,2927524,2927525,19013177,19013178,19016157,19016158,19098071,19098072,19098352,19124851,19126932,21026653,21027335,21032925,21032926,21036422,21037111,21062427,21065878,21075798,21082048,21085524,21095319,21095320,21095321,21101683,21121227,21124589,21124590,21134515,21135225,21144410,21150772,21150773,21173923,21174599,35130611,35131737,35132265,35134278,35139488,35139673,35142438,35144529,35150201,35150830,35154573,35156663,35157425,35158970,35160036,35161032,35161808,35748407,35752554,35763487,35771959,35831240,35868392,35884729,35887526,35887527,35887528,35887529,35887530,35887531,35887532,35898098,35898099,35898100,35898101,35898102,35898103,35898104,35898105,36035582,36035702,36065668,36066738,36066739,36214145,36214146,36219519,36219520,36222100,36222101,36227948,36227949,36247787,36247788,36247789,36247790,36257108,36258547,36259183,36260679,36261346,36263642,36268858,36269726,36270881,36271959,36273454,36419990,36419991,36419992,36503906,36506340,36784062,36784063,36784064,36784065,36784066,36784067,36784068,36784069,36784070,36784071,36784072,36784073,36784074,36784075,36784076,36784077,36784078,36784079,36784080,36784081,36784082,36784083,36784084,36789373,36789374,36789375,36789376,36789377,36789378,36789379,36790388,36790389,36810314,36811052,36811290,36811478,36811518,36811558,36813892,36814123,36921082,36925432,36930696,36933735,36944550,36954717,36960077,36962541,36963618,36966501,37593226,37593227,37593228,37593229,37593230,37593231,37593232,37593233,37593234,3759	RxNorm

Concept	Concept IDs	Ontology
	3235,37593236,37593237,40092426,40092427,40140735,40140736,40728575,40728576,40728577,40728578,40728579,40728580,40728581,40728582,40728583,40728584,40728585,40728586,40728587,40728588,40728590,40728591,40728592,40728593,40728594,40728595,40728596,40728597,40728598,40824876,40875109,40887929,40887930,40912734,40919328,40942873,40942874,40942875,40950077,40981174,41074933,41087373,41119259,41137780,41137781,41138323,41150148,41161757,41178853,41200355,41231414,41231415,41231894,41305582,42609380,42609381,42609382,42609383,42609385,42609386,42609387,42609388,42609389,42609391,42609392,42609393,42614154,42614186,42655765,42657477,42875993,42938126,42938127,42938128,42938129,42938130,42938131,43033953,43033954,43033955,43033956,43033957,43033958,43033959,43033960,43033961,43033962,43033963,43033964,43033965,43033966,43033967,43033968,43033969,43033970,43033971,43033972,43033973,43033974,43033975,43033976,43033977,43033978,43033979,43033980,43033981,43033982,43033983,43033984,43033985,43137354,43137356,43141060,43148294,43148295,43148296,43152118,43159470,43159471,43159472,43170353,43174257,43174258,43174259,43181369,43181370,43181371,43185107,43192320,43196110,43196111,43196112,43196113,43203391,43203392,43214216,43214218,43218027,43218028,43260389,43260390,43263990,43263991,43265819,43271308,43276874,43280329,43282186,43293040,43293041,43296571,43607040,43607041,43624964,43624965,43624966,43643214,43643215,43679267,43697114,43697115,43715016,43733042,43733043,43733044,43768974,43768975,43786938,43804933,43804934,43823039,43823040,44164136,44171663,44186778,44507580,44507581,44507582,44507583,44507584,44507585,44507586	
Phosphodiesterase type 5 inhibitors	1830593,1970939,2925235,35744644,36268748,36271404,44126915,44163128,44178187,41257458,43037443,43624629,43804437,44040758,44066892,36783105,36966897,40914087,41027303,41070085,41077579,2925212,21091007,21169741,35746874,35748866,35787664,43786438,44053802,44059753,44075073,44087762,44165475,40724106,40902586,40996308,43037420,43139632,43207195,36074971,36241998,36257435,36783082,36921221,36930707,1830710,21159946,36270193,36783059,36960113,40720333,43161759,43660796,43678772,44033811,44118379,40724083,40883161,40893812,41069870,41121240,41277069,2925258,21051831,35765443,35769759,36783036,36929757,42876298,43161736,43205606,43840627,40720285,40723937,40871568,40883138,40933746,40976411,995249,35757210,36066882,36783013,40723966,40840425,43732512,44046832,44098365,43150567,43165881,43174448,43216489,43216495,43588508,40851648,41164237,41215171,41246149,43036017,43150561,741670,1201174,2926417,2926423,21032149,36411232,43216472,43642674,43696608,40851886,41163999,42926079,43035994,43036000,43194654,36782990,36927510,36933461,36961919,37593405,40720356,995132,2925189,19102192,21045897,36035532,36035701,43786655,43822536,44072674,41195326,42480759,43037397,43161753,43606530,43768679,36964103,40851863,40996285,41121234,41132887,41183842,36270199,36505115,36782967,36814102,36882120,36926654,995155,2926494,21081260,35774056,36035555,36066859,44113616,42657790,42876181,42876304,43037374,43150590,43714507,41038804,41052255,41070108,41090076,41121257,41319951,36814125,36955891,40723943,40883144,40933752,41015000,1970933,2926486,21120444,35765460,35767713,36119657,43141238,43183617,43279331,43295576,44169288,44173023,41027297,41070091,41090059,41240069,42614146,43035931,36276651,36949911,36967567,40840410,40914081,40914093,1316265,2925206,21022417,21042090,21134115,36258615,43037414,43768456,44059759,36259943,36783076,36945240,40724100,40902580,41226398,2925195,2926440,21124228,35753011,35898109,36066842,43139615,36933973,36947301,41007529,41288307,41319943,43035977,21061618,21071565,21155801,35757193,36066853,36783122,43150584,43172765,44072580,44074904,36959340,36965254,41070102,41257226,42609389,43037368,2926477,21036045,35761384,36267654,42876189,43035940,43143737,43216483,44108189,41152824,41164225,41164231,41215177,41288516,41404388,36953252,40723954,40723960,40821779,40840419,41090068,2925298,35758776,40851880,40933761,41027311,41058486,43606538,43606544,43732744,43804445,44092508,41183850,41183856,41226638,42658076,43183625,43183631,1830716,2926431,2926434,19102278,21110758,21159940,43268563,43660790,43804646,44166918,41319937,42900540,43035983,43035986,43139609,43194646,35753017,35769742,36940216,36963771,40882912,40890486,1971079,2925252,19121064,21061624,21071559,35757199,43274073,43768447,41277052,42609383,43037460,43150578,43161742,43205612,36938493,40720316,41049587,41132655,41246166,41257232,35868989,35898203,36066404,36265098,36783030,36887885,2925223,2926480,	RxNorm

Concept	Concept IDs	Ontology
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Concept	Concept IDs	Ontology
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Concept	Concept IDs	Ontology
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Concept	Concept IDs	Ontology
	270198,36272706,41277068,42480758,43768678,43822535,36419295,36813535,40851862,40913877,40945436,41007528,1201173,19047693,21120435,36257409,36257440,36259948,44165474,44170644,43216471,43642673,43642679,44059758,44079578,44105497,40840407,40851885,40964978,41299272,43035999,43207194,1970944,2925240,2926491,21169738,35761389,36066881,43150566,43216494,43624628,43804436,44100949,44176787,41090073,41101557,41257463,41288521,43035945,43037448,36268824,40168409,40723965,40840430,41007743,41070084,995154,2925263,2926468,21049512,35765448,35772063,42876303,43037373,43150589,43840632,40976416,41038803,41070107,41090050,42657789,42876180,35774055,36066858,36272683,40723942,40883143,40933751,1366400,1971076,2925194,2926439,21071556,21110757,44118384,44166917,43037402,43139614,43194645,43606529,43678777,44087922,41058483,41121245,41132652,41288306,41319942,43035991,21135978,35753022,36782981,36924074,40720353,40927374,2926428,35757207,36783075,36783087,40902579,40902591,41226397,43037413,43183630,43768455,43786443,44111245,2926485,21036044,21173565,35761383,36257432,40720307,43216488,43804442,44085466,44163133,40723959,40840424,41070090,43037365,43141237,43150572,1830707,19079498,21061617,21067371,35898208,36265103,42876186,43150583,43284738,43290148,44082280,36783121,36814462,36966716,40723948,41038809,41152812,1830715,35746284,35898108,36066847,36119619,36273708,36934897,40724097,43035982,43822541,1316270,2925297,21159934,35788425,40996276,41183855,43139606,43176886,43216477,43606543,21065507,35765459,36258754,36407673,36783027,36928605,41070096,41090064,41164230,41288512,43035936,44163127,36930769,40834270,40840418,40871550,40914092,41027308,1970930,2925251,21061623,21159937,35757198,36066403,43205611,43274072,43661033,44030584,44178178,41038815,41246165,41257231,42609382,43037459,43161741,36407281,36814013,36887884,36946410,36949607,40990076,2925271,21100933,35769747,35898117,36066850,36119616,44082343,44181899,41270917,41308197,43172750,43194639,43714498,43822544,40724094,40882914,40945190,40945427,41058477,41081030,35774064,36066400,36262524,36277180,36919480,40720324,43768449,43858734,44027845,44072668,44159369,44187993,41152815,43172773,43183636,43279325,43588524,43750473,40723951,40883152,40914075,41027316,41038818,41090041,21032134,21085164,21169732,35759382,36783021,36783095,44159300,41404387,43035939,43205594,43262940,43295572,44062326,40723974,40871553,41038795,41202951,41257469,41288515,995148,35407830,35757204,36261242,36275308,36782076,43194662,43205617,44113621,44185623,37593413,40933757,41174821,42876309,43152329,43161747,783942,1734746,1971067,21051822,21110748,36035549,43037476,43139623,43218209,43660804,36412969,36782972,36921664,40720350,40851868,41132892,2925291,2926004,21022410,21022416,21045894,35753002,42614334,43284735,43606549,40865367,40976419,41183861,41215165,41308217,41308223,36259942,36269065,36419610,36782995,36783044,36925886,1830601,19065870,36946424,36949006,40720301,40871559,44046751,44161713,44169287,40983770,41007746,41164242,41319727,43183613,43624379,1830701,35748874,36267691,36920258,36945783,41121256,42658084,43257559,995140,2925277,21140140,35748860,35769753,35887795,44174411,40724088,40945433,41058471,41308203,42657806,43205625,36272703,36419298,36778487,36783064,36928485,37593421,2926416,35787669,36264141,36270190,36941612,36965920,43858728,44066803,44087767,44187999,41226612,43037425,43139637,43172779,43183642,43750467,40720330,40723982,41027322,41052257,41090047,41132878,1970947,19036979,36066878,36504484,36814734,36963985,44100943,40933743,41101551,41233988,43037439,43216500,43732514,995246,1316304,1830695,2925134,2925220,21081265,44121244,42658090,42876174,42926081,43035965,43036002,43696610,21149984,35744638,36267685,36891456,36936998,41164001,19121181,21051816,21153963,35755260,36035537,36035543,44111314,41069875,41115076,41226620,41277074,43161761,44092573,36933889,40720338,40720344,40996293,40996299,41038589,2926459,2926502,21117810,36035686,36035692,36419604,41215159,41257449,42657798,43037382,43273952,43624365,36783001,40945447,40964972,40976425,41007754,41215153,2926408,21032140,21145848,36269251,36783101,36953663,44085546,46275408,41195534,41246139,43037433,43174453,43268442,43732520,36958240,40715226,40823767,40924838,40933737,40976184,995240,19102546,21091009,35132763,35744632,35761403,43840620,44062183,44105414,44124447,43036008,43194668,43517398,43606761,43696616,43714518,40721028,40871573,40958821,41058463,41121268,43035959,35831290,36066870,36267679,36275302,36943533,36954304	

Concept	Concept IDs	Ontology
Soluble guanylate cyclase stimulators	21021815,21031550,21031551,21041432,21041433,21041434,21041435,21051239,21051240,21051241,21051242,21051243,21061041,21070992,21070993,21070994,21070995,21080669,21080670,21080671,21100341,21100342,21110163,21110164,21119887,21129670,21129671,21139561,21139562,21139563,21159359,21159360,21169147,21169148,21169149,35744958,35749153,35749154,35749155,35749156,35750497,35753317,35754131,35754721,35761651,35761652,35765732,35765733,35765734,35765735,35770051,35770872,35774324,35774325,36247520,36247521,36247567,36247568,36261137,36266105,36268875,36271659,36276469,36782720,36782721,36782722,36782723,36782724,36921304,36922749,36928720,36929676,36935853,36935986,36936552,36939531,36942515,36949310,36953476,36956618,36957328,36958718,36959671,40852172,40865493,40865494,40865495,40865496,40872033,40914362,40927682,40934254,40958958,40976689,40996764,41008035,41058982,41058983,41101853,41121750,41133189,41133190,41133191,41164535,41164536,41164537,41164538,41226955,41226956,41246633,41257765,41257766,41271055,43140539,43140540,43140541,43140543,43140544,43140545,43151549,43151550,43151551,43162714,43162715,43162716,43162717,43162718,43173721,43173722,43173723,43173724,43173725,43173726,43184573,43184574,43184575,43184576,43184577,43195576,43195577,43195578,43195579,43195580,43206462,43206463,43206464,43206465,43217446,43217447,44062460,44062461,44113910,44113911,44127047,44174483,44506421,44506422,44506423,44506427,44506428,44506429,44506454,44506455,44506456,44506457,44506458,44506459,44506614,44506615,44506617,44506618,44506619,44506639,44506640,44506642,44506643,44506644,44506752	RxNorm
Prostacyclin receptor agonists	586889,586975,588265,588849,589353,701473,701474,701475,701476,701477,701478,701479,701480,746828,746829,746830,746831,746832,746833,746834,746835,746836,746837,746838,746839,747668,747669,747670,747671,747672,747673,779831,779832,779833,779834,779835,779836,779837,779838,779839,779840,779841,779842,779843,779844,779845,779846,779847,779848,780188,780189,780190,780191,780192,780193,780194,780195,783662,783663,783664,783665,783666,783667,783668,783669,784638,784815,784816,784817,784818,784819,784820,784821,784822,784823,1302270,1302271,1302272,1302273,1302274,1302275,1327256,1327261,1327292,1327293,1327294,1327295,1327297,1327298,1344992,1344995,1354118,1354119,1356206,1356207,1356256,1356257,1718571,1718572,1718573,1718574,1718575,1718576,1734266,1734267,1734269,1734270,1734271,1734272,1735667,1735668,1735669,1735670,1735751,1735752,1758766,1758767,1758768,1758769,2026832,2026833,2026834,2029603,2905201,2905202,2905203,2905204,2923890,2923891,2925830,2925831,2925832,2925833,2925834,19016192,19016193,19016194,19016195,19045938,19054361,19080430,19096754,19096755,19096756,19096757,19100973,19101291,19104373,19110302,19112948,19112949,19115193,19115194,21028473,21028775,21028776,21032074,21032075,21035597,21038592,21049405,21049406,21051765,21055253,21058150,21061560,21067759,21067760,21067761,21071491,21071492,21077896,21087336,21094508,21097451,21100879,21104432,21106997,21108286,21110704,21110705,21120390,21120391,21120392,21120393,21123808,21126497,21126786,21136362,21136677,21140065,21140066,21140067,21149920,21156201,21169663,35129658,35130958,35131089,35131897,35132427,35139305,35142432,35142937,35147319,35148213,35149978,35153958,35155040,35155361,35157400,35157579,35158352,35158499,35407386,35407502,35408178,35409083,35409084,35411269,35411270,35411382,35413209,35413895,35413911,35413961,35413971,35413988,35413995,35414000,35414005,35414015,35414017,35414024,35414030,35414056,35414058,35414098,35414100,35414400,35414401,35414402,35414403,35414404,35419429,35419430,35419431,35419432,35419433,35604618,35604848,35604849,35604850,35604851,35604932,35604933,35604934,35604936,35604937,35604938,35604939,35604940,35604941,35604942,35604943,35604944,35604945,35604946,35604947,35604948,35604949,35604950,35604951,35604952,35604953,35604954,35604955,35604956,35604957,35604958,35604959,35604960,35604961,35604962,35604963,35606608,35744698,35748920,35753064,35753065,35754104,35757248,35757251,35761435,35761437,35762332,35765510,35770738,35771419,35774100,35775959,35776222,35776355,35776777,35777190,35777494,35777495,35777933,35785570,35785571,35785619,35785646,35785672,35785688,35785689,35867609,35867610,35867611,35868091,35868092,35868093,35896644,35896645,35896646,35896647,36037288,36052462,36052463,36052464,36054544,36054545,36054546,36054547,36054548,36054549,36054550,36054551,36054552,36054553,36058334,36058335,36058336,36058337,36058338,36058339,36065969,36065970,36065971,3	RxNorm

Concept	Concept IDs	Ontology
	6065972,36065973,36065974,36065975,36065976,36065977,36065978,36066276,3606627 7,36066278,36066279,36074120,36074121,36074122,36074123,36121391,36121392,36121 393,36121394,36214306,36214307,36214424,36214425,36222622,36228989,36235966,362 39680,36242322,36242338,36247974,36247975,36248106,36248107,36248460,36248461,3 6248481,36248482,36257948,36258301,36259124,36260489,36264257,36267405,3626891 9,36269012,36269144,36271056,36273760,36273880,36275039,36280701,36280717,36280 747,36280757,36280779,36280787,36403723,36408325,36409720,36409913,36409932,364 09975,36410108,36410109,36410168,36410179,36410194,36779130,36779131,36779132,3 6779133,36779134,36779135,36784353,36784354,36784355,36784356,36784357,3678435 8,36784359,36784360,36784361,36784362,36784363,36784364,36784365,36784366,36784 367,36784368,36784369,36787745,36787746,36787747,36787748,36787749,36787750,367 87751,36787752,36787753,36787754,36787755,36787756,36787757,36787758,36787759,3 6787760,36787761,36787762,36787763,36787764,36787765,36787766,36787767,3678776 8,36787769,36787770,36787771,36787772,36787773,36787774,36787775,36787776,36787 777,36787778,36787779,36787780,36787781,36787782,36787783,36787784,36787785,367 87786,36809190,36809206,36809216,36809236,36809253,36809315,36811253,36813084,3 6813437,36814004,36856411,36879330,36880108,36880109,36880512,36880883,3688149 6,36882045,36883161,36884129,36884640,36886585,36886795,36886818,36887145,36887 540,36887592,36887786,36888788,36890100,36890776,36892730,36892731,36893527,368 93733,36893920,36894418,36894869,36895679,36895694,36895711,36895740,36895773,3 6895774,36895803,36895807,36896184,36919949,36921787,36922998,36923006,3692339 0,36923928,36924419,36924430,36925271,36925279,36926644,36926854,36928384,36928 530,36930073,36930169,36930768,36931000,36931543,36932023,36932325,36933166,369 33441,36933474,36938467,36938708,36941969,36942154,36943430,36943452,36943580,3 6944369,36944525,36945538,36945786,36946840,36948465,36949398,36950092,3695018 6,36950556,36950631,36951654,36952068,36952476,36952558,36952564,36953765,36954 007,36954417,36954462,36954765,36955025,36955260,36956044,36957481,36958305,369 58387,36959506,36960539,36961916,36962209,36962391,36962470,36962758,36962784,3 6962867,36964176,36964810,36965153,36967098,36967180,36968328,36968350,3696902 3,36969417,36969667,36969719,36969823,40048977,40090704,40090705,40164835,40164 836,40164837,40165305,40165306,40165307,40165308,40226772,40719021,40719022,407 19023,40719024,40719025,40719026,40719027,40719028,40719029,40729362,40729363,4 0729364,40729365,40729366,40729367,40729368,40729369,40729370,40729371,4072937 2,40729373,40729374,40729375,40729376,40729377,40729378,40729379,40744869,40744 870,40744871,40744872,40744873,40744874,40744875,40744876,40744877,40754629,407 54630,40754631,40754632,40826841,40832497,40835782,40846730,40846731,40860073,4 0860459,40866872,40906982,40908903,40938334,40951523,40960411,40960412,4096936 9,40969370,40971151,40985071,40991658,40991659,40991660,41000691,41002528,41050 638,41053893,41053894,41085437,41085438,41086147,41094513,41116638,41116639,411 16640,41116641,41127603,41148132,41148857,41157259,41179941,41203807,41207112,4 1211377,41219539,41238392,41241574,41241575,41272391,41272392,41272393,4127239 4,41273168,41281381,41281383,41299989,41303556,41303557,41312721,41314565,41314 566,41314567,41327443,41328861,41328862,41329401,41329572,41329573,41330068,413 30861,41331534,41332212,41332881,41332882,41333175,41333406,41333591,41333592,4 1334111,41335185,41335186,41335461,41335608,41335609,41335610,41335875,4133611 6,41336293,41336294,41336936,41337436,41337835,41337836,41339292,41339409,41343 105,41343623,41345218,41345219,41345740,41407551,41407661,41408003,41408286,414 08472,41409345,41409754,41409843,41409897,41410139,41431044,41431081,41431227,4 1431441,41431549,41431659,41431786,41431809,41431963,41454381,41459653,4261416 6,42629306,42629307,42629308,42629309,42629310,42629311,42629312,42629313,42629 314,42656219,42656220,42656221,42656222,42656223,42656224,42656225,42656226,426 57296,42657297,42658541,42658542,42710270,42710773,42711180,42713900,42715520,4 2721981,42722710,42724495,42725861,42728065,42729629,42873590,43023011,4302301 2,43023013,43023014,43026840,43026841,43026842,43032839,43032840,43032841,43032 842,43032843,43032844,43032845,43032846,43032847,43032848,43037854,43037855,430 37856,43037857,43039121,43041815,43041816,43041817,43041818,43041819,43041820,4 3041821,43041822,43042732,43042733,43042734,43042735,43042736,43042737,4304273 8,43042739,43042740,43042741,43042742,43042743,43042744,43042745,43042746,43042 747,43042748,43042749,43042750,43042751,43042752,43042753,43042754,43042755,430	

Concept	Concept IDs	Ontology
	42756,43042757,43042758,43042759,43043171,43043172,43043173,43043174,43043175,43043176,43043177,43043178,43135122,43135123,43137381,43137382,43137383,43137384,43137385,43137386,43137387,43137388,43141233,43142344,43142345,43142346,43142590,43142591,43142592,43142824,43143023,43143755,43143756,43148320,43148321,43148322,43148323,43153741,43153742,43154898,43157266,43159503,43159504,43159505,43159506,43159507,43159508,43163435,43164488,43164489,43164490,43164757,43164758,43164977,43170386,43170387,43170388,43170389,43170390,43170391,43170392,43170393,43170394,43170395,43174444,43174445,43175783,43175784,43176187,43176188,43176908,43176909,43181408,43181409,43181410,43181411,43181412,43181413,43181414,43186419,43186420,43186665,43186666,43186667,43186668,43186669,43187096,43187860,43190089,43192351,43192352,43192353,43192354,43192355,43192356,43192357,43192358,43192359,43196295,43196296,43197410,43197411,43197412,43197717,43197718,43197719,43197720,43198132,43201166,43203422,43203423,43203424,43203425,43203426,43203427,43203428,43207190,43208309,43208310,43208311,43208564,43208565,43208566,43208567,43208568,43208789,43208790,43208975,43208976,43214252,43214253,43214254,43214255,43214256,43214257,43214258,43218208,43219312,43219313,43219572,43219573,43219574,43219575,43219576,43219982,43219983,43219984,43220725,43220726,43220727,43220728,43258564,43259146,43263985,43263986,43263987,43264553,43269446,43269447,43275607,43277402,43280325,43280326,43280327,43285805,43285806,43285807,43285808,43291170,43291171,43291777,43296563,43296564,43296565,43296566,43296567,43515699,43518073,43518115,43592742,43592743,43594075,43606779,43606780,43608531,43610720,43612039,43622487,43624655,43644733,43644734,43646929,43647891,43647892,43647893,43647894,43648221,43661060,43680767,43684219,43696834,43698665,43698666,43702226,43714763,43715290,43716422,43716450,43730505,43734574,43737684,43738085,43748418,43750703,43750704,43752431,43752477,43752478,43766409,43768703,43770520,43773697,43774048,43784518,43786674,43786675,43786676,43788302,43788340,43788341,43802406,43802407,43806365,43806406,43809997,43820532,43824576,43842643,43856648,43860786,43864382,44027860,44033823,44045738,44046851,44046852,44046853,44049346,44050777,44054735,44057234,44060782,44062351,44062352,44063809,44069530,44072690,44073576,44076501,44079592,44087626,44087627,44087628,44087938,44092597,44098481,44099467,44099468,44100971,44102403,44105513,44108794,44111333,44113512,44113801,44113802,44118488,44118489,44118490,44118491,44119351,44123428,44124531,44126941,44158914,44160636,44160837,44162268,44162269,44166079,44166080,44168216,44173557,44173558,44173559,44174427,44177307,44177308,44177309,44177310,44178198,44179460,44181029,44181030,44183756,44184732,44184733,44188582,44188583,44188584,44189319,44189345,44189346,44189383,44189437,44189524,44189525,44189617,44189618,44189619,44189663,44189858,44189927,44189928,44189965,44190042,44190043,44190044,44190045,44190046,44190047,44190073,44190074,44190243,44190556,44190699,44190700,44190701,44190789,44190790,44190791,44202852,44203015,44785331,44785334,44785335,44785338,44785339,44785342,44785343,44785346,44785531,44785532,44785533,44785534,44785535,44785536,44785537,44785538,44785789,44785790,44785792,44785793,44785794,44785795,44785796,44785797,44785798,44785799	
6 minute walking test	606289,40766814	SNOMED, LOINC
Echocardiography	710016,724754,724755,724756,1074281,1389749,2211762,2211763,2211764,2313799,2313800,2313867,2313868,2313869,2313870,2313871,2313872,2313873,2313874,2313875,2313876,2313877,2313878,2313882,2313883,2313884,2313913,2313914,2313942,2616263,2616264,2616265,2616266,2616267,2616268,2616269,2616270,2616271,2616272,2722250,2785849,2785850,2785851,2785852,2785853,2785854,2785855,2785856,2786044,2786045,2786046,2786047,2786048,2786049,2786050,2786051,2786052,2786053,2786054,2786055,2786056,2786057,2786058,2786059,2786060,2786061,2786062,2786063,2786064,2786065,2786066,2786067,2786407,2786410,2786413,2786416,2786419,2786422,2786425,2786617,2786620,2786623,2786626,2786629,2786632,2786635,2786638,2786641,2787377,2787379,2787571,2787573,2787575,2787577,2787579,2787581,2787583,2787585,2787587,2787589,2787591,2787593,2787595,2787597,2788411,2788609,2788611,2788613,2788615,2788617,2788619,2788621,2788623,2788625,2788627,2788629,2788631,3654311,3654312,	CPT4, SNOMED

Concept	Concept IDs	Ontology
	4019824,4034866,4084945,4098215,4098216,4138036,4147613,4151632,4160720,4161943,4162102,4171076,4171199,4179324,4196155,4197265,4199054,4199235,4199240,4202441,4203365,4203445,4216774,4225363,4230911,4234778,4250325,4265040,4267123,4301377,4305021,4307818,4316729,4327260,4329506,4329659,4330376,4331514,4331964,4334807,4334808,4335824,4335825,36717088,37153802,37153961,37157721,37158860,37206167,37209048,37311809,37311810,40479237,40488479,40491498,40492792,42535579,43020942,43021423,43021737,43022021,43533197,44514109,44805202,44805203,44805204,44809812,45876598,46257454,46273020,46273033	
NT-proBNP	3029187,3029435,42529224,42529225,42870364,46236287,46236288	LOINC
WHO functional class	715984,715985,715986,715987,715988	OMOP Extension
Right heart catheterisation	1126194,1126195,1126200,1126201,1126202,1389750,1389751,2108060,2313897,2313898,2313899,2313900,4029340,4029805,4148375,4185904,4218124,4223626,4243461,4338609,4338617,40756947,40757025,44809593,45890619	HCPCS, SNOMED, CPT4
Cardiovascular MRI	801003,801004,1448037,2211575,2211577,2211579,2785839,2785840,2785841,2785842,2785843,2785844,2785845,2785846,2785847,4082987,4160417,4171885,4197200,4235230,4267435,4267450,4304124,4331941,4333065,4333355,35610681,40483388,42535250,42537414,42537586,42537911,42539284,42710004,42710005,42710006,42710007,42710008,42710009,42710010,42710011,43020548,43533272,43533322,43533323,43533344,43533345,43533346,44802640,44806116,45765754,45770555	CPT4, SNOMED, HCPCS, ICD10PCS

*Cardiac arrhythmia was classified as “cardiac arrhythmia overall” and further categorized into atrial flutter, atrial fibrillation, SVT (supraventricular tachycardia), VT (ventricular tachycardia), VF (ventricular fibrillation), sick sinus syndrome, and AV block

Annex IV: Algorithm for identifying monotherapies, combination therapies, and any treatment cohorts

Algorithm 1 Input definitions and overall workflow

```
# Construct drug eras from exposures for ERAs, PDE-5i, PRAs, and SGCs
cdm[[allTreatmentsTable]] ← getDrugEras(cdm, drugs, gapEra)

# Define treatment instructions to construct monotherapies and combination therapies. Inclusion rules correspond to individual drug (eras) participating in a combination. Exclusion rules correspond to combination therapies that are supersets: are constructed using all drugs (eras) needed to construct the new combination therapy or monotherapy.
treatmentInstructions ← list of treatment definitions:
    name: ERA+PDE-5i+PRA
    inclusion cohorts: [ERA drug eras, PDE-5i drug eras, PRA drug eras]
    exclusion cohorts: []
    name: ERA+PDE-5i
    inclusion cohorts: [ERA drug eras, PDE-5i drug eras]
    exclusion cohorts: [ERA+PDE-5i+PRA]
    name: PDE-5i+PRA
    inclusion cohorts: [PDE-5i drug eras, PRA drug eras]
    exclusion cohorts: [ERA+PDE-5i+PRA]
    name: ERA+SGC
    inclusion cohorts: [ERA drug eras, SGC drug eras]
    exclusion cohorts: []
    name: SGC monotherapy
    inclusion cohorts: [SGC drug eras]
    exclusion cohorts: [ERA+SGC]
    name: PRA monotherapy
    inclusion cohorts: [PRA drug eras]
    exclusion cohorts: [ERA+PDE-5i+PRA, PDE-5i+PRA]
    name: PDE-5i monotherapy
    inclusion cohorts: [PDE-5i drug eras]
    exclusion cohorts: [ERA+PDE-5i, PDE-5i+PRA, ERA+PDE-5i+PRA]
    name: ERA monotherapy
    inclusion cohorts: [ERA drug eras]
    exclusion cohorts: [ERA+PDE-5i, ERA+SGC, ERA+PDE-5i+PRA]
# Construct drug combinations and monotherapies
cdm ← generateCombinationDependentCohorts(cdm, treatmentInstructions, allTreatmentTable, minLength = 30 days)

# Construct cohort corresponding to individuals that are treated with any of the combinations and monotherapies
cdm ← getAnyTreatmentCohort(cdm , allTreatmentsTable, treatmentInstructions$names)

# Get percentage of treated (treatment-specific) and untreated individuals per time-window. A person is untreated in a window if no treatment is taken in that time-window. A person is considered treated with a specific treatment, if the treatment intesects the specific time-window.
results ← geCharacterizationResultsPerWindow(cdm, allTreatmentsTable, pahTable, windows)
```

Algorithm 2 Generate combination dependent cohorts

```
function GENERATECOMBINATIONDEPENDENTCOHORTS(cdm, treatmentInstructions, allTreatmentTable, minLength)
    for instruction in treatmentInstructions do
        Extract name, inclusionRules, and exclusionRules
        # Build inclusion cohort
        if more than one inclusionRules exists then
            Intersect these cohorts → inclusion cohort
        else
            Use single cohort → inclusion cohort
        if exclusionRules are not empty then
            if more than one exclusionRules exists then
                Unite these cohorts → exclusion cohort
            else
                Use single cohort → exclusion cohort
            # Apply exclusion logic
            Intersect inclusion and exclusion cohorts
            Keep cohort segments exclusive to the inclusion cohort
        # Remove artifacts
        Filter out resulting cohort entries with duration <= minLength
        # Save resulting cohort
        Name resulting cohort using name provided
        Append resulting cohort to allTreatmentTable
    return cdm
```

Algorithm 3 Construct cohort of individuals that are on any combination therapy or monotherapy

```
function GETANYTREATMENTCOHORT(cdm, allTreatmentsTable, monotherapiesAndCombinationsNamesList)
    Extract monotherapies and combination therapies from allTreatmentTable
    Unite all monotherapy and combination therapy into a single cohort
    Append resulting cohort to allTreatmentTable
    return cdm
```

ANNEX V: Glossary

Additional definitions are available in the EMA Glossary of terms https://www.ema.europa.eu/en/about-us/glossaries.

Aggregated Data

Data collected and combined from multiple sources to generate summary information, typically anonymised.

Benefit-Risk Assessment

Evaluation of the positive therapeutic effects of a medicine compared to its risks (e.g., side effects).

Common Data Model (CDM)

A standardized data structure that enables data from multiple sources to be harmonized, making analysis consistent and reproducible. DARWIN EU® utilises the OMOP CDM maintained by the OHDSI community.

Complex Studies (C3)

Studies requiring the development or customisation of specific study designs, protocols, and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data. Examples include etiological studies measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome in a defined population considering sources of bias, potential confounding factors, and effect modifiers.

Coordination Centre (CC)

The central hub responsible for managing and overseeing the activities within DARWIN EU®. It is based at Erasmus University Medical Centre in Rotterdam, the Netherlands.

Data Access

The process of obtaining permission to use specific datasets for regulatory or scientific studies.

Data Quality Framework

A set of standards and procedures to ensure accuracy, completeness, timeliness, and consistency of data used in DARWIN EU®.

Data Source

A database or repository of structured health-related data, such as electronic health records (EHRs), insurance claims, or registries.

DARWIN EU®

The European Medicines Agency's (EMA) federated network of real-world data sources designed to generate evidence to support regulatory decision-making.

EMA (European Medicines Agency)

The regulatory body responsible for the evaluation and supervision of medicinal products in the EU, overseeing DARWIN EU®.

Evidence Generation

The process of analysing real-world data to produce scientific information that can inform healthcare or regulatory decisions.

Federated Network

A data infrastructure where data remain at their original location but can be analysed in a harmonised way across multiple partners using a common model and tools.

GDPR (General Data Protection Regulation)

The EU regulation governing the protection of personal data and privacy, crucial to how DARWIN EU® handles health data.

Health Technology Assessment (HTA)

A systematic evaluation of properties and impacts of health technology, often using DARWIN EU® data to support assessments.

Metadata

Descriptive information about a data source (e.g., its content, quality, and structure), essential for identifying relevant databases in DARWIN EU® studies.

Off-the-Shelf Studies (OTS)

Studies for which a standard protocol per study/analysis type and standardised analytics may be developed and applied or adapted, typically relating to a descriptive research question. This includes studies on disease epidemiology, for example, the estimation of the prevalence or incidence of health outcomes in defined time periods and population groups, or drug utilisation studies at the population or patient level.

OHDSI (Observational Health Data Sciences and Informatics)

An open-science collaborative community that develops tools and standards (including the OMOP CDM) to enable large-scale analytics of observational health data. OHDSI provides the technical and scientific foundation for DARWIN EU®'s analytical ecosystem.

Patient-Level Data

Data related to individuals, de-identified, used for longitudinal or detailed analyses.

OMOP (Observational Medical Outcomes Partnership)

A common data model (CDM) that standardises the structure and content of observational healthcare data, enabling systematic analysis across disparate datasets. DARWIN EU® uses the OMOP CDM to ensure interoperability and consistency in real-world evidence generation.

Real-World Data (RWD)

Data relating to individual health status or healthcare delivery that is collected from routine clinical practice rather than from randomised controlled trials.

Real-World Evidence (RWE)

Clinical evidence derived from the analysis of RWD, used to inform decisions by regulators, payers, or clinicians.

Regulatory Decision-Making

The process by which authorities like EMA assess data to authorise, monitor, or modify the use of medicines in the EU.

Routine Repeated Studies (RR)

Studies that are either Off-the-Shelf or Complex studies repeated on a regular basis, following the same protocol and study code, but with updated data and/or different data partners.

Study Protocol

A detailed plan describing how a specific real-world study will be conducted, including objectives, design, data sources, and analyses.

Very Complex Studies (C4)

Studies which cannot rely only on electronic health care databases, or which would require complex methodological work, for example, due to the occurrence of events that cannot be defined by existing diagnosis codes, including events that do not yet have a diagnosis code, where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations. These studies might require the collection of data prospectively, or the inclusion of new (not previously onboarded) data sources.