Study Report

DARWIN EU® – Paracetamol prescribing and paracetamol overdose in Europe: a descriptive analysis of trends and patient characteristics

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Version 3.0

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Public

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Study title[1]	DARWIN EU® – Paracetamol prescribing and paracetamol overdose in Europe: a descriptive analysis of trends and patient characteristics
Study report version	V3.0
Date	01/10/2025
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Research question and objectives	The aim of the study is to provide an overview of paracetamol prescribing and paracetamol overdose in Europe, and to characterise patients presenting with paracetamol overdose. The specific objectives of the study are: 1. To examine the incidence/prevalence of paracetamol prescribing (overall, and by age, sex, formulation, and country/database) 2. To examine the incidence of paracetamol overdose (overall, and by age, sex, country/database) 3. To characterise patients with paracetamol overdose, in terms of comorbidities, co-prescribed medications, prior paracetamol prescription, and incidence of short-term complications and mortality.
Countries of study	Denmark, France, Germany, Norway, Spain, Sweden, The Netherlands
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[1] This is a routine repeated study from P3-C1-007 with EUPAS1000000329.

LIST OF ABBREVIATIONS

Acronyms/terms	Description
APHM	Assistance Publique – Hôpitaux de Marseille
CDM	Common Data Model
CI	Confidence interval
CDWBordeaux	Clinical Data Warehouse of Bordeaux University Hospital
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
DUS	Drug utilisation study
EHR	Electronic Health Record
EMA	European Medicines Agency
EU	European Union
FAERS	Food and Drug Administration Adverse Event Reporting System
GP	General Practitioner
GDPR	General Data Protection Regulation
HI-SPEED	Health Impact - Swedish Population Evidence Enabling Data-linkage
H12O	Hospital Universitario 12 de Octubre
ICD-10-GM	Classification of Diseases, version 10 in the German Modification
InGef RDB	InGef Research Database
IPCI	Integrated Primary Care Information
IQVIA DA	IQVIA Disease Analyzer
NAPQI	N-acetyl-p-benzoquinoneimine
NLHR	Norwegian Linked Health Registry data
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OTC	Over The Counter
PY	Person-year
SCIFI-PEARL	Swedish COVID-19 Investigation for Future Insights - a Population Epidemiology Approach using Register Linkage
SHI	Statutory Health Insurance
SNOMED	Systematized Nomenclature of Medicine
UK	United Kingdom
WHO	World Health Organization

1. TITLE

DARWIN EU® - Paracetamol prescribing and paracetamol overdose in Europe: a descriptive analysis of trends and patient characteristics

2. DESCRIPTION OF STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Berta Raventós Talita Duarte-Salles	Erasmus MC
Data Scientist	Ger Inberg Cesar Barboza Maarten van Kessel Adam Black Ioanna Nika Ross Williams	Erasmus MC
Epidemiologist	Nicholas Hunt Guido van Leeuwen Melissa Leung*	Erasmus MC
Study Manager	Natasha Yefimenko	Erasmus MC
Data Partner**	**Names**	**Organisation**
DK-DHR	Claus Møldrup Elvira Bräuner Susanne Bruun	Danish Medicines Agency (DKMA)
APHM	Laurent Boyer Dorian Grousset	Assistance Publique – Hôpitaux de Marseille
InGef RDB	Raeleesha Norris Annika Vivirito Josephine Jacob Alexander Harms	InGef - Institut für angewandte Gesundheitsforschung Berlin GmbH
IPCI	Katia Verhamme Ger Inberg	Erasmus MC
NLHR	Saeed Hayati Nhung Trinh Hedvig Nordeng Maren Mackenzie Olson	University of Oslo
H12O	Juan Luis Cruz Bermudez Noelia Garcia Barrio Javier de la Cruz Paula Rubio Mayo	Fundación Investigación Biomédica Hospital 12 de Octubre

HI-SPEED	Huiqi Li Fredrik Nyberg Rickard Ljung Nicklas Pihlström	University of Gothenburg Swedish MPA

*Included in the study team on the 18th July 2025.
**Data partners do not have an investigator role. Data partners execute code at their data source and approve their results.

3. ABSTRACT

Title

DARWIN EU® – Paracetamol prescribing and paracetamol overdose in Europe: a descriptive analysis of trends and patient characteristics.

Rationale and background

Paracetamol (acetaminophen) is one of the most common causes of drug poisonings and can result in severe hepatic failure. Different regulatory interventions at national level have occurred to reduce the incidence of paracetamol overdose, but it is uncertain how paracetamol is prescribed across Europe and to what extent prescription may be involved in poisonings.

Research question and objectives

The aim of the study was to provide an overview of paracetamol prescribing and paracetamol overdose trends in selected European databases, and to characterise patients presenting with paracetamol overdose.

The specific objectives of the study were:

1. To examine the incidence/prevalence of paracetamol prescribing (overall, and by age, sex, formulation, and country/database).
2. To examine the incidence of paracetamol overdose (overall, and by age, sex, country/database).
3. To characterise patients with paracetamol overdose, in terms of comorbidities, co-prescribed medications, prior paracetamol prescription, and incidence of short-term complications and mortality.

Methods

Study design

Cohort studies comprising of:

1. Population-level drug utilisation study to assess incidence and prevalence of paracetamol prescribing (objective 1)
2. Population-level descriptive epidemiology study to estimate the incidence of paracetamol overdose (objective 2)
3. Patient-level characterisation study to characterise patients with a paracetamol overdose (objective 3)

Population

For objective 1 and 2, the study population comprised all individuals present in the database at any time from 1st January 2010 to 31st December 2023. For objective 3, the study population comprised individuals with paracetamol overdose for the first time in their patient history during the study period.

For incidence calculations (objective 1 and 2), individuals with a record of the outcome re-entered the study after a washout window so that multiple occurrences of the outcome could be captured. This washout window was 60 days following the end of the prescribed treatment for paracetamol prescribing and 365 days for paracetamol overdose. For objective 3, individuals with a prior history of paracetamol overdose any time prior to index date were excluded.

A year of observation history prior to index date was required for all individuals within selected databases. Individuals aged less than 1 year were excluded.

Variables

Drug of interest: Paracetamol.

Condition of interest: Paracetamol overdose.

Sample size

No sample size was calculated.

Data sources

1. Denmark, Danish Data Health Registries (DK-DHR)
2. France, Assistance Publique - Hôpitaux de Marseille (APHM)
3. Germany, InGef Research Database (InGef RDB)
4. The Netherlands, Integrated Primary Care Information (IPCI)
5. Norway, Norwegian Linked Health Registry data (NLHR)
6. Spain, Hospital Universitario 12 de Octubre (H12O)
7. Sweden, Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)

Statistical analysis

Objective 1 was conducted in all databases except for DK-DHR. Objectives 2 and 3 were conducted in DK-DHR, APHM, InGef RDB, and HI-SPEED.

Population-level drug utilisation study (objective 1): Incidence rates and period prevalence of paracetamol prescribing were calculated overall and stratified by sex, age, and formulation. Estimates were calculated overall and by calendar year.

Population-level descriptive epidemiology (objective 2): Incidence rates of paracetamol overdose were calculated overall and stratified by sex, age, and study period. Estimates were calculated overall and by calendar year.

Patient-level characterisation (objective 3): Characteristics were described using large-scale characterisation. Prespecified comorbidities and concomitant medications, prior paracetamol prescriptions, short-term complications, and mortality were also described. Results were stratified by sex and age groups. Covariates of interest were also reported as counts and proportions.

For all analyses, results were reported by country/database. A sensitivity analysis excluding the prior observation requirement was conducted. Any counts smaller than 5 were obscured to ensure privacy and confidentiality.

Results

Incidence per 100,000 person-years (PY) of paracetamol prescribing ranged between 2,166 in InGef RDB and 20,340 in NLHR. Prevalence ranged from 8.8% in InGef RDB to 36.9% in NLHR for the entire study period.

Incidence rates were higher among females than males across all databases, except for APHM, InGef RDB, and H12O, where estimates were similar by sex. Rates increased with age in all databases, except for InGef RDB, where the highest rates were observed among children aged 1 to 5 and 6 to 11 years. Oral tablet formulations were generally the most prescribed, although variations by age groups and healthcare settings existed. Prevalence results stratified by age, sex, and formulation aligned with those observed for incidence rates.

Incidence of paracetamol overdose per 100,000 PY was 31 (95% CI 31 to 31) in DK-DHR, 13 (12 to 15) in APHM, 2 (2 to 2) in InGef RDB, and 3 (2 to 3) in HI-SPEED. Incidence rates among females were 2–4 times larger than those observed for males. Individuals aged 1–17 years had higher incidence rates than those aged 18 or older in all databases, except for HI-SPEED, where no differences between these two age groups were observed.

Individuals with paracetamol overdose had a median age ranging from 21 to 32 years depending on the database and were predominantly females. Most frequently recorded baseline conditions included pain, anxiety disorders, and depressive disorders. In all databases except for APHM, approximately 30% had a depressive disorder or were prescribed antidepressants in the year leading up to a month prior to paracetamol overdose. Paracetamol ranked as the most prescribed ingredient in all databases, except for InGef RDB. In the month prior to paracetamol overdose, the proportion of individuals prescribed paracetamol were 1.6% in InGef RDB, 1.9% in APHM, 17.8% in HI-SPEED, and 16.3% in DK-DHR.

In the month following the paracetamol overdose, diagnoses indicating hepatic toxicity were observed in up to 12.0% of cases and renal toxicity in up to 4.2% of cases. All-cause mortality in the following 30 days was assessed in all databases, except for HI-SPEED, and was observed in >5 individuals in only DK-DHR, affecting 1.0% of paracetamol overdose cases.

Conclusion

Incidence and prevalence of paracetamol prescribing increased with age. Paracetamol overdose was most frequently observed in females and younger individuals, many of whom had a history of mental health conditions. Paracetamol prescribing in the month preceding paracetamol overdose varied between 1.6% and 17.8%. Hepatic toxicity was observed in less than 12% of overdose cases in the 30 days after paracetamol overdose. All-cause mortality was rare and affected less than 1.0% of cases.

These findings are consistent with those reported in the earlier DARWIN EU® study (EUPAS1000000329), strengthening the evidence base on prescribing and overdose patterns in Europe.

4. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or Update	Reason
1	13/05/2025	n/a	Update from initial study protocol P3-C1-007 (EUPAS1000000329)	This is a routine repeated study.

Comparison with previous protocols:

Study deliverables	P3-C1-007 (EUPAS1000000329)	P4-C2-002 (current study protocol)
Study period	2010-2023	2010-2023
Data partners:[1]		
- NAJS [Croatia]	X (Objective 1)	
- DK-DHR [Denmark]	X (Objective 1)	X (Objectives 2 and 3)
- APHM [France]		X
- CDWBordeaux [France]	X (Objective 3)	
- InGef RDB [Germany]		X
- IQVIA DA Germany [Germany]	X (Objective 1)	
- IPCI [The Netherlands]		X (Objective 1)
- NLHR [Norway]		X (Objective 1)
- EMBD-ULSEDV [Portugal]	X (Objective 1)	
- BIFAP [Spain]	X	
- H12O [Spain]		X (Objective 1)
- HI-SPEED [Sweden]		X
- CPRD GOLD [United Kingdom]	X	
- UKBB [United Kingdom]	X	
Reference study protocol	n/a	P3-C1-007 (EUPAS1000000329)
Changes from reference study protocol	n/a	Sensitivity analysis: remove the inclusion criteria of one year of prior database history analysis.

[1] Some data partners have been included to participate in specific objectives, which are noted in brackets.

5. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Final Study Protocol	May 2025	May 2025
Creation of Analytical code	May/June 2025	June 2025
Execution of Analytical Code on the data	June 2025	June 2025
Draft Study Report	July/August 2025	July 2025
Final Study Report	August 2025	August 2025
Draft Manuscript (if agreed on)	TBC	TBC
Final Manuscript (if agreed on)	TBC	TBC

6. RATIONALE AND BACKGROUND

Paracetamol (acetaminophen) is one of the most widely used medicines worldwide and is listed as an essential medicine by the World Health Organisation (WHO).(1) It has mild analgesic and antipyretic properties, and it is generally used to treat fever and pain. Paracetamol is readily available over the counter (OTC) in European countries, and in some countries it is available through non-pharmacy outlets.(2)

Paracetamol can be found in different pharmaceutical forms and in different doses. The usual dose recommended for an adult is 500mg to 1000mg, with a maximum daily dose of 3000 to 4000mg.(3) Preparations can include paracetamol alone or in combination with other substances, such as non-steroidal anti-inflammatory drugs or opioids, and it can be found in immediate release (short-acting) and modified release (long-acting) forms in some countries. Products containing modified-release paracetamol are no longer available in the EU, following a European Medicines Agency (EMA) recommendation to suspend the marketing of these products in December 2017.(4)

Paracetamol is generally considered safe when administered in appropriate doses and for short periods of time.(5) However, toxicity is common following paracetamol overdose, and it can result in severe hepatic failure. Inadvertent overdose can be the result of taking additional doses, repeated supratherapeutic ingestion, and duplication of therapy.

Paracetamol is principally metabolised by glucuronidation and sulfation.(6) Small amounts are converted into the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI), which is detoxified via conjugation with glutathione. Toxicity leads to overdose when there is insufficient glutathione available for conjugation of NAPQI, which may lead to hepatotoxicity and acute kidney injury.

Hepatotoxicity following paracetamol overdose usually results from massive overdoses (>30g/day), overdose with modified-release paracetamol, and delays to treatment. Additional risk factors include treatment with medications that induce the activity of the cytochrome CYP2E1 (e.g., carbamazepine, isoniazid), glutathione depletion (e.g., in individuals with malnutrition or anorexia), and chronic alcohol use.(7) Individuals with chronic liver disease are also at increased risk for hepatoxicity.(8) N-acetylcysteine is the most widely used antidote for paracetamol overdose. It works by replenishing cysteine, a rate-limiting factor for glutathione synthesis, which is essential for detoxification of NAPQI. The risk of developing hepatotoxicity is substantially reduced if treatment is initiated within 8 hours of ingestion.(9, 10) Severe cases may require liver transplantation or result in death.(11)

Paracetamol is one of the most common causes of drug poisonings, and it is one of the most common OTC analgesics used in suicidal overdoses. Based on available data, it has been estimated that paracetamol is involved in 6% of all global poisonings, 56% of cases of severe acute liver injury and acute liver failure, and

7% of drug-induced liver injuries, of which 0.4% are fatal cases.(12) Different regulatory interventions at national level have occurred over many years aimed at reducing the incidence of overdose, such as restriction in pack size and the total amount available to purchase OTC. However, it is uncertain how paracetamol is being prescribed across Europe and to what extent prescription of paracetamol is involved in paracetamol poisonings.

This present study builds on a previous DARWIN EU® study (EUPAS1000000329), which was informed by 8 databases from 7 European countries (Croatia, Denmark, France, Germany, Portugal, The Netherlands, Spain, and the United Kingdom [UK]). The objectives related to paracetamol overdose were informed by four databases, including data from France, Spain, and two databases from the UK. In this study, incidence rates of paracetamol prescribing per 100,000 PY ranged between 1,578 to 12,686, while prevalence ranged from 5.2% to 65.1%. In general, females exhibited higher figures than males, with values increasing with age. Incidence of paracetamol overdose ranged between 2 to 5 per 100,000 PY in primary care databases covering all ages, with higher rates observed in the 1 to 17 age group compared to older individuals, especially among females. Most individuals with paracetamol overdose were female, with a median age between 21 and 25 years, and many had a prior history of mental disorders (e.g. 14% to 42.4% had a prior history of depressive disorders). In the month prior, 2.1% to 16.7% had a prior prescription of paracetamol. In the month following paracetamol overdose, hepatic toxicity occurred in approximately <11% of cases and mortality in <1.5%.

This study replicates the earlier DARWIN EU® study to extend the evidence base on this topic, as well as expanding the geographical coverage and diversity across healthcare settings in Europe.

7. RESEARCH QUESTION AND OBJECTIVES

The aim of the study was to provide an overview of paracetamol prescribing and paracetamol overdose in the selected European databases, and to characterise patients presenting with paracetamol overdose.

The specific objectives of the study were:

1. To examine the incidence/prevalence of paracetamol prescribing (overall, and by age, sex, formulation, and country/database).
2. To examine the incidence of paracetamol overdose (overall, and by age, sex, country/database).
3. To characterise patients with paracetamol overdose, in terms of comorbidities, co-prescribed medications, prior paracetamol prescription, and incidence of short-term complications and mortality.

A description of the proposed objectives achieved in the study is described in **Table 1**. This study was built upon a previous DARWIN EU® study (EUPAS1000000329), and was based on the same protocol with updated data and different data partners, with the exception of an additional sensitivity analysis, described in more detail in **8.9.4 Sensitivity analysis**.

Table 1. Primary and secondary research questions and objectives.

A. Primary research question and objective.

Objective:	Objective 1: To examine the incidence/prevalence of paracetamol prescribing Objective 2: To examine the incidence of paracetamol overdose Objective 3: To characterise patients with paracetamol overdose
Hypothesis:	n/a

Population:	Objective 1 and 2: Overall population Objective 3: Patients with paracetamol overdose
Exposure:	n/a
Comparator:	n/a
Outcome:	Objective 1: Paracetamol prescription Objective 2: Paracetamol overdose Objective 3: n/a
Time (when follow up begins and ends):	2010–2023
Setting:	Routinely collected data from 7 databases in 7 European countries.
Main measure of effect:	Proportions, incidence, and prevalence

8. RESEARCH METHODS

8.1. Study type and study design

Retrospective cohort studies were conducted using routinely collected health data from 7 databases. The study comprised:

1. A population-level drug utilisation study (DUS) to assess incidence/prevalence of paracetamol prescribing among the general population (objective 1).
2. A population-level descriptive epidemiology study to assess incidence of paracetamol overdose among the general population (objective 2).
3. A patient-level characterisation to characterise patients with a paracetamol overdose (objective 3).

8.2. Study setting and data sources

This study was conducted using routinely collected data from 7 databases in 7 European countries selected from the DARWIN EU® Database Catalogue. All databases were previously mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

The selection process was based on the size of the databases, the number of individuals with the outcome of interest, geographical spread, and diversity of healthcare settings. The selection process primarily focused on databases that were recently incorporated to the DARWIN EU® network and were not part of the previous study (EUPAS1000000329), which included 8 databases from 7 countries (Croatia, Denmark, France, Germany, Portugal, Spain, United Kingdom). Databases participating in the previous study which were not involved in objectives related to paracetamol overdose (objective 2 and 3) were also considered if refined mappings for paracetamol overdose were available.

Based on the feasibility assessment performed, these databases were considered fit for purpose for at least part of the objectives of this study:

1. Denmark, Danish Data Health Registries (DK-DHR)
2. France, Assistance Publique - Hôpitaux de Marseille (APHM)
3. Germany, InGef Research Database (InGef RDB)
4. The Netherlands, Integrated Primary Care Information (IPCI)

5. Norway, Norwegian Linked Health Registry data (NLHR)
6. Spain, Hospital Universitario 12 de Octubre (H12O)
7. Sweden, Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)

Information on data sources with a justification for their choice in terms of ability to capture the relevant data is described in **Table 2**. While some databases include data extending beyond December 2023, the study data was restricted to this time point to ensure comparability with the previous study.

All databases, except DK-DHR, were used to inform objective 1. Objectives 2 and 3 were informed by only APHM, DK-DHR, InGef RDB, and HI-SPEED, due to limited counts for paracetamol overdose observed in the study feasibility assessment for other databases. DK-DHR was not considered for Objective 1, as results for this objective were already provided in the previous study (EUPAS1000000329). DK-DHR participated in the current study to support objectives 2 and 3, as refinements in the mapping process enabled the detection of paracetamol poisoning cases.

Table 21. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects[1]	Data lock for the last update	Calendar period covered by each data source[2]
Denmark	DK-DHR	Contribute to the diversity of data sources in terms of geography and healthcare settings. Observed records of individuals with paracetamol overdose.	Hospital care (IP, OP)	EHRs, registries, others.	5,984,000	2025–1–18	2010–2023
France	APHM	Contribute to the diversity of data sources in terms of geography and healthcare settings. Observed records of individuals with paracetamol overdose.	Hospital care (IP, OP)	Claims, EHRs, registries, biobank	249,900	2025–01–11	2014–2023
Germany	InGef RDB	Contribute to the diversity of data sources in terms of geography and healthcare settings. Observed records of individuals with paracetamol overdose.	Primary care, hospital care (IP, OP)	Claims	7,658,400	2024–11–24	2015–2023
Netherlands	IPCI	Contribute to the diversity of data sources in terms of geography and healthcare settings (Objective 1 only).	Primary care	EHRs	1,247,900	2024–10–21	2010–2023
Norway	NLHR	Provide data with nation-wide coverage. Contribute to the diversity of data sources in terms of geography and healthcare settings (Objective 1 only).	Primary care, hospital care (IP, OP)	Registries	5,500,000	2024–10–29	2018–2023
Spain	H12O	Contribute to the diversity of data sources in terms of geography and healthcare settings (Objective 1 only).	Hospital care (IP, OP)	EHRs, registries	294,500	2024–09–16	2010–2023

Sweden	HI-SPEED	Provide data with nation-wide coverage. Contribute to the diversity of data sources in terms of geography and healthcare settings. Observed records of individuals with paracetamol overdose.	Primary care[2], hospital care (OP, IP)	Registries	10,563,700	2024–09–10	2015–2023

APHM=Assistance Publique - Hôpitaux de Marseille; DK-DHR=Danish Data Health Registries; EHR=Electronic Health Record; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage; InGef RDB=InGef Research Database; IP=inpatient; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; OP=outpatient.

[1] Defined as the maximum number of individuals in observation in the last 6 months of data.

[2] Primary care data is only available for 40% of the population.

Denmark, Danish Data Health Registries (DK-DHR)

Danish health data is collected, stored, and managed in national health registers at the Danish Health Data Authority and covers the entire population which makes it possible to study the development of diseases and their treatment over time. There are no gaps in terms of gender, age, and geography in Danish health data due to mandatory reporting on all patients from cradle to grave, in all hospitals and medical clinics. Personal identification numbers enable linking of data across registers, so it captures data on all Danes throughout their lives, regardless of whether they have moved around the country. High data quality due to standardisation, digitisation and documentation means that Danish health data is not based on interpretation. The Danish Health Data Authority is responsible for the national health registers and for maintaining and developing standards and classifications in the Danish healthcare system. Legislation ensures balance between personal data protection and use. The current data release includes data on the entire Danish population of 5.9 million persons from 1995. It includes data from the following registries: The Central Person Registry, The National Patient Registry, The Register of Pharmaceutical Sales, The National Cancer Register, The Cause of Death registry, The Laboratory Database including Coronavirus disease 2019 test results and The Vaccination Registry (including COVID-19 vaccinations.

France, Assistance Publique – Hôpitaux de Marseille (APHM)

The APHM database includes all hospital stays across various care settings—acute care, psychiatric care, rehabilitation care, and home hospitalisation—capturing approximately 300,000 stays annually. In the source data, diagnoses are coded using International Classification of Diseases, version 10 (ICD-10). Drugs, procedures, and measurements are recorded using terminologies in line with the French DRG system, managed via the CORA software. The APHM database also captures comprehensive drug prescription and administration data, including UCD drug codes, Anatomical Therapeutic Chemical classifications, quantities, and dosages, managed through PHARMA software. Additionally, medical, and paramedical notes, such as hospitalisation reports, radiology, endoscopy, and consultation summaries, are recorded using AXIGATE software. Laboratory data, covering both prescriptions and test results, is also included.

Germany, InGef Research Database (InGef RDB)

The InGef database comprises anonymised longitudinal claims data of about 10 million individuals across more than 50 statutory health insurance providers (SHIs) throughout Germany. Data are longitudinally linked over a period of currently ten years. Patients can be traced across health care sectors. All patient-level and provider-level data in the InGef research database are anonymised to comply with German data protection regulations and German federal law. German SHI claims data available in the InGef database includes information on demographics (quarter and year of birth, gender, death date if applicable, region of residence on administrative district level); hospitalisations; outpatient services (diagnoses, treatments; specialities of physicians); dispensing of drugs; dispensing of remedies and aids; and sick leave and sickness allowance times. In addition, costs or cost estimates from SHI perspective are available for all important cost elements. All diagnoses in Germany are coded using the International Classification of Diseases, version 10 in the German Modification (ICD-10-GM). The persistence (membership over time) is rather high in the InGef database. During a time period of 5 years (2009 to 2013), 70.6% of insurance members survived and remained insured with the same SHI without any gap in their observational time. Persons leaving one of the participating SHIs and entering another participating SHI, can be linked during yearly database consistency updates and are thus not lost over time. The InGef database is dynamic in nature, i.e., claims data are updated in an ongoing process and new SHIs may join or leave the database. By law, only the last 10 years of data are allowed to be used. At every new release this window shifts, dropping older data and adding new data.

The Netherlands, Integrated Primary Care Information (IPCI)

The IPCI database is a longitudinal observational database containing routinely collected data from computer-based patient records of a selected group of General Practitioners (GP) throughout the Netherlands (N=723). IPCI was started in 1992 by the department of Medical Informatics of the Erasmus University Medical Center in Rotterdam with the objective to enable better post marketing surveillance of drugs. The current database includes patient records from 2006 on, when the size of the database started to increase significantly. In 2016, IPCI was certified as Regional Data Center. Since 2019 the data is also standardised to the OMOP CDM enabling collaborative research in a large network of databases within the Observational Health Data Sciences and Informatics (OHDSI) community. The primary goal of IPCI is to enable medical research. In addition, reports are generated to inform GPs and their organizations about the provided care. Contributing GPs are encouraged to use this information for their internal quality evaluation. The IPCI database is registered on the European Medicines Agency (EMA) ENCePP resources database (http://www.encepp.eu).

Norway, Norwegian Linked Health Registry data (NLHR)

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. 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. We harmonised data from the following registries: the Medical Birth Registry of Norway (i.e., pregnancy-related data), the Norwegian Prescription Registry (i.e., medications dispensed outside of hospitals), the Norwegian Patient Registry (i.e., data on diagnosis recorded in secondary care), Norway Control and Payment of Health Reimbursement (i.e., primary care data), the Norwegian Surveillance System for Communicable Diseases (i.e., data on test results of communicable diseases), the Norwegian Immunisation Registry (i.e., data on vaccination), the National Death Registry, and the National Registry. Linkage between the registries was facilitated using project-specific person ID generated from unique personal identification assigned at birth or immigration for all legal residents in Norway.

Spain, Hospital Universitario 12 de Octubre (H12O)

The H12O data source includes hospital data from a wide range of health-related information across various domains, including laboratory results, prescriptions, treatments, administrative details, and diagnoses. Additionally, data is gathered from other systems, such as the Pathological Anatomy system, which provides insights into sample analyses, and the cost system, which tracks the expenses associated with patient interactions at the hospital. Efforts are currently underway to integrate further data sources, including radiological information and Patient-Reported Outcome Measures.

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

The HI-SPEED study is a nationwide linked multi-register, regularly updated, observational study for timely response over time to scientific questions around effectiveness and safety of approved drugs that can arise suddenly, requiring rapid evidence for timely regulatory action - to protect patients' health and lives. The study data covers the whole Swedish population (about 10 million), with data on specialist care (National Patient Register), drug use (Prescribed Drug Register), cause of death (Cause-of-Death Register), sociodemographic data, and selected clinical data. Primary care visit diagnoses and procedures are available for 40% of the population (two largest Swedish regions). Most data start from 2015; prescription drug data on all prescriptions filled nationally are available from 2018. The study population and all data are updated quarter-yearly. HI-SPEED builds on the predecessor project “Swedish COVID-19 Investigation for Future Insights - a Population Epidemiology Approach using Register Linkage” (SCIFI-PEARL) that was

initiated in 2020 to conduct research on Covid-19 and pandemic-relations (https://www.gu.se/en/research/scifi-pearl).

8.3. Study period

The study spanned from 1st January 2010 to 31st December 2023. For objectives 1 and 2, incidence and prevalence were only calculated for complete calendar years observed in the database (e.g., if the end of available data was 1st June 2023, only data up to 31st December 2022 was considered).

For databases with incomplete coverage for the entire study period, the study period differed and was defined based on data availability. This affected APHM (2014–2023), InGef RDB (2015–2023), and NLHR (2018–2023). For HI- SPEED, the study period differed across objectives, starting in 2018 (start of prescription data) for objective 1, and 2015 (start of data availability on paracetamol overdose) for objectives 2 and 3.

8.4. Follow-up

Study participants were followed up from index date (see **Table 3**). For objectives 1 and 2, index date was defined as the latest of: study start date (1st January 2010, or start of data availability if later), or date at which they had one year of prior history. Individuals were followed up until the earliest date of any of the following events: study end (31st December 2023 or last complete calendar year), end of data availability (end of the last year with complete observation in the database for objectives 1 and 2), loss to follow-up, or date of death.

For the incidence calculations of objective 1 and 2, individuals did not contribute time to the study during a certain amount of time after the occurrence of the event. For objective 1, individuals with a paracetamol prescription did not contribute time to the study during the 60 days after the end of treatment. For objective 2, individuals with a paracetamol overdose did not contribute time to the study during the 365 days following the diagnosis of this event. For objective 3, we only considered first-ever events (i.e., individuals diagnosed with a paracetamol overdose for the first time, with this event taking place during the study period). For this objective, index date was defined as the date of paracetamol overdose.

Table 32. Operational definition of time 0 (index date) and other primary time anchors.

Study population names	Time Anchor Description (e.g. time 0, index date)	Number of entries[1]	Type of entry	Washout window	Care Setting	Code Type	Position[2]	Incident with respect to…
General population (objective 1)	Study entry date	Multiple entry	Incident, prevalent	[-60, -1]	IP, OP, OT	SNOMED	Any	Paracetamol prescribing
General population (objective 2)	Study entry date	Multiple entry	Incident	[-365, -1]	IP, OP, OT	SNOMED	Any	Paracetamol overdose
Individuals with paracetamol overdose (objective 3)	Date of paracetamol overdose	Single entry	Incident	[-Inf, -1]	IP, OP, OT	SNOMED	Any	Paracetamol overdose

Inf=any time prior; IP=inpatient; OP=outpatient; OT=other; SNOMED=Systematized Nomenclature of Medicine.
[1] To indicate whether individuals are allowed to enter the study population only once or multiple times
[2] To indicate whether diagnosis codes are required to be in the primary position (main reason for encounter)

8.5. Study population with inclusion and exclusion criteria

The source population comprised all individuals present in the database at any time during the period from 1st January 2010 to 31st December 2023 (or the last year with complete observation). All study participants were required to have at least 365 days of data visibility prior to index date. Therefore, children aged <1 year were excluded.

The operational definitions of the inclusion and exclusion criteria are presented by means of **Table 4** and **Table 5**, respectively.

Table 43. Operational definitions of inclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings	Applied to study populations:
Observation period during the study period	All individuals who were present in the selected databases during the period 01/01/2010–31/12/2023 (or last available date, if earlier)	After	n/a	IP, OP, OT	All study populations
Prior database history	Study participants were required to have 365 days of prior history observed before contributing observation time	Prior	[-365, 0]	OP	All study populations

IP=inpatient; n/a=not applicable; OP=outpatient; OT=other.

Table 54. Operational definitions of exclusion criteria.

Criterion	Details	Order of application	Assessment window [1]	Care Settings[2]	Applied to study populations:
Washout window for paracetamol prescribing	Individuals newly prescribed with paracetamol but with a previous prescription of paracetamol were not allowed to contribute time at risk during the 60 after the end of the prescription.	Prior	[-60, -1]	IP, OP, OT	General population (objective 1)
Washout window for paracetamol overdose (incidence)	Individuals with previous history of paracetamol overdose were not allowed to contribute time at risk during the 365 days after the paracetamol overdose diagnosis.	Prior	[-365, -1]	IP, OP, PT	General population (objective 2)
Washout window for paracetamol overdose (characterisation)	Individuals with previous history of paracetamol overdose any time prior index date were excluded.	Prior	[-Inf, -1]	IP, OP, OT	Individuals with paracetamol overdose (objective 3)

Inf=any time prior; IP=inpatient; n/a=not applicable; OP=outpatient; OT=other.

8.6. Variables

8.6.1. Exposures

This study has no exposure of interest.

8.6.2. Outcomes

The operational definition of the outcomes is presented in **Table 6**. It includes paracetamol prescribing (Objective 1) and paracetamol overdose (Objective 2).

The use of paracetamol was derived from prescription data, when available. In databases lacking prescription data, dispensation records were used. For consistency, all drug exposure data were referred to as prescriptions in this report.

For paracetamol prescribing, successive individual drug records (i.e., drug exposures) separated by less than 30 days were considered as the same continuous exposure (i.e., drug era). To calculate incidence rates, multiple exposures (i.e., single or continuous) to paracetamol prescribing were treated as separate outcomes after a washout window of 60 days following the end of the prescribed treatment. For paracetamol overdose, this window was defined as 365 days.

Concept lists used to define paracetamol and paracetamol overdose can be found in **Table S1** and **Table S2** in **Annex II**.

Table 65. Operational definitions of outcome.

Outcome name	Details	Primary outcome ?	Type of outcome	Washout window	Care Settings	Code Type	Diagnosis Position[1]	Applied to study populations
Paracetamol prescribing	A drug record of a paracetamol-containing product	Yes	Count	[-60, -1]	IP, OP, OT	RxNorm	n/a	General population (objective 1)
Paracetamol overdose	A diagnosis of paracetamol overdose or poisoning	Yes	Count	[-365, -1]	IP, OP, OT	SNOMED	Any	General population (objective 2)

Inf=any time prior; IP=inpatient; n/a=not applicable; OP=outpatient; OT=other; SNOMED=Systematized Nomenclature of Medicine.
[1] To indicate whether a diagnosis code is required to be in the primary position (main reason for encounter)

8.6.3. Other covariates

The operational definitions of the covariates included in this study are described in **Table 7**.

Population-level DUS on paracetamol prescribing (objective 1):

The covariates for stratification on the population-level DUS included sex, age groups, and formulation. Age groups were: 1–5; 6–11; 12–17; 18–29; and subsequent 10-year age bands (30–39, 40–49, etc.), up to ≥80 years. Formulations included oral tablets, capsules, oral liquid formulations, injectable liquid formulations, and rectal suppositories. Dose forms used to identify formulations are included in **Table S3** in **Annex II**.

Population-level descriptive epidemiology study on paracetamol overdose (objective 2):

The covariates for stratification on the population-level descriptive epidemiology study included sex and age groups (1–17; 18–49; 50–79; ≥80). Given the low preliminary counts for paracetamol overdose, a broader age category was also considered (1–17; >18).

Patient-level characterisation of patients with paracetamol overdose (objective 3):

For the patient-level characterisation study, covariates included sex, age groups (narrow: 1–17; 18–49; 50–79; ≥80; broad: 1–17; >18), comorbidities, concomitant medications, short-term complications of paracetamol overdose, and mortality. If the number of cases allows, this analysis will be stratified by study period (2010–2016; 2017–2023).

Characteristics were assessed using prespecified comorbidities and medications, and by means of large-scale characterisation. Comorbidities were assessed any time prior to 1 day before index date and 365 days prior to 1 day before index date. Concomitant medications were assessed 365 days prior to 31 days before index and 30 days prior to 1 day before index date. Short-term complications were assessed 0 to 30 days after index date. These included hepatic and renal toxicity. Mortality was assessed 0 to 30 days and 31 to 365 days after index date.

Prespecified conditions included alcoholism, chronic kidney disease, chronic liver disease, depression, anxiety, schizophrenia, obesity, cancer, arthrosis and arthritis, pain, fever, and infectious diseases. Prespecified conditions were assessed using the same windows as those applied for large-scale characterisation, with a few exceptions. Fever and infectious diseases were assessed from 30 days prior to 1 day before index date. For pain, this time window was also applied in addition to those used for large-scale characterisation.

Prespecified medications included enzyme-inducing medications (e.g., carbamazepine, isoniazid) and medications found in concomitant overdosing, such as benzodiazepines, opioid analgesics, nonsteroid anti-inflammatory drugs, antipsychotics, and antidepressants.(13) Prior paracetamol prescribing was also of interest and was described 365 days prior to 31 days before index date, and 30 days prior to 1 day before index date. The same assessment window was applied for prespecified medications.

A list of concept sets for pre-specified conditions, short-term complications, and medications are detailed in **Annex II** (**Table S4** - **Table S7**).

Table 76. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings	Code Type	Diagnosis Position[1]	Applied to study populations
Sex	Female, Male	Categorical	0	n/a	n/a	n/a	All
Age groups	Objective 1: 1–5; 6–11; 12–17; 18–29; 10–year bands. Objective 2 and 3: Narrow: 1–17; 18–49; 50–79; ≥80; Broad: 1–17; >18.	Categorical	0	n/a	n/a	n/a	All
Comorbidities	Large scale characterisation and prespecified conditions[2]	Binary	[-Inf, -1], [-365,-1]	IP, OP, OT	SNOMED	Any	Individuals with paracetamol overdose

	Fever, infectious diseases, and pain	Binary	[-30,-1]	IP, OP, OT	SNOMED	Any	Individuals with paracetamol overdose
Concomitant medications	Large scale characterisation and prespecified medications[3]	Binary	[-365,-31], [-30,-1]	IP, OP, OT	RxNorm	Any	Individuals with paracetamol overdose
Short-term complications	Hepatic toxicity, renal toxicity, and death	Binary	[0,30]	IP, OP, OT	SNOMED	Any	Individuals with paracetamol overdose
Mortality	Mortality	Binary	[0,30], [31,365]	IP, OP, OT	Date of death	n/a	Individuals with paracetamol overdose

Inf=any time prior; IP=inpatient; n/a=not applicable; OP=outpatient; OT=other; SNOMED=Systematized Nomenclature of Medicine.
[1] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)
[2] These include: alcoholism, chronic kidney disease, chronic liver disease, depression, anxiety, schizophrenia, obesity, cancer, arthrosis and arthritis, and pain.
[3] These include: carbamazepine, isoniazid, benzodiazepines, opioid analgesics, nonsteroid anti-inflammatory drugs, antipsychotics, and antidepressants.

8.7. Study size

No sample size was calculated for this study, given its descriptive nature. Our primary focus was to explore trends of paracetamol prescribing and paracetamol overdose and to describe individuals with paracetamol overdose.

8.8. Data transformation

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed and quality control checks were performed. After all the tests were passed (see **Annex I**), the final 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 before returning them to the Coordination Centre. Sometimes multiple execution iterations were performed, and additional finetuning of the code base was needed. The study results of all data sources were checked, after which they were made available to the study team, and the Dissemination Phase started. All results were locked and timestamped for reproducibility and transparency.

8.9. Statistical methods

8.9.1. Main summary measures

Results were presented by counts, proportions, mean, median, standard deviation, interquartile range, incidence rates, and prevalence proportions.

8.9.2. Main statistical methods

Population-level DUS on paracetamol prescribing (objective 1):

Annual incidence rates of paracetamol prescribing were calculated as the number of new prescriptions per 100,000 person-years (PY) of the population at risk during the study period. Those study participants who

experienced the outcome during the study period were able to re-enter the study and contribute time to the incidence calculations after a 60-day washout window following the end of treatment (see **8.4 Follow-up**).

The period prevalence of paracetamol use was calculated as the proportion of study participants who were prescribed a paracetamol-containing product on an annual basis. There was no restriction based on individuals' observability within calendar years in the database (i.e., participants were considered even if they were present in the database for only one day in the entire year).

Incidence and prevalence were calculated with 95% confidence intervals (CI). Incidence per 100,000 PY were rounded to the nearest whole number. Analyses were reported overall and stratified by age groups, sex, and formulation (see **8.6.3 Other covariates**).

Population-level descriptive epidemiology study on paracetamol overdose (objective 2):

Annual incidence rates of paracetamol overdose with 95% CI were calculated following the same approach as for objective 1. Individuals were able to re-enter the study following a 365-day washout after the occurrence of the outcome.

Incidence rates per 100,000 PY were rounded to the nearest whole number. Analyses were stratified by sex and age groups (see **8.6.3 Other covariates**).

Patient-level characterisation of patients with paracetamol overdose (objective 3):

Characteristics were described by database using prespecified conditions and medications and by means of large-scale characterisation. Analyses were reported overall and, if counts allowed, stratified by study period (2010–2016; 2017–2023). Results by study period were reported for databases with complete data across any of the study periods considered. As an example, for a database starting in 2015, we will only report results, overall and stratified by study period, for 2017–2023. Results for 2010–2016 will be omitted to avoid misleading comparisons.

The presence of risk factors, prior paracetamol prescribing, short-term complications, and death were reported as counts and percentages. To facilitate the reporting of the results, only the top 10 conditions and the top 10 medications identified through large-scale characterisation are described in the report.

Results are presented separately for each database, and no meta-analysis of results has been conducted. Cell suppression (cell counts <5) has been applied as required by databases to protect individuals' privacy.

8.9.3. Missing values

Variables used in the study were based on the recorded diagnoses and prescription codes available in the data, where the absence of a record was considered as the study participant not having been diagnosed with the condition or prescribed the drug of interest. For incidence and prevalence calculations, individuals with part of their follow-up missing were censored at the time of follow-up or end of data availability, and the reported figures assumed that censoring occurred at random.

8.9.4. Sensitivity analysis

We performed a sensitivity analysis removing the inclusion criterion of one year of prior database history (**Table 8**). This analysis was considered of interest given that many databases included in the study were derived from hospital settings only and define observation periods using different approaches (e.g., first to last visit, start to end of the data availability). In these databases, the requirement of one year of prior history can hinder the identification of individuals whose index date (e.g., diagnosis of paracetamol overdose) falls within their first year of observation, which will now be included. On the other hand, the lack of prior data might reduce the ability to identify prior health events, including prior history of the outcomes of interest and prior conditions and medications for characterisation. This also impacts databases whose data availability starts after the study start date (1st January 2010) and individuals aged <1 year. For

this analysis, data from the first year of the database was included. However, individuals aged <1 year were excluded.

Table 8. Sensitivity analyses – rationale, strengths, and limitations.

	What is being varied? How?	Why?	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Prior database history (365 days)	Excluded from the sensitivity analysis.	The impact of this requirement on the included population.	- Do not exclude individuals with <365 days of prior observation. - Include data from the first year of data availability.	Less prior observation time to capture previous health events, including outcome occurrences and prior comorbidities or medication use.

For all analyses, cell suppression was applied as required by databases to protect individuals' privacy. Cell counts <5 were masked.

8.10. Deviations from protocol

Since the last publication of the protocol, the protocol has been amended to incorporate the following changes:

1. **Study period modification for APHM**

   The study period for APHM was initially described as beginning in 2010, but was modified to start in 2014, based on the start of data availability of this database (i.e., 2015, considering the 365 days prior history requirement in the main analysis). This has been amended accordingly in **8.3 Study Period** and **10.2 Limitations of the research methods**. Considering this, stratification by study period (2010–2016; 2017–2023) in patient-level characterisation of individuals with paracetamol overdose (objective 3) was only possible in DK-DHR, which was the only database that provided data for the entire study period (see **8.9.2 Main statistical methods**).

2. **Inclusion of individuals aged <1 in the sensitivity analysis**

   In the original version of the protocol, we required all study participants to have at least 365 days of data visibility prior to index date. As a result, children aged <1 year were excluded. In the sensitivity analysis (where this requirement was removed), we had intended to include individuals under 1 year as an additional age category. However, in practice, individuals aged <1 year were not included in either the primary analysis (as per the original protocol) or the sensitivity analysis (representing a deviation from the protocol). This deviation occurred due to an unintended omission during the development of the analytical code. The impact of this deviation is expected to be limited. For objective 1 and 2, individuals were included to the denominator for incidence and prevalence calculations once they reached one year of age. For objective 3, this deviation represented the exclusion of approximately 51 individuals with a paracetamol overdose aged <1 year at index date (n=41 in DK-DHR; n<5 in APHM; n=10 in InGef RDB; n=0 in HI-SPEED). Further details can be found in **Tables S8-9** in **Annex II**.

3. **Mortality in HI-SPEED 0 to 30 days after paracetamol overdose**

   Reporting of mortality from 0 to 30 days after paracetamol overdose was not described in HI-SPEED. During the study, it was observed that contributing causes of death were mapped as conditions occurring at the date of death (even though they might occur any time prior). This led to an overestimation of mortality at time 0. For this reason, we have not reported the estimates of

mortality at time 0 to 30 in HI-SPEED. Estimates of mortality occurring between 31 and 365 days after the overdose should not be affected by this issue.

9. RESULTS

All results are available in a web application (Shiny App) at: https://data.darwin-eu.org/EUPAS1000000584/.

Considerations regarding the interpretation of results have been described in **10.5. Other information**. These include: 1) the study period covered by each data source in relation to prior history requirements; 2) additional context for understanding some artefactual increases in annual incidence trends; and 3) further information to aid interpretation of comorbidities and medication use.

9.1. Participants

Details on attrition and the number of individuals contributing to the denominator population created for incidence calculations for objective 1 are described by database in **Table 9**. All databases, except DK-DHR, contributed to this objective, including data from 30,889,960 individuals (n=972,282 in APHM; n=9,433,229 in InGef RDB; n=2,511,115 in IPCI; n=5,832,427 in NLHR; n=953,612 in H12O; n=11,187,295 in HI-SPEED).

For objective 2, this denominator was also used to calculate incidence of paracetamol overdose for databases participating in this objective (APHM, InGef RDB, and HI-SPEED), except for HI-SPEED, which had additional data (from 2015 onwards). Additionally, individuals in DK-DHR contributed to the denominator population for objective 2. A total of 28,753,828 individuals participated in objective 2 (n=6,921,679 in DK-DHR; n=972,282 in APHM; n=9,433,229 in InGef RDB; n=11,426,638 in HI-SPEED).

Table 9. Study attrition of individuals included in the denominator for objectives 1 and 2 (where applicable).

	DK-DHR (Obj 2)	APHM (Obj 1&2)	InGef RDB (Obj 1&2)	IPCI (Obj 1)	NLHR (Obj 1)[3]	H12O (Obj 1)	HI-SPEED (Obj 1)	HI-SPEED (Obj 2)
Starting population	8,593,356	2,329,771	10,512,283	2,870,221	6,114,138	2,218,528	11,739,647	11,739,647
Birth date available	8,593,356	2,329,771	10,512,283	2,870,221	6,114,138	2,218,528	11,739,647	11,739,647
Sex available	8,593,356	2,328,230	10,512,283	2,870,221	6,114,138	2,218,257	11,739,647	11,739,647
Satisfied age criteria during the study period, based on year of birth	8,484,906	2,304,534	10,423,421	2,858,836	6,065,401	2,203,389	11,653,562	11,653,562
Individuals with observation time available during study period (2010–2023)[1]	7,248,363	2,178,990	10,274,573	2,822,862	6,004,439	1,551,752	11,276,375	11,653,517
Prior history requirement fulfilled during the study period	7,248,363	2,178,990	10,274,573	2,822,862	6,004,439	1,551,752	11,276,375	11,653,517
Individuals with observation time available after applying age and prior observation	6,921,679	972,282	9,433,229	2,511,115	5,832,427	953,612	11,187,295	11,426,638

DK-DHR=Danish Data Health Registries; APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.
[1] Study period start differed in APHM (2014), InGef RDB (2015), NLHR (2018), and HI-SPEED (2018 for objective 1; 2015 for objective 2 and 3).

Table 10 details the attrition and the number of individuals contributing to the characterisation of individuals with paracetamol overdose in DK-DHR (n=21,425), APHM (n= 524), InGef RDB (n=1,084), and HI-SPEED (n=1,980).

Table 10. Study attrition of individuals included in objective 3.

	DK-DHR	APHM	InGef RDB	HI-SPEED
Qualifying initial records (first event)	30,335	1,168	1,416	2,444
Require prior observation of 365 days[1]	30,043	617	1,191	1,980
Require cohort start date within study period (2010–2023) and age >1[1]	21,425	524	1,084	1,980

DK-DHR=Danish Data Health Registries; APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.
[1] Study period start differed in APHM (2014), InGef RDB (2015), and HI-SPEED (2015 for objective 3).

Table 11 provides information on the demographic characteristics of individuals prescribed with paracetamol during the study period, assessed at the date of their first-ever prescription. This cohort differs from the paracetamol outcome cohort used for incidence and prevalence calculations, which is not limited to first-ever prescriptions, and has been included for descriptive purposes only.

A total of 6,429,210 individuals received their first prescription of paracetamol during the study period (**Table 11**). The number of individuals included ranged from 164,930 in APHM to 3,314,617 in HI-SPEED. The distribution was similar across sex, with a slightly higher proportion of females compared to males. Individuals with unknown sex were captured in APHM (n=27) and excluded from denominators for incidence calculations (see **Table 9**). Median age ranged from 29 years in InGef RDB to 59 years in IPCI. The duration of the first prescription ranged from 3 days in H12O to 35 days in HI-SPEED (see **10.2 Limitations of research methods**).

Table 11. Demographic characteristics of paracetamol users at date of first prescription during the study period.

		APHM	InGef RDB	IPCI	NLHR	H12O	HI-SPEED
Number of individuals		164,930	434,662	196,477	2,143,702	174,822	3,314,617
Cohort start date (min)[1]		2015-01-01	2016-01-01	2010-01-01	2018-01-01	2010-01-01	2018-01-01
Cohort end date (max)[2]		2024-12-03	2024-12-31	2023-12-31	2023-12-31	2025-06-18	2024-08-30
Age in years, median [min; q25 – q75; max]		48 [1; 26 – 69; 108]	29 [1; 7 – 55; 103]	59 [1; 41 – 73; 105]	51 [1; 35 – 67; 109]	54 [1; 35 – 73; 105]	58 [1; 41 – 73; 112]
Age group in years, N (%)	1 to 5	9,925 (6.0%)	88,441 (20.4%)	7,031 (3.6%)	8,521 (0.4%)	6,927 (4.0%)	33,352 (1.0%)
	6 to 11	6,969 (4.2%)	80,264 (18.5%)	3,823 (2.0%)	8,505 (0.4%)	4,980 (2.9%)	30,229 (0.9%)
	12 to 17	8,694 (5.3%)	19,102 (4.4%)	4,583 (2.3%)	53,000 (2.5%)	5,474 (3.1%)	71,221 (2.2%)
	18 to 29	22,520 (13.7%)	32,010 (7.4%)	13,685 (7.0%)	297,181 (13.9%)	15,720 (9.0%)	297,725 (9.0%)
	30 to 39	21,030 (12.8%)	33,894 (7.8%)	16,863 (8.6%)	294,855 (13.8%)	21,716 (12.4%)	352,984 (10.7%)
	40 to 49	16,741 (10.2%)	41,432 (9.5%)	24,177 (12.3%)	335,226 (15.6%)	22,460 (12.9%)	416,034 (12.6%)
	50 to 59	18,893 (11.5%)	54,974 (12.7%)	31,247 (15.9%)	372,865 (17.4%)	24,573 (14.1%)	530,381 (16.0%)
	60 to 69	20,972 (12.7%)	37,214 (8.6%)	32,745 (16.7%)	327,603 (15.3%)	22,356 (12.8%)	533,973 (16.1%)
	70 to 79	20,734 (12.6%)	26,328 (6.1%)	32,682 (16.6%)	275,952 (12.9%)	22,795 (13.0%)	588,313 (17.8%)
	> 80	18,452 (11.2%)	21,003 (4.8%)	29,641 (15.1%)	169,994 (7.9%)	27,821 (15.9%)	460,405 (13.9%)
Sex, N (%)	Female	90,735 (55.0%)	230,711 (53.1%)	117,903 (60.0%)	1,176,242 (54.9%)	98,863 (56.6%)	1,864,217 (56.2%)

		APHM	InGef RDB	IPCI	NLHR	H12O	HI-SPEED
	Male	74,168 (45.0%)	203,951 (46.9%)	78,574 (40.0%)	967,460 (45.1%)	75,959 (43.5%)	1,450,400 (43.8%)
	Unknown	27 (0.02%)	-	-	-	-	-
Duration of the prescription in days, median [min; q25 – q75; max]		4 [1; 2 – 8; 1,509]	30 [1; 30 – 30; 2,974]	14 [1; 8 – 22; 4,794]	34 [1; 11 – 34; 2,190]	3 [1; 2 – 8; 3,867]	35 [1; 18 – 71; 2,434]

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage; min=minimum; max=maximum; q25=25th percentile; q75=75th percentile.

[1] Study period start differed in APHM (2014), InGef RDB (2015), NLHR (2018), and HI-SPEED (2018 for objective 1; 2015 for objective 2 and 3).

[2] Cohort end dates after 2024-01-01 correspond to individuals included in the cohort before 2023-12-31 (i.e., individuals who initiated treatment before the end of the year who continued after).

Table 12 details information on demographic characteristics of the individuals with paracetamol overdose assessed at index date (i.e., date of the event). Most individuals were females, with proportions ranging from 70.1% in DK-DHR to 75.8% in APHM. The median age ranged from 21 years (InGef RDB) to 32 years (HI-SPEED). The highest frequency of paracetamol overdose was observed among individuals aged 18–49 years. Out of all individuals with paracetamol overdose, the proportion of individuals aged 1–17 ranged from 20.2% in HI-SPEED to 35.7% in InGef RDB. Individuals aged ≥80 years represented a small proportion of cases, accounting for less than 5% across all databases.

DK-DHR was the only database included in objectives related to paracetamol overdose that contributed data for the entire study period, with cases roughly split between 2010–2016 and 2017–2023 (**Table 12**).

Table 712. Demographic characteristics of individuals diagnosed with paracetamol overdose.

		DK-DHR	APHM	InGef RDB	HI-SPEED
Number of individuals		21,425	524	1,084	1,980
Cohort start date (min)[1]		2010-01-01	2015-05-17	2016-01-11	2016-01-02
Cohort end date (max) [1]		2024-01-01	2023-12-31	2024-01-01	2023-12-28
Age, median [min; q25 – q75; max]		24 [1; 17 – 48; 101]	22 [1; 16 – 38; 95]	21 [1; 16 – 39; 89]	32 [1; 19 – 54; 102]
Age group (broad), N (%)	1 to 17	6,140 (28.7%)	162 (30.9%)	387 (35.7%)	400 (20.2%)
	> 18	15,285 (71.3%)	362 (69.1%)	697 (64.3%)	1,580 (79.8%)
Age group (narrow), N (%)	1 to 17	6,140 (28.7%)	162 (30.9%)	387 (35.7%)	400 (20.2%)
	18 to 49	10,340 (48.3%)	274 (52.2%)	532 (49.1%)	960 (48.5%)
	50 to 79	4,164 (19.4%)	76 (14.5%)	149 (13.8%)	527 (26.6%)
	≥80	781 (3.6%)	12 (2.3%)	16 (1.5%)	93 (4.7%)
Sex, N (%)	Female	15,014 (70.1%)	397 (75.8%)	816 (75.3%)	1,480 (74.8%)
	Male	6,411 (29.9%)	127 (24.2%)	268 (24.7%)	500 (25.3%)
Study period[2]	2010-2016	10,982	40	116	306
	2017-2023	10,443	484	698	1,674

DK-DHR=Danish Data Health Registries; APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage; min=minimum; max=maximum; q25=25th percentile; n/a =Not applicable; q75=75th percentile.

[1] Cohort end dates on 2024-01-01 correspond to individuals included in the cohort on or before 2023-12-31 (i.e., cohort duration was set programmatically to 1 day for analysis purposes).

[2] Study period start differed in APHM (2014), InGef RDB (2015), and HI-SPEED (2018 for objective 1; 2015 for objective 3).

9.2. Paracetamol prescribing

9.2.1. Incidence

Incidence rates per 100,000 PY of paracetamol prescribing for the entire period ranged between 2,166 in InGef RDB and 20,340 in NLHR (**Table 13**).

Over the study period, incidence rates of paracetamol prescribing increased in NLHR, H12O, and APHM; remained stable in HI-SPEED and InGef RDB; and decreased in IPCI (**Figure 1**)**.** Increases in incidence rates during the first year with available estimates were observed in NLHR and HI-SPEED (2018), while an increase in the last year was observed in APHM (2023). Potential reasons behind these increases are described in section **10.5 Other information**.

Table 13. Incidence rates of paracetamol prescribing for the entire study period by database.

Database name[1]	Number of individuals	Number of events[2]	Person-years (PY)	Incidence per 100,000 PY (95% CI)[3]
APHM	971,051	343,351	4,011,801	8,559 (8,530 to 8,587)
InGef RDB	9,428,897	1,241,387	57,313,261	2,166 (2,162 to 2,170)
IPCI	2,506,471	483,182	12,672,769	3,813 (3,802 to 3,824)
NLHR	5,831,827	5,934,061	29,174,862	20,340 (20,323 to 20,356)
H12O	953,275	372,426	7,254,557	5,134 (5,117 to 5,150)
HI-SPEED	11,186,636	8,029,520	56,863,744	14,121 (14,111 to 14,130)

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage; CI=confidence interval; PY=person-year.
[1] Study period spanned from 2010 to 2023. Study period start differed in APHM (2014), InGef RDB (2015), NLHR (2018), and HI-SPEED (2018 for objective 1; 2015 for objective 2 and 3).
[2] Number of incident paracetamol prescriptions, defined with a 60-day washout.
[3] Incidence estimates are rounded to the nearest whole number.

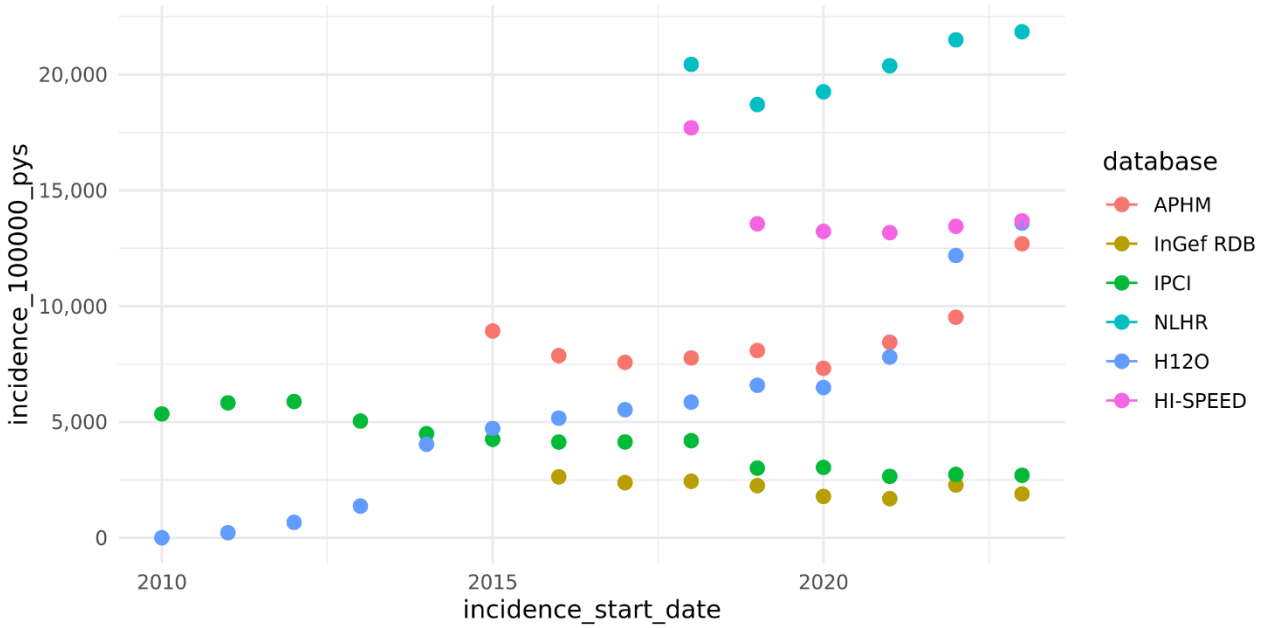

Figure 1. Annual incidence rates of paracetamol prescribing (2010–2023).

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

Trends in incidence rates by sex and age group were similar to overall trends across all databases (**Figure 2** and **Figure 3**). Incidence rates were similar between males and females in APHM, InGef RDB, and H120, whereas rates were higher among females than males in IPCI, NLHR, and HI-SPEED (**Figure 2**). In these latter databases, the overall incidence per 100,000 PY among females was estimated at 4,993 (95% CI 4,976 to 5,011) in IPCI, 25,409 (25,382 to 25,435) in NLHR, and 17,491 (17,476 to 17,507) in HI-SPEED. Corresponding figures for males (in the same order and units) were 2,604 (2,592 to 2,617), 15,573 (15,553 to 15,593), and 10,929 (10,917 to 10,941), respectively.

Incidence rates of paracetamol prescribing increased with increasing age in all databases, except InGef RDB (**Figure 3**), in which incidence rates per 100,00 PY were highest among the age group of 1–5 years (28,547 [28,479 to 28,614] over the study period) and second highest among the age group of 6–11 years. The largest difference in incidence rates per 100,000 PY between age groups was observed in NLHR: from 494 (485 to 503) in the age group 6 to 11 years to 53,827 (53,691 to 53,964) in the age group ≥80 years. Incidence results over the entire study period, stratified by sex and by age groups, can be found in the Shiny App.

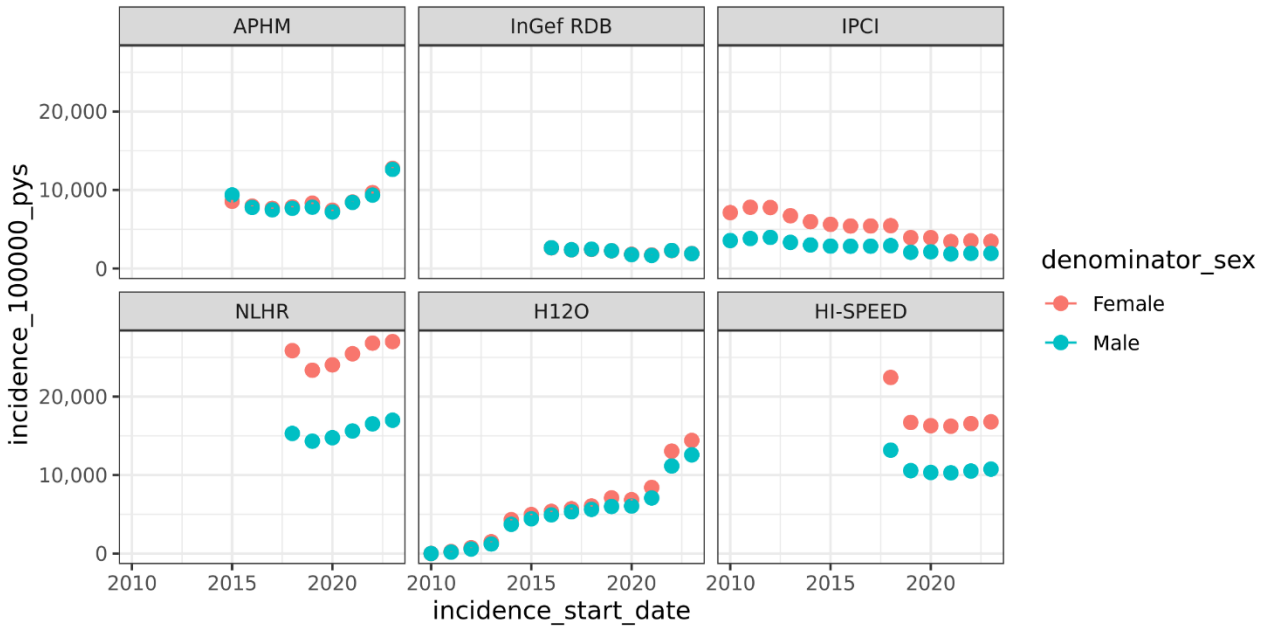

Figure 2. Annual incidence rates of paracetamol prescribing by sex (2010–2023).

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

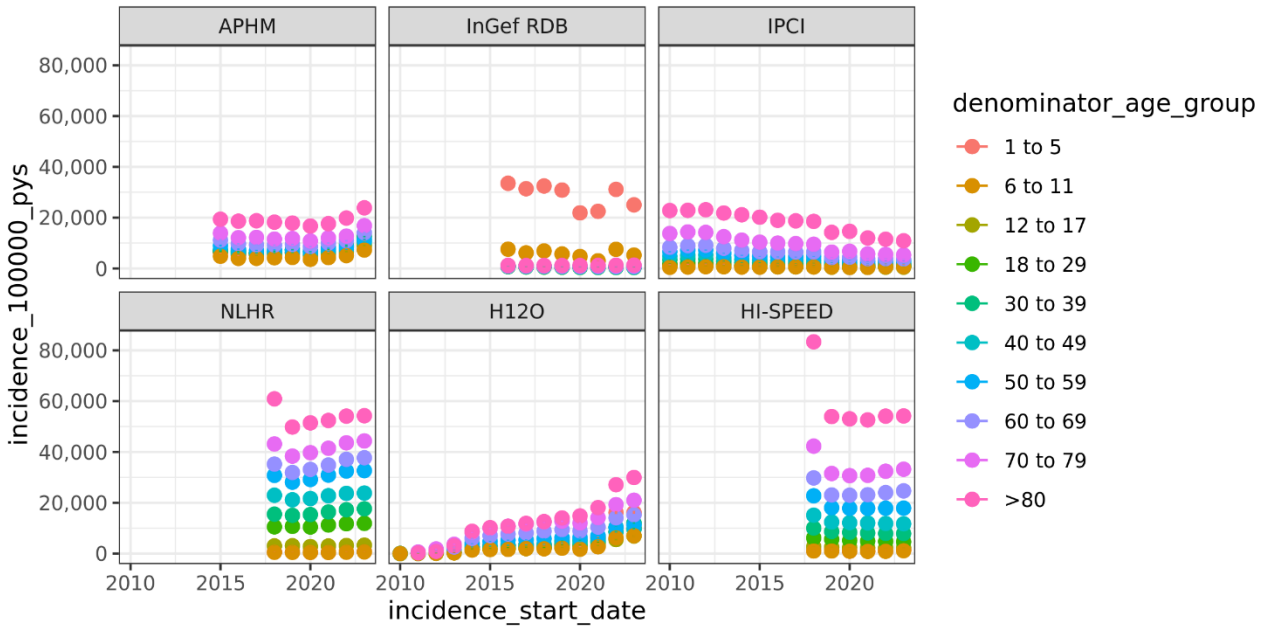

Figure 3. Annual incidence rates of paracetamol prescribing by age group (2010–2023).

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

The most frequently prescribed formulation of paracetamol differed between databases: injectable liquid (until 2017) and oral capsules (from 2018) in APHM; rectal suppositories in InGef RDB; oral tablets in IPCI, NLHR, and HI-SPEED; and injectable liquid in H12O (**Figure 4**). Overall, trends in paracetamol prescribing by formulation remained generally stable throughout the study period. However, trends increased for oral capsules in APHM, injectable liquid formulations in H12O, and oral tablets in NLHR, while they decreased for oral tablets in IPCI.

In NLHR, incidence of oral tablets prescribing was particularly high (20,160 per 100,000 PY [20,144 to 20,176]) and close to the prescribing of paracetamol of any formulation (20,340 per 100,000 PY [20,323 to 20,356]). In other databases, incidence rates per 100,000 PY of oral tablets ranged from 654 (652 to 656) in InGef RDB to 3,557 (3,547 to 3,568) in IPCI. For oral capsules, incidence rates (per 100,000 PY) were estimated at 4,825 (4,803 to 4,846) in APHM, 19 (19 to 19) in InGef RDB, 5 (5 to 6) in IPCI, and had 0 or < 5 incident events in NLHR, H12O, and HI-SPEED. For oral liquid formulations, incidence figures (per 100,000 PY) ranged from 28 (27 to 29) in IPCI to 496 (494 to 498) in InGef RDB.

Incidence of injectable formulations ranged from 0 to 5 per 100,000 PY in all databases, except for APHM and H12O, which obtained (3,619 [3,600 to 3,637] and 3,132 [3,119 to 3,145] per 100,000 PY, respectively). Incidence of rectal suppositories ranged from 0 in H12O to 1,030 per 100,000 PY (1,027 to 1,032) in InGef RDB, with zero events captured in HI-SPEED.

Formulation details were not consistently captured for all paracetamol drug records across databases, particularly in HI-SPEED, where a substantial discrepancy was observed between overall incidence of paracetamol prescribing and that estimated for the specific formulations studied (**Figure 4**). Further information can be found in **10.2 Limitations of the research methods**).

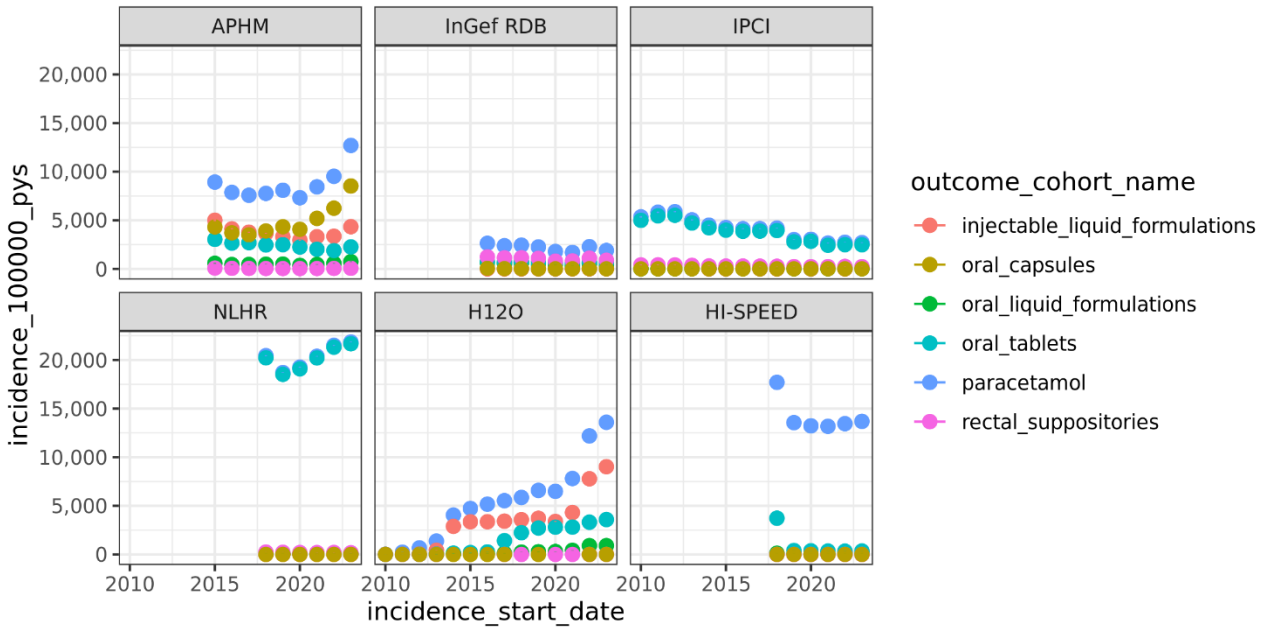

Figure 4. Annual incidence rates of paracetamol prescribing by formulation (2010–2023).

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

Incidence rates of oral paracetamol tablets were higher among females than males across all databases, except for APHM and InGef RDB, where rates were similar by sex (**Figure S1**). Incidence rates of rectal suppositories were also higher among females than males in IPCI and NLHR, while the opposite pattern was observed in InGef RDB. In APHM, rates of oral capsules, oral liquid formulations, and injectable formulations were lower among females than males (**Figure S1**).

In general, the overall trend of increasing incidence rates of paracetamol prescribing with increasing age was reflected across all databases (**Figure S2**). Incidence rates were highest in the age group 1 to 5 years, followed by the age group 6 to 11 years, of oral liquid formulations in APHM, InGef RDB, H12O, and HI-SPEED; and of rectal suppositories in InGef RDB.

Overall results stratified by database and covariates of interest, as well as results combining multiple stratifications, can be explored in the Shiny App.

9.2.2. Prevalence

Table 14 describes period prevalence estimates over the entire study period (i.e., number of individuals with a paracetamol prescription divided by all participants present in the database at any time during the study period). Prevalence over the study period was lowest in InGef RDB (8.8% [95% CI 8.8 to 8.8]) and highest in NLHR (36.9% [36.9 to 36.9]).

Table 148. Prevalence of paracetamol prescribing over the entire study period by database.

Database[1]	Number of individuals	Number of cases	Prevalence, % (95% CI)
APHM	972,282	219,728	22.6 (22.5 to 22.7)
InGef RDB	9,433,229	829,540	8.8 (8.8 to 8.8)
IPCI	2,511,115	257,535	10.3 (10.2 to 10.3)
NLHR	5,832,427	2,152,114	36.9 (36.9 to 36.9)
H12O	953,612	184,040	19.3 (19.2 to 19.4)
HI-SPEED	11,187,295	3,326,812	29.7 (29.7 to 29.8)

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage; CI=confidence interval.
[1] Study period spanned from 2010 to 2023. Study period start differed in APHM (2014), InGef RDB (2015), NLHR (2018), and HI-SPEED (2018 for objective 1; 2015 for objective 2 and 3).

The trends of the annual prevalence of paracetamol prescribing prevalence (**Figure 5**) were similar to the trends of the annual incidence: the annual prevalence increased in NLHR, H12O, and APHM; remained stable in HI-SPEED and InGef RDB; and decreased in IPCI. Please note that the annual values are lower than the estimates of prevalence in **Table 14**, as these were calculated over the entire study period.

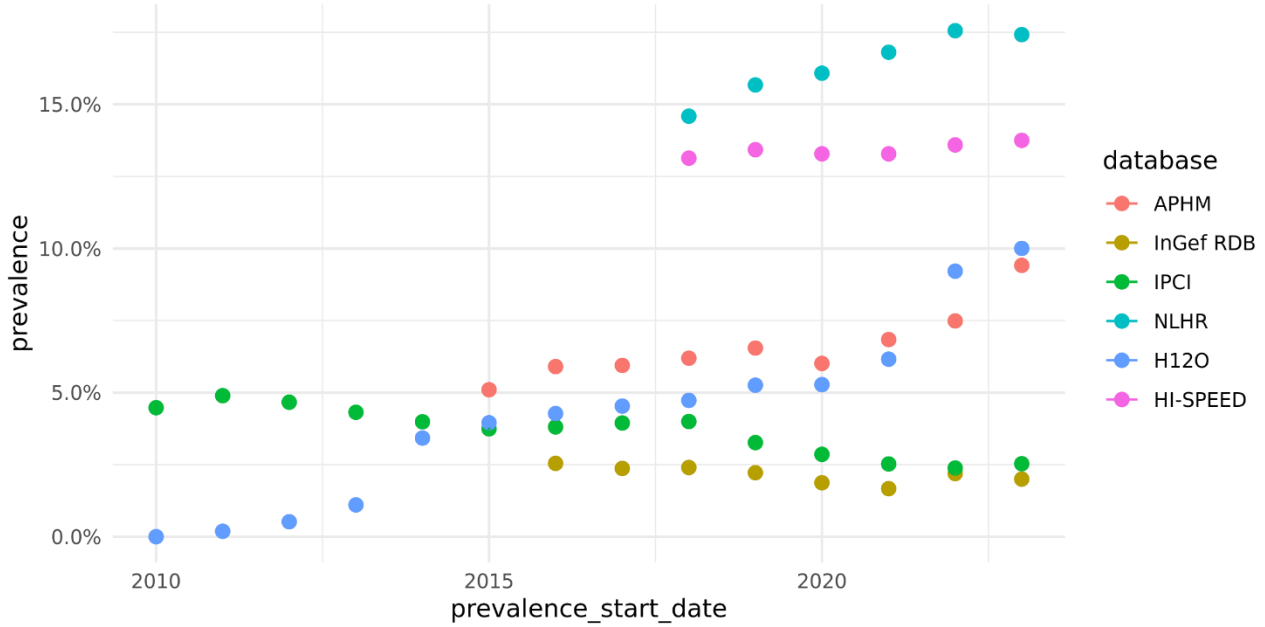

Figure 5. Annual prevalence of paracetamol prescribing (2010–2023).

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

Across all databases, the trends of prevalence by sex were similar to the trends of the overall prevalence. Prevalence of paracetamol prescribing was similar between males and females in APHM, InGef RDB, and H12O, whereas prevalence (%) was higher among females than males in IPCI (12.5 [12.5 to 12.6] versus 7.9 [7.8 to 7.9] over the study period), NLHR (41 [40.9 to 41.1] versus 32.9 [32.8 to 33]), and HI-SPEED (33.7 [33.7 to 33.7] versus 25.8 [25.8 to 25.9]).

As described for incidence rates, prevalence of paracetamol prescribing increased with increasing age in all databases, except InGef RDB, in which prevalence (%) was highest among the age group of 1–5 years (45.5 [45.4 to 45.6]) and second highest among the age group of 6–11 years. The largest difference in prevalence (%) between age groups was observed in HI-SPEED: from 2.2 (2.2 to 2.2) in the age group 6 to 11 years to 63.5 (63.4 to 63.6) in the age group ≥80 years.

Overall results considering the entire study period can be found in the Shiny App. The trends of the annual prevalence of paracetamol prescribing prevalence stratified by age and sex can be found in **Figure 6** and **Figure 7.**

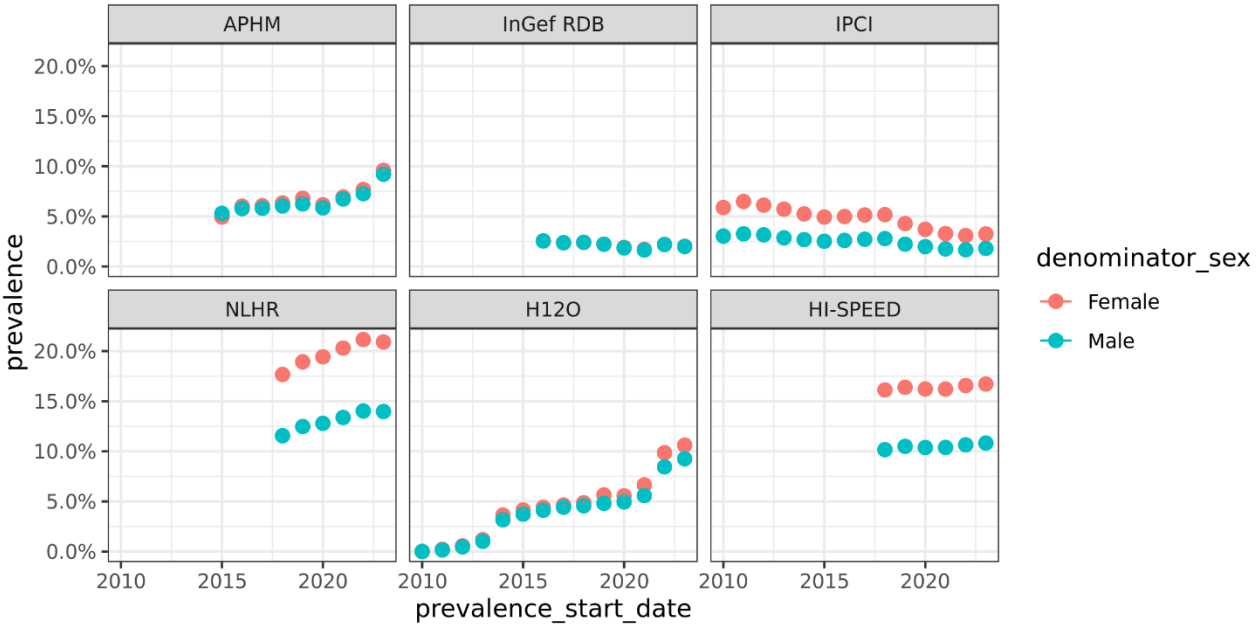

Figure 6. Annual prevalence of paracetamol prescribing by sex (2010–2023).

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

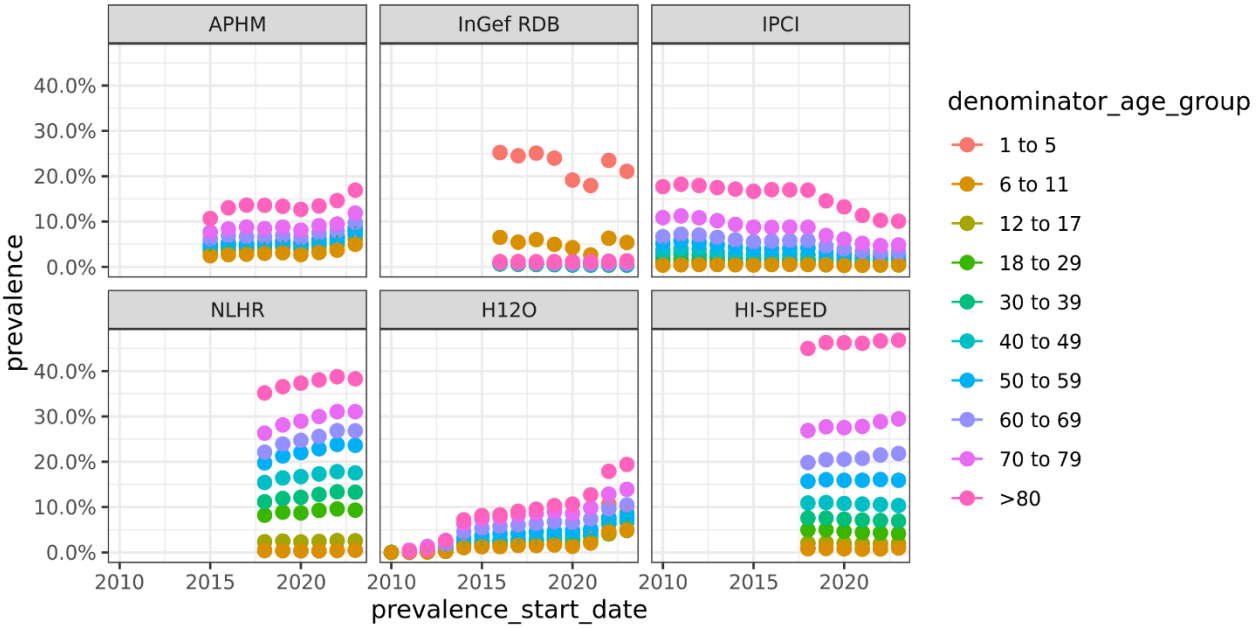

Figure 7. Annual prevalence of paracetamol prescribing by age group (2010–2023).

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

As observed for incidence rates, the highest prevalence of paracetamol prescribing was observed for injectable liquid (until 2017) and oral capsules (from 2018) in APHM; rectal suppositories in InGef RDB; oral tablets in IPCI, NLHR, and HI-SPEED; and injectable liquid in H12O (**Figure 8**)**.** Prevalence trends of injectable liquid formulations were similar between APHM and H12O and obtained similar figures when assessed

during the entire study period (11.3% [11.2 to 11.3] and [15.4% (15.3 to 15.4], respectively). Prevalence of paracetamol prescribing increased over the study period for oral capsules in APHM, injectable liquid formulations in H12O, and oral tablets in NLHR; decreased for oral tablets in IPCI; and remained stable for the other remaining formulations across the remaining databases.

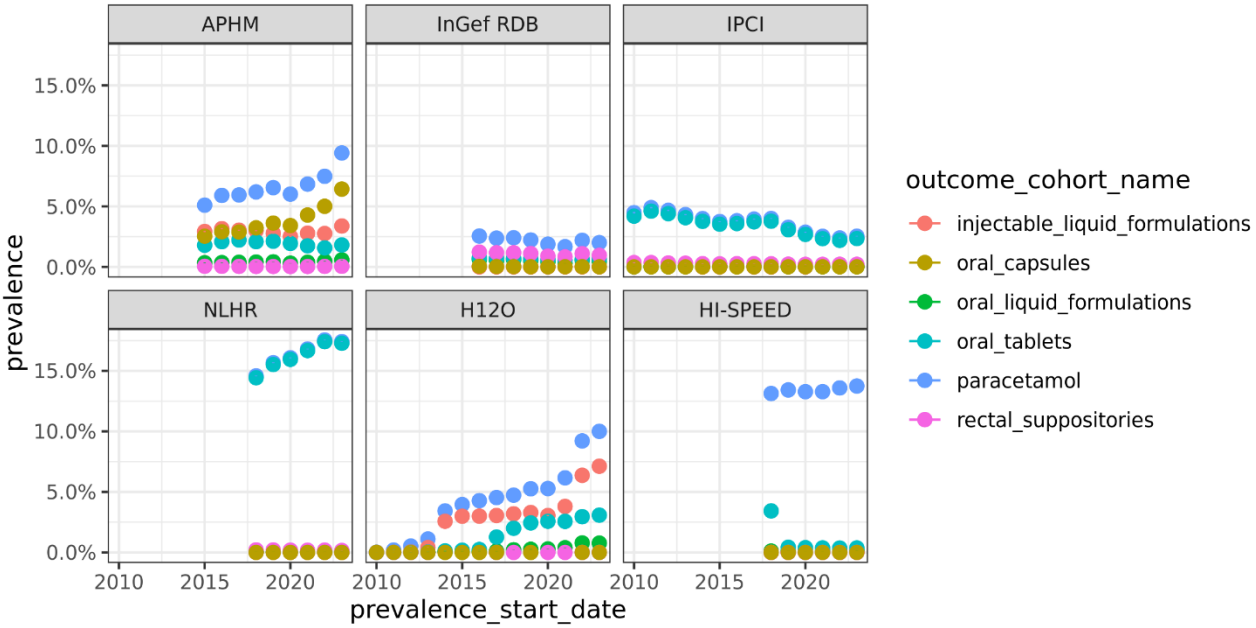

Figure 8. Annual prevalence of paracetamol prescribing by formulation (2010–2023).

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

The prescribing prevalence of oral paracetamol tablets was higher among females than males across all databases (**Figure S3**). This pattern was also observed for injectable liquid formulations in H12O, oral capsules in APHM, and rectal suppositories in IPCI and NLHR. Prevalence of oral liquid formulations was slightly higher among males than females in APHM and H12O. Prevalence of injectable liquid formulations was similar between both sexes in H12O, and oral liquid formulations and rectal suppositories in InGef RDB. Of the remaining formulations and across the remaining databases, the prescribing prevalence was close to 0% among both sexes.

The overall trend of increasing prevalence of paracetamol prescribing with increasing age was reflected across all databases in the prescribing prevalence of oral tablets, in APHM and H12O for injectable liquid formulations, and in APHM for oral capsules (**Figure S4**). In the remaining databases, prevalence of the two latter formulations was close to 0% across all age groups. Prevalence was highest in the age group 1 to 5 years, followed by the age group 6 to 11 years, of oral liquid formulations in APHM, InGef RDB, H12O, and HI-SPEED; and of rectal suppositories in InGef RDB. The prescribing prevalence of rectal suppositories in IPCI was highest in the age group ≥80 years, followed by the age group 70 to 79 years. In the remaining databases, the prescribing prevalence of rectal suppositories was close to 0% across all age groups, as was the case for oral liquid formulations in IPCI and NLHR.

Overall results stratified by database and covariates of interest, as well as results combining multiple stratifications, can be explored in the Shiny App.

9.3. Paracetamol overdose

9.3.1. Incidence

The overall incidence per 100,000 PY was 31 (95% CI 31 to 31) in DK-DHR, 13 (12 to 15) in APHM, 2 (2 to 2) in InGef RDB, and 3 (2 to 3) in HI-SPEED. Rates were 2–4 times larger in females than males and were generally higher in individuals aged 1–17 years compared to those aged 18 or older, except in HI-SPEED, where no differences between these age groups were observed (**Table 15**).

Table 159. Incidence of paracetamol overdose for the entire study period by database.

Results[1]	Database[2]	Number of events	Number of individuals	Person-Years (PY)	Incidence per 100,000 PY (95% CI)[3]
Overall	DK-DHR	24,246	6,921,649	78,138,486	31 (31 to 31)
	APHM	545	972,277	4,074,760	13 (12 to 15)
	InGef RDB	1,110	9,433,219	57,677,552	2 (2 to 2)
	HI-SPEED	2,054	11,426,628	80,715,609	3 (2 to 3)
Female	DK-DHR	17,355	3,463,502	39,360,806	44 (43 to 45)
	APHM	413	512,882	2,200,376	19 (17 to 21)
	InGef RDB	841	4,695,319	28,930,410	3 (3 to 3)
	HI-SPEED	1,542	5,670,442	40,164,742	4 (4 to 4)
Male	DK-DHR	6,891	3,458,147	38,777,681	18 (17 to 18)
	APHM	132	459,395	1,874,383	7 (6 to 8)
	InGef RDB	269	4,737,900	28,747,142	1 (1 to 1)
	HI-SPEED	512	5,756,186	40,550,867	1 (1 to 1)
1 to 17 years	DK-DHR	6,458	2,101,340	15,379,201	42 (41 to 43)
	APHM	167	228,073	806,569	21 (18 to 24)
	InGef RDB	391	2,086,678	9,466,587	4 (4 to 5)
	HI-SPEED	404	3,010,253	16,128,079	3 (2 to 3)
> 18 years	DK-DHR	17,788	5,793,433	62,759,285	28 (28 to 29)
	APHM	378	784,751	3,268,191	12 (10 to 13)
	InGef RDB	719	7,939,343	48,210,965	1 (1 to 2)
	HI-SPEED	1,650	9,293,676	64,587,530	3 (2 to 3)

DK-DHR=Danish Data Health Registries; APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage; CI=confidence interval; PY=person-year.
[1] Results stratified by additional age groups can be found in the Shiny App.
[2] Study period start differed in APHM (2014), InGef RDB (2015), and HI-SPEED (2015 for objective 3).
[3] Incidence estimates rounded to the nearest whole number.

Trends remained relatively stable over time, with a modest upward trend observed in APHM (**Figure 9**). Results stratified by sex showed differences in rates across age groups for some databases (**Figure 10**). Incidence rates per 100,000 PY of paracetamol overdose were higher among females aged 1–17 years than females aged ≥18 years in DK-DHR and APHM (DK-DHR: 71 [69 to 73] versus 38 [37 to 39]; APHM: 40 [33 to 47] versus 15 [13 to 16]). Rates were similar between both age groups among females in InGef RDB and HI-SPEED, and among males across all databases.

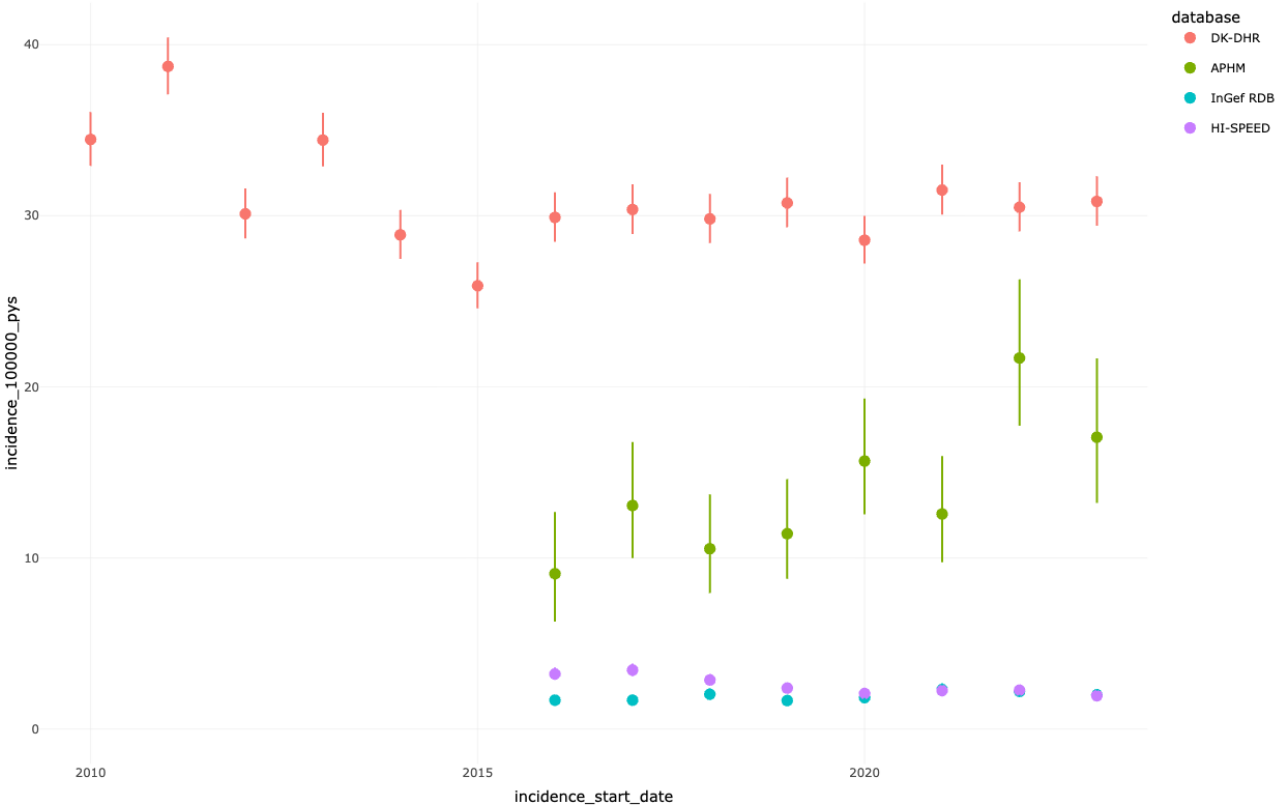

Figure 9. Annual incidence rates of paracetamol overdose (2010–2023)

DK-DHR=Danish Data Health Registries; APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

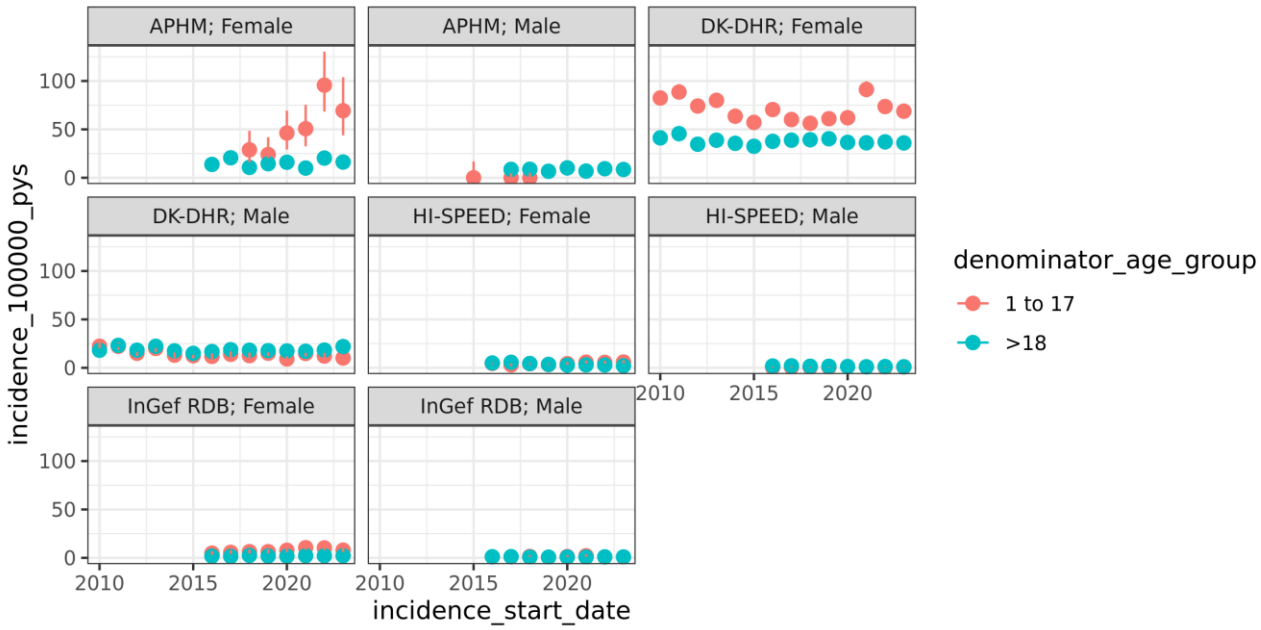

Figure 10. Annual incidence rates of paracetamol overdose in each database, by sex and age group.

DK-DHR=Danish Data Health Registries; APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

Results stratified by narrow age groups and results stratified by narrow age groups and sex combined can be explored in the Shiny App.

9.4. Characterisation of individuals with paracetamol overdose

In this section we describe the characterisation of 25,013 individuals with paracetamol overdose (n=21,425 in DK-DHR; n=524 in APHM; n=1,084 in InGef RDB; n=1,980 in HI-SPEED). Most individuals with paracetamol overdose were females, with proportions ranging from 70.1% in DK-DHR to 75.8% in APHM. Median age across all databases ranged from 21 to 25 years, except for HI-SPEED, where it was 32 years. Further details on demographic characteristics can be found in **9.1 Participants**.

Regarding clinical characteristics, individuals with paracetamol overdose were described based on prespecified comorbidities and medications, and by means of large-scale characterisation. Results are reported using frequencies and percentages calculated relative to the number of cases in each database.

9.4.1. Prespecified conditions and medications

Considerations for the interpretation of the frequency of conditions and medications reported in this section are described in **10.3 Interpretation**.

Conditions

The proportion of individuals with conditions of interest assessed using all prior history to 1 day before index date differed across databases (**Table 16**). In general, DK-DHR and HI-SPEED had the highest number of individuals with records of comorbidities of interest prior to index date, whereas APHM had the lowest. When considering all prior history, the most frequent conditions were pain (67.9% in DK-DHR; 10.7% in APHM; 25.6% in InGef RDB; 55.2% in HI-SPEED), anxiety disorders (22.0% in DK-DHR; 5.2% in APHM; 21.1% in InGef RDB; 47.5% in HI-SPEED), and depressive disorders (37.9% in DK-DHR; 8.2% in APHM; 37.6% in InGef RDB; 39.6 % in HI-SPEED). The least frequent conditions were alcoholism and chronic kidney disease, which were captured in <2 % of individuals across data sources. This pattern was also observed for the recording of conditions in the year prior to index date with lower proportions of cases.

The proportion of individuals with a record of pain in the month prior to index date ranged from 2.7% in InGef RDB to 17.3% in DK-DHR, with <5 cases captured in APHM. . Records of fever and infectious diseases in the month prior were limited. Fever was captured in <1% of cases and infectious diseases were captured in less <7% of cases across databases (**Table 17**).

Table 1610. Number and percentage of prespecified comorbidities among individuals with paracetamol overdose.

Prespecified comorbidities	Databases[1]							
	DK-DHR		APHM		InGef RDB		HI-SPEED	
	[-Inf, -1][2]	[-365, -1]	[-Inf, -1]	[-365, -1]	[-Inf, -1]	[-365, -1]	[-Inf, -1]	[-365, -1]
Alcoholism	287 (1.3%)	53 (0.2%)	<5	<5	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anxiety disorder	4,719 (22%)	2,094 (9.8%)	27 (5.2%)	15 (2.9%)	229 (21.1%)	148 (13.7%)	941 (47.5%)	717 (36.2%)
Arthritis arthrosis	4,265 (19.9%)	869 (4.1%)	<5	<5	46 (4.2%)	18 (1.7%)	253 (12.8%)	133 (6.7%)
Cancer	1,163 (5.4%)	477 (2.2%)	<5	<5	19 (1.8%)	10 (0.9%)	88 (4.4%)	50 (2.5%)
Chronic kidney disease	159 (0.7%)	88 (0.4%)	<5	<5	17 (1.6%)	8 (0.7%)	32 (1.6%)	22 (1.1%)
Chronic liver disease	252 (1.2%)	127 (0.6%)	<5	0 (0%)	11 (1%)	5 (0.5%)	65 (3.3%)	41 (2.1%)
Depressive disorder	8,120 (37.9%)	5,123 (23.9%)	43 (8.2%)	21 (4%)	408 (37.6%)	321 (29.6%)	785 (39.6%)	561 (28.3%)
Obesity	1,968 (9.2%)	529 (2.5%)	18 (3.4%)	<5	74 (6.8%)	42 (3.9%)	167 (8.4%)	72 (3.6%)
Pain	14,556 (67.9%)	8,866 (41.4%)	56 (10.7%)	21 (4%)	277 (25.6%)	143 (13.2%)	1,092 (55.2%)	697 (35.2%)
Schizophrenia	1,114 (5.2%)	730 (3.4%)	<5	<5	26 (2.4%)	23 (2.1%)	34 (1.7%)	26 (1.3%)

DK-DHR=Danish Data Health Registries; APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage; Inf=any time prior.
[1] Study period spanned from 2010 to 2023.Study period start differed in APHM (2014), InGef RDB (2015), and HI-SPEED (2015 for objective 3).
[2] Time windows are expressed in days relative to index date (i.e., date of paracetamol overdose).

Table 17. Number and percentage of acute conditions among individuals with paracetamol overdose.

Prespecified conditions/events	Time window[2]	Databases[1] DK-DHR	APHM	InGef RDB	HI-SPEED
Fever	[-30,-1]	31 (0.1%)	0 (0%)	0 (0%)	8 (0.4%)
Infectious diseases	[-30,-1]	1,319 (6.2%)	<5	18 (1.7%)	80 (4%)
Pain	[-30,-1]	3,712 (17.3%)	<5	29 (2.7%)	212 (10.7%)

DK-DHR=Danish Data Health Registries; APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.
[1] Study period spanned from 2010 to 2023. Study period start differed in APHM (2014), InGef RDB (2015), and HI-SPEED (2015 for objective 3).
[2] Time windows are expressed in days relative to index date (i.e., date of paracetamol overdose).

Short-term complications were assessed 30 days after index date. Hepatic and renal toxicity were assessed as coded conditions and did not consider laboratory test results. Hepatic toxicity was more frequently observed than renal toxicity and was found in 2.8% of individuals in DK-DHR, 12% of individuals in APHM, 5.1% in InGef RDB, and 8.5% in HI-SPEED (**Table 18**). For renal toxicity, corresponding figures (in the same order) were 0.8%, 4.2%, 2.5%, and 3.5%. Mortality within 30 days after index date occurred in insufficient counts for assessment (i.e., <5) in APHM and InGef RDB and in 1.00.% of individuals in DK-DHR. Mortality 31 to 365 days after paracetamol overdose was observed in <5 individuals in APHM and less than 2.5% of cases across the other data sources. Mortality 0 to 30 days after paracetamol overdose was not reported in HI-SPEED (see **8.10 Deviations from protocol** for further details).

Table 18. Number and percentage of short-term complications and mortality among individuals with paracetamol overdose.

Prespecified conditions/events	Time window[2]	Databases[1] DK-DHR	APHM	InGef RDB	HI-SPEED
Hepatic toxicity	[0, 30]	598 (2.8%)	63 (12.0%)	55 (5.1%)	168 (8.5%)
Renal toxicity	[0, 30]	166 (0.8%)	22 (4.2%)	27 (2.5%)	69 (3.5%)
Mortality[3]	[0, 30]	218 (1.0%)	<5	<5	n/a
	[31, 365]	489 (2.3%)	<5	14 (1.3%)	38 (2.2%)

DK-DHR=Danish Data Health Registries; APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage; n/a=not applicable
[1] Study period spanned from 2010 to 2023. Study period start differed in APHM (2014), InGef RDB (2015), and HI-SPEED (2015 for objective 3).
[2] Time windows are expressed in days relative to index date (i.e., date of paracetamol overdose).
[3] Mortality 0 to 30 days after index date was not reported in HI-SPEED.

Results stratified by sex, age groups, and study period can be explored in the Shiny App. In general, the proportion of females with anxiety disorders and depressive disorders was greater than the proportion of males with these conditions. Regarding short-term complications, results were similar by sex, albeit slightly higher for males compared to females. Sex differences were more pronounced in HI-SPEED, where 11.2% of males had hepatotoxicity (compared to 7.6% among females) and 20.6% died 0 to 30 days after index date (compared to 12.0% in females). Regarding age groups, comorbidities and complications were less

frequently recorded among individuals aged 1 to 17 years compared to those aged 18 or older. No individuals aged 1 to 17 years died in the month following index date. Short-term complications were more frequently captured among individuals aged 50 to 79 years compared to other age groups.

Medications

When considering the year leading up to a month before paracetamol overdose (i.e., -365 to -31 days prior to index date), the most frequent prespecified medications were paracetamol, antidepressants, nonsteroid anti-inflammatory drugs, and benzodiazepines (**Table 19**). The percentages of individuals with prespecified medications among individuals diagnosed with paracetamol overdose were similar between DK-DHR, InGef RDB, and HI-SPEED, but lower in APHM. For example, 27–30% of cases in the former three databases had a record of antidepressants and 15–16% of antipsychotics, compared to <4% of cases in APHM. Among prespecified medications, the less frequently prescribed were isoniazid (with 0 or <5 counts) and carbamazepine (with >5 counts in DK-DHR and HI-SPEED only). The ranking of the most and least frequent prespecified medications was similar when assessed during the month prior to index date, with lower frequencies.

The percentages of individuals prescribed paracetamol during the year leading up to a month before index date were 3.7% in InGef RDB, 10.3% in APHM, 23.5% in HI-SPEED, and 26.4% in DK-DHR. In the month prior to index date, the corresponding percentages were 1.6% in InGef RDB, 1.9% in APHM, 17.8% in HI-SPEED, and 16.3% in DK-DHR.

Results stratified by sex, age group, and study period can be explored in the Shiny App. The percentage of females with prescription of antidepressants or antipsychotics was higher than the percentage of males. The percentage of individuals with prespecified medications was higher among adults (aged ≥18 years) than children (aged 1 to 17 years). The highest percentage of individuals aged 1 to 17 years prescribed with antidepressants or benzodiazepines was observed in InGef RDB (21.2% and 2.1%, respectively), followed by HI-SPEED (20.8% and 1.3%, respectively).

Table 19. Number and percentage of individuals with prespecified medications among individuals diagnosed with paracetamol overdose.

Prespecified medications	Databases[1]							
	DK-DHR		APHM		InGef RDB		HI-SPEED	
	[-365, -31][2]	[-30, -1]	[-365, -31]	[-30, -1]	[-365, -31]	[-30, -1]	[-365, -31]	[-30, -1]
Antidepressants	5,823 (27.2%)	4,574 (21.3%)	22 (4.2%)	13 (2.5%)	330 (30.4%)	181 (16.7%)	601 (30.4%)	542 (27.4%)
Antipsychotics	3,190 (14.9%)	1,948 (9.1%)	20 (3.8%)	12 (2.3%)	166 (15.3%)	105 (9.7%)	306 (15.5%)	251 (12.7%)
Benzodiazepines	3,134 (14.6%)	2,012 (9.4%)	27 (5.2%)	17 (3.2%)	103 (9.5%)	50 (4.6%)	427 (21.6%)	346 (17.5%)
Carbamazepine	60 (0.3%)	36 (0.2%)	<5	0 (0%)	<5	<5	9 (0.5%)	5 (0.3%)
Isoniazid	<5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	<5	<5
Nonsteroid anti-inflammatory drugs (NSAIDs)	4,745 (22.1%)	1,753 (8.2%)	18 (3.4%)	<5	272 (25.1%)	78 (7.2%)	267 (13.5%)	153 (7.7%)
Opioids	3,062 (14.3%)	1,742 (8.1%)	22 (4.2%)	<5	92 (8.5%)	48 (4.4%)	265 (13.4%)	147 (7.4%)
Paracetamol	5,665 (26.4%)	3,491 (16.3%)	54 (10.3%)	10 (1.9%)	40 (3.7%)	17 (1.6%)	465 (23.5%)	353 (17.8%)

DK-DHR=Danish Data Health Registries; APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

[1] Study period spanned from 2010 to 2023. Study period start differed in APHM (2014), InGef RDB (2015), and HI-SPEED (2015 for objective 3).

[2] Time windows are expressed in days relative to index date (i.e., date of paracetamol overdose).

9.4.2. Large-scale characterisation

In the large-scale characterisation, all comorbidities and comedications recorded within pre-defined time windows of interest among individuals with paracetamol overdose were described. To facilitate the reporting of the results, only the top 10 conditions and the top 10 medications are described in the report. The results presented in this section include those based on a time window ranging from one year prior to one day before index date for conditions, and from 30 days to one day before index date for medications. The time windows used for conditions in this section thus differ from those reported for prespecified conditions, which were based on all prior history for assessment. This distinction was made to capture the more relevant conditions occurring closer to index date.

All results can be explored in the Shiny App, including results beyond the top 10 conditions and top 10 medications; results obtained using other time windows for assessment; and results stratified by covariates of interest.

Some of the conditions and medications reported provided in the large-scale characterisation differ in number from those reported in the previous section, when assessed as pre-specified conditions or medications. Reasons behind these discrepancies are explained in detail in **10.5 Other information.**

Conditions

In general, mental health and pain-related disorders were among the most frequently observed in the top 10 conditions identified through large-scale characterisation (**Table 20**). Pain was the most recorded condition among individuals with paracetamol overdose in DK-DHR (pain, 33.9%; severe pain, 10.7%) and ranked as the third (pain of truncal structure, 14.7%) and fifth most common condition (11.3%) in HI-SPEED. In contrast, it was not observed among the ten most recorded conditions in APHM and InGef RDB.

The proportion of mental-health related conditions observed in the top 10 was 3/10 in DK-DHR, 8/10 in InGef RDB, and 5/10 in HI-SPEED. In APHM, only 7 conditions were recorded in >5 individuals during the year prior to paracetamol overdose: the most recorded condition was intentional self-poisoning (6.1%), followed by poisoning by benzodiazepine-related tranquilizer (4.4%). No poisoning-related codes were among the top 10 conditions in any of the other databases. Alcoholism-related codes were observed in only InGef RDB.

Table 2011. Top 10 most recorded conditions among individuals diagnosed with paracetamol overdose, one year prior to 1 day before index date.

Database[1]			
DK-DHR	**APHM[2]**	**InGef RDB**	**HI-SPEED**
Pain: 7,268 (33.9%)	Intentional self-poisoning: 32 (6.1%)	Moderate major depression, single episode: 151 (13.9%)	Anxiety disorder: 560 (28.3%)
Depressive disorder: 4,627 (21.6%)	Poisoning by benzodiazepine-based tranquilizer: 23 (4.4%)	Emotionally unstable personality disorder: 105 (9.7%)	Disease: 464 (23.4%)
Insomnia: 2,558 (11.9%)	Emotional state finding: 17 (3.2%)	Severe major depression, single episode, without psychotic features: 105 (9.7%)	Pain of truncal structure: 291 (14.7%)
Severe pain: 2,297 (10.7%)	Psychosocial problems related to unwanted pregnancy: 14 (2.7%)	Severe recurrent major depression without psychotic features: 81 (7.5%)	Major depression, single episode: 260 (13.1%)
Esophageal reflux finding: 1,997 (9.3%)	Personality disorder: 10 (1.9%)	Acute alcohol intoxication: 75 (6.9%)	Pain: 224 (11.3%)

Database[1]			
DK-DHR	**APHM[2]**	**InGef RDB**	**HI-SPEED**
Infectious disease: 1,987 (9.3%)	Poisoning: 10 (1.9%)	Moderate recurrent major depression: 68 (6.3%)	Borderline personality disorder: 201 (10.2%)
Mental disorder: 1,905 (8.9%)	Poisoning by drug AND/OR medicinal substance: 10 (1.9%)	Posttraumatic stress disorder: 64 (5.9%)	Attention deficit hyperactivity disorder: 197 (9.9%)
Eczema: 1,794 (8.4%)	n/a	Essential hypertension: 62 (5.7%)	Essential hypertension: 195 (9.8%)
Asthma: 1,673 (7.8%)	n/a	Adjustment disorder: 58 (5.3%)	Disorder of musculoskeletal system: 173 (8.7%)
Cystitis: 1,615 (7.5%)	n/a	Alcohol dependence: 52 (4.8%)	Acute stress disorder: 165 (8.3%)

DK-DHR=Danish Data Health Registries; APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage; n/a=Not applicable.
[1] Study period spanned from 2010 to 2023. Study period start differed in APHM (2014), InGef RDB (2015), and HI-SPEED (2015 for objective 3).
[2] Conditions with <5 counts have been omitted (n/a).

In general, conditions recorded from all prior history up to one day before index date were similar to those described in the year prior, with variations in frequency. In APHM, additional conditions were recorded in >5 individuals with paracetamol overdose and could thus be presented among the ten most recorded conditions. Using data from all prior history up to one day before index date in APHM, 7/10 most reported conditions were related to mental health and 2/10 to poisoning.

In DK-DHR, 4/10 most recorded conditions in adults, versus 3/10 in children, were mental health-related. In APHM, only two conditions (emotional state finding and intentional self-poisoning, both 7.4%) had counts in >5 children with paracetamol overdose and three (poisoning by benzodiazepine-based tranquilizer, 5.8%; intentional self-poisoning, 5.5%; and psychosocial problems related to unwanted pregnancy, 3.9%) in adults. More of the ten most common conditions in children versus adults were mental health-related in both InGef RDB (8/10 versus 6/10) and HI-SPEED (7/10 versus 4/10). Another substance was noted among the ten most recorded conditions in adults, but not children, in both InGef RDB (acute alcohol intoxication and alcohol dependence) and HI-SPEED (disorder caused by psychoactive substance).

Results stratified by sex and results stratified by study period (assessed in DK-DHR only) were similar to the results reported in the overall population.

Medications

Paracetamol was the most recorded medication at ingredient level during the month prior to the diagnosis of paracetamol overdose in all databases, except InGef RDB (**Table 21**). In InGef RDB, the most recorded medication was ibuprofen (5.2%), which was also among the ten most recorded medications in DK-DHR (6.0%). In APHM, paracetamol was the only medication recorded among >5 individuals with paracetamol overdose (5.2%). Medications that were among the ten most recorded in multiple databases were: sertraline (DK-DHR, InGef RDB, and HI-SPEED), ethinyl oestradiol (DK-DHR and InGef RDB), quetiapine (DK-DHR and InGef RDB), melatonin (DK-DHR and HI-SPEED), and pantoprazole (DK-DHR and InGef RDB). In InGef RDB, psychoanaleptics (fluoxetine and venlafaxine) were among the most recorded medications, whereas this was the case for psycholeptics in HI-SPEED (zopiclone, propiomazine, and hydroxyzine) and DK-DHR (melatonin), and antihistamines (trimeprazine and promethazine) in HI-SPEED. In InGef RDB, the analgesic dipyrone was also among the ten most recorded medications.

Table 2112. Top 10 most recorded medications at ingredient-level among individuals diagnosed with paracetamol overdose, 30 days to 1 day before index date.

Database[1]			
DK-DHR	**APHM[2]**	**InGef RDB**	**HI-SPEED**
acetaminophen: 3,396 (15.8%)	acetaminophen: 10 (1.9%)	ibuprofen: 56 (5.2%)	acetaminophen: 353 (17.8%)
ethinyl estradiol: 2,270 (10.6%)	n/a	quetiapine: 52 (4.8%)	zopiclone: 219 (11.1%)
levonorgestrel: 1,558 (7.3%)	n/a	pantoprazole: 51 (4.7%)	propiomazine: 177 (8.9%)
ibuprofen: 1,282 (6%)	n/a	dipyrone: 48 (4.4%)	omeprazole: 169 (8.5%)
sertraline: 1,291 (6%)	n/a	ethinyl oestradiol: 45 (4.2%)	melatonin: 160 (8.1%)
pantoprazole: 1,132 (5.3%)	n/a	fluoxetine: 35 (3.2%)	trimeprazine: 143 (7.2%)
potassium chloride: 997 (4.7%)	n/a	amoxicillin: 32 (3.0%)	sertraline: 132 (6.7%)
quetiapine: 9,33 (4.3%)	n/a	sertraline: 33 (3.0%)	promethazine: 126 (6.4%)
citalopram: 848 (4.0%)	n/a	venlafaxine: 33 (3.0%)	vitamin B12: 105 (5.3%)
melatonin: 860 (4.0%)	n/a	levothyroxine: 26 (2.4%)	hydroxyzine: 103 (5.2%)

DK-DHR=Danish Data Health Registries; APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage; n/a=Not applicable.
[1] Study period spanned from 2010 to 2023. Study period start differed in APHM (2014), InGef RDB (2015), and HI-SPEED (2015 for objective 3).
[2] Ingredients with <5 counts have been omitted (n/a).

Results using data from one year before up to the month prior to index date were similar to those using data from the month prior to index date in DK-DHR, InGef RDB, and HI-SPEED, except for SARS-CoV-2 vaccines being among the ten most common medications in DK-DHR (8.7%) and HI-SPEED (12.8%). In APHM, additional medications were recorded in >5 individuals with paracetamol overdose and could thus be presented among the ten most recorded medications. Using data from the year before up to one month prior to index date in APHM, 3/10 most recorded medications were analgesics, including paracetamol as the most common, and 5/10 were for the alimentary tract and metabolism (e.g., pantoprazole, 4.8%).

In the stratified analysis of most frequent medications during the month prior to index date, medications for the cardiovascular system (e.g., atorvastatin and ramipril) were among the ten most recorded medications for males, but not females in DK-DHR (4/10 most common medications), InGef RDB (1/10), and HI-SPEED (2/10). The results of the stratified analysis on children (age 1–17 years) versus adults (≥18 years) yielded results in each subgroup that were similar to the overall results.

Stratification by study period in DK-DHR yielded results in each subgroup that were similar to the overall results.

9.5. Sensitivity analysis

A sensitivity analysis was conducted to investigate the impact of removing the requirement of 365 days of database history. Removing this requirement led to the inclusion of over 2.5 million more individuals than in the main analysis in the total denominator population for objective 1 and 2 (**Table S8**). For objective 3, the sensitivity analysis allowed the inclusion of 1,354 additional individuals (**Table S9**). Differences in the number of individuals included were particularly pronounced in APHM, where approximately 50% of the population was excluded due to the prior history requirement. In this database, the number of individuals included in the denominator populations for incidence and prevalence calculations (objective 1 and 2) increased from 972,282 to 2,125,496, and the number of individuals with paracetamol overdose (objective

3) from 524 to 1,027. This was also observed in H12O, where approximately 37% of the population were excluded due to the prior history requirement (**Table S8**).

Demographic characteristics of individuals prescribed with paracetamol were similar to those reported in the main analysis, except for InGef RDB, where the median age at the first recorded prescription of paracetamol was lower (12 [q25-q75: 4-50] years versus 29 [7-55] years). Results for incidence and prevalence of paracetamol prescribing were similar to those reported in the main analysis, with some exceptions. In APHM, incidence rates per 100,000 PY were higher in the sensitivity analysis than in the main analysis (12,493 [95% CI 12,462 to 12,524] versus 8,559 [8,530 to 8,587]) (**Figure 11**). In APHM, trends of annual prevalence of in-patient paracetamol prescribing also obtained higher estimates in the sensitivity analysis than those reported in the main analysis (**Figure S5**). However, this was not reflected in overall figures considering the entire study period (20% [95% CI 19.9 to 20.0] in the sensitivity analysis versus 22.6% [22.5 to 22.7] in the main analysis). This was also observed for H12O, which showed similar trends over time but lower prevalence in the sensitivity analysis (H12O: 15.2% [15.1% to 15.2%] versus 19.3% [19.2% to 19.4%]).

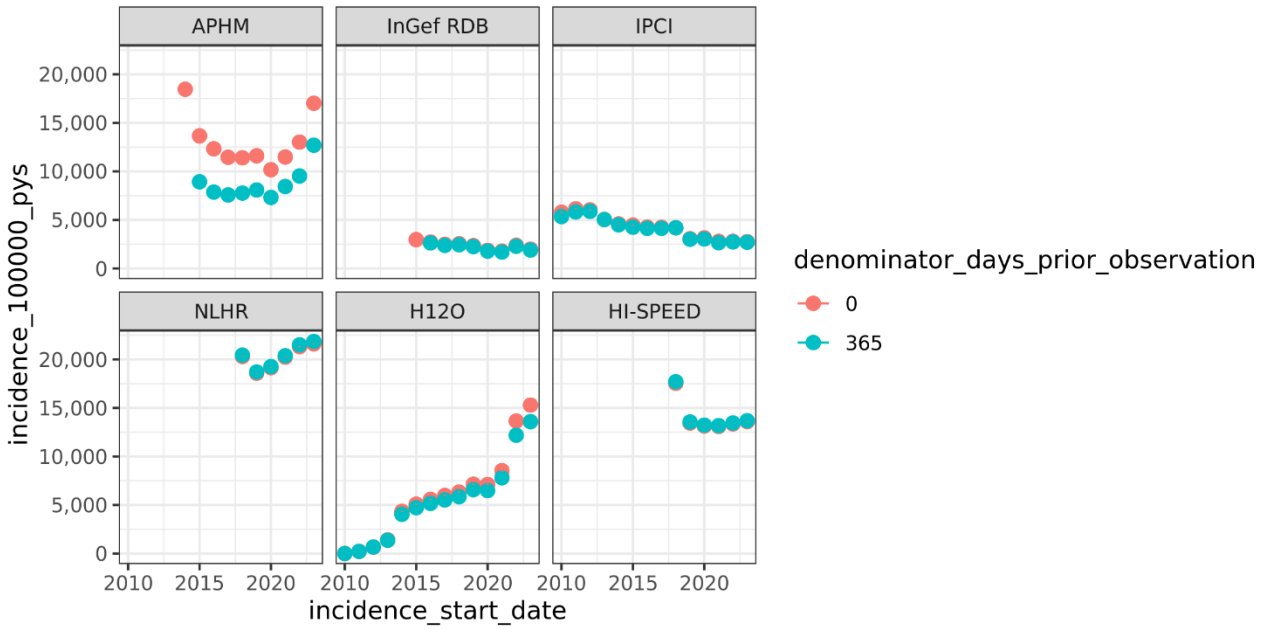

Figure 11. Annual incidence rates of paracetamol prescribing in the sensitivity analysis (0 days prior history) versus main analysis (365 days prior history).

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

Similarly, incidence results of paracetamol overdose obtained in the sensitivity analysis were consistent with those reported in the main analysis across databases, except for APHM (**Figure 12**). In this database, the overall incidence rate in the sensitivity analysis were approximately 1.5 times as high as in the main analysis (20 [95% CI 19 to 22] versus 13 [12 to 15]).

Removing the requirement of prior history allowed the reporting of incidence and prevalence for the first year of available data in databases where observability started later than 2010 (see **10.5 Other information** for further details)**.** The additional data point for 2014 in APHM showed substantially higher incidence of paracetamol prescribing and paracetamol overdose compared to subsequent years. Differences observed in APHM were likely driven by how observability is defined in the data, which has been explained in detail in **10.3 Interpretation**.

The characterisation of individuals with paracetamol overdose was consistent with the findings of the main analysis. In APHM, 11 individuals (1.1%) had a record of mortality in the month after paracetamol overdose in the sensitivity analysis versus <5 individuals in the main analysis.

For all objectives, results stratified by covariates of interest were consistent with those reported in the main analysis. All results related to the sensitivity analysis can be explored in the Shiny App.

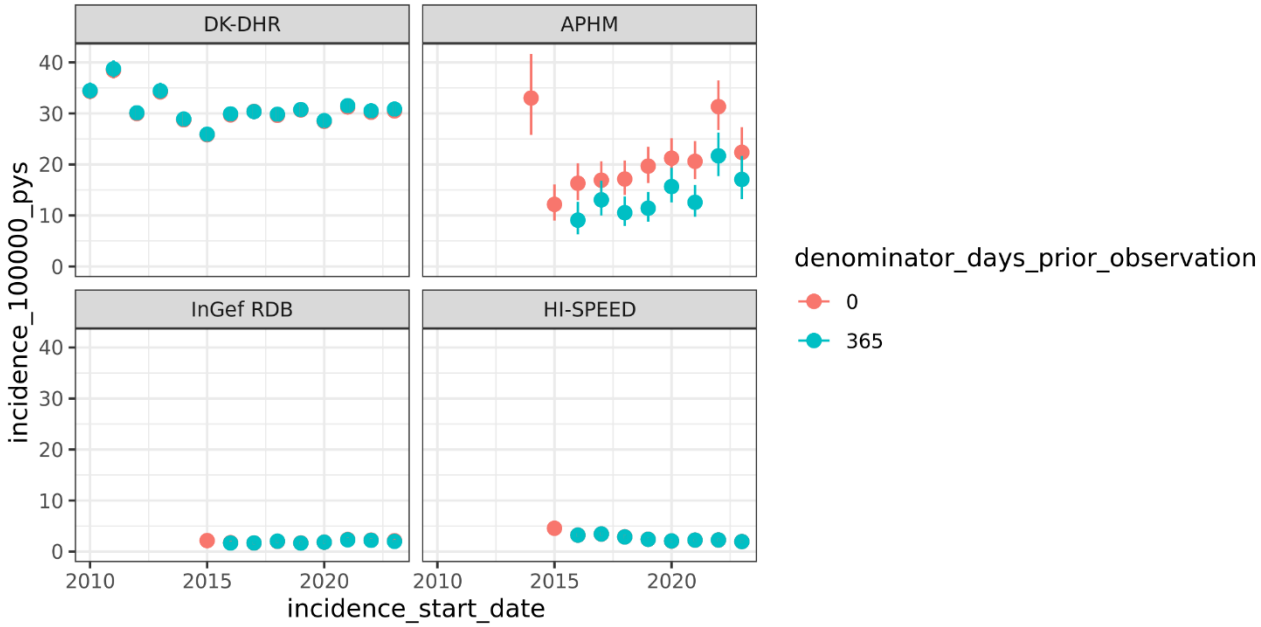

Figure 12. Annual incidence rates of paracetamol overdose in the sensitivity analysis (0 days prior history) versus main analysis (365 days prior history).

DK-DHR=Danish Data Health Registries; APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

10. DISCUSSION

10.1. Key results

In this study, which was built upon a previous DARWIN EU® study (EUPAS1000000329), we estimated: 1) incidence and prevalence of paracetamol prescribing; 2) incidence rates of paracetamol overdose; and 3) characterised those identified with paracetamol overdose. Incidence and prevalence of paracetamol prescribing were derived from 6 databases across 6 countries (France, APHM; Germany, InGef RDB; The Netherlands, IPCI; Norway, NLHR; Spain, H12O; and Sweden, HI-SPEED). Results of paracetamol overdose were informed by DK-DHR, APHM, InGef RDB, and HI-SPEED. Some of the databases included did not provide data for the entire study period (2010–2023) and contributed fewer years of data based on the start of their data availability (APHM: 2014; InGef RDB: 2015; NLHR: 2018; HI-SPEED: 2015, with data on drug records starting on 2018).

Incidence and prevalence of paracetamol prescribing:

Incidence per 100,000 PY of paracetamol prescribing ranged between 2,166 in InGef RDB and 20,340 in NLHR. Rates were higher among females than males across all databases, except for APHM, InGef RDB, and H12O, where estimates were similar by sex. All databases showed a gradient of increasing rates with age, except for InGef RDB, where the highest rates were observed among children aged 1 to 5 and 6 to 11 years.

Oral tablets had the highest incidence rates in IPCI, NLHR, and HI-SPEED, while oral capsules, rectal suppositories, and injectable liquids were most common in APHM, InGef RDB, and H12O, respectively. Incidence of injectable liquid formulations was low across all data sources (<5 per 100,000 PY) except for APHM and H12O, which exhibited higher rates (3,619 and 3,132 per 100,000 PY, respectively). Children aged 1 to 5 years and 6 to 11 years had the highest rates for oral formulations in APHM, InGef RDB, H12O, and HI-SPEED, with a similar pattern observed for rectal suppositories in InGef RDB.

Prevalence of paracetamol prescribing ranged from 8.8% in InGef RDB to 36.9% in NLHR for the entire study period, with trends by sex, age group and formulation generally mirroring those obtained for incidence rates.

Estimates obtained in the current study were generally consistent with the ranges reported in the previous study (see **6. Rationale and Background**), except for NLHR, where incidence rates were higher. Sex and age patterns also aligned with previous findings. The age distribution in InGef RDB, with rates decreasing as age increased, mirrored that observed in IQVIA Disease Analyzer (IQVIA DA) Germany, a primary care database from the same country included in the previous study.

Incidence of paracetamol overdose:

Incidence rates of paracetamol overdose per 100,000 PY were 31 (95% CI 31 to 31) in DK-DHR, 13 (12 to 15) in APHM, 2 (2 to 2) in InGef RDB, and 3 (2 to 3) in HI-SPEED. The overall incidence of paracetamol overdose remained stable over the study period across databases included. Estimates for InGef RDB and HI-SPEED in the current study were consistent with those reported for primary care databases from Spain and the UK in the previous study (between 2 to 5 per 100,000 PY). The previous study found substantially higher incidence rates in females, especially among those aged 1–17 years, which was also observed in DK-DHR and APHM in the current study.

Characterisation of patients with paracetamol overdose:

We identified and described 25,013 individuals with paracetamol overdose (n=21,425 in DK-DHR; n=524 in APHM; n=1,084 in InGef RDB; n=1,980 in HI-SPEED). Most individuals were female, with a median age of 21 to 32 years. Age and sex distribution were similar to those in the previous study, although females represented a higher proportion of cases in the current study (range: 70.1% to 75.8% vs. 55.4% to 67.3%).

When considering all prior history, the most frequent conditions were pain, anxiety disorders, and depressive disorders. The most frequent prespecified medications (i.e., -365 to -31 days prior to index date) were paracetamol, antidepressants, nonsteroid anti-inflammatory drugs, and benzodiazepines. Depressive disorders and antidepressants were observed in 37–40% and 27–30% of cases across databases, with lower proportions observed in APHM (8.2% and 4.2%, respectively). When analysed using large-scale characterisation, the most recorded conditions during the year up to paracetamol overdose were related to mental health or pain, which is consistent with findings obtained in the previous study. In APHM, 6.1% of individuals with paracetamol overdose had a record of intentional self-poisoning and 4.4% of poisoning by benzodiazepine-based tranquilizers. These findings align with those reported in the previous study in a hospital database from the same country (Clinical Data Warehouse of Bordeaux University Hospital; CDWBordeaux), where poisonings from psychotropic agents and benzodiazepine-based tranquilizers were documented in 5.8% and 4.2% of individuals with paracetamol overdose.

Paracetamol was the most recorded medication during the month prior to the diagnosis of paracetamol overdose in all databases except InGef RDB. The percentages of cases prescribed paracetamol the month prior to index date were 1.6% in InGef RDB, 1.9% in APHM, 17.8% in HI-SPEED, and 16.3% in DK-DHR, which aligned with findings obtained in the previous study (range: 2.1% to 16.7%).

Hepatotoxicity up to one month after paracetamol overdose ranged from 2.8% in DK-DHR to 12.0% in APHM. For renal toxicity, estimates ranged from 0.8% to 4.2%. These results were consistent with those reported in the prior study, which showed a range of 0.4% to 10.9% for hepatotoxicity and 0.3% to 4.8% for renal toxicity.

Mortality within 30 days after index date occurred in <5 individuals in APHM and InGef RDB and was observed in 1.0% of individuals in DK-DHR. Mortality 31 to 365 days after paracetamol overdose was observed in <5 individuals in APHM and less than 2.5% of cases across the remaining data sources. These findings were comparable to those from the previous study, which reported mortality ranging from 0.2% to 1.3% within 30 days and from 1.2% to 6.1% between 31 to 365 days.

Sensitivity analysis:

Results of the sensitivity analysis were similar to those of the main analysis, except for APHM. Removing the prior history requirement led to the inclusion of more individuals, particularly in APHM and H12O, both inpatient databases, where approximately 50% and 37% of the population had been excluded due to this requirement.

In APHM, trends in annual incidence of paracetamol prescribing and paracetamol overdose were consistently higher than those reported in the main analysis, particularly in the first year of available data (2014). Trends in annual prevalence of paracetamol prescribing also showed higher estimates when removing the prior history requirement. However, this was not reflected in the overall estimates of period prevalence when considering the entire study period. This analysis was not performed in the previous study.

10.2. Limitations of the research methods

Database-specific limitations:

The study was informed by routinely collected health care data and so data quality issues inherent to observational studies need to be considered. As such, the recording of events (e.g., comorbidities, medications) may vary across databases and might be inaccurately recorded or incomplete. In addition, results only reflect events occurring in the healthcare settings covered by each database, and therefore conditions diagnosed outside the healthcare institutions covered by each data partner were not captured. The same occurred for medications in all databases, except for DK-DHR, HI-SPEED, and NLHR, where linkage to national registries containing data on all prescriptions filled nationally was available (i.e., all medications dispensed outside of hospitals).

Information on conditions was based on diagnoses recorded in hospital settings in all databases, except for IPCI (which only participated in the assessment of paracetamol prescribing) and HI-SPEED (which included primary care data for 40% of individuals included). While primary care data was available in InGef RDB, the assessment of conditions was based on using inpatient diagnoses due to the convention used to map outpatient diagnoses in InGef RDB. In this database, outpatient diagnoses are recorded quarterly without exact diagnosis dates and are represented as observations (rather than conditions) using concepts such as "history of event within 3 months". The impact of this is limited, as we expected most cases of paracetamol overdose to be recorded in hospital settings. However, this might have resulted in an underestimation of comorbidities diagnosed and managed in primary care settings.

Some of the databases included did not provide data for the entire study period (2010–2023) and contributed fewer years of data based on the start of their data availability (APHM: 2014; InGef RDB: 2015; NLHR: 2018; HI-SPEED: 2015, with data on drug records starting on 2018). A year of observation history prior to index date was required for all individuals included, which reduced the study period by one year in the main analysis for databases where observability started later than 2010 (i.e., APHM, InGef RDB).

Artefactual increases in incidence rates were observed in the first year of available data in both main and sensitivity analysis, especially in databases that began contributing data after 2010, but did not delay the study start by one year to apply the prior history requirement (i.e., NLHR, HI-SPEED). Artefactual increases were also observed in the last year of data for APHM. Both cases relate to how observation periods are defined in the data and have been discussed in detail in **10.5 Other information**.

Paracetamol prescribing:

Although the use of paracetamol was derived from different sources of data, all records were referred to as prescription for simplicity. The use of routinely collected records likely caused underestimation of paracetamol use given its ease of access as an OTC medication. The underestimation is likely greatest in databases from countries with fewer restrictions on the availability of paracetamol sold OTC, which have been described in more detail in **10.3 Interpretation**.

Upon reviewing diagnostics results for drug exposures, two important aspects were noted. First, accurate information on treatment duration was not available across all data sources. Information on drug exposure end dates was unavailable and was automatically set to a specific number of days after the drug exposure start date in the source data. In InGef RDB it was set to 29 days after, resulting in prescription durations of 30 days for most records (**Table 11**). The lack of accurate information on treatment duration can affect the results obtained for incidence and prevalence, as the end date recorded in the data does not correspond to the actual treatment date. However, considering that we estimated incidence and prevalence figures annually, the impact of this is likely minor. Secondly, some drug records were mapped using concept classes with no information on dose form. Examples include records mapped at ingredient-level (i.e., “acetaminophen”) and clinical drug component (e.g., “acetaminophen 500MG”). This was particularly relevant for H12O and HI-SPEED, where according to diagnostic results, 46.8% and 95.6% of records were mapped using concept classes with no information on dose form (**Figure 4** and **Figure 8**).

Paracetamol overdose:

Based on the feasibility assessment, counts on paracetamol overdose were limited in some databases, and therefore, it was only assessed in 4 databases (DK-DHR, APHM, InGef RDB, and HI-SPEED). The extent of capture of paracetamol overdose is dependent on sufficient granularity of event recording. In this study, we only considered diagnoses that explicitly specified poisoning or overdoses caused by paracetamol and therefore, results presented in this study likely represent an underestimation of cases. In addition, we could not distinguish between accidental and deliberate paracetamol overdose, which limited our understanding of the underlying circumstances of these events.

Data availability started in 2014 or 2015 in all databases included in this analysis, except for DK-DHR. The amount of data available before index date likely affected the ability to capture prior health events, especially for conditions when assessed considering all prior data. This limitation is particularly relevant for HI-SPEED, where data on prior medication use only became available starting in 2018. Due to these constraints, stratification by time period was performed only in DK-DHR.

Mortality within 0 to 30 days after paracetamol overdose was not reported in HI-SPEED (see **8.10 Deviations from protocol**). This was due to the convention used for recording contributing causes of death, which were not available in other data sources included in this study, and were mapped as conditions occurring on the date of death. Consequently, it was not possible to reliably differentiate between conditions with accurately recorded diagnosis dates and those assigned the date of death, leading to an overestimation of mortality on day 0. For the characterisation of patients (objective 3), individuals with a prior diagnosis of paracetamol overdose preceding the recording of a contributing cause of death for the same event were not affected, as patient characteristics were assessed at the time of the first occurrence of the event. However, we cannot confirm that this was the case for all individuals, as in some cases the event may have been recorded solely as a contributing cause of death (i.e., on the date of death), with no prior record of a diagnosis on the date the event occurred. This could be a contributing factor to the higher median age observed in HI-SPEED (32 years) compared to other databases (range: 21 to 25 years).

Lastly, data on some covariates of interest (e.g., amount of paracetamol taken at overdose, delayed presentation to care, whether it was taken alone or in combination with other products) was not available and was not described in the study. Moreover, the age group classification used in this study did not allow for estimating incidence across more specific age groups among children (1–17 years, accounting for 20.2–35.7% of individuals with paracetamol overdose in our study). This distinction would be valuable for

estimating incidence among young children, whose overdoses are often due to unsupervised ingestions and medication errors, and adolescents, where self-harm may play an important role.

10.3. Interpretation

Paracetamol prescribing:

Incidence and prevalence of paracetamol prescribing were generally consistent with the ranges reported in the previous DARWIN EU® study (EUPAS1000000329), and showed similar patterns in terms of age, sex and formulations. However, as reported in the prior study, substantial variability across databases existed. Differences in healthcare settings (e.g., primary care versus secondary care) or types of data (e.g., electronic health records versus claims data) are likely contributors to these disparities. Geographical differences have been found in other studies,(14, 15) and likely play a role in the variations observed in our findings. National differences in analgesic use may also be relevant. As our analysis focused on paracetamol only, we were unable to assess its use in relation to other analgesics. Future studies incorporating a broader range of analgesic medications could enhance understanding of both intra- and inter-country differences in paracetamol prescribing.

Previous studies have shown that paracetamol users are more frequently females and older populations.(15-17) This is in line with our results in which we generally found higher incidence and prevalence of prescriptions among females, with overall figures increasing with age. Differences by sex were observed in IPCI, NLHR, and HI-SPEED, but not in APHM, H12O, and InGef RDB. These discrepancies may stem from differences in healthcare settings and the types of data included, as databases that included only primary care data (i.e., IPCI) or national records of dispensed prescriptions (i.e., NLHR, HI-SPEED) differed compared to those with hospital (i.e., APHM, H12O) or only claims data (i.e., InGef RDB). Similarly, the higher incidence rates observed among children in IQVIA DA Germany (in the previous study) and InGef RDB (in the current study) may reflect geographical differences in how paracetamol is accessed, with adults primarily purchasing OTC and children mainly obtaining prescriptions.

Rates stratified across formulations varied greatly across data sources, with oral tablets showing the highest incidence rates across most data sources. Oral liquid formulations and rectal suppositories were predominantly seen in children aged 1 to 5 and 6 to 11 years. These results align with those reported in the previous study and appear to be consistent with clinical practice, as these formulations are used for treating pain or fever in children, with rectal suppositories being used in cases of emesis or when oral administration is difficult. Injectable liquid formulations were mostly recorded in hospital databases, obtaining similar figures for incidence rates and prevalence in databases with information on drugs from inpatient settings (i.e., APHM and H12O).

Importantly, our results represent trends of prescribed/dispensed paracetamol, and do not account for paracetamol obtained with OTC purchases.(18) Among the countries included in this study, the Netherlands has no pack size restrictions on OTC paracetamol sales. In Norway, up to 5g paracetamol per pack can be purchased from non-pharmacy outlets (versus up to 10g OTC). In the other countries included, paracetamol is only available in pharmacies, with pack size limits up to 8g OTC in France and up to 10g OTC in both Germany and Sweden.

Different regulatory actions have been implemented at national level,(2) and might have played a role in the observed trends of paracetamol prescribing observed in this study. As an example, paracetamol sales from non-pharmacy outlets were introduced in Sweden in 2009 and were associated with increase in paracetamol poisonings.(19) In 2015, Sweden withdrew sales of mild analgesics including paracetamol (10g) from non-pharmacy outlets sold as regular tablets.(2) The short-term effects of these regulatory actions were not reflected in prescribing trends analysed in this study, as HI-SPEED only had drug data starting in 2018.

Paracetamol overdose:

A recent review estimated a weighted mean rate of paracetamol poisoning at 7.4 per 100,000 population per year (range 0.1–63.3) across 24 countries, including Denmark, Germany, and Sweden.(7) Our estimates were below this point estimate in InGef RDB and HI-SPEED (2 per 100,000 PY and 3 per 100,000 PY, respectively) and exceeded it in APHM and DK-DHR (13 per 100,000 PY and 31 per 100,000 PY, respectively), but were within the reported range. Differences were also seen in countries common to both studies, such as Sweden, which obtained one of the highest rates across all countries included in the review (>50 per 100,000 population per year) and one of the lowest rates in our study. These differences may stem from different case definitions and data sources, as most data in the review was based on poison information centres. As noted in the limitations section, we only considered diagnoses that explicitly specified poisoning or overdoses due to paracetamol, and therefore, cases documented using broader or less specific diagnostic terms may have been missed.

Incidence rates of paracetamol overdose varied across databases, with DK-DHR reporting rates twice as high as those observed in APHM, and between 8 and 13 times higher than those in InGef RDB and HI-SPEED. While these differences could be partially explained by variations in the type of data and healthcare settings covered, they could also reflect a true difference in rates between countries: it was reported previously that most countries with paracetamol for purchase only in pharmacies (e.g., France, Germany, and Sweden) have a lower rate of paracetamol-related poisoning enquiries than countries with paracetamol for purchase outside of pharmacies (e.g., Denmark).(7) In Sweden, a population-based registry study reported an increase in incidence rates per 100,000 population from 11.5 in 2009 to 16.2 in 2013, suggesting a 40% increase in the incidence of paracetamol-related poisonings four years after introducing paracetamol sales from non-pharmacy outlets.(19)

Regarding age and sex distribution, our findings are consistent with those reported in other studies, showing females to be more affected than males. Prior evidence has also shown that paracetamol is more commonly used by young people who self-harm, especially females.(20-23) This is consistent with findings obtained in our study, where rates among females aged 1–17 years in DK-DHR and APHM were substantially higher than those observed for other age and sex groups, and align with evidence from primary care databases from Spain in the UK included in the prior DARWIN EU® study.

A recent review reported a global case fatality rate of paracetamol overdose of 0.4% (range: 0.1% to 2.3%).(7) These findings broadly align with the all-cause mortality at 30 days obtained in this study (1.0% in DK-DHR; <5 events in APHM and InGef RDB) and the previous DARWIN EU® study (range: 0.2% to 1.3%). A prior population-based study conducted in Sweden reported a stable 30-day mortality of 3.2% following paracetamol overdose, with 2.4% having a diagnosis indicating a hepatic injury.(19) The proportion of individuals with hepatic toxicity align with that observed in DK-DHR (2.8%) but is lower than that reported for other databases (ranging from 5.1% in InGef RDB to 12% in APHM).

The extent to which overdoses captured in our study correspond to intentional overdoses is unknown. The global rate of intentional paracetamol overdose per 100,000 PY was estimated at 5.4 (range: 0.2 to 31.9) in a recent review.(7) A recent study using data from the United States Food and Drug Administration Adverse Event Reporting System (FAERS) found that paracetamol was the most reported drug used in deliberate self-poisoning (10.1% of deliberate self-poisoning; 16.7% including secondary suspects).(18) 41.1% of FAERS reports included in the study were from Europe. Globally, 67.1% of deliberate self-poisoning FAERS records with paracetamol were from females, the median reported age was 31 years, and 5.1% included psychiatric comorbidity. This was similar to our study population of individuals with paracetamol overdose: 70.1–75.8% were females, the median age was 21–32, and prevalence of depressive disorder ever before overdose was 8.2–39.7%. In the study using FAERS reports, 54% of cases of deliberate self-poisoning with paracetamol involved another substance: primarily other analgesics, including ibuprofen and tramadol, and alcohol. In our study, analgesics were among the most recorded medications, and alcohol was noted among the ten most common conditions in the year up to paracetamol overdose only in InGef RDB (acute alcohol

intoxication: 6.9%; alcohol dependence: 4.8%). The similarity in characteristics of our study populations with paracetamol overdose (intentional or unintentional) and the population described with FAERS records of deliberate self-poisoning with paracetamol, together with the difference in the case fatality rates reported in literature for paracetamol overdose intended or unintended (0.4%) versus intended only (24.3%; 32% in multiple drug intake), highlights the need for attention especially for individuals with prior record of intentional self-poisoning (6.1% in APHM).

The prevalence of comorbidities and medications use observed prior to paracetamol overdose differed across databases, with the lowest estimates obtained in APHM. These variations in recording are likely due to differences in healthcare settings from which the data were sourced, with APHM primarily reflecting inpatient care. In APHM, the exclusion of many individuals due to the prior history requirement (i.e. up to 50%) suggests that many individuals with paracetamol overdose entered the database at the time of the event, limiting available information on prior comorbidities and medication use. The fact that APHM is an inpatient database likely explains why hepatic toxicity and renal toxicity obtained the highest estimates in APHM. The low number of fatalities observed (i.e., reporting <5 fatalities in both time windows studied) might be partially explained by the low number of individuals with paracetamol overdose included in APHM (n=524) and the limitation that this database captures only in-hospital deaths.

Impact of prior history requirement:

Most results of the sensitivity analysis (no history prior to index date) were similar to those of the main analysis (at least 365 days of history prior to index date), except for APHM. Differences observed in APHM were likely driven by how observability is defined in the data. Imposing a one-year of prior history requirement excluded individuals whose index date (e.g., denominator entry for objective 1 or 2; date of paracetamol overdose for objective 3) occurred during the first year of observation. While this can affect all databases, it is particularly relevant in databases where observation is defined from one's first to last recorded entry, which is the case for APHM. This did not have a significant impact in other databases included in the study, such as health registries (e.g., DK-DHR, NLHR, HI-SPEED) or primary care databases (e.g., IPCI), where observation offers a more longitudinal coverage across the entire lifespan of individuals.

Some artefactual increases in incidence rates were observed in the first year of available data in both main and sensitivity analysis, especially in databases that began contributing data after 2010, but did not delay the study start by one year when applying the prior history requirement (i.e., NLHR, HI-SPEED). This also relates on how observability is defined in the data and has been discussed in detail in **10.5 Other information**.

10.4. Generalisability

This study included data from 7 databases from 7 different European countries (Denmark, France, Germany, The Netherlands, Norway, Spain, Sweden). However, not all data sources could inform all objectives, with objectives related to paracetamol overdose informed by data from four countries (Denmark, France, Germany, and Sweden).

We consider our findings to largely reflect population-level incidence and prevalence of paracetamol prescribing, as well as incidence of paracetamol overdose, particularly for health registries from Denmark (DK-DHR), Norway (NLHR), and Sweden (HI-SPEED). All three contain information on diagnoses recorded in secondary care settings, with NLHR and HI-SPEED also providing primary care data (covering approximately 40% of individuals in HI-SPEED) and include national records of dispensed medications. Therefore, results from these databases are broadly generalisable to their respective national populations.

IPCI is considered broadly representative of the population in the Netherlands,(24) and therefore, incidence and prevalence of paracetamol prescribing derived from this database are likely to be generalisable to the population living in the Netherlands in primary care settings. The representativeness of APHM, InGef RDB, and H12O to the populations of their respective countries and healthcare settings is unknown and, therefore, findings from these databases should not be generalised to their entire countries.

Considering both the current and the previous study (EUPAS1000000329), evidence provided in the context of DARWIN EU® was informed by a total of 14 databases from 10 countries. Of those, 13 participated in the objective related to paracetamol prescribing (all except CDWBordeaux, which participated in the characterisation objective only), and 7 participated in objectives related to paracetamol overdose (8 considering the characterisation objective).

It should be noted that some databases included were from the same country in both studies, including France, Germany, and Spain. However, healthcare settings and types of data differed, which hinders the comparison of results from the same country. This happened for all three countries, except for France, where both databases included data from hospital settings (APHM and CDWBordeaux).

As discussed in previous sections, both studies yielded generally consistent findings, particularly in the characterisation of individuals with paracetamol overdose. Although there were some differences in the absolute estimates of incidence and prevalence of paracetamol prescribing, the distribution by age, sex, and formulation was largely consistent across databases. This pattern also holds true for incidence rates of paracetamol overdose.

While we consider our results to largely reflect population-level incidence and prevalence of paracetamol prescribing and be largely representative of individuals diagnosed with paracetamol overdose in the respective countries and healthcare settings, results should not be generalised to Europe as differences in population characteristics and access to paracetamol OTS vary by country.

10.5. Other information

Please see below additional information for interpretation of results:

1. **Prior history requirements and study periods**

   Some of the databases included did not provide data for the entire study period (2010–2023) and contributed fewer years of data (i.e., APHM, InGef RDB, HI-SPEED, NLHR). In some cases, the study period start concurred with the start date of data collection or availability (i.e., APHM: 2014; InGef RDB: 2015; HI-SPEED: 2015 for objective 2 and 3). For these databases, the requirement of one year of prior history reduced the study period by one year for the main analysis (e.g., APHM: 2015; InGef RDB: 2016; HI-SPEED: 2016 for objective 2 and 3). The requirement of one year of prior history did not affect NLHR or HI-SPEED (Objective 1), as individuals were in observation before 2018. For both registries, observability is defined in the data from the start of data collection or from birth, whichever occurred later. In HI-SPEED, the start of data collection is 2015. For NLHR, observability begins in 2008, though data on conditions and medications are only captured from 2018 onwards.

2. **Artefactual increases in incidence rates**

   We observed some artefactual increases in annual incidence rates assessed in this study, which mostly occurred during the first and last years of data.

   Artefactual increases in the first year of data were observed in databases that began contributing data after the study start (2010) but did not delay the study start by one year to apply the prior history requirement. As explained in the previous point, this was the case for HI-SPEED (objective 1) and NLHR, which could provide data since the first year of data availability. This likely caused the artefactual increase in incidence rates of paracetamol prescribing observed in 2018 (**Figure 1**). This pattern was not observed in databases where data availability began years before the study start (e.g., IPCI), and it did not appear to introduce major artefacts in databases that started after 2010 and applied a one-year delay to the study start to account for the prior history requirement of 365 days (i.e., APHM, InGef RDB).

   Regarding paracetamol overdose, no artefacts during the first year of data were detected in HI-SPEED, as for the main analysis the study start (2015) was delayed by one year to fulfil the prior

history requirement (from 2016 onwards) (**Figure 9**). Some artefacts were observed in the sensitivity analysis when data from 2015 was included (**Figure 12**). However, these were less pronounced than those observed in 2018 for paracetamol prescribing (**Figure 11**).

Artefacts in the sensitivity analysis were mostly observed in APHM, which contributed data from the first year of available data (2014) after removing the prior history requirement, resulting in increased incidence rates during the first year of data (**Figure 11** and **Figure 12**).

We also observed artefacts in the last year of data in APHM (**Figure 1** and **Figure 9**), which are also likely to be caused by the strategy used to define observability in the data. In APHM, observation ends at the date of the last visit or encounter with the healthcare system, resulting in fewer people under observation in the final years. Consequently, the denominator presents an artefactual decrease whilst the incident events remain, incrementing incidence rates over the last points of available data. While this artefact was particularly pronounced for paracetamol prescribing (**Figure 1**), it also occurred for paracetamol overdose. However, this was less noticeable in the observed trends as the number of events peaked in 2022 (**Figure 9**). However, denominators for incidence calculations in APHM decreased in 2023 in both cases.

3. **Characterisation of patients with paracetamol overdose: Comorbidities and medication use**

   When interpreting the occurrence of comorbidities and medications, note that frequencies described in this report represent the number of individuals with a record of the condition of interest within the specified time window. These frequencies may differ from the actual prevalence of the disease, as they do not account for its duration. For example, a cancer diagnosis recorded two years before index date is likely relevant in the year preceding index date but is not included in the time assessment of one year prior if no record of the disease exists within that period. For medications, individuals with a record of a drug of interest during the time interval were considered to be actively taking the medication, even if the prescription began earlier. For example, if a prescription for a drug spans six months up to one month after index date, it is included in the one-month-prior time window, regardless of its initial start date.

   In the large-scale characterisation, all comorbidities and comedications recorded within pre-defined time windows of interest among individuals with paracetamol overdose were described. Conditions identified through large-scale characterisation are based on individual concept-level codes and may differ from those reported as pre-specified conditions. For example, pain was reported in 41.4% of individuals in DK-DHR when assessed as a pre-specified condition, compared to 33.9% when assessed through large-scale characterisation, using the same one-year assessment window. These discrepancies arise because the pre-specified condition was defined using a combination of concepts (outlined in **Appendix II**), whereas the large-scale characterisation estimate reflects the recording of a single concept only.

11. CONCLUSION

Incidence rates per 100,000 PY of paracetamol prescribing ranged between 2,166 to 20,340, and prevalence from 8.8% to 36.9%. Incidence and prevalence of paracetamol prescribing increased with age except for InGef RDB, where the opposite pattern was observed. Females reported higher estimates compared to males in databases with primary care data (i.e., IPCI) or national records of dispensed prescriptions (i.e., NLHR, HI-SPEED).

Oral tablet formulations were generally the most prescribed, although variations by database existed. Oral liquid formulations were more frequently prescribed among individuals aged 1 to 5 years, and injectable liquid formulations were primarily recorded in hospital databases.

Incidence of paracetamol overdose per 100,000 PY was 31 (95% CI 31 to 31) in DK-DHR, 13 (12 to 15) in APHM, 2 (2 to 2) in InGef RDB, and 3 (2 to 3) in HI-SPEED. Incidence rates observed among females were 2–4 times bigger than those observed for males. Individuals aged 1–17 years obtained higher rates than those aged 18 or older in all databases except for HI-SPEED, where no differences between these two age groups were observed.

Individuals with paracetamol overdose had a median age of 21 to 32 years and were predominantly females. Most frequently recorded conditions prior to paracetamol overdose included pain, anxiety disorders, and depressive disorders. In all databases except for APHM, approximately 30% had a depressive disorder in the year prior or were prescribed antidepressants in the year leading up to a month prior to paracetamol overdose. Paracetamol ranked as the most prescribed ingredient during the year leading up to, and in the month preceding paracetamol overdose in all databases, except for InGef RDB. Paracetamol prescribing in the month preceding paracetamol overdose varied in size and was estimated at 1.6% in InGef RDB, 1.9% in APHM, 17.8% in HI-SPEED, and 16.3% in DK-DHR.

Diagnoses indicating hepatic toxicity were observed in up to 12.0% of cases and renal toxicity was in up to 4.2% of cases in the month following the paracetamol overdose. All-cause mortality in the following 30 days was rare and occurred in less than 1.0% of cases.

The findings reported in this study demonstrate consistency with those reported in the earlier DARWIN EU® study (EUPAS1000000329), strengthening the evidence on this topic in Europe.

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13. ANNEXES

ANNEX I. Additional information

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 standardised analytics wherever possible. Each data partner executed the study code against their data source containing individual-level 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 individual-level data and performing only a central analysis, local analyses were run, which generate non-identifiable aggregate summary results.

QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, all data partners ran the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness, and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions. Completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

The Systematized Nomenclature of Medicine (SNOMED) codes of the conditions and outcomes of interest were derived from ATLAS. The codes were then reviewed by two clinical epidemiologists to consider their relevance and accuracy. In addition, the "*CohortDiagnostics"* R package (https://github.com/OHDSI/CohortDiagnostics) was run to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error. This allowed for a

consideration of the validity of the study cohort of individuals with the selected conditions and outcomes in each of the databases and informed decisions around whether multiple definitions were required.

ANNEX II. Additional information

Table S1. Code list for paracetamol.

Concept ID[1]	Concept name
1125315	Paracetamol

[1] All descendants included.

Table S2. Code list for definition of paracetamol overdose.

Concept ID	Concept name
4322306	Poisoning caused by acetaminophen
4173525	Acetaminophen overdose
4166500	Accidental acetaminophen overdose
4055123	Intentional paracetamol overdose
4159373	Accidental acetaminophen poisoning
4157354	Intentional paracetamol poisoning

Table S3. Dose forms for paracetamol formulations.

Formulation	Dose forms[1]
Oral tablets	Chewable tablet, Chewable extended release oral tablet, delayed release oral tablet, disintegrating oral tablet, effervescent oral tablet, disintegrating oral tablet, effervescent oral tablet, extended release oral tablet, oral tablet, oral tablet with sensor
Oral capsule	Oral capsule, delayed release oral capsule, extended release oral capsule
Oral liquid solutions	Oral solution, powders for oral solution, granules for oral solution, oral powder, oral suspension, oral granules, granules for oral suspension, powder for oral suspension, tablet for oral suspension
Injectable formulations	Injection, injectable solution, intravenous solution, intravenous suspension, intramuscular prolonged release suspension, intramuscular solution, intravenous solution; injection, injection; intravenous solution, prefilled syringe.
Rectal suppository	Rectal suppository

[1] All codes belonging to specified dose forms containing paracetamol were included.

Table S4. Code list for pre-specified conditions.

Concept ID[1]	Pre-specified comorbidity
4218106	Alcoholism
4212540	Chronic liver disease
46271022	Chronic kidney disease
440383	Depressive disorders
442077	Anxiety disorders

435783	Schizophrenia
433736	Obesity
443392	Cancer
4167092, 80180, 4291025	Arthritis/arthrosis
4329041	Pain
437663	Fever
432250	Infectious disease

[1] All descendants included.

Table S5. Code list for hepatic toxicity.

Concept ID	Concept name
4026032	Acute hepatic failure
4184847	Acute hepatic failure due to drugs
4243475	Acute hepatitis
36676901	Acute infantile liver failure with multisystemic involvement syndrome
4169242	Acute toxic hepatitis
4139051	Allergic hepatitis
4318541	Cholestatic hepatitis
37396401	Decompensated cirrhosis of liver
4222609	Drug-induced cholestatic hepatitis
4342774	Drug-induced chronic hepatitis
4143008	Drug-induced cirrhosis of liver
4144765	Drug-induced disorder of liver
4231815	Drug-induced hepatic necrosis
4340942	Drug-induced hepatitis
45769564	End stage liver disease
1340280	Exacerbation of chronic active hepatitis
1340484	Exacerbation of toxic liver disease
4340389	Fulminant hepatic failure
4342883	Hepatic ascites
46273476	Hepatic ascites co-occurrent with chronic active hepatitis due to toxic liver disease
377604	Hepatic coma
46269814	Hepatic coma due to acute hepatic failure
46269949	Hepatic coma due to subacute liver failure
4029488	Hepatic encephalopathy
42710029	Hepatic encephalopathy in fulminant hepatic failure
4245975	Hepatic failure
4309163	Hepatic failure as a complication of care
196455	Hepatorenal syndrome

4308408	Hepatorenal syndrome as a complication of care
42536533	Hypersensitivity disease of liver caused by drug
4059281	Subacute hepatic failure
4342773	Subfulminant hepatic failure
4046016	Toxic cirrhosis
4055223	Toxic hepatitis
4055224	Toxic liver disease
4059297	Toxic liver disease with acute hepatitis
4058694	Toxic liver disease with cholestasis
4059299	Toxic liver disease with chronic active hepatitis
4055225	Toxic liver disease with chronic lobular hepatitis
4059298	Toxic liver disease with chronic persistent hepatitis
4058695	Toxic liver disease with fibrosis and cirrhosis of liver
4026136	Toxic liver disease with hepatic necrosis
4052963	Toxic noninfectious hepatitis
4059287	Toxic portal cirrhosis

Table S6. Code list for renal toxicity.

Concept ID	Concept name
4030519	Acute drug-induced renal failure
4137752	Acute drug-induced tubulointerstitial nephritis
37116430	Acute kidney failure stage 1
37116431	Acute kidney failure stage 2
37116432	Acute kidney failure stage 3
37395516	Acute kidney injury due to acute tubular necrosis due to circulatory failure
37395521	Acute kidney injury due to acute tubular necrosis due to circulatory failure with histological evidence
37395514	Acute kidney injury due to acute tubular necrosis due to hypovolaemia
37395519	Acute kidney injury due to acute tubular necrosis due to hypovolaemia with histological evidence
37395518	Acute kidney injury due to acute tubular necrosis with histological evidence
36716182	Acute kidney injury due to circulatory failure
36716183	Acute kidney injury due to hypovolemia
44809061	Acute kidney injury stage 1
44809062	Acute kidney injury stage 2
44809063	Acute kidney injury stage 3
45757442	Acute nontraumatic kidney injury
197329	Acute renal failure due to acute cortical necrosis
4311129	Acute renal failure due to ischemia
45757466	Acute renal failure due to tubular necrosis

44809170	Acute renal failure induced by poison
45757398	Acute renal failure on dialysis
197320	Acute renal failure syndrome
4160274	Acute renal failure with oliguria
4126305	Acute renal impairment
36716946	Acute renal insufficiency
432961	Acute renal papillary necrosis with renal failure
4126120	Acute toxic nephropathy
444044	Acute tubular necrosis
606419	Acute tubular necrosis caused by toxin
606418	Acute tubular necrosis due to mixed ischemic and toxic causes
4128067	Acute-on-chronic renal failure
4244418	Analgesic nephropathy
37312165	Atypical hemolytic uremic syndrome
4128228	Chronic drug-induced renal disease
4128206	Chronic drug-induced tubulointerstitial nephritis
4126442	Chronic toxic interstitial nephritis
604484	Dependence on prolonged intermittent renal replacement therapy due to renal failure
4019967	Dependence on renal dialysis
4159967	Diarrhea-negative hemolytic uremic syndrome
36716200	Drug-induced membranous nephropathy
4043348	Drug-induced nephrogenic diabetes insipidus
4208918	Drug-induced tubulointerstitial nephritis
4030520	End stage renal failure on dialysis
4128200	End stage renal failure untreated by renal replacement therapy
4125970	End stage renal failure with renal transplant
193782	End-stage renal disease
197253	Hemolytic uremic syndrome
4267646	Hemolytic uremic syndrome of childhood
4302298	Hemolytic uremic syndrome, adult type
196455	Hepatorenal syndrome
4308408	Hepatorenal syndrome as a complication of care
4126432	Hyperkalemic renal tubular acidosis
193519	Impaired renal function disorder
42536547	Ischemia of kidney
600855	Nephritis caused by drug
4126424	Nephrotoxic acute renal failure
4048200	Nephrotoxic serum nephritis
45770903	Prerenal renal failure

4126427	Pulmonary renal syndrome
4153876	Renal failure as a complication of care
192359	Renal failure syndrome
42538752	Renal hypersensitivity caused by drug
4030518	Renal impairment
36716945	Renal insufficiency
36716169	Renal papillary necrosis caused by analgesic drug
37397038	Renal tubulopathy with encephalopathy and liver failure syndrome
4126119	Toxic nephropathy
4139414	Transient acute renal failure

Table S7. Code list for pre-specified medications.

Concept ID[1]	Pre-specified comorbidity
740275	Carbamazepine
1782521	Isoniazid
21604635, 21604653, 21604565	Benzodiazepines
21604254	Opioid analgesics
21603933	Nonsteroid anti-inflammatory drugs[2]
21604490	Antipsychotics
21604686	Antidepressants
1125315	Paracetamol

[1] All descendants included.
[2] Excluding all descendants of: 21604004, 21604002, 21604013, 40254364, 216039

Table S8. Study attrition of individuals in the sensitivity analysis included in the denominator for objectives 1 and 2 (where applicable).

	DK-DHR (Obj 2)	APHM(Obj 1&2)	InGef RDB (Obj 1&2)[1]	IPCI (Obj 1)	NLHR (Obj 1)[2]	H12O (Obj 1)	HI-SPEED (Obj 1)[3]	HI-SPEED (Obj 2)[3]
Starting population	8,593,356	2,329,771	10,512,283	2,870,221	6,114,138	2,218,528	11,739,647	11,739,647
Birth date available	8,593,356	2,329,771	10,512,283	2,870,221	6,114,138	2,218,528	11,739,647	11,739,647
Sex available	8,593,356	2,328,230	10,512,283	2,870,221	6,114,138	2,218,257	11,739,647	11,739,647
Satisfied age criteria during the study period based on year of birth	8,484,906	2,304,534	10,423,421	2,858,836	6,065,401	2,203,389	11,653,562	11,653,562
Individuals with observation time available during study period	7,248,363	2,178,990	10,274,573	2,822,862	6,004,439	1,551,752	11,276,375	11,653,517
Individuals with observation time available after applying age and prior observation	7,240,430	2,125,496	10,253,218	2,802,511	6,000,740	1,524,024	11,273,746	11,649,370

DK-DHR=Danish Data Health Registries; APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.
[1] Study period for InGef RDB spans from 2015 onwards.
[2] Study period for NLHR spans from 2018 onwards.
[3] The denominators and study periods in HI-SPEED differ between objectives 1 and 2. Study period for objective 1 spans from 2018 onwards; study period for objective 2 spans from 2015 onwards.

Table S9. Study attrition of individuals in the sensitivity analysis included in objective 3.

	DK-DHR	APHM	InGef RDB	HI-SPEED
Qualifying initial records (first event)	30,335	1,168	1,416	2,444
Require cohort_start_date within study period[1]	21,639	1,029	1,308	2,444
Require age >1	21,598	1,027	1,298	2,444

DK-DHR=Danish Data Health Registries; APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.
[1] For InGef RDB and HI-SPEED, the study period spanned from 2015 onwards. For NLHR, the study period spanned from 2018 onwards.

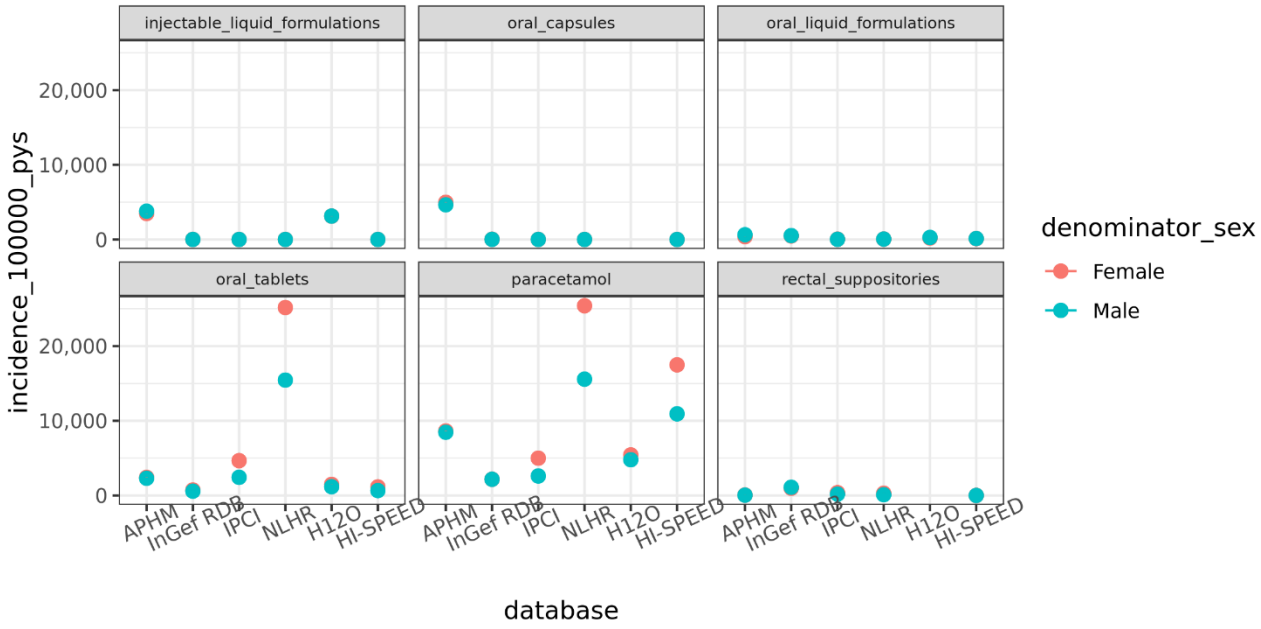

Figure S1. Incidence rates of paracetamol by formulation and sex.

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

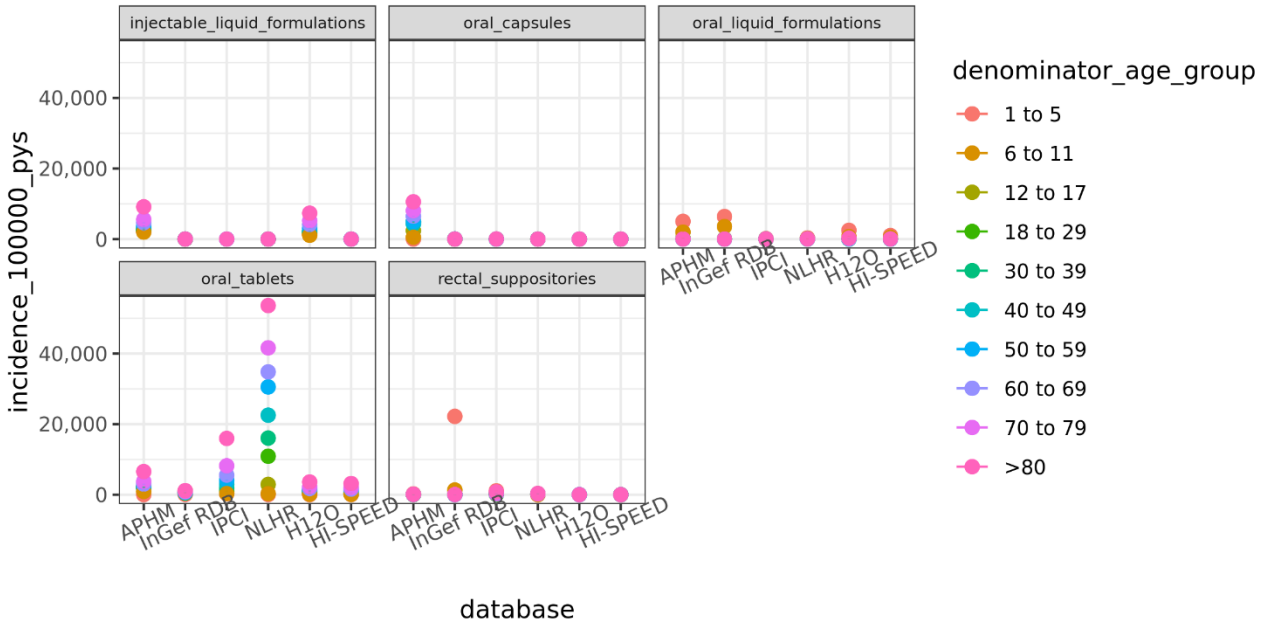

Figure S2. Incidence rates of paracetamol by formulation and age group.

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

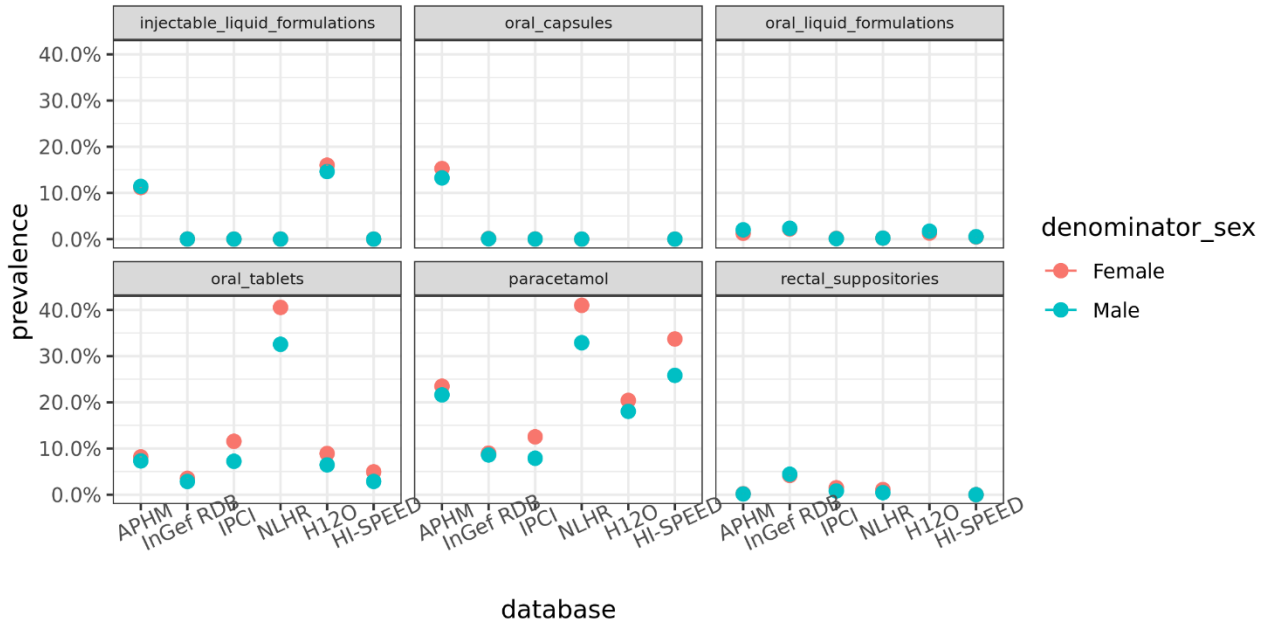

Figure S3. Prevalence of paracetamol prescribing by formulation and sex.

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

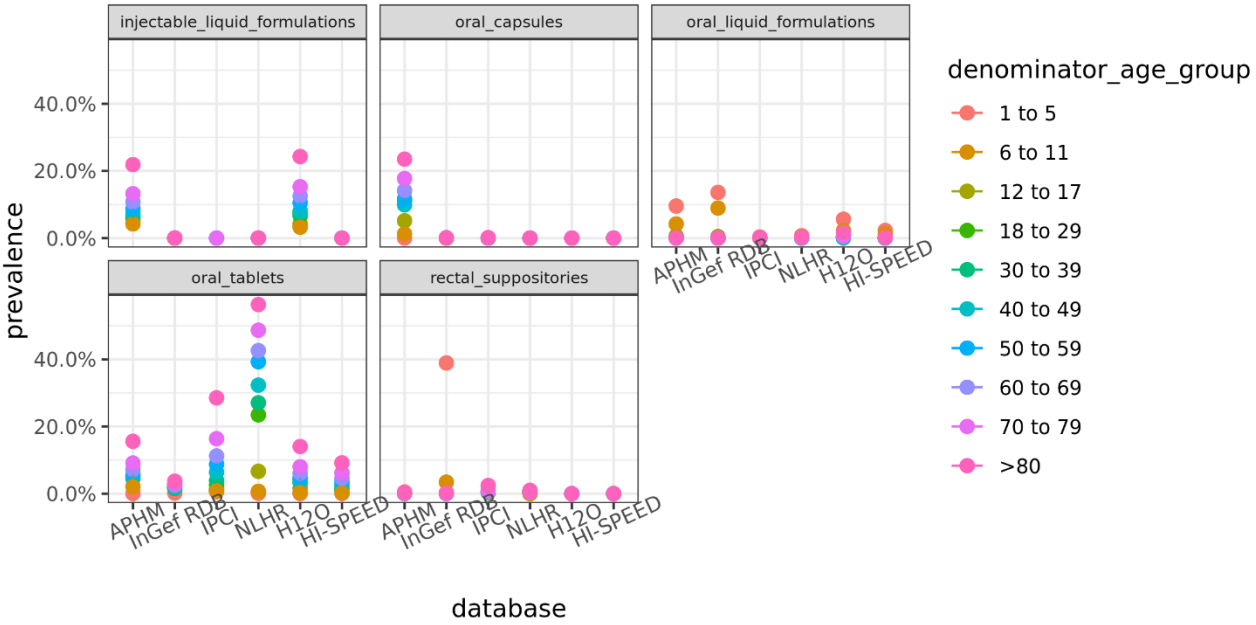

Figure S4. Prevalence of paracetamol prescribing by formulation and age group.

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.

Figure S5. Annual prevalence of paracetamol prescribing by calendar year in the sensitivity analysis (0 days prior history) versus main analysis (365 days prior history).

APHM=Assistance Publique - Hôpitaux de Marseille; InGef RDB=InGef Research Database; IPCI=Integrated Primary Care Information; NLHR=Norwegian Linked Health Registry data; H12O=Hospital Universitario 12 de Octubre; HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage.