Study Report

P3-C1-007

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

20/02/2025

Version 2.0

Contents

Study title	DARWIN EU® – Paracetamol prescribing and paracetamol overdose in Europe: a descriptive analysis of trends and patient characteristics
Study report version	V2.0
Date	20/02/2025
EU PAS number	EUPAS1000000329
Active substance	Paracetamol
Medicinal product	Not applicable
Research question and objectives	The aim of the study was 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 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.
Countries of study	Croatia, Denmark, France, Germany, Portugal, Spain, United Kingdom.
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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 roles	Names	Organisations
Principal Investigator	Berta Raventós Talita Duarte-Salles	Erasmus MC
Data Scientist	Ger Inberg Cesar Barboza Maarten van Kessel Adam Black Ross Williams	Erasmus MC
Epidemiologist	Nicolas Hunt Julieta Politi Guido van Leeuwen	Erasmus MC
Data partner name*	**Data Partner member names**	**Organisations**
BIFAP	Elisa Martin-Merino Miguel-Angel Maciá-Martinez Juan-Ignacio Díaz-Hernández Ana Llorente-Garcia	Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)
CDWBordeaux	Romain Griffier Guillaume Verdy	Bordeaux University Hospital
CPRD GOLD	Antonella Delmestri	University of Oxford
IQVIA DA Germany	Gargi Jadhav Isabella Kacmarczyl Akram Mendez Hanne van Ballegooijen Dina Vojinovic	IQVIA
DK-DHR	Claus Møldrup Elvira Bräuner Susanne Bruun Tine Iskov Kopp Cæcilie Brinth Christiansen	Danish Medicines Agency (DKMA)

Study team roles	Names	Organisations
EMBD-USEDV	Firmino Machado Ana Pinto Luís Malheiro Luís Ruano Mesquita Bastos	Clinical Academic Center Egas Moniz Health Alliance
NAJS	Pero Ivanko Marko Čavlina Antea Jezidžić Marija Švajda	Croatian Institute of Public Health
UKBB	Antonella Delmestri	University of Oxford

*Data partners' role is only to execute code at their data source, review and approve their results. These people do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for these people is not needed.

3. DATA SOURCES

Country	Name of Database	Health Care setting[1]	Type of Data[2]	Number of subjects[3]	Data lock for the last update
Spain	BIFAP	Primary care, hospital care (IP)	EHRs, claims, registries	22M	22-05-2024
France	CDWBordeaux	Hospital care (IP, OP)	EHRs, claims	2.2M	22-02-2024
UK	CPRD GOLD	Primary care	EHRs	17.4M	04-03-2024
Denmark	DK-DHR	Hospital care (IP, OP)	EHRs, registries, others	8.5M	21-05-2024
Portugal	EMBD-ULSEDB	Hospital care (IP, OP)	EHRs, registries	563k	31-08-2023
Germany	IQVIA DA Germany	Primary care	EHRs	43.1M	30-09-2023
Croatia	NAJS	Primary care, hospital care (IP, OP)	Registries	5.4M	17-11-2023
UK	UKBB	Primary care, hospital care (IP, OP)	EHRs, registries, biobank	502k	01-03-2020

1. IP = inpatient, OP = outpatient
2. EHR = electronic health records
3. This number corresponds to all-patients recorded in the data

4. ABSTRACT

Title

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

Rationale and background

Paracetamol is one of the most common causes of drug poisoning and can result in severe hepatic failure. Different regulatory interventions at national level have been implemented 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 study.

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 of December 2023 (or the latest year with complete observation). For objective 3, the study included individuals diagnosed with paracetamol overdose for the first time in their patient history.

Individuals aged less than 1 year were excluded. A year of observation history prior to index date was required for all individuals within selected databases except CDWBordeaux. For objective 3, individuals with a prior history of paracetamol overdose any time prior to index date were excluded.

Variables

The drug of interest was paracetamol, and the condition of interest was paracetamol overdose.

Data sources

1. Base de datos para la investigación Farmacoepidemiológica en el Ámbito Público (BIFAP), Spain
2. Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France
3. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
4. Danish Data Health Registries (DK-DHR), Denmark

5. Egas Moniz Health Aliance database – Entre o Douro e Vouga (EMBD- ULSEDV), Portugal
6. IQVIA Disease Analyzer (IQVIA DA) Germany, Germany
7. Croatian National Public Health Information System (NAJS), Croatia
8. UK BioBank (UKBB), United Kingdom

Statistical analysis

Objective 1 was conducted in all databases except for CDWBordeaux. Objective 2 was conducted in BIFAP, CPRD GOLD, and UKBB. Objective 3 was conducted in BIFAP, CDWBordeaux, CPRD GOLD, and UKBB.

Incidence rates of paracetamol prescribing and overdose and period prevalence of paracetamol prescribing with 95% confidence intervals (CI) were calculated overall and stratified by sex, age, and formulation. Estimates were calculated yearly. For incidence calculations, individuals with a record of the outcome of interest were allowed to re-enter the study after a certain amount of time (i.e. washout window) so further occurrences of the outcome could be captured. This washout window was defined as 60 days following the end of the prescribed treatment for paracetamol prescribing and 365 days for paracetamol overdose. Characteristics of patients with paracetamol overdose were described based on pre-specified conditions and medications, and by means of large-scale characterisation. Covariates of interest were reported as counts and proportions.

For all analyses, results were reported by country/database, and any counts smaller than 5 were obscured to ensure privacy and confidentiality.

Results

Incidence rates of paracetamol prescribing per 100,000 person-years ranged between 5,625 in UKBB to 12,686 in BIFAP. Prevalence of paracetamol prescribing ranged from 5.2% in IQVIA DA Germany to 65.1% in BIFAP. In general, figures were higher among females than males and increased with age. When stratified by formulation, oral tablet formulations had the highest estimates of prescribing, while injectable liquid formulations were generally the least prescribed. Oral liquid formulations and rectal suppositories were more frequently prescribed among individuals aged 1 to 5 years.

Incidence of paracetamol overdose per 100,000 was 2 (95% CI: 2 to 2) in BIFAP, 5 (5 to 5) in CPRD GOLD and 21 (20 to 23) in UKBB. Incidence of paracetamol overdose was higher among females, reaching three times the rate observed among males in BIFAP, and higher among individuals aged 1 to 17 years compared to those aged 18 or older, particularly among females.

We identified 8,370 patients with paracetamol overdose (n=2,480 in BIFAP; n=2,125 in CDWBordeaux; n=3,140 in CPRD GOLD; n=625 in UKBB). Females represented 55.4% to 67.3% of cases. Median age at paracetamol overdose diagnosis was 21 to 25 years across databases with information on all ages. The most frequent pre-specified conditions considering all prior history were pain (ranging from 17.1% to 73.5%), depressive disorder (ranging from 14.0% to 42.4%), anxiety disorders (ranging from 9.7% to 21.0%) and arthritis and arthrosis (ranging from 1.3% to 29.3%). The most frequent pre-specified medications prescribed in the year leading up to a month before index date (-365 to -31 days) were antidepressants (ranging from 3.1% to 37.3%), benzodiazepines (ranging from 5.8% to 29.3%) and paracetamol. Prior paracetamol prescriptions in the year leading up to a month before index date (-365 to -31 days) were recorded for 37.2% of patients in BIFAP, 7.2% in CDWBordeaux, 22.3% in CPRD GOLD, and 17.1% in UKBB in the year leading up to a month before the OD. In the month prior, corresponding figures (in the same order) were 16.7%, 2.1%, 12.2%, and 10.6%. Records of poisoning, overdose, suicidal thoughts and self-inflicted injuries were captured in the year prior through large-scale characterisation in some databases. In

the month following the paracetamol overdose, coded hepatic toxicity was observed in less than 11% of cases, renal toxicity in less than 5% of patients, and mortality in less than 1.5% of cases.

Conclusion

Incidence and prevalence of paracetamol prescribing were higher among females than males and increased with age. Incidence of paracetamol was higher among females, especially those aged 1 to 17 years. An identifiable proportion of patients with paracetamol overdose had a prior history of mental health problems and were prescribed with antidepressants, benzodiazepines. In the four databases examined, paracetamol was prescribed in the year prior to paracetamol overdose between in 7.2% to 37.2% of cases. Hepatic toxicity following paracetamol overdose occurred in approximately less than 11% of cases.

5. LIST OF ABBREVIATIONS

Acronyms/terms	Description
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
BIFAP	Base de datos para la investigación Farmacoepidemiológica en el Ámbito Público
CDM	Common Data Model
CDW	Clinical Data Warehouse
CDWBordeaux	Clinical Data Warehouse of Bordeaux University Hospital
CI	Confidence Interval
CIPH	Croatian Institute of Public Health
CPRD GOLD	Clinical Practice Research Datalink GOLD
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
EHR	Electronic Health Record
EMA	European Medicines Agency
EMBD- ULSEDV	Egas Moniz Health Aliance database – Entre o Douro e Vouga
EU	European Union
GDPR	General Data Protection Regulation
GP	General Practitioner
IQVIA DA	IQVIA Disease Analyzer
NAJS	Croatian National Public Health Information System
NAPQI	N-acetyl-p-benzoquinoneimine
NSAIDs	Nonsteroid Anti-inflammatory Drugs (NSAIDs),
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OTC	Over The Counter
PY	Person-Years
UK	United Kingdom
UKBB	UK BioBank
WHO	World Health Organization

6. AMENDMENTS AND UPDATES

None.

7. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Draft Study Protocol	23rd August	23rd August
Final Study Protocol	30th September 2024	30th September 2024
Creation of Analytical code	September/October 2024	September/October 2024
Execution of Analytical Code on the data	October 2024	November/December 2024
Draft Study Report	November 2024	28th January 2025
Final Study Report	November/December 2024	February 2025

8. RATIONALE AND BACKGROUND

Paracetamol (acetaminophen) is one of the most widely used medicines worldwide and is listed by the World Health Organisation (WHO) as an essential medicine.(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 it is available through non-pharmacy outlets in some countries.(2)

Paracetamol can be found in different pharmaceutical forms and in different doses. The usual adult recommended dose is 500mg to 1000mg, with a maximum daily dose of 3000 to 4000mg/day.(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 not available in the European Union (EU), as the European Medicines Agency (EMA) recommended suspending 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. However, toxicity is common following paracetamol overdose, and it can result in severe hepatic failure. Inadvertent overdose can result from taking additional doses, repeated supratherapeutic ingestion, and duplication of therapy.

Paracetamol is principally metabolised by glucuronidation and sulfation.(5) Small amounts are converted into the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI), which is detoxified via conjugation with glutathione. Toxicity results in 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. Other risk factors include treatment with medications that induce the activity of the cytochrome CYP2E1 (e.g. carbamazepine, isoniazid),

glutathione depletion (e.g. in patients with malnutrition or anorexia) and chronic alcohol use.(6) Chronic liver disease patients are also at increased risk for hepatoxicity.(7) 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 detoxifying NAPQI. The risk of developing hepatotoxicity is substantially reduced when treatment is initiated within 8 hours of ingestion.(8, 9) Severe cases may require liver transplantation or result in death.(10)

Paracetamol is one of the most common causes of drug poisoning, 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 severe acute liver injury and acute liver failure and 7% of drug-induced liver injury, with 0.4% of fatal cases.(11) Different regulatory interventions at national level have been implemented over many years aimed at reducing the incidence of overdose, such as restrictions in pack size and the total amount available to purchase OTC.(2) However, it is uncertain how paracetamol is being prescribed across Europe and to what extent prescription of paracetamol is involved in paracetamol poisonings.

9. 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.

10. RESEARCH METHODS

10.1 Study type and study design

The study types with related study designs are described in the **Table 1** below and were selected from the Catalogue of Data Analytics.

Retrospective cohort studies were conducted using routinely collected health data from 8 databases. The study was comprised of:

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).

Table 1 Description of potential study types and related study designs.

Study type	Study design	Study classification
Population Level DUS	Population Level Cohort	Off the shelf
Population-level descriptive epidemiology	Population-level cohort	Off the shelf
Patient-level characterisation	Cohort analysis	Off the shelf

10.2 Study setting and data sources

This study was conducted using routinely collected data from 8 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, the suitability of denominator population for population-level rates, geographical spread, and diversity of healthcare settings. Based on the feasibility assessment performed, the suggested databases were considered fit for purpose for at least some of the study objectives:

1. Base de datos para la investigación Farmacoepidemiológica en el Ámbito Público (BIFAP), Spain
2. Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France
3. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom (UK)
4. Danish Data Health Registries (DK-DHR), Denmark
5. Egas Moniz Health Aliance database – Entre o Douro e Vouga (EMBD- ULSEDV), Portugal
6. IQVIA Disease Analyzer (IQVIA DA) Germany, Germany
7. Croatian National Public Health Information System (NAJS), Croatia
8. UK BioBank (UKBB), UK

Information on data sources used with a justification for their choice in terms of ability to capture the relevant data is described in **Table 2.**

All databases except CDWBordeaux were used to inform objective 1. Objective 2 were informed by BIFAP, CPRD GOLD, and UKBB. Objective 3 were informed by BIFAP, CDWBordeaux, CPRD GOLD, and UKBB. Other databases did not contribute to objectives 2 and 3 due to limited counts for paracetamol overdose observed in the study feasibility assessment.

BIFAP contributed to objectives 2 and 3 using data from 2014 onwards to ensure a higher coverage of hospital data, which is available for approximately 70% of patients starting from that year. In addition, the analysis was restricted to participants registered in regions with hospital linkage only. These restrictions were implemented to ensure that denominators for incidence calculations of paracetamol overdose were consistent. This restriction was not applied to objective 1 but was implemented for objective 3 to maintain consistency.

Table 2. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting[1]	Type of Data[2]	Number of subjects[3]	Feasibility count of paracetamol overdose[4]	Data lock for the last update
Spain	BIFAP	Linkage to hospital records is available for some geographical areas. Time periods of availability for hospital data differ across geographic areas. Observed records of individuals with paracetamol overdose. Suitable denominator population for population-level rates Contribute to the diversity of data sources in terms of geography and healthcare settings.	Primary care, hospital care (IP)[5]	EHRs, claims, registries	22.M	1,200	22-05-2024
France	CDWBordeaux	Observed records of individuals with paracetamol overdose occurring within hospital settings. Contribute to the diversity of data sources in terms of geography and healthcare settings.	Hospital care (IP, OP)	EHRs, claims	2.2 M	2,200	22-02-2024
UK	CPRD GOLD	Observed records of individuals with paracetamol overdose. Suitable denominator population for population-level rates Contribute to the diversity of data sources in terms of geography and healthcare settings.	Primary care	EHRs	17.4 M	4,800	04-03-2024
Denmark	DK-DHR	Contribute to the diversity of data sources in terms of geography and healthcare settings.	Hospital care (IP, OP)	EHRs, registries, others.	8.5 M	<5	21-05-2024
Portugal	EMBD-ULSEDV	Contribute to the diversity of data sources in terms of geography and healthcare settings.	Hospital care (IP, OP)	EHRs, registries	563 k	100	31-08-2023

Germany	IQVIA DA Germany	Suitable denominator population for population-level rates Contribute to the diversity of data sources in terms of geography and healthcare settings.	Primary care	EHRs	43.1 M	100	30-09-2023
Croatia	NAJS	Contribute to the diversity of data sources in terms of geography and healthcare settings.	Primary care, hospital care (IP, OP)		5.4 M	100	17-11-2023
UK	UKBB	Contribute to Objective 2 and 3, with limited counts on paracetamol overdose. Complement evidence from the UK with data from other healthcare settings.	Primary care, hospital care (IP, OP)	EHRs, registries, biobank	502 k	300	01-03-2020

[1] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

[2] EHR = electronic health records

[3] This number corresponds to all-patients recorded in the data.

[4] Person counts provided as part of the feasibility assessment using preliminary concepts. All counts are rounded up to the nearest multiple of 100.

[5] Hospital data is available for 7 out of 9 Spanish regions included in BIFAP. However, hospital data is available during different time periods for each region. From 2014 onwards, hospital linkage is available for approximately over 70% of patients, with the regions with linkage available reaching almost 100% of patients

Pharmacoepidemiological Research Database for Public Health Systems (BIFAP), Spain

BIFAP (http://www.bifap.org/?lang=en) is a longitudinal population-based data source of medical patient records of the Spanish National Health Service. It includes data from 9 of Spain's 17 autonomous regions. Population currently included represents 36% of the total Spanish population. The Spanish National Health Service provides universal access to health services through the Regional Healthcare Services. Primary care physicians, both general practitioners (GP) and paediatricians, act as gatekeepers of the system and exchange information with other levels of care to ensure the continuity of care. Most of the population (98.9%) is registered with a primary care physician and most drug prescriptions are written at the primary care level. BIFAP includes a collection of databases linked at individual patient level. The main one is the Primary care Database given the central role of primary care physicians in the Spanish National Health Service.

There are additional important structural databases like the medicines dispensed at community pharmacies and the patients' hospital diagnosis at discharge that can be linked to BIFAP. Hospital data is available for 7 out of 9 Spanish regions included in BIFAP. However, hospital data is available during different time periods for each region. From 2014 onwards, hospital linkage is available for approximately over 70% of patients, with the regions with linkage available reaching almost 100% of patients. Additional databases are also linked for a subset of patients (hospital pharmacy, cause of death registry).

BIFAP program is a non-profit program financed by the Spanish Agency of Medicines and Medical Devices (AEMPS), a government agency belonging to the Ministry of Health in collaboration with the Regional health authorities. The main use of BIFAP is for research purposes to evaluate the adverse and beneficial effects of drugs and drug utilisation patterns in the general population under real conditions of use.

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

The clinical data warehouse (CDW) of the Bordeaux University Hospital comprises EHRs on more than 2 million patients, with data collection starting in 2005. The hospital complex is made up of three main sites and comprises a total of 3,041 beds (2021 figures). The database currently holds information about patient characteristics (demographics), visits (inpatient and outpatient), conditions and procedures (billing codes), drugs (outpatient prescriptions and inpatient orders and administrations), measurements (laboratory tests and vital signs) and dates of death (in or out-hospital death). The hospital production information system data are loaded daily into a CDW in i2b2 format. A specific Extract, Transform & Load process from i2b2 to OMOP has been set up to standardise the data to the OMOP format. Currently, this mapping process is launched manually when needed. The data is integrated into the OMOP CDM version and is stored in Oracle version 19c.

Clinical Practice Research Datalink GOLD (CPRD GOLD), UK

The Clinical Practice Research Datalink (CPRD) GOLD is a database of anonymised electronic health records (EHRs) from GP clinics in the UK that use the Vision® software system for their management. 98% of the population in the UK is registered with a GP primarily responsible for non-emergency care and referrals to secondary care as needed. Participating GPs provide CPRD EHRs for all registered patients who did not specifically request to opt out of data sharing. GOLD currently contains data from 985 up-to-standard GP practices and for nearly 21 million patients whose data quality is routinely assessed by CPRD as acceptable for clinical research. More than 3 million of these patients are alive and registered in 401 contributing practices. Based on the latest UK population estimates from the UK Office of National Statistics, GOLD covers 4.6% of the current UK population and includes 4.9% of currently contributing GP practices. GOLD contains data from all four UK constituent countries, and the current regional distribution of its GP practices is 5.7% in England, 55.6% in Scotland, 28.4% in Wales, and 10.2% in Northern Ireland (May 2022).

GOLD data include the patient's demographic, biological measurements, clinical symptoms and diagnoses, referrals to specialists/hospital and their outcomes (based on referral letters between primary and secondary care), laboratory tests/results, and prescribed medications. GOLD has been assessed and found broadly representative of the UK general population regarding age, gender, and ethnicity. GOLD has been widely used internationally for observational research to produce nearly 3,000 peer-reviewed publications, making GOLD the most influential UK clinical database so far. In 2019, CPRD launched AURUM and has since encouraged practices from England to move from the software that feeds GOLD (Vision®) to the one that feeds AURUM (Emis®). GOLD data from 2019, therefore, mainly represents Wales/Scotland/Northern Ireland, and AURUM represents England. However, GOLD data collected before 2019 fully represent the UK. CPRD provides an updated list of practices that moved from GOLD to AURUM for each build release. The license also covers data from the Hospital Episode Statistics/Office for National Statistics, which can be requested on a study-by-study basis as linked data. This data only covers England and is planned to be mapped to OMOP.

Danish Data Health Registries (DK-DHR), Denmark

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, and Coronavirus disease 2019 test and vaccination Registries.

Egas Moniz Health Aliance database – Entre o Douro e Vouga (EMBD- ULSEDV), Portugal

The database comprises clinical information of patients admitted at a public hospital center, located in Santa Maria da Feira, Portugal. It includes administrative, sociodemographic, and clinical data (medical and nursing) of over 500 thousand patients with ages ranging from 0 to 100 years. The hospital center includes departments of all medical specialties, comprising data from surgery, outpatient, ward, accident and emergency and intensive care units.

IQVIA Disease Analyzer (IQVIA DA) Germany, Germany

IQVIA Disease Analyzer (DA) Germany is a database of de-identified electronic medical records from specialised and GP practices in Germany since 1992. This dataset encompasses approximately 3% of all outpatient practices within Germany, ensuring a substantial representation of the national healthcare landscape. The sampling methods used for practice selection, taking into account physician's demographics, specialty focus, community size category and federal state location, was instrumental in constructing a database that accurately mirrors the diverse spectrum of healthcare providers in the country. Consequently, data within IQVIA DA Germany database has been demonstrated to be representative of general and specialised practices throughout Germany.

The database contains demographics records, basic medical data, disease diagnosis, and prescription records. While the database partly records information on deaths and procedures, it currently does not support linkage with external data sources. Routine updates are conducted at regular intervals. The quality of data is assessed based on several criteria including completeness of information and correctness (e.g. linkage between diagnosis and prescriptions).

Croatian National Public Health Information System (NAJS), Croatia

The National Public Health Information System (Nacionalni javnozdravstveni informacijski sustav - NAJS) is an organised system of information services by Croatian Institute of Public Health (CIPH). NAJS enables data collecting, processing, recording, managing and storing of health-related data from health care providers as well as production and management of health information. NAJS contains medical and public health data collected and stored in health registries and other health data collections including cancer registry, mortality, work injuries, occupational diseases, communicable and non-communicable diseases, health events, disabilities, psychosis and suicide, diabetes, drug abuse and others.

UK Biobank (UKBB), UK

UK Biobank (UKBB) is a powerful biomedical database that can be accessed globally to enable new discoveries to improve public health. UKBB contains in-depth genetic, biomarker, imaging and health information from over half a million volunteers living in the UK aged 40–69 years at the time of recruitment (2006–2010).(12) UKBB has collected an unprecedented amount of biological and medical data as part of a large-scale long term prospective study. With their consent they regularly provide blood, urine and saliva samples, as well as detailed information about their lifestyle which is then linked to their health-related records (e.g. primary care data, hospital data, cancer registry) to provide a deeper understanding of how individuals experience diseases. Since 2012 UKBB database, the largest and richest of its kind, is opened to applications from researchers. The resource is available in a strictly anonymised format to scientists from the UK and around the world, subject to verification that the research is health-related and in the public interest. Researchers are required to publish their results in an open-source publication site or in an academic journal and return their findings to the UKBB. At the time of writing nearly 3,600 research applications have been approved for the usage of UKBB data and 3,239 peer-reviewed articles based on them have been published.

10.3 Study period

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

For BIFAP, the study period began on the 1st of January 2014 for objectives 2 and 3 to ensure higher coverage of hospital linkage. For NAJS, the study start date was set as the 1st of January 2017 for all objectives. Please see “15.2 Limitations of research methods” for further details.

10.4 Follow-up

Study participants were followed up from index date. For objective 1 and 2, index date was defined as the latest of: study start date (1st January 2010, except for BIFAP and NAJS), or date at which they have one year of prior history. For CDWBordeaux, index date was defined as the study start date or the date of entry in the database (whichever occurs last). Individuals were followed up until the earliest date of any of following events: study end (31st of December 2023 or last complete calendar year), end of data availability

(end of the last year with complete observation in the database for objective 1 and 2), or 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 outcome 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. patients diagnosed for the first time with a paracetamol overdose, with this event taking place during the study period). For this objective, index date was defined as the date of paracetamol overdose.

Table 3. Operational definition of time 0 (index date) and other primary anchors.

Study population name(s)	Time Anchor Description (e.g. time 0, index date)	Number of entries [1]	Type of entry	Washout window[2]	Care Setting [3]	Code Type	Diagnosis position[4]	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
Patients with paracetamol overdose (objective 3)	Date of paracetamol overdose	Single entry	Incident	[-Inf, 1]	IP, OP, OT	SNOMED	Any	Paracetamol overdose

[1] Indicate whether patients are allowed to enter the study population only once or multiple times
[2] Relative to index date (day 0). Inf= Any time prior
[3] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable
[4] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

10.5 Study population with in and exclusion criteria

The source population comprised all individuals present in the database at any time during the period from 1st of January 2010 to 31st of December 2023 (or last year with complete observation). All patients were required to have at least 365 days of data visibility prior to index date. Therefore, children aged <1 year were excluded. This requirement did not hold for the CDWBordeaux. For this database, we required 0 days of prior data availability as their observation period starts at the date of a first visit or hospitalisation.

For BIFAP (objective 2 and 3 only), we excluded participants registered in the two regions that do not have hospital linkage and restricted data from 2014 onwards.

Table 4. Operational definitions of inclusion criteria.

Criterion	Details	Order of application	Assessment window[1]	Care Settings[2]	Code Type	Diagnosis position[3]	Applied to study populations
Observation period during the study period	All individuals present in the period 01/01/2010-31/12/2023 (or last available date)	After	n/a	IP, OP, OT	n/a	n/a	All study populations
Prior database history	Study participants will be required to have 365 days of prior history observed before contributing observation time	Prior	[-365, 0]	OP	n/a	n/a	All study populations except CDWBordeaux.

[1] Relative to index date (day 0).
[2] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

Table 5. Operational definitions of exclusion criteria.

Criterion	Details	Order of application	Assessment window [1]	Care Settings[2]	Code Type	Diagnosis position[3]	Applied to study populations:
Washout window for paracetamol prescribing	Individuals newly prescribed with paracetamol with a previous prescription of paracetamol 60 days prior index date will be excluded	Prior	[-60,1]	IP, OP, OT	n/a	n/a	General population (objective 1)
Washout window for paracetamol overdose (incidence)	Individuals newly diagnosed with a paracetamol overdose with previous history of that same outcome 365 days prior to index date will be excluded.	Prior	[-365, 1]	IP, OP, PT	n/a	n/a	General population (objective 2)
Washout window for paracetamol overdose (characterisation)	Individuals newly diagnosed with a paracetamol overdose with previous history of that same outcome any time prior index date will be excluded.	Prior	[-Inf,1]	IP, OP, OT	n/a	n/a	Patients with paracetamol overdose (objective 3)

[1] Relative to index date (day 0). Inf= Any time prior
[2] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

10.6 Variables

10.6.1 Exposures

The study has no exposure of interest.

10.6.2 Outcome/s

Outcomes included paracetamol prescribing and paracetamol overdose.

The use of paracetamol was derived from prescription data. In DK-DHR and BIFAP, data was derived from dispensation records, and in UKBB, from self-reported medication use. For simplicity, all records were referred to as prescriptions. Successive individual prescriptions (i.e. drug exposures) separated by less than 30 days were considered 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 **Supplementary Table I- 1** and **Supplementary Table I- 2.**

Table 6. Operational definitions of outcome.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care Settings[2]	Code Type	Diagnosis Position[3]	Applied to study populations
Paracetamol prescribing	A prescription with 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)

[1] Relative to index date (day 0). Inf= Any time prior
[2] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

10.6.3 Other covariates

The study covariates are described conceptually, and the context or rationale for the choices are provided in this section. The operational definition of the covariates is described in **Appendix I.**

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

The covariates for stratification on the population level DUS were sex, age groups, and formulation. Age groups included were: 1-5; 6-11; 12-17; 18-29 and subsequently 10-year age bands (30-39, 40-49, etc.) up to >80 years or more (i.e. implemented as 80 to 130 years of age). Formulations included oral tablets, capsules, oral liquid formulations, injectable liquid formulations, and rectal suppositories. Dose forms used to identify formulations are included in **Supplementary Table I- 3**.

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

The covariates for stratification on the population level descriptive epidemiology study included were 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 were 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 described using pre-specified comorbidities and medications and by means of large-scale characterisation. Comorbidities were measured for 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 days before index date. Short-term complications were assessed in the 30 days after index date and will include hepatic and renal toxicity. Mortality was also be assessed 0 to 30 days after index date and 31 to 365 days after index date.

Pre-specified conditions included alcoholism, chronic kidney disease, chronic liver disease, depressive disorders, anxiety disorders, schizophrenia, obesity, cancer, arthrosis and arthritis, pain, fever and infectious diseases. Pre-specified 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 the index date. For pain, this time window was also applied in addition to those used for large-scale characterisation.

Pre-specified medications were enzyme inducing medications (e.g. carbamazepine, isoniazid), and medications found in concomitant overdosing. These medications were benzodiazepines, opioid analgesics, nonsteroid anti-inflammatory drugs (NSAIDs), antipsychotics and antidepressants.(13) Prior paracetamol prescribing was also of interest and was reported 365 days prior to 31 days before index date, and 30 to 1 day before index date. The same assessment window was applied for pre-specified medications.

A list of concept sets for pre-specified conditions are detailed in **Supplementary Table I-4**. Lists of concept sets for short-term complications are detailed in **Supplementary Table I- 5** and **Supplementary Table I- 6**, and medications in **Supplementary Table I- 7.**

Table 7. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window [1]	Care Settings[2]	Code Type	Diagnosis Position[3]	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;	Categorical	0	n/a	n/a	n/a	All

	>80; Broad: 1-17; >18.						
Comorbidities	Large scale characterisation and pre-specified conditions[4]	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 pre-specified medications[5]	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

[1] Relative to index date (day 0). Inf= Any time prior

[2] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

[4] These include: alcoholism, chronic kidney disease, chronic liver disease, depressive disorders, anxiety disorders, schizophrenia, obesity, cancer, arthrosis and arthritis, and pain.

[5] These include: carbamazepine, isoniazid, benzodiazepines, opioid analgesics, nonsteroid anti-inflammatory drugs (NSAIDs), antipsychotics and antidepressants.

10.7 Study size

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

10.8 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 section “12 Quality Control”), 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 fine tuning of the code base was needed. The study results of all data sources were checked after which they were made available to the team and the Dissemination Phase started. All results were locked and timestamped for reproducibility and transparency.

10.9 Statistical methods

10.9.1 Main summary measures

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

10.9.2 Main statistical methods

The type of analysis by study type is described in **Table 8**.

Table 8. Description of study types and type of analysis.

Study type	Study classification	Type of analysis
Population Level DUS	Off-the-shelf	- Population-based incidence rates - Population-based prevalence of use of a drug/drug class
Population-level descriptive epidemiology	Off-the-shelf	- Incidence rates of the condition of interest
Patient-level characterisation	Off-the-shelf	- Large-scale characterisation - Patient-level characteristics

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 a yearly basis. There was no restriction based on individuals' observability within calendar years in the database (i.e., participants were considered even if they were not present in the database for 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 "10.6.3 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 of Objective 1. Individuals were able to re-enter the study following a 365-day washout after the occurrence of the outcome.

Incidence per 100,000 PY were rounded to the nearest whole number. Analyses were stratified by sex and age groups (see "10.6.3 Other covariates").

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

Characteristics were described by database using pre-specified 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). 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 of medications 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.

10.9.3 Missing values

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

10.9.4 Sensitivity analysis

No sensitivity analyses were performed.

11. DATA MANAGEMENT

Data management

All databases were mapped to the OMOP CDM. This enabled the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is 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. Each data partner has executed the study code against their database containing patient-level data and has returned the results set which only contained aggregated data. The results from each of the contributing data sites have been combined in tables and figures for the study report.

Data storage and protection

For this study, participants from various EU member states have processed personal data from individuals which is collected in national/regional electronic health record databases. 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 databases used in this study have been 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 are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.

These output files do not contain any data that allow identification of subjects included in the study. The DRE implements further security measures to ensure a high level of stored data protection to comply with

the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

12. QUALITY CONTROL

General database quality control

Several 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, data partners have run 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

Concepts and phenotypes of interest have been developed and assessed using the following R packages: “CodelistGenerator”, "CohortDiagnostics”, and “DrugExposureDiagnostics”. The study code was based on three R packages to (1) estimate incidence rates and period prevalence (“IncidencePrevalence”), and (2) characterise patients (“PatientProfiles” and “CohortCharacteristics”). Details on how “IncidencePrevalence” operates are available elsewhere.(14) These packages include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing.

13. RESULTS

All results are available in a web application (“Shiny App”) at: https://data-dev.darwin-eu.org/P3-C1-007-Paracetamol/.

13.1 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 CDWBordeaux contributed to this objective, including data from 78,042,138 individuals (n= 20,754,789 in BIFAP; n=10,701,809 in CPRD GOLD; n= 6,923,875 in DK-DHR; n=374,742 in EMBD-ULSEDV; n=17,124,145 in IQVIA DA Germany; n=4,536,282 in NAJS; n=502,350 in UKBB).

For Objective 2, this denominator was also used to calculate incidence of paracetamol overdose for databases participating in this objective (BIFAP, CPRD GOLD and UKBB), with additional restrictions applied for BIFAP only. A total of 27,649,325 individuals participated in Objective 2 (n=16,445,166 in BIFAP; n=10,701,809 in CPRD GOLD; n=502,350 in UKBB).

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

	BIFAP (Obj 1)[1]	BIFAP (Obj 2)[1]	CPRD GOLD (Obj 1 & 2)	DK-DHR (Obj 1)	EMBD-ULSEDV (Obj 1)	IQVIA DA Germany (Obj 1)	NAJS (Obj 1)[2]	UKBB (Obj 1 & 2)
Starting population	22,580,036	22,580,036	17,521,504	8,500,891	562,686	43,553,860	5,448,809	502,362
Birth date available	22,580,036	22,580,036	17,521,504	8,500,891	562,686	43,553,860	5,448,809	502,362
Sex available	22,580,036	22,580,036	17,521,504	8,500,891	562,686	43,526,439	5,448,808	502,362
Satisfied age criteria during the study period based on year of birth	22,489,206	22,489,206	17,487,712	8,431,294	560,946	43,475,404	5,405,466	502,362
Individuals with observation time available during study period	21,851,109	20,991,013	11,915,387	7,248,505	454,030	38,220,862	4,576,007	502,350
Prior history requirement fulfilled during the study period	20,754,789	20,045,565	10,701,809	6,923,880	374,742	17,124,145	4,536,283	502,350

	BIFAP (Obj 1)[1]	BIFAP (Obj 2)[1]	CPRD GOLD (Obj 1 & 2)	DK-DHR (Obj 1)	EMBD-ULSEDV (Obj 1)	IQVIA DA Germany (Obj 1)	NAJS (Obj 1)[2]	UKBB (Obj 1 & 2)
Individuals with observation time available after applying age and prior observation	20,754,789	20,045,565	10,701,809	6,923,875	374,742	17,124,145	4,536,283	502,350
Individuals registered in hospital-linked areas	n/a	16,445,166	n/a	n/a	n/a	n/a	n/a	n/a

[1] The denominator for Objective 1 differs from the denominator for Objective 2 in BIFAP.

[2] Only applicable to BIFAP (Objective 2), with data from 2014 onwards. n/a = not applicable

[3] Study period for NAJS spans from 2017 onwards.

Table 10 details the attrition and the number of individuals contributing to the characterisation of patients with paracetamol overdose in BIFAP (n=2,480), CDWBordeaux (n=2,125), CPRD GOLD (n=3,140) and UKBB (n=625).

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

	BIFAP	CDWBordeaux	CPRD GOLD	UKBB
Qualifying initial records	3,175	2,758	7,372	3,064
Require first event	2,960	2,309	6,622	1,904
Require prior observation of 365 days[1]	2,683	n/a	5,589	1,750
Require cohort_start_ date within study period and age >1[2]	2,624	2,125	3,140	625
Exclude individuals outside-hospital areas[3]	2,480	n/a	n/a	n/a

[1] The prior history requirement was not applied in CDWBordeaux. n/a = not applicable.
[2] Reasons for exclusion have been combined to avoid reporting exclusions of <5 cases. For BIFAP, the study period spanned from 2014 onwards.
[3] Applicable to BIFAP only.

Table 11 provides information on the demographic characteristics of patients 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 (see "13.2 Outcome data"), which is not limited to first-ever prescriptions, and has been included for descriptive purposes only.

A total of 11,599,393 individuals received their first prescription of paracetamol during the study period. The number of individuals included ranged from 526,853 in IQVIA DA Germany to 7,023,728 in BIFAP. The distribution was similar across sex, with a slightly higher proportion of females compared to males. Median age ranged from 40 years in IQVIA DA Germany to 63 years in UKBB. The duration of the first prescription ranged from 1 day in EMBD-ULSEDV to 30 days in NAJS and UKBB (see "15.2 Limitations of research methods" for more details).

Table 12 details information on demographic characteristics of patients with paracetamol overdose assessed at index date (date of the event). The majority of individuals were females, with proportions ranging from 55.4% in UKBB to 74.2% in CDWBordeaux. The median age was approximately 21 years across most databases, except for UKBB, where age was higher (median [q25 – q75]: 57 [50–65]). The highest

frequency of paracetamol overdose were among individuals aged 1–17 and 18–49 years in databases covering all age groups. Of all people with paracetamol overdose, the proportion of individuals aged 1–17 ranged from 29.0% in CPRD GOLD to 41.7% in BIFAP. Individuals aged over 80 years represented a small proportion of cases, accounting for less than 4% across all databases.

The number of paracetamol overdoses captured between 2010 and 2016 was lower than the number of events recorded between 2017 and 2023 and CDWBordeaux (429 vs. 1,696), while the opposite pattern, with smaller differences, was observed in CPRD GOLD (1,765 vs. 1,375). In BIFAP, 170 cases were observed between 2014 and 2016, compared to 2,310 between 2017 and 2023. In UKBB, the last cases of paracetamol prescribing or paracetamol overdose were captured in 2017.

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

		BIFAP	CPRD GOLD	DK-DHR	EMBD-ULSEDV	IQVIA DA Germany	NAJS	UKBB
Number of individuals		7,023,728	1,421,130	1,381,712	144,298	526,852	1,062,968	38,705
Cohort start date (min)[1]		2010-01-01	2010-01-01	2010-01-01	2010-01-01	2010-01-02	2017-01-01	2010-01-04
Cohort end date (max)[2]		2023-12-31	2024-06-12	2024-03-15	2023-12-31	2023-12-31	2024-06-07	2018-02-15
Age, median [min; q25 – q75; max]		42 [1; 26 – 59; 112]	45 [1; 28 – 62; 114]	50 [1; 32 – 66; 108]	46 [1; 25 – 64; 108]	40 [1; 19- 60; 99]	56 [1; 37 – 70; 107]	63 [40; 56 – 68; 79]
Age group, N (%)	1 to 5	436,022 (6.2%)	94,929 (6.7%)	12,591 (0.9%)	12,039 (8.3%)	51,170 (9.7%)	55,458 (5.2%)	-
	6 to 11	335,341 (4.8%)	39,866 (2.8%)	13,626 (1.0%)	5,729 (4.0%)	39,274 (7.5%)	25,281 (2.4%)	-
	12 to 17	437,852 (6.2%)	48,714 (3.4%)	54,852 (4.0%)	6,363 (4.4%)	33,511 (6.4%)	26,200 (2.5%)	-
	18 to 29	883,986 (12.6%)	200,531 (14.1%)	209,841 (15.2%)	18,345 (12.7%)	74,292 (14.1%)	85,422 (8.0%)	-
	30 to 39	1,087,491 (15.5%)	208,042 (14.6%)	183,006 (13.2%)	17,096 (11.9%)	61,468 (11.7%)	100,153 (9.4%)	-

		BIFAP	CPRD GOLD	DK-DHR	EMBD-ULSEDV	IQVIA DA Germany	NAJS	UKBB
	40 to 49	1,128,697 (16.1%)	217,869 (15.3%)	213,087 (15.4%)	20,155 (14.0%)	61,105 (11.6%)	130,822 (12.3%)	3,584 (9.3%)
	50 to 59	1,052,841 (15.0%)	211,708 (14.9%)	224,445 (16.2%)	20,728 (14.4%)	69,358 (13.2%)	170,121 (16.0%)	9,483 (24.5%)
	60 to 69	802,163 (11.4%)	189,248 (13.3%)	209,775 (15.2%)	17,726 (12.3%)	50,688 (9.6%)	198,489 (18.7%)	18,447 (47.7%)
	70 to 79	499,821 (7.1%)	127,812 (9.0%)	172,715 (12.5%)	15,123 (10.5%)	45,277 (8.6%)	158,843 (15.0%)	7,191 (18.6%)
	> 80	359,514 (5.1%)	82,411 (5.8%)	87,774 (6.4%)	10,994 (7.6%)	40,709 (7.7%)	112,179 (10.6%)	-
Sex, N (%)	Female	3,635,814 (51.8%)	747,439 (52.6%)	721,094 (52.2%)	76,574 (53.1%)	287,439 (54.6%)	625,689 (58.9%)	21,240 (54.9%)
	Male	3,387,914 (48.2%)	673,691 (47.4%)	660,618 (47.8%)	67,724 (46.9%)	239,088 (45.4%)	437,279 (41.1%)	17,465 (45.1%)
Duration of the prescription, median [min; q25 – q75; max]		8 [1; 6-14; 5,099]	14 [1; 8-28; 5,228]	8 [1; 16-50; 5,160]	1 [1; 1-1; 190]	7 [1; 5-7; 4,780]	30 [1; 30-30; 2,183]	30 [1; 30-34; 2,701]

[1] For NAJS, the study start was restricted to 2017 onwards.

[2] Cohort end dates in 2024 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. Demographic characteristics of individuals diagnosed with paracetamol overdose.

		BIFAP[1]	CDWBordeaux	CPRD GOLD	UKBB
Number of individuals		2,480	2,125	3,140	625
Cohort start date (min)[1]		2014-01-22	2010-07-01	2010-01-01	2010-01-15
Cohort end date (max) [1]		2023-12-31	2024-06-12	2024-01-01	2017-03-31
Age, median [min; q25 – q75; max]		21 [1; 14 – 45; 95]	21 [1; 15 – 39; 100]	25 [1; 17 – 44; 112]	57 [41; 50 – 65; 77]
Age group (broad), N (%)	1 to 17	1,033 (41.7%)	806 (37.9%)	912 (29.0%)	-
	> 18	93 (3.8%)	38 (1.8%)	61 (1.9%)	-
Age group (narrow), N (%)	1 to 17	1,033 (41.7%)	806 (37.9%)	912 (29.0%)	-
	18 to 49	927 (37.4%)	994 (46.8%)	1,656 (52.7%)	129 (20.6%)
	50 to 79	427 (17.2%)	287 (13.5%)	511 (16.3%)	496 (79.4%)
	> 80	93 (3.8%)	38 (1.8%)	61 (1.9%)	-
Sex, N (%)	Female	1,669 (67.3%)	1,577 (74.2%)	2,008 (64.0%)	346 (55.4%)
	Male	811 (32.7%)	548 (25.8%)	1,132 (36.1%)	279 (44.6%)
Study period[2]	2010-2016	170	429	1,765	602
	2017-2023	2,310	1,696	1,375	23

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

[2] For BIFAP, the study start was restricted to 2014 onwards and to individuals registered in areas with hospital linkage. Data availability for UKBB spanned up to 01-03-2020.

13.2 Outcome data

Table 13 presents the number of incident outcome records identified across data partners. In total, we identified 84,203,320 paracetamol prescriptions and 8,879 paracetamol overdoses. Counts reflect the number of incident events captured based on the outcome definitions used for incidence calculations, which include a 60-day washout period for paracetamol prescribing and a 365-day washout period for paracetamol overdose. As a result, the counts do not correspond directly to the number of events described in Section “13.1 Participants”, since individuals were allowed to experience multiple outcomes during follow up.

Table 13. Outcome of incident records by database during the study period[1]

	BIFAP	CDWBordeaux	CPRD GOLD	DK-DHR	EMBD-ULSEDB	IQVIA DA Germany	NAJS	UKBB
Records of paracetamol prescribing[2], N	59,821,318	n/a	10,941,308	8,783,770	443,996	1,529,117	2,392,818	290,993
Records of paracetamol overdose[3], N	2,551	2,125	3,345	n/a	n/a	n/a	n/a	858

[1] Study period spanned from 2010 to 2023 (or end of available data if earlier), except for BIFAP for paracetamol overdose (2014 onwards, restricting study population to individuals registered in areas with hospital linkage), and NAJS (2017 onwards).

[2] Incident records, defined using a 60-day washout

[3] Incident records, defined using a 365-day washout. Records for CDWBordeaux (participating in Objective 3 only) correspond to the number of subjects with a first-ever event, with all prior history considered for washout.

13.3 Paracetamol prescribing

13.3.1. Incidence

In this section, we present incidence rates for paracetamol prescribing. For the calculation of incidence rates, multiple events per person were allowed with a washout of 60 days between paracetamol records.

Overall incidence rates are described by database in **Table 14** and shown by calendar year in

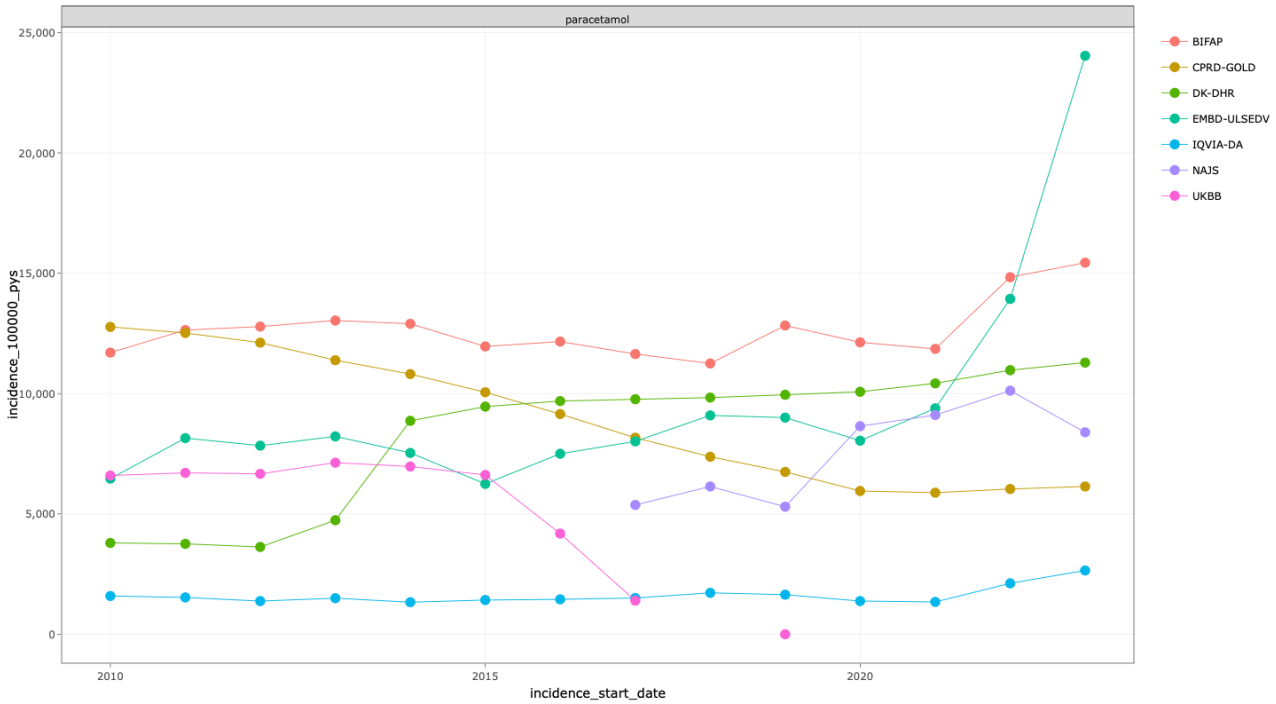


Figure *1*. Incidence rates per 100,000 PY of paracetamol prescribing for the entire period ranged between 5,625 in UKBB and 12,686 in BIFAP. Trends showed an upward trajectory in most databases, except for CPRD GOLD (which exhibited a descending trend throughout the study period, stabilising after 2020); and UKBB (which saw an abrupt decrease after 2015 onwards). An abrupt increase in incidence was observed for DK-DHR in 2014 and EMBD-ULSEDV in 2022 and 2023.

Table 14. Incidence rates of paracetamol prescribing for the entire study period by database.

Database name[1]	N of persons	Number of events[2]	Person-years (PY)	Incidence per 100,000 PY (95% CI)[3]
BIFAP	20,676,039	59,821,318	471,549,476	12,686 (12,683 to 12,689)
CPRD GOLD	10,562,849	10,941,308	115,450,667	9,477 (9,471 to 9,483)
DK-DHR	6,901,718	8,783,770	106,057,522	8,282 (8,277 to 8,288)
EMBD-ULSEDV	374,656	443,996	5,030,068	8,827 (8,801 to 8,853)

Database name[1]	N of persons	Number of events[2]	Person-years (PY)	Incidence per 100,000 PY (95% CI)[3]
IQVIA DA Germany	17,120,103	1,529,117	96,930,210	1,578 (1,575 to 1,580)
NAJS	4,535,263	2,392,818	31,525,488	7,590 (7,580 to 7,600)
UKBB	502,038	290,993	5,172,928	5,625 (5,605 to 5,646)

[1] Study period for NAJS spanned from 2017 onwards.

[2] Number of incident paracetamol prescriptions, defined with a 60-day washout.

[3] Incidence estimates are rounded to the nearest whole number.

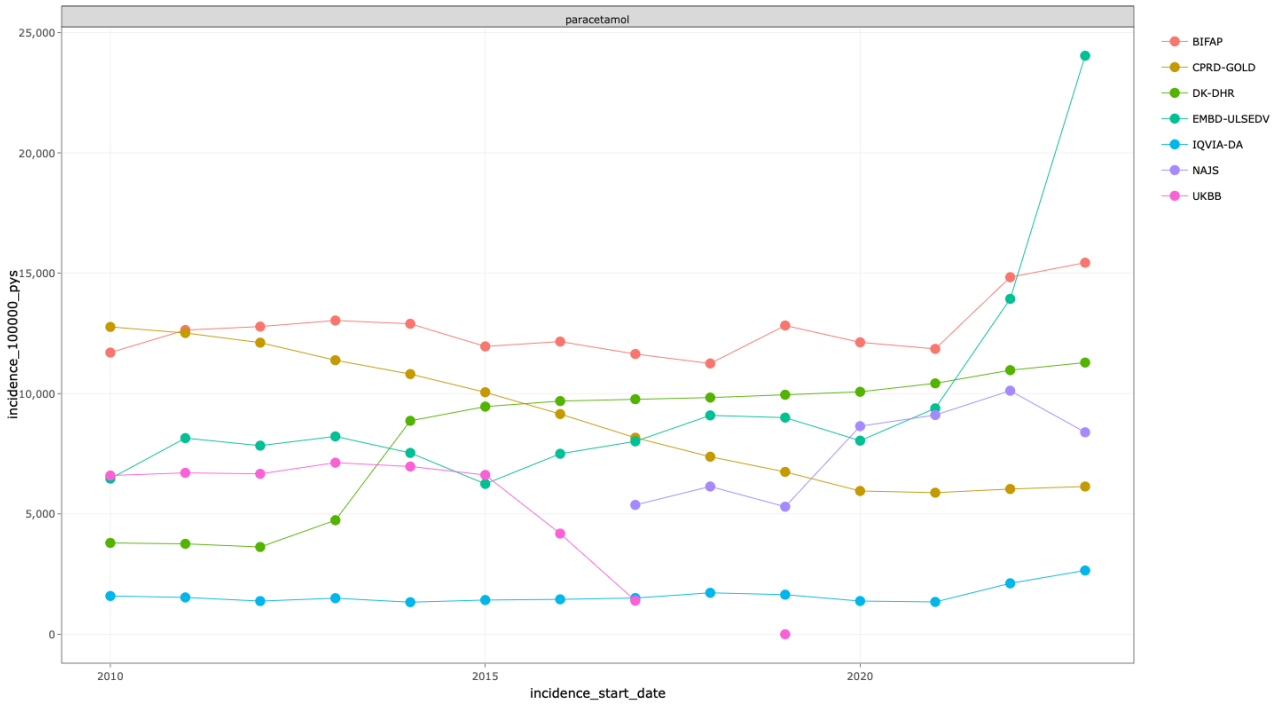


Figure 1. Incidence rates of paracetamol prescribing by calendar year.

Yearly incidence stratified by sex and by age groups are shown in

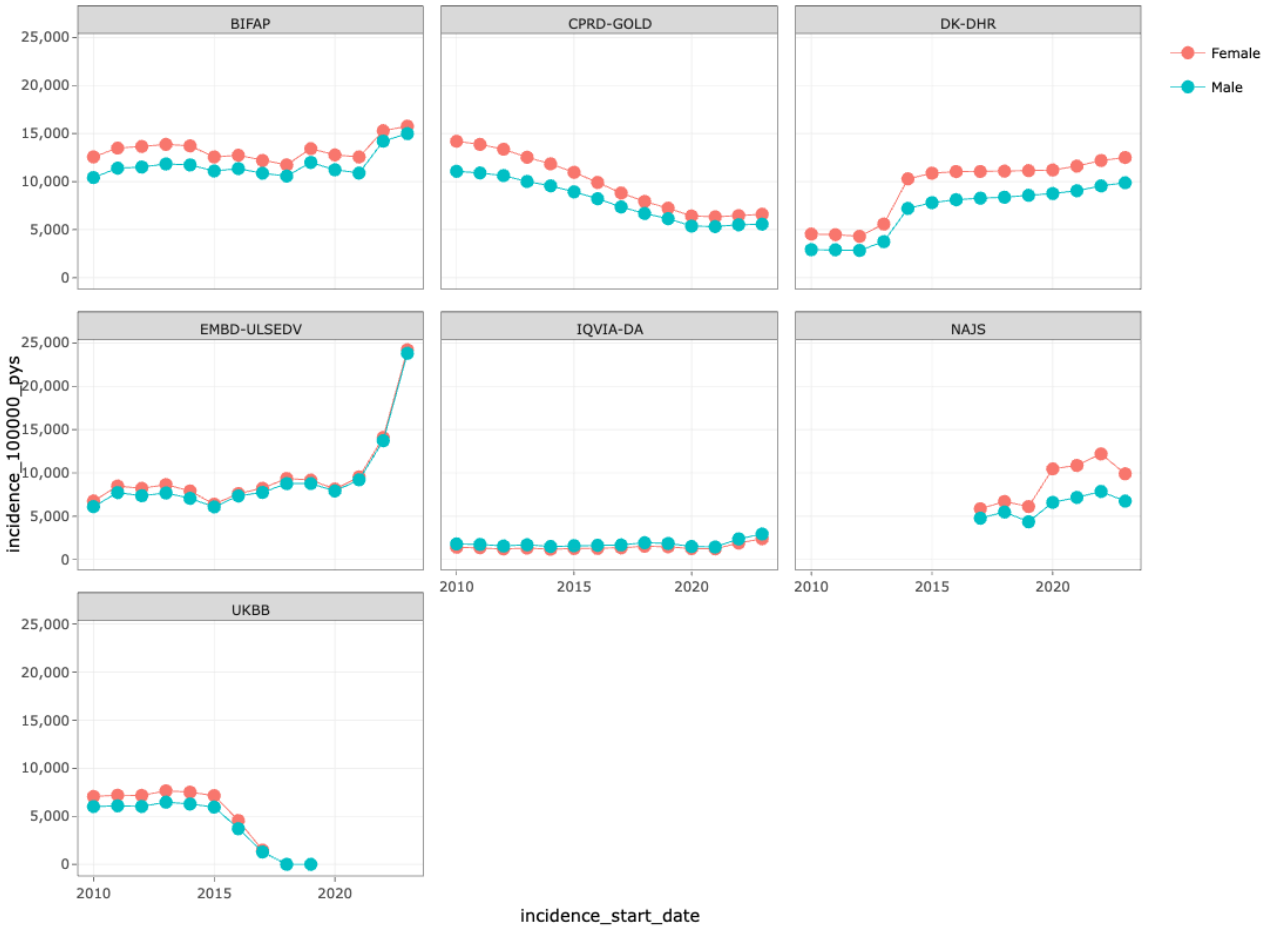


Figure *2* and

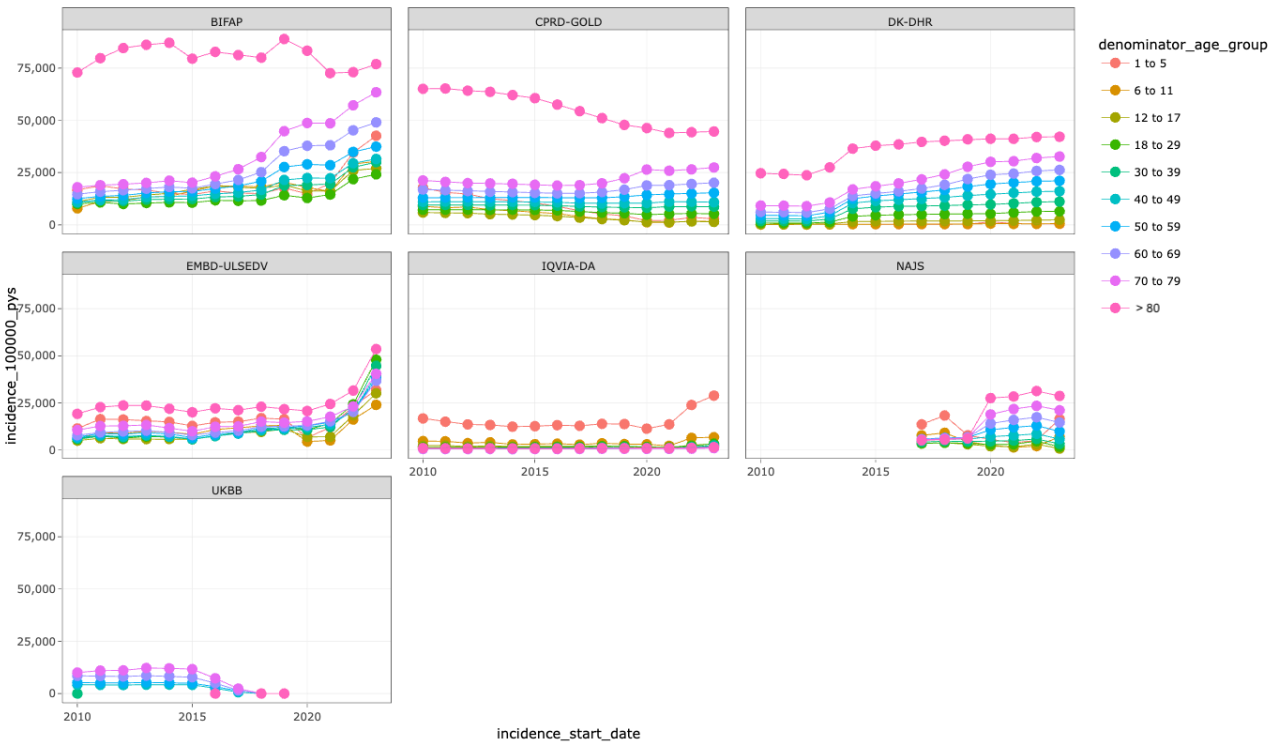


Figure *3*, respectively. Trends by sex and age groups were similar to those reported overall in

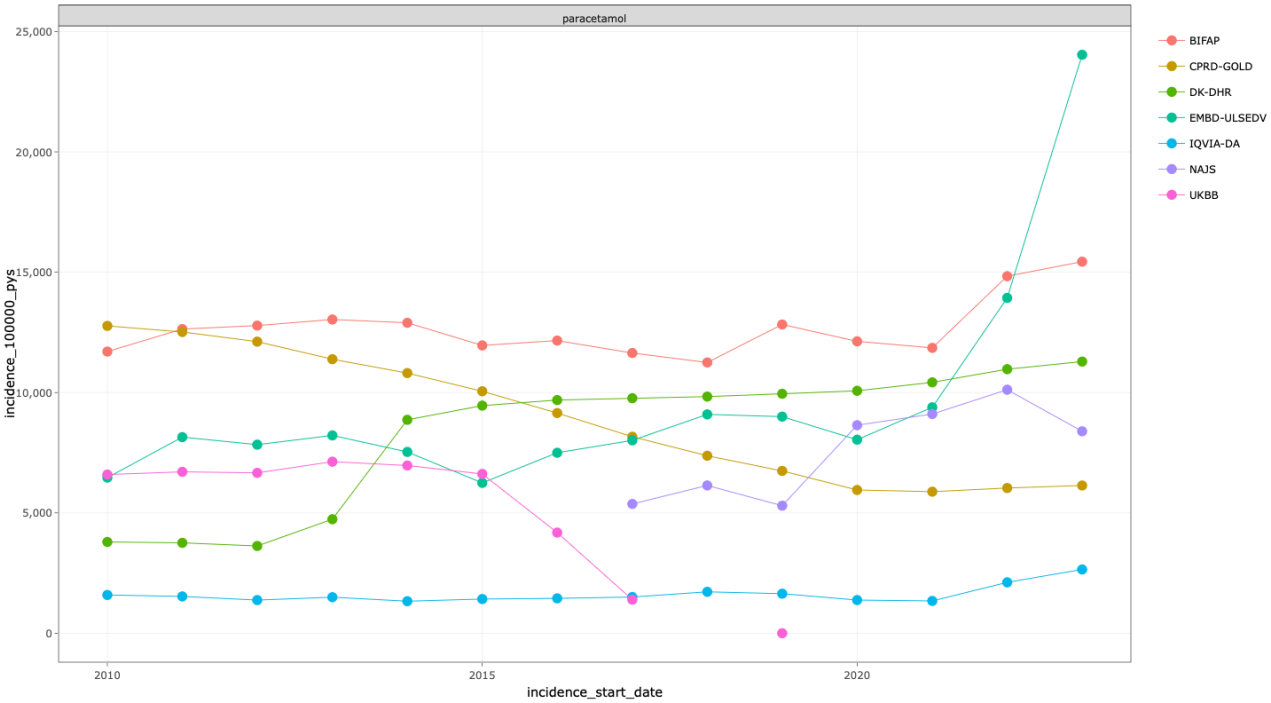
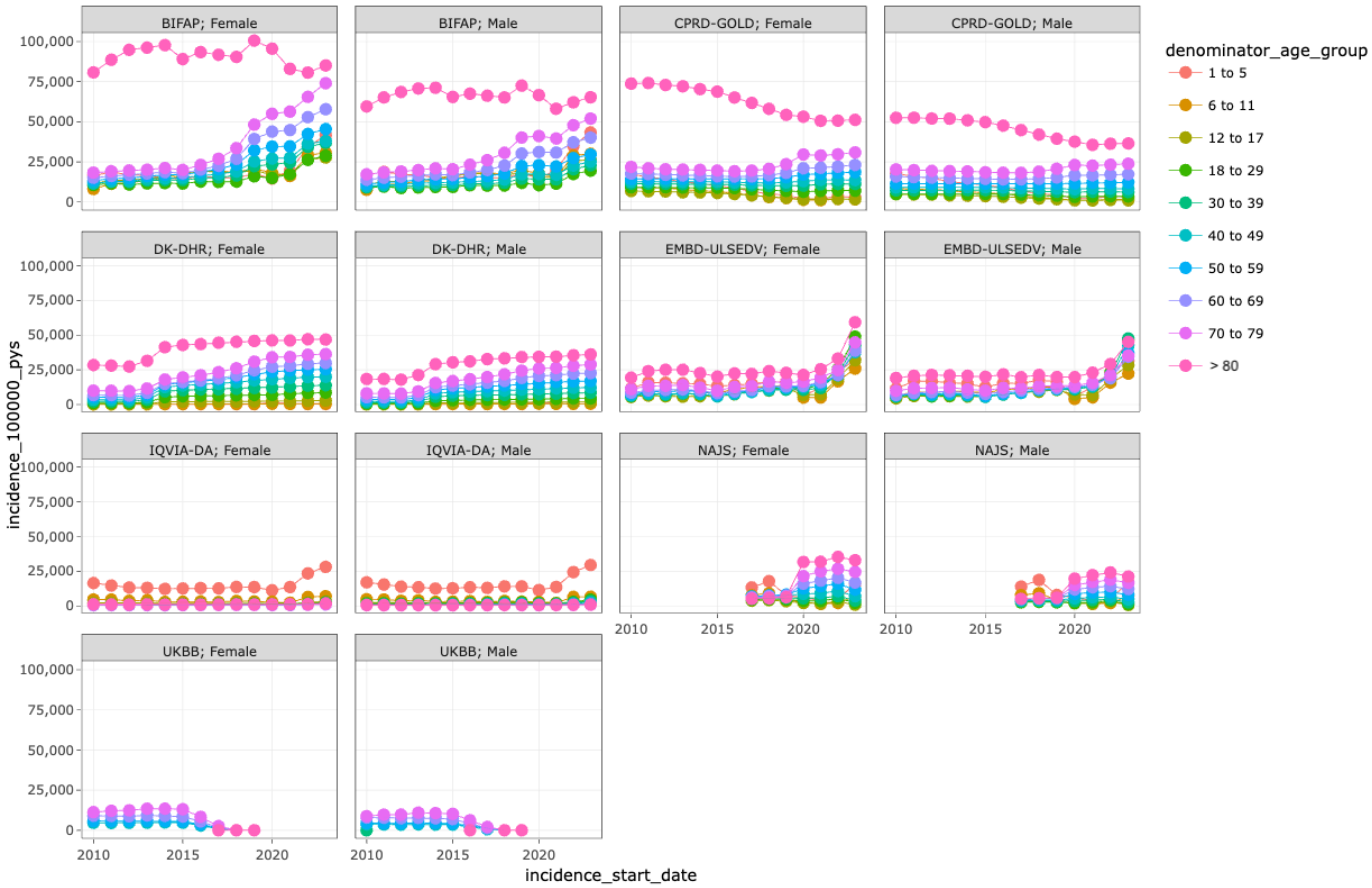


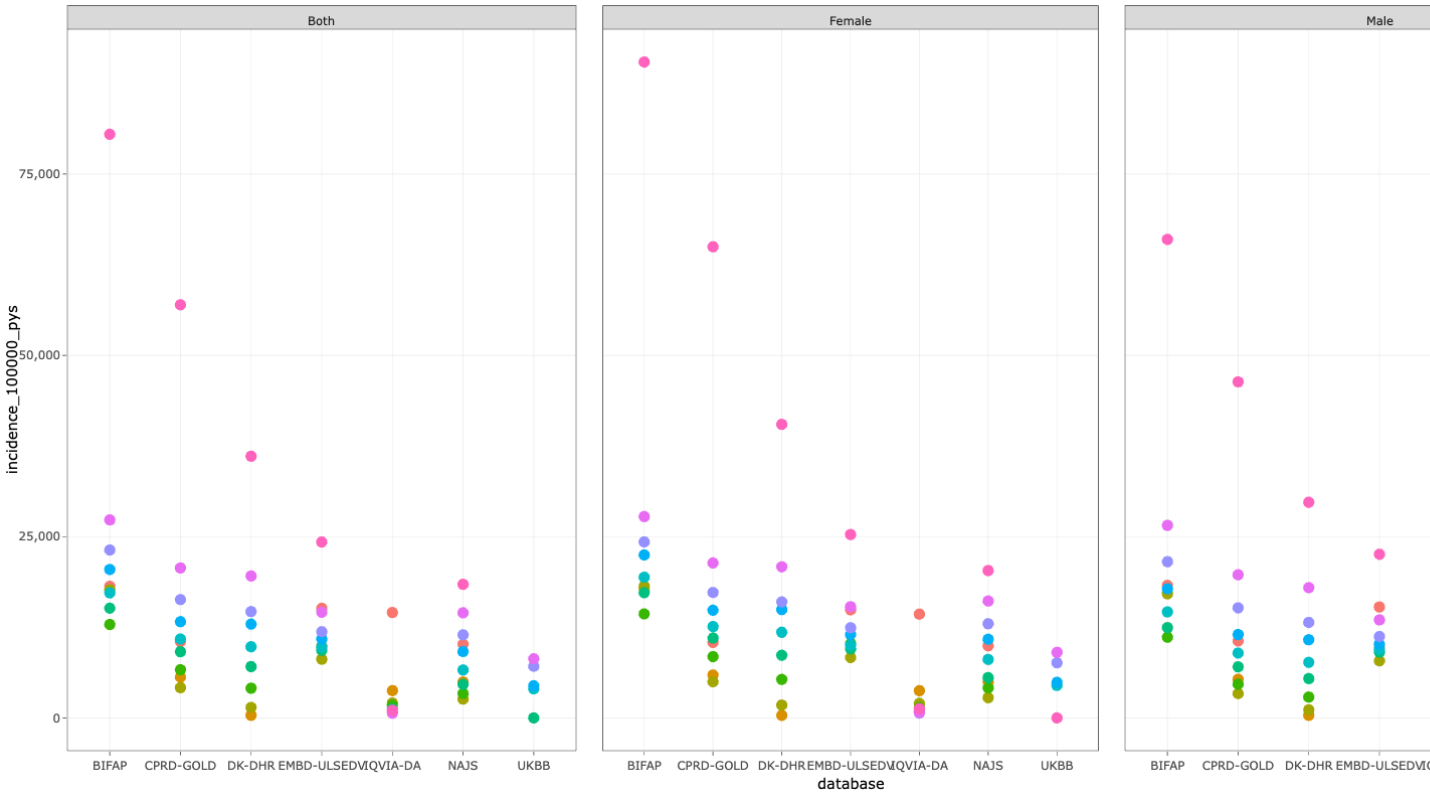
Figure *1*, with the exception of BIFAP, where the overall trends differed from those observed by age group. Incidence showed an upward trajectory across most age groups, while incidence among those aged >80 remained stable and resembled trends seen in the general population.

Incidence rates were higher among females than males across most databases except for IQVIA DA Germany, where incidence rates were slightly higher among males (incidence rates per 100,000 PY: 1,780

[95% CI 1,776 to 1,785] vs 1,424 [1,421 to 1,428]). Regarding age groups, most databases showed a gradient of increasing incidence rates with age. The gap between incidence rates across age groups was particularly pronounced among individuals aged >80 and 70 to 79 years, particularly in BIFAP and CPRD GOLD, where incidence rates among individuals aged >80 years was six time bigger than in the general population (incidence rates per 100,000 PY: 80,470 [80,416 to 80,541] vs. 12,686 [12,683 to 12,689] in BIFAP; 56,972 [56,872 to 57,072] vs. 9,477 [9,471 to 9,483] in CPRD GOLD). This was also observed to a lesser extent in DK-DHR and EMBD-ULSEDV. Results stratified by age and sex (combined) showed similar results, with the gap in incidence rates between the >80 and 70 to 79 age groups being more pronounced in females than males (



Supplementary Figure II- ***1*** and



Supplementary Figure II-*2*).

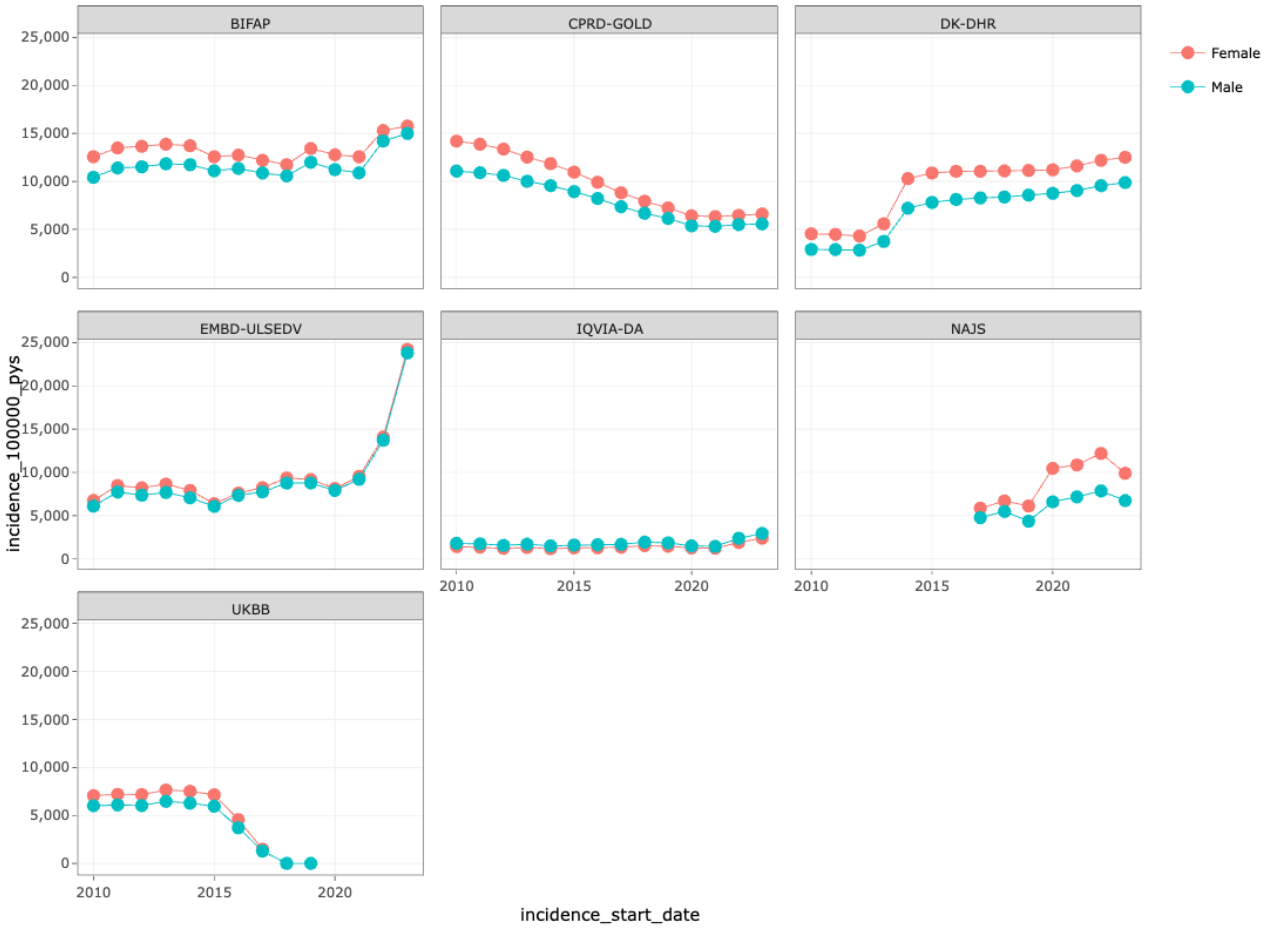


Figure 2. Incidence rates of paracetamol prescribing by calendar year and sex.

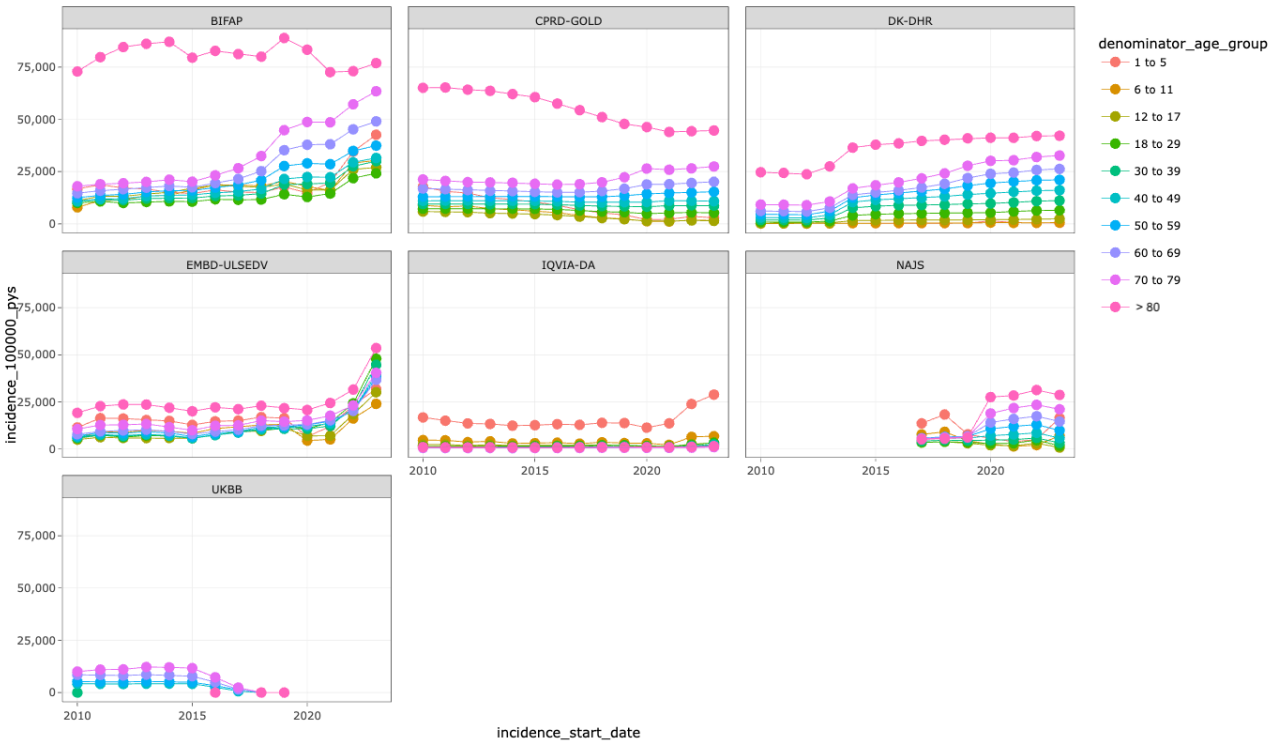


Figure 3. Incidence rates of paracetamol prescribing by calendar year and age groups.

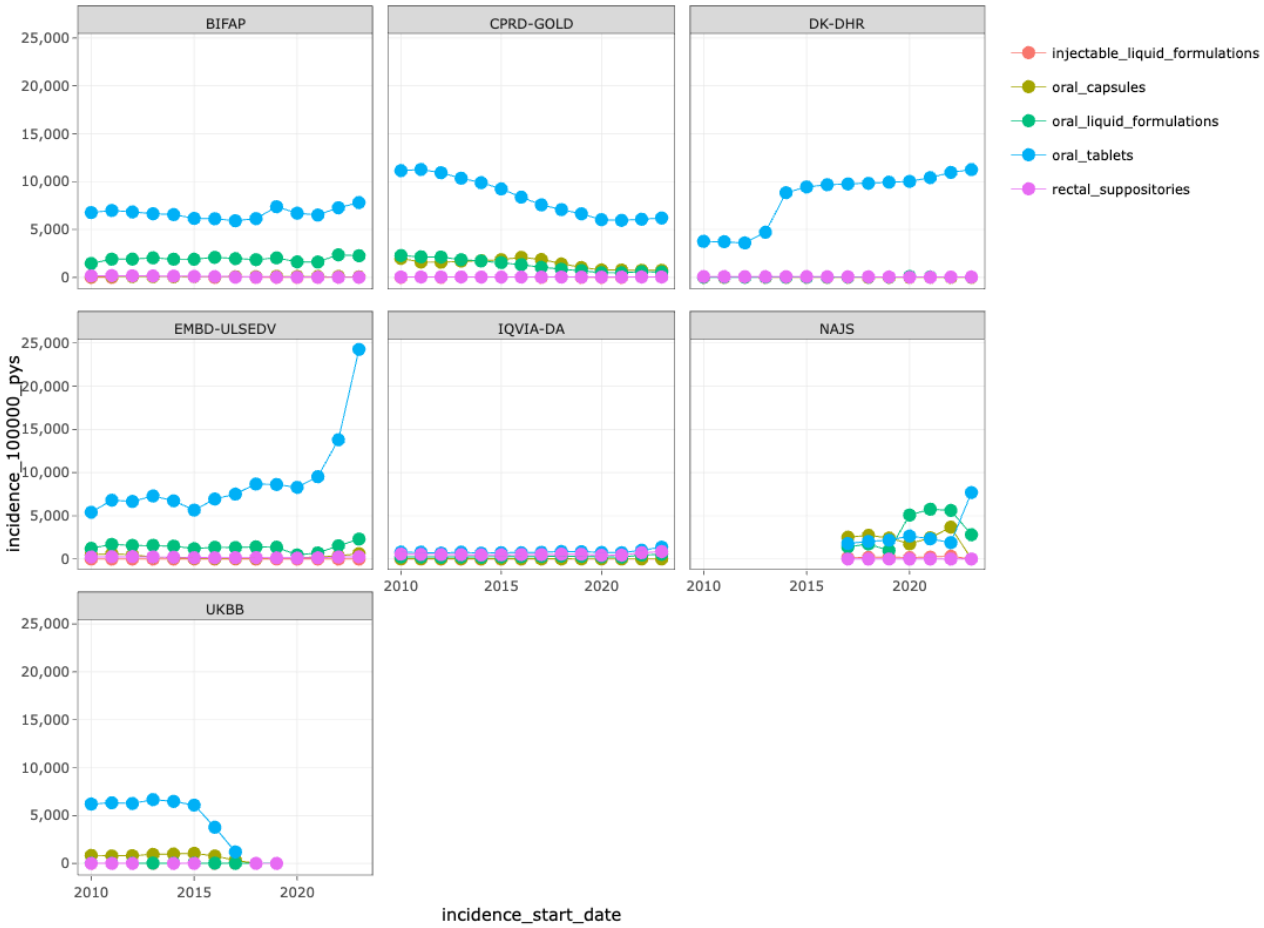


Figure 4 shows yearly incidence rates stratified by formulations. Oral tablets obtained significantly higher incidence rates compared to other formulations across all databases except NAJS and mimic trends of incidence rates for paracetamol overall. NAJS was an exception to this, with the highest incidence rates obtained for oral liquid formulations followed by oral tablets. Oral capsules obtained the second-highest incidence rates in CPRD GOLD and UKBB, while oral liquid formulations held this position in BIFAP and EMBD-ULSEDV, and rectal suppositories in IQVIA DA Germany. In DK-DHR, incidence of other formulations other than oral tablets showed low number to 0 events. Injectable liquid formulations were the least captured formulation across databases, with incidence > 1 per 100,000 PY in NAJS (179 [177 to 181]), IQVIA DA Germany (3 [3 to 3]), and BIFAP (1 [1 to 1]) only. Formulations with less than 100 incident events during the entire study period included injectable liquid formulations (CPRD GOLD, DK-DHR EMBD-ULSEDV and UKBB), oral capsules (DK-DHR) and rectal suppositories (NAJS, UKBB).

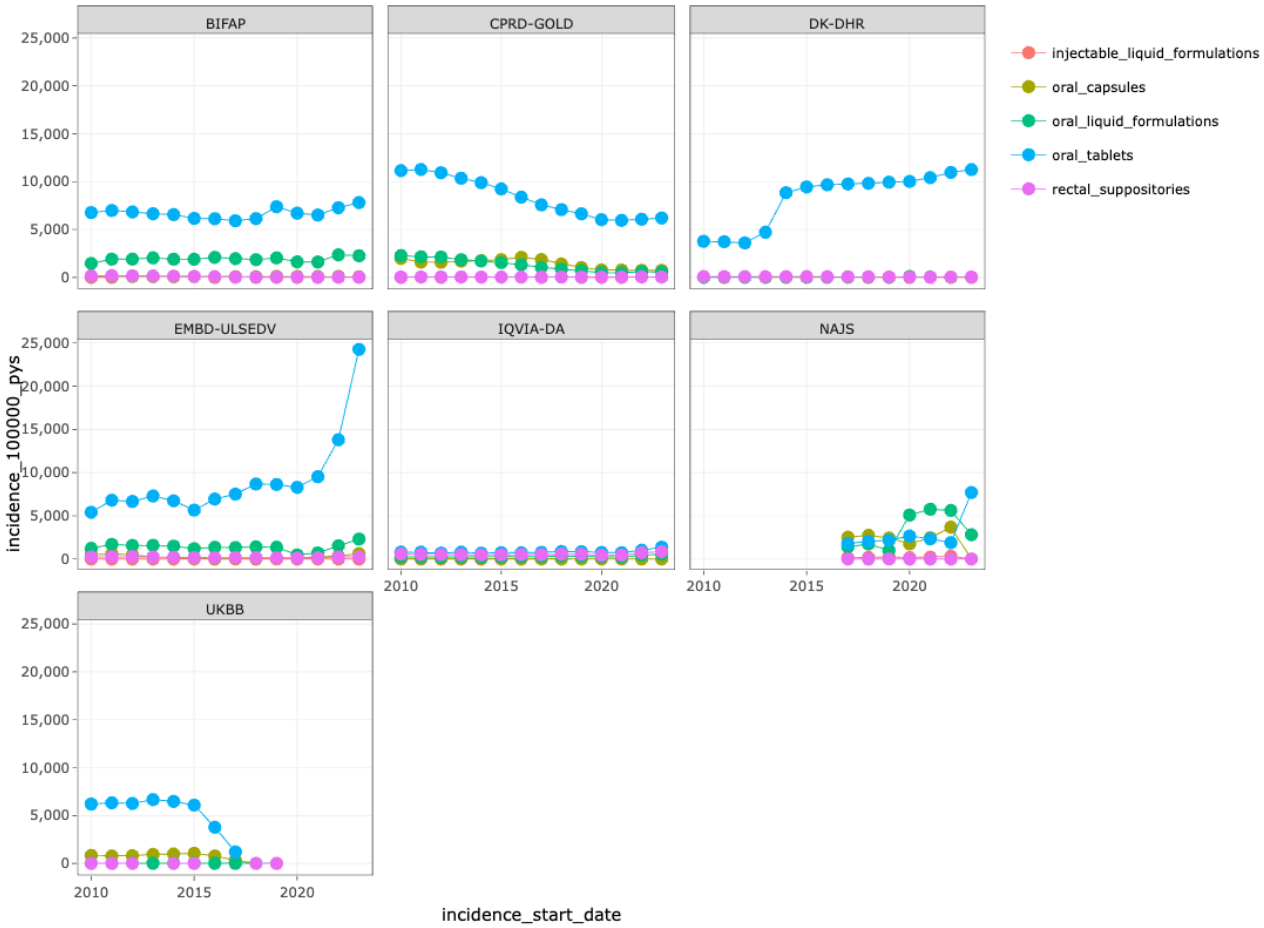


Figure 4. Incidence rates of paracetamol prescribing by calendar year and formulations.

Incidence rates by formulations were additionally stratified by age and sex. In general, results stratified by sex showed similar results to those obtained for paracetamol overall, with incidence rates of oral tables being higher among females compared to males (e.g. incidence rates per 100,000 PY in BIFAP: 7,794 [7,790 to 7,799] vs. 5,280 [5,276 to 5,285]). This was also observed across all formulations, except for oral liquid formulations in BIFAP and EMBD-ULSEDV, and rectal suppositories in IQVIA DA Germany (

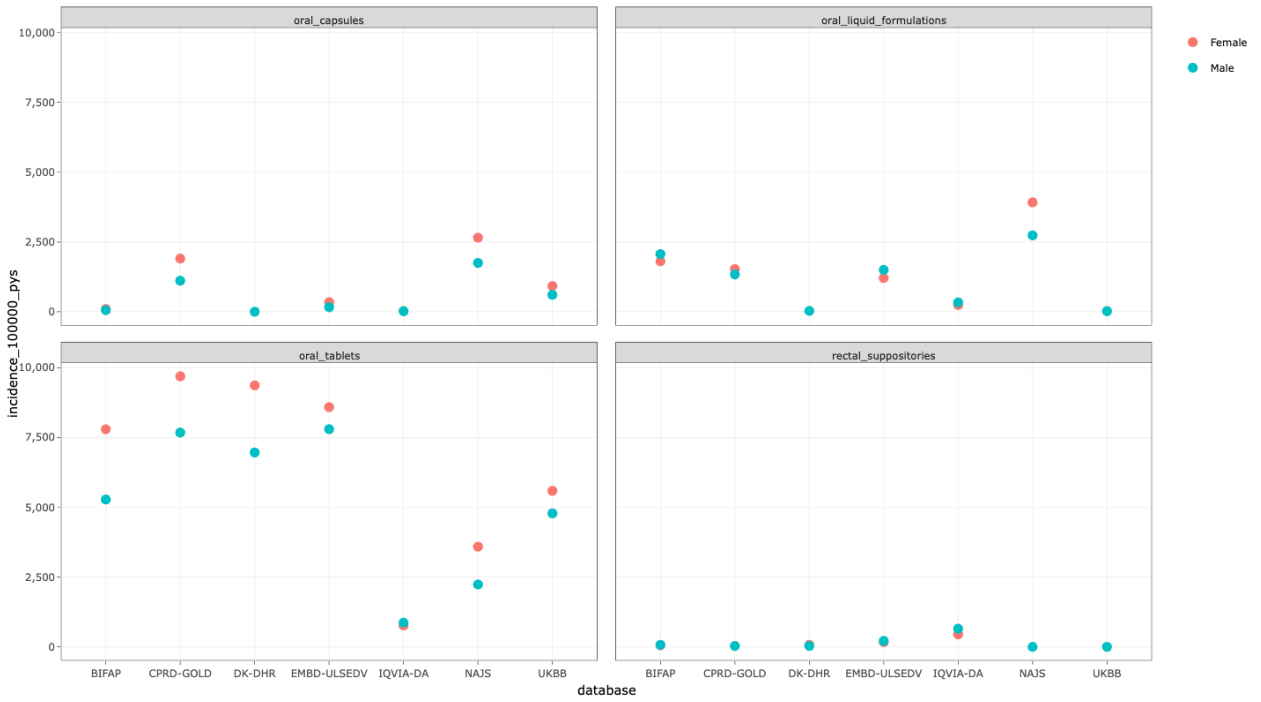


Figure 5). Regarding age groups, oral tablets and oral capsules (where counts available) showed similar patterns that those obtained for paracetamol overall, with incidence rates increasing with age. For rectal suppositories, incidence rates were higher among individuals aged 1-5 years in BIFAP, CPRD GOLD, EMBD-ULSEDV and IQVIA DA Germany. Similarly, oral liquid formulations obtained higher incidence rates among individuals aged 1-5 years in BIFAP, CPRD GOLD, EMBD-ULSEDV, NAJS, and IQVIA DA Germany, and were followed by rates among individuals aged 6-11 years (except for NAJS, which was followed by individuals aged > 80 years) (

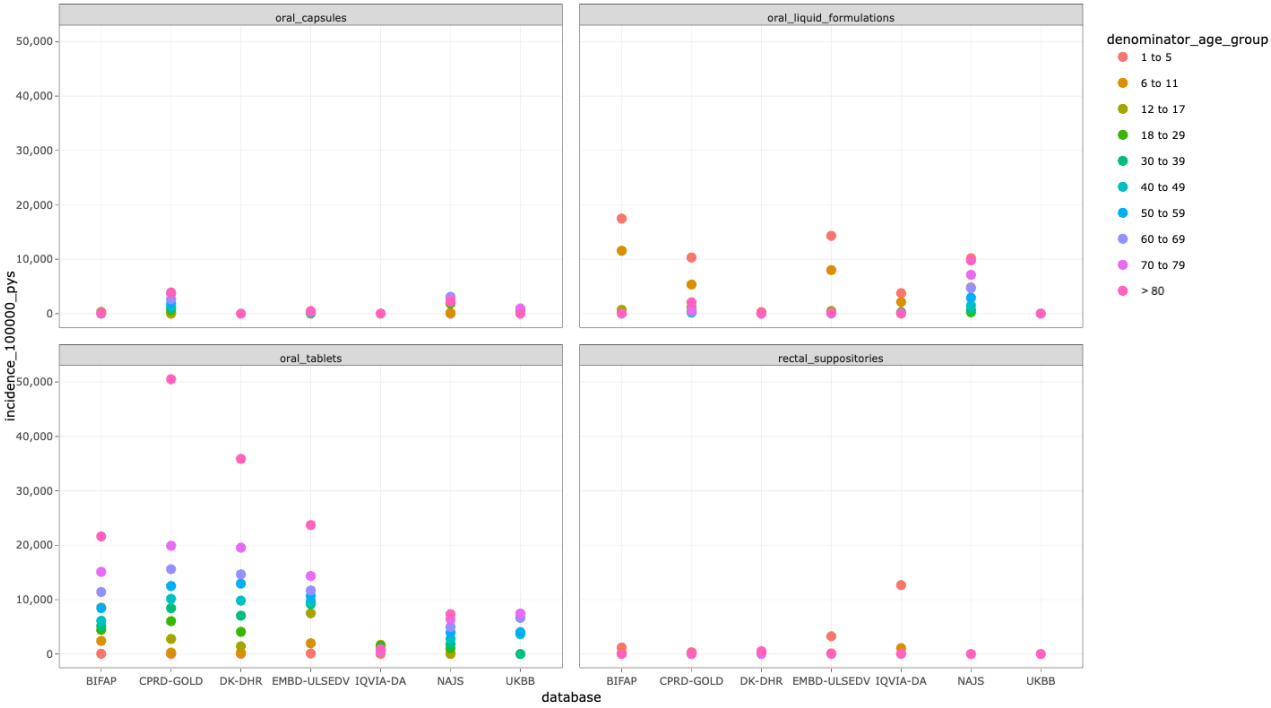


Figure *6*). Results of liquid injectable formulations are not shown in

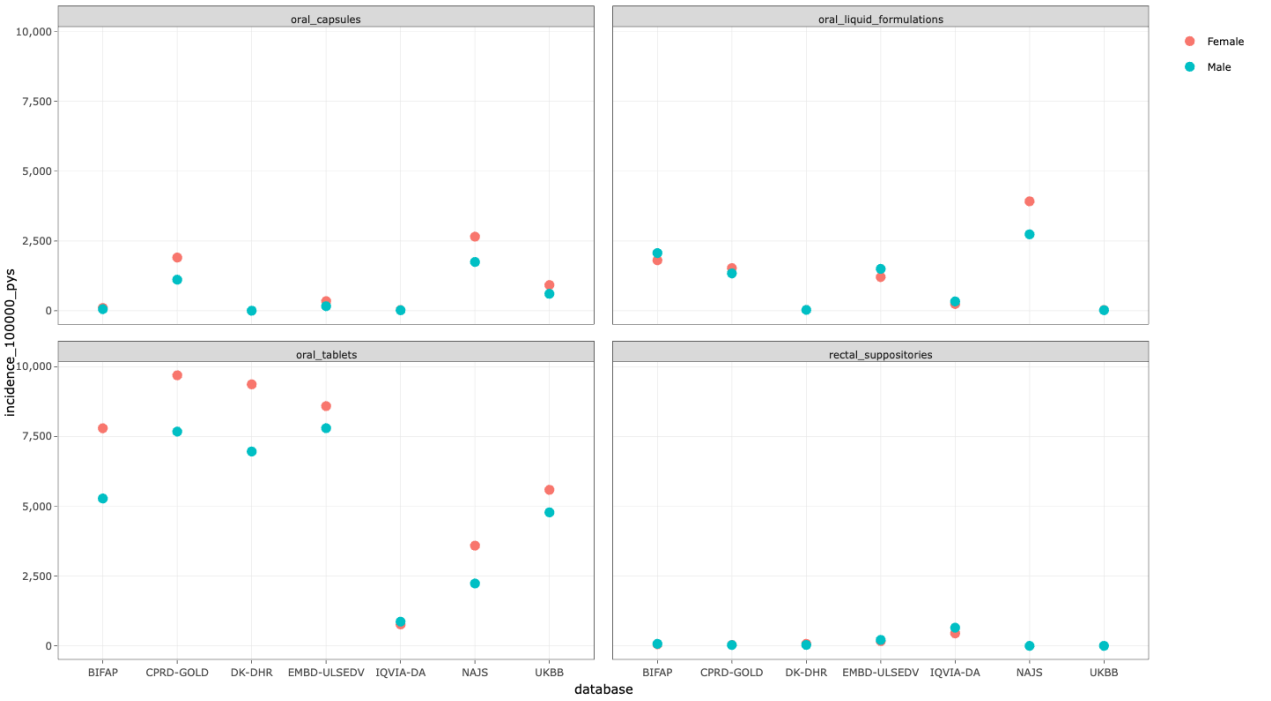


Figure *5* and

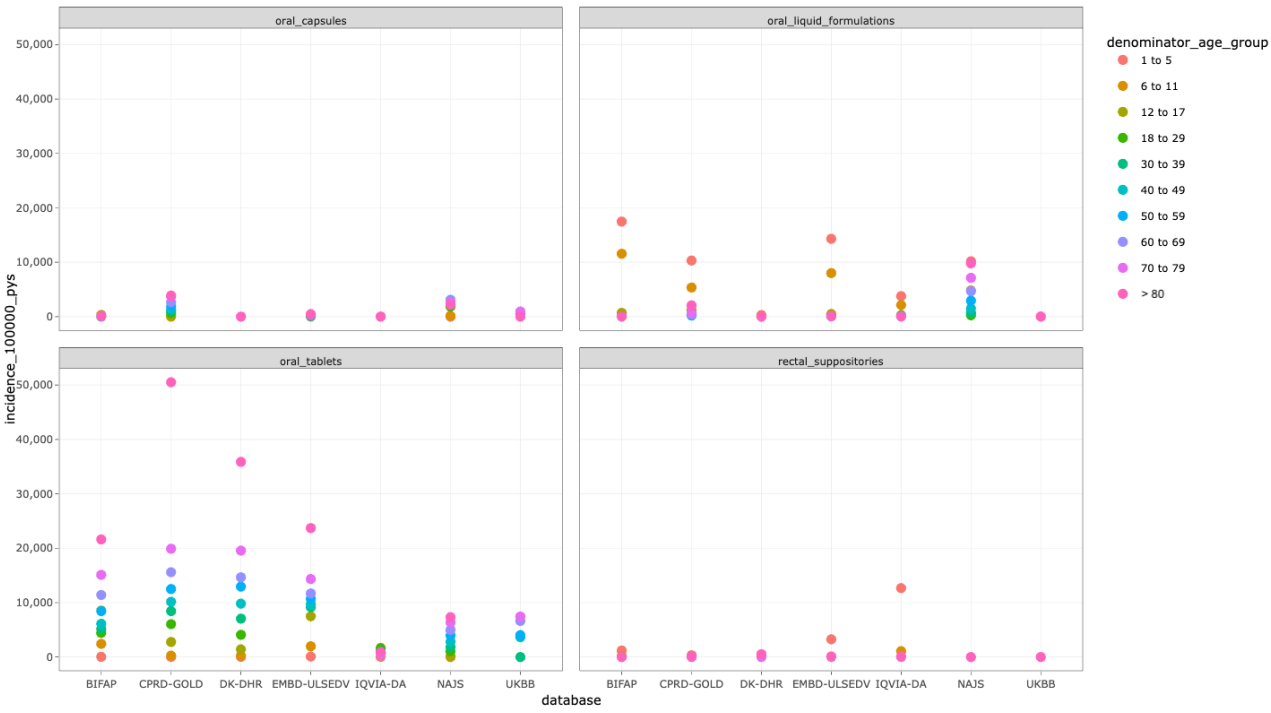


Figure *6* but can be explored in the Shiny App.

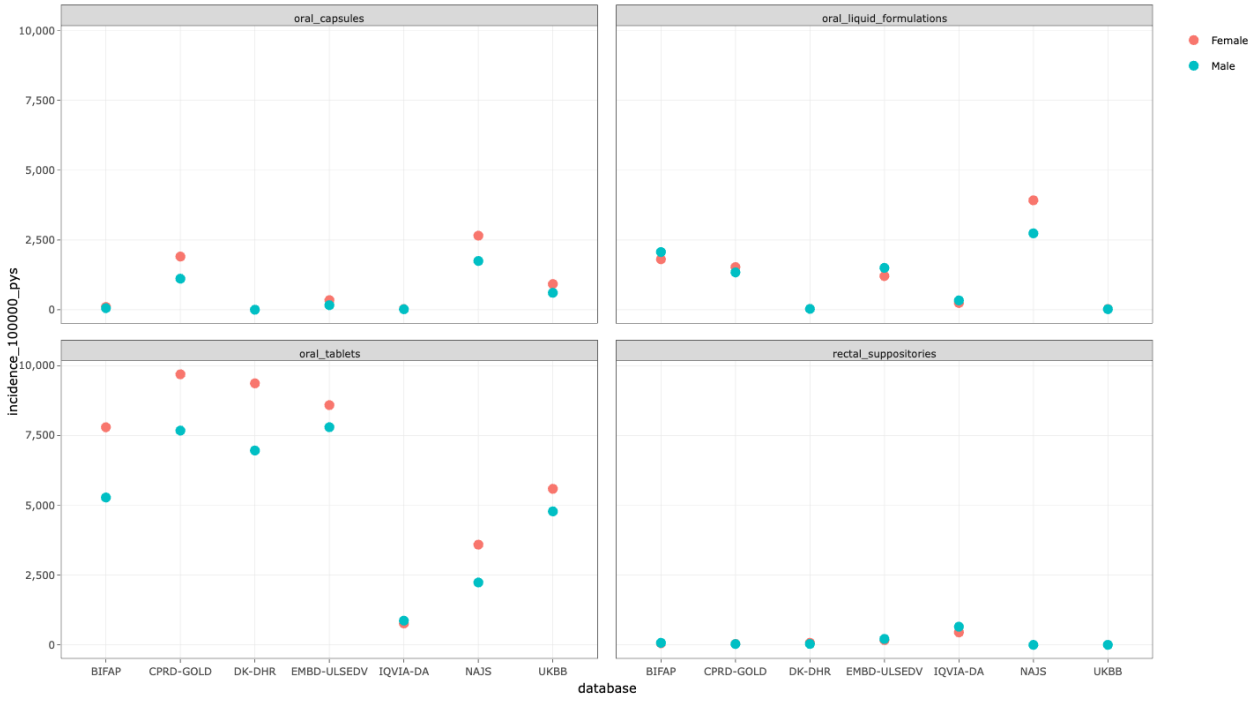


Figure 5. Incidence rates of paracetamol prescribing stratified by formulation and sex.

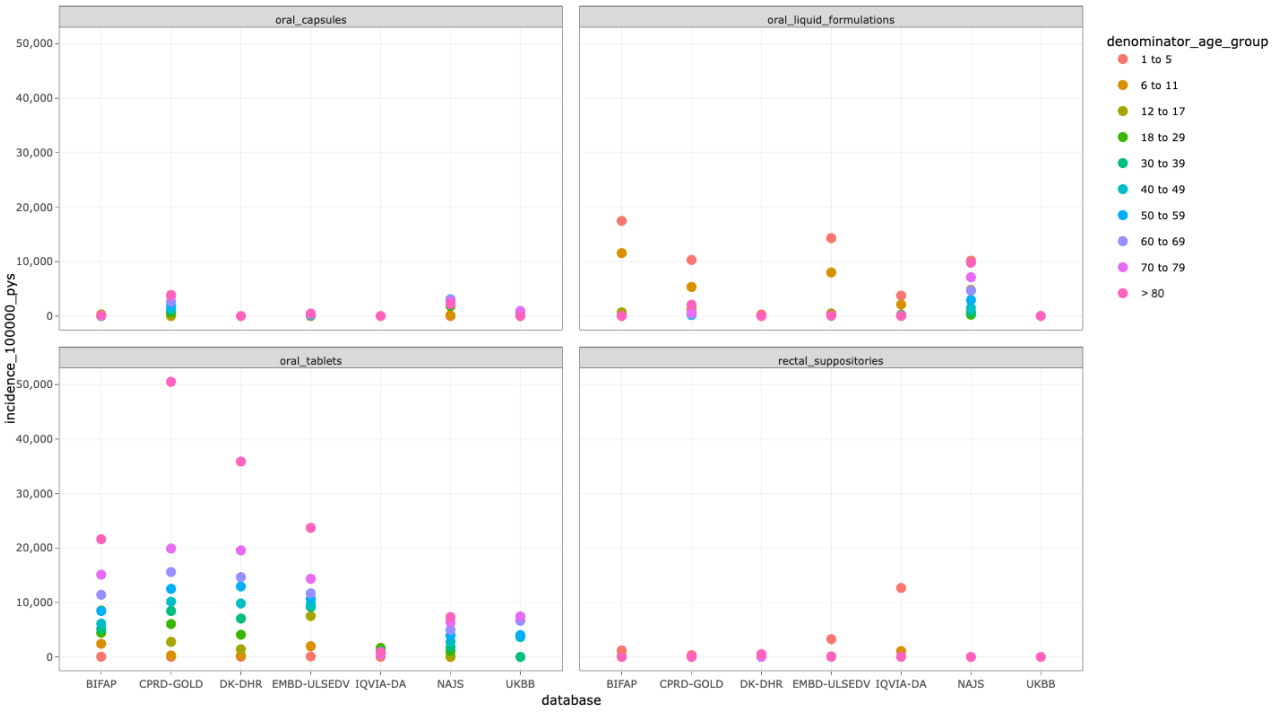


Figure 6. Incidence rates of paracetamol prescribing stratified by formulation and age groups.

Overall results stratified by database and covariates of interest can be found in the **Supplementary Table II- 1**. Yearly estimates, along with results combining multiple stratifications (e.g. formulation and sex), can be explored in the Shiny App.

13.3.2. Prevalence

In this section, we present prevalence of paracetamol prescribing. Prevalence was calculated as the proportion of participants who were prescribed a paracetamol-containing product within time intervals of interest (period prevalence).

Table 15 describes prevalence estimates considering 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 ranged from 5.2% (95% CI 5.2 to 5.3) in IQVIA DA Germany to 65.1% (65.1 to 65.2) in BIFAP. Estimates were below 32% across databases except for BIFAP and EMBD ULSEDV (53.1% [52.9 to 53.2]).

Table 15. Prevalence of paracetamol prescribing of the entire study period by database.

Database[1]	N population	N cases	Prevalence (95%CI)
BIFAP	20,754,789	13,520,681	65.1 (65.1 to 65.2)

Database[1]	N population	N cases	Prevalence (95%CI)
CPRD GOLD	10,701,809	3,361,899	31.4 (31.4 to 31.4)
DK-DHR	6,923,875	1,888,858	27.3 (27.3 to 27.3)
EMBD-ULSEDV	198,920	374,742	53.1 (52.9 to 53.2)
IQVIA DA Germany	17,124,145	896,091	5.2 (5.2 to 5.2)
NAJS	1,236,781	4536283	27.3 (27.2 to 27.3)
UKBB	502,350	87,236	17.4 (17.3 to 17.5)

[1] Study period from NAJS spanned from 2017 onwards.

Prevalence estimates by calendar year are shown in

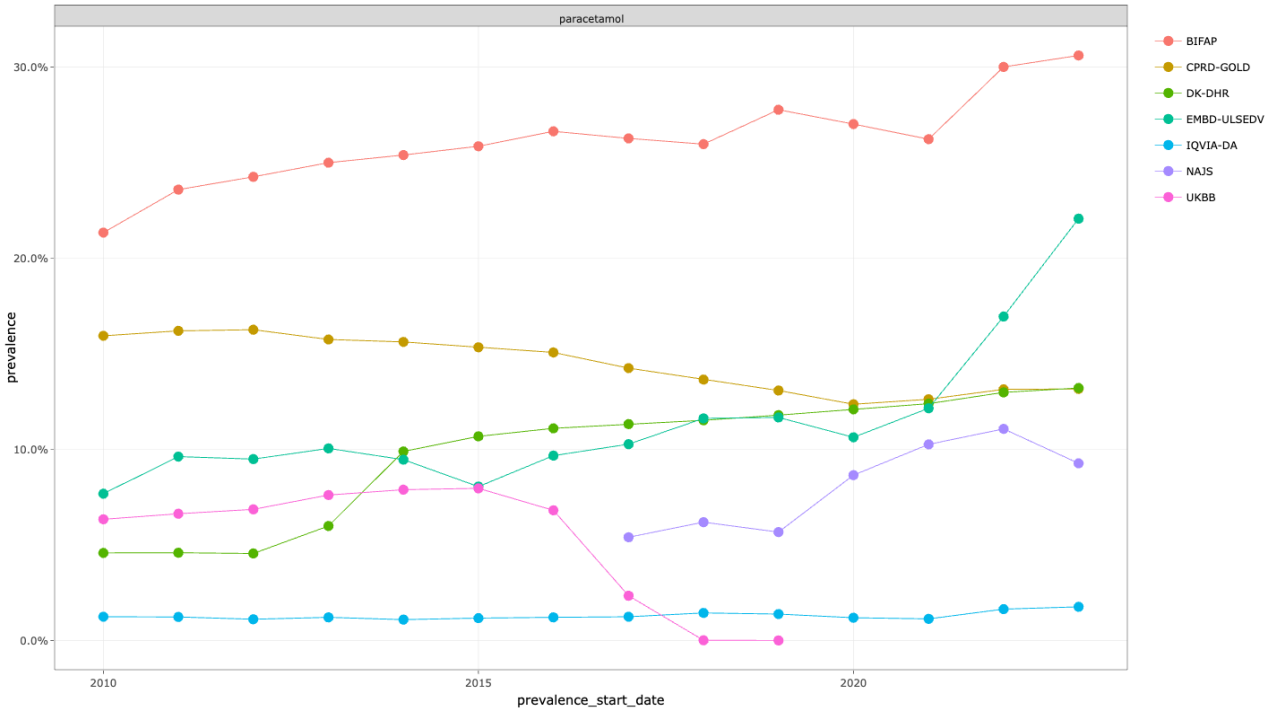


Figure 7. As observed for incidence rates, trends showed an upward trajectory in most databases, except for CPRD GOLD (which exhibited a descending trend throughout the study period, stabilising after 2020); and UKBB (which saw an abrupt decrease after 2015 onwards). As observed in incidence rates, prevalence of paracetamol prescribing in EMBD-ULSDEV increased over the last two years of available data.

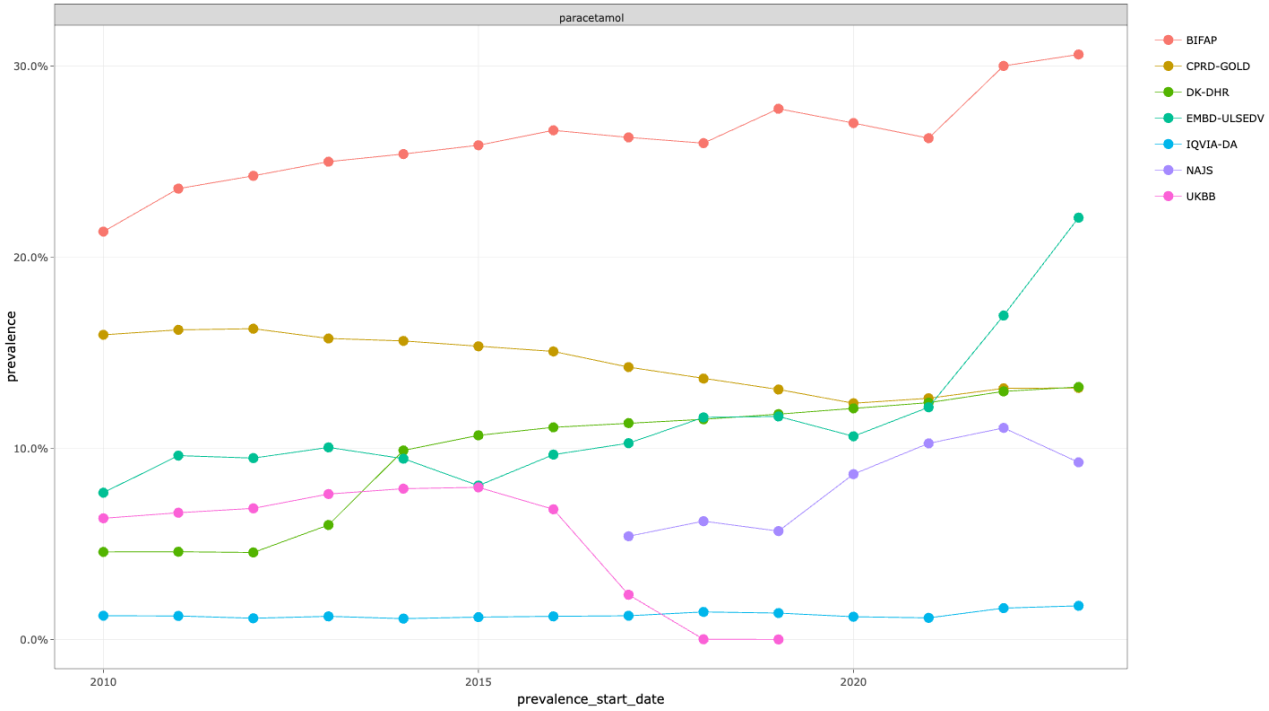


Figure 7. Prevalence of paracetamol prescribing by calendar year.

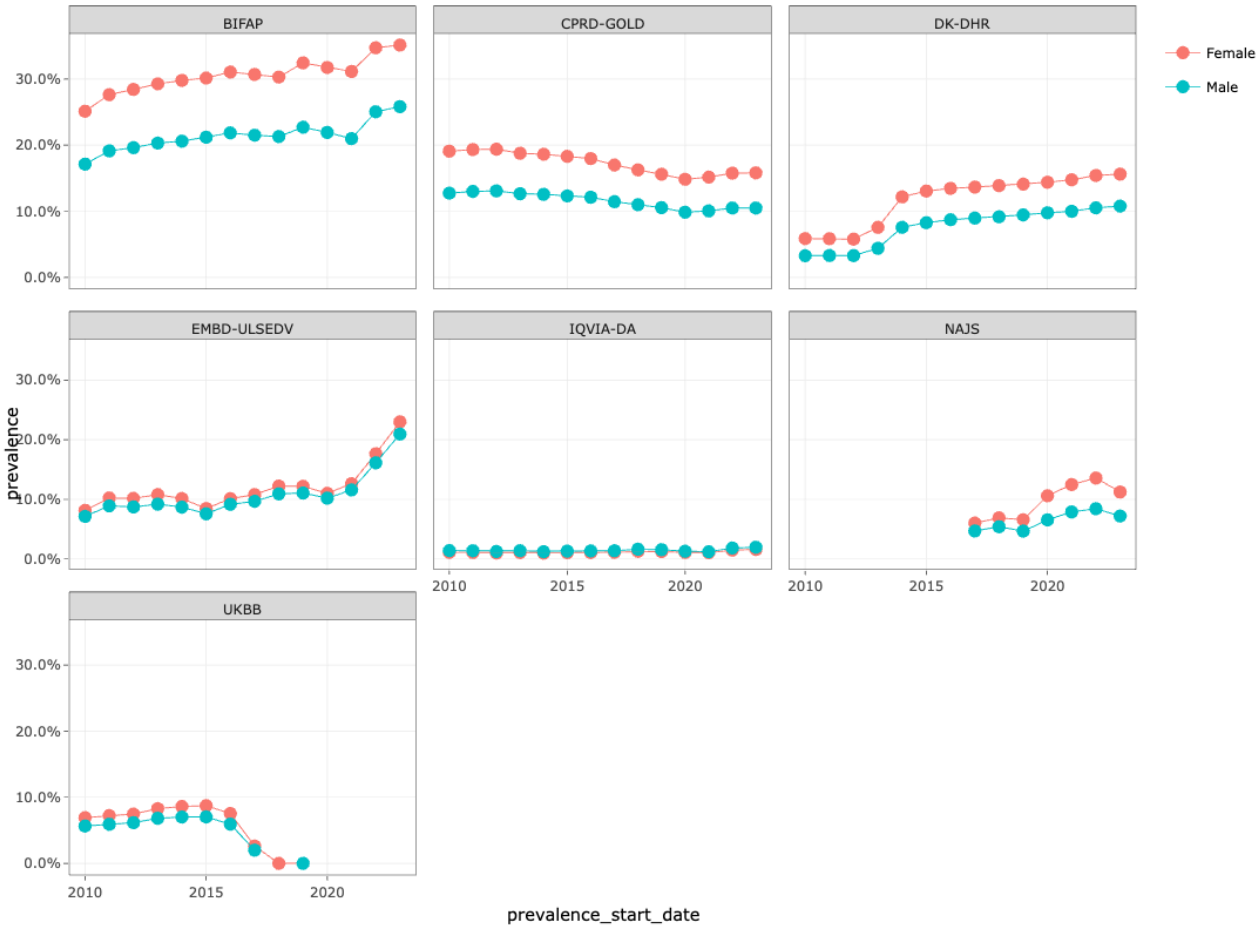

BIFAP
CPRD-GOLD
DK-DHR
EMBD-ULSEDV
IQVIA-DA
NAJS
UKBB
Female
Male
prevalence
30.0%
20.0%
10.0%
0.0%
2010
2015
2020
prevalence_start_date

Figure *8* and

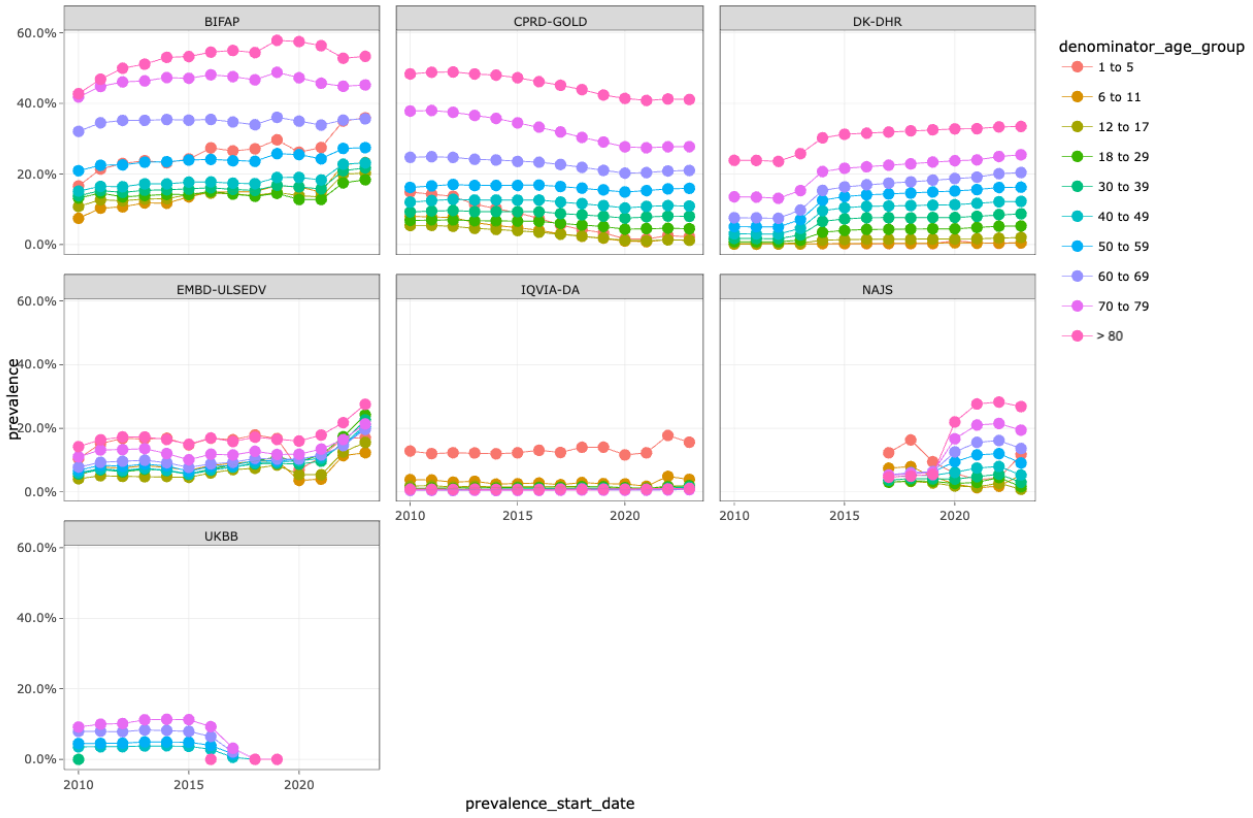
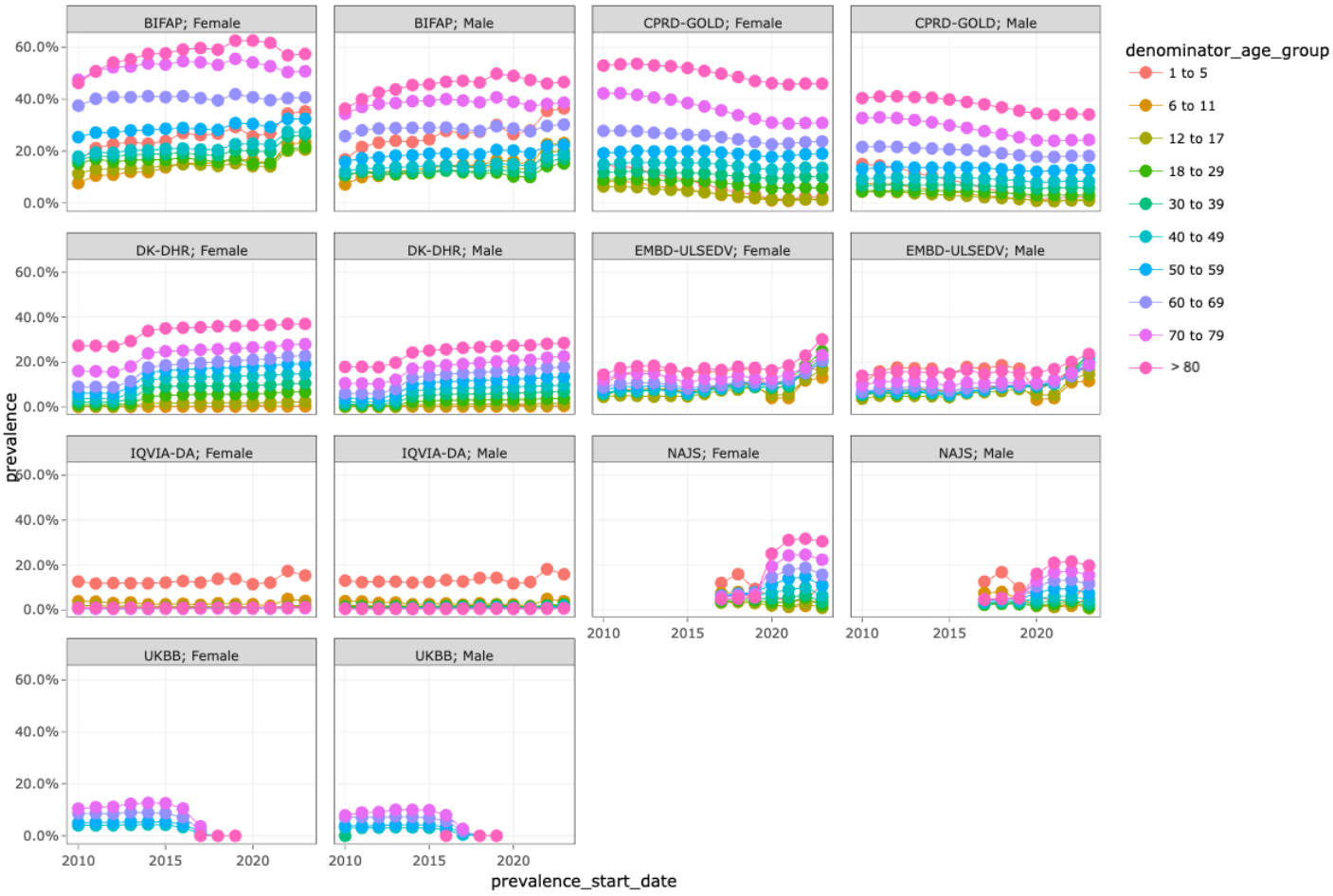
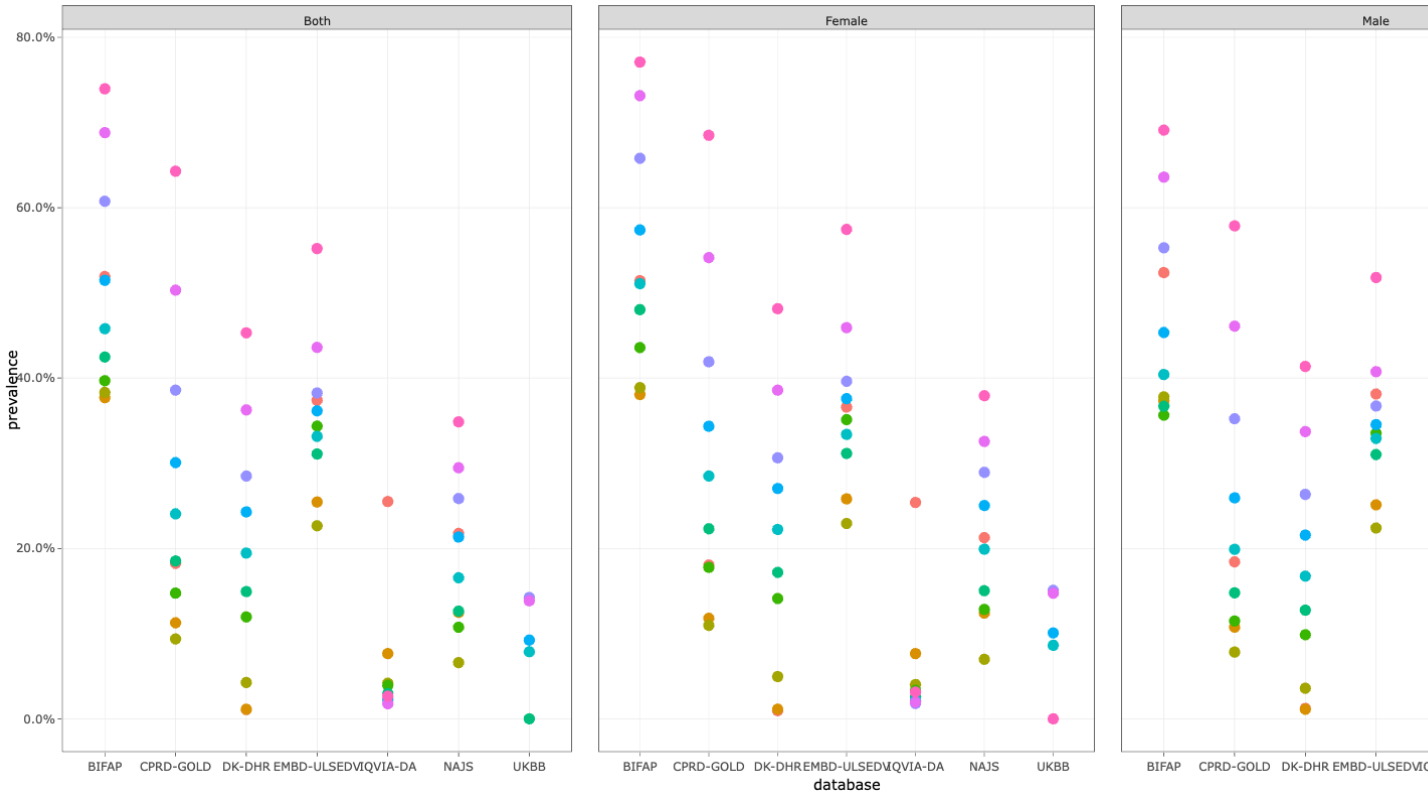


Figure *9* present results stratified by sex and age groups, respectively. Prevalence trends across sex and aged groups mirrored those observed for incidence rates, with higher prevalence among females compared to males, along with an increase in prevalence with age. As seen with incidence results, IQVIA DA Germany showed different patterns, with higher prevalence among males compared to females, and individuals aged 1 to 5 years exhibiting the highest prevalence among all age groups. Unlike incidence results, individuals aged 1 to 5 years exhibited the higher prevalence than subsequent older age groups in BIFAP and CPRD GOLD (e.g. in BIFAP: 51.9% [51.9 to 52.0] in the 1-5 age group vs. 37.7% [37.6 to 37.8] in the 6-11 age

group). Prevalence stratified by age and sex (combined) are shown in



Supplementary Figure II- *3* and



Supplementary Figure II- *4*, and can be explored in the Shiny App.

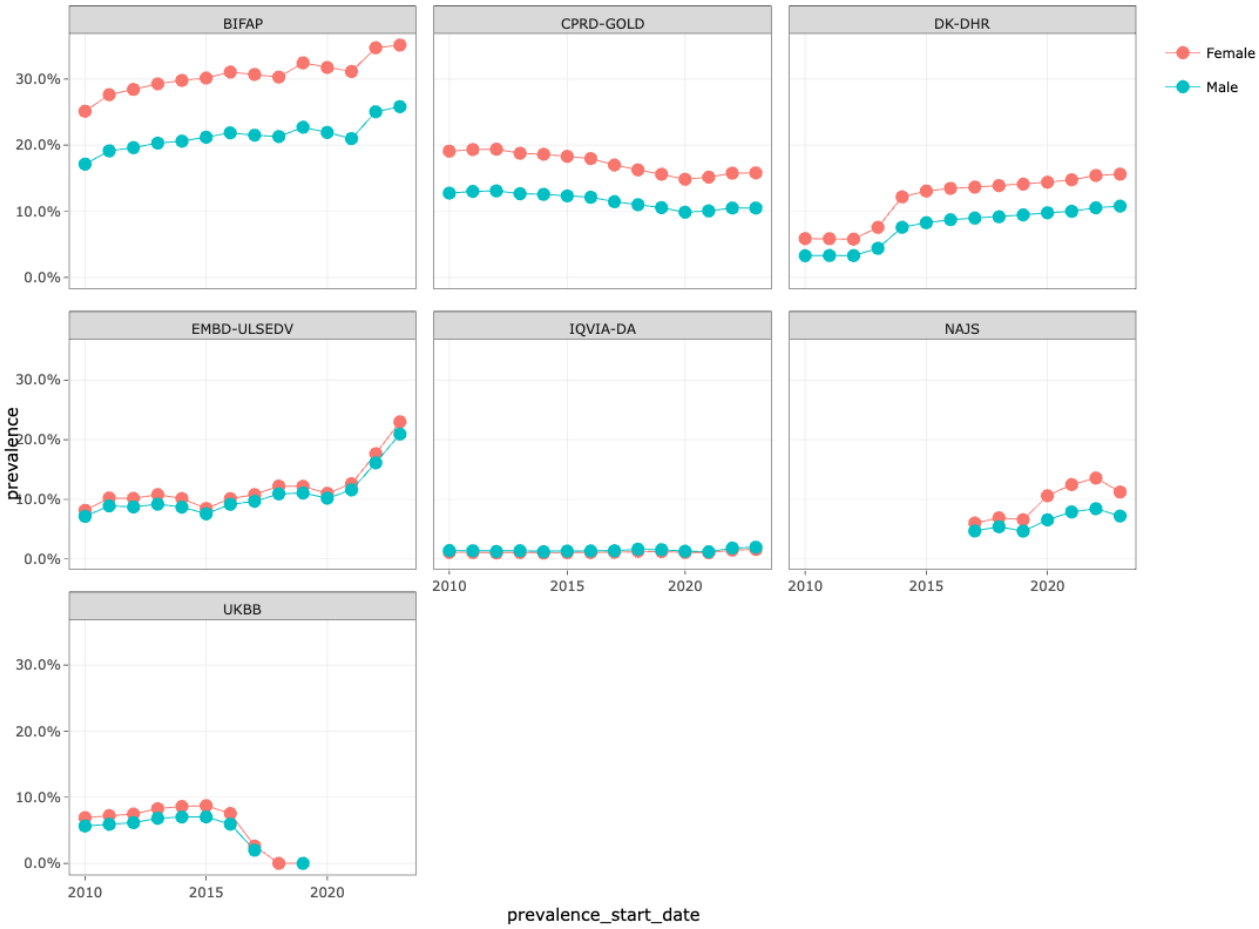


Figure 8. Prevalence of paracetamol prescribing by calendar year and sex.

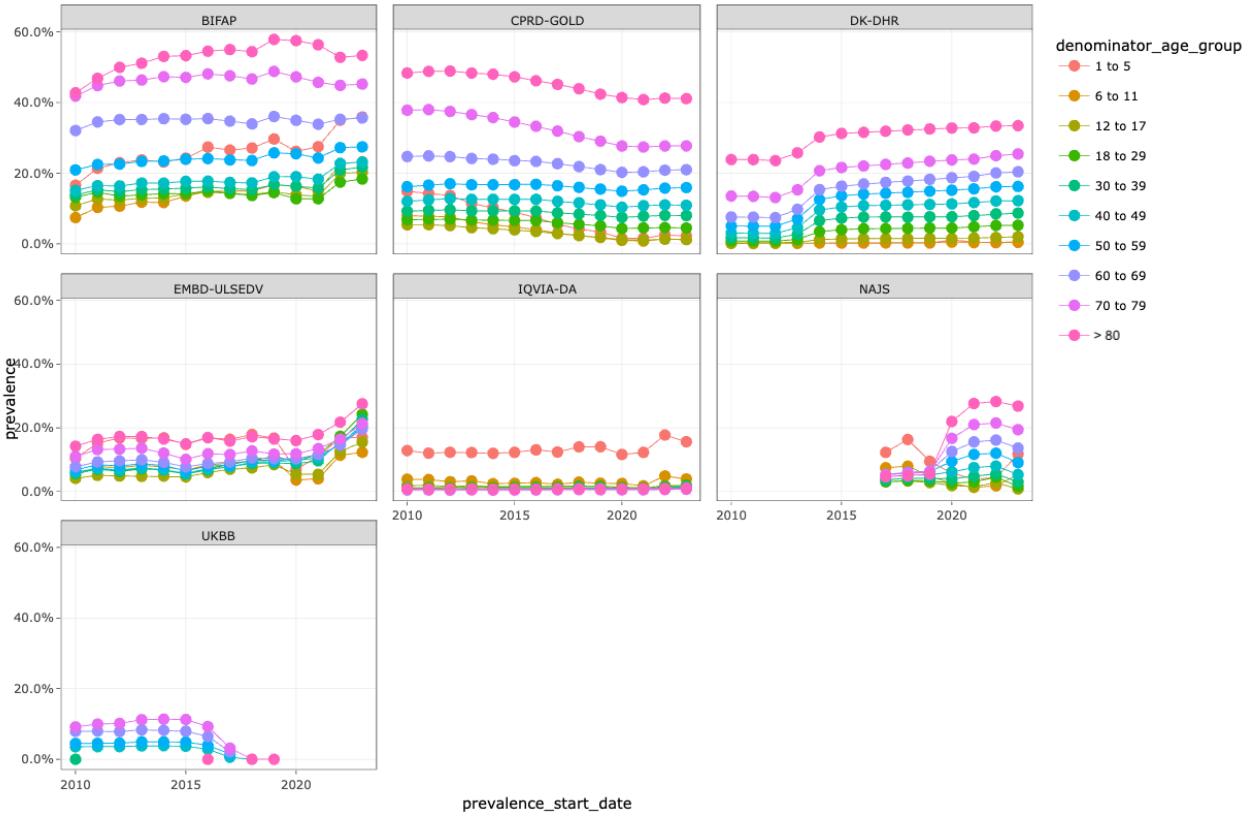


Figure 9. Prevalence of paracetamol prescribing by calendar year and age group.

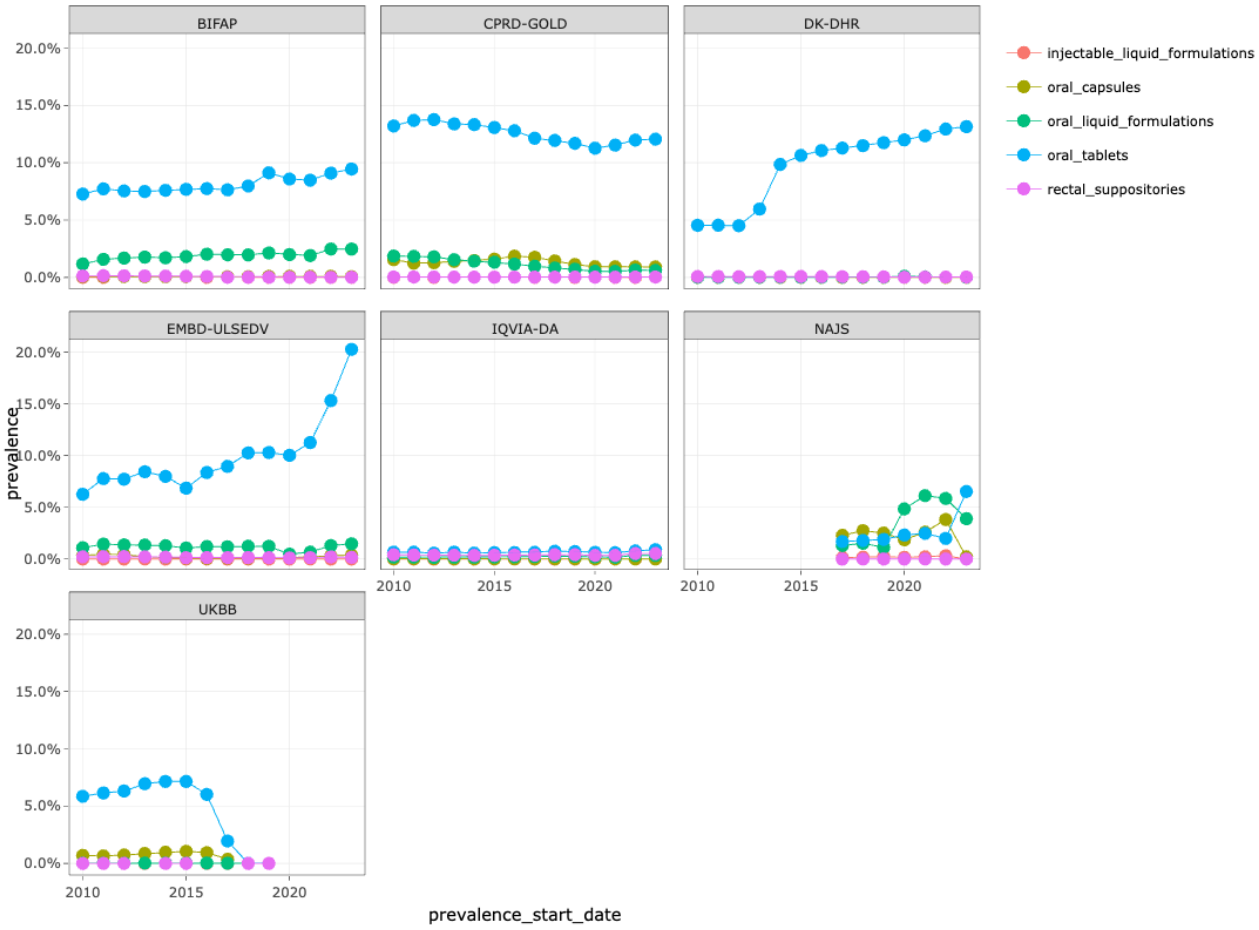


Figure *10* shows prevalence results stratified by formulations. In general, formulations with the highest and lowest prevalence aligned with those observed for incidence rates, with oral tablets obtaining the highest prevalence across data partners except for NAJS, in which the formulation with the highest prevalence varied between oral liquid, oral capsules and oral tablets across the captured years. Formulations with less than 100 events during the entire study period included injectable liquid formulations (DK-DHR, CPRD GOLD, EMBD ULSEDV, UKBB), oral capsules (DK-DHR) and rectal suppositories (NAJS).

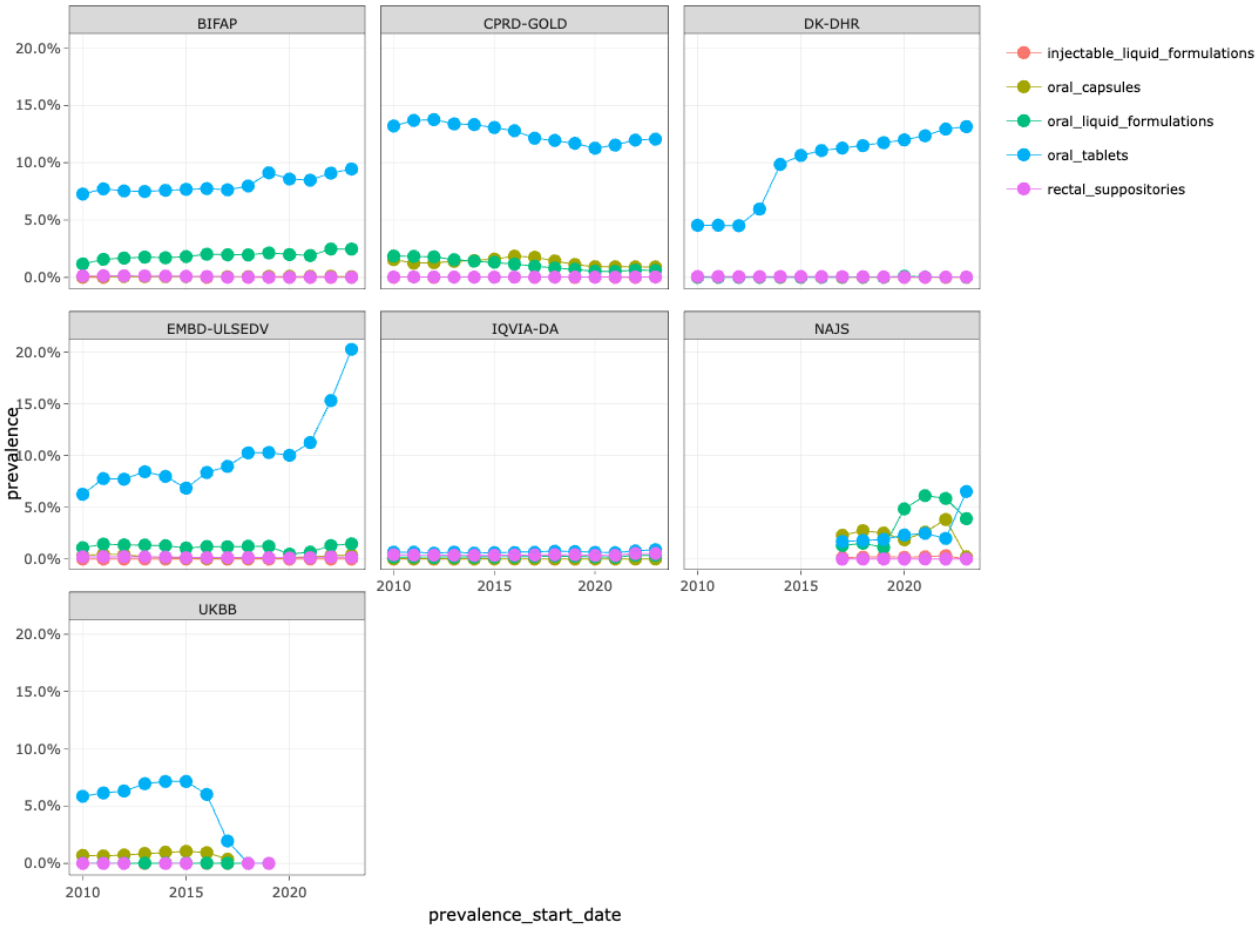


Figure 10. Prevalence of paracetamol prescribing by calendar year and formulation.

Prevalence of each formulation was additionally stratified by age and sex, with results illustrated in

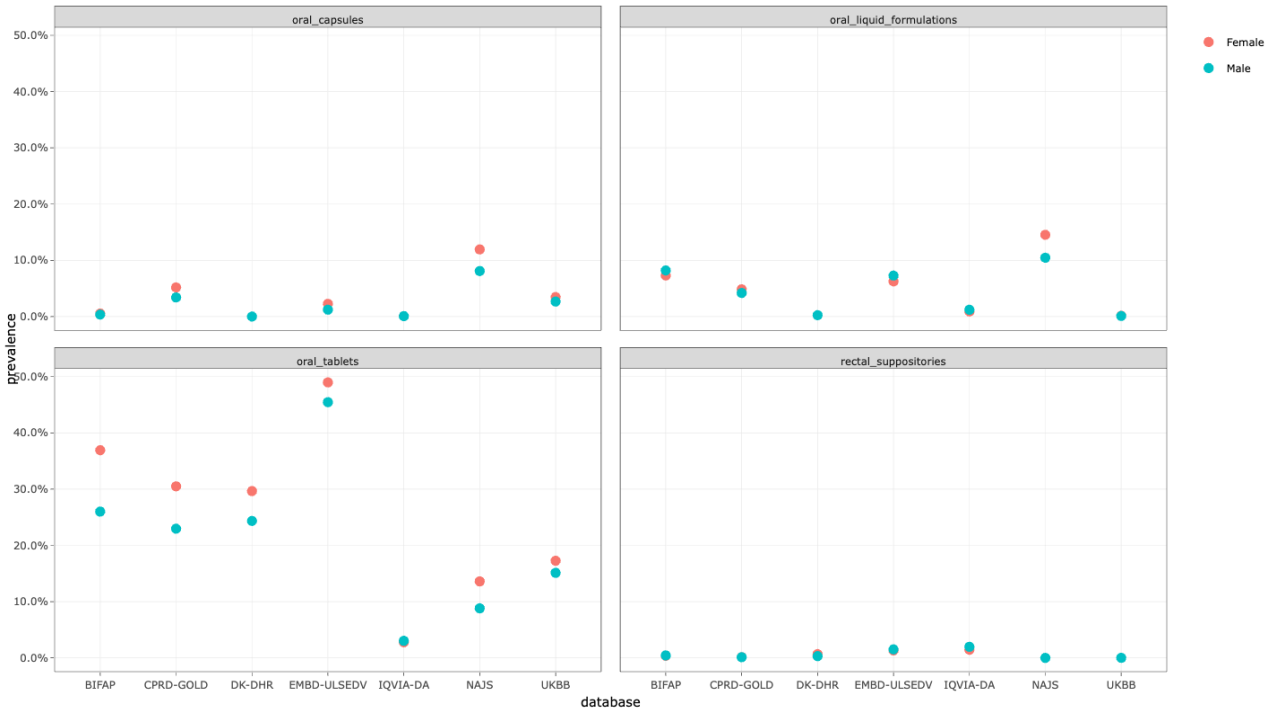


Figure *11* and

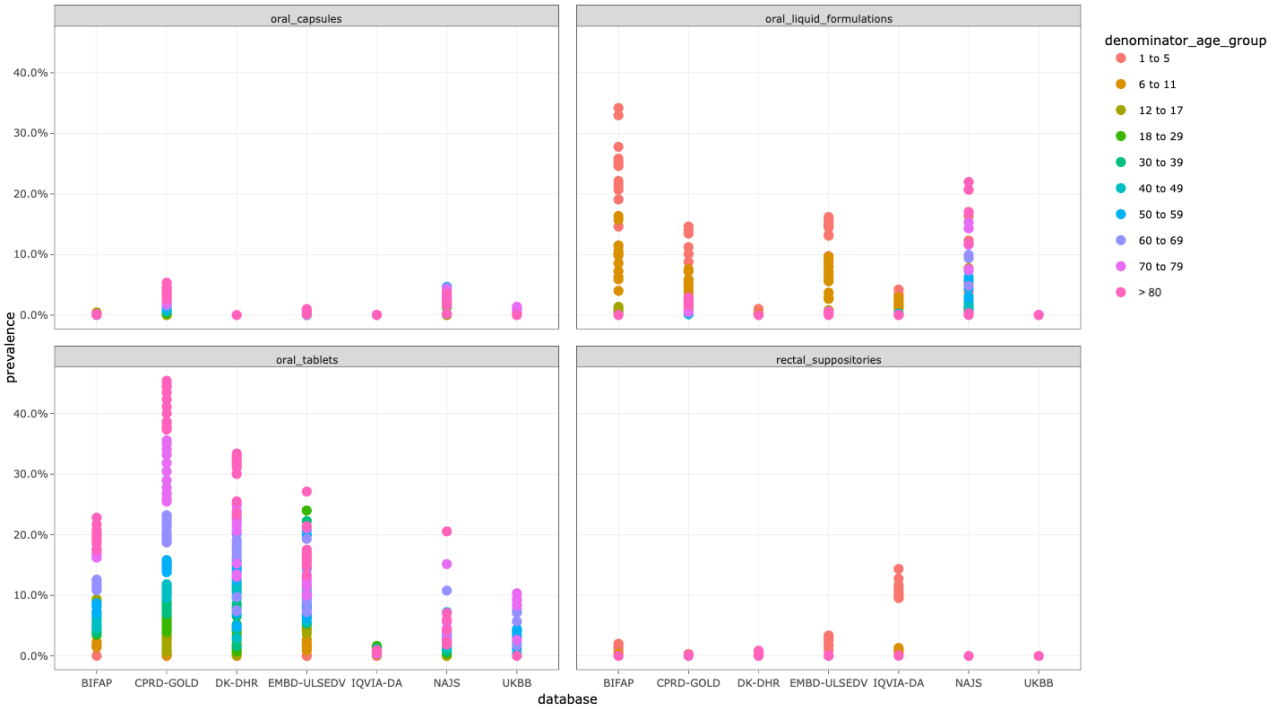


Figure *12*. Patterns across sex and age groups were similar to those observed for incidence. Prevalence was higher among females across all formulations except for oral liquid formulations (in BIFAP, EMBD-ULSEDV and IQVIA DA Germany) and rectal suppositories (in IQVIA DA Germany). Individuals aged 1-5 years obtained the highest prevalence for oral liquid formulations (in BIFAP, CPRD GOLD, EMBD-ULSEDV, IQVIA

DA Germany) and rectal suppositories (in BIFAP, EMBD-ULSEDV and IQVIA DA Germany). Individuals aged >80 obtained the highest prevalence of oral liquid formulations in NAJS (21.9% [21.8 to 22.0]) and rectal suppositories in DK-DHR (2.5% [2.5 to 2.5]). Results for injectable formulations showed greater prevalence among females compared to males, with figures increasing with age (results available in the Shiny App).

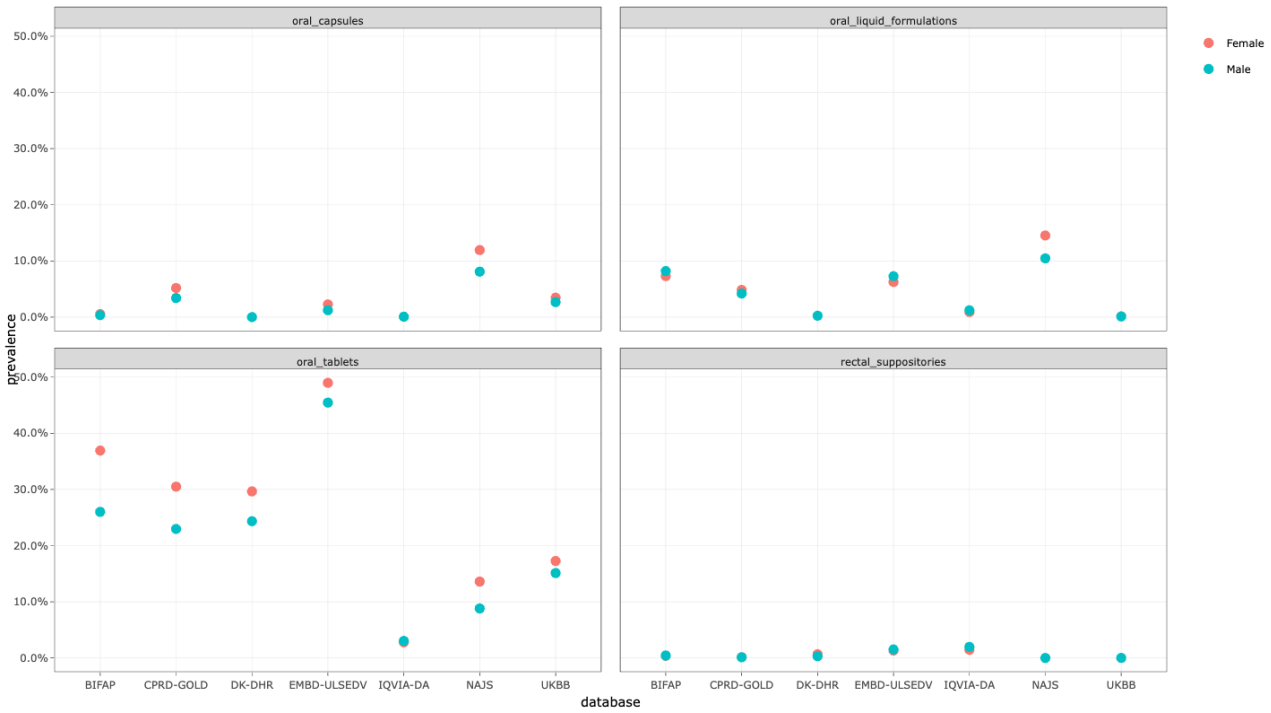


Figure 11. Prevalence of paracetamol prescribing by formulation and sex.

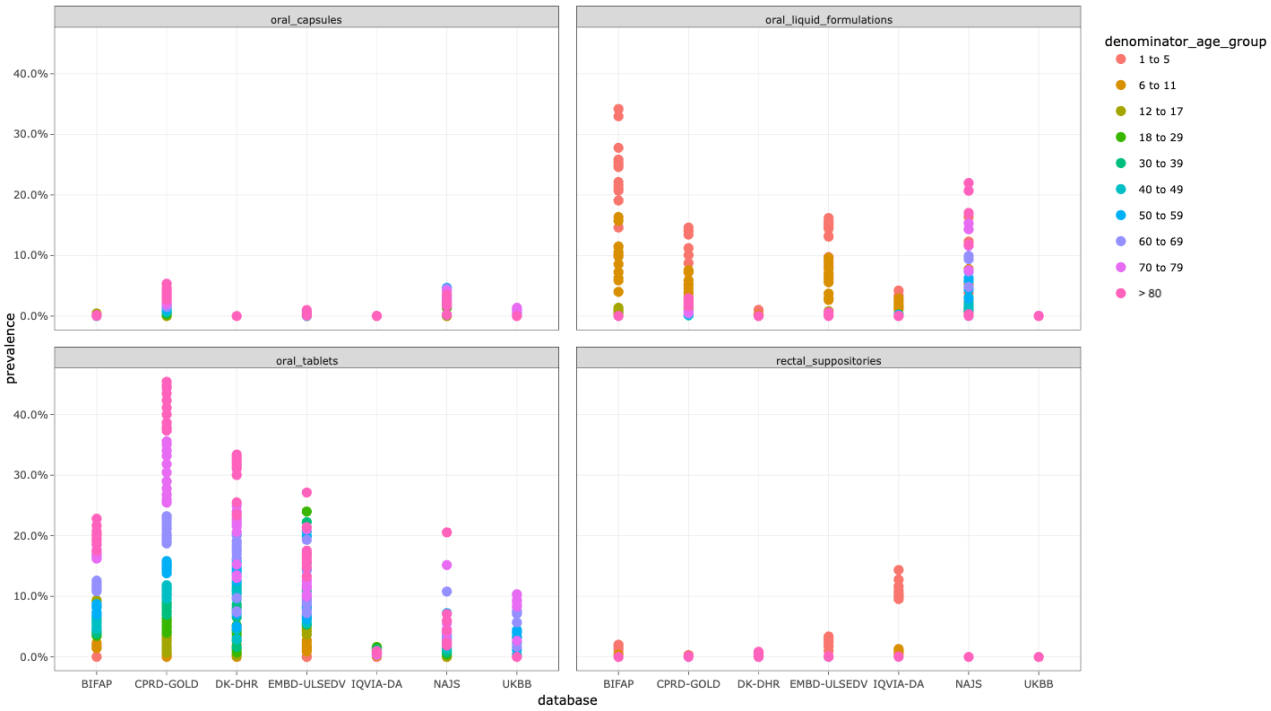


Figure 12. Prevalence of paracetamol prescribing by formulation and age group.

Overall results stratified by database and covariates of interest can be found in **Supplementary Table II- 2.** Yearly estimates, along with results combining multiple stratifications (e.g. formulation and sex), can be explored in the Shiny App.

13.4 Paracetamol overdose

13.4.1 Incidence

In this section we described incidence of paracetamol overdose. For incidence calculations, multiple events per person were allowed if separated by more than 365 days.

Overall incidence results for the entire study period can be found in **Table 16**, and by calendar year in

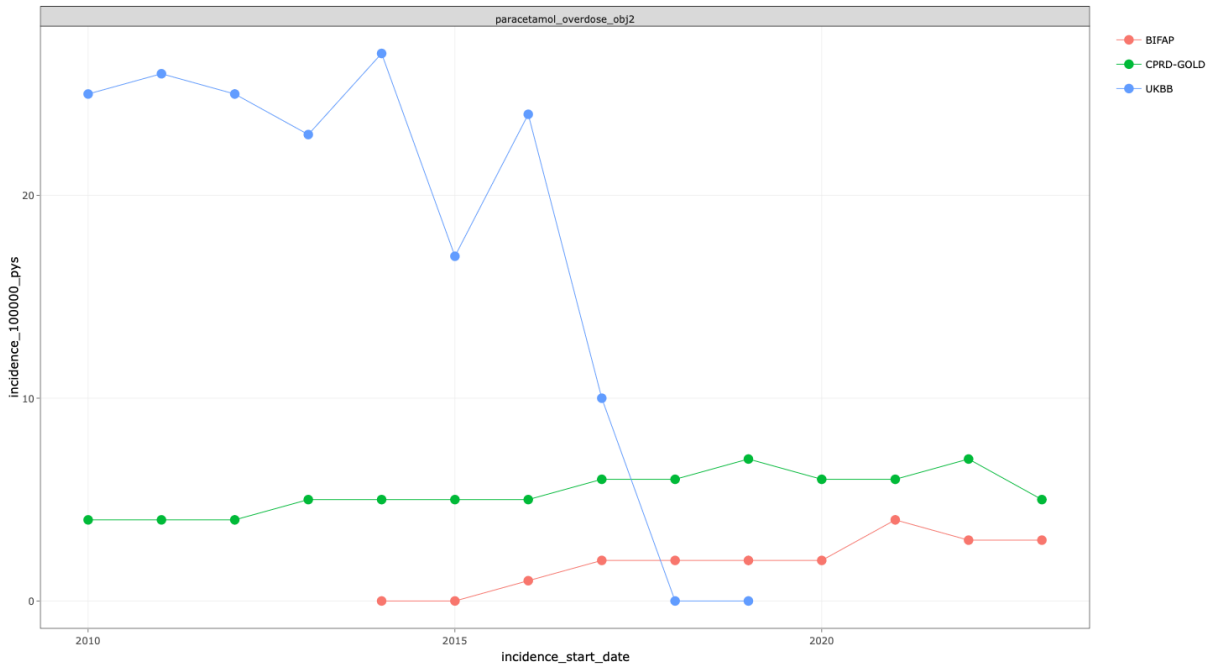
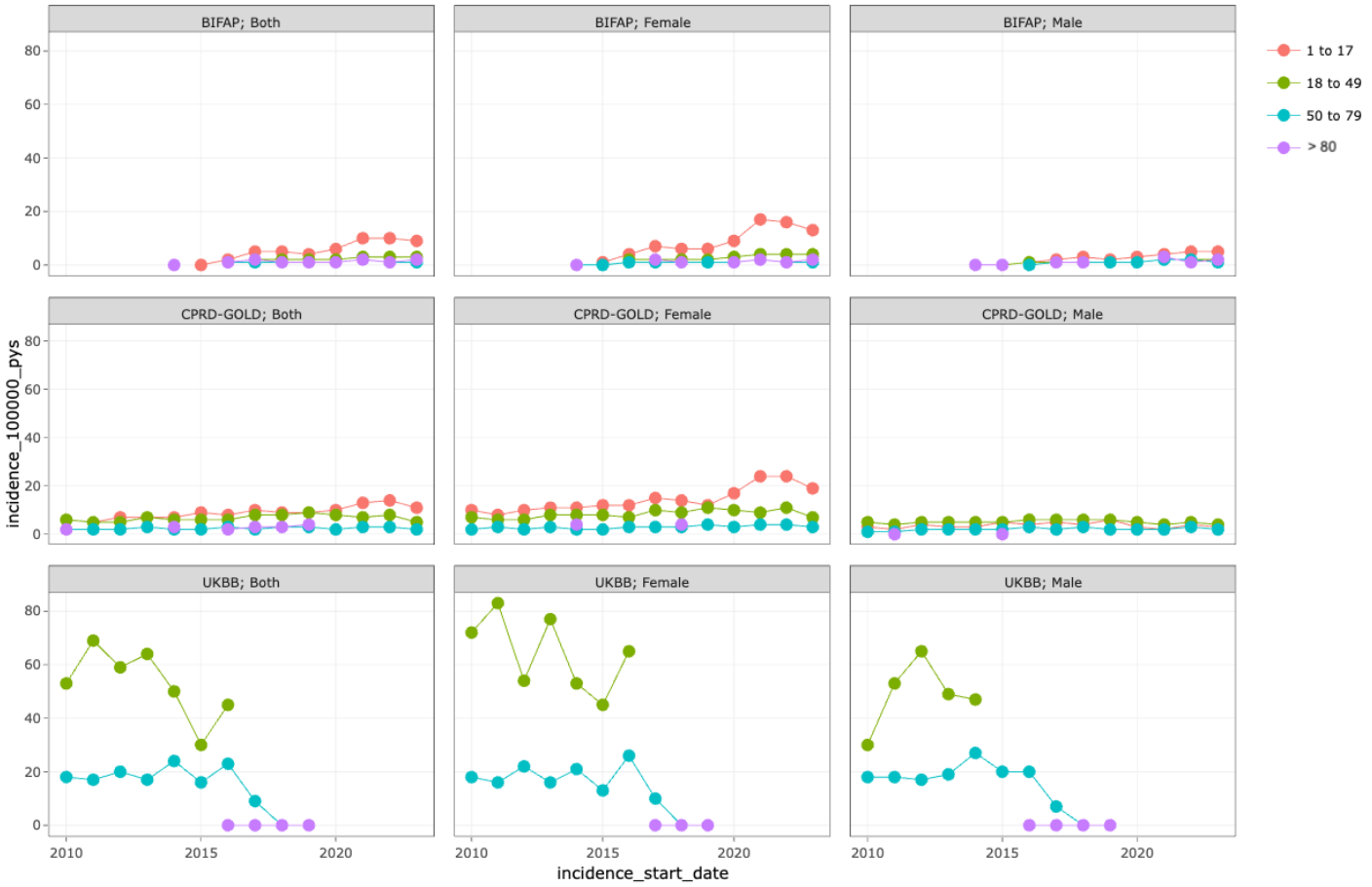


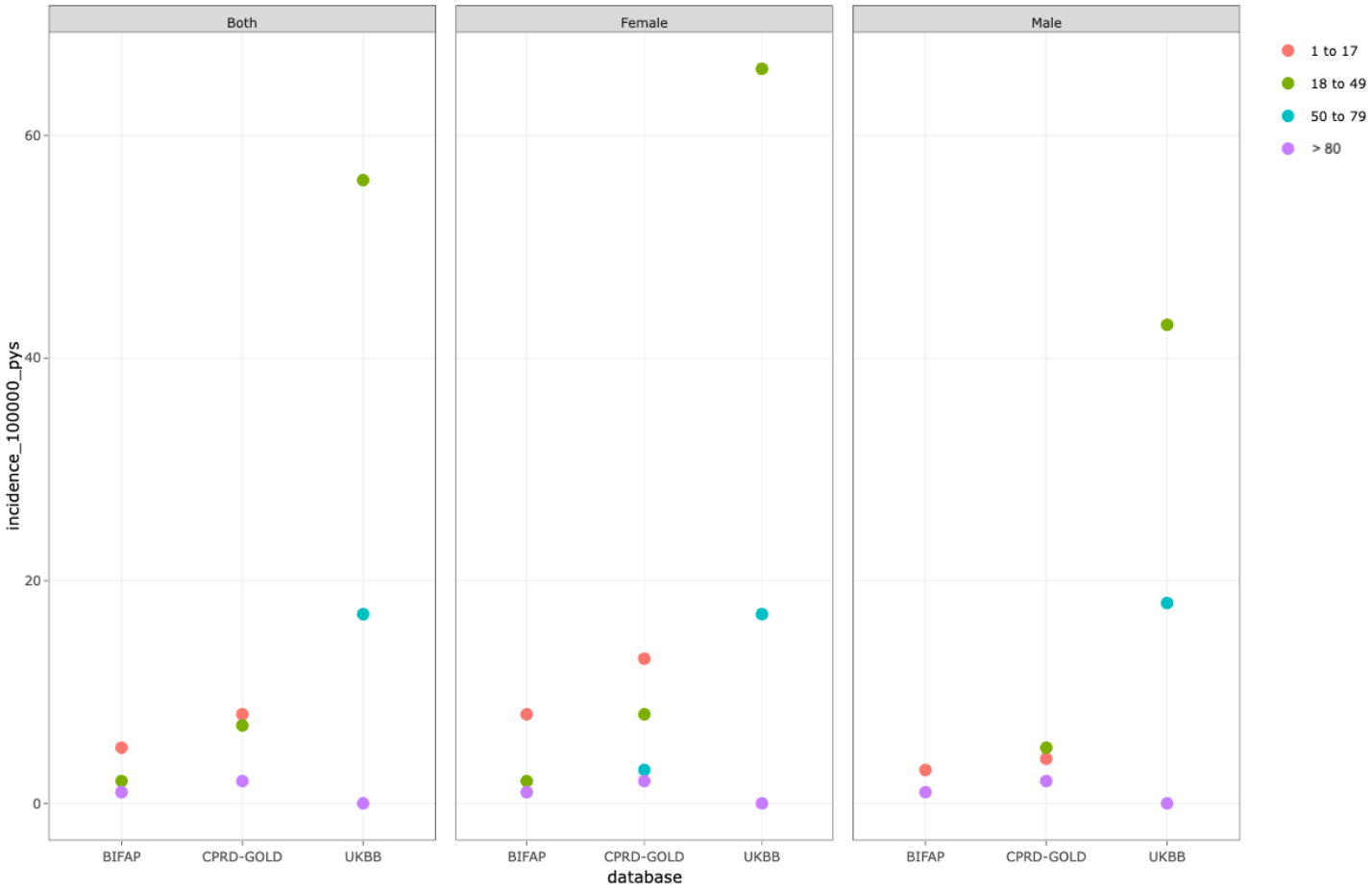
Figure *13*. Incidence rates per 100,000 PY were 2 (95% CI 2 to 2) in BIFAP, 5 (5 to 5) in CPRD GOLD and 21 (20 to 23) in UKBB. In BIFAP, incidence rates showed an upward trend, reaching a peak in 2021. A more modest upward trend was also observed in CPRD GOLD, which appeared to stabilise after 2017 and saw a decrease in estimates in 2023. In UKBB, rates followed a decreasing pattern, with a sharp decrease in 2017, concurring with the last year with cases captured (see "13.1 Participants").

Table 16 details results for the entire study period stratified by sex and age groups (broad categories). Incidence rates were consistently higher among females than males. The gap in incidence rates between females and males was particularly pronounced in BIFAP and CPRD GOLD, and was less notable in UKBB. In BIFAP and CPRD GOLD, individuals aged 1 to 17 years exhibited higher incidence rates compared to those aged > 18 years. This gap was particularly pronounced among females and appeared to have widened after 2020 (**Figure 14**).

Figures illustrating results stratified by narrow age groups can be found in


BIFAP; Both
BIFAP; Female
BIFAP; Male
CPRD-GOLD; Both
CPRD-GOLD; Female
CPRD-GOLD; Male
UKBB; Both
UKBB; Female
UKBB; Male
incidence_100000_pys
incidence_start_date
1 to 17
18 to 49
50 to 79
> 80

Supplementary Figure II-*5* and



Supplementary Figure II- *6*, incidence rates decreasing with age. Results stratified by age and sex (combined) can be found in **Supplementary Table II-3.**

Table 16. Incidence of paracetamol overdose for the entire study period by database.

Results[1]	Database[2]	N events	N persons	Person-years	Incidence per 100,000 person-years (95%CI) [3]
Overall	BIFAP	2,551	16,445,144	131,730,698	2 (2 to 2)
	CPRD GOLD	3,345	10,701,718	63,661,681	5 (5 to 5)
	UKBB	858	502,350	4,038,831	21 (20 to 23)
Female	BIFAP	1,726	8,485,107	68,407,502	3 (2 to 3)
	CPRD GOLD	2,170	5,425,642	32,079,087	7 (6 to 7)

Results[1]	Database[2]	N events	N persons	Person-years	Incidence per 100,000 person-years (95%CI)[3]
	UKBB	485	273,291	2,207,113	22 (20 to 24)
Male	BIFAP	825	7,960,037	63,323,197	1 (1 to 1)
	CPRD GOLD	1,175	5,276,076	31,582,593	4 (4 to 4)
	UKBB	373	229,059	1,831,718	20 (18 to 23)
1 to 17 years	BIFAP	1,075	3,468,567	20,675,601	5 (5 to 6)
	CPRD GOLD	978	2,549,550	11,937,685	8 (8 to 9)
> 18 years	BIFAP	947	8,656,475	56,576,650	2 (2 to 2)
	CPRD GOLD	1,768	5,650,278	27,039,852	7 (6 to 7)
	UKBB	232	103,430	417,747	56 (49 to 63)

[1] Results stratified by additional age groups can be found in the Appendix.

[2] Study period in BIFAP was restricted to 2014 onwards and to patients registered in areas with hospital linkage.

[3] Incidence estimates are rounded to the nearest whole number.

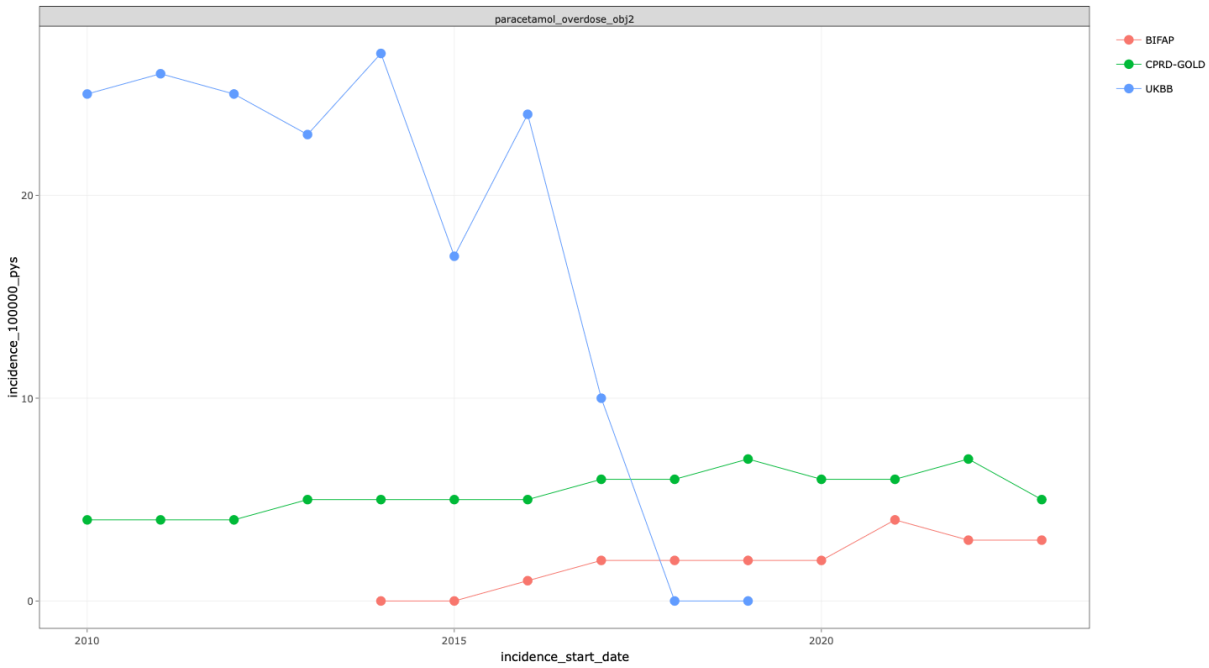


Figure 13. Incidence rates of paracetamol overdose by calendar year.

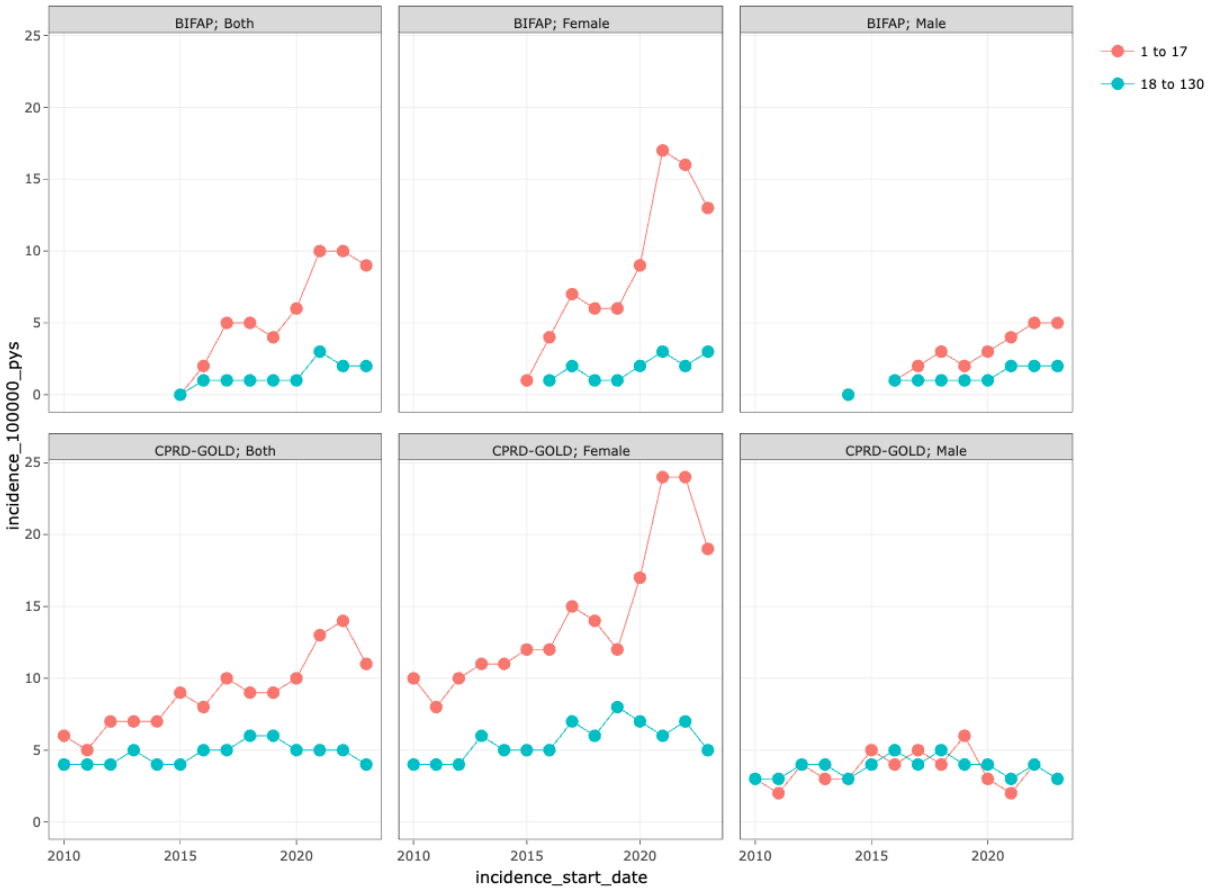


Figure 14. Incidence rates of paracetamol overdose in BIFAP and CPRD GOLD, by calendar year, sex and age groups.

13.5. Characterisation of patients

In this section we described the characterisation of 8,370 individuals with paracetamol overdose (n=2,480 in BIFAP; n=2,125 in CDWBordeaux; n=3,140 in CPRD GOLD; n=625 in UKBB). Patients were described based on pre-specified 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.

13.5.1. Pre-specified conditions and medications

In this section we will describe results of pre-specified comorbidities and medications. In **Table 17**, the frequency of pre-specified conditions is described for each database considering time windows spanning from all prior history to 1 day before index date, and 31 to 1 day prior to index date. **Table 18** includes short-term complications (hepatic toxicity and renal toxicity), mortality, and conditions assessed using different time windows. Considerations for the interpretation of the frequency of conditions and medications reported in this section are described in “15.3 Interpretation”.

The proportion of patients with conditions of interest differed across databases. In general, UKBB had the highest number of patients with records of comorbidities of interest prior to index date, whereas CDWBordeaux had the lowest. The frequency of pre-specified comorbidities in primary care databases was similar, with some exceptions. Compared to BIFAP, CPRD GOLD had higher proportions of patients with a history of anxiety disorders (BIFAP vs. CPRD GOLD: 10.9% vs. 19.9%) and depressive disorders (19.4% vs. 28.8%). The opposite pattern was seen for obesity, which was assessed as a coded condition and did not consider weight measurements (BIFAP vs. CPRD GOLD: 9.1% vs. 2.5%).

When considering all prior history as the time window, the least frequent conditions were chronic liver disease (ranging from 0.42% in CDWBordeaux to 1.9% in UKBB), schizophrenia (ranging from 0.5% in CDWBordeaux to 1.2% in UKBB), and chronic kidney disease (ranging from <5 cases in CDWBordeaux to 4% in UKBB). This pattern was also observed for the recording of conditions in the year prior to index date with lower proportions of cases.

When assessed in the month prior, pain was present in less than 7% of individuals across databases. Records of fever and infectious diseases were also very limited. Fever had insufficient counts for assessment (<5) or was documented in less than 1% of records (in BIFAP only). Infectious diseases were captured in less 6% of cases across databases.

Short-term complications were captured 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 captured than renal toxicity. Hepatic toxicity was found in 10.9% of patients in BIFAP, 7.1% of patients in CDWBordeaux, and in less than 1% of patients in CPRD GOLD and UKBB. For renal toxicity, corresponding figures were 4.8%, 2.1%, 0.3% and, 3.5%.

Mortality occurred in less than 1.5% of patients within the first month following index date, with figures ranging from 1.2% in CPRD GOLD to 6.1% in UKBB when assessed 31 to 365 days after index date.

Results stratified by sex are included in **Supplementary Table II- 4**. Results stratified by age groups and study period are not included due to limited counts and can be explored in the Shiny App. In general, the proportion of females with anxiety disorders, depressive disorders and pain was greater than the proportion of males with these conditions. Compared to females, males had higher proportions of alcoholism and were more affected by complications of paracetamol overdose, including hepatotoxicity, renal toxicity, and death in the year after. As an example, in CDWBordeaux, 10.0% of males had

hepatotoxicity (compared to 6.1% among females), 4.9% had renal toxicity (compared to 2.4% among females), and 3.7% died 31 to 365 days after index date (compared to 1.7% among females).

Comorbidities and complications were less frequently recorded among individuals aged 1 to 17 years compared to those aged 18 or older. In CDWBordeaux, depressive disorders and anxiety disorders were more frequent among this age group compared to those aged 18 or older (depressive disorders: 9.2% vs 3.1%; anxiety disorders: 9.2% vs 6.3%). Hepatotoxicity was present in approximately <5% of cases, and renal toxicity in 1.36%, where available. Mortality was 0 to <5 cases across all databases. Among cases aged >80 years, arthritis/arthrosis was found in 45.2% of cases in BIFAP and 50.8% of cases in CPRD GOLD. All results can be explored in the Shiny App.

Table 17. Number and% of pre-specified comorbidities among individuals with paracetamol overdose.[1]

Pre-specified comorbidities	BIFAP		CDWBordeaux		CPRD GOLD		UKBB	
	[-Inf, -1]	[-365, -1]	[-Inf, -1]	[-365, -1]	[-Inf, -1]	[-365, -1]	[-Inf, -1]	[-365, -1]
Alcoholism	142 (5.7%)	72 (2.9%)	105 (4.9%)	57 (2.7%)	258 (8.2%)	82 (2.6%)	77 (12.3%)	40 (6.4%)
Anxiety disorder	269 (10.9%)	126 (5.1%)	205 (9.7%)	115 (5.4%)	626 (19.4%)	224 (7.1%)	131 (21.0%)	45 (7.2%)
Arthritis arthrosis	291 (11.7%)	49 (2.0%)	28 (1.3%)	6 (0.3%)	278 (8.9%)	39 (1.2%)	183 (29.3%)	47 (7.5%)
Cancer	70 (2.8%)	28 (1.1%)	22 (1.0%)	7 (0.3%)	55 (1.8%)	20 (0.6%)	72 (11.5%)	21 (3.4%)
Chronic kidney disease	43 (1.7%)	20 (0.8%)	<5	<5	52 (1.7%)	7 (0.2%)	25 (4.0%)	8 (1.3%)
Chronic liver disease	25 (1.0%)	9 (0.4%)	<5	8 (0.4%)	22 (0.7%)	7 (0.2%)	12 (1.9%)	5 (0.8%)
Depressive disorder	481 (19.4%)	186 (7.5%)	298 (14.0%)	157 (7.4%)	905 (28.8%)	286 (9.1%)	265 (42.4%)	116 (18.6%)
Obesity	225 (9.1%)	35 (1.4%)	45 (2.1%)	16 (0.8%)	78 (2.5%)	12 (0.4%)	43 (6.9%)	10 (1.6%)
Pain	1,823 (73.5%)	646 (26.1%)	364 (17.1%)	161 (7.6%)	2,295 (73.1%)	1,046 (33.3%)	419 (67.0%)	154 (24.6%)
Schizophrenia	29 (1.2%)	10 (0.4%)	11 (0.5%)	5 (0.2%)	40 (1.3%)	5 (0.2%)	14 (2.2%)	6 (1.0%)

[1] Time windows are expressed in days relative to index date (i.e. date of paracetamol overdose). Inf = All prior history.

Table 18. Number and % of additional pre-specified conditions, short-term complications and mortality among individuals with paracetamol overdose.

Pre-specified conditions/events	Time window[1]	BIFAP	CDWBordeaux	CPRD GOLD	UKBB
Fever	[-30,-1]	17 (0.7%)	<5	0	0
Infectious diseases	[-30,-1]	133 (5.4%)	17 (0.8%)	65 (2.1%)	14 (2.2%)
Pain	[-30,-1]	104 (4.2%)	39 (1.8%)	205 (6.5%)	31 (5.0%)
Hepatic toxicity	[0, 30]	270 (10.9%)	151 (7.1%)	11 (0.4%)	5 (0.8%)
Renal toxicity	[0, 30]	118 (4.7%)	65 (3.1%)	8 (0.3%)	22 (3.5%)
Mortality	[0, 30]	11 (0.4%)	20 (0.9%)	7 (0.2%)	5 (0.8%)
Mortality	[31, 365]	41 (1.6%)	47 (2.2%)	38 (1.2%)	38 (6.8%)

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

The frequency of pre-specified medications is described for each database considering the month prior to index date, and one year to 31 days before index date in **Table 19**.

When considering the year leading up to a month before index date (i.e. -365 to -31 days prior to index date), the most frequent pre-specified medications were paracetamol (ranging from 7.2% in CDWBordeaux to 37.2% in BIFAP), antidepressants (ranging from 3.1% to 22.5% in BIFAP) and benzodiazepines (ranging from 5.8% in CDWBordeaux to 29.3% in BIFAP). The prescription of NSAIDs was particularly high in BIFAP compared to other databases, with 44.8% and 16.7% of patients being prescribed NSAIDs during the year leading up to a month before the index date, and during the month prior to the index date, respectively. In other databases, these figures were below 12% and 5%, respectively. Among pre-specified medications, the less frequently prescribed were isoniazid (with 0 or <5 counts) and carbamazepine (with >5 counts in BIFAP and CPRD GOLD only). The ranking of the most and least frequent pre-specified medications was similar when assessed during the month prior to index date, with lower frequencies.

The proportion of patients prescribed paracetamol the year leading up to a month before index date was 37.2% in BIFAP, 7.2% in CDWBordeaux, 22.3% in CPRD GOLD, and 17.1% in UKBB. During the month prior, corresponding figures (in the same order) were 16.7%, 2.1%, 12.2%, and 10.6%.

Results stratified by sex, age group and study period can be found in **Supplementary Table II-5**, **Supplementary Table II- 6** and **Supplementary Table II- 7**. Females had higher proportion of prescriptions of antidepressants and benzodiazepines compared to males, and individuals aged 1 to 17 years had lower counts of pre-specified medications compared to those older (aged 18 or older). The highest number of individuals aged 1 to 17 years prescribed with antidepressants or benzodiazepines was observed in BIFAP (9.2% and 7.2%, respectively), and was followed by CPRD GOLD (5.9% and 1.9%, respectively).

Table 19. Number and % of pre-specified medications among individuals diagnosed with paracetamol overdose.[1]

Pre-specified medications	BIFAP		CDWBordeaux		CPRD GOLD		UKBB	
	[-365, -31]	[-30, -1]	[-365, -31]	[-30, -1]	[-365, -31]	[-30, -1]	[-365, -31]	[-30, -1]
Antidepressants	559 (22.5%)	471 (19.0%)	65 (3.0%)	25 (1.2%)	1170 (37.3%)	956 (30.5%)	137 (21.9%)	110 (17.6%)
Antipsychotics	361 (14.6%)	276 (11.1%)	89 (4.2%)	28 (1.3%)	382 (12.2%)	262 (8.3%)	32 (5.1%)	12 (1.9%)
Benzodiazepines	727 (29.3%)	524 (21.1%)	123 (5.8%)	46 (2.2%)	575 (18.3%)	322 (10.3%)	61 (9.8%)	35 (5.6%)
Carbamazepine	10 (0.4%)	5 (0.2%)	<5	0 (0%)	20 (0.6%)	17 (0.5%)	<5	<5
Isoniazid	<5	<5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nonsteroid antiinflammatory drugs (NSAIDs)	1112 (44.8%)	479 (19.3%)	53 (2.5%)	19 (0.9%)	524 (16.7%)	152 (4.8%)	69 (11.0%)	25 (4%)
Opioids	291 (11.7%)	125 (5.0%)	58 (2.7%)	24 (1.1%)	617 (19.7%)	339 (10.8%)	92 (14.7%)	54 (8.6%)
Paracetamol	922 (37.1%)	414 (16.7%)	153 (7.2%)	44 (2.1%)	699 (22.3%)	384 (12.2%)	107 (17.1%)	66 (10.6%)

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

13.5.2. Large-scale characterisation

In large-scale characterisation, all comorbidities and comedications recorded within pre-defined time windows of interest among patients with paracetamol overdose were described. To facilitate the reporting of the results, only the top 10 conditions and the top 10 of medications are described in the report. Results without the top 10 restriction can be explored in the Shiny App.

For simplicity, the results presented in this section include those based on a time window ranging from one year prior to one day before the index date for conditions, and from 30 days to one day before the index date for medications. Please note that the time windows used for conditions in this section differ from those reported for pre-specified conditions, which were based on all prior history for assessment. This distinction was made to capture more relevant conditions occurring closer to the index date. Results for top 10 conditions and top 10 medications assessed using other time windows can be found in the Shiny App.

Conditions

The ten most frequently recorded conditions in people with paracetamol overdose by database are described in **Table 20**. In general, these conditions appeared commonly related to symptoms and were acute in nature, with variations across databases. Examples include upper respiratory tract infections, urinary tract infections, the common cold, headache, nausea and vomiting, sore throat symptom, and abdominal pain. In UKBB, chronic conditions also ranked among the most frequent, including asthma and type 2 diabetes mellitus. Clinical findings recorded as conditions were also captured, including blood pressure findings or emotional state findings. Depressive disorders were captured among the most frequently recorded conditions in CDWBordeaux (5.6%), CPRD GOLD (4.4%) and UKBB (14.1%). Codes reflecting depressed mood or anxiety were captured among 13.2% and 4.4% of patients in CPRD GOLD, respectively.

Prior history of overdose (i.e. not specific to any particular drug) was captured in 15.7% of patients in CPRD GOLD. Prior history of poisonings from psychotropic agents and benzodiazepine-based tranquilizers were documented in 5.8% and 4.2% of patients in CDWBordeaux, with no additional information available on whether the cause was intentional or accidental. Records of suicidal thoughts were noted in 4.0% of patients in BIFAP. In CDWBordeaux, self-inflicted injury was captured in 3.1% of patients. Codes for nicotine dependence were recorded across all databases except for CPRD GOLD, ranging from 4.1% in BIFAP to 6.6% in UKBB, with the latest also capturing alcohol dependence among 5.1% of patients.

The top 10 conditions, considering all prior history before index date can be explored in the Shiny App. In general, conditions recorded from all prior history up to one day before the index date were similar to those described in the year prior, with variations in frequency. Prior history of poisonings from psychotropic agents and benzodiazepine-based tranquilizers remained among the most frequent conditions in CDWBordeaux (9.7% and 10.0%, respectively). In UKBB, most of the captured codes were related to emotional state findings (e.g., feeling worried, mood swings) or characteristics (e.g., white constitutive skin colour).

Table 20. Top 10 most recorded conditions among patients diagnosed with paracetamol overdose, one year prior to 1 day before index date.

BIFAP	CDWBordeaux	CPRD GOLD	UKBB
Viral upper respiratory tract infection: 187 (7.5%)	Emotional state finding: 127 (7.9%)	Blood pressure finding: 1142 (36.4%)	O/E Diastolic BP reading: 164 (26.2%)

BIFAP	CDWBordeaux	CPRD GOLD	UKBB
Fever: 134 (5.4%)	Poisoning by psychotropic agent: 93 (5.8%)	Overdose: 494 (15.7%)	O/E Systolic BP reading: 164 (26.2%)
Infectious gastroenteritis: 130 (5.2%)	Depressive disorder: 91 (5.6%)	Depressed mood: 413 (13.2%)	Depressive disorder: 88 (14.1%)
Urinary tract infectious disease: 113 (4.6%)	Headache: 71 (4.4%)	Finding of pulse rate: 337 (10.7%)	Essential hypertension: 85 (13.6%)
Common cold: 107 (4.3%)	Poisoning by benzodiazepine-based tranquilizer: 68 (4.2%)	Cough: 248 (7.9%)	O/E pulse rhythm regular: 46 (7.4%)
Nicotine dependence: 101 (4.1%)	Nausea and vomiting: 65 (4.0%)	Abdominal pain: 202 (6.4%)	Harmful pattern of use of nicotine: 41 (6.6%)
Suicidal thoughts: 100 (4.0%)	Feeling unhappy: 58 (3.6%)	Anxiety: 139 (4.4%)	Asthma: 37 (5.9%)
Abdominal pain: 98 (4.0%)	Alcohol dependence: 56 (3.5%)	Depressive disorder: 138 (4.4%)	Alcohol dependence: 32 (5.1%)
Coronavirus infection: 97 (3.9%)	Self-inflicted injury: 50 (3.1%)	Eruption: 127 (4.0%)	Abnormal vision: 31 (5.0%)
Acute pharyngitis: 87 (3.5%)	Tobacco dependence syndrome: 50 (3.1%)	Sore throat symptom: 125 (4.0%)	Type 2 diabetes mellitus without complication: 31 (5.0%)

Results for the frequency of comorbidities stratified by sex, age groups (broad categories) and study periods are included in **Appendix II**. Results stratified by sex were similar to the results reported in the overall population (**Supplementary Table II- 8** and **Supplementary Table II- 9**). In BIFAP, the number of cases with suicidal thoughts and intentional self- poisoning was slightly higher among females compared to males (females vs. males: 4.3% vs. 3.5% and 4.0% vs. 2.3%, respectively). In CDWBordeaux, a higher proportion of males were diagnosed with tobacco dependence or alcohol dependence or intoxications. Both sexes had similar proportions of poisoning by psychotropic agents (approximately 5%), with females having higher proportion of cases with records of self-inflected injury compared to males (3.9% in females vs. <5 counts in males). In CPRD GOLD, the proportion of females with overdose was higher compared to males (16.7% vs. 14.1%). This was also observed for depressed mood (14.7% vs. 10.3%) and, to a lesser extent, for depressive disorders (4.7% vs. 3.9%)

Results stratified by age groups (1-17; >18 years old) are included in **Supplementary Table II- 10** and **Supplementary Table II-11**. In BIFAP, the top 10 captured codes among individuals aged 1-17 years old included acute common infections, similar to those reported in the overall results. Codes related to intentional self-poisoning, suicidal thoughts, and self-inflicted injuries appeared in the top 10 list of conditions among individuals aged 18 and older, with proportions of approximately 4-5%. In CDWBordeaux, codes related to self-inflicted injuries and poisoning by psychotropic agents were detected among the top

10 conditions for patients aged 1-17 years, with proportions ranging from approximately 5% to 6.5%. In CPRD GOLD, the proportion of patients with prior records of overdose was lower among those aged 1 to 17 yeas compared to older groups (1-17 years vs. >18 years: 12.2% vs. 17.2%). Other conditions or emotional states included in this ranking were generalised anxiety disorder, conduct disorder, being a victim of psychological abuse, and feeling unhappy.

Results stratified by study period are included in **Supplementary Table II- 12** and **Supplementary Table II-13**, and were similar to those reported for the entire study period.

Medications

Table 21 lists the top 10 most recorded medications at ingredient-level the month prior to the diagnosis of paracetamol overdose. Paracetamol was listed as the most frequently recorded medication, ranging from 2.7% in CDWBordeaux to 16.7% in BIFAP, as described in prior sections. Benzodiazepines were also captured among the most frequently prescribed medication, with ingredients of this class being captured in the top 10 medications across the four databases. BIFAP showed the highest proportion of individuals exposed to this drug class, with lorazepam, clonazepam or lormetazepam, being captured in approximately 5 to 10% of cases. Fluoxetine and antipsychotics, including quetiapine and cyamemazine, were also recorded in some databases, albeit with proportions of less than 5%.

Ingredients with analgesic effects were also captured, including NSAIDs (ibuprofen: 7.4% in BIFAP; ketoprofen: 0.7% in CDWBordeaux), dipyrone (4.4% in BIFAP), codeine (6.7% in UKBB) and tramadol (1.0% in CDWBordeaux). Additionally, other ingredients commonly used in the treatment of chronic conditions were documented, such as simvastatin, amlodipine, ramipril, and proton pump inhibitors, among others.

Results using one year before up to the month prior to index date for assessment can be found in the Shiny App. In general, ingredients captured aligned with those reported the month prior, with some variations in terms of frequency.

Table 21. Top 10 most recorded medications at ingredient-level among patients diagnosed with paracetamol overdose, 30 to 1 days before index date.

BIFAP	CDWBordeaux	CPRD GOLD	UKBB
acetaminophen: 414 (16.7%)	acetaminophen: 44 (2.7%)	acetaminophen: 384 (12.2%)	acetaminophen: 66 (10.6%)
lorazepam: 239 (9.6%)	sodium: 41 (2.5%)	omeprazole: 280 (8.9%)	simvastatin: 50 (8%)
omeprazole: 217 (8.8%)	glucose: 38 (2.4%)	codeine: 250 (8.0%)	codeine: 42 (6.7%)
ibuprofen: 183 (7.4%)	metoclopramide: 25 (1.6%)	citalopram: 208 (6.6%)	omeprazole: 41 (6.6%)
fluoxetine: 128 (5.2%)	alprazolam: 18 (1.1%)	fluoxetine: 207 (6.6%)	citalopram: 36 (5.8%)
clonazepam: 126 (5.1%)	cyamemazine: 17 (1.1%)	albuterol: 206 (6.6%)	amlodipine: 30 (4.8%)

BIFAP	CDWBordeaux	CPRD GOLD	UKBB
lormetazepam: 120 (4.8%)	tramadol: 16 (1.0%)	sertraline: 203 (6.5%)	albuterol: 29 (4.6%)
quetiapine: 109 (4.4%)	diazepam: 14 (0.9%)	mirtazapine: 169 (5.4%)	lansoprazole: 29 (4.6%)
dipyrone: 108 (4.4%)	ketoprofen: 12 (0.7%)	diazepam: 168 (5.4%)	ramipril: 24 (3.8%)
amoxicillin: 93 (3.8%)	oxazepam: 12 (0.7%)	thiamine: 132 (4.2%)	fluoxetine: 22 (3.5%)

Results for the frequency of medications stratified by sex, age groups and study periods are included in **Appendix II** (same tables as those specified for conditions) and were similar to those reported overall. Antidepressants and benzodiazepines were more frequently captured among females and those aged 18 or older (**Supplementary Table II-11** and **Supplementary Table II- 12**).

13.6 Other analysis

Not applicable.

14. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

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

15. DISCUSSION

15.1 Key results

In this study, covering the period from 2010 to 2023, 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 7 databases across 6 countries (BIFAP, Spain; CPRD GOLD, UK; EMBD-ULSEDV, Portugal; DK-DHR, Denmark; IQVIA DA Germany, Germany; NAJS, Croatia; and UKBB, UK). Results of paracetamol overdose were informed by BIFAP, CDWBordeaux (from France, used for patient-level characterisation only), CPRD GOLD and UKBB.

Incidence and prevalence of paracetamol prescribing:

Incidence per 100,000 PY of paracetamol prescribing differed across databases and ranged between 5,625 in UKBB and 12,686 in BIFAP. Incidence rates were higher among females than males across most databases except for IQVIA DA Germany. Regarding age groups, most databases showed a gradient of increasing incidence rates with age. This was particularly evident in BIFAP and CPRD GOLD, where incidence rates among individuals aged >80 years was six time bigger than in the general population.

Regarding paracetamol formulations, the highest incidence rates was found for oral tablets when compared to other formulations across data sources, except for NAJS, where the highest incidence rates were found for oral liquid formulations. The second-highest incidence rates in CPRD GOLD and UKBB were oral capsules, while oral formulations held this position in BIFAP and EMBD-ULSEDV, and rectal suppositories in IQVIA DA Germany. In DK-DHR, incidence of other formulations other than oral tablets showed low number to 0 events. Injectable liquid formulations were the least captured formulation across databases, with incidence > 1 per 100,000 PY in NAJS, IQVIA DA Germany, and BIFAP only. Results by formulation stratified by age and sex showed similar results to those obtained for paracetamol overall. Females had higher incidence rates across formulations except for oral liquid formulations in BIFAP and EMBD-ULSEDV, and rectal suppositories in IQVIA DA Germany. Regarding age groups, incidence rates of rectal suppositories were higher among individuals aged 1-5 years in BIFAP, EMBD-ULSEDV and IQVIA DA Germany. Similarly, oral liquid formulations obtained higher incidence rates among individuals aged 1-5 years in BIFAP, CPRD GOLD, EMBD-ULSEDV, and IQVIA DA Germany and were followed by rates among individuals aged 6-11 years (except for NAJS, which was followed by individuals aged > 80 years).

Prevalence of paracetamol prescribing ranged from 5.2% in IQVIA DA Germany to 65.1% in BIFAP for the entire study period. In general, results by sex and age group mirrored those obtained for incidence rates, with higher prevalence among females compared to males and increased prevalence with age, with some exceptions. Prevalence was higher among males compared to females for oral liquid formulations (in BIFAP, EMBD-ULSEDV and IQVIA DA Germany) and rectal suppositories (in IQVIA DA Germany). Individuals aged 1-5 years obtained the highest prevalence rates for oral liquid formulations (in BIFAP, CPRD GOLD, EMBD-ULSEDV, IQVIA DA Germany) and rectal suppositories (in BIFAP, EMBD-ULSEDV and IQVIA DA Germany). Individuals aged >80 obtained the highest prevalence of oral liquid formulations in NAJS (21.9% [21.8 to 22.0]) and rectal suppositories in DK-DHR (2.5% [2.5 to 2.5]).

Incidence of paracetamol overdose:

Incidence of paracetamol overdose per 100,000 PY was 2 (2 to 2) in BIFAP, 5 (5 to 5) in CPRD GOLD and 21 (20 to 23) in UKBB. In BIFAP, incidence rates showed an upward trend, reaching a peak in 2021. A more modest upward trend was also observed in CPRD GOLD, which appeared to stabilise after 2017 and saw a decrease in estimates in 2023. In UKBB, rates followed a decreasing pattern, with a sharp drop starting in 2017 and no events captured in 2018 and 2019.

Incidence rates were consistently higher among females than males across all databases, particularly in BIFAP and CPRD GOLD. Individuals aged 1 to 17 years exhibited higher incidence rates compared to those aged > 18 years. This gap was particularly pronounced among females and appeared to have widened after 2020.

Characterisation of patients with paracetamol overdose:

We identified and described 8,370 individuals with paracetamol overdose (n=2,480 in BIFAP; n=2,125 in CDWBordeaux; n=3,140 in CPRD GOLD; n=625 in UKBB). Most individuals with paracetamol overdose were females, with percentages ranging from 55.4% in UKBB to 74.2% in CDWBordeaux. Median age at diagnosis ranged from 21 to 25 years, except for UKBB where median age was 57 years.

When considering all prior history, the most frequent pre-specified conditions were pain (ranging from 17.1% in CDWBordeaux to 73.5% in BIFAP), depressive disorder (ranging from 14.0% in CDWBordeaux to

42.4% in UKBB), anxiety disorders (ranging from 9.7% in CDWBordeaux to 21.0% in UKBB) and arthritis and arthrosis (ranging from 1.3% in CDWBordeaux to 29.3% in UKBB).

When considering the year leading up to a month before index date, the most frequent pre-specified medications were paracetamol (ranging from 7.3% in CDWBordeaux to 37.2% in BIFAP), antidepressants (ranging from 3.1% to 22.5% in BIFAP) and benzodiazepines (ranging from 5.8% in CDWBordeaux to 29.3% in BIFAP). The prescription of NSAIDs was particularly high in BIFAP, with 44.8% of patients being prescribed NSAIDs compared to figures below 12% in other databases.

The proportion of patients prescribed with paracetamol the year up to a month leading to index date was 37.2% in BIFAP, 7.2% in CDWBordeaux, 22.3% in CPRD GOLD, and 17.1% in UKBB. During the month prior, corresponding figures (in the same order) were 16.7%, 2.1%, 12.2%, and 10.6%.

In the month following the diagnosis of paracetamol overdose, hepatic toxicity was found in 10.9% of patients in BIFAP, 7.1% of patients in CDWBordeaux, and in less than 1% of patients in CPRD GOLD and UKBB. For renal toxicity, corresponding figures were 4.8%, 2.1%, 0.3% and, 3.5%. Deaths occurred in less than 1.5% of patients within the first month following index date, with figures ranging from 1.2% in CPRD GOLD to 6.1% in UKBB when assessed 31 to 365 days after index date.

Results of pre-specified conditions and medications were similar to overall results when stratified by age, sex and study period. In general, the proportion of females with anxiety disorders, depressive disorders and pain was greater than the proportion of males with these conditions. This pattern was also observed for medications such as antidepressants and benzodiazepines. Compared to females, males had higher proportions of alcoholism and are more affected by complications of paracetamol overdose (where counts available), and mortality in the year after.

When analysed using large-scale characterisation, the most frequently recorded conditions the year prior to index date were symptomatic and acute (e.g. respiratory tract infections, urinary tract infections, abdominal pain). Records of depressive disorders also ranked among the most frequent in CDWBordeaux, CPRD GOLD (along with anxiety disorders) and UKBB. Overdose was captured in 15.7% of patients in CPRD GOLD. Poisonings from psychotropic agents and benzodiazepine-based tranquilizers were documented in 5.8% and 4.2% of patients in CDWBordeaux. Records of suicidal thoughts were noted in 4.0% of patients in BIFAP, and self-inflicted injury in 3.1% of patients in CDWBordeuax. Records related to nicotine dependence were also captured among the most frequently recorded across databases (except for CPRD GOLD). Most frequently recorded medications the month prior to index date were paracetamol and benzodiazepines. Other agents included ingredients with analgesic effects (e.g. ibuprofen, dipyrone, codeine), and ingredients commonly used in the treatment of chronic conditions (e.g. simvastatin, amlodipine, omeprazole).

Results of large-scale characterisation were similar when stratified by sex, age groups or study period.

15.2 Limitations of the research methods

Database-specific limitations:

This study only reflects outcomes occurring in the healthcare settings covered by each database. Data from UKBB differed from other sources included in this study, as it was not collected for medical or administrative purposes. UKBB data is sourced from volunteers aged 40-69 at the time of recruitment who consented to participate and were followed prospectively, and is not representative of the general UK population.(15) While its results can provide important insights on health-related characteristics, caution should be exercised when interpreting prevalence or incidence rates, as its suitability for calculation of population-level estimates is limited, and results cannot be generalised to broader populations.

In some databases, the observation period of patients was calculated based on the last visit, observation or interaction of the patient with the health care system. This methodology impacts the individuals considered "at risk" for the outcomes of interest of the study (i.e., the individuals included in the denominator populations) during the latest years of available data from the latest data lock, where healthy and/or non-frequent users of the health care system will not be considered active. This was particularly relevant for EMDB-ULSEDV, where the denominator used to calculate incidence and prevalence of paracetamol prescribing in the last two years of the observation period has presented an artefactual decrease. As the number of events has remained constant, this artefact has resulted in an increase of incidence and prevalence estimates in 2022 and 2023.

Regarding study periods, BIFAP contributed to objectives 2 and 3 using data from 2014 onwards to ensure a higher coverage of hospital data. Data was additionally restricted to participants registered in regions with hospital linkage only (see "10.2 Study setting and data sources"). However, some regions may not have consistent linkage throughout the study period, which might have affected our ability to capture cases. The study period was also restricted for NAJS, which provided data from 2017 onwards only, as earlier data might include information on duplicated patients. All databases had data up to 2023 except for UKBB, which had data up to 2020. This information should be considered when interpreting results, particularly when comparing results by study period (2010-2016 vs. 2017-2023).

Paracetamol prescribing:

The use of paracetamol was derived from prescription data. In DK-DHR and BIFAP, data was derived from dispensation records, and in UKBB, from self-reported medication usage. In this report, all records were referred to as prescription for simplicity. Paracetamol records might likely represent an underestimation of use given its ease of access as an OTC medication. In addition, information on whether paracetamol prescriptions correspond to immediate or modified release forms was not reported in the study.

Upon reviewing diagnostics results for drug exposures, two important aspects were noted. First, accurate information on treatment duration was not available across all data partners. Information on drug exposure end dates was unavailable and was automatically set in the source data to 30 days after the drug exposure start date. In EMBD-ULSEDV, it was set to one day after. 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 yearly, the impact of this is likely very minor. Second, some drug records were mapped at ingredient-level and had no information on dose form. This was particularly relevant for BIFAP, where 36% of drug records are mapped at the ingredient level.(16)

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 (BIFAP, CDWBordeaux, CPRD GOLD, UKBB). 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.

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. Glutathione depletion (described using codes for malnutrition or anorexia) and liver transplantation had limited feasibility counts in the selected databases and were not assessed in this study.

15.3 Interpretation

Paracetamol prescribing:

Previous studies have shown that paracetamol users are more frequently women and older populations.(17-19) This is in line with our results in which we found higher incidence and prevalence of prescriptions among females, with overall figures increasing with age.

Incidence and prevalence of paracetamol prescribing obtained in this study differed substantially across databases. Geographical differences have been found in other studies,(17, 20) and likely play a role in the variations observed in our findings. In addition, differences in healthcare settings (e.g., primary care vs. secondary care) are likely contributors to these disparities. The lowest prevalence of paracetamol prescribing obtained in this study was found in IQVIA DA Germany (5.2%) and is consistent with estimates derived from population-based surveys among adults in Germany.(18) BIFAP showed the highest prevalence of paracetamol prescribing (65.1%), which is similar but higher to that reported in France, where half of the population aged > 15 years or older were found to buy prescribed paracetamol at least once in a year.(19)

Rates stratified across formulations varied greatly across data sources, with oral tablets showing the highest incidence rates across most data partners. Oral liquid formulations and rectal suppositories were predominantly seen in children aged 1 to 5. These results were expected given that 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 the least captured and were not observed across all databases.

Our results represent trends of prescribed/dispensed paracetamol, and do not account for paracetamol obtained with OTC purchases. Different regulatory actions have been implemented at national level,(2) and might have played a role in the observed trends of paracetamol observed in this study. As an example, the increase in incidence rates observed in DK-DHR in 2014 has been previously observed in other studies and has been probably attributed to legislative changes, where larger pack sizes of paracetamol were restricted to prescription only in 2013 in Denmark.(17)

Paracetamol overdose:

Incidence rates of paracetamol overdose observed in this study were substantially lower than those reported in other studies using self-harm episodes presenting to hospital care.(21, 22) A previous study using data from the Multicentre Study of Self-harm in England estimated incidence rates of pure paracetamol poisoning to be 90 (84.3 to 96) per 100,000.(22) Reasons behind these discrepancies are unclear and might be related to methodological reasons related to case and denominator definitions, the healthcare settings where data was sourced, and the reliability of the data and recording of events. 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 patient who self-harm, especially females, which was also seen in our data.(21-24)

Incidence rates of paracetamol overdose varied across databases, with UKBB reporting figures four times higher than those observed in CPRD GOLD and ten times greater than those in BIFAP. The observed discrepancies in UKBB are likely to be explained by the nature of this database, which differs from other databases in terms of type of data (e.g. patient-reported questionnaire data, EHR, claims) and patient

characteristics (i.e. volunteers aged 40 to 69 at recruitment).(12, 25) Incidence of paracetamol overdose was higher in CPRD GOLD compared to BIFAP. This finding is consistent with prior evidence describing rates of self-harm by overdose of paracetamol being higher in the UK compared to other European countries.(26, 27) The frequency of short-term complications and mortality observed in BIFAP and CDWBordeaux aligned with that seen in prior studies,(6) and was higher than that observed in CPRD GOLD. Comorbidities and medication use also varied across data sources, with UKBB reporting the highest number cases and CDWBordeaux the lowest. Such differences are likely due to the nature of the data. For instance, variations in the recording of short-term complications are likely to be attributed to the healthcare settings from which the data was sourced, with CPRD GOLD being derived from primary care data only. When interpreting the occurrence of comorbidities and medications, note that frequencies described in this report represent the number of patients 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 the 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 the index date, it is included in the one-month-prior time window, regardless of its initial start date.

The extent to which overdoses captured in our study correspond to intentional overdoses is unknown. A study using nationally representative data from the United States estimated that 70% of emergency department visits for acetaminophen overdose involved intentional self-harm, with the remaining visits representing unintentional overdoses caused by unsupervised ingestions by children (13.4%) or overuse of a drug for medicinal effect and medication errors (16.7%).(23) In our study, individuals aged 1 to 17 years accounted for between 29.0% to 41.7% of paracetamol overdoses. The age group classification used in this study does not allow for estimating incidence across more specific age groups. 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.

According to Casey et. al, 60% patients presenting to hospital care following self-harm episodes with paracetamol had history of previous self-harm, with 39% receiving psychiatric treatment at the time of the overdose, and 49% having received such treatment in the past.(22) In our study, approximately 10-20% of patients had a prior record of anxiety disorders and 14-42% of depressive disorders. Codes related to prior history of poisoning, overdose, and self-inflicted injuries were captured among the most frequently recorded conditions in the year before index date in some databases. The proportion of patients with these records was <6% except for overdose, which was present in 15.73% of patients in CPRD GOLD. While these estimates are lower than those previously reported,(22) our findings suggest that some patients had prior acts of self-harm, which highlight the need for attention given that individuals who present to care for self-harm are at considerable risk of subsequent suicide.(28) In terms of treatments, between 3.1% and 27.3% of patients had been prescribed antidepressants, and between 5.8% and 29.3% had received benzodiazepine prescriptions in the year leading up to one month before the index date. Such findings are relevant as they suggest that a substantial proportion of patients received treatment for mental health problems, and because these drugs are among the most frequently involved medications in intentional overdoses.(13, 29) The proportion of patients who concomitantly overdosed with paracetamol and other medications was not assessed in the present study and has been estimated at approximately one-third.(13) According to our findings, up to 17% of patients were prescribed with paracetamol the month prior of the paracetamol overdose. However, the extent to which paracetamol obtained through prescription contributed to the overdose is unclear and cannot be assessed with the current study.

15.4 Generalisability

This study included data from 8 databases from 7 different European countries (Croatia, Denmark, France, Germany, Portugal, The Netherlands, Spain, UK). However, not all data sources could inform all objectives, with incidence of paracetamol overdose being informed by data from three databases from 2 countries (BIFAP from Spain, and CPRD GOLD and UKBB from the UK). The characterisation of patients with paracetamol overdose was informed by BIFAP, CPRD GOLD, UKBB, and CDWBordeaux (France). In addition, data sources had limitations advising caution in interpretation of results (e.g. lower capture of complications following paracetamol overdose in CPRD GOLD, lack of representativeness in UKBB). 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 health settings, results should not be generalised to Europe as differences in population characteristics and access to paracetamol OTS may vary by country.

16. CONCLUSION

Incidence rates and prevalence of paracetamol prescribing differed by data source. Incidence rates per 100,000 ranged between 5,625 to 12,686, and prevalence from 5.2% to 65.1%. In general, figures of paracetamol prescribing were higher among females than males and increased with age. When stratified by formulation, oral tablet formulations had the highest estimates, while injectable liquid formulations were generally the least prescribed. Oral liquid formulations and rectal suppositories were more frequently prescribed among individuals aged 1 to 5 years.

Incidence of paracetamol overdose per 100,000 was 2 (2 to 2) in BIFAP, 5 (5 to 5) in CPRD GOLD and 21 (20 to 23) in UKBB, which was lower than expected based upon published literature. Where available, rates among individuals aged 1 to 17 years were higher than those aged 18 or older. This gap was particularly pronounced among females and appeared to have widened after 2020.

Individuals with paracetamol overdose were more frequently female, with a median age of 21 to 25 years (in databases with all ages captured). Most frequent pre-specified conditions considering all prior history were pain, depressive disorder, anxiety disorders and arthrosis/arthritis, while the most frequent medications in the month prior were paracetamol, antidepressants and benzodiazepines. Records of suicidal thoughts, poisoning by psychotropic agents, overdose or self-inflected injuries prior to paracetamol overdose were also captured. In the month following the paracetamol overdose, hepatic toxicity was observed in less than 11% of cases, renal toxicity was found in less than 5% of patients, and mortality in less than 1.5% of cases.

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18. ANNEXES

Appendix I: List with concept definitions

Supplementary Table I-1. Code list for paracetamol.

Concept ID[1]	Concept name
1125315	Paracetamol

[1] All descendants included.

Supplementary Table I- 2. Code list for 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

Supplementary Table I- 3. Dose forms for paracetamol formulations

Formulation	Dose forms[1]
Oral tablets	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
Rectal suppository	Rectal suppository

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

Supplementary Table I- 4. 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.

Supplementary Table I- 5. 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

Supplementary Table I- 6. 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

Supplementary Table I- 7. 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, 2160393

Appendix II: Supplemental tables and figures

Supplementary Table II- 1. Incidence rates of paracetamol prescribing by database, overall and stratified by covariates of interest.

Database[1]	Strata	N events	N persons	Person-Years (PY)	Incidence per 100,000 PY (95% CI)[2]
BIFAP	Overall	59,821,318	20,676,039	471,549,476	12,686 (12,683 to 12,689)
BIFAP	Female	36,751,562	10,617,413	275,773,212	13,327 (13,322 to 13,331)
BIFAP	Male	23,069,756	10,058,626	195,776,264	11,784 (11,779 to 11,789)
BIFAP	>1	59,821,318	20,676,039	471,549,476	12,686 (12,683 to 12,689)
BIFAP	1 to 5	2,918,217	2,429,608	16,081,819	18,146 (18,125 to 18,167)
BIFAP	6 to 11	2,023,025	2,863,805	11,546,917	17,520 (17,496 to 17,544)
BIFAP	12 to 17	2,036,229	2,898,493	11,540,210	17,645 (17,620 to 17,669)
BIFAP	18 to 29	4,266,904	4,803,296	33,106,681	12,888 (12,876 to 12,901)
BIFAP	30 to 39	5,948,221	5,658,424	39,298,797	15,136 (15,124 to 15,148)
BIFAP	40 to 49	7,622,127	6,099,273	44,214,951	17,239 (17,227 to 17,251)
BIFAP	50 to 59	8,859,670	5,393,140	43,292,832	20,465 (20,451 to 20,478)
BIFAP	60 to 69	9,974,985	4,226,170	43,074,877	23,157 (23,143 to 23,172)
BIFAP	70 to 79	9,395,187	3,141,805	34,404,850	27,308 (27,290 to 27,325)
BIFAP	> 80	6,398,362	2,218,131	7,950,371	80,479 (80,416 to 80,541)
BIFAP	Oral tablets	17,126,923	20,737,515	255,239,951	6,710 (6,707 to 6,713)
BIFAP	Oral capsules	147,132	20,754,707	187,713,267	78 (78 to 79)
BIFAP	Oral liquid formulations	4,040,355	20,742,216	209,078,508	1,932 (1,931 to 1,934)
BIFAP	Rectal suppositories	119,578	20,754,785	187,939,769	64 (63 to 64)
BIFAP	Injectable liquid formulations	1,827	20,754,788	187,449,561	1 (1 to 1)
CPRD GOLD	Overall	10,941,308	10,562,849	115,450,667	9,477 (9,471 to 9,483)
CPRD GOLD	Female	6,570,832	5,335,820	63,552,755	10,339 (10,331 to 10,347)

Database[1]	Strata	N events	N persons	Person-Years (PY)	Incidence per 100,000 PY (95% CI)[2]
CPRD GOLD	Male	4,370,476	5,227,029	51,897,912	8,421 (8,413 to 8,429)
CPRD GOLD	> 1	10,941,308	10,562,849	115,450,667	9,477 (9,471 to 9,483)
CPRD GOLD	1 to 5	464,729	1,278,000	4,419,810	10,515 (10,484 to 10,545)
CPRD GOLD	6 to 11	258,174	1,324,114	4,598,804	5,614 (5,592 to 5,636)
CPRD GOLD	12 to 17	188,298	1,312,305	4,517,833	4,168 (4,149 to 4,187)
CPRD GOLD	18 to 29	727,359	2,575,271	10,959,457	6,637 (6,622 to 6,652)
CPRD GOLD	30 to 39	942,448	2,376,384	10,324,234	9,129 (9,110 to 9,147)
CPRD GOLD	40 to 49	1,345,294	2,242,423	12,369,390	10,876 (10,858 to 10,894)
CPRD GOLD	50 to 59	1,692,139	2,012,355	12,750,088	13,272 (13,252 to 13,292)
CPRD GOLD	60 to 69	1,987,210	1,647,520	12,175,899	16,321 (16,298 to 16,344)
CPRD GOLD	70 to 79	1,925,814	1,145,045	9,315,095	20,674 (20,645 to 20,703)
CPRD GOLD	> 80	1,259,505	725,620	2,210,747	56,972 (56,872 to 57,072)
CPRD GOLD	Oral tablets	9,287,118	10,589,090	105,777,411	8,780 (8,774 to 8,786)
CPRD GOLD	Oral capsules	1,024,295	10,692,622	67,437,777	1,519 (1,516 to 1,522)
CPRD GOLD	Oral liquid formulations	981,257	10,695,358	68,451,720	1,434 (1,431 to 1,436)
CPRD GOLD	Rectal suppositories	20,980	10,701,757	63,706,027	33 (32 to 33)
CPRD GOLD	Injectable liquid formulations	56	10,701,809	63,664,048	0 (0 to 0)
DK-DHR	Overall	8,783,770	6,901,718	106,057,522	8,282 (8,277 to 8,288)
DK-DHR	Female	5,368,976	3,449,086	57,186,952	9,388 (9,381 to 9,396)
DK-DHR	Male	3,414,794	3,452,632	48,870,570	6,987 (6,980 to 6,995)
DK-DHR	> 1	8,783,770	6,901,718	106,057,522	8,282 (8,277 to 8,288)
DK-DHR	1 to 5	16,766	1,212,616	4,297,946	390 (384 to 396)
DK-DHR	6 to 11	19,057	1,315,219	5,395,429	353 (348 to 358)
DK-DHR	12 to 17	82,047	1,387,393	5,694,294	1,441 (1,431 to 1,451)

Database[1]	Strata	N events	N persons	Person-Years (PY)	Incidence per 100,000 PY (95% CI)[2]
DK-DHR	18 to 29	512,593	2,002,611	12,513,322	4,096 (4,085 to 4,108)
DK-DHR	30 to 39	735,728	1,841,715	10,404,959	7,071 (7,055 to 7,087)
DK-DHR	40 to 49	1,219,998	1,880,249	12,428,638	9,816 (9,799 to 9,833)
DK-DHR	50 to 59	1,638,389	1,855,342	12,663,321	12,938 (12,918 to 12,958)
DK-DHR	60 to 69	1,742,642	1,663,526	11,882,348	14,666 (14,644 to 14,688)
DK-DHR	70 to 79	1,709,202	1,230,631	8,732,473	19,573 (19,544 to 19,602)
DK-DHR	> 80	1,044,507	672,339	2,894,849	36,082 (36,012 to 36,151)
DK-DHR	Oral tablets	8,742,817	6,901,933	105,878,829	8,257 (8,252 to 8,263)
DK-DHR	Oral capsules	0	6,923,875	78,174,073	0
DK-DHR	Oral liquid formulations	23,065	6,923,854	78,210,525	29 (29 to 30)
DK-DHR	Rectal suppositories	41,292	6,923,764	78,215,589	53 (52 to 53)
DK-DHR	Injectable liquid formulations	39	6,923,875	78,174,069	0
EMBD-ULSEDV	Overall	443,996	374,656	5,030,068	8,827 (8,801 to 8,853)
EMBD-ULSEDV	Female	252,578	196,295	2,775,207	9,101 (9,066 to 9,137)
EMBD-ULSEDV	Male	191,418	178,361	2,254,861	8,489 (8,451 to 8,527)
EMBD-ULSEDV	> 1	443,996	374,656	5,030,068	8,827 (8,801 to 8,853)

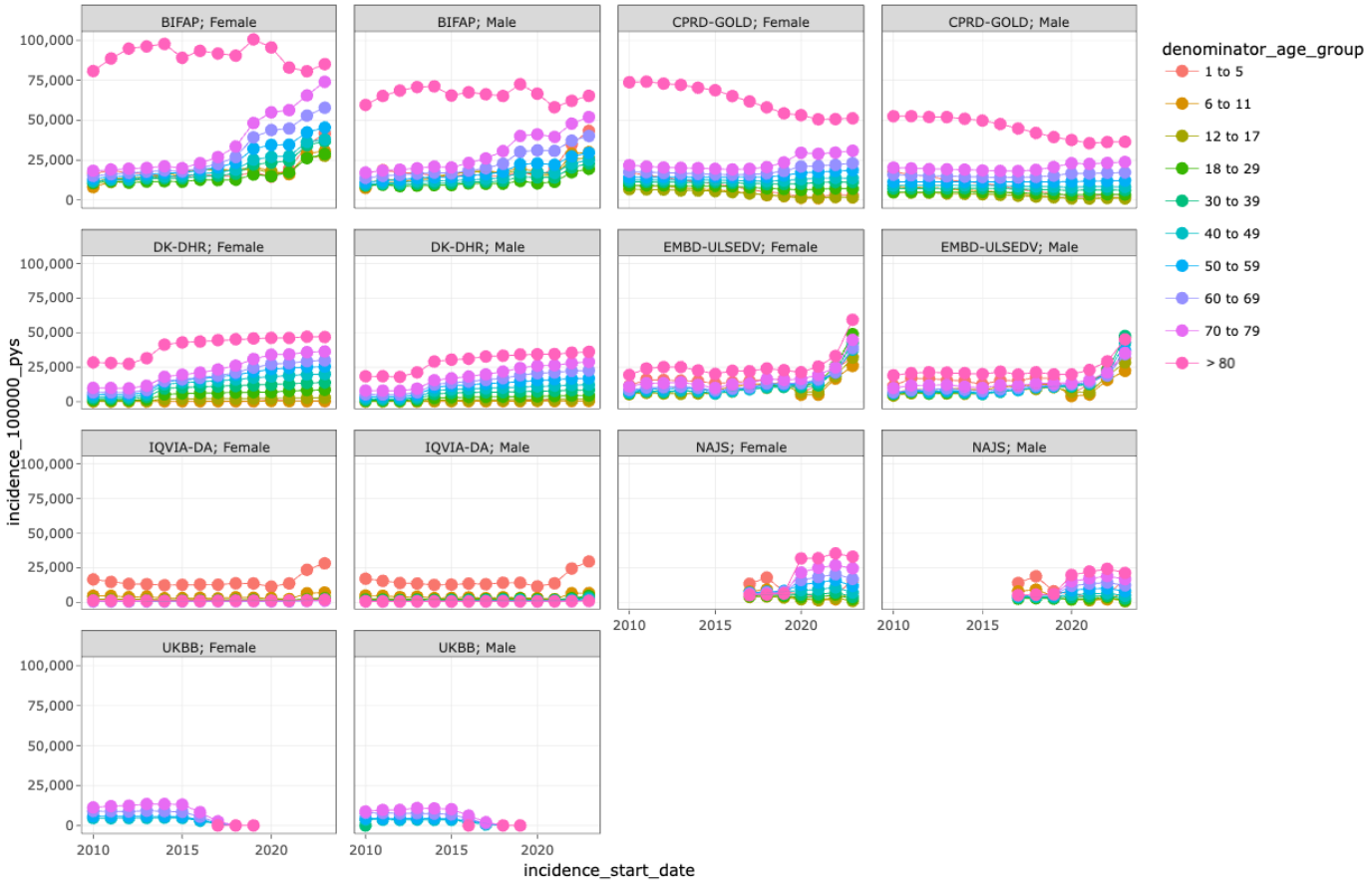
Database[1]	Strata	N events	N persons	Person-Years (PY)	Incidence per 100,000 PY (95% CI)[2]
EMBD-ULSEDV	1 to 5	33,197	46,783	219,604	15,117 (14,955 to 15,280)
EMBD-ULSEDV	6 to 11	20,497	54,051	207,033	9,900 (9,765 to 10,037)
EMBD-ULSEDV	12 to 17	17,278	55,728	213,389	8,097 (7,977 to 8,219)
EMBD-ULSEDV	18 to 29	47,009	83,909	478,816	9,818 (9,729 to 9,907)
EMBD-ULSEDV	30 to 39	44,369	90,667	475,959	9,322 (9,235 to 9,409)
EMBD-ULSEDV	40 to 49	54,600	100,677	558,948	9,768 (9,687 to 9,851)
EMBD-ULSEDV	50 to 59	62,910	99,401	577,746	10,889 (10,804 to 10,974)
EMBD-ULSEDV	60 to 69	59,071	85,120	496,878	11,888 (11,793 to 11,985)
EMBD-ULSEDV	70 to 79	57,233	66,305	392,662	14,576 (14,456 to 14,696)
EMBD-ULSEDV	> 80	47,672	41,370	196,564	24,253 (24,035 to 24,471)
EMBD-ULSEDV	Oral tablets	383,933	374,676	4,661,491	8,236 (8,210 to 8,262)
EMBD-ULSEDV	Oral capsules	8,754	374,740	3,388,414	258 (253 to 264)
EMBD-ULSEDV	Oral liquid formulations	48,030	374,721	3,575,481	1,343 (1,331 to 1,355)
EMBD-ULSEDV	Rectal suppositories	6,489	374,740	3,386,335	192 (187 to196)
EMBD-ULSEDV	Injectable liquid formulations	0	374,742	3,371,108	0
IQVIA DA Germany	Overall	1,529,117	17,120,103	96,930,210	1,578 (1,575 to 1,580)
IQVIA DA Germany	Female	786,818	9,723,511	55,239,153	1,424 (1,421 to 1,428)
IQVIA DA Germany	Male	742,299	7,396,592	41,691,057	1,780 (1,776 to 1,785)
IQVIA DA Germany	> 1	1,529,117	17,120,103	96,930,210	1,578 (1,575 to 1,580)
IQVIA DA Germany	1 to 5	514,019	1,087,795	3,536,271	14,536 (14,496 to 14,575)
IQVIA DA Germany	6 to 11	150,304	1,326,318	3,995,129	3,762 (3,743 to 3,781)
IQVIA DA Germany	12 to 17	82,202	1,440,316	3,996,469	2,057 (2,043 to 2,071)

Database[1]	Strata	N events	N persons	Person-Years (PY)	Incidence per 100,000 PY (95% CI)[2]
IQVIA DA Germany	18 to 29	158,044	2,759,796	9,074,858	1,742 (1,733 to 1,750)
IQVIA DA Germany	30 to 39	117,113	2,825,431	9,492,228	1,234 (1,227 to 1,241)
IQVIA DA Germany	40 to 49	116,487	3,408,448	12,503,749	932 (926 to 937)
IQVIA DA Germany	50 to 59	133,521	4,204,038	16,538,080	807 (803 to 812)
IQVIA DA Germany	60 to 69	97,190	3,854,680	14,680,379	662 (658 to 666)
IQVIA DA Germany	70 to 79	84,759	3,298,258	13,012,474	651 (647 to 656)
IQVIA DA Germany	> 80	73,928	1,969,741	6,977,747	1,059 (1,052 to 1,067)
IQVIA DA Germany	Oral tablets	759,084	17,122,902	93,668,845	810 (809 to 812)
IQVIA DA Germany	Oral capsules	19,960	17,124,110	92,038,235	22 (21 to 22)
IQVIA DA Germany	Oral liquid formulations	258,513	17,123,751	92,477,726	280 (278 to 281)
IQVIA DA Germany	Rectal suppositories	503,066	17,121,792	94,030,627	535 (534 to 536)
IQVIA DA Germany	Injectable liquid formulations	2,469	17,124,143	91,984,487	3 (3 to 3)
NAJS	Overall	2,392,818	4,535,263	31,525,488	7,590 (7,580 to 7,600)
NAJS	Female	1,477,412	2,321,119	16,679,747	8,858 (8,843 to 8,872)
NAJS	Male	915,406	2,214,144	14,845,741	6,166 (6,153 to 6,179)
NAJS	> 1	2,392,818	4,535,263	31,525,488	7,590 (7,580 to 7,600)
NAJS	1 to 5	158,267	457,124	1,554,758	10,180 (10,129 to 10,230)
NAJS	6 to 11	91,553	535,841	1,847,190	4,956 (4,924 to 4,989)
NAJS	12 to 17	46,437	552,327	1,782,097	2,606 (2,582 to 2,630)
NAJS	18 to 29	134,091	911,559	3,991,030	3,360 (3,342 to 3,378)
NAJS	30 to 39	178,933	944,619	3,875,340	4,617 (4,596 to 4,639)
NAJS	40 to 49	265,596	975,027	4,019,200	6,608 (6,583 to 6,633)
NAJS	50 to 59	383,535	994,729	4,188,475	9,157 (9,128 to 9,186)
NAJS	60 to 69	472,451	971,920	4,126,353	11,450 (11,417 to 11,482)

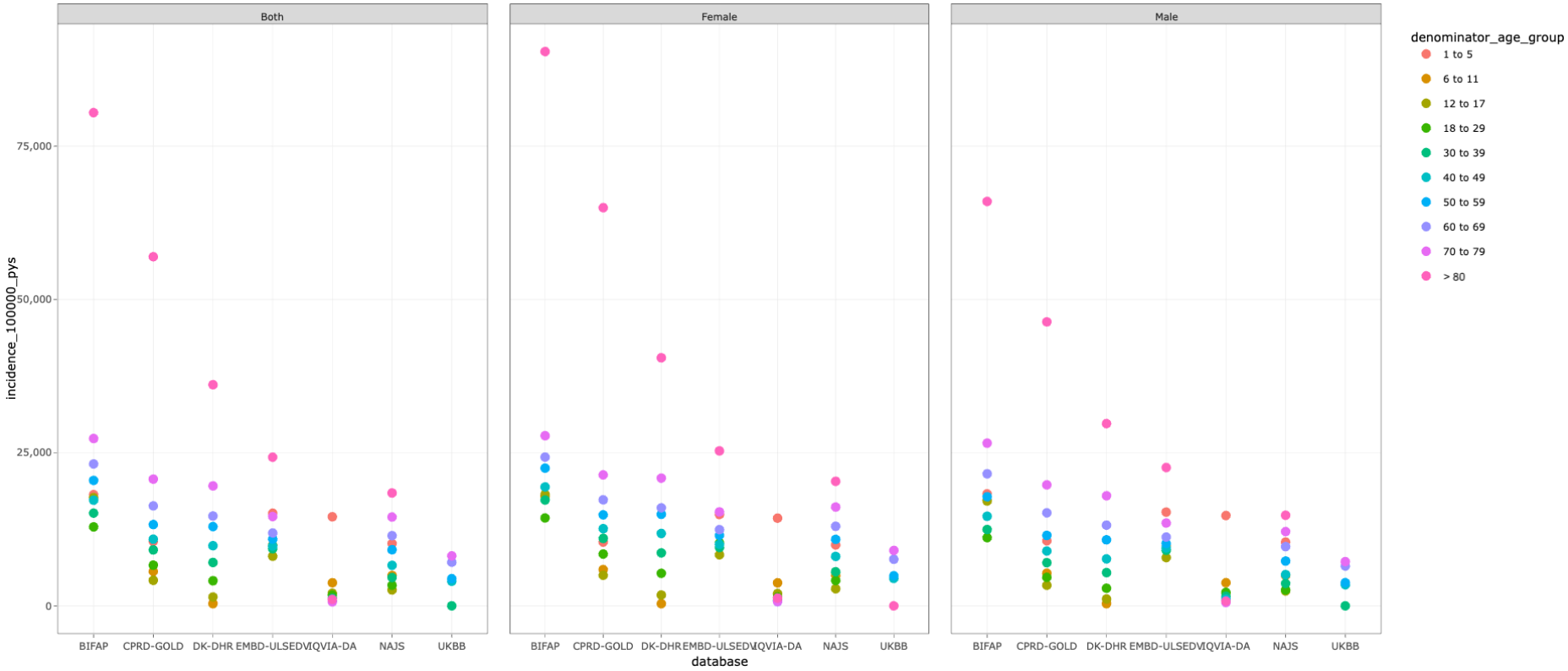
Database[1]	Strata	N events	N persons	Person-Years (PY)	Incidence per 100,000 PY (95% CI)[2]
NAJS	70 to 79	388,961	699,532	2,683,063	14,497 (14,451 to 14,543)
NAJS	> 80	256,992	415,989	1,395,264	18,419 (18,348 to 18,490)
NAJS	Oral tablets	862,210	4,535,779	29,272,623	2,945 (2,939 to 2,952)
NAJS	Oral capsules	638,945	4,536,272	28,791,220	2,219 (2,214 to 2,225)
NAJS	Oral liquid formulations	989,578	4,535,876	29,529,853	3,351 (3,345 to 3,358)
NAJS	Rectal suppositories	0	4,536,283	28,352,778	0 (0 to 0)
NAJS	Injectable liquid formulations	50,764	4,536,260	28,353,644	179 (177 to 181)
UKBB	Overall	290,993	502,038	5,172,928	5,625 (5,605 to 5,646)
UKBB	Female	175,075	273,100	2,904,487	6,028 (6,000 to 6,056)
UKBB	Male	115,918	228,938	2,268,442	5,110 (5,081 to 5,140)
UKBB	> 1	290,993	502,038	5,172,928	5,625 (5,605 to 5,646)
UKBB	30 to 39	0	53	8	0 (0 to 47,142)
UKBB	40 to 49	19,127	103,272	476,113	4,017 (3,961 to 4,075)
UKBB	50 to 59	56,429	254,079	1,273,099	4,432 (4,396 to 4,469)
UKBB	60 to 69	148,669	351,213	2,087,596	7,122 (7,085 to 7,158)
UKBB	70 to 79	61,953	192,537	760,060	8,151 (8,087 to 8,216)
UKBB	Oral tablets	264,977	502,112	5,064,153	5,232 (5,213 to 5,252)
UKBB	Oral capsules	32,145	502,331	4,127,321	779 (770 to 787)
UKBB	Oral liquid formulations	955	502,350	4,040,487	24 (22 to 25)
UKBB	Rectal suppositories	41	502,350	4,038,854	1 (1 to 1)
UKBB	Injectable liquid formulations	0	502,350	4,038,836	0 (0 to 0)

[1] Study period spanned from 2010 to 2023 (or end of available data). For BIFAP, the study period was restricted to 2014 onwards and to individuals registered in areas with hospital linkage. For NAJS, study period was restricted to 2014 onwards

[2] Incidence estimates are rounded to the nearest whole number.



Supplementary Figure II- 1. Incidence of paracetamol prescribing by calendar year, sex and age groups.



Supplementary Figure II-2. Incidence of paracetamol prescribing by sex and age groups.

Supplementary Table II- 2. Prevalence of paracetamol prescribing, overall and stratified by covariates of interest.

Database[1]	Strata	N population	N cases	Prevalence (95% CI)
BIFAP	Overall	20,754,789	13,520,681	65.14 (65.12 to 65.17)
BIFAP	Female	10,667,669	7,388,241	69.26 (69.23 to 69.29)
BIFAP	Male	10,087,120	6,132,440	60.79 (60.76 to 60.82)
BIFAP	> 1	20,754,789	13,520,681	65.14 (65.12 to 65.17)
BIFAP	1 to 5	2,443,588	1,268,671	51.92 (51.86 to 51.98)
BIFAP	6 to 11	2,871,812	1,082,677	37.7 (37.64 to 37.76)
BIFAP	12 to 17	2,905,586	1,113,436	38.32 (38.26 to 38.38)
BIFAP	18 to 29	4,807,565	1,908,254	39.69 (39.65 to 39.74)
BIFAP	30 to 39	5,664,170	2,405,764	42.47 (42.43 to 42.51)
BIFAP	40 to 49	6,111,882	2,798,356	45.79 (45.75 to 45.83)
BIFAP	50 to 59	5,421,038	2,790,163	51.47 (51.43 to 51.51)
BIFAP	60 to 69	4,277,729	2,598,736	60.75 (60.7 to 60.8)
BIFAP	70 to 79	3,219,300	2,215,100	68.81 (68.76 to 68.86)
BIFAP	> 80	2,319,696	1,715,692	73.96 (73.91 to 74.02)
BIFAP	Oral tablets	20,754,789	6,562,893	31.62 (31.6 to 31.64)
BIFAP	Oral capsules	20,754,789	93,600	0.45 (0.45 to 0.45)

Database[1]	Strata	N population	N cases	Prevalence (95% CI)
BIFAP	Oral liquid formulations	20,754,789	1,607,403	7.74 (7.73 to 7.76)
BIFAP	Rectal suppositories	20,754,789	83,519	0.4 (0.4 to 0.41)
BIFAP	Injectable liquid formulations	20,754,789	1,188	0.01 (0.01 to 0.01)
CPRD GOLD	Overall	10,701,809	3,361,899	31.41 (31.39 to 31.44)
CPRD GOLD	Female	5,425,701	1,911,043	35.22 (35.18 to 35.26)
CPRD GOLD	Male	5,276,108	1,450,856	27.5 (27.46 to 27.54)
CPRD GOLD	> 1	10,701,809	3,361,899	31.41 (31.39 to 31.44)
CPRD GOLD	1 to 5	1,279,350	233,430	18.25 (18.18 to 18.31)
CPRD GOLD	6 to 11	1,324,527	149,273	11.27 (11.22 to 11.32)
CPRD GOLD	12 to 17	1,312,659	123,058	9.37 (9.32 to 9.42)
CPRD GOLD	18 to 29	2,578,458	380,691	14.76 (14.72 to 14.81)
CPRD GOLD	30 to 39	2,386,588	442,126	18.53 (18.48 to 18.57)
CPRD GOLD	40 to 49	2,264,743	544,959	24.06 (24.01 to 24.12)
CPRD GOLD	50 to 59	2,050,998	616,640	30.07 (30 to 30.13)
CPRD GOLD	60 to 69	1,702,932	656,950	38.58 (38.5 to 38.65)
CPRD GOLD	70 to 79	1,212,011	609,839	50.32 (50.23 to 50.41)

Database[1]	Strata	N population	N cases	Prevalence (95% CI)
CPRD GOLD	> 80	810,250	520,809	64.28 (64.17 to 64.38)
CPRD GOLD	Oral tablets	10,701,809	2,866,722	26.79 (26.76 to 26.81)
CPRD GOLD	Oral capsules	10,701,809	460,360	4.3 (4.29 to 4.31)
CPRD GOLD	Oral liquid formulations	10,701,809	484,132	4.52 (4.51 to 4.54)
CPRD GOLD	Rectal suppositories	10,701,809	13,911	0.13 (0.13 to 0.13)
CPRD GOLD	Injectable liquid formulations	10,701,809	45	0 (0 to 0)
DK-DHR	Overall	6,923,875	1,888,858	27.28 (27.25 to 27.31)
DK-DHR	Female	3,464,435	1,036,839	29.93 (29.88 to 29.98)
DK-DHR	Male	3,459,440	852,019	24.63 (24.58 to 24.67)
DK-DHR	> 1	6,923,875	1,888,858	27.28 (27.25 to 27.31)
DK-DHR	1 to 5	1,212,641	13,235	1.09 (1.07 to 1.11)
DK-DHR	6 to 11	1,315,236	14,787	1.12 (1.11 to 1.14)
DK-DHR	12 to 17	1,387,454	59,043	4.26 (4.22 to 4.29)
DK-DHR	18 to 29	2,002,928	239,633	11.96 (11.92 to 12.01)
DK-DHR	30 to 39	1,843,085	275,381	14.94 (14.89 to 14.99)
DK-DHR	40 to 49	1,884,245	366,703	19.46 (19.41 to 19.52)

Database[1]	Strata	N population	N cases	Prevalence (95% CI)
DK-DHR	50 to 59	1,865,209	453,087	24.29 (24.23 to 24.35)
DK-DHR	60 to 69	1,681,166	479,207	28.5 (28.44 to 28.57)
DK-DHR	70 to 79	1,255,552	455,202	36.26 (36.17 to 36.34)
DK-DHR	> 80	706,737	320,231	45.31 (45.2 to 45.43)
DK-DHR	Oral tablets	6,923,875	1,869,673	27 (26.97 to 27.04)
DK-DHR	Oral capsules	6,923,875	0	0 (0 to 0)
DK-DHR	Oral liquid formulations	6,923,875	16,652	0.24 (0.24 to 0.24)
DK-DHR	Rectal suppositories	6,923,875	33,955	0.49 (0.49 to 0.5)
DK-DHR	Injectable liquid formulations	6,923,875	35	0 (0 to 0)
EMBD-ULSEDV	Overall	374,742	198,920	53.08 (52.92 to 53.24)
EMBD-ULSEDV	Female	196,340	106,577	54.28 (54.06 to 54.5)
EMBD-ULSEDV	Male	178,402	92,343	51.76 (51.53 to 51.99)
EMBD-ULSEDV	> 1	374,742	198,920	53.08 (52.92 to 53.24)
EMBD-ULSEDV	1 to 5	46,803	17,505	37.4 (36.96 to 37.84)
EMBD-ULSEDV	6 to 11	54,064	13,761	25.45 (25.09 to 25.82)
EMBD-ULSEDV	12 to 17	55,743	12,629	22.66 (22.31 to 23.01)

Database[1]	Strata	N population	N cases	Prevalence (95% CI)
EMBD-ULSEDV	18 to 29	83,928	28,835	34.36 (34.04 to 34.68)
EMBD-ULSEDV	30 to 39	90,696	28,197	31.09 (30.79 to 31.39)
EMBD-ULSEDV	40 to 49	100,692	33,392	33.16 (32.87 to 33.45)
EMBD-ULSEDV	50 to 59	99,427	35,939	36.15 (35.85 to 36.45)
EMBD-ULSEDV	60 to 69	85,145	32,564	38.25 (37.92 to 38.57)
EMBD-ULSEDV	70 to 79	66,342	28,926	43.6 (43.22 to 43.98)
EMBD-ULSEDV	> 80	41,424	22,864	55.2 (54.72 to 55.67)
EMBD-ULSEDV	Oral tablets	374,742	177,309	47.31 (47.16 to 47.47)
EMBD-ULSEDV	Oral capsules	374,742	6,615	1.77 (1.72 to 1.81)
EMBD-ULSEDV	Oral liquid formulations	374,742	25,265	6.74 (6.66 to 6.82)
EMBD-ULSEDV	Rectal suppositories	374,742	5,295	1.41 (1.38 to 1.45)
EMBD-ULSEDV	Injectable liquid formulations	374,742	0	0 (0 to 0)
IQVIA DA Germany	Overall	17,124,145	896,091	5.23 (5.22 to 5.24)
IQVIA DA Germany	Female	9,725,590	469,345	4.83 (4.81 to 4.84)
IQVIA DA Germany	Male	7,398,555	426,746	5.77 (5.75 to 5.78)
IQVIA DA Germany	> 1	17,124,145	896,091	5.23 (5.22 to 5.24)

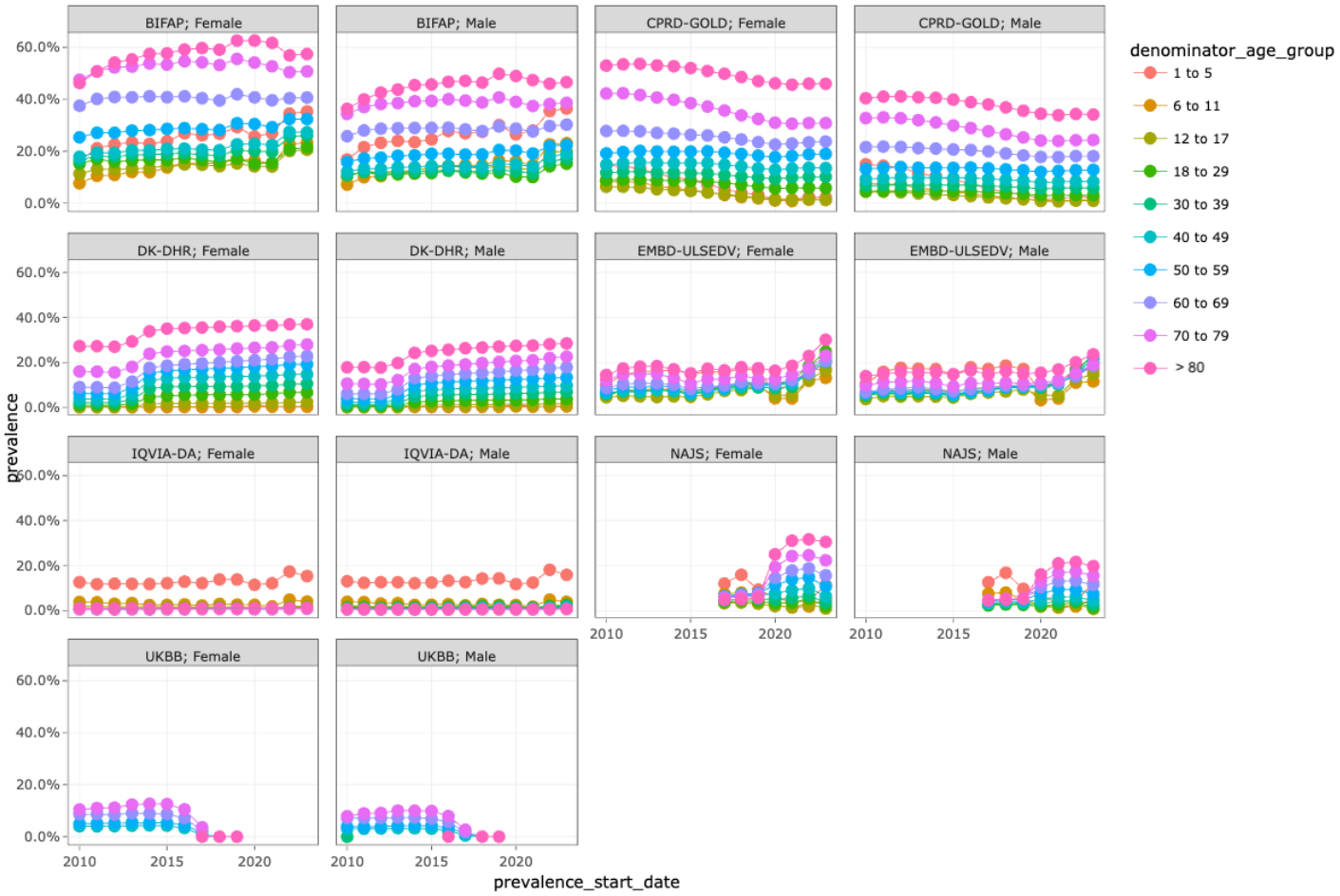
Database[1]	Strata	N population	N cases	Prevalence (95% CI)
IQVIA DA Germany	1 to 5	1,090,289	278,147	25.51 (25.43 to 25.59)
IQVIA DA Germany	6 to 11	1,326,688	101,593	7.66 (7.61 to 7.7)
IQVIA DA Germany	12 to 17	1,440,663	60,249	4.18 (4.15 to 4.21)
IQVIA DA Germany	18 to 29	2,760,337	108,368	3.93 (3.9 to 3.95)
IQVIA DA Germany	30 to 39	2,825,754	84,038	2.97 (2.95 to 2.99)
IQVIA DA Germany	40 to 49	3,408,696	82,677	2.43 (2.41 to 2.44)
IQVIA DA Germany	50 to 59	4,204,342	92,368	2.2 (2.18 to 2.21)
IQVIA DA Germany	60 to 69	3,854,953	68,506	1.78 (1.76 to 1.79)
IQVIA DA Germany	70 to 79	3,298,501	58,399	1.77 (1.76 to 1.78)
IQVIA DA Germany	> 80	1,970,011	52,384	2.66 (2.64 to 2.68)
IQVIA DA Germany	Oral tablets	17,124,145	495,675	2.89 (2.89 to 2.9)
IQVIA DA Germany	Oral capsules	17,124,145	12,802	0.07 (0.07 to 0.08)
IQVIA DA Germany	Oral liquid formulations	17,124,145	177,571	1.04 (1.03 to 1.04)
IQVIA DA Germany	Rectal suppositories	17,124,145	286,457	1.67 (1.67 to 1.68)
IQVIA DA Germany	Injectable liquid formulations	17,124,145	1,827	0.01 (0.01 to 0.01)
NAJS	Overall	4,536,283	1,236,781	27.26 (27.22 to 27.31)

Database[1]	Strata	N population	N cases	Prevalence (95% CI)
NAJS	Female	2,321,632	725,959	31.27 (31.21 to 31.33)
NAJS	Male	2,214,651	510,822	23.07 (23.01 to 23.12)
NAJS	> 1	4,536,283	1,236,781	27.26 (27.22 to 27.31)
NAJS	1 to 5	457,754	99,658	21.77 (21.65 to 21.89)
NAJS	6 to 11	536,224	67,046	12.5 (12.42 to 12.59)
NAJS	12 to 17	552,384	36,444	6.6 (6.53 to 6.66)
NAJS	18 to 29	911,640	98,034	10.75 (10.69 to 10.82)
NAJS	30 to 39	944,871	119,390	12.64 (12.57 to 12.7)
NAJS	40 to 49	975,781	161,550	16.56 (16.48 to 16.63)
NAJS	50 to 59	996,339	212,630	21.34 (21.26 to 21.42)
NAJS	60 to 69	975,615	252,292	25.86 (25.77 to 25.95)
NAJS	70 to 79	705,165	207,815	29.47 (29.36 to 29.58)
NAJS	> 80	421,833	147,054	34.86 (34.72 to 35)
NAJS	Oral tablets	4,536,283	511,071	11.27 (11.24 to 11.3)
NAJS	Oral capsules	4,536,283	456,361	10.06 (10.03 to 10.09)
NAJS	Oral liquid formulations	4,536,283	569,027	12.54 (12.51 to 12.57)
NAJS	Rectal suppositories	4,536,283	0	0 (0 to 0)

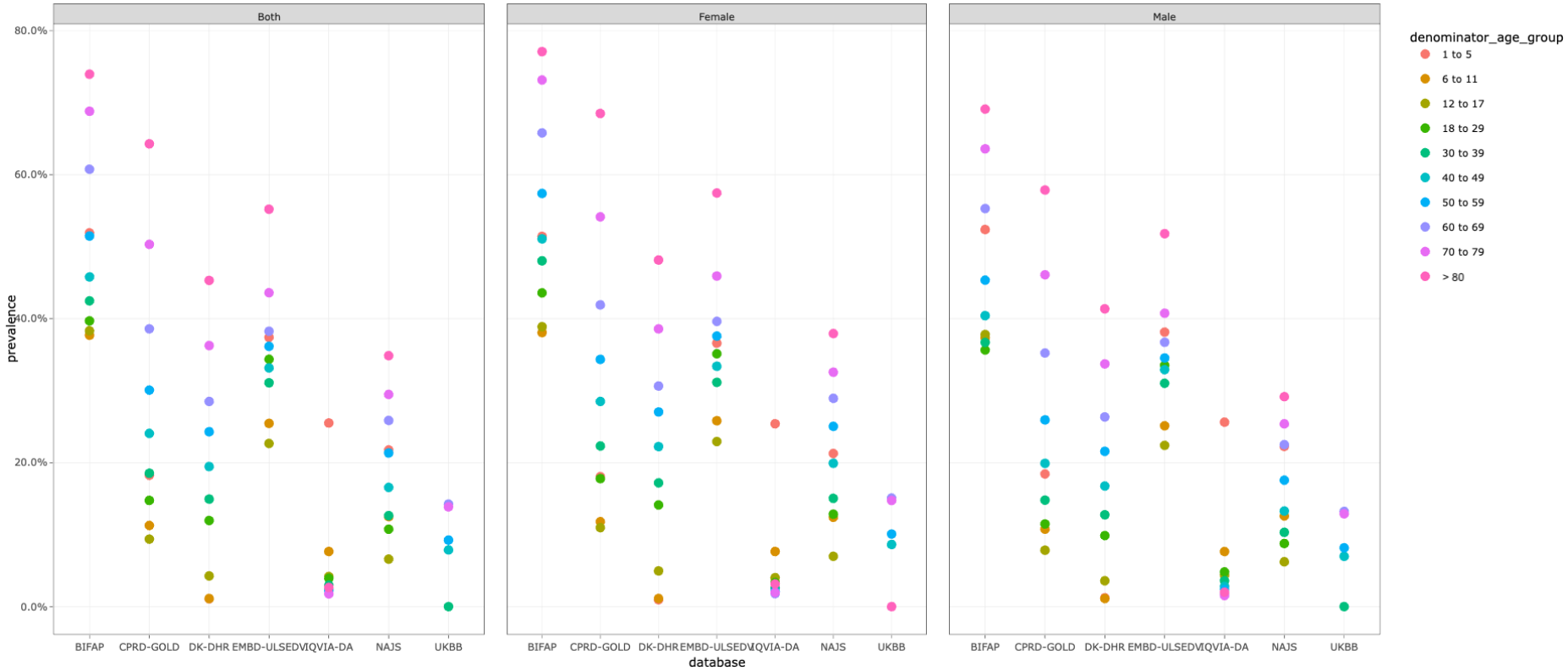
Database[1]	Strata	N population	N cases	Prevalence (95% CI)
NAJS	Injectable liquid formulations	4,536,283	47,593	1.05 (1.04 to 1.06)
UKBB	Overall	502,350	87,236	17.37 (17.26 to 17.47)
UKBB	Female	273,291	50,322	18.41 (18.27 to 18.56)
UKBB	Male	229,059	36,914	16.12 (15.97 to 16.27)
UKBB	> 1	502,350	87,236	17.37 (17.26 to 17.47)
UKBB	30 to 39	53	0	0 (0 to 6.76)
UKBB	40 to 49	103,431	8,155	7.88 (7.72 to 8.05)
UKBB	50 to 59	254,605	23,523	9.24 (9.13 to 9.35)
UKBB	60 to 69	352,345	50,161	14.24 (14.12 to 14.35)
UKBB	70 to 79	193,279	26,793	13.86 (13.71 to 14.02)
UKBB	> 80	2,600	<5	*
UKBB	Oral tablets	502,350	81,849	16.29 (16.19 to 16.4)
UKBB	Oral capsules	502,350	15,586	3.1 (3.06 to 3.15)
UKBB	Oral liquid formulations	502,350	629	0.13 (0.12 to 0.14)
UKBB	Rectal suppositories	502,350	36	0.01 (0.01 to 0.01)
UKBB	Injectable liquid formulations	502,350	0	0 (0 to 0)

[1] Study period spanned from 2010 to 2023 (or end of available data if earlier). For BIFAP, the study period was restricted to 2014 onwards and to individuals registered in areas with hospital linkage. For NAJS, study period was restricted to 2014 onwards

* Results have been suppressed.



Supplementary Figure II- 3. Prevalence of paracetamol prescribing by calendar year, sex and age groups.



Supplementary Figure II- 4. Prevalence of paracetamol prescribing by sex and age groups.

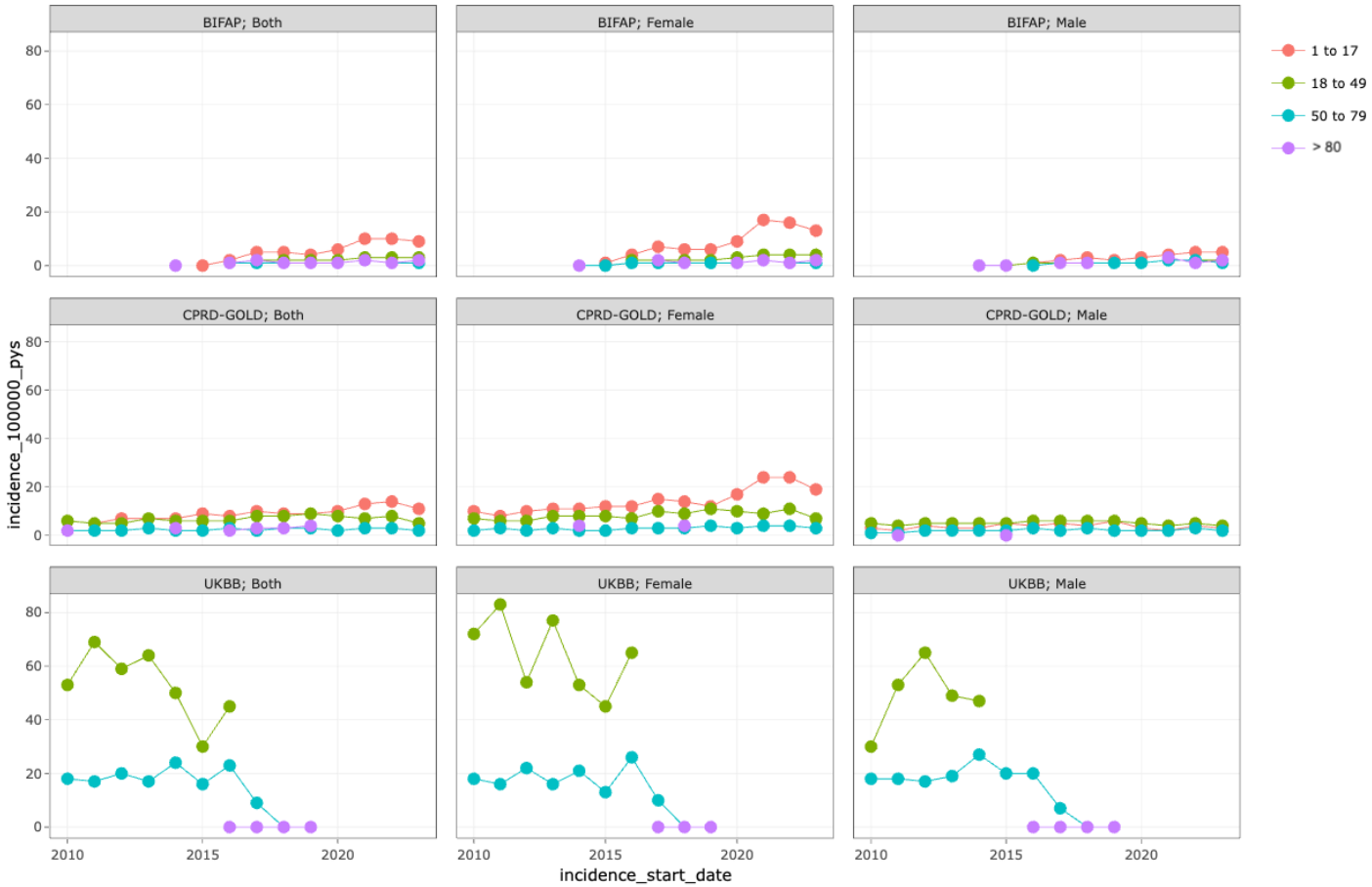
Supplementary Table II- 3. Incidence rates of paracetamol overdose, overall and by covariates of interest.

Database[1]	Sex	Age group (years)	N events	N persons	Person-Years (PY)	Incidence per 100,000 PY (95% CI)[2]
BIFAP	Both	> 1	2,551	16,445,144	131,730,698	2 (2 to 2)
BIFAP	Both	1 to 17	1,075	3,468,567	20,675,601	5 (5 to 6)
BIFAP	Both	18 to 49	947	8,656,475	56,576,650	2 (2 to 2)
BIFAP	Both	50 to 79	435	6,776,202	45,452,368	1 (1 to 1)
BIFAP	Both	> 80	94	1,809,461	9,025,958	1 (1 to 1)
BIFAP	Female	> 1	1,726	8,485,107	68,407,502	3 (2 to 3)
BIFAP	Female	1 to 17	798	1,687,637	10,046,763	8 (7 to 9)
BIFAP	Female	18 to 49	625	4,374,805	28,706,512	2 (2 to 2)
BIFAP	Female	50 to 79	247	3,519,607	23,913,350	1 (1 to 1)
BIFAP	Female	> 80	56	1,104,091	5,740,775	1 (1 to 1)
BIFAP	Male	> 1	825	7,960,037	63,323,197	1 (1 to 1)
BIFAP	Male	1 to 17	277	1,780,930	10,628,838	3 (2 to 3)
BIFAP	Male	18 to 49	322	4,281,670	27,870,138	1 (1 to 1)
BIFAP	Male	50 to 79	188	3,256,595	21,539,018	1 (1 to 1)
BIFAP	Male	> 80	38	705,370	3,285,183	1 (1 to 2)

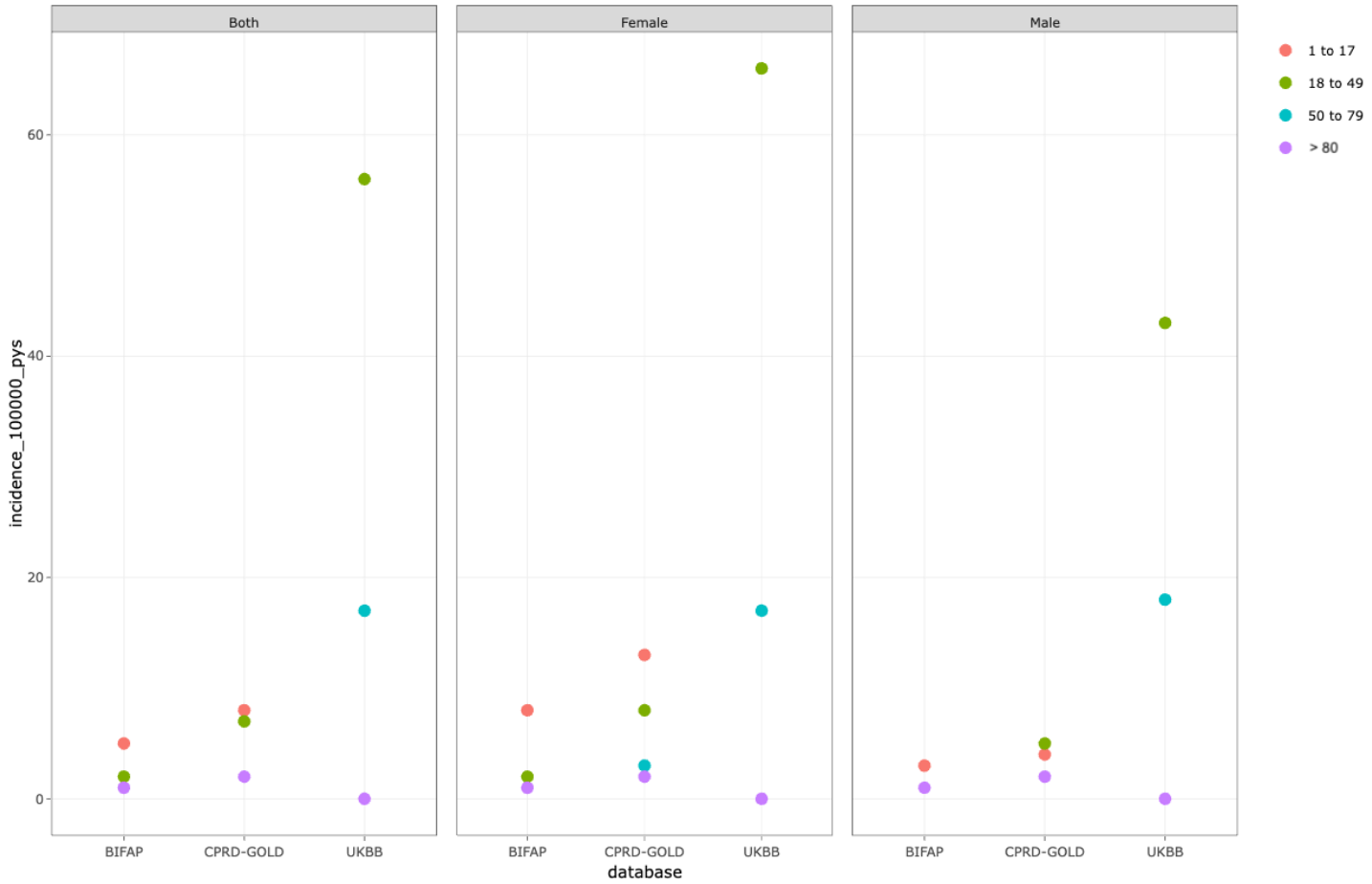
CPRD GOLD	Both	> 1	3,345	10,701,718	63,661,681	5 (5 to 5)
CPRD GOLD	Both	1 to 17	978	2,549,550	11,937,685	8 (8 to 9)
CPRD GOLD	Both	18 to 49	1,768	5,650,278	27,039,852	7 (6 to 7)
CPRD GOLD	Both	50 to 79	530	3,630,602	21,410,128	2 (2 to 3)
CPRD GOLD	Both	> 80	63	810,249	3,273,476	2 (1 to 2)
CPRD GOLD	Female	> 1	2,170	5,425,642	32,079,087	7 (6 to 7)
CPRD GOLD	Female	1 to 17	754	1,247,550	5,832,640	13 (12 to 14)
CPRD GOLD	Female	18 to 49	1,068	2,842,491	13,380,501	8 (8 to 8)
CPRD GOLD	Female	50 to 79	303	1,822,202	10,864,336	3 (2 to 3)
CPRD GOLD	Female	> 80	40	488,415	2,001,137	2 (1 to 3)
CPRD GOLD	Male	> 1	1,175	5,276,076	31,582,593	4 (4 to 4)
CPRD GOLD	Male	1 to 17	224	1,302,000	6,105,045	4 (3 to 4)
CPRD GOLD	Male	18 to 49	700	2,807,787	13,659,350	5 (5 to 6)
CPRD GOLD	Male	50 to 79	227	1,808,400	10,545,792	2 (2 to 2)
CPRD GOLD	Male	> 80	23	321,834	1,272,339	2 (1 to 3)
UKBB	Both	> 1	858	502,350	4,038,831	21 (20 to 23)
UKBB	Both	18 to 49	232	103,430	417,747	56 (49 to 63)
UKBB	Both	50 to 79	620	492,610	3,618,929	17 (16 to 19)

UKBB	Both	> 80	0	2,600	1,710	0 (0 to 216)
UKBB	Female	> 1	485	273,291	2,207,113	22 (20 to 24)
UKBB	Female	18 to 49	150	56,614	226,671	66 (56 to 78)
UKBB	Female	50 to 79	331	268,335	1,979,313	17 (15 to 19)
UKBB	Female	> 80	0	1,290	836	0 (0 to 441)
UKBB	Male	> 1	373	229,059	1,831,718	20 (18 to 23)
UKBB	Male	18 to 49	82	46,816	191,076	43 (34 to 53)
UKBB	Male	50 to 79	289	224,275	1,639,616	18 (16 to 20)
UKBB	Male	> 80	0	1,310	874	0 (0 to 422)

[1] Study period spanned from 2010 to 2023 (or end of available data if earlier). For BIFAP, the study period was restricted to 2014 onwards and to individuals registered in areas with hospital linkage. For NAJS, study period was restricted to 2014 onwards.
[2] Incidence estimates are rounded to the nearest whole number.



Supplementary Figure II-5. Incidence rates of paracetamol overdose by calendar year, sex, age groups (narrow categories).



Supplementary Figure II- 6. Incidence of paracetamol overdose by sex and age groups (narrow categories).

Supplementary Table II- 4. Number and% of pre-specified comorbidities by sex.

Pre-specified comorbidities[1]	BIFAP		CDWBordeaux		CPRD GOLD		UKBB	
	Females	Males	Females	Males	Females	Males	Females	Males
Alcoholism	72 (4.31%)	70 (8.63%)	49 (3.11%)	56 (10.22%)	122 (6.08%)	136 (12.01%)	22 (6.36%)	55 (19.71%)
Anxiety disorder	209 (12.52%)	60 (7.4%)	167 (10.59%)	38 (6.93%)	459 (22.86%)	167 (14.75%)	75 (21.68%)	56 (20.07%)
Arthritis arthrosis	196 (11.74%)	95 (11.71%)	22 (1.4%)	6 (1.09%)	178 (8.86%)	100 (8.83%)	95 (27.46%)	88 (31.54%)
Cancer	35 (2.1%)	35 (4.32%)	10 (0.63%)	12 (2.19%)	28 (1.39%)	27 (2.39%)	40 (11.56%)	32 (11.47%)
Chronic kidney disease	20 (1.2%)	23 (2.84%)	<5	<5	38 (1.89%)	14 (1.24%)	16 (4.62%)	9 (3.23%)
Chronic liver disease	9 (0.54%)	16 (1.97%)	*	*	14 (0.7%)	8 (0.71%)	*	*
Depressive disorder	351 (21.03%)	130 (16.03%)	233 (14.77%)	65 (11.86%)	628 (31.27%)	277 (24.47%)	161 (46.53%)	104 (37.28%)
Obesity	146 (8.75%)	79 (9.74%)	30 (1.9%)	15 (2.74%)	59 (2.94%)	19 (1.68%)	23 (6.65%)	20 (7.17%)
Schizophrenia	14 (0.84%)	15 (1.85%)	*	*	16 (0.8%)	24 (2.12%)	*	*
Fever	<5	<5	<5	<5	<5	<5	<5	<5

Pre-specified comorbidities[1]	BIFAP		CDWBordeaux		CPRD GOLD		UKBB	
	Females	Males	Females	Males	Females	Males	Females	Males
Infectious disease	<5	<5	<5	<5	<5	<5	<5	<5
Pain	<5	<5	<5	<5	<5	<5	<5	<5
Hepatotoxicity	171 (10.25%)	99 (12.21%)	96 (6.09%)	55 (10.04%)	*	*	<5	<5
Mortality (0 to 30 days)	*	*	12 (0.76%)	8 (1.46%)	*	*	*	*
Mortality (31 to 365 days)	18 (1.08%)	23 (2.84%)	27 (1.71%)	20 (3.65%)	17 (0.85%)	21 (1.86%)	15 (4.34%)	23 (8.24%)
Renal toxicity	63 (3.77%)	55 (6.78%)	38 (2.41%)	27 (4.93%)	*	*	5 (1.45%)	17 (6.09%)

[1] Results correspond to the assessment window of 1 year up to 1 day before index date, with some ex: pain, fever and infectious diseases are reported30 to1 day prior to index date; hepatic toxicity and renal toxicity 0 to 30 days after index date. Results for other time windows can be found in the Shiny App.

* Results have been suppressed for all strata where one group has < 5 counts.

Supplementary Table II-5. Number and% of pre-specified medications by sex.

Pre-specified medications[1]	BIFAP		CDWBordeaux		CPRD GOLD		UKBB	
	Females	Males	Females	Males	Females	Males	Females	Males
Antidepressants	358 (21.45%)	113 (13.93%)	*	*	676 (33.67%)	280 (24.73%)	62 (17.92%)	48 (17.2%)
Antipsychotics	196 (11.74%)	80 (9.86%)	*	*	182 (9.06%)	80 (7.07%)	5 (1.45%)	7 (2.51%)
Benzodiazepines	365 (21.87%)	159 (19.61%)	34 (2.16%)	12 (2.19%)	222 (11.06%)	100 (8.83%)	23 (6.65%)	12 (4.3%)
Carbamazepine	<5	<5	0 (0%)	0 (0%)	9 (0.45%)	8 (0.71%)	<5	<5
Isoniazid	0 (0%)	<5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nonsteroid anti-inflammatory drugs	324 (19.41%)	155 (19.11%)	12 (0.76%)	7 (1.28%)	97 (4.83%)	55 (4.86%)	14 (4.05%)	11 (3.94%)
Opioids	87 (5.21%)	38 (4.69%)	*	*	206 (10.26%)	133 (11.75%)	27 (7.8%)	27 (9.68%)
Paracetamol	275 (16.48%)	139 (17.14%)	32 (2.03%)	12 (2.19%)	228 (11.35%)	156 (13.78%)	33 (9.54%)	33 (11.83%)

[1] Results correspond to the assessment window of one month up to one day before index date. Results for other time windows can be found in the Shiny App.

* Results have been suppressed for all strata where one group has < 5 counts.

Supplementary Table II- 6. Number and% of pre-specified medications by age groups (broad categories).

Pre-specified medications[1]	BIFAP		CDWBordeaux		CPRD GOLD		UKBB[2]
	1-17	>18	1-17	>18	1-17	>18	>18
Antidepressants	95 (9.2%)	376 (25.98%)	16 (1.99%)	9 (0.68%)	54 (5.92%)	902 (40.48%)	110 (17.6%)
Antipsychotics	61 (5.91%)	215 (14.86%)	16 (1.99%)	12 (0.91%)	12 (1.32%)	250 (11.22%)	12 (1.92%)
Benzodiazepines	74 (7.16%)	450 (31.1%)	15 (1.86%)	31 (2.35%)	6 (0.66%)	316 (14.18%)	35 (5.6%)
Carbamazepine	0 (0%)	5 (0.35%)	0 (0%)	0 (0%)	0 (0%)	17 (0.76%)	<5
Isoniazid	*	*	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nonsteroid anti-inflammatory drugs	139 (13.46%)	340 (23.5%)	5 (0.62%)	14 (1.06%)	20 (2.19%)	132 (5.92%)	25 (4%)
Opioids	*	*	*	*	*	*	54 (8.64%)
Paracetamol	115 (11.13%)	299 (20.66%)	10 (1.24%)	34 (2.58%)	16 (1.75%)	368 (16.52%)	66 (10.56%)

[1] Results correspond to the assessment window of one month up to one day before index date. Results for other time windows and age groups can be found in the Shiny App.

[2] UKBB includes individuals aged 40 to 69 at recruitment.

* Results have been suppressed for all strata where one group has < 5 counts.

Supplementary Table II- 7. Number and% of pre-specified medications by study period.

Pre-specified medications[1]	BIFAP		CDWBordeaux		CPRD GOLD		UKBB	
	2016-2010	2017-2023	2016-2010	2017-2023	2016-2010	2017-2023	2016-2010	2017-2023
Antidepressants	31 (18.24%)	440 (19.05%)	*	*	478 (27.08%)	478 (34.76%)	110 (18.27%)	0 (0%)
Antipsychotics	18 (10.59%)	258 (11.17%)	5 (1.17%)	23 (1.36%)	139 (7.88%)	123 (8.95%)	12 (1.99%)	0 (0%)
Benzodiazepines	39 (22.94%)	485 (21%)	8 (1.86%)	38 (2.24%)	194 (10.99%)	128 (9.31%)	35 (5.81%)	0 (0%)
Carbamazepine	0 (0%)	5 (0.22%)	0 (0%)	0 (0%)	11 (0.62%)	6 (0.44%)	*	*
Isoniazid	*	*	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nonsteroid anti-inflammatory drugs	41 (24.12%)	438 (18.96%)	*	*	93 (5.27%)	59 (4.29%)	25 (4.15%)	0 (0%)
Opioids	10 (5.88%)	115 (4.98%)	*	*	176 (9.97%)	163 (11.85%)	54 (8.97%)	0 (0%)
Paracetamol	37 (21.76%)	377 (16.32%)	7 (1.63%)	37 (2.18%)	207 (11.73%)	177 (12.87%)	66 (10.96%)	0 (0%)

[1] Results correspond to the assessment window of one month up to one day before index date. Results for other time windows can be found in the Shiny App. Data availability differs across data sources. Data lock for last update are: BIFAP: 22-05-2024; CDWBordeaux: 22-02-2024; CPRD GOLD: 04-03-2024; UKBB: 01-03-2020. BIFAP contributed data from 2014 onwards.

* Results have been suppressed for all strata where one group has < 5 counts.

Supplementary Table II- 8. Top 10 conditions and medications captured through large-scale characterisation among females.

Domain	BIFAP	CDWBordeaux	CPRD GOLD	UKBB
Conditions	Viral upper respiratory tract infection: 122 (7.31%)	Emotional state finding: 104 (8.62%)	Blood pressure finding: 819 (40.79%)	O/EDiastolic BP reading: 90 (26.01%)
	Urinary tract infectious disease: 91 (5.45%)	Poisoning by psychotropic agent: 70 (5.8%)	Overdose: 335 (16.68%)	O/ESystolic BP reading: 90 (26.01%)
	Fever: 86 (5.15%)	Depressive disorder: 66 (5.47%)	Depressed mood: 297 (14.79%)	Depressive disorder: 52 (15.03%)
	Infectious gastroenteritis: 81 (4.85%)	Feeling unhappy: 52 (4.31%)	Finding of pulse rate: 225 (11.21%)	Essential hypertension: 34 (9.83%)
	Coronavirus infection: 73 (4.37%)	Headache: 52 (4.31%)	Cough: 164 (8.17%)	Asthma: 28 (8.09%)
	Suicidal thoughts: 72 (4.31%)	Poisoning by benzodiazepine-based tranquilizer: 51 (4.23%)	Abdominal pain: 156 (7.77%)	Cervical smearnegative: 22 (6.36%)
	Common cold: 69 (4.13%)	Nausea and vomiting: 48 (3.98%)	Cervical smearnegative: 112 (5.58%)	O/Epulse rhythm regular: 22 (6.36%)
	Abdominal pain: 67 (4.01%)	Self-inflicted injury: 47 (3.89%)	Anxiety: 105 (5.23%)	Abnormal vision: 21 (6.07%)
	Intentional self-poisoning: 67 (4.01%)	Victim of psychological abuse: 42 (3.48%)	Sore throat symptom: 99 (4.93%)	O/Eblood pressure reading: 20 (5.78%)
	Nicotine dependence: 67 (4.01%)	Generalised anxiety disorder: 40 (3.31%)	Depressive disorder: 94 (4.68%)	Urine glucose test negative: 19 (5.49%)

Domain	BIFAP	CDWBordeaux	CPRD GOLD	UKBB
Medications	acetaminophen: 275 (16.48%)	sodium: 36 (2.98%)	acetaminophen: 228 (11.35%)	acetaminophen: 33 (9.54%)
	lorazepam: 165 (9.89%)	glucose: 33 (2.73%)	fluoxetine: 162 (8.07%)	codeine: 23 (6.65%)
	omeprazole: 141 (8.45%)	acetaminophen: 32 (2.65%)	omeprazole: 162 (8.07%)	omeprazole: 23 (6.65%)
	ibuprofen: 124 (7.43%)	metoclopramide: 23 (1.91%)	codeine: 153 (7.62%)	citalopram: 22 (6.36%)
	fluoxetine: 111 (6.65%)	alprazolam: 16 (1.33%)	sertraline: 146 (7.27%)	simvastatin: 22 (6.36%)
	clonazepam: 88 (5.27%)	cyamemazine: 13 (1.08%)	citalopram: 142 (7.07%)	albuterol: 16 (4.62%)
	lormetazepam: 86 (5.15%)	tramadol: 13 (1.08%)	albuterol: 136 (6.77%)	calcium carbonate: 12 (3.47%)
	quetiapine: 77 (4.61%)	diazepam: 9 (0.75%)	ethinyl estradiol: 122 (6.08%)	levothyroxine: 12 (3.47%)
	dipyrone: 76 (4.55%)	hydroxyzine: 9 (0.75%)	diazepam: 113 (5.63%)	cholecalciferol: 11 (3.18%)
	ethinyl estradiol: 67 (4.01%)	sertraline: 9 (0.75%)	mirtazapine: 101 (5.03%)	diazepam: 11 (3.18%)

[1] Results correspond to the assessment window of 365 days up to one day before index date for conditions and 30 up to 1 day before index date for medications. Results for other time windows can be found in the Shiny App.

Supplementary Table II- 9. Top 10 conditions and medications captured through large-scale characterisation among males.

Domain	BIFAP	CDWBordeaux	CPRD GOLD	UKBB
Conditions	Viral upper respiratory tract infection: 65 (8.01%)	Alcohol dependence: 30 (7.35%)	Blood pressure finding: 323 (28.53%)	O/E Diastolic BP reading: 74 (26.52%)
	Infectious gastroenteritis: 49 (6.04%)	Depressive disorder: 25 (6.13%)	Overdose: 159 (14.05%)	O/E Systolic BP reading: 74 (26.52%)
	Fever: 48 (5.92%)	Emotional state finding: 23 (5.64%)	Depressed mood: 116 (10.25%)	Essential hypertension: 51 (18.28%)
	Common cold: 38 (4.69%)	Poisoning by psychotropic agent: 23 (5.64%)	Finding of pulse rate: 112 (9.89%)	Depressive disorder: 36 (12.9%)
	Nicotine dependence: 34 (4.19%)	Restlessness and agitation: 20 (4.9%)	Cough: 84 (7.42%)	Alcohol dependence: 26 (9.32%)
	Abdominal pain: 31 (3.82%)	Tobacco dependence, continuous: 20 (4.9%)	Abdominal pain: 46 (4.06%)	O/E pulse rhythm regular: 24 (8.6%)
	Acute otitis media: 31 (3.82%)	Headache: 19 (4.66%)	Chest pain: 46 (4.06%)	Harmful pattern of use of nicotine: 23 (8.24%)
	Hyperlipidemia: 29 (3.58%)	Tobacco dependence syndrome: 19 (4.66%)	Eruption: 45 (3.98%)	Type 2 diabetes mellitus without complication: 21 (7.53%)
	Suicidal thoughts: 28 (3.45%)	Acute alcoholic intoxication in alcoholism: 17 (4.17%)	Depressive disorder: 44 (3.89%)	Pure hypercholesterolemia: 19 (6.81%)
	Vomiting: 27 (3.33%)	Nausea and vomiting: 17 (4.17%)	Exercise grading: 39 (3.45%)	Chest pain: 16 (5.73%)

Domain	BIFAP	CDWBordeaux	CPRD GOLD	UKBB
Medications	acetaminophen: 139 (17.14%)	acetaminophen: 12 (2.94%)	acetaminophen: 156 (13.78%)	acetaminophen: 33 (11.83%)
	omeprazole: 76 (9.37%)	diazepam: 5 (1.23%)	omeprazole: 118 (10.42%)	simvastatin: 28 (10.04%)
	lorazepam: 74 (9.12%)	glucose: 5 (1.23%)	codeine: 97 (8.57%)	amlodipine: 21 (7.53%)
	ibuprofen: 59 (7.27%)	oxazepam: 5 (1.23%)	albuterol: 70 (6.18%)	lansoprazole: 20 (7.17%)
	clonazepam: 38 (4.69%)	pyridoxine: 5 (1.23%)	mirtazapine: 68 (6.01%)	codeine: 19 (6.81%)
	amoxicillin: 34 (4.19%)	sodium: 5 (1.23%)	citalopram: 66 (5.83%)	omeprazole: 18 (6.45%)
	lormetazepam: 34 (4.19%)	thiamine: 5 (1.23%)	thiamine: 65 (5.74%)	ramipril: 16 (5.73%)
	aspirin: 33 (4.07%)	Haemophilus influenzae type b, capsular polysaccharide inactivated tetanus toxoid conjugate vaccine: <5	sertraline: 57 (5.04%)	aspirin: 15 (5.38%)
	dipyrone: 32 (3.95%)	acellular pertussis vaccine, inactivated: <5	diazepam: 55 (4.86%)	atorvastatin: 14 (5.02%)
	quetiapine: 32 (3.95%)	albuterol: <5	simvastatin: 53 (4.68%)	citalopram: 14 (5.02%)

Supplementary Table II- 10. Top 10 conditions and medications captured through large-scale characterisation among individuals aged 1-17 years.

Domain	BIFAP	CDWBordeaux	CPRD GOLD
Conditions	Viral upper respiratory tract infection: 120 (11.62%)	Emotional state finding: 79 (12.87%)	Blood pressure finding: 169 (18.53%)
	Fever: 103 (9.97%)	Feeling unhappy: 45 (7.33%)	Overdose: 111 (12.17%)
	Common cold: 71 (6.87%)	Self-inflicted injury: 39 (6.35%)	Depressed mood: 90 (9.87%)
	Infectious gastroenteritis: 64 (6.2%)	Victim of psychological abuse: 38 (6.19%)	Cough: 76 (8.33%)
	Acute otitis media: 56 (5.42%)	Generalised anxiety disorder: 31 (5.05%)	Finding of pulse rate: 64 (7.02%)
	Acute tonsillitis: 53 (5.13%)	Poisoning by psychotropic agent: 31 (5.05%)	Upper respiratory infection: 61 (6.69%)
	Acute pharyngitis: 52 (5.03%)	Headache: 28 (4.56%)	Sore throat symptom: 52 (5.7%)
	Coronavirus infection: 48 (4.65%)	Conduct disorder: 27 (4.4%)	Abdominal pain: 50 (5.48%)
	Vomiting: 47 (4.55%)	Nausea and vomiting: 27 (4.4%)	Acute tonsillitis: 41 (4.5%)
	Conjunctivitis: 44 (4.26%)	Nightmares: 26 (4.23%)	Eruption: 41 (4.5%)
Medications	acetaminophen: 115 (11.13%)	acetaminophen: 10 (1.63%)	ethinyl estradiol: 38 (4.17%)
	ibuprofen: 113 (10.94%)	glucose: 10 (1.63%)	albuterol: 34 (3.73%)
	fluoxetine: 69 (6.68%)	sertraline: 10 (1.63%)	fluoxetine: 33 (3.62%)
	lorazepam: 44 (4.26%)	cyamemazine: 9 (1.47%)	levonorgestrel: 32 (3.51%)
	amoxicillin: 41 (3.97%)	sodium: 9 (1.47%)	amoxicillin: 25 (2.74%)

Domain	BIFAP	CDWBordeaux	CPRD GOLD
	aripiprazole: 29 (2.81%)	alprazolam: 8 (1.3%)	desogestrel: 21 (2.3%)
	risperidone: 18 (1.74%)	hydroxyzine: 8 (1.3%)	beclomethasone: 19 (2.08%)
	ethinyl estradiol: 16 (1.55%)	metoclopramide: 7 (1.14%)	melatonin: 17 (1.86%)
	desloratadine: 15 (1.45%)	diazepam: 6 (0.98%)	acetaminophen: 16 (1.75%)
	lormetazepam: 15 (1.45%)	fluoxetine: 5 (0.81%)	sertraline: 15 (1.64%)

[1] Results correspond to the assessment window of one year up to one day before index date. Results for other time windows and age groups can be found in the Shiny App.

Supplementary Table II-11. Top 10 conditions captured through large-scale characterisation among individuals aged 18 or older.

Domain	BIFAP	CDWBordeaux	CPRD GOLD	UKBB
Condition	Nicotine dependence: 96 (6.63%)	Depressive disorder: 68 (6.79%)	Blood pressure finding: 973 (43.67%)	O/E Diastolic BP reading: 164 (26.24%)
	Urinary tract infectious disease: 90 (6.22%)	Poisoning by psychotropic agent: 62 (6.19%)	Overdose: 383 (17.19%)	O/E Systolic BP reading: 164 (26.24%)
	Low back pain: 68 (4.7%)	Poisoning by benzodiazepine-based tranquilizer: 53 (5.29%)	Depressed mood: 323 (14.5%)	Depressive disorder: 88 (14.08%)
	Viral upper respiratory tract infection: 67 (4.63%)	Emotional state finding: 48 (4.8%)	Finding of pulse rate: 273 (12.25%)	Essential hypertension: 85 (13.6%)
	Anxiety disorder: 66 (4.56%)	Alcohol dependence: 47 (4.7%)	Cough: 172 (7.72%)	O/E pulse rhythm regular: 46 (7.36%)

Domain	BIFAP	CDWBordeaux	CPRD GOLD	UKBB
	Infectious gastroenteritis: 66 (4.56%)	Headache: 43 (4.3%)	Abdominal pain: 152 (6.82%)	Harmful pattern of use of nicotine: 41 (6.56%)
	Intentional self-poisoning: 66 (4.56%)	Tobacco dependence, continuous: 41 (4.1%)	Depressive disorder: 120 (5.39%)	Asthma: 37 (5.92%)
	Abdominal pain: 65 (4.49%)	Tobacco dependence syndrome: 40 (4%)	Anxiety: 114 (5.12%)	Alcohol dependence: 32 (5.12%)
	Suicidal thoughts: 65 (4.49%)	Nausea and vomiting: 38 (3.8%)	Cervical smear negative: 112 (5.03%)	Abnormal vision: 31 (4.96%)
	Self-inflicted injury: 63 (4.35%)	Acute alcoholic intoxication in alcoholism: 34 (3.4%)	Backache: 109 (4.89%)	Type 2 diabetes mellitus without complication: 31 (4.96%)
Medications	acetaminophen: 299 (20.66%)	acetaminophen: 34 (3.4%)	acetaminophen: 368 (16.52%)	acetaminophen: 66 (10.56%)
	omeprazole: 203 (14.03%)	sodium: 32 (3.2%)	omeprazole: 271 (12.16%)	simvastatin: 50 (8%)
	lorazepam: 195 (13.48%)	glucose: 28 (2.8%)	codeine: 245 (11%)	codeine: 42 (6.72%)
	clonazepam: 112 (7.74%)	metoclopramide: 18 (1.8%)	citalopram: 207 (9.29%)	omeprazole: 41 (6.56%)
	lormetazepam: 105 (7.26%)	tramadol: 12 (1.2%)	sertraline: 188 (8.44%)	citalopram: 36 (5.76%)
	dipyrone: 96 (6.63%)	oxazepam: 11 (1.1%)	fluoxetine: 174 (7.81%)	amlodipine: 30 (4.8%)

Domain	BIFAP	CDWBordeaux	CPRD GOLD	UKBB
	quetiapine: 96 (6.63%)	alprazolam: 10 (1%)	albuterol: 172 (7.72%)	albuterol: 29 (4.64%)
	tramadol: 83 (5.74%)	ketoprofen: 10 (1%)	mirtazapine: 168 (7.54%)	lansoprazole: 29 (4.64%)
	mirtazapine: 73 (5.04%)	morphine: 9 (0.9%)	diazepam: 165 (7.41%)	ramipril: 24 (3.84%)
	calcifediol: 70 (4.84%)	cyamemazine: 8 (0.8%)	thiamine: 130 (5.83%)	fluoxetine: 22 (3.52%)

Supplementary Table II- 12. Top 10 conditions and medications identified through large-scale characterisation by study period (2010-2016).

Domain	BIFAP	CDWBordeaux	CPRD GOLD	UKBB
Conditions	Pharyngitis: 16 (9.41%)	Emotional state finding: 29 (9.29%)	Blood pressure finding: 672 (38.07%)	O/E Diastolic BP reading: 163 (27.08%)
	Infectious gastroenteritis: 14 (8.24%)	Depressive disorder: 25 (8.01%)	Overdose: 286 (16.2%)	O/E Systolic BP reading: 163 (27.08%)
	Upper respiratory infection: 14 (8.24%)	Poisoning by psychotropic agent: 24 (7.69%)	Depressed mood: 216 (12.24%)	Depressive disorder: 86 (14.29%)
	Common cold: 12 (7.06%)	Poisoning by benzodiazepine-based tranquilizer: 19 (6.09%)	Finding of pulse rate: 164 (9.29%)	Essential hypertension: 83 (13.79%)
	Abdominal pain: 10 (5.88%)	Headache: 18 (5.77%)	Cough: 160 (9.07%)	O/E pulse rhythm regular: 45 (7.48%)

Domain	BIFAP	CDWBordeaux	CPRD GOLD	UKBB
	Headache: 9 (5.29%)	Poisoning by nonopioid analgesic: 17 (5.45%)	Abdominal pain: 112 (6.35%)	Harmful pattern of use of nicotine: 41 (6.81%)
	Urinary tract infectious disease: 9 (5.29%)	Nausea and vomiting: 15 (4.81%)	Depressive disorder: 92 (5.21%)	Asthma: 37 (6.15%)
	Viral upper respiratory tract infection: 9 (5.29%)	Self-inflicted injury: 15 (4.81%)	Upper respiratory infection: 84 (4.76%)	Abnormal vision: 31 (5.15%)
	Vomiting: 9 (5.29%)	Fatigue: 13 (4.17%)	Eruption: 82 (4.65%)	Alcohol dependence: 31 (5.15%)
	Acute respiratory infections: 8 (4.71%)	Alcohol dependence: 12 (3.85%)	Backache: 79 (4.48%)	Type 2 diabetes mellitus without complication: 30 (4.98%)
Medications	acetaminophen: 37 (21.76%)	acetaminophen: 7 (2.24%)	acetaminophen: 207 (11.73%)	acetaminophen: 66 (10.96%)
	omeprazole: 20 (11.76%)	alprazolam: 7 (2.24%)	omeprazole: 152 (8.61%)	simvastatin: 50 (8.31%)
	lorazepam: 16 (9.41%)	sodium: 6 (1.92%)	citalopram: 136 (7.71%)	codeine: 42 (6.98%)
	ibuprofen: 13 (7.65%)	acetylcysteine: <5	albuterol: 122 (6.91%)	omeprazole: 41 (6.81%)
	diazepam: 11 (6.47%)	albumin human, USP: <5	codeine: 118 (6.69%)	citalopram: 36 (5.98%)
	amoxicillin: 10 (5.88%)	albuterol: <5	fluoxetine: 113 (6.4%)	amlodipine: 30 (4.98%)
	dipyrone: 10 (5.88%)	alginate: <5	diazepam: 103 (5.84%)	albuterol: 29 (4.82%)

Domain	BIFAP	CDWBordeaux	CPRD GOLD	UKBB
	clonazepam: 9 (5.29%)	amoxicillin: <5	sertraline: 77 (4.36%)	lansoprazole: 29 (4.82%)
	mirtazapine: 9 (5.29%)	benzyl alcohol: <5	mirtazapine: 74 (4.19%)	ramipril: 24 (3.99%)
	lormetazepam: 8 (4.71%)	budesonide: <5	thiamine: 74 (4.19%)	fluoxetine: 22 (3.65%)

[1] Results correspond to the assessment window of one year up to one day before index date. Results for other time windows can be found in the Shiny App. Data availability differs across data sources. Data lock for last update are: BIFAP: 22-05-2024; CDWBordeaux: 22-02-2024; CPRD GOLD: 04-03-2024; UKBB: 01-03-2020. BIFAP contributed data from 2014 onwards.

Supplementary Table II- 13. Top 10 conditions and medications identified through large-scale characterisation stratified by study period (2017-2023).

Domain	BIFAP	CDWBordeaux	CPRD GOLD
Conditions	Viral upper respiratory tract infection: 178 (7.71%)	Emotional state finding: 98 (7.52%)	Blood pressure finding: 470 (34.18%)
	Fever: 126 (5.45%)	Poisoning by psychotropic agent: 69 (5.3%)	Overdose: 208 (15.13%)
	Infectious gastroenteritis: 116 (5.02%)	Depressive disorder: 66 (5.07%)	Depressed mood: 197 (14.33%)
	Urinary tract infectious disease: 104 (4.5%)	Headache: 53 (4.07%)	Finding of pulse rate: 173 (12.58%)
	Coronavirus infection: 97 (4.2%)	Nausea and vomiting: 50 (3.84%)	Abdominal pain: 90 (6.55%)

Domain	BIFAP	CDWBordeaux	CPRD GOLD
	Nicotine dependence: 97 (4.2%)	Feeling unhappy: 49 (3.76%)	Cough: 88 (6.4%)
	Suicidal thoughts: 97 (4.2%)	Poisoning by benzodiazepine-based tranquilizer: 49 (3.76%)	Anxiety: 76 (5.53%)
	Common cold: 95 (4.11%)	Alcohol dependence: 44 (3.38%)	Suicidal thoughts: 68 (4.95%)
	Abdominal pain: 88 (3.81%)	Tobacco dependence syndrome: 39 (2.99%)	Self-injurious behavior: 63 (4.58%)
	Acute pharyngitis: 86 (3.72%)	Tobacco dependence, continuous: 38 (2.92%)	Anxiety disorder: 57 (4.15%)
Medications	acetaminophen: 377 (16.32%)	acetaminophen: 37 (2.84%)	acetaminophen: 177 (12.87%)
	lorazepam: 223 (9.65%)	glucose: 36 (2.76%)	codeine: 132 (9.6%)
	omeprazole: 197 (8.53%)	sodium: 35 (2.69%)	omeprazole: 128 (9.31%)
	ibuprofen: 170 (7.36%)	metoclopramide: 24 (1.84%)	sertraline: 126 (9.16%)
	fluoxetine: 126 (5.45%)	cyamemazine: 14 (1.07%)	mirtazapine: 95 (6.91%)
	clonazepam: 117 (5.06%)	diazepam: 13 (1%)	fluoxetine: 94 (6.84%)
	lormetazepam: 112 (4.85%)	tramadol: 13 (1%)	albuterol: 84 (6.11%)
	quetiapine: 103 (4.46%)	alprazolam: 11 (0.84%)	citalopram: 72 (5.24%)
	dipyrone: 98 (4.24%)	ketoprofen: 11 (0.84%)	propranolol: 67 (4.87%)
	amoxicillin: 83 (3.59%)	oxazepam: 11 (0.84%)	folic acid: 66 (4.8%)