Study Report

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DARWIN EU® - Prescription trends of ketamine and esketamine

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CONTENTS

Study title	DARWIN EU® - Prescription trends of ketamine and esketamine
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Country(-ies) of study	Denmark, Finland, France, Germany, the United Kingdom.
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TITLE

DARWIN EU® - Prescription trends of ketamine and esketamine

1. DESCRIPTION OF STUDY TEAM

Study team role	Names	Organisation
Principal Investigator/ Epidemiologist	Dina Vojinovic	IQVIA
Data Scientist	Isabella Kaczmarczyk	IQVIA
Data Partner*	**Names**	**Organisation**
CDW Bordeaux	Romain Griffier Guillaume Verdy	CHUBX
CPRD GOLD	Hezekiah Omulo Mandickel Kamtengeni	University of Oxford
DK-DHR	Claus Møldrup Elvira Bräuner Susanne Bruun	DKMA
FinOMOP-HUS	Kimmo Porkka Eric Fey Salma Rachidi Valtteri Nieminen Alexey Ryzhenkov	FinOMOP
IMASIS	Juan Manuel Ramírez-Anguita Angela Leis Miguel-Angel Mayer	PSMAR
IQVIA DA Germany	Gargi Jadhav Akram Mendez	IQVIA

*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.

2. DATA SOURCES

This study was conducted using routinely collected data from 6 data sources in 6 European countries (5 EU countries and the United Kingdom). All databases were previously mapped to the OMOP Common Data Model (CDM).

1. Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux), France
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), the United Kingdom
3. Danish Data Health Registries (DK-DHR), Denmark
4. Hospital District of Helsinki and Uusimaa (FinOMOP-HUS), Finland
5. Institut Municipal Assistència Sanitària Information System (IMASIS), Spain
6. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

Detailed information on data sources is described below.

Country	Name of Data source	Health Care setting	Type of Data	Number of subjects	Data lock for the last update
France	CDW Bordeaux	Hospital outpatient, inpatient care and ICU	EHR	2.4 million	22/02/2024
The United Kingdom	CPRD GOLD	Primary care	EHR	17.5 million	17/08/2024
Denmark	DK-DHR	Registry	Registry	8.6 million	18/01/2025
Finland	FinOMOP-HUS	Hospital outpatient and inpatient care	EHR	2.6 million	04/08/2025
Spain	IMASIS	Hospital outpatient, inpatient care and ICU	EHR	1.7 million	04/09/2024
Germany	IQVIA DA Germany	Primary care and outpatient specialist care	EHR	45.2 million	14/01/2025

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, CPRD GOLD = Clinical Practice Research Datalink GOLD, DK-DHR = Danish Data Health Registries, FinOMOP-HUS = Hospital District of Helsinki and Uusimaa, IMASIS = Institut Municipal Assistència Sanitària Information System, IQVIA DA Germany = IQVIA Disease Analyzer Germany, EHR = Electronic Health Record, ICU = Intensive Care Unit.

3. ABSTRACT

Title

DARWIN EU® – Prescription trends of ketamine and esketamine

Rationale and background

Ketamine and esketamine are authorised for use in anaesthesia and for sedation in medical procedures, as well as for managing treatment-resistant depression. The non-medical use of ketamine has become a growing concern within the European Union (EU), prompting law enforcement actions to monitor its illicit trafficking and misuse. To better understand the scope of this issue, this study has been initiated to separately examine legitimate prescription trends for ketamine and esketamine.

Research question and objectives

Research question

What were the prescription trends of ketamine and esketamine over the last 10 years in Europe?

Study objectives

1. To estimate the monthly and annual incidence rate for ketamine and for esketamine prescriptions, overall and stratified by age, sex, route of administration and country/data source.
2. To estimate the monthly and annual prevalence for ketamine and for esketamine prescriptions, overall and stratified by age, sex, route of administration and country/data source.
3. To characterise individuals initiating treatment with ketamine and with esketamine in terms of demographics, indication for prescribing, comorbidities and concomitant medication at the treatment initiation. Results were stratified by country/data source.
4. To estimate the initial dose at treatment initiation, treatment duration of the first drug era and cumulative duration of use for ketamine and for esketamine, where available. Results were stratified by data source.

Methods

Study design

- Population-level cohort study (*Objective 1* and *2*, Population-level drug utilisation for ketamine and for esketamine).
- New drug user cohort study (*Objective 3* and *Objective 4*, Patient-level drug utilisation with regard to demographics, indication of use, comorbidities, concomitant medication, initial dose, treatment duration of the first drug era and cumulative duration of use, where available).

Study period

1st of January 2014 to 31st December 2023 (or latest available date)

Population

Population-level utilisation of ketamine and esketamine: population-level drug utilisation analyses included all individuals registered in the respective data source between 1st of January 2014 and 31st of December 2023, with at least one year of data visibility prior to becoming eligible for study inclusion. Therefore, children aged <1 year of age were excluded.

Patient-level utilisation of ketamine and esketamine: patient-level drug utilisation analysis included all new users of ketamine and esketamine in the period between 1st of January 2014 and 31st of December 2023,

with at least one year of data visibility prior to becoming eligible for study inclusion and no use of the respective medication during one year period preceding the study inclusion. Children aged <1 year of age were excluded.

Variables

Drugs of interest:

- Ketamine, WHO ATC code N01AX03
- Esketamine, WHO ATC code N01AX14 and N06AX27

Data source

1. Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux), France
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), the United Kingdom
3. Danish Data Health Registries (DK-DHR), Denmark
4. Hospital District of Helsinki and Uusimaa (FinOMOP-HUS), Finland
5. Institut Municipal Assistència Sanitària Information System (IMASIS), Spain
6. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

Sample size

No sample size has been calculated as this is a descriptive study.

Statistical analysis

Population-level utilisation of pre-specified medicines of interest: monthly and annual incidence rates (expressed as number of new users of ketamine and esketamine per 1,000 person-years) and annual period prevalence of ketamine and esketamine prescriptions (expressed as the proportion of users in the study population) were estimated. The statistical analyses were performed based on OMOP-CDM mapped data using *IncidencePrevalence* R package. The results were presented overall and stratified by age, sex, route of administration and country/data source.

Patient-level utilisation of pre-specified medicines of interest: patient-level characterisation, including demographics (age, sex), indication for prescribing, comorbidities and concomitant medication, was assessed at the date of new incident prescription for ketamine and for esketamine (index date) and in the period of one year prior to the index date. The initial dose was estimated, and the minimum, quartiles and maximum values were provided. The treatment duration of the first drug era and cumulative duration of use were calculated and summarised providing the minimum, quartiles and maximum, where available. Statistical analyses were conducted using the *CohortCharacteristics*, *PatientProfiles*, and *DrugUtilisation* R packages based on OMOP-CDM mapped data. The analyses were stratified by country/data source.

Sensitivity analyses were conducted by removing the inclusion criterion requiring 365 days of prior observation to assess its impact on cohort size and study estimates.

For all analyses a minimum cell counts of 5 was used when reporting results, with any smaller counts obscured.

Results

Incidence rates and prevalence of ketamine and esketamine prescriptions – Population-level utilisation

Ketamine prescription records were identified in five data sources (CDW Bordeaux, CPRD GOLD, FinOMOP-HUS, IMASIS, and IQVIA DA Germany), while esketamine prescriptions were recorded in four data sources (DK-DHR, FinOMOP-HUS, IMASIS, and IQVIA DA Germany).

Overall, the monthly and annual incidence rates of ketamine prescriptions were very low and stable over time in primary care settings, including CPRD GOLD and IQVIA DA Germany, with rates consistently below 1 per 1,000 person-years (PYs). In contrast, hospital-based data sources showed low incidence rates that increased from 2021 onwards. In IMASIS, monthly incidence increased from 0.35 per 1,000 PYs in 2014 to 4.8 per 1,000 PYs in 2023, and in CDW Bordeaux from 0.35 per 1,000 PYs in 2014 to 2.13 per 1,000 PYs in 2023. In contrast, FinOMOP-HUS data source showed no recorded ketamine prescriptions prior to 2020, followed by a slight increase with monthly incidence rates reaching 0.11 per 1,000 PYs by 2023. Similar trends were observed for annual incidence rates. The results of sensitivity analyses were consistent with those observed in the primary analyses. Esketamine use remained extremely low across contributing data sources, with both monthly and annual incidence rates generally below 0.02 per 1,000 PYs in the primary care data source (IQVIA DA Germany), the hospital-based data source (IMASIS), and the registry (DK-DHR). In contrast, data from the FinOMOP-HUS indicated minimal recorded use of esketamine in 2014, with incidence rates around 0.3 per 1,000 PYs. A gradual and sustained increase was observed over time, reaching an annual incidence rate of approximately 11 per 1,000 PYs by 2023.

When stratified by age, incidence rates of ketamine use tended to be higher in older adults, particularly in those aged 55 years and older, with the lowest rates in younger age groups. No age-related differences were observed for esketamine, except in FinOMOP-HUS where higher incidence rates were observed among older age groups. Analyses stratified by sex showed no notable differences in ketamine between males and females across most data sources, except for CDW Bordeaux, where higher rates among males were observed after 2020. Esketamine prescription records were comparable between sexes. Regarding the route of administration, parenteral ketamine prescriptions accounted for the highest incidence rates in hospital settings in CDW Bordeaux and IMASIS. For esketamine, monthly and annual incidence rates did not differ by route of administration for most data sources. In FinOMOP-HUS, the highest incidence rates were observed for unknown route of administration.

Prevalence patterns closely mirrored those observed for incidence. Ketamine prevalence remained below 0.01% in primary care data sources throughout the study period but increased slightly in hospital data sources, reaching 0.04% in IMASIS, 0.004% in FinOMOP-HUS, and 0.02% in CDW Bordeaux by 2023. Age and sex stratifications showed higher prevalence among older individuals and a modest male predominance in CDW Bordeaux after 2020. Esketamine prevalence remained uniformly low across all strata and data sources, with slight increases in FinOMOP-HUS among older age groups (aged 55 years and older). Parenteral administration was the predominant route of use for ketamine in hospital-based setting of in CDW Bordeaux and IMASIS. In FinOMOP-HUS, a substantial proportion of esketamine prescriptions had an unknown route of administration. Sensitivity analyses, based on a larger sample size, consistently supported the primary findings and provided additional evidence, further strengthening the main observation.

Characterisation of new users of ketamine or esketamine – Patient-level utilisation

The number of individuals prescribed ketamine ranged from 48 individuals in IQVIA DA Germany to 3,646 individuals in IMASIS when one year of prior data visibility was required. Common pre-specified conditions reported in the year prior to new ketamine prescriptions among these individuals were anxiety, cancer, and depression. The frequency of recorded surgical procedures or records of anaesthesia or sedation around the date of ketamine prescription differed across the data sources. Depression, hypertension, and pain were the most common conditions among ketamine users in the year prior to their treatment. Medication related to pain management, electrolyte balance, anaesthesia and gastrointestinal health management, anxiety and sleep disorders were most commonly prescribed among ketamine users across the data sources in the year prior up to their ketamine prescription. The sensitivity analyses confirmed the robustness of these findings.

The number of individuals prescribed esketamine ranged from 9 individuals in IMASIS and 51 individuals in IQVIA DA Germany to 53,657 individuals in FinOMOP-HUS across different data sources if one year of prior data visibility was required. Common pre-specified conditions among new users of esketamine were cancer, chronic pain, and depression. The frequency of recorded surgical procedures or records of anaesthesia or sedation around the date of esketamine prescription differed across the data sources. Depression, pain, and essential hypertension were the most common conditions recorded among new esketamine users in the year prior to treatment. Medication related to pain management, electrolyte balance, anaesthesia and gastrointestinal health management, anxiety and sleep disorders was the most commonly prescribed among esketamine users. The sensitivity analyses confirmed the robustness of these findings.

Treatment characteristics of ketamine or esketamine – Patient-level drug utilisation

The median initial daily dose of ketamine ranged between 16.7 milligrams in IQVIA DA Germany and 200 milligrams in CPRD GOLD, while the recorded median initial daily dose of esketamine ranged between 8 milligrams in IQVIA DA Germany and 33 milligrams in DK-DHR, irrespective of the prior data visibility criterion. The median duration that individuals were exposed to ketamine ranged from 0 days in CDW Bordeaux and IMASIS to 29 days in IQVIA DA Germany, while the median total number of days exposed to ketamine ranged from 1 day in CDW Bordeaux and IMASIS to 30 days in IQVIA DA Germany, irrespective of the prior data visibility criterion. The median duration that individuals were exposed to esketamine ranged from 1 day in FinOMOP-HUS to 29 days in DK-DHR, IMASIS, and IQVIA DA Germany, while the median total number of days exposed to esketamine ranged from 1 day in FinOMOP-HUS to 212 days in IMASIS among new users with at least one year prior data visibility and from 1 day in FinOMOP-HUS to 224 days in IMASIS without the prior data visibility criterion.

Discussion

This multi-data source drug utilisation study provides an overview of ketamine and esketamine prescription patterns across six European healthcare data sources between 2014 and 2023. The study reveals distinct patterns of ketamine and esketamine prescriptions across different healthcare settings. Ketamine prescriptions were consistently infrequent in primary care settings, with little variation over time. In contrast, hospital-based data sources showed a gradual increase in ketamine prescribing since 2021. Esketamine prescriptions remained rare across all data sources, except in FinOMOP-HUS where gradual increase over time was observed.
Ketamine and esketamine are often prescribed among individuals with a record of depression or pain, or individuals that undergo surgical procedures or have a record of anaesthesia or sedation. This corresponds with their intended use as anaesthetic or analgesic agents, or to treat treatment-resistant depression.
These findings provide important baseline information for ongoing monitoring of ketamine and esketamine utilisation in clinical practice.

4. LIST OF ABBREVIATIONS

Acronyms/term	Description
ATC	Anatomical Therapeutic Chemical classification system
CDM	Common Data Model
CDW	Clinical Data Warehouse
CM	Clinical Modification
CPRD	Clinical Practice Research Datalink
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DK-DHR	Danish Data Health Registries
DOI	Declaration of interests
DQD	Data Quality Dashboard
DUS	Drug Utilisation Study
ED	Emergency Department
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUDA	European Union Drug Agency
GP	General Practitioner
GDPR	General Data Protection Regulation
ICD	International Classification of Diseases
ICU	Intensive Care Unit
ID	Index date
IMASIS	Institut Municipal Assistència Sanitària Information System
IP	Inpatient
MA	Marketing Authorisation
NA	Not applicable
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
OT	Other
PAS	Post-Authorization Studies
SD	Standard deviation
SNOMED	Systematized Nomenclature of Medicine
WHO	World Health Organisation

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	7th February 2025	Sensitivity analysis	Sensitivity analysis without 365 days prior history inclusion criteria	Based on the results of cohort diagnostics, the inclusion criterion requiring 365 days of prior history impacted the sample size.

6. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Final Study Protocol	16th December 2024	9th January 2025
Creation of Analytical code	December 2024	December/February 2025
Execution of Analytical Code on the data	December 2024/January 2025	January/April 2025, October 2025
Interim Study Report (if applicable)	30th January 2025	29th April 2025
Draft Study Report	30th April 2025	30th April 2025
Final Study Report	30th May 2025	29th January 2026

7. RATIONALE AND BACKGROUND

Ketamine and esketamine are authorised for use in anaesthesia and for sedation in medical procedures, as well as for managing treatment-resistant depression [1]. The non-medical use of ketamine has recently emerged as a drug threat within the European Union (EU) [2]. Law enforcement authorities from several EU Member States have expressed increasing concerns regarding the illicit trafficking and recreational misuse of ketamine, prompting coordinated actions to address and better understand this issue. In response, an operational initiative has been developed, aiming to refine the criminal intelligence surrounding ketamine distribution networks across Europe. This initiative is designed to monitor trends and identify patterns in the trafficking and unauthorised use of ketamine within the EU [2].

However, to comprehensively assess the scope of ketamine's distribution and its misuse potential, it is crucial to examine legitimate prescription trends for ketamine and its derivative esketamine, both of which are used in medical settings. The European Union Drug Agency (EUDA) has prioritised this area of study to quantify the volume of legally prescribed ketamine and esketamine across EU Member States. By investigating prescription patterns, this study aims to provide valuable data to support ongoing efforts to monitor and mitigate emerging drug-related risks in the EU.

8. RESEARCH QUESTION AND OBJECTIVES

Research question

What were the prescription trends of ketamine and esketamine over the last 10 years in Europe?

Study objectives

1. To estimate the monthly and annual incidence rate for ketamine and for esketamine prescriptions, overall and stratified by age, sex, route of administration and country/data source.
2. To estimate the monthly and annual prevalence for ketamine or esketamine prescriptions, overall and stratified by age, sex, route of administration and country/data source.
3. To characterise individuals initiating treatment with ketamine or esketamine in terms of demographics, indication for prescribing, comorbidities and concomitant medication at the treatment initiation. Results were stratified by country/data source.
4. To estimate the initial dose at treatment initiation, treatment duration of the first drug era and cumulative duration of use for ketamine and for esketamine, where available. Results were stratified by data source.

Description of the proposed objectives to be achieved in the study (**Table 1**).

Table 1. Primary and secondary research questions and objective.

A. Objective 1 and 2.

Objective:	**Objective 1:** To estimate the monthly and annual incidence rate for ketamine and for esketamine prescriptions, overall and stratified by age, sex, route of administration and country/data source. **Objective 2:** To estimate the monthly and annual prevalence for ketamine and for esketamine prescriptions, overall and stratified by age, sex, route of administration and country/data source.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	All individuals registered in the respective data source between 1st of January 2014 and 31st of December 2023, with at least one year of data visibility prior becoming eligible for study inclusion. Children aged <1 year of age were excluded.
Exposure:	Not applicable
Comparator:	None
Outcome:	Ketamine and esketamine prescriptions
Time *(when follow up begins and ends):*	Follow-up started on the respective date of the latest of the following: 1) study start date (1st of January 2014) or 2) date at which individual has 1 year of prior history. End of follow up is defined as the earliest of the following: 1) end of study period (31st of December 2023), 2) end of data availability, 3) loss to follow up or 4) death, whichever came first.
Setting:	General practitioner, hospital, and registry setting using data from the following 6 data sources: CDW Bordeaux (France), CPRD GOLD (the United Kingdom), DK-DHR (Denmark), FinOMOP-HUS (Finland), IMASIS (Spain), and IQVIA DA Germany (Germany).
Main measure of effect:	Number of prescriptions of ketamine and esketamine, overall and stratified by country/data source. For hospital data sources, in addition to overall number of prescriptions, the data was stratified by intensive care unit (ICU)/non-ICU status. Monthly and annual incidence rates (expressed as number of new users of ketamine and esketamine per 1,000 person-years), overall and stratified by age, sex, route of administration and country/data source. Annual period prevalence of ketamine and esketamine prescriptions (expressed as proportion), overall and stratified by age, sex, route of administration and country/data source.

B. Objective 3 and 4.

Objective:	**Objective 3**: To characterise individuals initiating treatment with ketamine or esketamine in terms of demographics, indication for prescribing, comorbidities and concomitant medication at the treatment initiation. Results were stratified by country/data source. **Objective 4**: To estimate the initial dose at treatment initiation, treatment duration of the first drug era and cumulative duration of use for ketamine and esketamine, where available. Results were stratified by data source.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	All new users of ketamine and esketamine in the period between 1st of January 2014 and 31st of December 2023, with at least one year of data visibility prior to becoming eligible for study inclusion and no use of the respective medication in the previous 1 year. Children aged <1 year of age were excluded.
Exposure:	Not applicable
Comparator:	None
Outcome:	Ketamine and esketamine prescriptions
Time *(when follow up begins and ends):*	Follow up started at the day of new incident prescription/dispensation of ketamine and esketamine (index date). End of follow-up was defined as earliest of following: 1) end of study period (31st of December 2023), 2) end of data availability, 3) loss to follow up or 4) death, whichever came first.
Setting:	General practitioner, hospital, and registry setting using data from the following 6 data sources: CDW Bordeaux (France), CPRD GOLD (the United Kingdom), DK-DHR (Denmark), FinOMOP-HUS (Finland), IMASIS (Spain) and IQVIA DA Germany (Germany).
Main measure of effect:	Age, sex, frequency of comorbidities and concomitant medication for new users of ketamine and esketamine at the index date and in a 1 year prior to the index date, stratified by country/data source. Frequency and percentage of diagnosis from the pre-specified list, used as proxy to assess indications for prescribing ketamine and esketamine, at the index date and in 1 year prior to the index date, stratified by country/data source. Initial dose of treatment of ketamine and esketamine, stratified by country/data source. Duration of first treatment era of ketamine and esketamine expressed as minimum, p25, median, p75 and maximum, stratified by country/data source. Cumulative treatment duration of ketamine and esketamine expressed as minimum, p25, median, p75 and maximum, stratified by country/data source.

9. RESEARCH METHOD

9.1. Study type and study design

The study types with related study designs are described below and were selected from the Draft Catalogue of Data analytics.

A cohort study was conducted using routinely collected health data from 6 data sources. The study comprised two consecutive parts:

- Population-level cohort study (*Objectives 1* and *2*, Population-level drug utilisation of ketamine and esketamine).

- New drug user cohort study (*Objectives 3* and *4*, Patient-level drug utilisation with regard to demographics, indication of use, comorbidities, concomitant medication, initial dose, treatment duration of the first drug era and cumulative duration of use, where available).

9.2. Study setting and data sources

This study was conducted using routinely collected data from 6 data sources in 6 European countries (5 EU countries and the United Kingdom). All data sources were previously mapped to the OMOP Common Data Model (CDM).

1. Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux), France
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), the United Kingdom
3. Danish Data Health Registries (DK-DHR), Denmark
4. Hospital District of Helsinki and Uusimaa (FinOMOP-HUS), Finland
5. Institut Municipal Assistència Sanitària Information System (IMASIS), Spain
6. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

For this study, we have selected 6 data sources that were considered fit for purpose from the data sources available in the DARWIN EU® Database Catalogue. The selection process was based on several key criteria. Firstly, the number of individuals prescribed ketamine and esketamine within each data source was evaluated to guarantee sufficient data for analysis. Secondly, the geographical distribution of the data sources was taken into account to ensure a diverse and representative sample. Additionally, the experience gained from data sources that had previously participated in similar DARWIN EU® studies was also taken into account, leveraging their proven reliability and data quality.
Information on these data sources with a justification for their choice in terms of ability to capture the relevant data is described in **Table 2**.

The selected data sources were relevant for this study because they encompass secondary care and outpatient specialist care settings where ketamine and esketamine may be prescribed or dispensed. CPRD GOLD covers primary care setting but general practitioners receive information about patient contacts with secondary care. However, not all data sources included both medications. Regarding reliability of data sources, the data partners were asked to describe their internal data quality process on the source data as part of the DARWIN EU® onboarding procedure. To further ensure data quality, we utilised the Achilles tool, which systematically characterised the data and presented it in a dashboard format that was inspected. The generated data characteristics such as age distribution, condition prevalence per year, data density, and measurement value distribution were compared against expectations for the data. Additionally, the data quality dashboard (DQD) provided more objective checks on plausibility consistently across the data sources. In terms of relevance, a more general-purpose diagnostic tools, *CohortDiagnostics* (https://github.com/darwin-eu-dev/CohortDiagnostics) and *DrugExposureDiagnostics* R packages (https://darwin-eu.github.io/DrugExposureDiagnostics/), were developed. *CohortDiagnostics* R package evaluated phenotype algorithms for OMOP CDM datasets, offering a standard set of analytics for understanding patient capture including data generation. It provided additional insights into cohort characteristics, record counts and index event misclassification. *DrugExposureDiagnostics* R package assessed ingredient specific diagnostics for drug exposure records. Furthermore, timeliness was guarded by extracting the release dates for each dataset in the network and monitoring when data were out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it was important to have clear understanding of the time period covered by each released data source, as this can vary across different domains. To facilitate this, the CdmOnboarding (and Achilles) packages contained a ‘data density’ plot. This plot displayed the number of records per OMOP domain on a monthly basis. This allowed to get insights when data collection started, when new sources of data were added and when until when data was included.

Table 2. Description of the selected data sources.

Country	Name of Data source	Justification for Inclusion	Health Care setting	Type of Data	Number of subjects	Data lock for the last update
France	CDW Bordeaux	Data source covers secondary care setting where ketamine and esketamine may be prescribed/dispensed	Hospital outpatient, inpatient care, and ICU	EHR	2.4 million	22/02/2024
The United Kingdom	CPRD GOLD	Data source covers settings where ketamine and esketamine may be prescribed/dispensed	Primary care	EHR	17.5 million	17/08/2024
Denmark	DK-DHR	Data source covers secondary care setting where ketamine and esketamine may be prescribed/dispensed	Registry	Registry	8.6 million	18/01/2025
Finland	FinOMOP-HUS	Data source covers secondary care setting where ketamine and esketamine may be prescribed/dispensed	Hospital outpatient and inpatient care	EHR	2.9 million	20/10/2025
Spain	IMASIS	Data source covers secondary care setting where ketamine and esketamine may be prescribed/dispensed	Hospital outpatient, inpatient care and ICU	EHR	1.7 million	04/09/2024
Germany	IQVIA DA Germany	Data source covers primary care/outpatient specialist care setting where ketamine and esketamine may be prescribed/dispensed	Primary care and outpatient specialist care	EHR	45.2 million	14/01/2025

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, CPRD GOLD = Clinical Practice Research Datalink GOLD, DK-DHR = Danish Data Health Registries, FinOMOP-HUS = Hospital District of Helsinki and Uusimaa, IMASIS = Institut Municipal Assistència Sanitària Information System, IQVIA DA Germany = IQVIA Disease Analyzer Germany, EHR = Electronic Health record, ICU = Intensive Care Unit.

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

The clinical data warehouse of the Bordeaux University Hospital comprises electronic health records 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 data source currently holds information about the person (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) [3].

Clinical Practice Research Datalink GOLD (CPRD GOLD), the United Kingdom

The Clinical Practice Research Datalink (CPRD) GOLD is a data source of anonymised electronic health records (EHR) from General Practitioner (GP) clinics in the UK that use the Vision® software system for their management [4]. The source population encompasses 98% of the UK, registered with GPs responsible for non-emergency care and referrals. Participating GPs provide CPRD EHR for all registered patients who did not specifically request to opt out of data sharing. Covering 4.6% of the current UK population, GOLD includes 4.9% of contributing GP practices, providing comprehensive information within its defined source population. 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 patient's demographic, biological measurements, clinical symptoms and diagnoses, referrals to specialist/hospital and their outcome, laboratory tests/results, and prescribed medications. GPs receive information about patient contacts with secondary care, but this information must be manually entered into the patient record and therefore, may be incomplete. GOLD has been assessed and found broadly representative of the UK general population in terms of age, gender, and ethnicity [4]. GOLD has been widely used internationally for observational research to produce nearly 3,000 peer-reviewed publications, making GOLD the most influential UK clinical data source so far [5-7].

In terms of quality checks, the integrity, structure and format of the data is reviewed. Collection-level validation ensures integrity by checking that data received from practices contain only expected data files and ensures that all data elements are of the correct type, length and format. Duplicate records are identified and removed. Transformation-level validation checks for referential integrity between records ensure that there are no orphan records included in the data source (for example, that all event records link to a patient), while research-quality-level validation covers the actual content of the data. CPRD provides a patient-level data quality metric in the form of a binary 'acceptability' flag. This is based on recording and internal consistency of key variables including date of birth, practice registration date and transfer out date.

Danish Data Health Registries (DK-DHR), Denmark

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 birth to death, 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. The high quality of Danish health data is attributed to standardisation, digitisation and comprehensive documentation, which together enhance accuracy, consistency and reliability, minimising potential for interpretation errors. 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.

Hospital District of Helsinki and Uusimaa (FinOMOP-HUS), Finland

The HUS data lake is a comprehensive, integrated data source derived in real time from all patients who visit the HUS hospitals and receiving treatment [8]. HUS is responsible for specialised healthcare in Finlands Uusimaa region and treatment of many rare and severe diseases that are nationally centralised to HUS. HUS's catchment area covers a population of about 2.2 million people: 2.4 million outpatient clinic visits, 670,00 patients treated, 84,000 surgical procedures, 710 specialist care emergency clinic visits per day. All visits, examinations, laboratory test, procedures, and treatments are recoded in the HUS IT systems and integrated into the data lake. The data lake stores decades of clinical information in digital format, data from both past and current source systems are available.

Institut Municipal Assistència Sanitària Information System (IMASIS), Spain

The Institut Municipal Assistència Sanitària Information System (IMASIS) is the Electronic Health Record (EHR) system of Parc de Salut Mar Barcelona (PSMar) which is a complete healthcare services organisation. Currently, this information system includes and shares the clinical information of two general hospitals (Hospital del Mar and Hospital de l'Esperança), one mental health care centre (Centre Dr. Emili Mira) and one social-healthcare centre (Centre Fòrum) including emergency room settings, which are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information more than 1 million patients with at least one diagnosis and who have used the services of this healthcare system since 1990 and from different settings such as admissions, outpatients, emergency room and major ambulatory surgery. The diagnoses are coded using the International Classification of Diseases, Ninth and Tenth revision, Clinical Modification (ICD-9-CM and ICD-10-CM). The average follow-up period per patient in years is 6.37 (SD±6.82). IMASIS-2 is the anonymised relational data source of IMASIS which is used for mapping to OMOP including additional sources of information such as the Tumours Registry.

IQVIA Disease Analyzer (DA) Germany, Germany

IQVIA Disease Analyzer (DA) Germany is a data source of de-identified electronic medical records from specialised and general primary practices (GP) in Germany since 1992 [9]. 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, community size category and federal state location, was instrumental in constructing a data source that accurately mirrors the diverse spectrum of healthcare providers in the country. Consequently, data within IQVIA DA Germany data source has been demonstrated to be representative of general practices throughout Germany.

The data source contains demographics records, basic medical data, disease diagnosis according to International Classification of Diseases, 10th revision (ICD-10), and prescription records. While the data source partly records information on deaths and procedures, it currently does not support linkage with external data sources and therefore, information on mortality is incomplete. Routine updates are conducted at regular intervals. Data quality is assessed based on several criteria, including completeness of information and correctness (e.g., linkage between diagnosis and prescriptions).

No registration or approval is required for drug utilisation studies. As previously demonstrated, IQVIA DA Germany is suitable for pharmacoepidemiologic and pharmacoeconomic studies.

9.3. Study period

The study period was from 1st of January 2014 until the earliest of 31st of December 2023 or the date of the last update for each respective data source (please see **Table 2** for more details on the last update for each data source).

9.4. Follow-up

For population-level utilisation study for ketamine and for esketamine prescriptions, follow-up started when study participants fulfilled inclusion criteria (i.e. present in the data source between 1st of January 2014 and 31st of December 2023 and with at least one year of data visibility). End of follow-up was defined as earliest of end of study period (31st of December 2023), end of data availability, loss to follow-up or death, whichever came first.

For patient-level utilisation study of ketamine and esketamine, study participants were followed from the date of new incident prescription of ketamine and esketamine (index date) until end of study period (31st December 2023), end of data availability, loss to follow up or death, whichever came first.

The operational definitions of the index date and other primary time anchors are presented by means of **Table 3**.

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

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics/validation	Source of algorithm
All participants from the respective data source eligible for the study – Incident use of ketamine or esketamine	Study entry date	Multiple entries	Incident	[-365, -1]	IP, OP, OT	SNOMED	n/a	Prior use of ketamine or esketamine	n/a	n/a
All participants from the respective data source eligible for study – Prevalent use of ketamine or esketamine	Study entry date	Multiple entries	Prevalent	n/a	IP, OP, OT	SNOMED	n/a	n/a	n/a	n/a
All study participants from the data source initiating new treatment with ketamine or esketamine – Characterisation	Date of new prescription of ketamine or esketamine	Multiple entries	Incident	[-365, -1]	IP, OP, OT	RxNorm	n/a	Prior use of ketamine or esketamine	n/a	n/a

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

An example of entry and exit into the denominator population is shown in **Figure 1**. In this example, person ID 1 has already sufficient prior history before the study start date and the observation period ends after the study end date, so person ID 1 will contribute during the complete study period. Person ID 2 and 4 enter the study only when they have sufficient prior history. Person ID 3 leaves when exiting the data source (the end of observation period). Lastly, person ID 5 has two observation periods in the data source. The first period contributes time from study start until end of observation period, the second starts contributing time again once sufficient prior history is reached and exits at study end date.

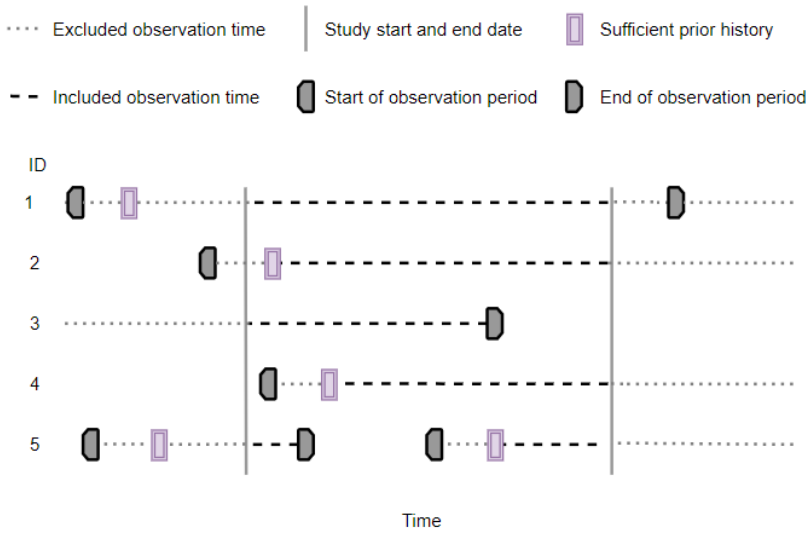


Figure 1. Included observation time for the denominator population.

9.5. Study population with in and exclusion criteria

Population-level drug utilisation of ketamine and esketamine

The study population included all individuals registered in the data source between 1st of January 2014 and 31st of December 2023, with at least one year of data visibility prior to becoming eligible for study inclusion.

Additional eligibility criteria applied for:

- Incidence rates calculation: the observation time of participants prescribed ketamine or esketamine was excluded during use and 1 year afterwards.
- Incidence rates and prevalence calculation stratified by age, sex and route of administration: age specific cohorts had age-boundary eligibility criteria, sex specific cohorts had sex eligibility criteria and cohort defined based on the route of administration had route of administration eligibility criteria.

Patient-level utilisation of ketamine and esketamine

All new users of ketamine and esketamine in the period between 1st of January 2014 and 31st of December 2023 (or latest date available). Notably, all individuals needed to have at least one year of data visibility prior to the date of their new prescription. “New use” referred to a prescription/dispensation of ketamine or esketamine in the study period and without any use of respective medicine in the previous 1 year.
The operational definitions of the inclusion exclusion criteria are presented by means of **Table 4.**

Table 4. Operational definitions of inclusion criteria.

Criterion	Details	Order of application *	Assessment window	Care Settings [1]	Code Type	Diagnosis position[2]	Applied to study populations:	Measurement characteristics / validation	Source for algorithm
Observational period in the data source during the period 2014–2023 (or the latest date available)	All individuals present in the data source in the period 2014–2023 (or the latest date available)	n/a	n/a	IP, OP, OT	n/a	n/a	All study population	n/a	n/a
Prior data source history	Study participants were required to have 365 days of prior history observed before contributing observation time	Prior	[-365, 0]	IP, OP, OT	n/a	n/a	All study population	n/a	n/a
Washout period	Individuals who initiated treatment were required to have not used selected pre-specified medication of interest 1 year before a “new” prescription	Prior	[-365, -1]	IP, OP, OT	n/a	n/a	All study population	n/a	n/a

[1] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable;
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter);
*Order of application specifies whether the eligibility criterion is applied before or after selection of the study entry date. For instance, selecting 'after' means that the first possible study entry date is chosen, followed by the application of the inclusion and/or exclusion criteria.

9.6. Variables

9.6.1 Exposure

Not applicable.

9.6.2 Outcome/s

For this study, outcome of interest was prescription (during study period) of ketamine or esketamine.
The list of medication of interest is described in **ANNEX I**. The operational definition of outcome is presented by means of **Table 5.**

Table 5. Operational definitions of outcome.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics/ validation	Source of algorithm
Ketamine or esketamine	Code list provided in **ANNEX I**	Yes	Count	[-365, -1]	IP, OP, OT	RxNorm	n/a	All individuals present in the data source during the study period	n/a	n/a

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

9.6.3 Other covariates, including confounders, effect modifiers and other variables

Population-level utilisation study (incidence rates and prevalence of ketamine and esketamine)

Covariates for stratification in population-level utilisation included:

- Calendar month
- Calendar year
- Age categories:
    - All adults: 15–64 years old
    - Young adults: 15–34 years old
    - Detailed breakdown: <5, 5–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, >85 years old
- Sex: both, males, and females
- Route of administration: nasal, oral, parenteral, topical, unknown

Patient-level utilisation study (Characterisation of cohort with prescription of ketamine and esketamine)

The other variables for patient-level utilisation included:

- A list of pre-specified conditions was used as a proxy to assess indication of use, including both authorised and non-authorised indications (the frequency of conditions of interest was assessed at the index date and within 1 year prior to the index date):
    - Depression (including treatment resistant depression)
    - Acute pain
    - Chronic pain
    - Cancer
    - Bipolar disorder
    - Anxiety disorder
    - Post-traumatic stress disorder
    - Migraine
    - Epilepsy
    - Other
    - Missing
- Additional entries were used as a proxy to assess use for sedation, anaesthesia, diagnostics procedures, and surgical interventions (the frequency of additional entries was assessed at the index date and in a window of 2 days before and 2 days after the index date).
- The top 10 of most frequent diagnostic codes as a proxy for comorbidities from large-scale characterisation (the frequency of comorbidities was assessed at the index date and in 1 year prior to the index date).

- The top 10 of most frequently prescribed drugs in each data source from large-scale characterisation (the frequency of comedication was assessed at the index date and in 1 year prior to the index date).

The operational definition of the covariates is described in **Table 6**. The index date was the start of the (new) incident prescription during the study period. The list of concepts for prespecified conditions of interest is described in **ANNEX I**.

Table 6. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics/ validation	Source for algorithm
Indication of use	Check for pre-specified conditions of interest related to use of ketamine and esketamine	Counts	At ID and in window around ID [-365, ID]	IP, OP, OT	SNOMED	n/a	All eligible individuals within the data source considered for objective 3 (new user cohort)	n/a	n/a
Comorbidities	Large-scale characterisation with regard to underlying comorbidity	Counts	At ID and in window around ID [-365, ID]	IP, OP, OT	SNOMED	n/a	All eligible individuals within the data source considered for objective 3 (new user cohort)	n/a	n/a
Concomitant medication	Large-scale characterisation with regard to underlying comorbidity	Counts	At ID and in window around ID [-365, ID]	IP, OT, OT	RxNorm	n/a	All eligible individuals within the data source considered for objective 3 (new user cohort)	n/a	n/a

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

9.7. Study size

No formal sample size calculation was conducted for this descriptive drug utilisation study, as the primary objective was to describe prescription trends for ketamine and esketamine, irrespective of sample size. Based on a preliminary feasibility assessment, the expected number of person counts for ketamine differed across data sources and ranged from 100 in DK-DHR to 9,800 person counts in CDW Bordeaux. For esketamine, the person counts varied from 100 in IQVIA DA Germany to 71,600 in FinOMOP-HUS.

9.8. Data transformation

Analyses were conducted separately for each data source. Before study initiation, test runs of the analytics were performed on a subset of the data sources and on a simulated set of patients and quality control checks were performed. After all the tests were passed, 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. 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.

9.9. Statistical methods

This section described the details of the analysis approach and rationale for the choice of analysis, with reference to the D1.3.8.1 Draft Catalogue of Data Analysis which described the type of analysis in function of the study type.
In principle the type of analysis by study type was fixed, as could be observed from **Table 7**.

Table 7. Description of study types and type of analysis.

Study type	Study classification	Type of analysis
Population Level DUS	Off-the-shelf	- Number of prescriptions - Population-based incidence rates - Population-based prevalence for ketamine and for esketamine
Patient Level DUS	Off-the-shelf	- Characterisation of patient-level features - Frequency and percentage of pre-specified conditions as proxy for indication/s - Frequency and percentage of recorded diagnostic codes - Frequency and percentage of comedication - Estimation of minimum, p25, median, p75, and maximum initially prescribed dose - Estimation of minimum, p25, median, p75, and maximum treatment duration (first drug area) - Estimation of minimum, p25, median, p75, and maximum cumulative treatment duration

DUS = drug utilisation study.

9.9.1 Patient privacy protection

Cell suppression was applied as required by data sources to protect people's privacy. Cell counts <5 were masked.

9.9.2 Main statistical methods

R-packages

We used the R packages *IncidencePrevalence* for population-level estimation of drug utilisation and *CohortCharacteristics*, *PatientProfiles* and *DrugUtilisation* for patient-level drug utilisation analyses including patient-level characterisation.

Drug exposure calculations

Drug eras were defined as follows: exposure starts at the date of the first prescription after a washout of 365 days. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM, using the start and end date of the exposure. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) using the following specifications: two drug eras were merged into one continuous drug era if the distance in days between end of the first era and start of the second era is ≤ 30 days. The time between the two joined eras was considered as exposed by the first era as shown in **Figure 2**, first row.

Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

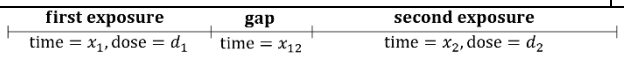


Figure 2. Gap era joint mode.

New user cohort

New users were selected based on their incident prescriptions of ketamine or esketamine after the start of the study. For each patient, at least one year of data visibility was required prior to a prescription. Individuals who initiated treatment are required to not have been exposed to the drug of interest for at least one year prior to the current prescription. If the start date of a prescription did not fulfil the exposure washout criteria of 1 year of no use, the whole exposure was eliminated. New drug user cohort study was used to characterise patient-level drug utilisation in terms of demographics, pre-specified conditions (proxy for indication of use), recorded diagnostic codes, and comedication at the date of incident prescription of ketamine or esketamine.

9.9.3 Methods to derive parameters of interest

Calendar time

Calendar time was determined on the calendar month and calendar year during which the index prescription was issued. The calendar time for subsequent prescriptions was based on the calendar month and calendar year they were issued following the washout period of 365 days.

Age

Age at index date was calculated using January 1st of the year of birth as a proxy for the actual birthday. Date/month was either not present or could not be made available for governance reasons. If available, the date was often set to the first of the month for patient's privacy. The following age groups were used for stratification for population-level analyses:

- All adults: 15–64 years old
- Young adults: 15–34 years old
- Detailed breakdown: <5, 5–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, >85 years old

Sex

Results for population-level analyses were presented overall and stratified by sex.

Indication

Indication was determined based on recordings of pre-defined conditions (see section 9.6.3 – other variables), at the date of the prescription of the respective drug (index date) [primary definition] or during assessment windows 365 before index date. If none of the specific indications was recorded on index date or during the assessment window, but there was a record for any other condition, the person was considered having an "other" indication.

Characterisation of patient-level features

Large-scale patient-level characterisation was conducted. Concepts in the "condition" domain were assessed at the index date and in the window around the index date (1 year prior to the index date). The top 10 diagnostic codes were presented.

9.9.4 Methods to obtain point estimates with confidence intervals of measures of occurrence or association

Population-level drug utilisation study

Incidence and prevalence calculations were conducted for ketamine and for esketamine.

Number of prescriptions

The overall number of prescription records of ketamine and esketamine was provided. For hospital data sources, in addition to overall number of prescriptions, the data was also stratified by healthcare setting including intensive care unit (ICU)/non-ICU setting.

Incidence calculations

Annual incidence rates of ketamine or esketamine prescriptions were calculated as the number of new users with ketamine or esketamine treatment episodes starting after 1 year of no use per 1,000 person-years of the population at risk of getting exposed during the period for each calendar year. Those study participants who enter the denominator population then contributed time at risk up to start of their new ketamine or esketamine prescription during the study period. Multiple prescriptions were allowed, with participants' time contributions paused during a defined outcome washout period of 365 days. Participants without drug exposure contributed time at risk as described above. Time-at-risk of participants who died

were censored at the time of death. Similarly, time at risk of participants who were lost to follow-up were censored at the time of loss to follow-up [last contact]. Participants with data until the end of the study period without experiencing exposure were administratively censored at the end of the study period. Incidence rates were given together with 95% Poisson confidence intervals.

An illustration of the calculation of incidence of selected pre-specified medication of interest is shown below in **Figure 3**. Patient ID 1 and 4 contributed time at risk up to the point at which they become incident users of selected pre-specified medication of interest. Patient ID 2 and 5 were not seen to use pre-specified medication of interest and so contributed time at risk but no incident outcomes. Meanwhile, patient ID 3 first contributed time at risk starting at the day when the washout period of a previous exposure, before study start, has ended, and ending when the next exposure of pre-specified medication of interest was starting. A second period of time at risk again started after the washout period. For person ID 4, only the first and third exposures of pre-specified medication of interest counted as incident use, while the second exposure starts within the washout period of the first exposure. The time between start of the first exposure until the washout period after the second exposure was not considered as time at risk.

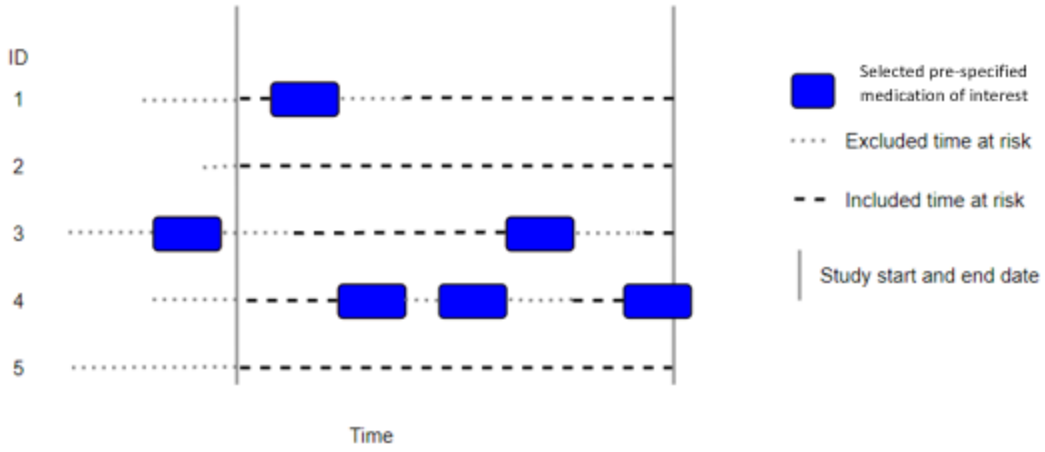


Figure 3. Incidence example.

Prevalence calculations

Prevalence was calculated as monthly and annual period prevalence, which summarises the total number of individuals who use the drug of interest during a given month and year divided by the population at risk of getting exposed during that month and year. Therefore, period prevalence gave the proportion of individuals exposed at any time during a specified interval. Binomial 95% confidence intervals was calculated.

An illustration of the calculation of period prevalence is shown below in **Figure 4**. Between time t+2 and t+3, study participants ID1 and ID4 were identified as users of pre-selected medication of interest, giving a prevalence of 40%. Meanwhile, for the period t to t+1 all five participants also have some observation time during the year with one of the five study participants being a user of pre-selected medication of interest.

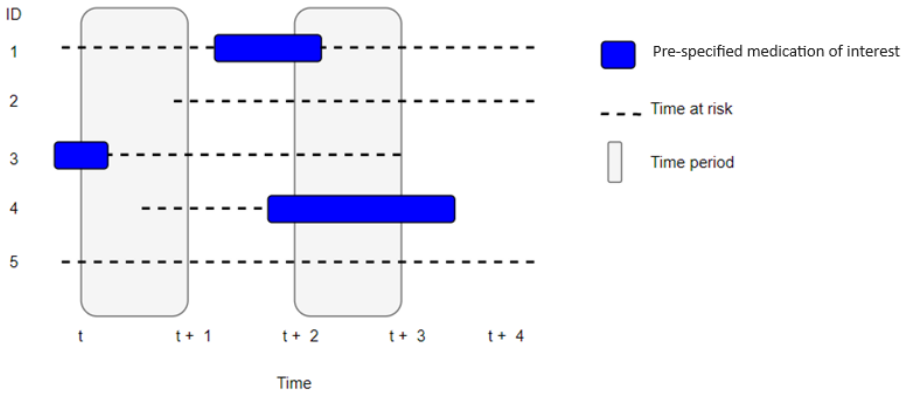


Figure 4. Period prevalence example.

Patient-level drug utilisation study

New drug user patient-level characteristics on index date

For concepts extracted at the index date, the number of persons (N, %) with a record within the pre-specified time windows was provided.

Indication

The number of persons (N, %) with a record of the respective pre-specified condition or procedure was provided. If a person had a record of more than one specific indication, that person was included in both specific indication groups separately.

Treatment duration

Treatment duration was calculated as the duration of the first treatment era during the study period. Treatment duration was summarised providing the minimum, quartiles, maximum duration of treatment era. For data sources, where duration cannot be calculated due to e.g., missing information on quantity or dosing, treatment duration was not provided. Cumulative duration was also calculated during the study period and was summarised by providing the minimum, quartiles, and maximum.

9.9.5 Methods to deal with missing data

For the drug utilisation studies we assumed that the absence of a prescription record meant that the person did not receive the respective drug. For indications, we assumed that the missingness of a record of the respective condition meant that that condition was not the indication for the drug prescription.

9.9.6 Sensitivity analysis

Please see **section 9.11** Deviations from the protocol.

9.10. Evidence synthesis

Results from analyses described in **section 9.9** were presented separately for each data source and no meta-analysis of results was conducted.

9.11. Deviations from the protocol

Based on the results of cohort diagnostics, the inclusion criterion requiring 365 days of prior history impacted the sample size. Therefore, a sensitivity analysis was performed without this criterion.

10. DATA MANAGEMENT

10.1. Data management

All data sources were mapped to the OMOP common data model. This enabled the use of standardised analytics and tools across the network since the structure of the data and the terminology system was 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 executed the study code against their data source containing patient-level data and then returned the results set which only contained aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

10.2. Data storage and protection

For this study, data sources from various EU member states process personal data from patients 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 data sources used in this study are 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 were run, which generate non-identifiable aggregate summary results.

11. QUALITY CONTROL

General data source quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it is expected that data partners ran the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provided numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that described the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality was 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 had one or more subcategories and were 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

When defining cohorts for medicinal products, a systematic search of possible codes for inclusion was identified using *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This software allowed the user to define a search strategy and using this then queried the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition,

DrugExposureDiagnostics was run to assess the use of different codes across the data sources contributing to the study.

The study code was based on four R packages namely the *CohortCharacteristics*, *PatientProfiles*, *IncidencePrevalence*, and *DrugUtilisation* packages. These packages included numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R packages were made publicly available via GitHub.

12. RESULTS

The full set of the results from this study can be assessed through an interactive web-application ("Shiny app") at EUPAS1000000436. This resource provides access to overall findings as well as detailed incidence and prevalence metrics, including the number of events, population size, and person-years (PYs) for each data source, stratified by calendar month and year throughout the study period.

12.1. Population-level drug utilisation

12.1.1 Participants

Table 8 shows the total number of individuals included in the estimation of incidence rates for ketamine and esketamine within the context of the population-level drug utilisation study. The results are stratified by data source and further presented by calendar year. Ketamine prescriptions were identified in five out of the six data sources included in this study: CDW Bordeaux, CPRD GOLD, FinOMOP-HUS, IMASIS, and IQVIA DA Germany. In contrast, esketamine prescription records were observed in four out of the six data sources, specifically DK-DHR, FinOMOP-HUS, IMASIS, and IQVIA DA Germany.

Table 8. Number of individuals during the study period, per calendar year and data source.

	Ketamine					Esketamine			
Year	CDW Bordeaux	CPRD-GOLD	FinOMOP-HUS	IMASIS	IQVIA DA Germany	DK-DHR	FinOMOP-HUS	IMASIS	IQVIA DA Germany
2014	581,590	6,217,453	-	319,859	7,301,904	5,597,856	1,348,319	319,877	7,301,907
2015	602,064	5,717,187	-	318,217	7,756,542	5,631,584	1,392,638	318,238	7,756,543
2016	616,294	4,898,921	1,430,162	315,558	8,136,543	5,675,562	1,430,064	315,580	8,136,546
2017	622,430	4,438,517	1,458,302	313,049	8,690,483	5,713,668	1,458,148	313,067	8,690,485
2018	619,344	4,139,939	1,481,772	311,830	9,047,536	5,744,829	1,481,564	311,860	9,047,536
2019	606,874	3,995,468	1,524,099	311,457	9,097,230	5,770,154	1,523,722	311,492	9,097,231
2020	580,220	3,759,092	1,547,418	311,167	9,257,275	5,794,321	1,546,905	311,202	9,257,274
2021	536,225	3,432,664	1,547,833	298,485	9,261,994	5,820,251	1,546,841	298,527	9,261,990
2022	486,216	3,132,252	1,475,729	273,083	8,841,468	5,852,376	1,474,255	-	8,841,467
2023	410,760	2,980,749	1,270,082	232,219	7,590,384	5,905,840	1,268,645	232,282	7,590,381

CDW Bordeaux = Clinical Data Warehouse Bordeaux; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-HUS = Hospital District of Helsinki and Uusimaa; IMASIS = Institut Municipal Assistència Sanitària Information System; IQVIA DA Germany = IQVIA Disease Analyzer Germany. "-" Suppressed rows due to the censored event counts.

12.1.2 Descriptive data and main results

12.1.2.1 Incidence rates for ketamine and for esketamine over time

Figures 5–8 present the monthly and annual incidence rates of ketamine and esketamine, expressed as the number of treatment episodes of the drugs of interest per 1,000 PYs across different data sources during the study period from 2014 to 2023. The primary analysis included individuals who met the inclusion criterion of having at least one year of data visibility prior to being eligible for study inclusion (**Figures 5A–8A**). Additionally, a sensitivity analysis was performed to assess the robustness of the findings, removing the requirement of one year of prior data visibility (**Figures 5B–8B**).

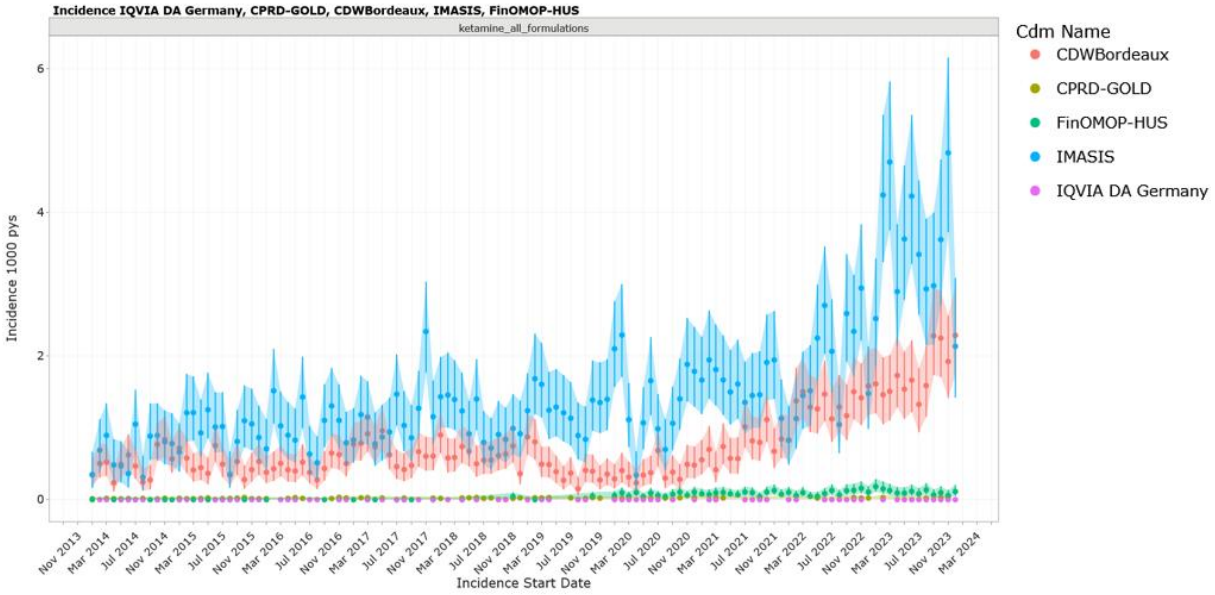
Overall, monthly and annual incidence rates of ketamine prescriptions showed distinct trends across various data sources (**Figures 5A–6A**). In primary care data sources, including CPRD GOLD and IQVIA DA Germany, both the monthly and annual incidence rates of ketamine use were very low and stable over time, with incidence rates below 1 per 1,000 PYs. In contrast, hospital-based data sources such as CDW Bordeaux and IMASIS displayed initially low monthly and annual incidence rates, followed by an increase from 2021 onwards. In IMASIS, the monthly incidence rates increased from 0.35 per 1,000 PYs in 2014 to 4.8 per 1,000 PYs in 2023, while in CDW Bordeaux they ranged from 0.35 per 1,000 PYs in 2014 to 2.13 per 1,000 PYs in 2023. A similar pattern was observed for annual incidence rates. In FinOMOP-HUS, ketamine prescriptions were recorded only at very low levels prior to 2020. A slight increase was observed thereafter, with monthly and annual incidence rates reaching 0.11 per 1,000 PYs by 2023.

The results of the sensitivity analysis for ketamine were consistent with those observed in the primary analysis (**Figures 5B–6B**). In the primary care data sources, the incidence rates of ketamine prescriptions were very low and stable over time, with no notable differences in monthly or annual estimates compared to the primary analysis. Hospital-based data sources generally showed a similar temporal trend as in the primary analysis, however, the monthly incidence rate estimates were slightly higher (CDW Bordeaux: 0.66 per 1,000 PYs in 2014 to 3.2 per 1,000 PYs in 2023; IMASIS: 0.48 per 1,000 PYs in 2014 to 4.98 per 1,000 PYs in 2023). In contrast, the monthly incidence rates in FinOMOP-HUS were comparable with those observed in the primary analysis. A similar pattern per hospital-based data source was observed for annual incidence rates.

Figures 7–8 present the monthly and annual incidence rates for esketamine prescriptions across various data sources. Both monthly and annual incidence rates were consistently very low across the primary care data source (IQVIA DA Germany), the hospital-based data source (IMASIS), and the registry (DK-DHR), with incidence rates generally below 0.02 per 1,000 PYs (**Figures 7A–8A**). In contrast, data from the FinOMOP-HUS indicated minimal recorded use of esketamine in 2014, with incidence rates around 0.3 per 1,000 PYs, followed by a gradual and sustained increase over time, reaching approximately 11 per 1,000 PYs by 2023 (**Figures 7A–8A**).

The sensitivity analysis of esketamine yielded results consistent with those of the primary analysis with unchanged trends over time (**Figures 7B–8B**).

A



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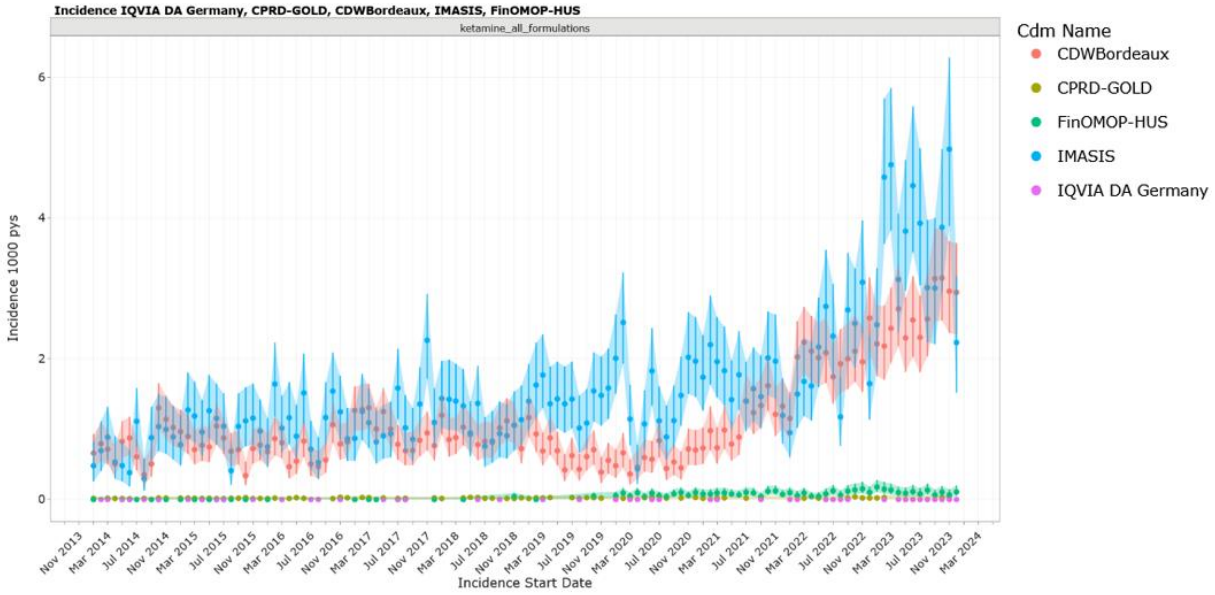
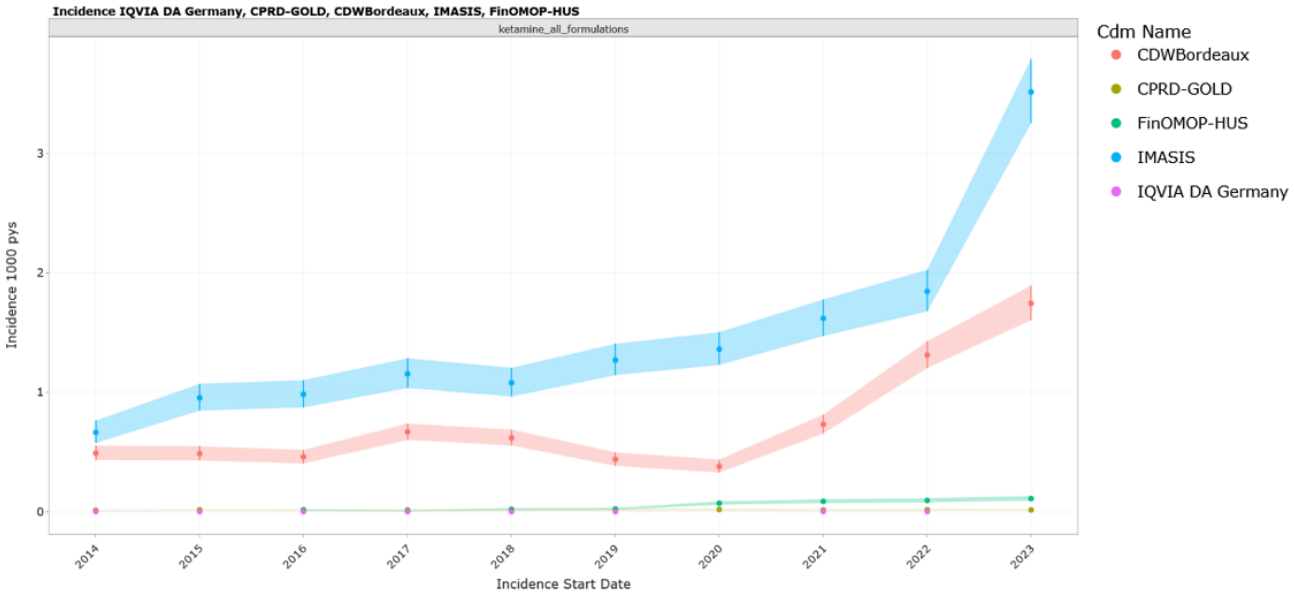


Figure 5. Monthly incidence rates of ketamine prescriptions across data sources during the study period. Panel A shows incidence rates from the primary analysis, which was restricted to the study population with at least one year of data visibility prior to becoming eligible for study inclusion. Panel B presents the results from the sensitivity analysis, which did not require prior data visibility.

A



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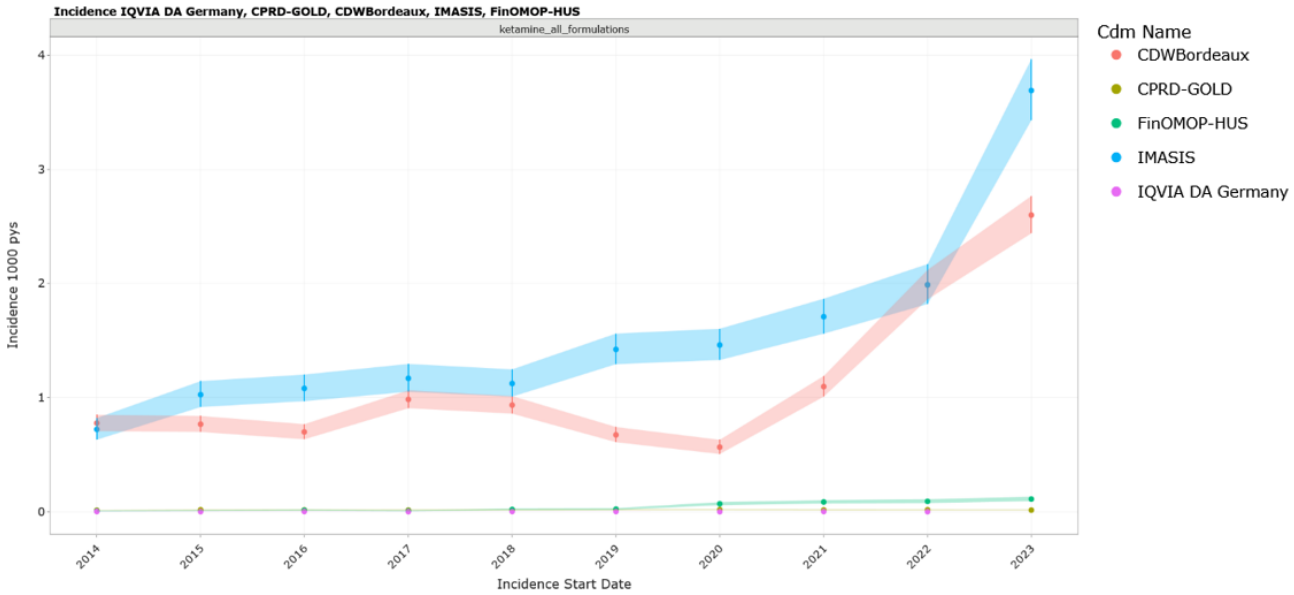
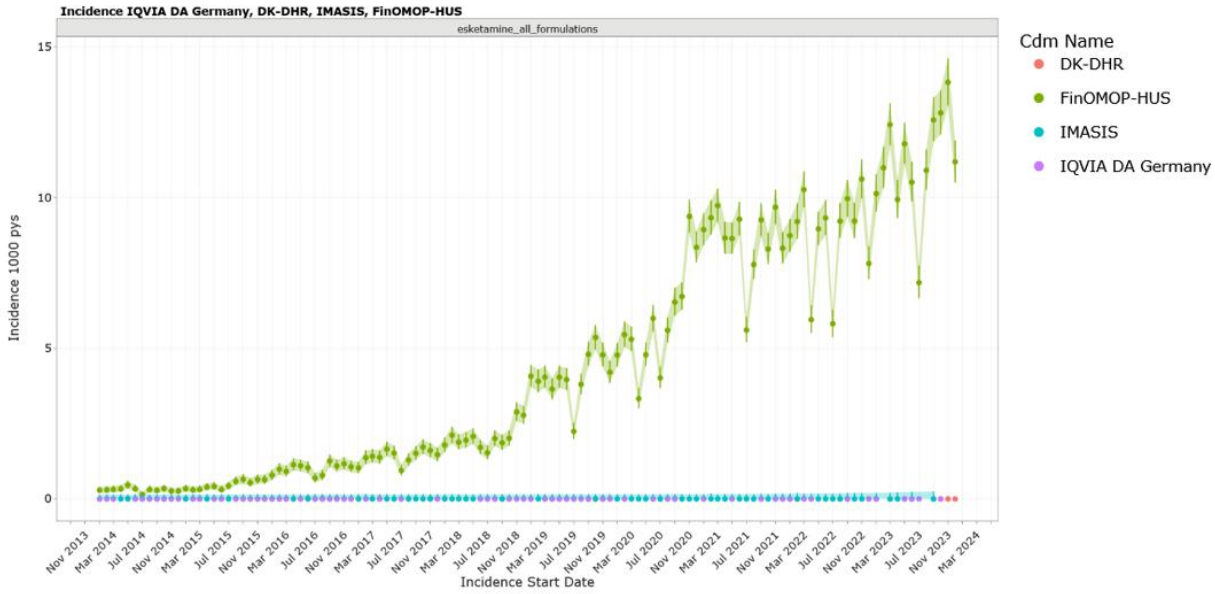


Figure 6. Annual incidence rates of ketamine prescriptions across data sources during the study period. Panel A shows incidence rates from the primary analysis restricted to the study population with at least one year of data visibility prior to becoming eligible for study inclusion. Panel B presents results from the sensitivity analysis, which did not require prior data visibility.

A



B

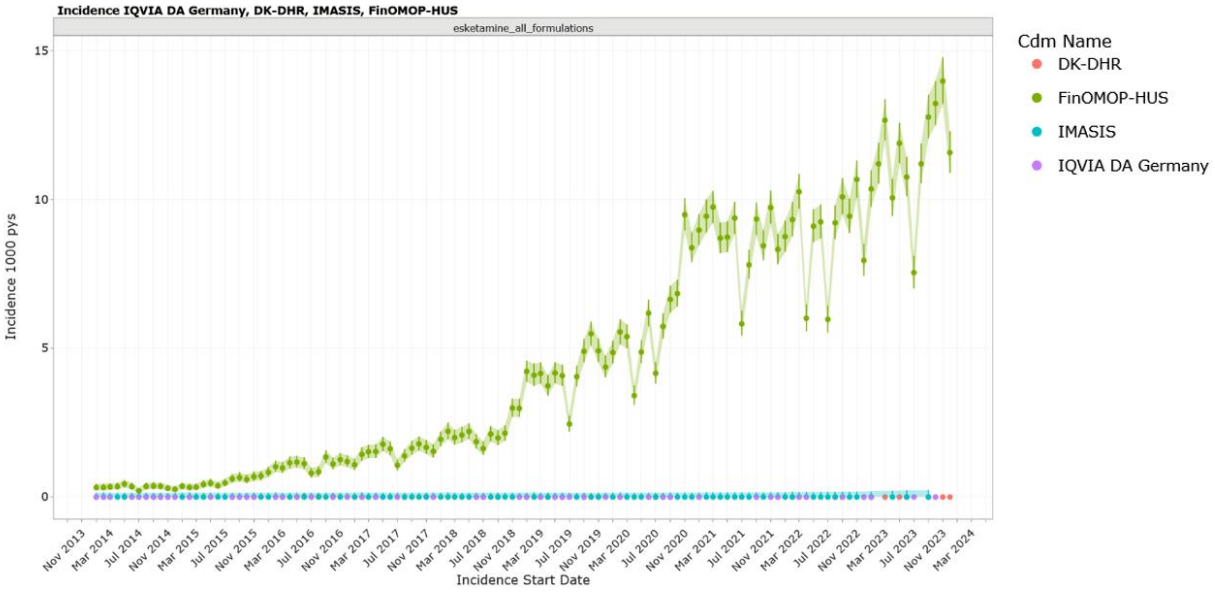
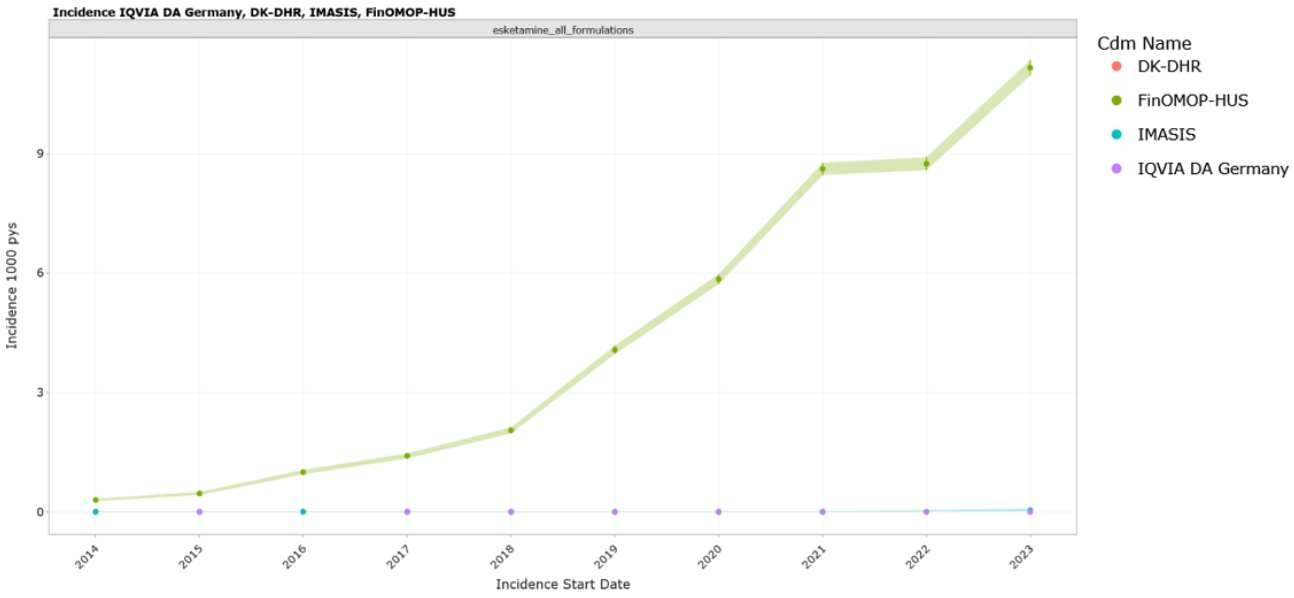


Figure 7. Monthly incidence rates of esketamine prescriptions across data sources during the study period. Panel A shows incidence rates from the primary analysis restricted to the study population with at least one year of data visibility prior to becoming eligible for study inclusion. Panel B presents the results from the sensitivity analysis, which did not require prior data visibility.

A



B

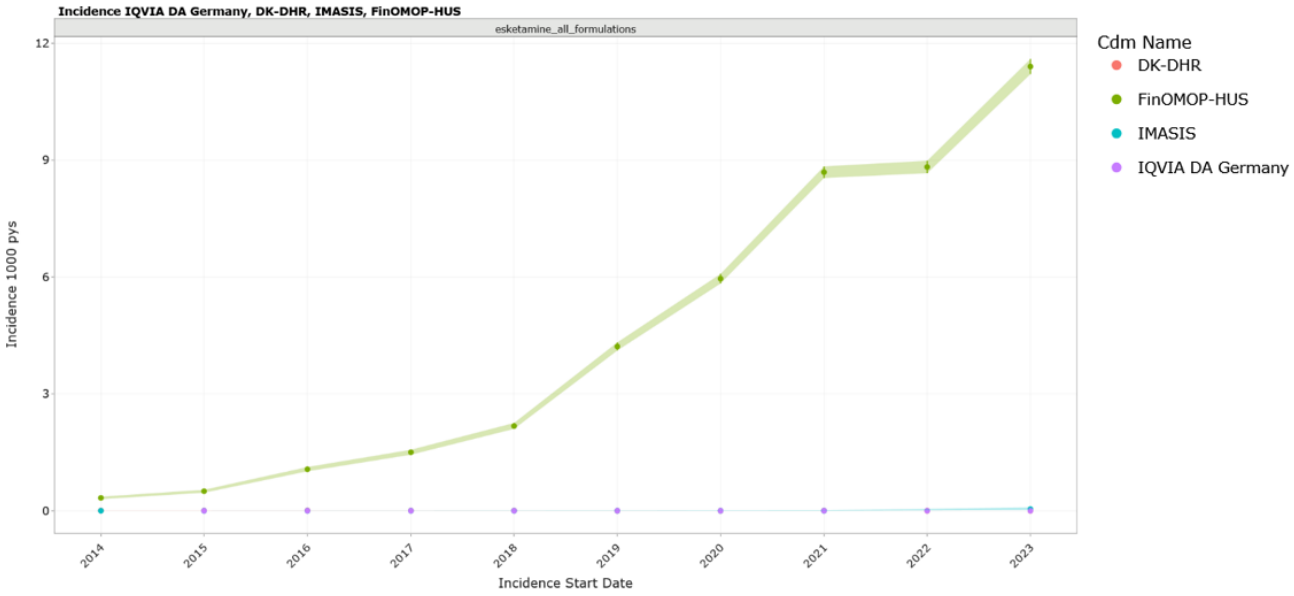


Figure 8. Annual incidence rates of esketamine prescriptions across data sources during the study period. Panel A displays results from the primary analysis, limited to individuals with at least one year of prior data visibility before becoming eligible for inclusion. Panel B presents the sensitivity analysis, without a prior observation requirement.

12.1.2.2 Incidence rates for ketamine and for esketamine over time by age groups

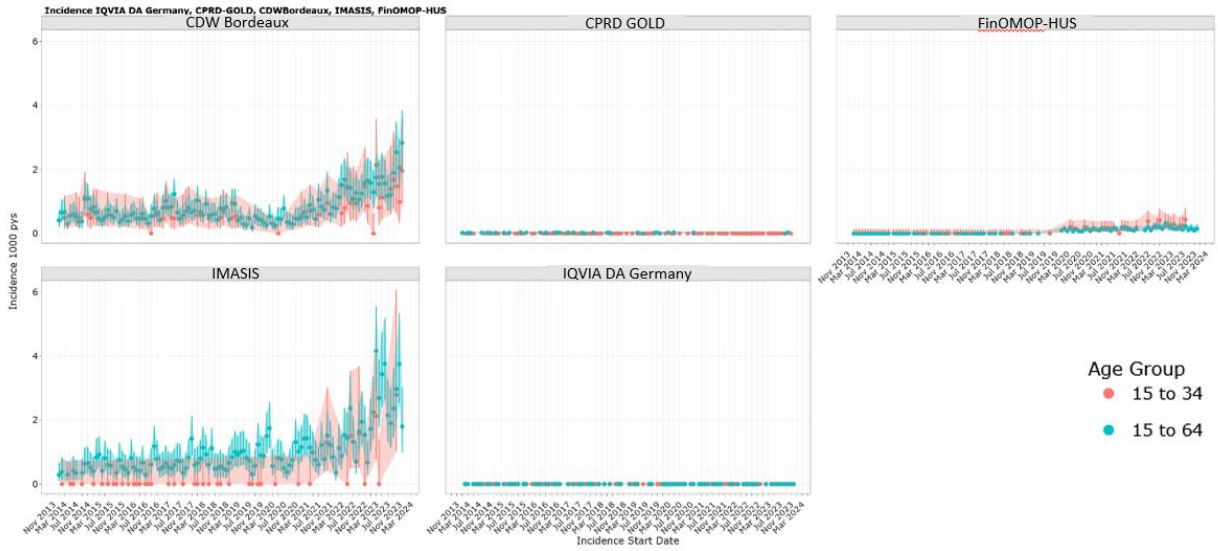
Figures 9–12 show the monthly and annual incidence rates of ketamine and esketamine use in young adults (15 to 34 years) and broader adult population (15 to 64 years). Additionally, **Figures 1–4** in **ANNEX III** provide further stratification, displaying incidence rates by more granular age categories. The primary analysis included individuals who met the inclusion criterion of having at least one year of data visibility prior to being eligible for study inclusion (**Figures 9A–12A, Figures 1A–4A** in **ANNEX III**). Additionally, a sensitivity analysis was performed to assess the robustness of the findings, removing the requirement of one year of prior data visibility (**Figures 9B–12B, Figures 1B–4B** in **ANNEX III**).

Across hospital-based data sources, monthly and annual incidence rates of ketamine remained low overall and showed similar trends between the broader adult group and young adults (**Figures 9A–10A)**. Incidence rates in primary care data sources were very low, showed no variation over time, and were also comparable between these age groups (**Figures 9A–10A**). The results from sensitivity analyses were consistent with the primary analyses (**Figures 9B–10B**).

Further granular age stratification revealed that incidence rates of ketamine use tended to be higher in older age groups, particularly among individuals aged 55 years and older (**Figures 1A–2A** in **ANNEX III)**. Incidence rates were lowest in the youngest age groups. This pattern was observed for both monthly and annual incidence rates of ketamine in hospital data sources CDW Bordeaux and IMASIS but was not evident in primary care data and in FinOMOP-HUS. The results from the sensitivity analyses were consistent with the primary analyses (**Figures 1B–2B** in **ANNEX III**).

For esketamine, both monthly and annual incidence rates were very low and comparable between young and older adults and more granular age categories in most data sources (**Figures 11A–12A, Figures 3A–4A** in **ANNEX III)**. In contrast, FinOMOP-HUS showed higher incidence rates in older age groups, particularly among individuals older than 55–64 years (**Figures 11B–12B, Figures 3B–4B** in **ANNEX III)**. These findings were consistent in both the primary and sensitivity analyses.

A



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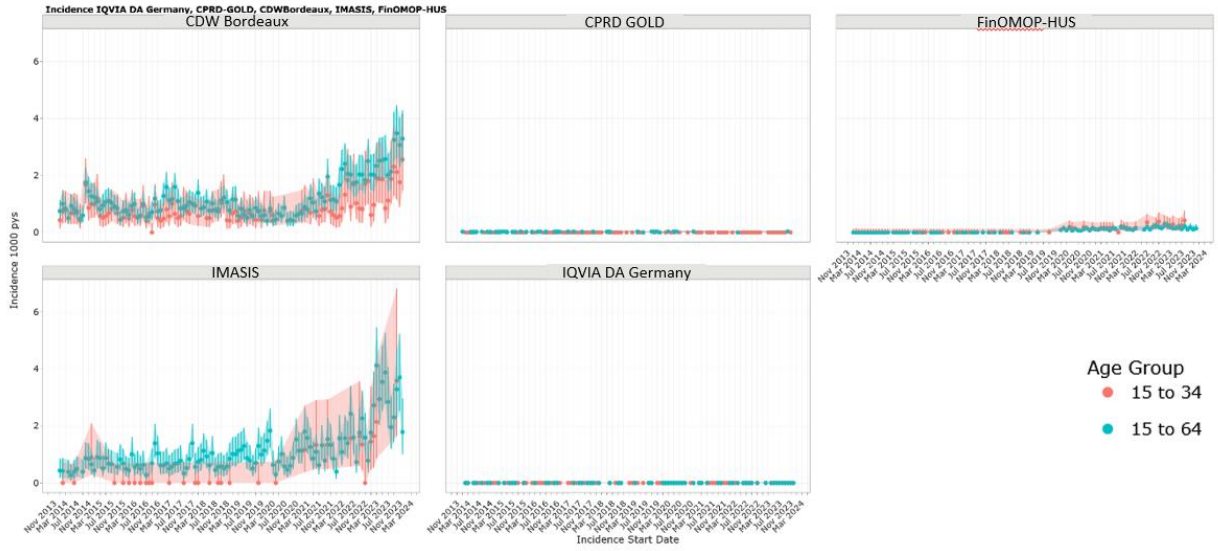
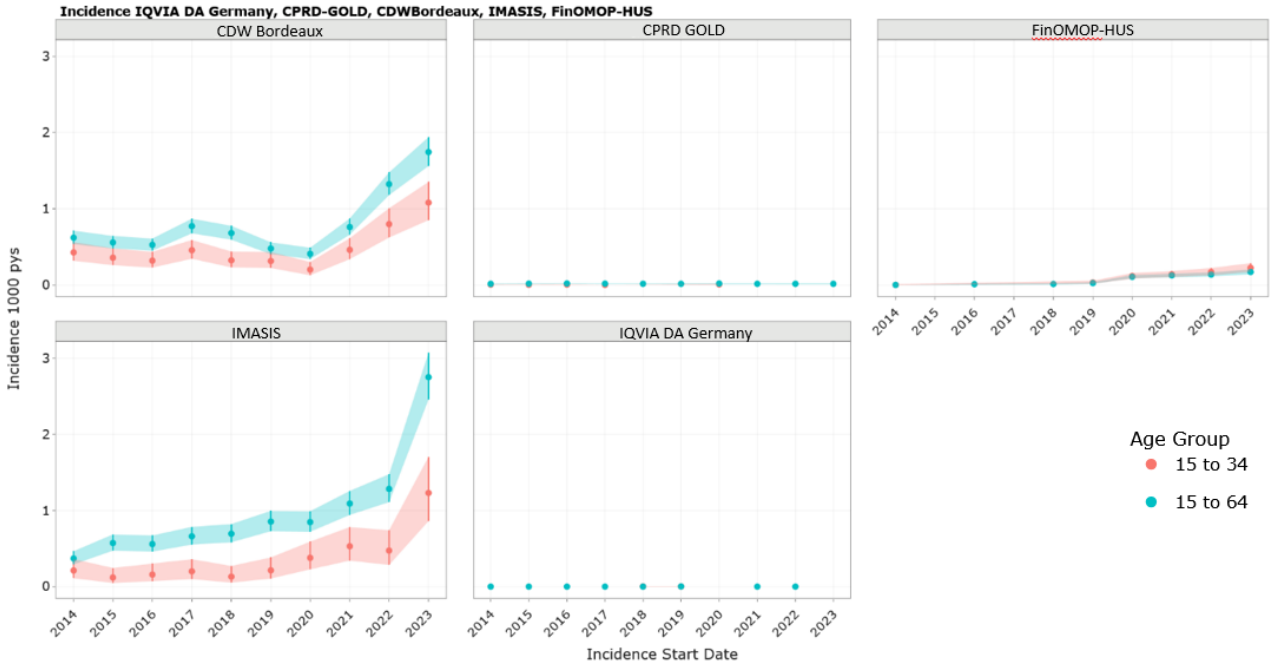


Figure 9. Monthly incidence rates of ketamine prescriptions across data sources during the study period stratified by age groups, including all adults (15–64 years) and young adults (15–34 years). Panel A shows incidence rates restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



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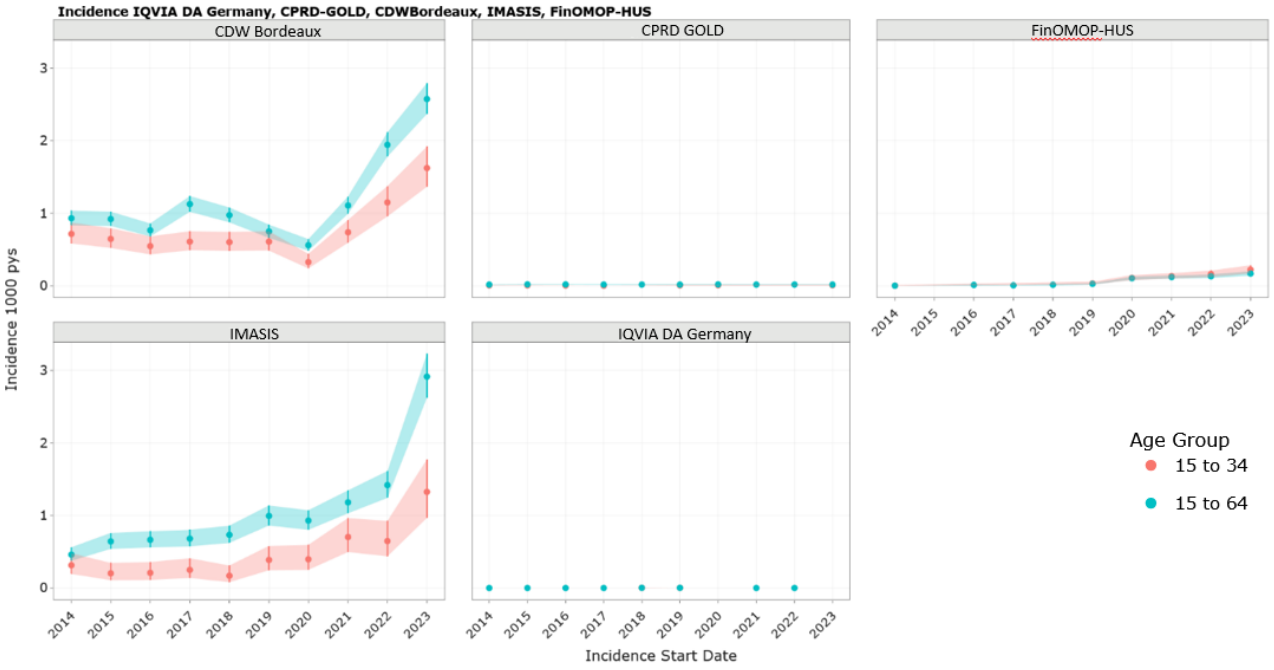
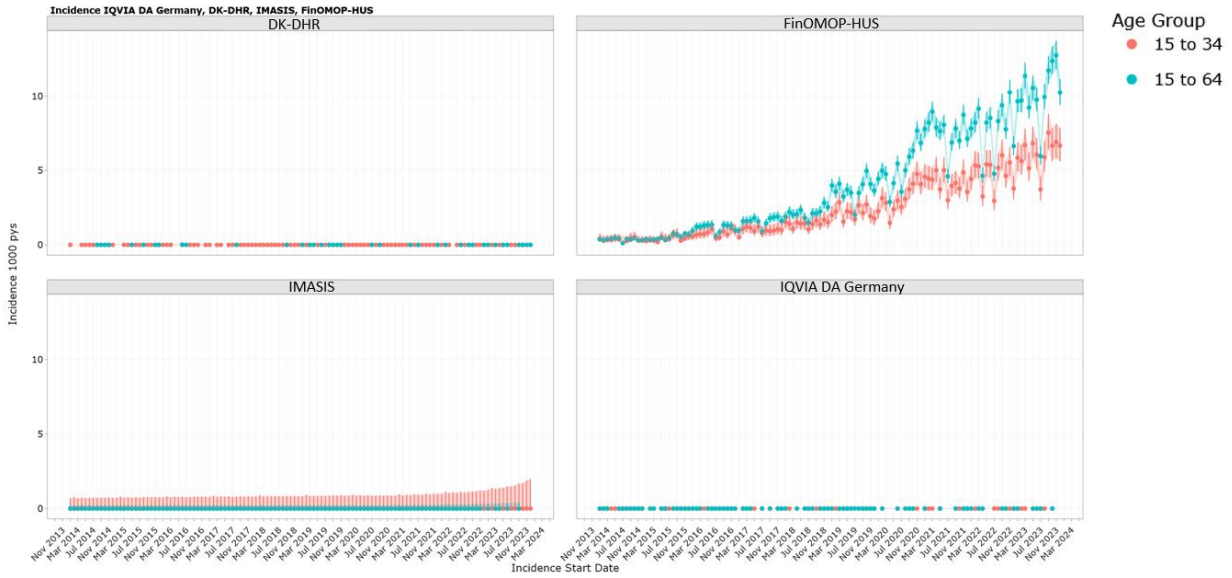


Figure 10. Annual incidence rates of ketamine prescriptions across data sources during the study period stratified by age groups, including all adults (15–64 years) and young adults (15–34 years). Panel A shows incidence rates restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



B

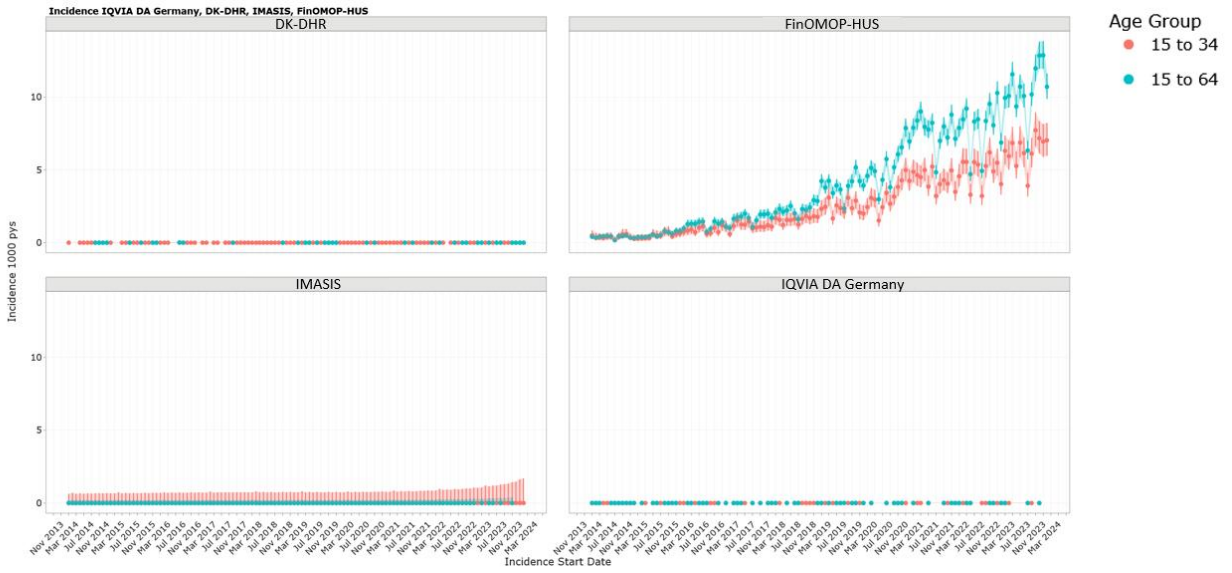
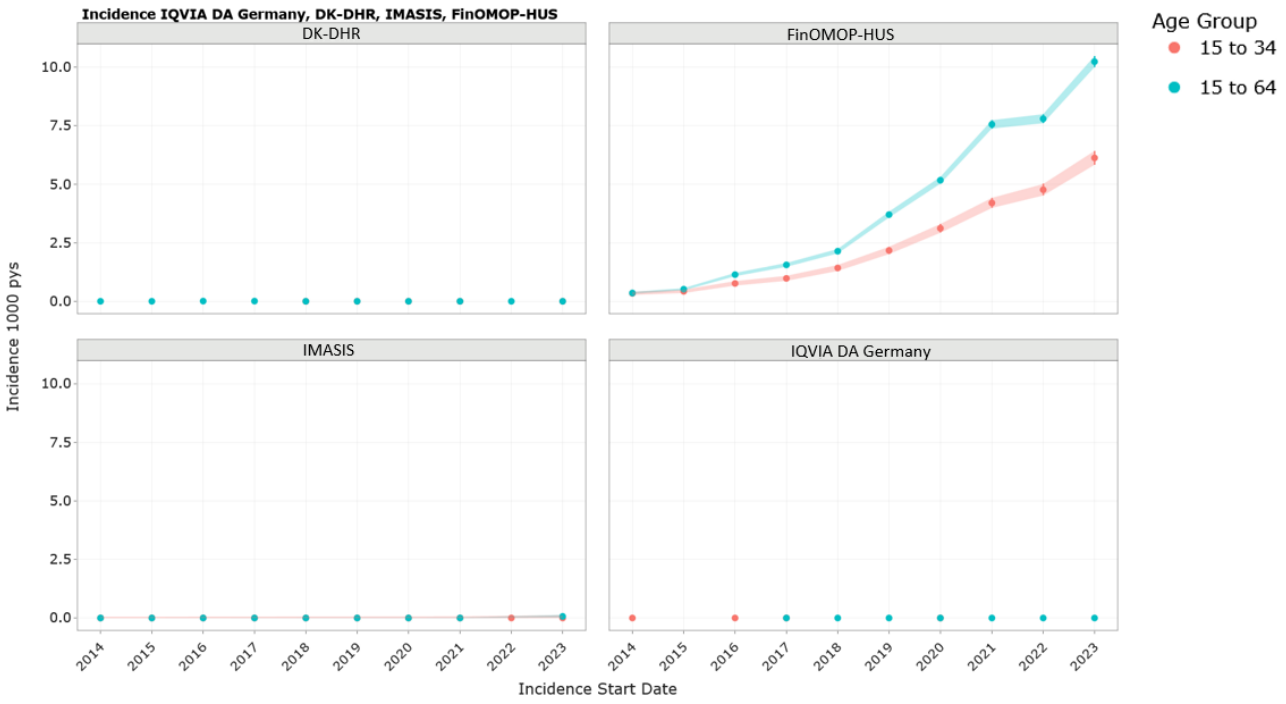


Figure 11. Monthly incidence rates of esketamine prescriptions across data sources during the study period stratified by age groups. Panel A shows incidence rates restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



B

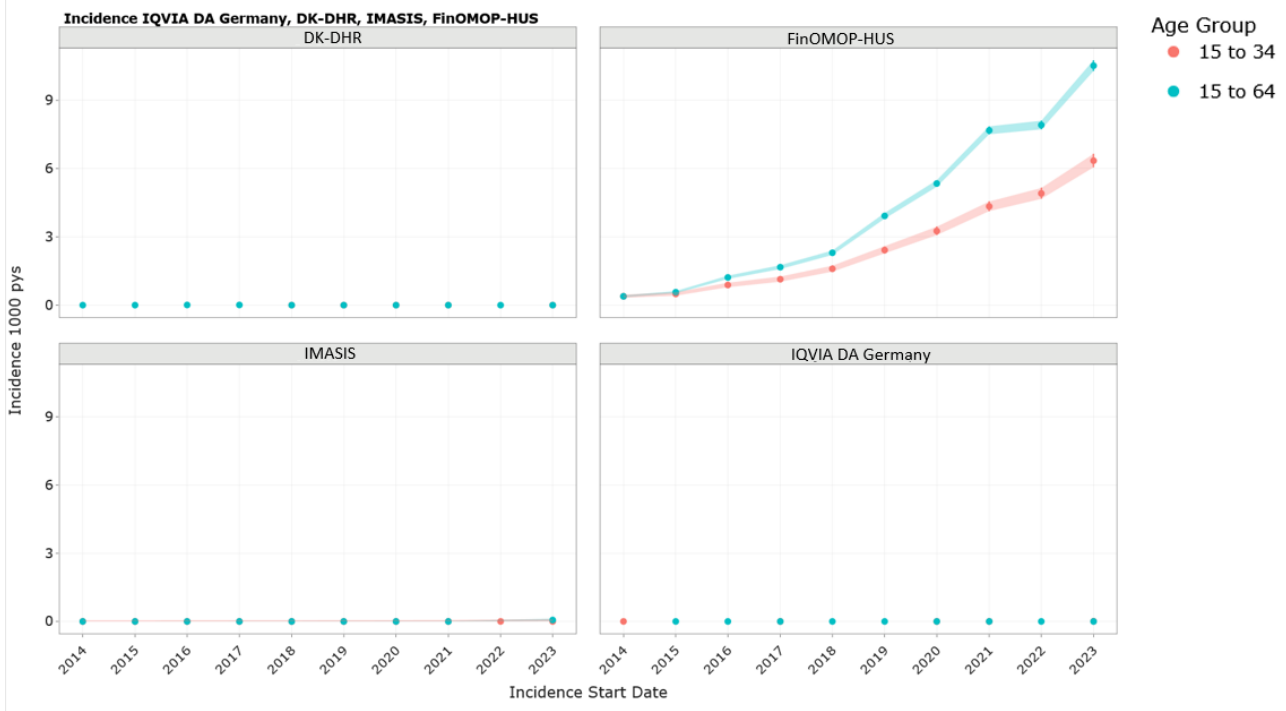


Figure 12. Annual incidence rates of esketamine prescriptions across data sources during the study period stratified by age groups. Panel A shows incidence rates restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

12.1.2.3 Incidence rates for ketamine and for esketamine over time by sex

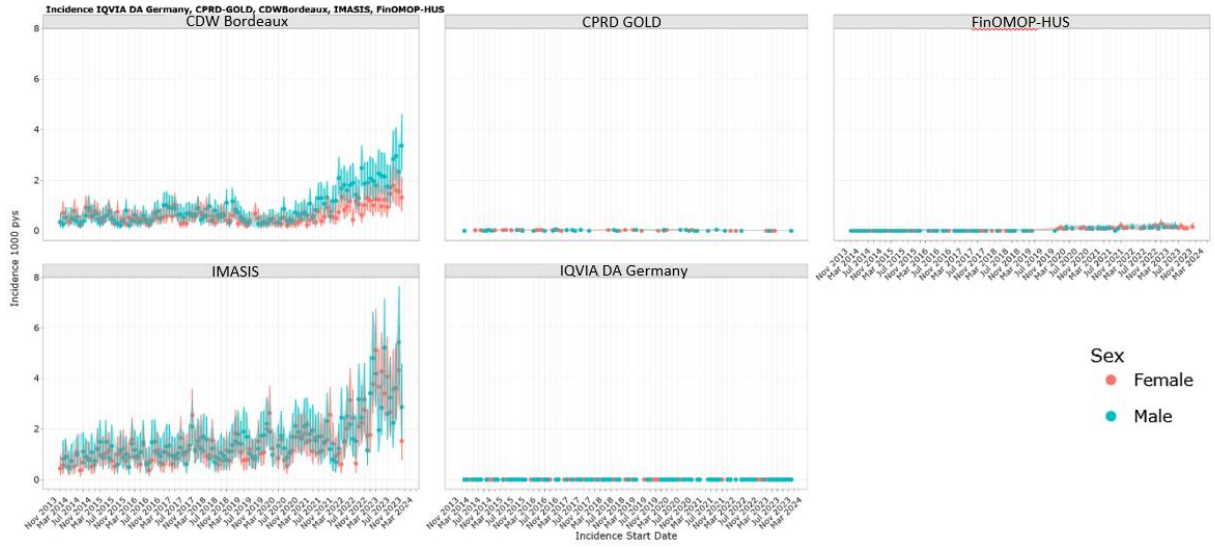
Figures 13–16 present the monthly and annual incidence rates of ketamine and esketamine stratified by sex.

Overall, distinct trends were observed across the different data sources in the primary analysis of ketamine incidence rates (**Figures 13A–14A**). In the primary care data sources (CPRD-GOLD and IQVIA DA Germany) and the hospital-based data sources FinOMOP-HUS and IMASIS, incidence rates for ketamine were comparable between males and females, with no notable sex-based differences in prescribing patterns. CDW Bordeaux, another hospital-based data source, showed comparable incidence rates for both sexes until 2020, after which a divergence emerged, with higher incidence rates observed among males compared to females (**Figures 13A–14A**).

The sensitivity analysis, which removed the requirement for one year of prior data visibility, largely corroborated the primary findings (**Figures 13B–14B**). The divergence between sexes in CDW Bordeaux became slightly more pronounced toward the end of the observation period (**Figures 13B–14B**).

For esketamine, the primary analysis showed no significant difference between incidence rates in males and females in DK-DHR, IMASIS, and IQVIA DA Germany, while the incidence rates were higher in males in FinOMOP-HUS (**Figures 15A–16A**). The results from the sensitivity analysis were comparable to the results from the primary analysis (**Figures 15B–16B**).

A



B

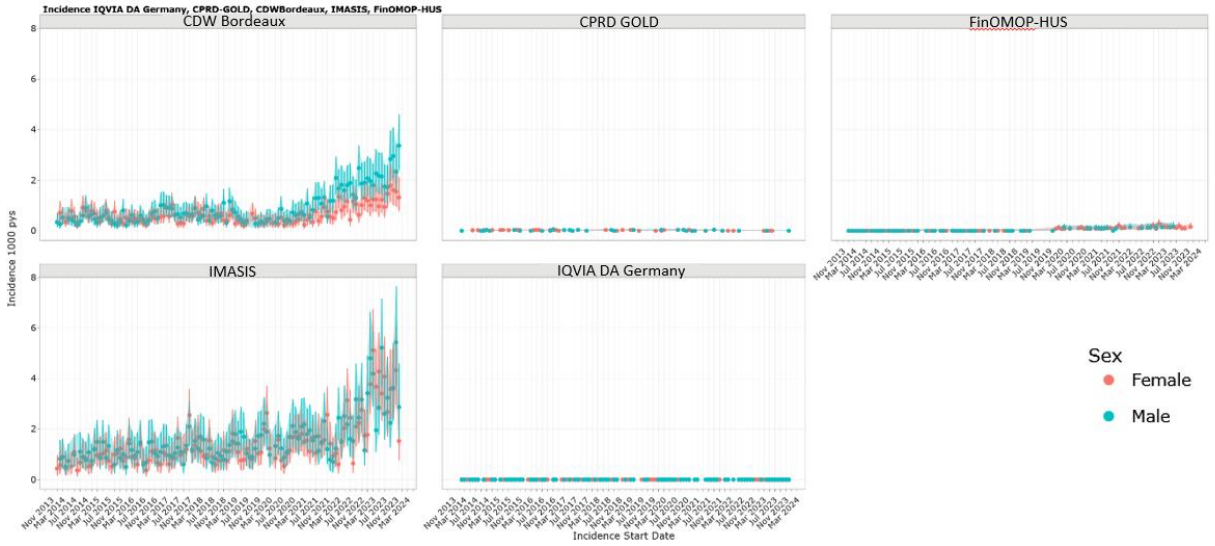
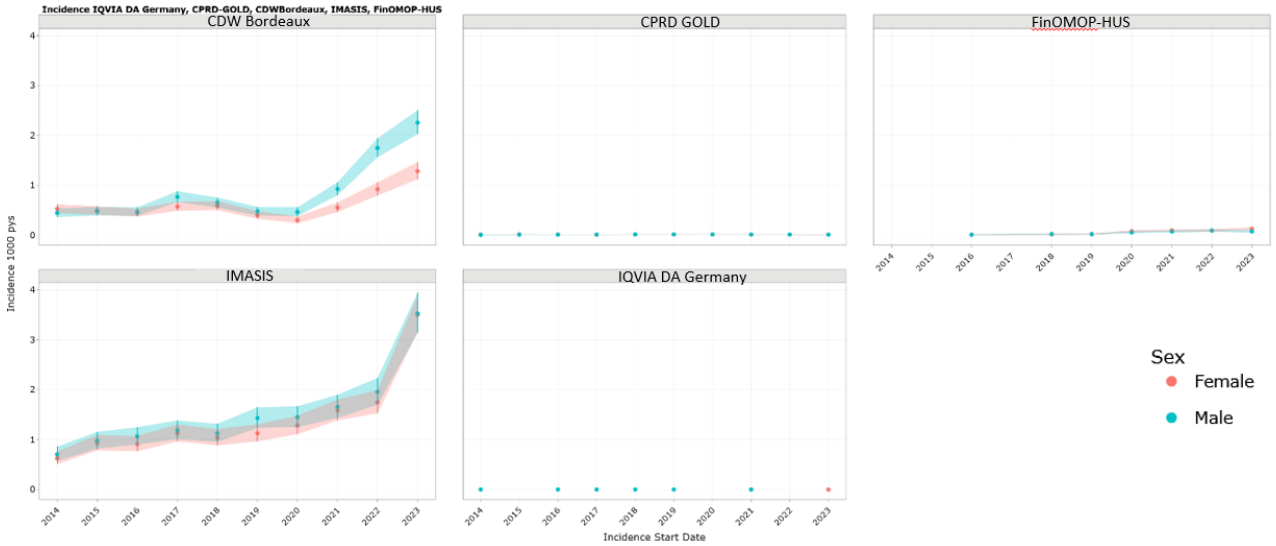


Figure 13. Monthly incidence rates of ketamine prescriptions across data sources during the study period stratified by sex. Panel A shows incidence rates restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



B

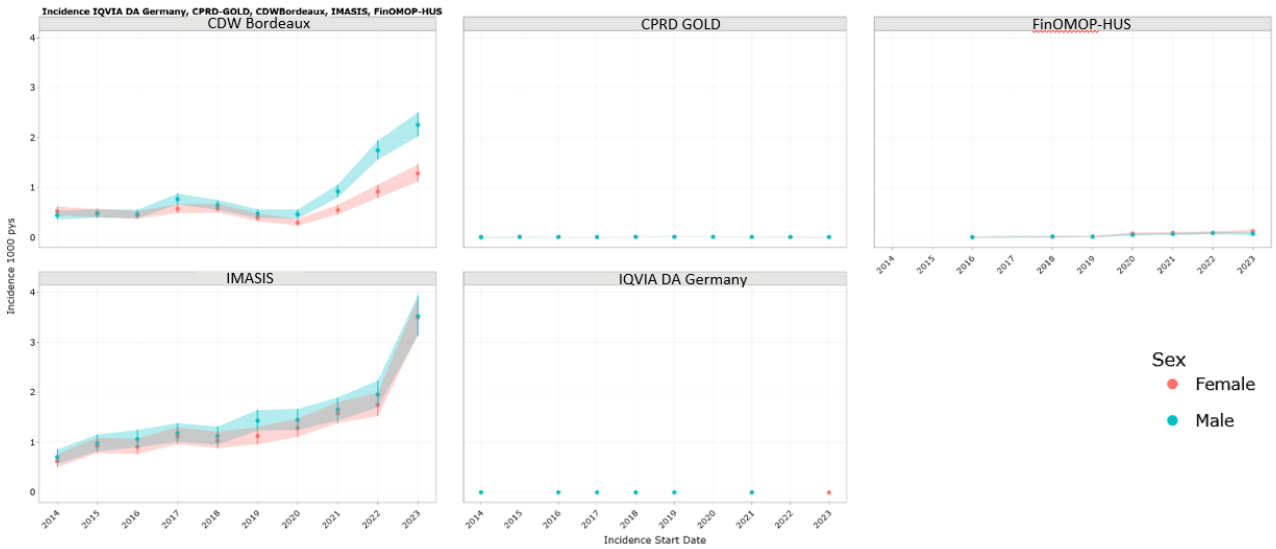
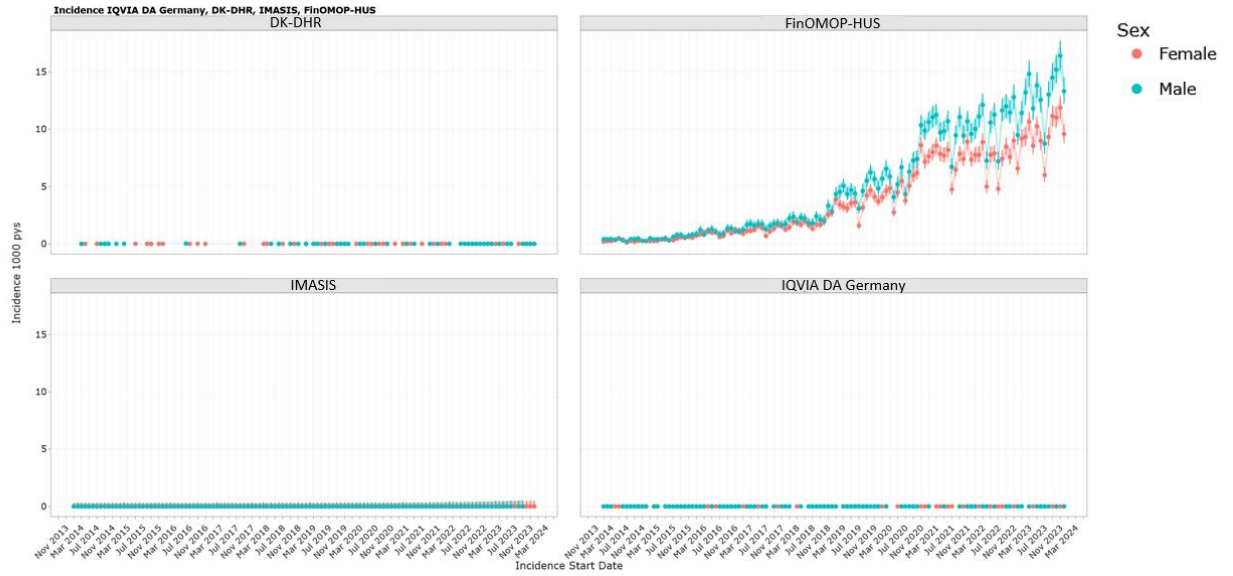


Figure 14. Annual incidence rates of ketamine prescriptions across data sources during the study period stratified by sex. Panel A shows incidence rates restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



B

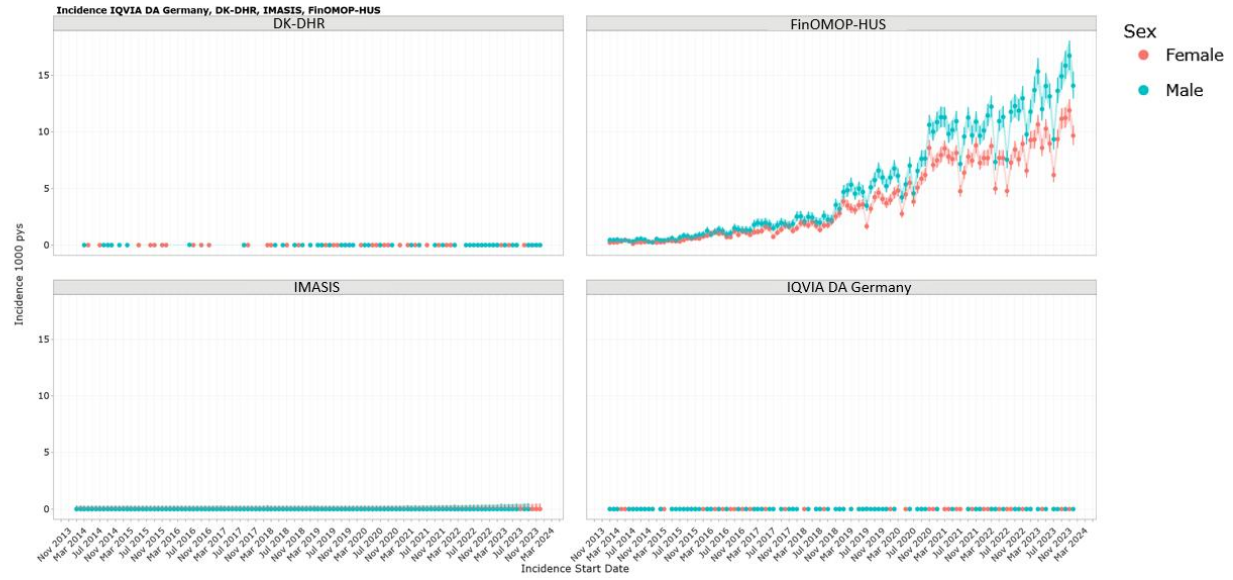
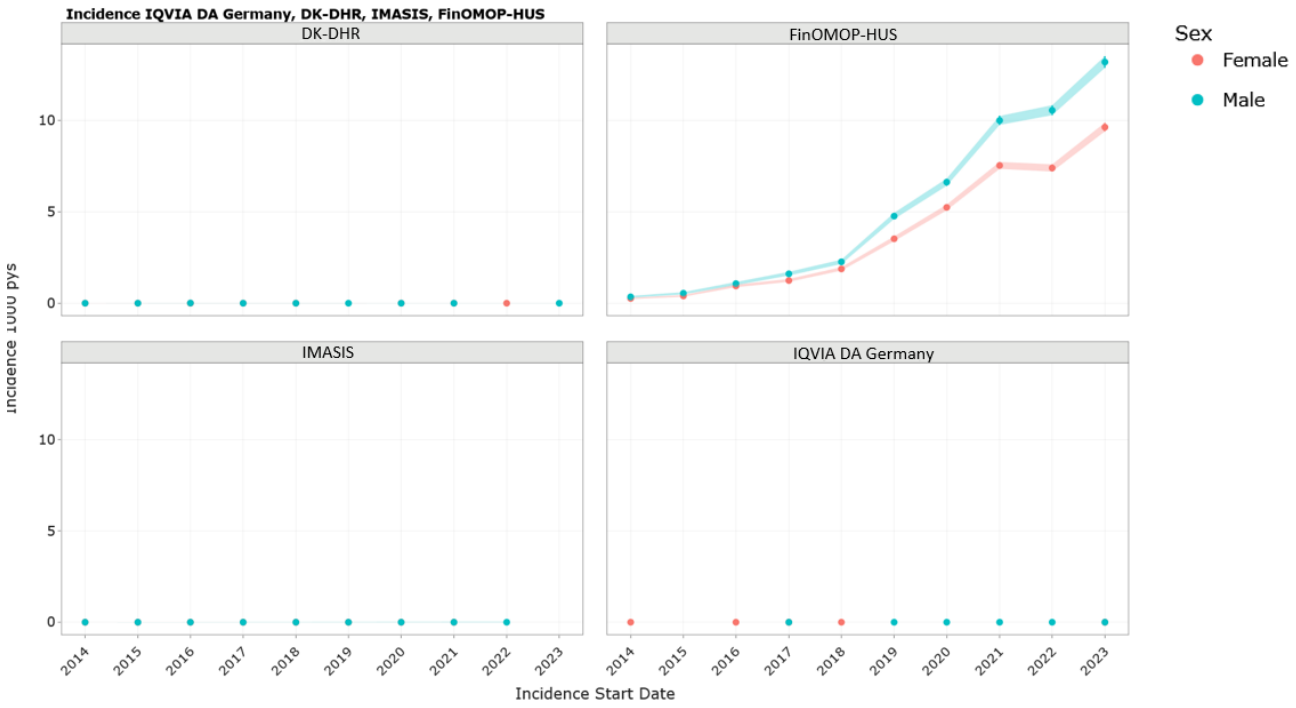


Figure 15. Monthly incidence rates of esketamine prescriptions across data sources during the study period stratified by sex. Panel A shows incidence rates restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



B

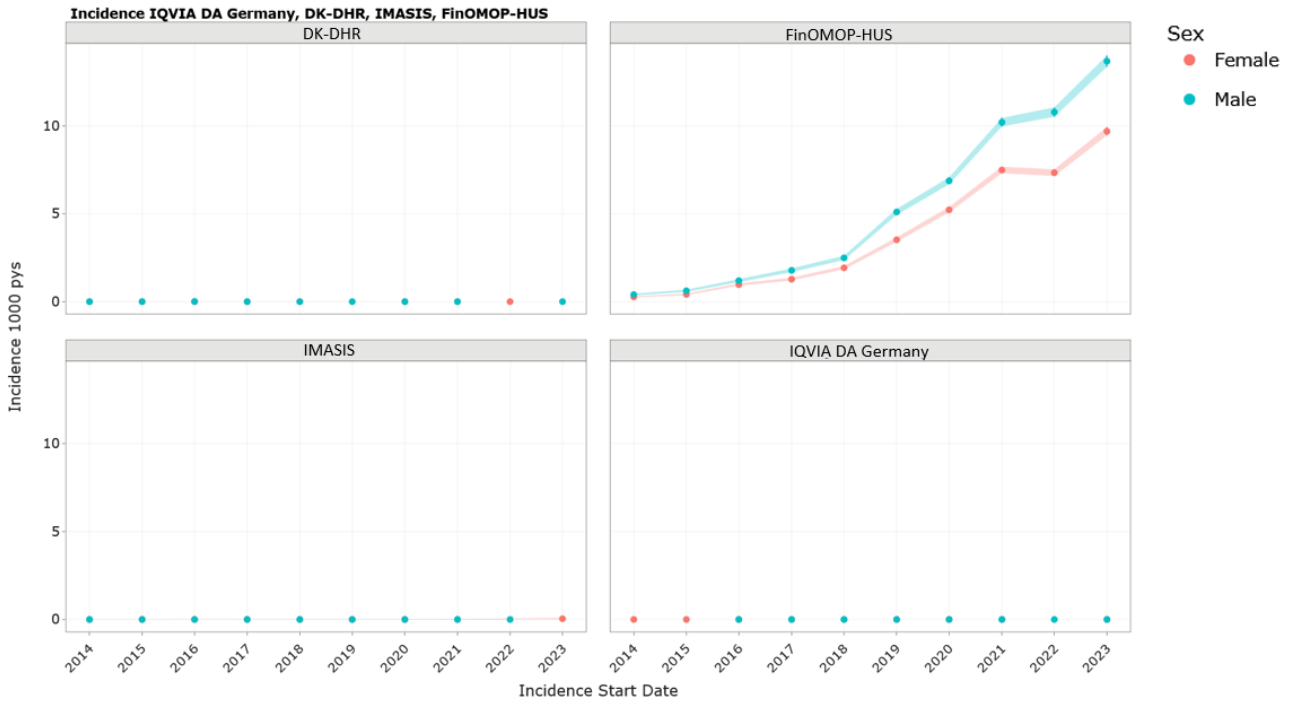


Figure 16. Annual incidence rates of esketamine prescriptions across data sources during the study period stratified by sex. Panel A shows incidence rates restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

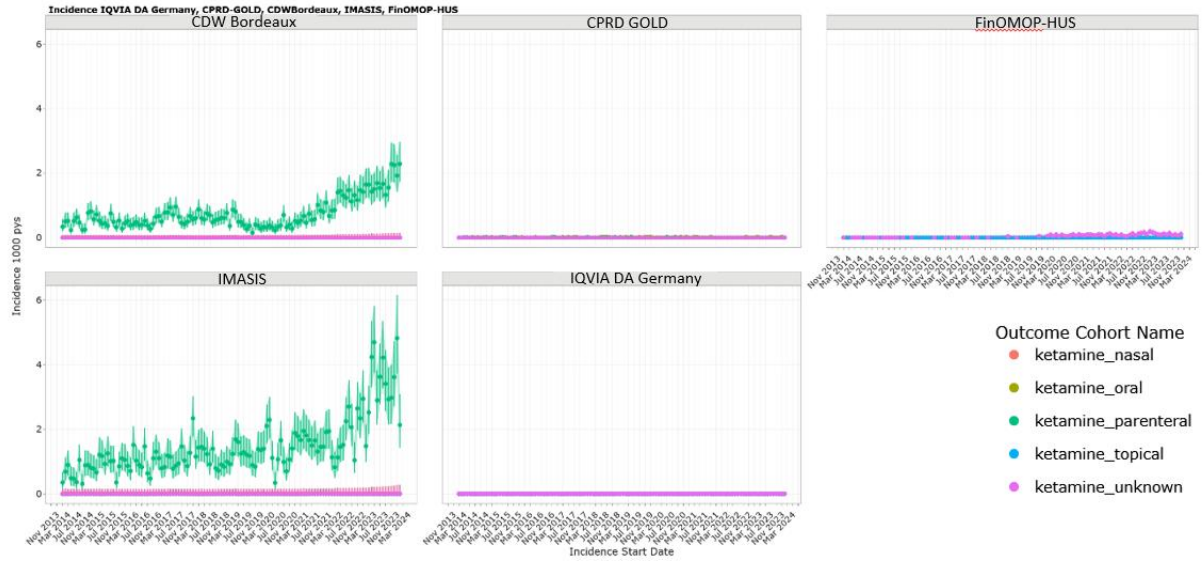
12.1.2.4 Incidence rates for ketamine and for esketamine over time by route of administration

Figures 17–20 display the monthly and annual incidence rates of ketamine and esketamine prescriptions, stratified by route of administration, across multiple data sources during the study period. The primary analysis is displayed in **Figures 17A–20A** and a sensitivity analysis in **Figures 17B–20B**.

Parenteral ketamine had the highest incidence rates in the hospital data sources CDW Bordeaux and IMASIS. In CDW Bordeaux, monthly incidence rates ranged from 0.34 per 1,000 PYs in 2014 to 2.29 per 1,000 PYs in 2023, while in IMASIS, monthly incidence rates increased from 0.35 per 1,000 PYs in 2014 to 4.83 per 1,000 PYs in 2023 in IMASIS (**Figure 17A**). These trends were similarly reflected in the annual incidence rates (**Figure 18A**), indicating that parenteral administration was the primary driver of ketamine use in CDW Bordeaux and IMASIS. In FinOMOP-HUS, prescription records with an unknown route of administration showed slightly higher incidence rates towards the end of study period compared with other routes (**Figures 17A–18A**). In CPRD GOLD and IQVIA DA Germany, monthly and annual incidence rates did not differ by route of administration. Sensitivity analyses confirmed the overall patterns observed in the primary analysis (**Figures 17B–18B**).

For esketamine, monthly incidence rates did not differ by route of administration in DK-DHR, IQVIA DA Germany, and IMASIS (**Figure 19A**). These findings were consistent with the annual incidence rates (**Figure 19A**). In FinOMOP-HUS, the highest incidence rates were observed for unknown route of administration (**Figures 19A–20A**). Sensitivity analyses yielded comparable results (**Figures 19B–20B**).

A



B

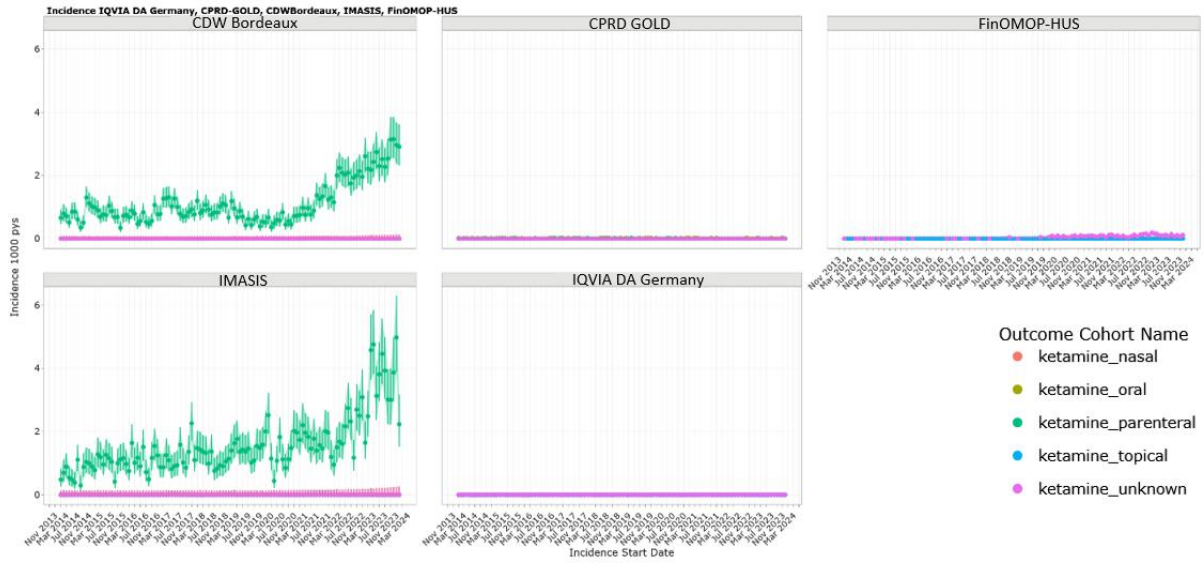
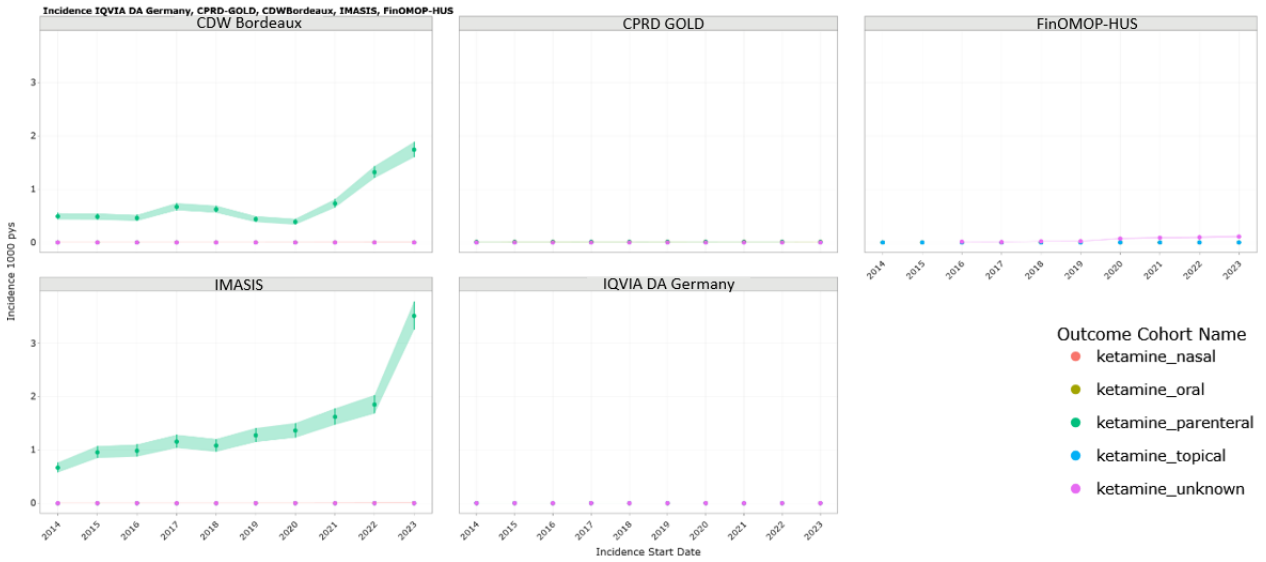


Figure 17. Monthly incidence rates of ketamine prescriptions across data sources during the study period stratified by route of administration. Panel A shows incidence rates restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

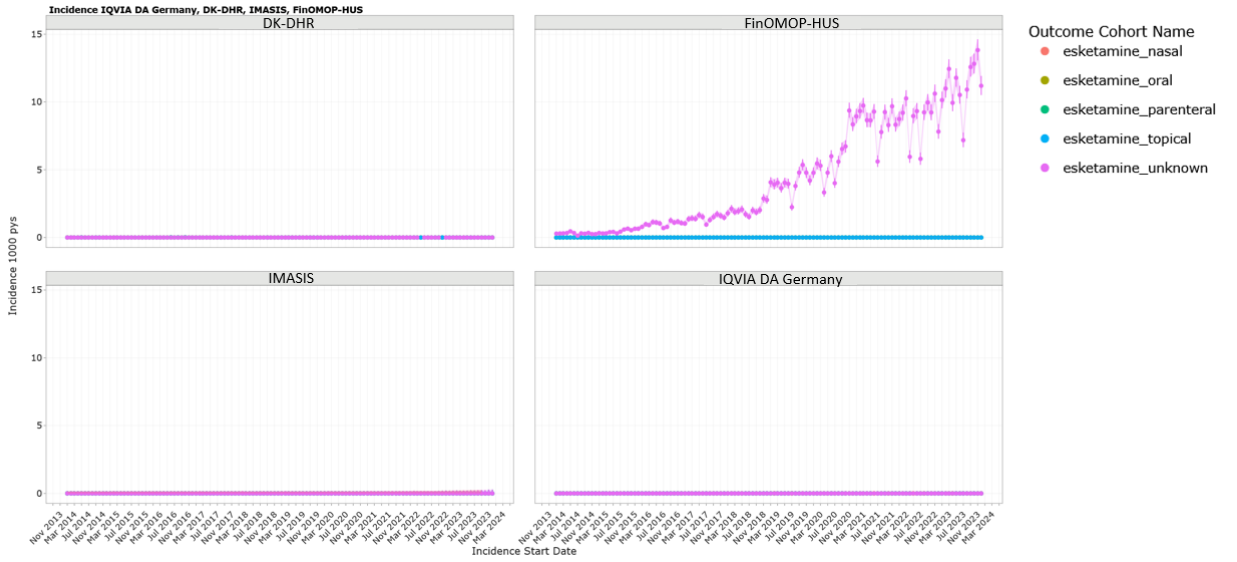
A



B

Figure 18. Annual incidence rates of ketamine prescriptions across data sources during the study period stratified by route of administration. Panel A shows incidence rates restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



B

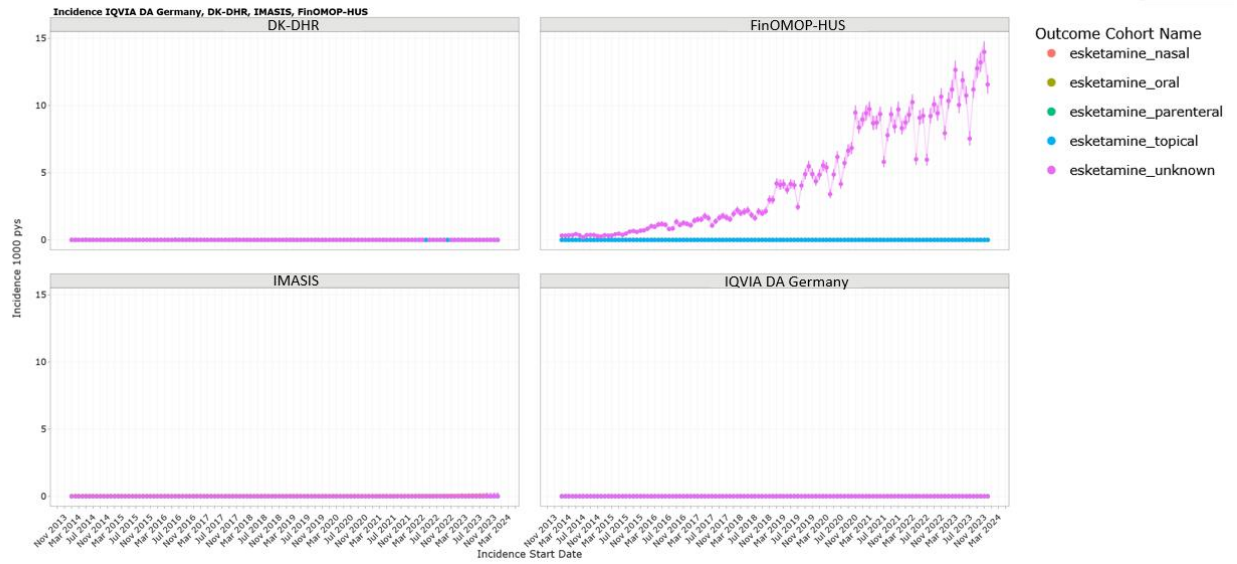
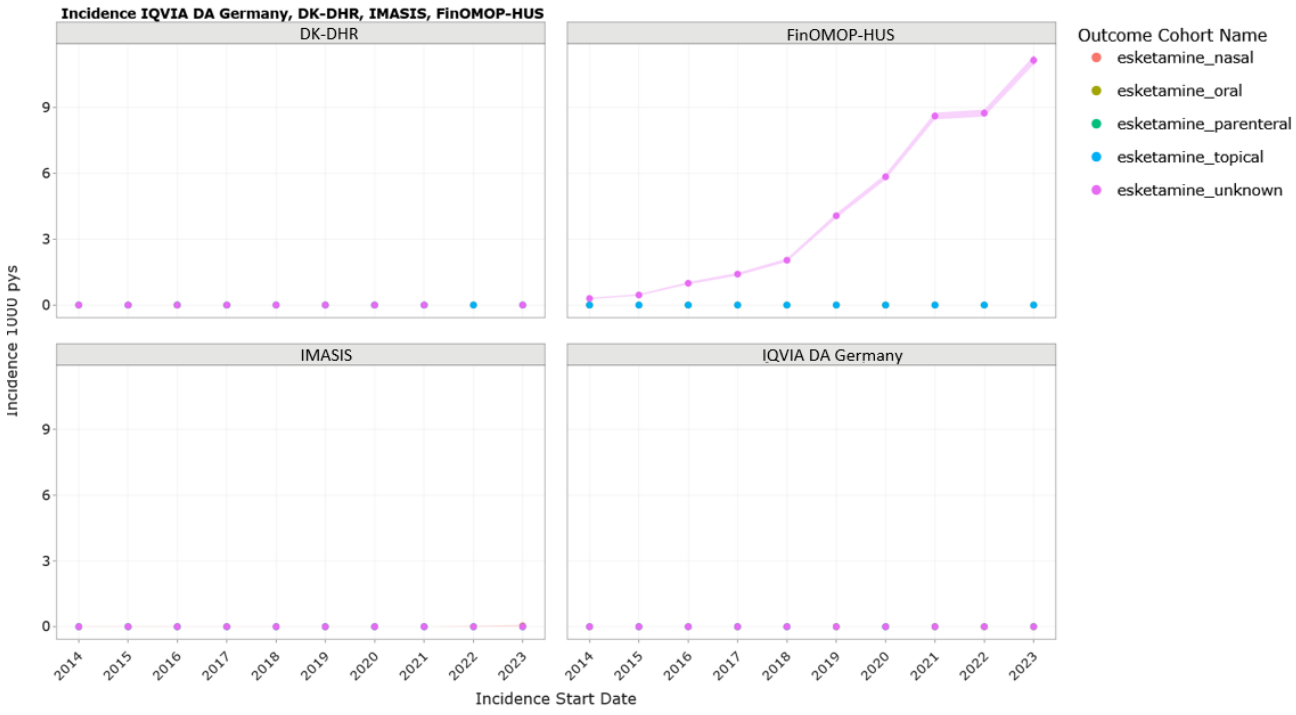


Figure 19. Monthly incidence rates of esketamine prescriptions across data sources during the study period stratified by route of administration. Panel A shows incidence rates restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



B

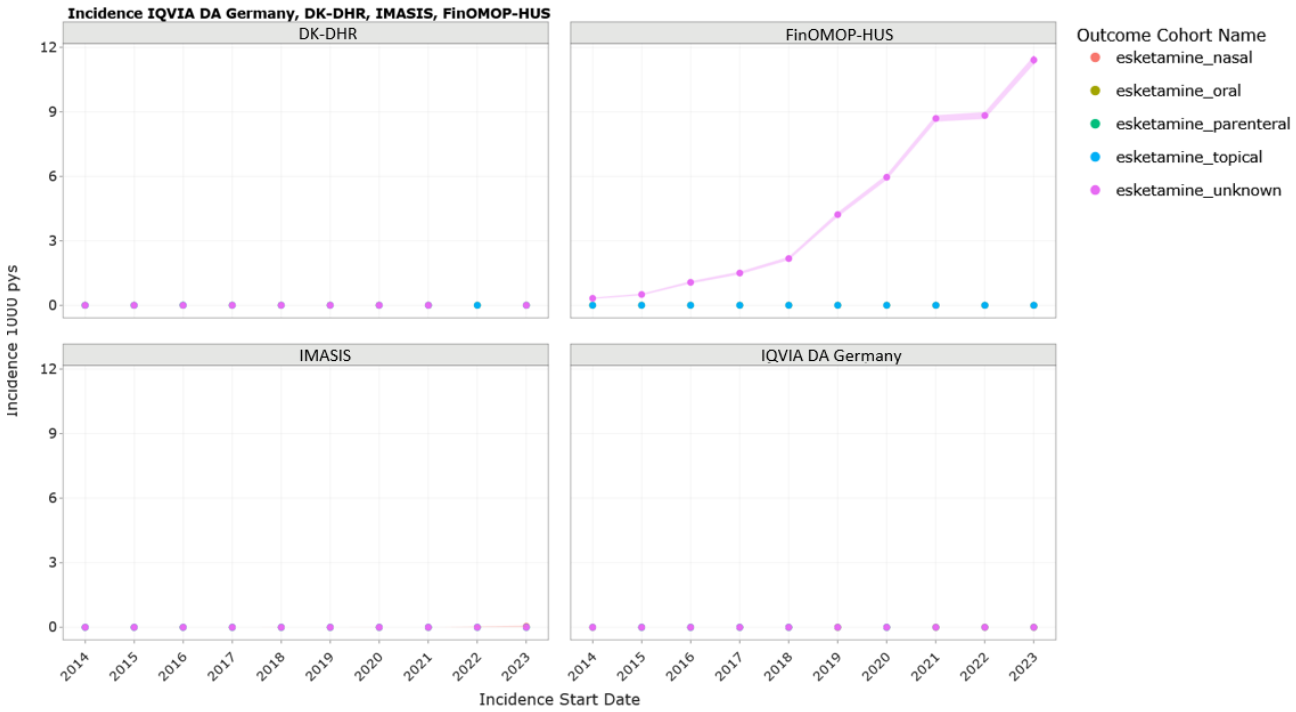


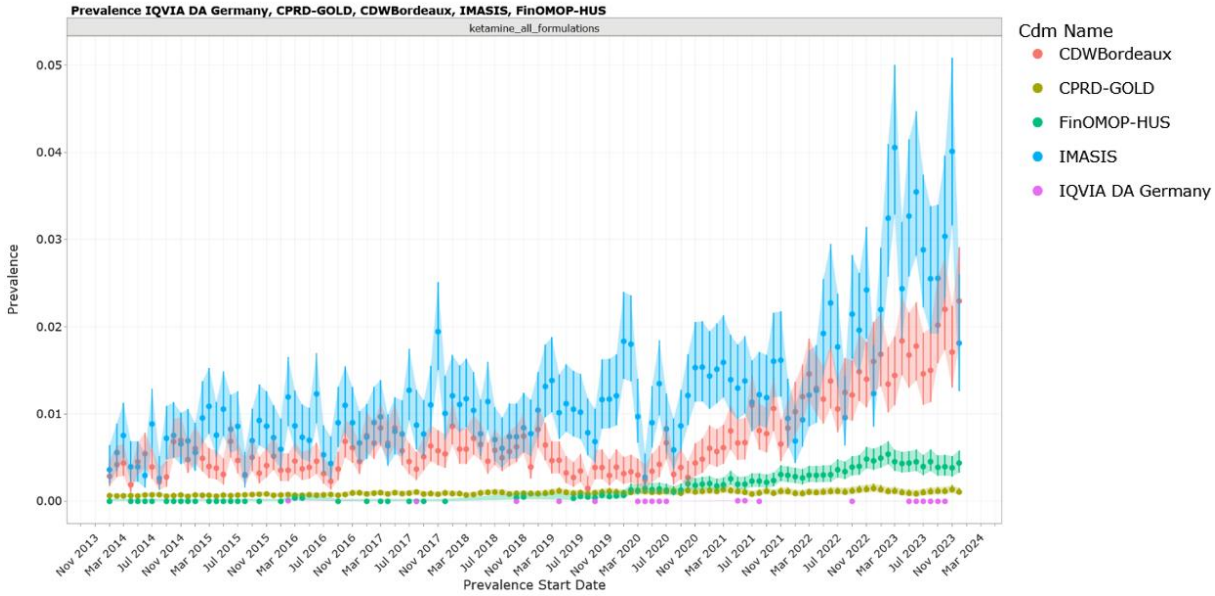
Figure 20. Annual incidence rates of esketamine prescriptions across data sources during the study period stratified by route of administration. Panel A shows incidence rates restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

12.1.2.5 Prevalence for ketamine and for esketamine over time

The trends and patterns observed in prevalent use of ketamine closely mirrored those of incident use (**Figures 21–22**). Overall, the prevalence of ketamine use was very low and remained stable over time in the primary care data sources including CPRD GOLD and IQVIA DA Germany, with both monthly and annual prevalence consistently below 0.01% (**Figures 21–22**). In contrast, prevalence of ketamine prescriptions in hospital data sources including CDW Bordeaux, FinOMOP-HUS, and IMASIS was initially low, followed by a slight increase from 2021 onwards (**Figure 21A**). In IMASIS, monthly prevalence increased slightly from < 0.01% in 2014 to 0.04% in 2023, in FinOMOP-HUS from 0.0004% in 2016 to 0.004% in 2023, and in CDW Bordeaux from < 0.01% in 2014 to 0.02% in 2023. A similar pattern was observed in annual prevalence, with estimates ranging from 0.06% in 2014 to 0.29% in 2023 in IMASIS, 0.001% in 2016 to 0.01% in 2023 in FinOMOP-HUS, and 0.05% in 2014 to 0.15% in 2023 in CDW Bordeaux (**Figure 22A**). The results of the sensitivity analysis were consistent with those from the primary analysis (**Figures 21B–22B**).

Figures 23–24 further illustrate trends in esketamine use across selected data sources. The prevalence of esketamine use was very low across the data sources including DK-DHR, IMASIS, and IQVIA DA Germany, with monthly and annual prevalence below 0.01% (**Figures 23A–24A**). In IMASIS, no esketamine prescriptions were recorded until 2022, after which a slight increase in number of esketamine prescriptions was observed. FinOMOP-HUS showed a similar trend to that observed for incident use (**Figures 23A–24A**). Sensitivity analyses again demonstrated consistent patterns across data sources (**Figures 23B–24B**).

A



B

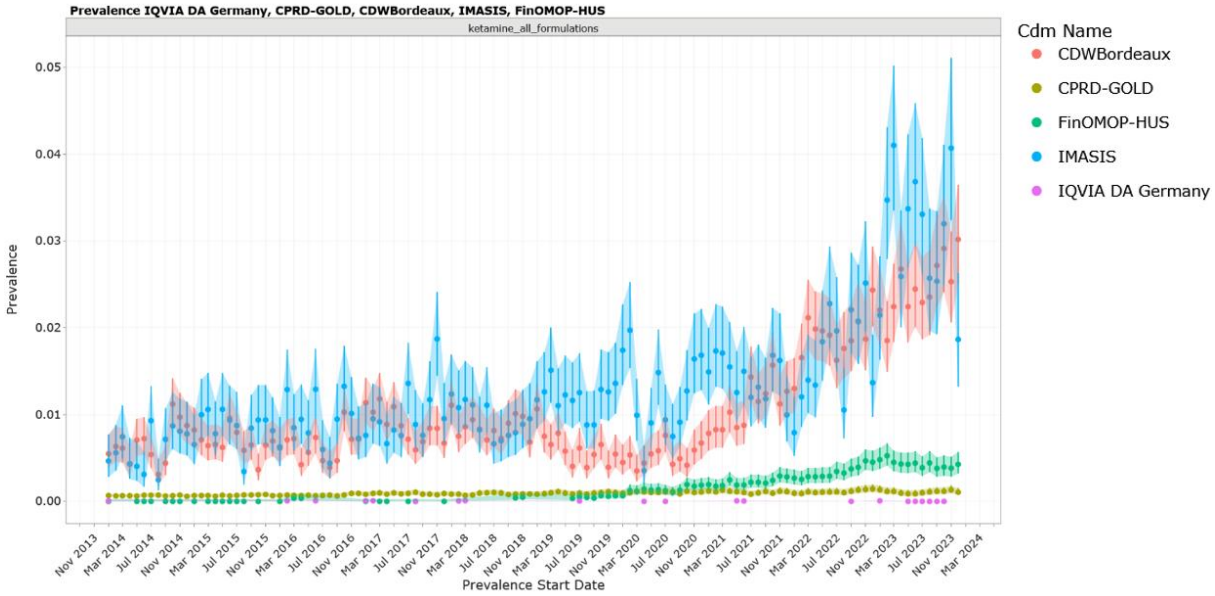
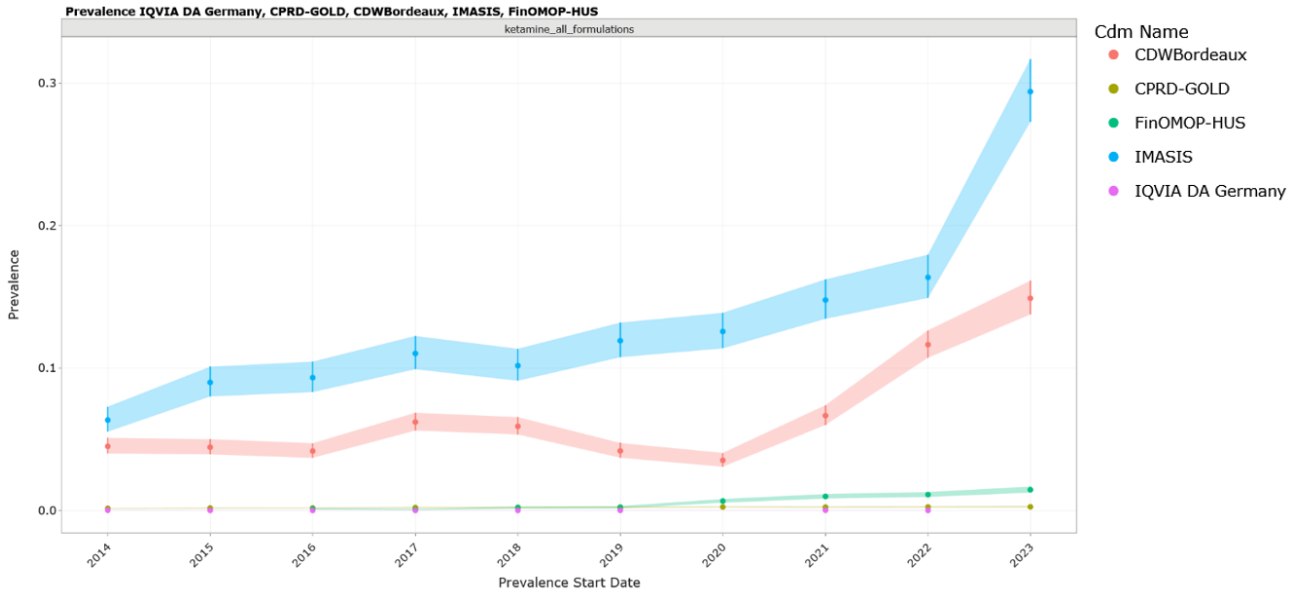


Figure 21. Monthly prevalence of ketamine prescriptions across data sources during the study period. Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B presents the results from the sensitivity analysis, which did not require prior data visibility.

A



B

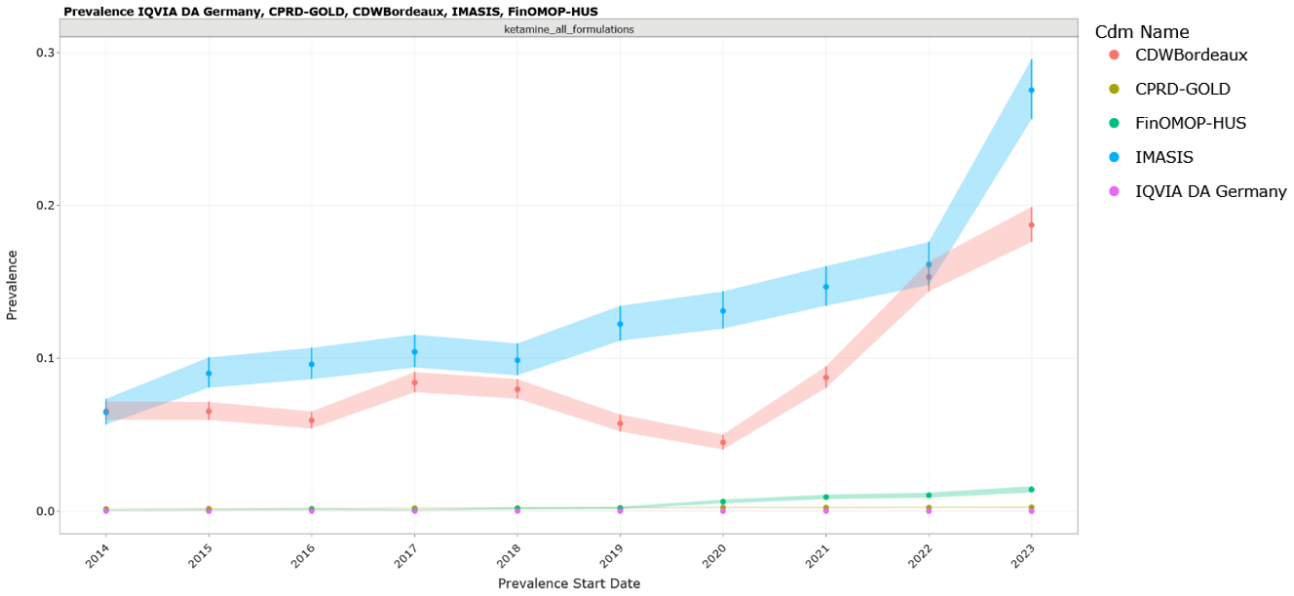
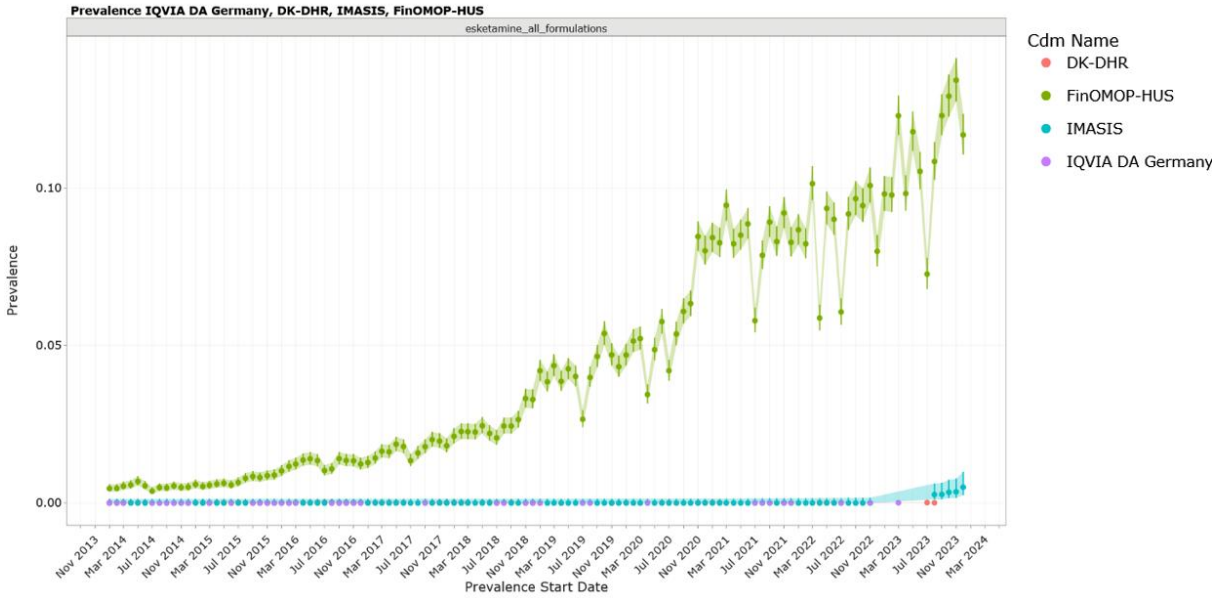


Figure 22. Annual prevalence of ketamine prescriptions across data sources during the study period. Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B presents the results from the sensitivity analysis, which did not require prior data visibility.

A



B

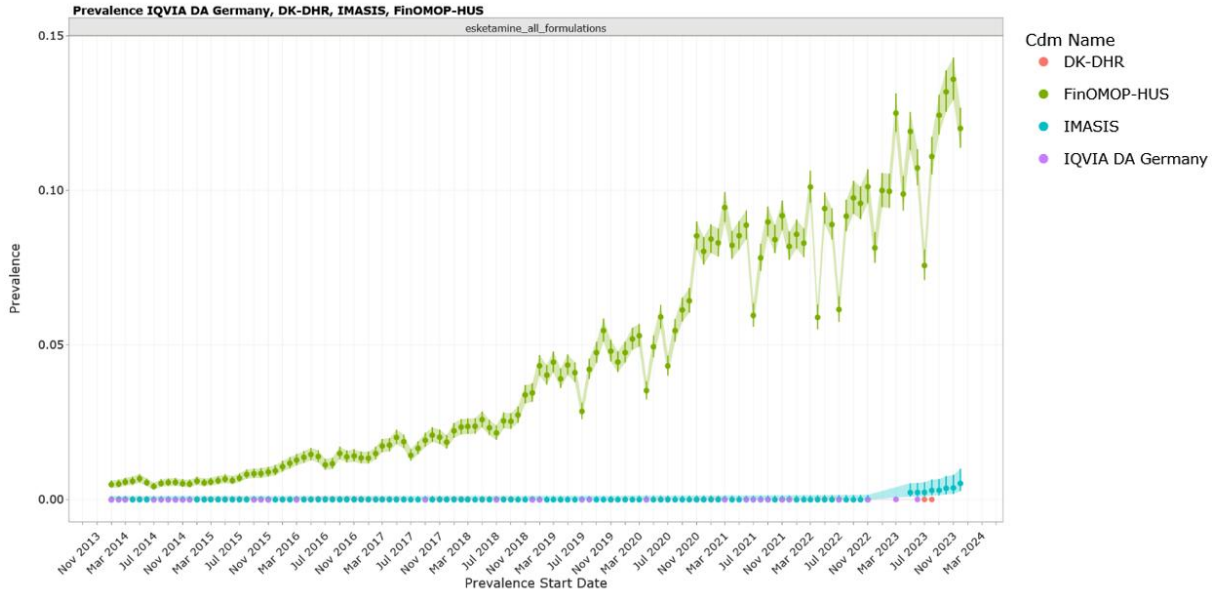
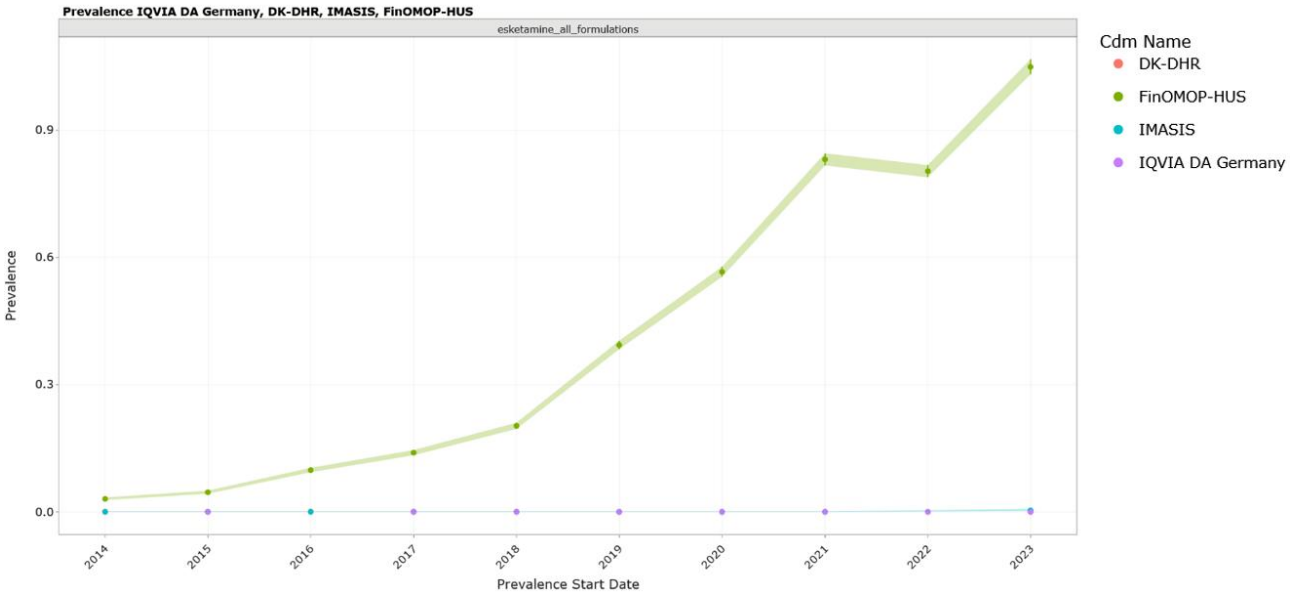


Figure 23. Monthly prevalence of esketamine prescriptions across data sources during the study period. Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B presents the results from the sensitivity analysis, which did not require prior data visibility.

A



B

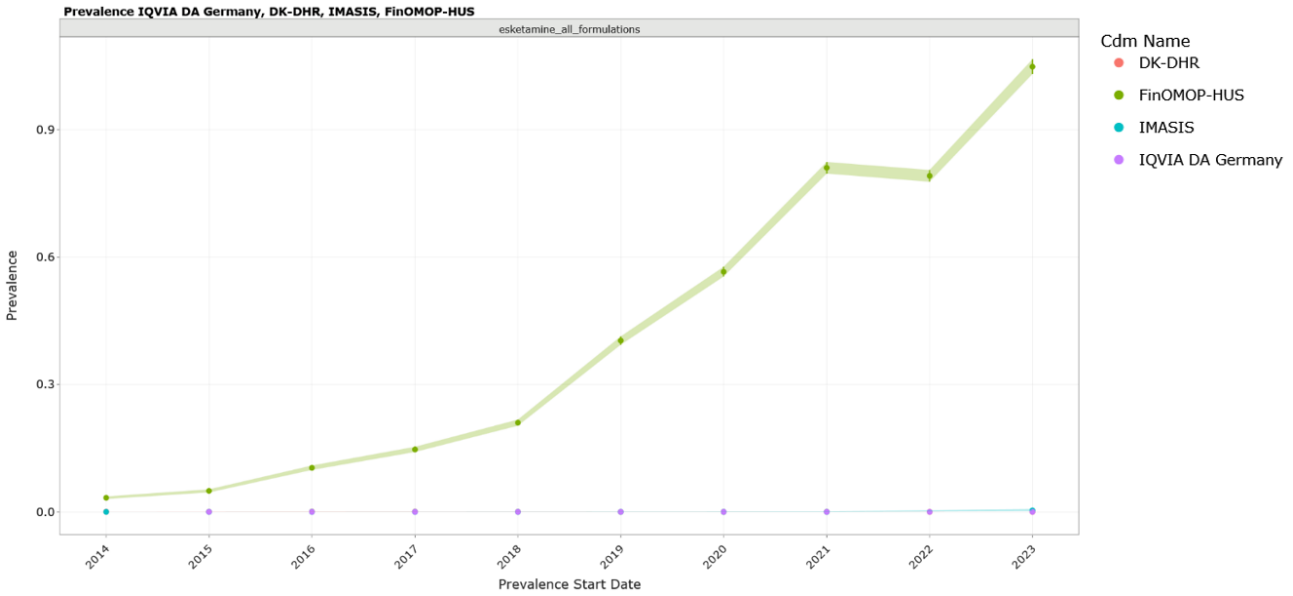


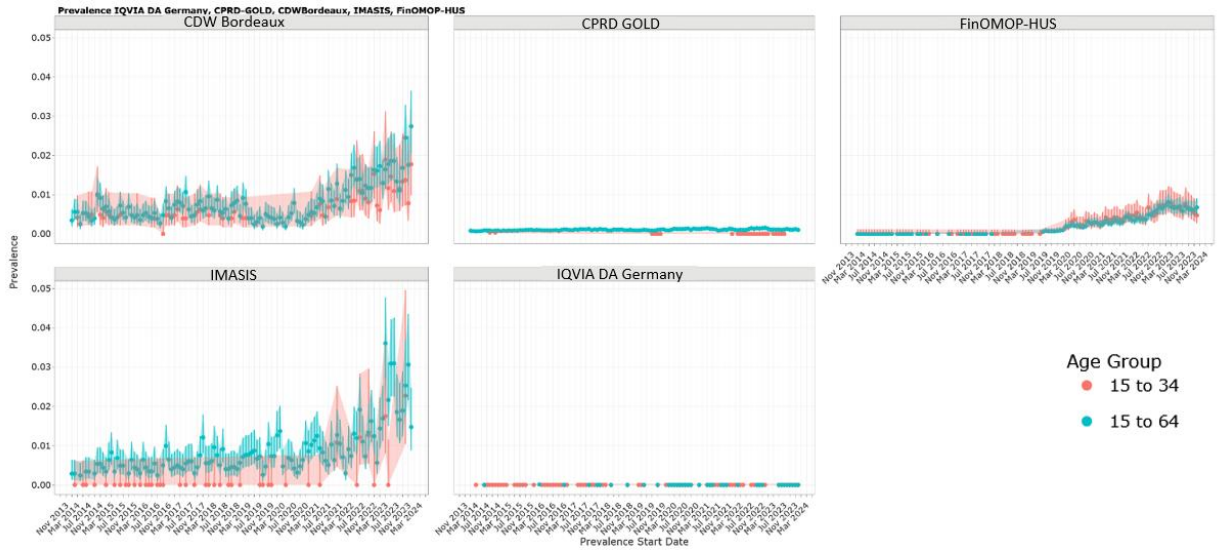
Figure 24. Annual prevalence of esketamine prescriptions across data sources during the study period. Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B presents the results from the sensitivity analysis, which did not require prior data visibility.

12.1.2.6 Prevalence for ketamine and for esketamine over time by age groups

Prevalence estimates stratified by age mirrored the patterns observed in incidence rates (**Figures 25–28, Figures 5–8** in **ANNEX III**). Across hospital-based data sources, prevalence of ketamine use remained low in the broader adult population (15–64 years) and young adults (15–34 years) (**Figures 25–26, Figures 5–6** in **ANNEX III**). This trend was evident for both monthly and annual prevalence estimates (**Figures 25A–26A**). Prevalence in primary care data sources was uniformly low and stable over time, with no differences between age groups. Further stratification by narrower age bands revealed that prevalence of ketamine use was higher among older individuals, particularly in those aged 55 years and older, while the lowest prevalence was observed in the youngest age groups (**Figures 5–6** in **ANNEX III**). This gradient was apparent in hospital data sources CDW Bordeaux and IMASIS but not in primary care settings or FinOMOP-HUS.

For esketamine, prevalence was uniformly low and showed limited variation across age groups and data sources (**Figures 27–28, Figures 7–8** in **ANNEX III**). In FinOMOP-HUS slightly higher prevalence was observed in the broader adult population and among older age groups, especially those aged 55–64 years, 65–74 years, and above 75 years. These findings were consistent in both the primary and sensitivity analyses.

A



B

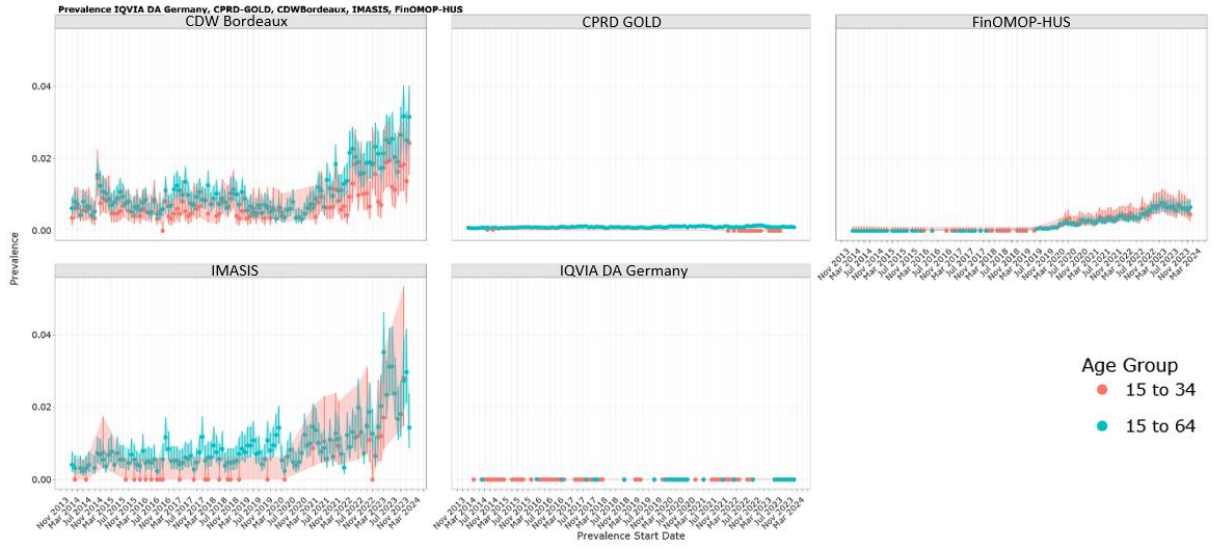
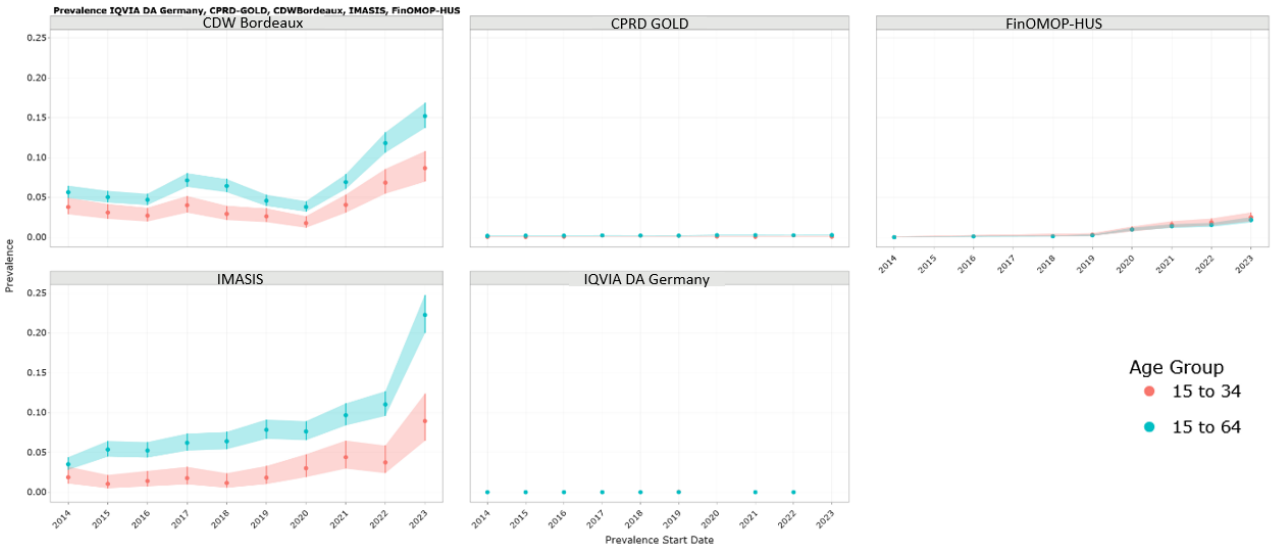


Figure 25. Monthly prevalence of ketamine prescriptions across data sources during the study period stratified by age groups, including all adults (15–64 years) and young adults (15–34 years). Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



B

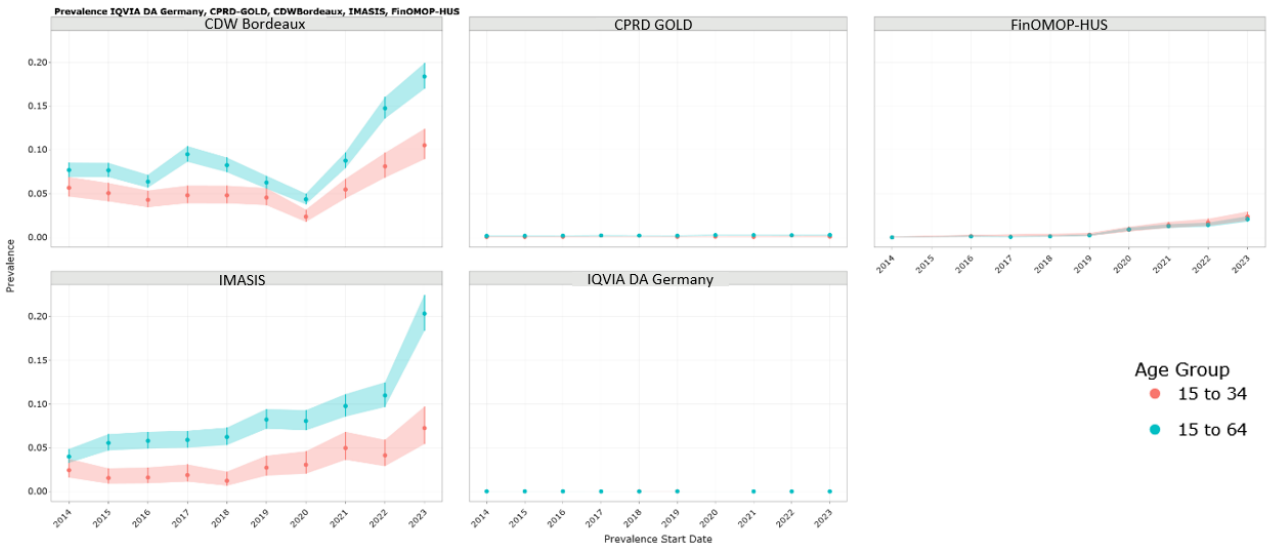
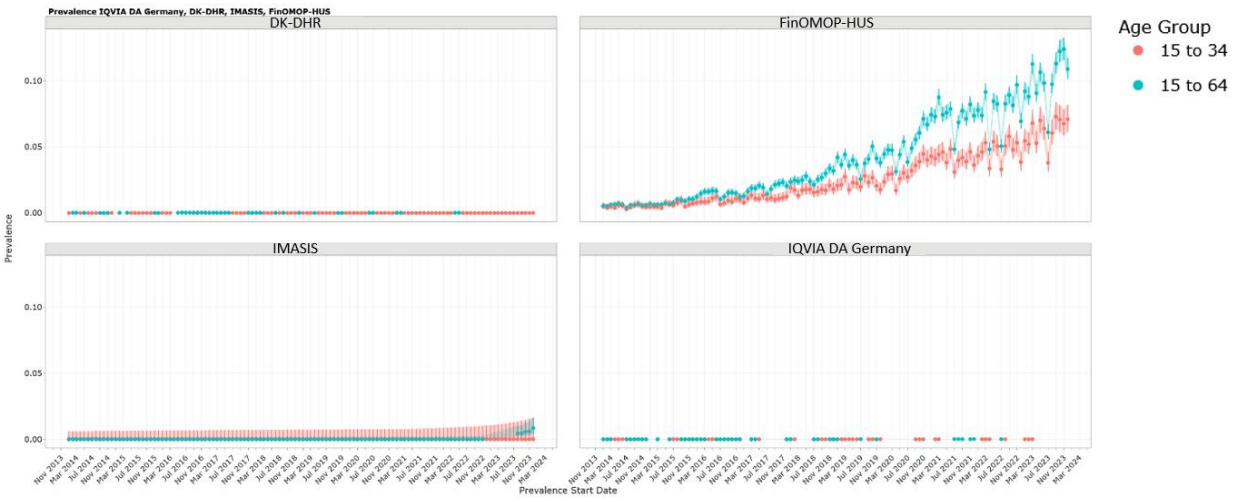


Figure 26. Annual prevalence of ketamine prescriptions across data sources during the study period stratified by age groups, including all adults (15–64 years) and young adults (15–34 years). Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



B

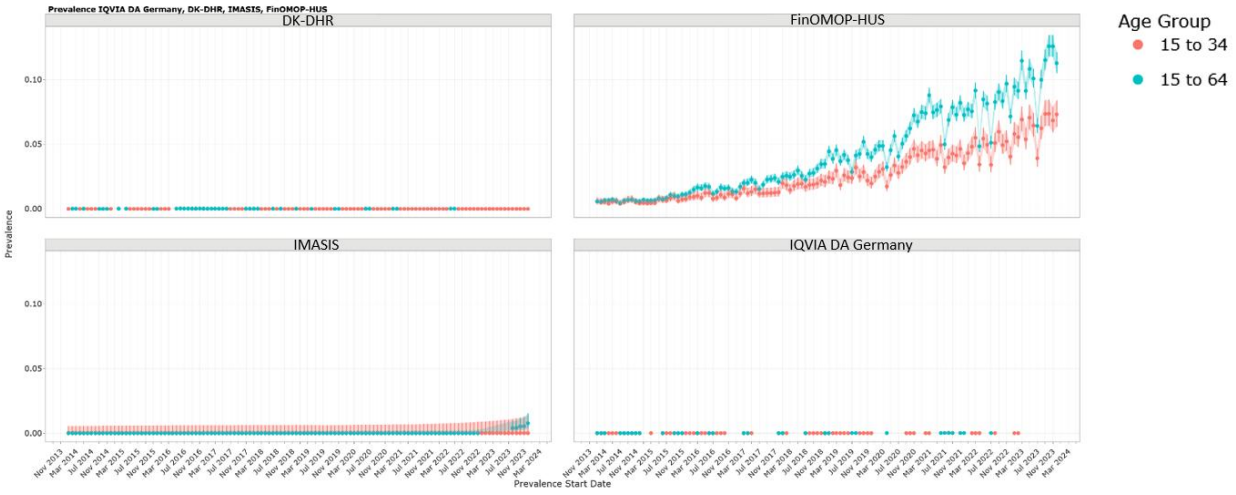
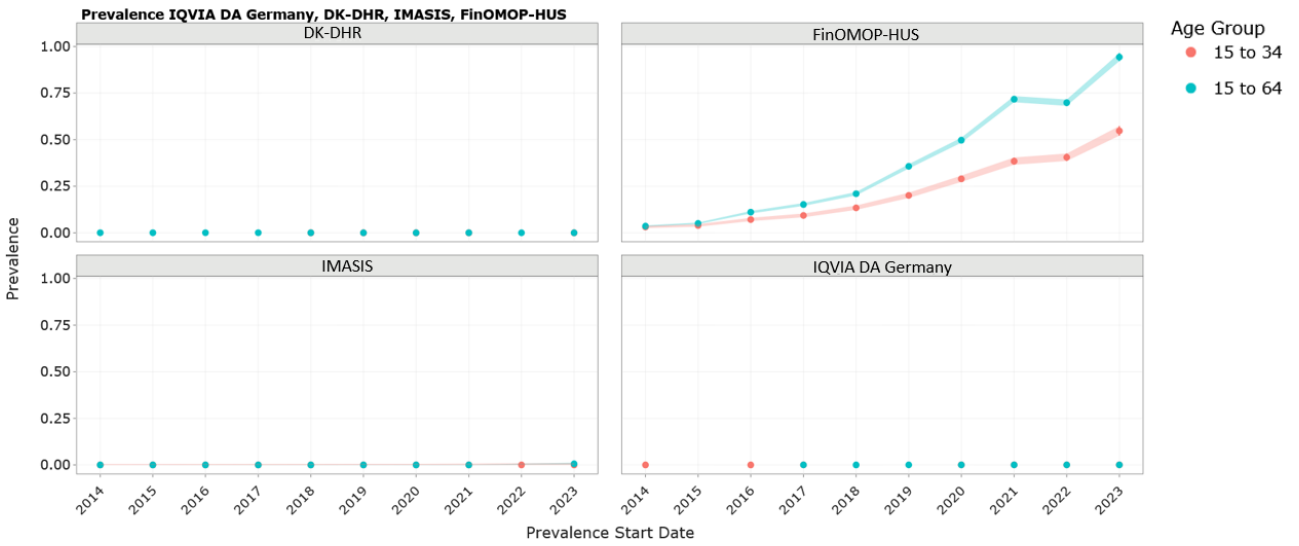


Figure 27. Monthly prevalence of esketamine prescriptions across data sources during the study period stratified by age groups, including all adults (15–64 years) and young adults (15–34 years). Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



B

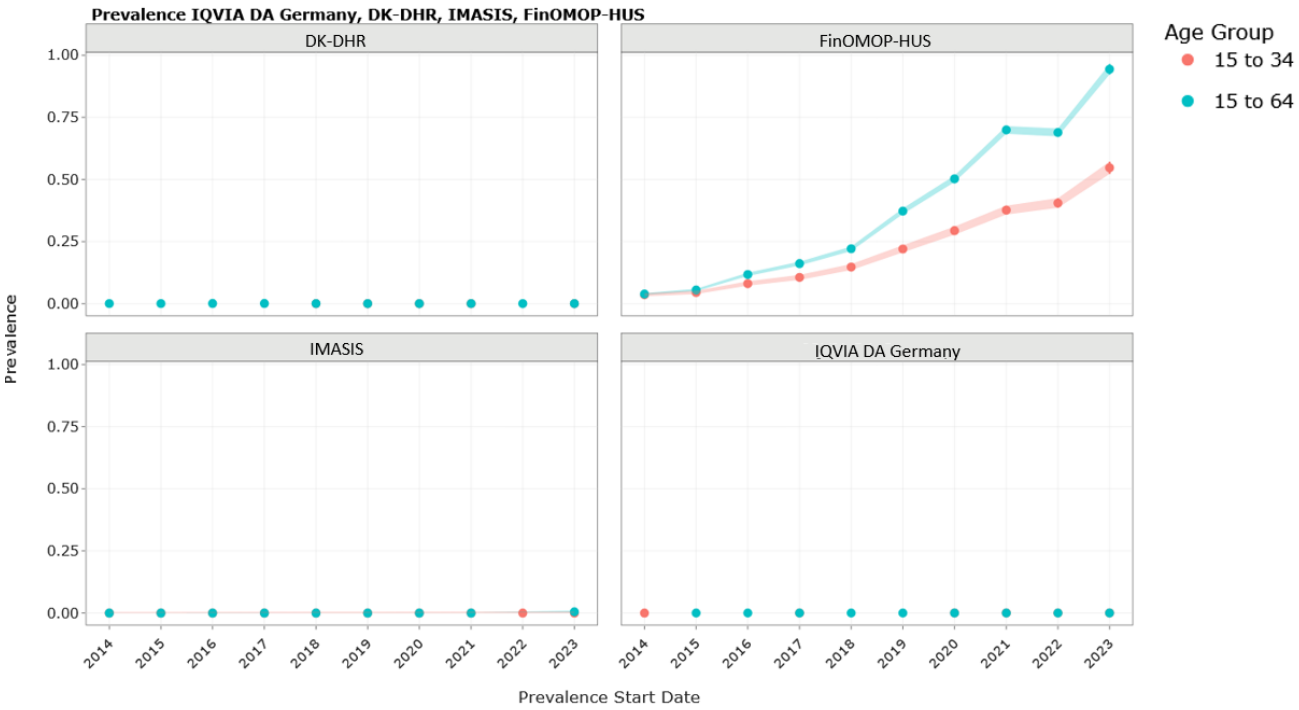


Figure 28. Annual prevalence of esketamine prescriptions across data sources during the study period stratified by age groups, including all adults (15–64 years) and young adults (15–34 years). Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

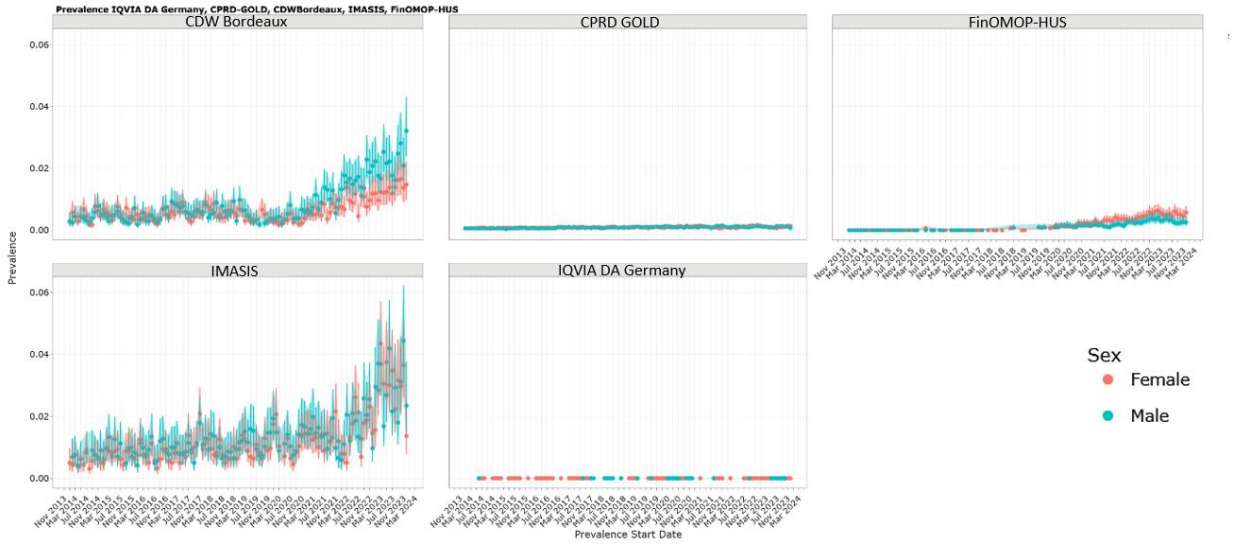
12.1.2.7 Prevalence for ketamine and for esketamine over time by sex

Figures 29–32 present the monthly and annual prevalence of ketamine and esketamine use, stratified by sex, during the study period. Overall, the same patterns and trends which were observed in the incidence analyses stratified by sex were observed in the prevalence estimates.

In the primary care data sources (CPRD GOLD and IQVIA DA Germany) and the hospital-based data sources (IMASIS and FinOMOP-HUS), prevalence of ketamine use was comparable between males and females, with no evidence of systematic sex-based differences. In CDW Bordeaux, prevalence remained similar between sexes until 2020, after which slightly higher prevalence was consistently observed among males (**Figures 29A–30A**). The sensitivity analysis confirmed these findings and further highlighted the divergence in CDW Bordeaux toward the latter part of the study period (**Figures 29B–30B**).

For esketamine, prevalence estimates were broadly comparable between sexes across all data sources, with only a male predominance noted in FinOMOP-HUS (**Figures 31A–32A**). These patterns remained stable in the sensitivity analysis (**Figures 31B–32B**).

A



B

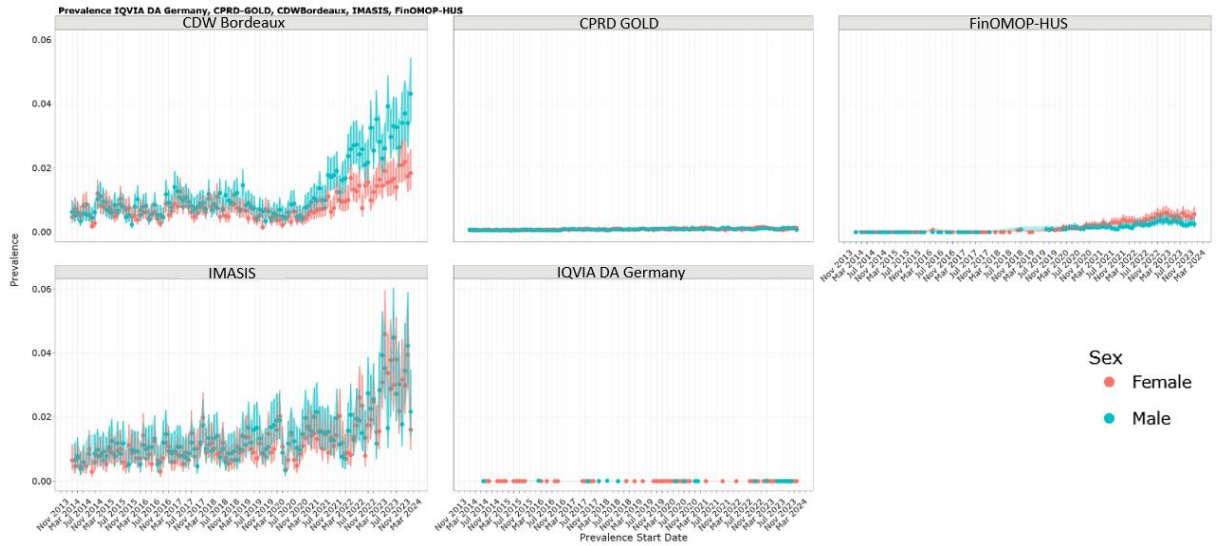
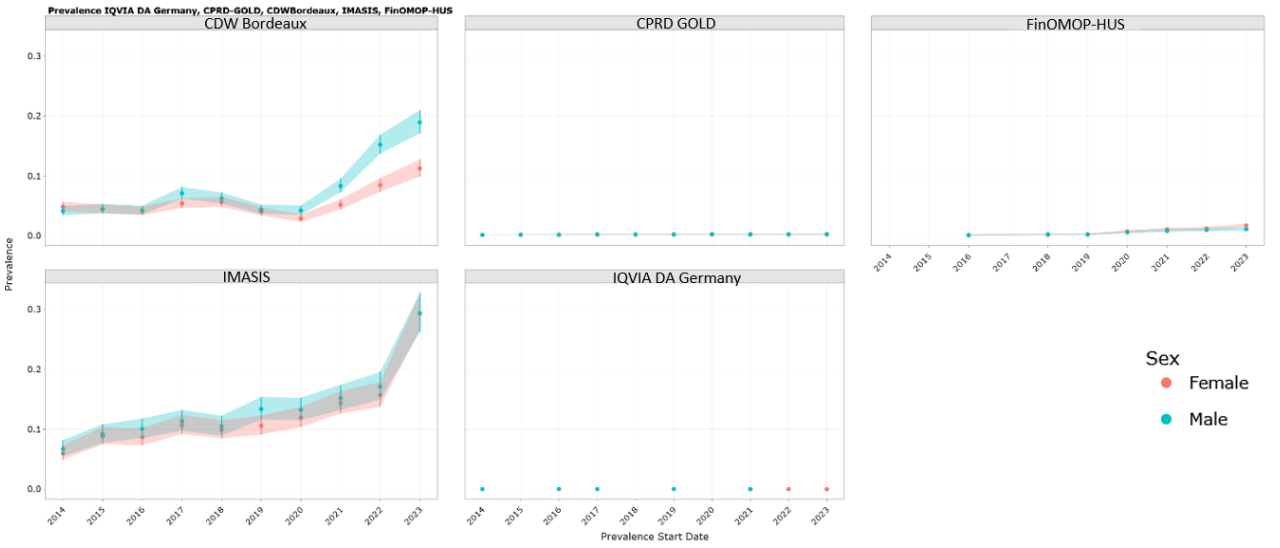


Figure 29. Monthly prevalence of ketamine prescriptions across data sources during the study period stratified by sex. Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



B

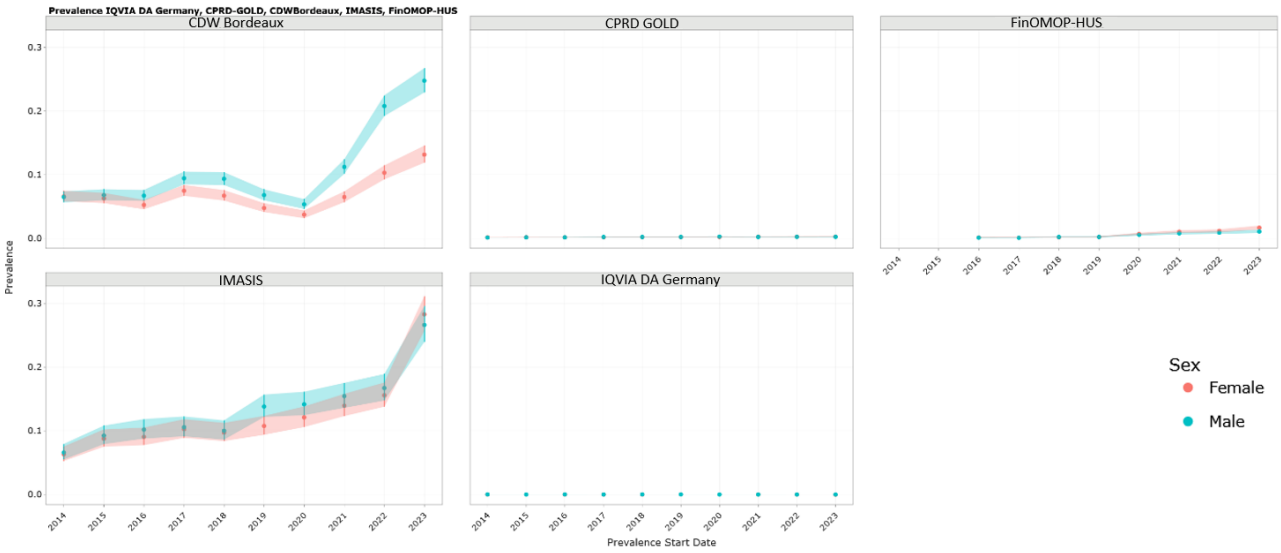
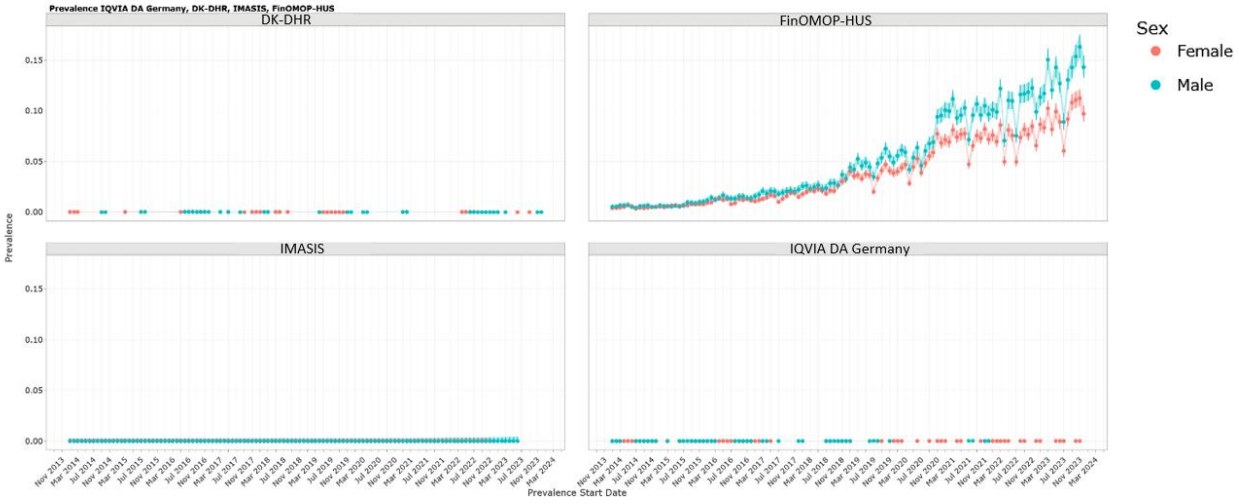


Figure 30. Annual prevalence of ketamine prescriptions across data sources during the study period stratified by sex. Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



B

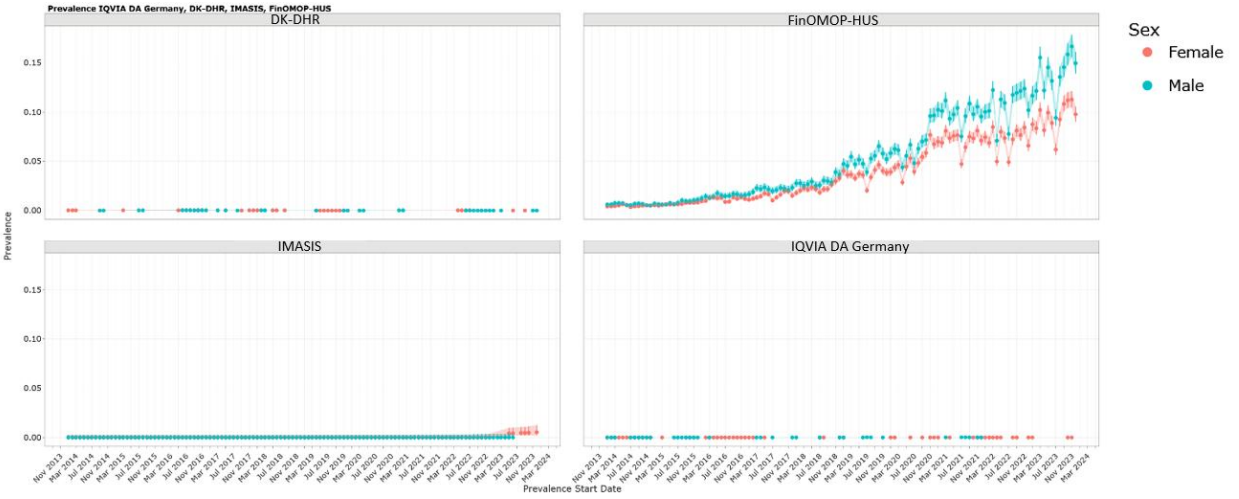
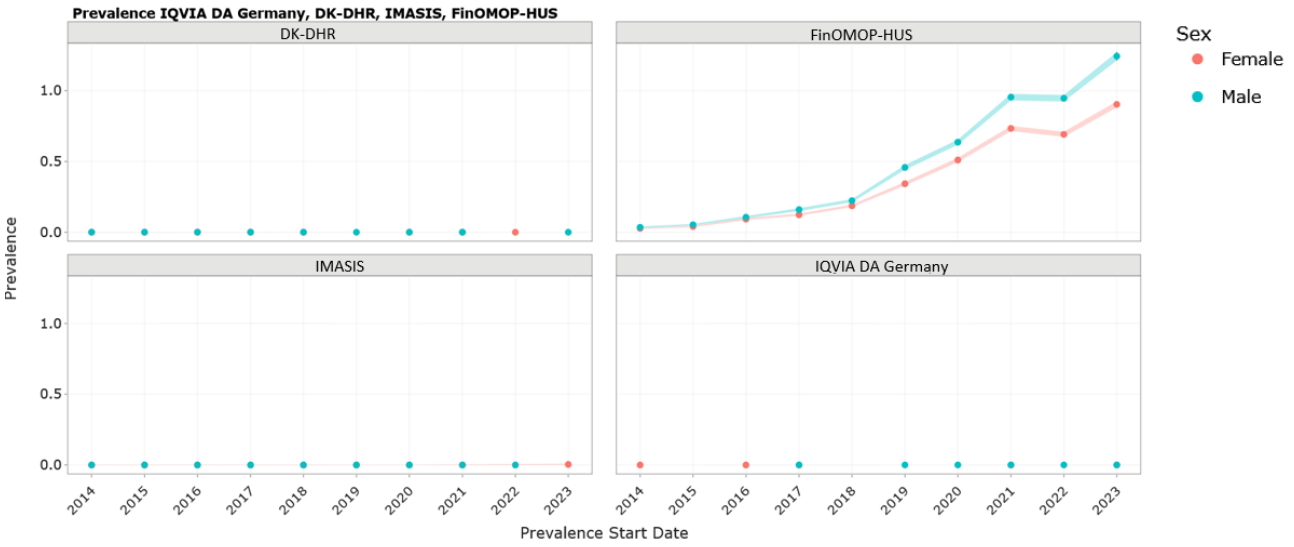


Figure 31. Monthly prevalence of esketamine prescriptions across data sources during the study period stratified by sex. Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



B

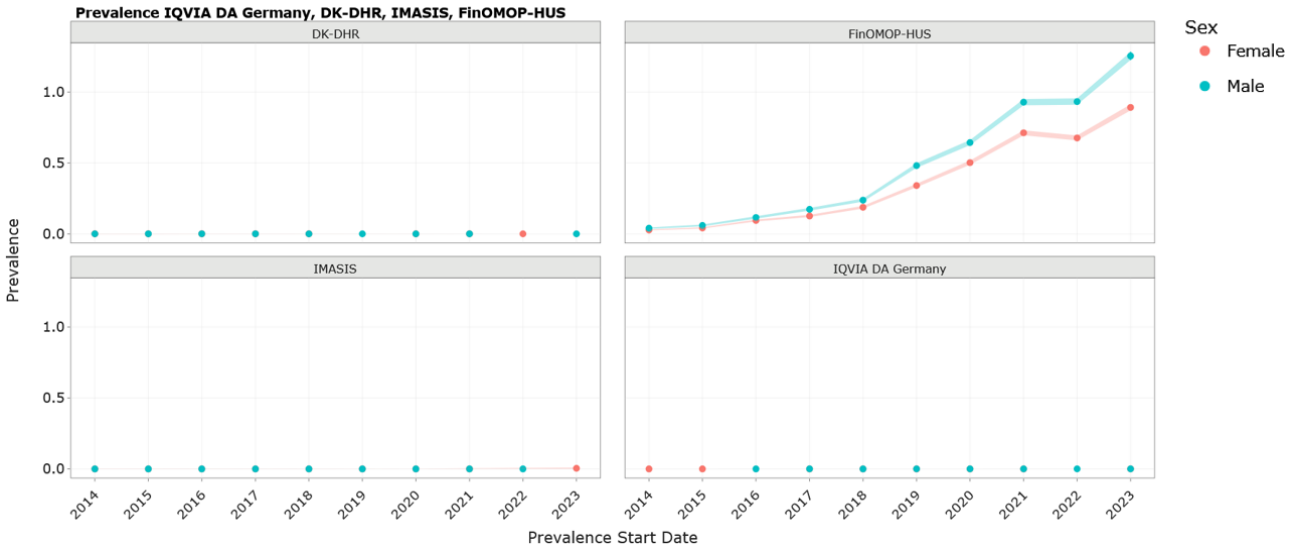


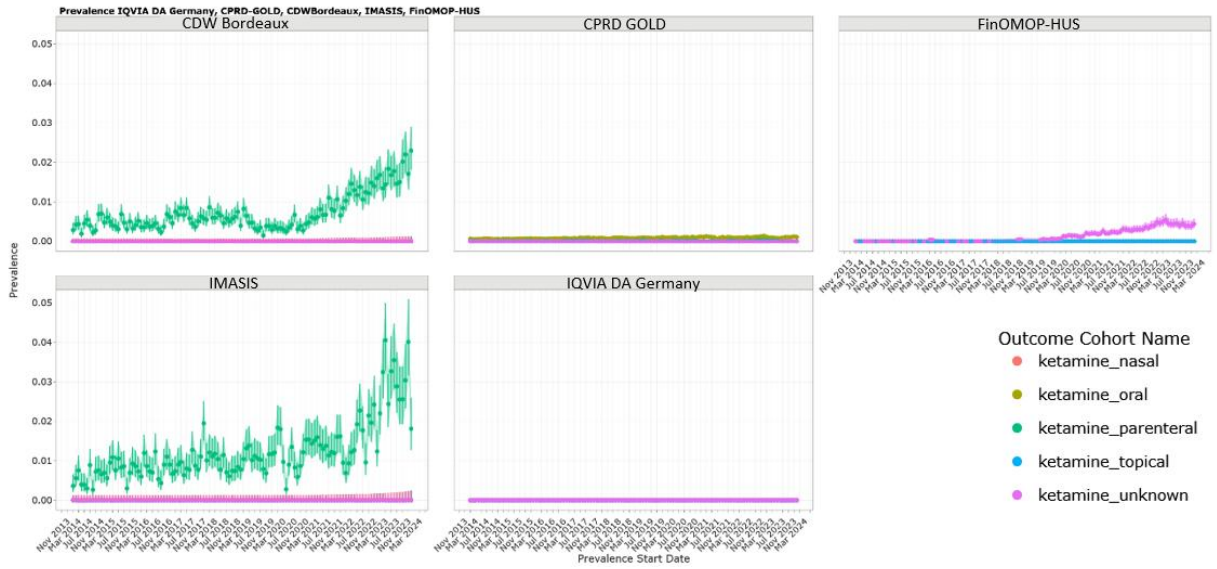
Figure 32. Annual prevalence of esketamine prescriptions across data sources during the study period stratified by sex. Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

12.1.2.8 Prevalence for ketamine and for esketamine over time by route of administration

Prevalence estimates of ketamine and esketamine prescriptions, stratified by route of administration, followed patterns consistent with those observed in the incidence analyses (**Figures 33–36**). In hospital data sources (CDW Bordeaux and IMASIS), parenteral administration of ketamine accounted for the highest prevalence, while in the hospital data source FinOMOP-HUS the highest prevalence was observed for an unknown route of administration (**Figures 33A–34A**).

For esketamine, monthly and annual prevalence did not differ by route of administration in DK-DHR, IMASIS, and IQVIA DA Germany (**Figures 35A–36A**). In FinOMOP-HUS a substantial proportion of esketamine prescriptions had an unknown route of administration, consistent with findings reported in the incidence analysis. The sensitivity analyses further reinforced the observed patterns across data sources (**Figures 33B–36B**).

A



B

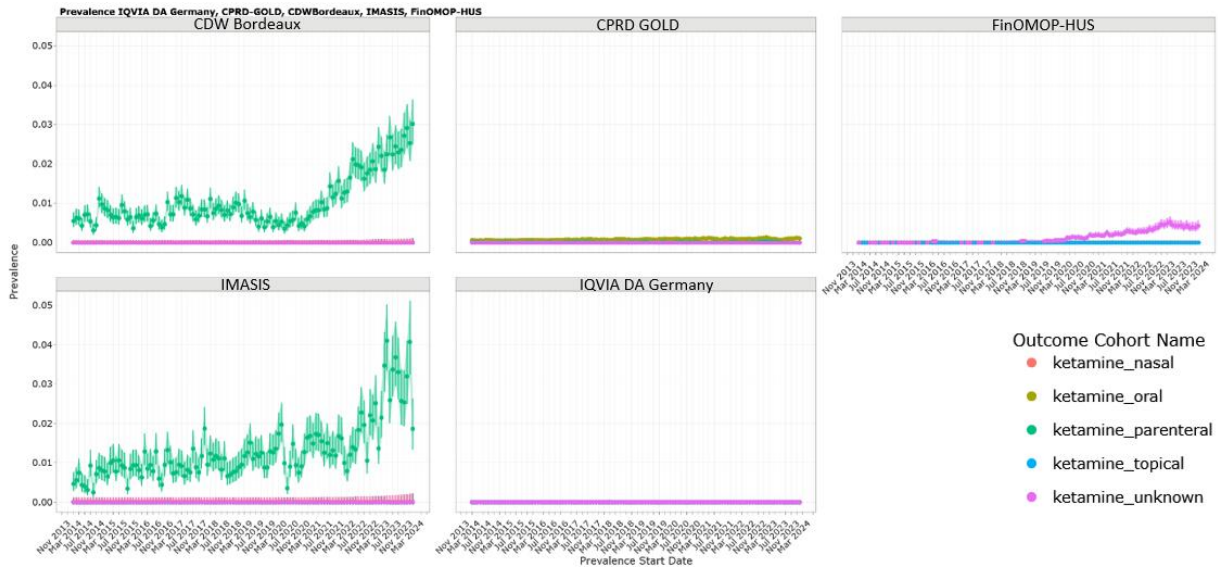
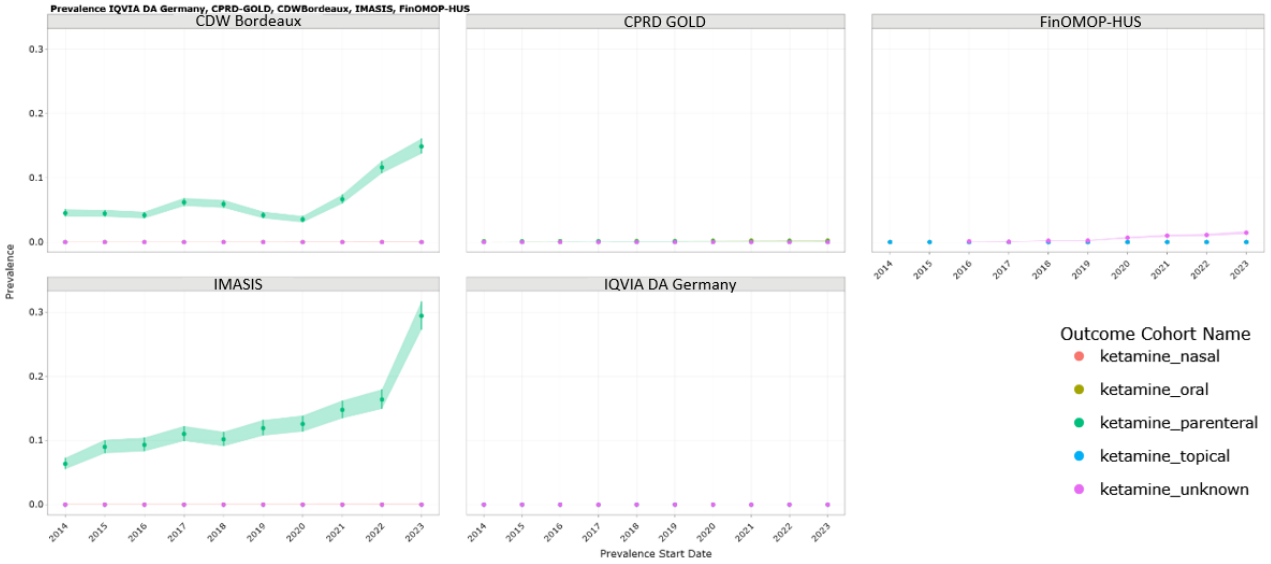


Figure 33. Monthly prevalence of ketamine prescriptions across data sources during the study period stratified by route of administration. Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



B

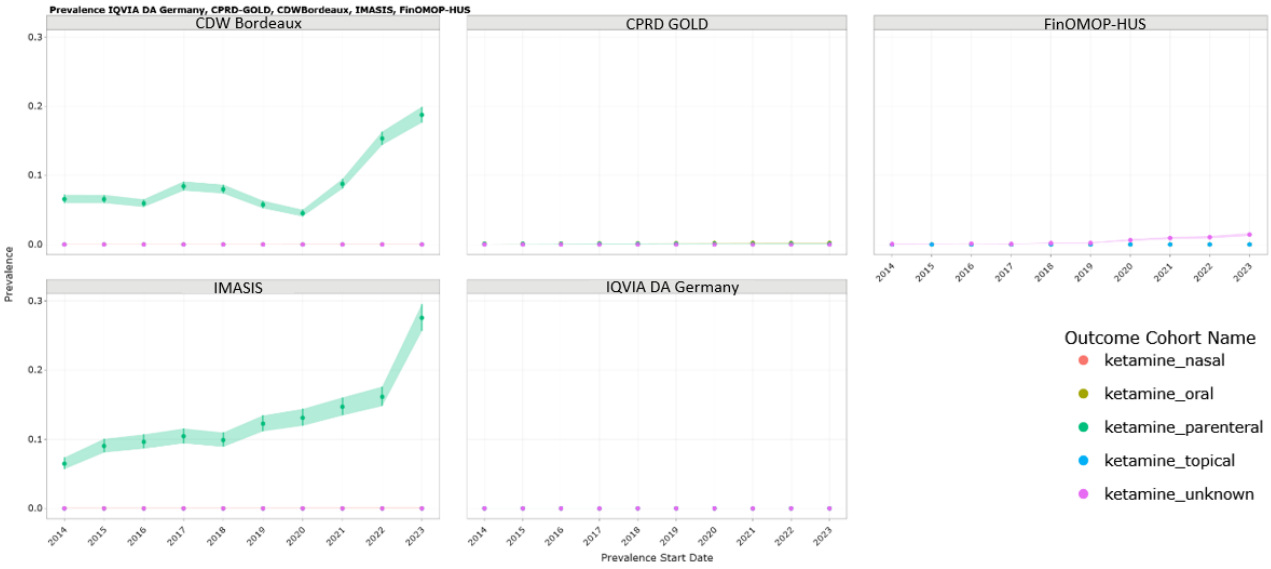
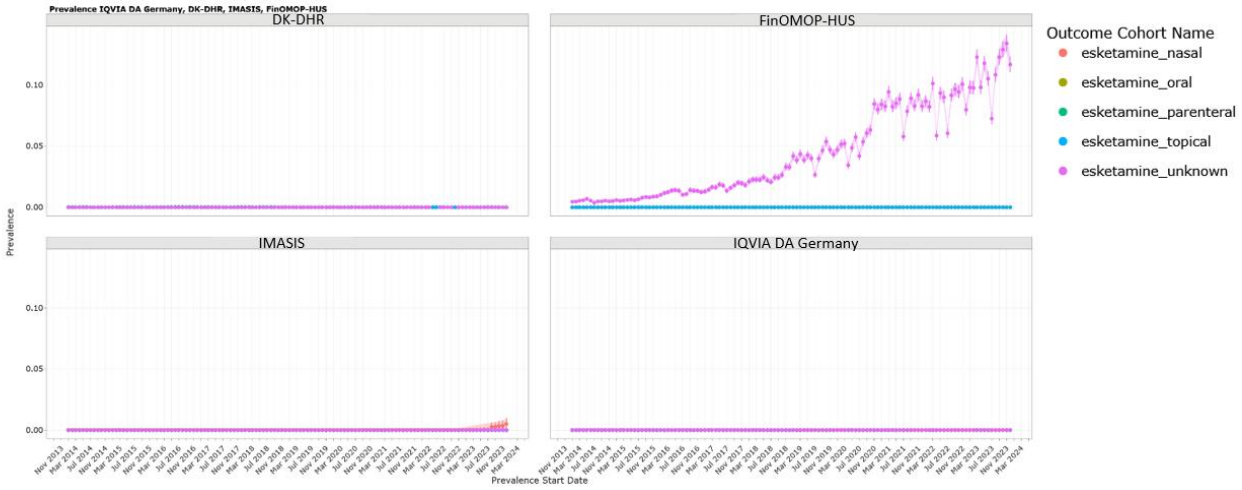


Figure 34. Annual prevalence of ketamine prescriptions across data sources during the study period stratified by route of administration. Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



B

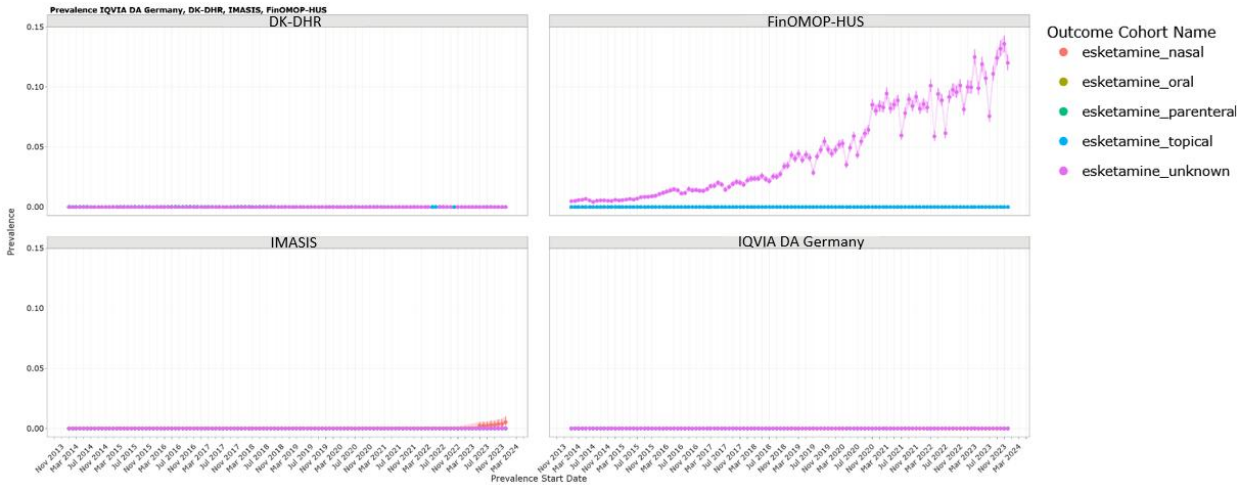
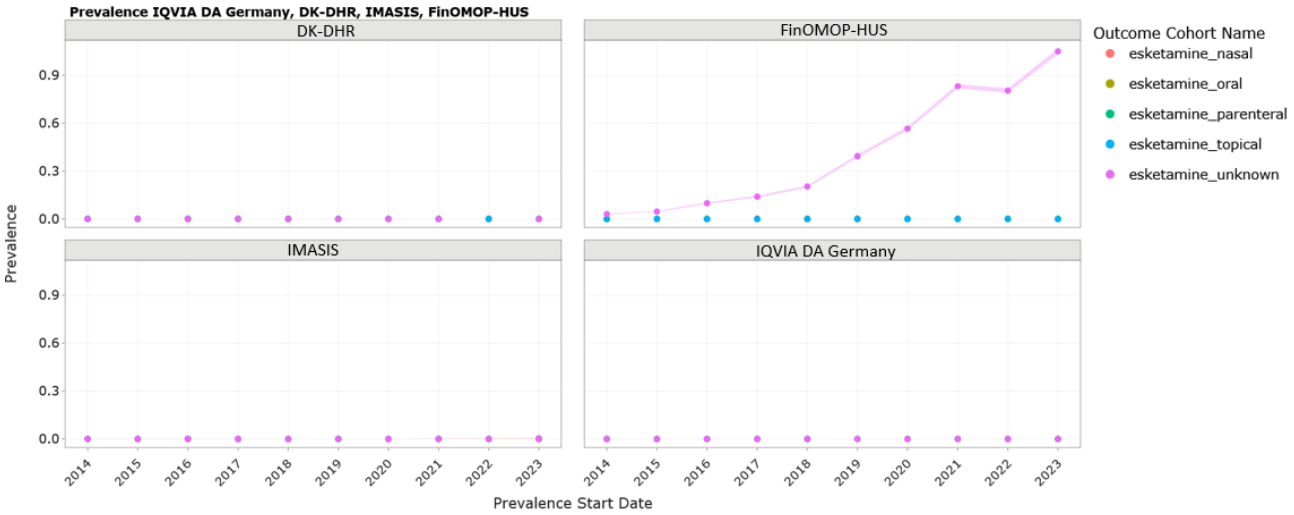


Figure 35. Monthly prevalence of esketamine prescriptions across data sources during the study period stratified by route of administration. Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



B

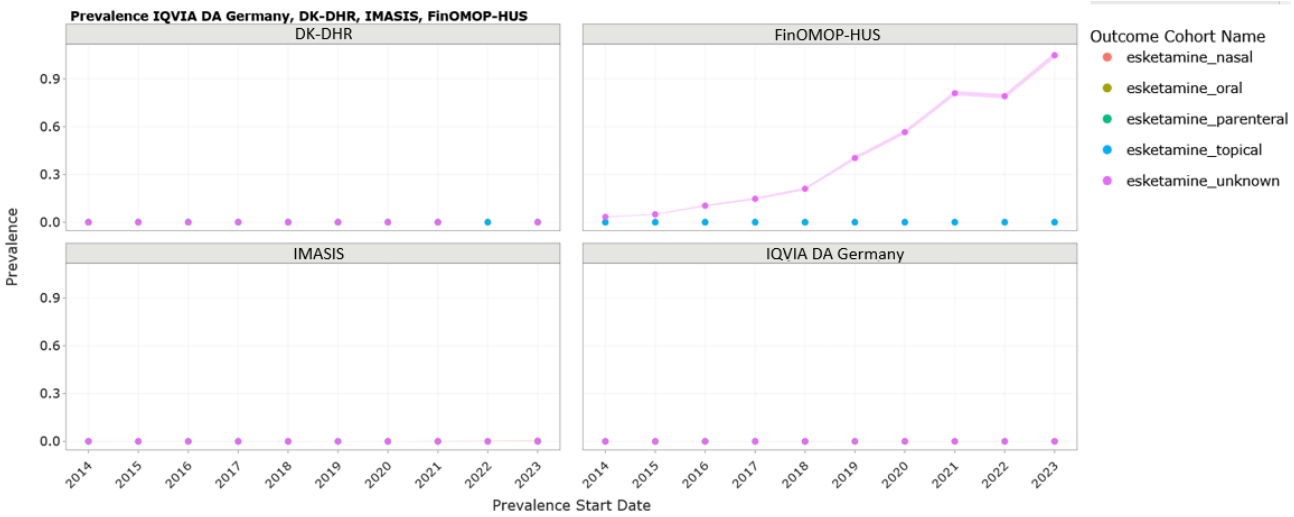


Figure 36. Annual prevalence of esketamine prescriptions across data sources during the study period stratified by route of administration. Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

12.2. Patient characterisation

12.2.1 Demographic characteristics of the study population

Table 9 provides a detailed overview of demographic characteristics of individuals prescribed ketamine and esketamine at the time of new prescription across data sources between 2014 and 2023.

If at least one year of prior data visibility was required, the median age of new users of ketamine at the time of prescription ranged from 34 years in IQVIA DA Germany to 66 years in the IMASIS. The median age of new users of esketamine ranged from 47 years in IQVIA DA Germany to 60 years in DK-DHR and FinOMOP-HUS. The proportion of males among new users of ketamine was higher in CDW Bordeaux (56.21%) and IQVIA DA Germany (56.45%) and comparable in CPRD GOLD (50.95%), while females were the majority in FinOMOP-HUS (60.77%) and IMASIS (51.40%). Most new users of esketamine were male in DK-DHR (55.31%) and IQVIA DA Germany (63.41%), while the majority was female in IMASIS (55.56%), and the sex distribution was balanced in FinOMOP-HUS (50.48% males).

If at least one year of prior data visibility was not required, the median age of new users of ketamine at the time of prescription ranged from 36 years in the FinOMOP-HUS to 65 years in the IMASIS. The median age of new users of esketamine ranged from 47 years in IQVIA DA Germany to 60 years in DK-DHR and FinOMOP-HUS. The proportion of males among new users of ketamine was higher in CDW Bordeaux (58.68%) and IQVIA DA Germany (55.96%). In contrast, females accounted for a higher proportion in FinOMOP-HUS (60.00%), while CPRD GOLD and IMASIS showed equal proportions of males and females. Most new users of esketamine were male in the DK-DHR (55.31%), FinOMOP-HUS (51.76%), and IQVIA DA Germany (58.93%), while the majority was female in the IMASIS (60.00%).

Table 9. Demographic characteristics of individuals who are prescribed ketamine or esketamine at the time of a new prescription, presented by drug of interest, data source, and prior observation criterion.

	Prior observation required*						No prior observation required*					
	CDW Bordeaux	CPRD GOLD	DK-DHR	FinOMOP-HUS	IMASIS	IQVIA DA Germany	CDW Bordeaux	CPRD GOLD	DK-DHR	FinOMOP-HUS	IMASIS	IQVIA DA Germany
Ketamine												
Number of records	3,254	475	0	543	3,739	62	5,666	513	0	560	4,225	109
Number of individuals	3,154	468	0	507	3,646	48	5,529	505	0	524	4,127	92
Cohort start date (minimum)	7-1-2014	10-1-2014	-	17-2-2014	3-1-2014	8-1-2014	2-1-2014	10-1-2014	-	11-2-2014	3-1-2014	8-1-2014
Cohort end date (maximum)	30-1-2024	9-6-2024	-	15-5-2025	29-12-2023	5-4-2023	30-1-2024	9-6-2024	-	14-5-2025	29-12-2023	5-4-2023
Age at index (years), median (IQR)	58 (41–67)	62 (51–69)	-	36 (26–50)	66 (53–77)	34 (18–58)	58 (40–68)	61 (51–69)	-	36 (25–50)	65 (51–76)	51 (22–69)
Age range (years)	1–97	6–96	-	<10–>90	1–101	2–93	1–97	6–96	-	<10–>90	1–101	2–93
Sex, n (%)												
• Female	1,424 (43.76)	233 (49.05)	-	330 (60.77)	1,922 (51.40)	24 (38.71)	2,340 (41.30)	253 (49.32)	-	336 (60.00)	2,146 (50.79)	45 (41.28)
• Male	1,829 (56.21)	242 (50.95)	-	213 (39.23)	1,817 (48.60)	35 (56.45)	3,325 (58.68)	260 (50.68)	-	224 (40.00)	2,079 (49.21)	61 (55.96)
• Missing	<5	-	-	-	-	<5	<5	-	-	-	-	<5
Esketamine												
Number of records	0	0	226	57,276	9	82	0	0	226	60,933	10	112
Number of individuals	0	0	224	53,657	9	51	0	0	224	57,210	10	80
Cohort start date (minimum)	-	-	16-1-2014	1-1-2014	15-12-2022	24-4-2014	-	-	16-1-2014	1-1-2014	15-12-2022	24-4-2014
Cohort end date (maximum)	-	-	26-10-2023	19-12-2024	12-7-2024	12-1-2024	-	-	26-10-2023	18-7-2025	12-7-2024	12-1-2024

	Prior observation required*						No prior observation required*					
	CDW Bordeaux	CPRD GOLD	DK-DHR	FinOMOP-HUS	IMASIS	IQVIA DA Germany	CDW Bordeaux	CPRD GOLD	DK-DHR	FinOMOP-HUS	IMASIS	IQVIA DA Germany
Age at index (years), median (IQR)	-	-	60 (51–68)	60 (44–72)	52 (51–58)	47 (22–61)	-	-	60 (51–58)	60 (43–72)	54 (51–62)	47 (25–63)
Age range (years)	-	-	19–96	<10–>90	47–64	1–87	-	-	<10–>90	1–101	47–71	1–93
Sex, n (%)												
• Female	-	-	101 (44.69)	28,361 (49.52)	5 (55.56)	28 (34.15)	-	-	101 (44.69)	29,391 (48.23)	6 (60.00)	43 (38.39)
• Male	-	-	125 (55.31)	28,915 (50.48)	<5	52 (63.41)	-	-	125 (55.31)	31,538 (51.76)	<5	66 (58.93)
• Missing	-	-	-	-	-	<5	-	-	-	<5	-	<5

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; CPRD GOLD = Clinical Practice Research Datalink GOLD; IQVIA DA Germany = IQVIA Disease Analyzer Germany; DK-DHR = Danish Data Health Registries; FinOMOP-HUS = Hospital District of Helsinki and Uusimaa; IMASIS = Institut Municipal Assistència Sanitària Information System; *Indicates whether the criterion of at least one year of data visibility prior to the prescription date is applied or not.

12.2.2 Participants

Table 10 provides the number of individuals newly prescribed ketamine or esketamine and the corresponding number of records across data sources between 1st of January 2014 and 31st of December 2023. Eligibility criteria also included no prior use of the respective medication in the previous year and at least one year of data visibility prior to the date of prescription or dispensation. As part of the sensitivity analysis, the counts without the criterion of at least one year of data visibility prior to the prescription or dispensation date are also included.

Overall, there were 7,823 new users of ketamine if prior observation was required (CDW Bordeaux: 3,154, CPRD GOLD: 468, FinOMOP-HUS: 507, IMASIS: 3,646, IQVIA DA Germany: 48) and 10,779 new users of ketamine if prior observation was not required (CDW Bordeaux: 5,529, CPRD GOLD: 505, FinOMOP-HUS: 526, IMASIS: 4,127, IQVIA DA Germany: 92) (**Table 10**). Also, there were 53,941 new users of esketamine if prior observation was required (DK-DHR: 224, FinOMOP-HUS: 53,657, IMASIS: 9, IQVIA DA Germany: 51) and 58,718 new users of esketamine if prior observation was not required (DK-DHR: 224, FinOMOP-HUS: 58,404, IMASIS: 10, IQVIA DA Germany: 80).

Applying the prior observation criterion, IMASIS contributed the largest proportion of new users of ketamine, accounting for 46.60% of the total. FinOMOP-HUS contributed the largest proportion of new users of esketamine, accounting for 99.47% of the total. No qualifying treatment initiations were identified for ketamine in DK-DHR and for esketamine in CDW Bordeaux and CPRD GOLD.

For CDW Bordeaux and IMASIS, we also assessed whether ketamine and esketamine were prescribed in an intensive care unit (ICU) setting or a non-ICU setting, as shown in **Table 1** of **ANNEX II**. In both data sources, the majority of ketamine and esketamine prescriptions were in a non-ICU setting, irrespective of the prior observation criterion.

Table 10. Study attrition of participants based on prescribing of ketamine or esketamine and relevant inclusion criteria, presented by drug of interest, data source, and prior observation criterion.

	CDW Bordeaux		CPRD GOLD		DK-DHR		FinOMOP-HUS		IMASIS		IQVIA DA Germany	
	Records (n)*	Individuals (n)**	Records (n)*	Individuals (n)**	Records (n)*	Individuals (n)**	Records (n)*	Individuals (n)**	Records (n)*	Individuals (n)**	Records (n)*	Individuals (n)**
Criteria	**Ketamine - prior observation required*** **											
Database population	-	2,363,709	-	17,521,504	-	8,593,356	-	2,933,113	-	1,747,852	-	45,156,504
Initial qualifying events	15,700	9,947	7,340	1,280	309	115	15,518	6,712	8,574	5,913	1,109	971
Join exposures separated by 30 or less days	11,039	9,947	2,584	1,280	155	115	7,282	6,712	6,200	5,913	1,066	971
Require prior use washout of 365 days	10,204	9,947	1,320	1,280	120	115	6,797	6,712	6,075	5,913	999	971
Require 1-year prior observation	5,511	5,334	1,206	1,173	114	110	6,517	6,432	5,310	5,160	414	395
Require cohort_start_date between 2014-01-01 to 2023-12-31	3,254	3,154	475	468	0	0	543	507	3,739	3,646	62	48
No recorded death after the index date	3,254	3,154	475	468	0	0	543	507	3,739	3,646	62	48
Criteria	**Ketamine - no prior observation required*** **											
Database population	-	2,363,709	-	17,521,504	-	8,593,356	-	2,933,113	-	1,747,852	-	45,156,504
Initial qualifying events	15,700	9,947	7,340	1,280	309	115	15,518	6,712	8,574	5,913	1,109	971
Join exposures separated by 30 or less days	11,039	9,947	2,584	1,280	155	115	7,282	6,712	6,200	5,913	1,066	971
Require prior use washout of 365 days	10,204	9,947	1,320	1,280	120	115	6,797	6,712	6,075	5,913	999	971
Require cohort_start_date between 2014-01-01 to 2023-12-31	5,710	5,573	513	505	0	0	6,797	6,712	4,225	4,127	114	97
No recorded death after the index date	5,666	5,529	513	505	0	0	562	526	4,225	4,127	109	92
Criteria	**Esketamine - prior observation required*** **											
Database population	-	2,363,709	-	17,521,504	-	8,593,356	-	2,933,113	-	1,747,852	-	45,156,504
Initial qualifying events	0	0	0	0	612	470	121,759	81,949	63	17	198	104

	CDW Bordeaux		CPRD GOLD		DK-DHR		FinOMOP-HUS		IMASIS		IQVIA DA Germany	
	Records (n)*	Individuals (n)**	Records (n)*	Individuals (n)**	Records (n)*	Individuals (n)**	Records (n)*	Individuals (n)**	Records (n)*	Individuals (n)**	Records (n)*	Individuals (n)**
Join exposures separated by 30 or less days	0	0	0	0	510	470	99,463	81,949	18	17	183	104
Require prior use washout of 365 days	0	0	0	0	473	470	89,177	81,949	17	17	150	104
Require 1 year prior observation	0	0	0	0	472	469	82,788	75,808	16	16	103	62
Require cohort_start_date between 2014-01-01 to 2023-12-31	0	0	0	0	226	224	57,276	53,657	9	9	82	51
No recorded death after the index date	0	0	0	0	226	224	57,276	53,657	9	9	82	51
Criteria	**Esketamine - no prior observation required*** **											
Database population	-	2,363,709	-	17,521,504	-	8,593,356	-	2,933,113	-	1,747,852	-	45,156,504
Initial qualifying events	0	0	0	0	612	470	121,759	81,949	63	17	198	104
Join exposures separated by 30 or less days	0	0	0	0	510	470	99,463	81,949	18	17	183	104
Require prior use washout of 365 days	0	0	0	0	473	470	89,177	81,949	17	17	150	104
Require cohort_start_date between 2014-01-01 to 2023-12-31	0	0	0	0	226	224	89,177	81,949	10	10	113	81
No recorded death after the index date	0	0	0	0	226	224	62,140	58,404	10	10	112	80

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; CPRD GOLD = Clinical Practice Research Datalink GOLD; IQVIA DA Germany = IQVIA Disease Analyzer Germany; DK-DHR = Danish Data Health Registries; FinOMOP-HUS = Hospital District of Helsinki and Uusimaa; IMASIS = Institut Municipal Assistència Sanitària Information System; *Number of records = number of prescriptions; **Number of individuals = number of unique individuals; ***Indicates whether the criterion of at least one year of data visibility prior to the prescription date is applied or not.

12.2.3 Main results

12.2.3.1 Pre-specified conditions and procedures

Tables 11A–11B display the frequency of pre-specified conditions (within one year prior to the index date) and procedures (in a window of 2 days before and 2 days after the index date) of interest in individuals being prescribed ketamine and esketamine. The index date refers to the date of a new prescription for each new treatment. For clarity, the results from the time window "at index date" are omitted from this table but are presented in the "shiny app" EUPAS1000000436. The results are presented by drug of interest and, as part of the sensitivity analysis, whether the criterion of at least one year of data visibility prior to the prescription date is applied or not.

If at least one year of prior data visibility was required, the most frequent pre-specified conditions recorded in the year prior to ketamine prescriptions were anxiety, cancer, and depression (**Table 11A**). The frequency of anxiety ranged from 3.8% in CPRD-GOLD to 29.3% in FinOMOP-HUS. For cancer, the frequencies ranged from 7.4% in FinOMOP-HUS to 44.6% in CDW Bordeaux. Depression records ranged from 1.3% in CPRD GOLD to 68.3% in FinOMOP-HUS. Notably, many ketamine users had an unknown condition, ranging from 15.7% in FinOMOP-HUS to 56.5% in IMASIS, indicating that these individuals had records of conditions that were not included in the pre-specified list. In IQVIA DA Germany, a large proportion (35.5%) had no recorded conditions in the year prior to the ketamine prescription.

For esketamine, the most frequent pre-specified conditions recorded in the year prior to the esketamine prescriptions were cancer, chronic pain, and depression (**Table 11B**). The frequency of cancer records ranged from 7.3% in IQVIA DA Germany to 93.8% in DK-DHR. For chronic pain, the frequencies ranged from 0.8% in FinOMOP-HUS to 69.5% in DK-DHR. Depression records ranged from 3.2% in FinOMOP-HUS to 100% in IMASIS. Notably, many esketamine users in IQVIA DA Germany and FinOMOP-HUS had an unknown condition, representing 20.7% and 70.2% of the esketamine users, respectively, indicating that these individuals had records of conditions that were not included in the pre-specified list. In IQVIA DA Germany, a large proportion (54.9%) had no recorded conditions in the year prior to their esketamine prescription.

The pattern of most frequent pre-specified conditions was similar if the one year of prior data visibility criterion was not applied, with anxiety, cancer, and depression being most common among ketamine users and cancer, chronic pain, and depression being most common among esketamine users. Again, a significant proportion of ketamine and esketamine users had records of conditions other than the ones pre-specified. In IQVIA DA Germany, 22.9% of ketamine users and 45.5% of esketamine users had no recorded condition in the year prior to their prescription of ketamine or esketamine.

Among ketamine users, if at least one year of prior data visibility was required, the frequency of sedation or anaesthesia procedures recorded during the two days before to two days after the ketamine prescription ranged from 0.1% in IMASIS to 9.0% in FinOMOP-HUS (**Table 11A**). There were no records of sedation or anaesthesia procedures in the primary care data sources CPRD GOLD and IQVIA DA Germany among ketamine users in this time window. For surgical procedures, the frequencies ranged from 5.2% in FinOMOP-HUS to 75.8% in IMASIS during the two days before to two days after the ketamine prescription. There were no or less than five records of surgical procedures in CPRD GOLD and IQVIA DA Germany among ketamine users during this time window. The frequency of unknown procedures ranged from 8.1% in IMASIS to 82.0% in CDW Bordeaux. In IQVIA DA Germany, counts for unknown procedures were below 5. Several ketamine users had no recorded procedures during this time window across all data sources, with frequencies ranging from 9.9% in CDW Bordeaux to 95.2% in IQVIA DA Germany.

Among ketamine users, if no prior data visibility was required, the frequency of sedation or anaesthesia procedures recorded during the two days before to two days after the ketamine prescription ranged from

0.1% in IMASIS to 9.3% in FinOMOP-HUS. There were no records of sedation or anaesthesia procedures in CPRD GOLD and IQVIA DA Germany among ketamine users in this time window. For surgical procedures, the frequencies ranged from 5.4% in FinOMOP-HUS to 75.1% in IMASIS during the two days before to two days after the ketamine prescription. There were no or fewer than five records of surgical procedures in CPRD GOLD and IQVIA DA Germany among ketamine users during this time window. The frequency of unknown procedures ranged from 4.6% in IQVIA DA Germany to 83.9% in CDW Bordeaux. Several ketamine users had no recorded procedures during this time window across all data sources, with frequencies ranging from 6.9% in CDW Bordeaux to 95.0% in IQVIA DA Germany.

Among esketamine users, if at least one year of prior data visibility was required, sedation or anaesthesia procedures during the two days before to two days after the esketamine prescription were only recorded in FinOMOP-HUS (87.2%) (**Table 11B**). For surgical procedures, 69.8% of the individuals prescribed esketamine had a record of surgical procedures during this time window in FinOMOP-HUS. There were no records of sedation or anaesthesia or surgical procedures in DK-DHR, IMASIS, and IQVIA DA Germany among esketamine users in this time window. The frequency of unknown procedures was 4.8% in FinOMOP-HUS and 46.5% in DK-DHR. No procedures were recorded for 7.4% in FinOMOP-HUS to 100% in IQVIA DA Germany among esketamine users during this time window.

Among esketamine users, if no prior data visibility was required, sedation or anaesthesia procedures during the two days before to two days after the esketamine prescription were only recorded in FinOMOP-HUS (86.9%). For surgical procedures, 69.2% of the individuals prescribed esketamine had the record in FinOMOP-HUS. There were no or fewer than five records of sedation or anaesthesia or surgical procedures in DK-DHR, IMASIS, and IQVIA DA Germany. The frequency of unknown procedures was 5.0% in FinOMOP-HUS and 46.5% in DK-DHR. No procedures were recorded for 7.5% in FinOMOP-HUS to 99.1% in IQVIA DA Germany.

Table 11A. Frequency of pre-specified conditions of interest in individuals being prescribed ketamine in a window around the index date, presented by data source and prior observation criterion.

	Prior observation required*					No prior observation required*				
	CDW Bordeaux (n = 3,254)	CPRD GOLD (n = 475)	FinOMOP-HUS (n = 543)	IMASIS (n = 3,739)	IQVIA DA Germany (n = 62)	CDW Bordeaux (n = 5,666)	CPRD GOLD (n = 513)	FinOMOP-HUS (n = 562)	IMASIS (n = 4,225)	IQVIA DA Germany (n = 109)
Conditions										
acute pain, n (%)	360 (11.1)	<5	10 (1.8)	9 (0.2)	<5	603 (10.6)	<5	10 (1.8)	13 (0.3)	<5
anxiety disorder, n (%)	750 (23.0)	18 (3.8)	159 (29.3)	177 (4.7)	8 (12.9)	1,215 (21.4)	19 (3.7)	160 (28.6)	186 (4.4)	11 (10.1)
bipolar disorder, n (%)	39 (1.2)	0	68 (12.5)	14 (0.4)	<5	47 (0.8)	0	68 (12.1)	15 (0.4)	<5
cancer, n (%)	1,450 (44.6)	196 (41.3)	40 (7.4)	1,035 (27.7)	7 (11.3)	2,599 (45.9)	207 (40.4)	45 (8.0)	1,202 (28.4)	33 (30.3)
chronic pain, n (%)	475 (14.6)	12 (2.5)	30 (5.5)	231 (6.2)	<5	589 (10.4)	13 (2.5)	30 (5.4)	243 (5.8)	14 (12.8)
depression, n (%)	329 (10.1)	6 (1.3)	371 (68.3)	417 (11.2)	<5	460 (8.1)	6 (1.2)	374 (66.8)	433 (10.2)	5 (4.6)
epilepsy, n (%)	121 (3.7)	<5	9 (1.7)	36 (1.0)	<5	166 (2.9)	<5	10 (1.8)	37 (0.9)	<5
migraine, n (%)	27 (0.8)	<5	23 (4.2)	46 (1.2)	<5	36 (0.6)	<5	24 (4.3)	51 (1.2)	<5
none, n (%)	33 (1.0)	14 (2.9)	8 (1.5)	38 (1.0)	22 (35.5)	59 (1.0)	22 (4.3)	8 (1.4)	44 (1.0)	25 (22.9)
not in observation, n (%)	0	0	0	0	0	0	0	0	0	0
post-traumatic stress disorder, n (%)	11 (0.3)	0	21 (3.9)	0	0	15 (0.3)	0	21 (3.8)	0	0
unknown, n (%)	946 (29.1)	237 (49.9)	85 (15.7)	2,112 (56.5)	19 (30.6)	1,768 (31.2)	254 (49.5)	93 (16.6)	2,397 (56.7)	32 (29.4)
Procedures										
none, n (%)	322 (9.9)	201 (42.3)	126 (23.2)	605 (16.2)	59 (95.2)	391 (6.9)	217 (42.3)	130 (23.2)	726 (17.2)	104 (95.0)
not in observation, n (%)	0	0	0	0	0	0	0	0	0	0
sedation anaesthesia, n (%)	71 (2.2)	0	49 (9.0)	5 (0.1)	0	126 (2.2)	0	52 (9.3)	6 (0.1)	0
surgical procedure, n (%)	201 (6.2)	<5	28 (5.2)	2,833 (75.8)	0	411 (7.3)	<5	30 (5.4)	3,172 (75.1)	0

	Prior observation required*					No prior observation required*				
	CDW Bordeaux (n = 3,254)	CPRD GOLD (n = 475)	FinOMOP-HUS (n = 543)	IMASIS (n = 3,739)	IQVIA DA Germany (n = 62)	CDW Bordeaux (n = 5,666)	CPRD GOLD (n = 513)	FinOMOP-HUS (n = 562)	IMASIS (n = 4,225)	IQVIA DA Germany (n = 109)
unknown, n (%)	2,668 (82.0)	270 (56.8)	361 (66.5)	301 (8.1)	<5	4,755 (83.9)	292 (56.9)	370 (66.1)	327 (7.7)	5 (4.6)

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; CPRD GOLD = Clinical Practice Research Datalink GOLD; IQVIA DA Germany = IQVIA Disease Analyzer Germany; DK-DHR = Danish Data Health Registries; FinOMOP-HUS = Hospital District of Helsinki and Uusimaa; IMASIS = Institut Municipal Assistència Sanitària Information System. Number of records is displayed per medication per data source. Data sources without any records for the respective medication are omitted from the table. The frequency of the conditions assessed within one year prior to the index and the frequency of the procedures assessed in a window of 2 days before and 2 days after the index date is displayed. *Indicates whether the criterion of at least one year of data visibility prior to the prescription date is applied or not.

Table 11B. Frequency of pre-specified conditions of interest in individuals being prescribed esketamine in a window around the index date, presented by data source and prior observation criterion.

	Prior observation required*				No prior observation required*			
	DK-DHR (n = 226)	FinOMOP-HUS (n = 57,276)	IMASIS (n = 9)	IQVIA DA Germany (n = 82)	DK-DHR (n = 226)	FinOMOP-HUS (n = 60,933)	IMASIS (n = 10)	IQVIA DA Germany (n = 112)
Conditions								
acute pain, n (%)	11 (4.9)	1,800 (3.1)	0	0	11 (4.9)	2,028 (3.3)	0	<5
anxiety disorder, n (%)	87 (38.5)	1,557 (2.7)	<5	<5	87 (38.5)	1,584 (2.6)	<5	7 (6.3)
bipolar disorder, n (%)	0	389 (0.7)	0	<5	0	391 (0.64)	0	<5
cancer, n (%)	212 (93.8)	11,977 (20.9)	<5	6 (7.3)	212 (93.8)	12,688 (20.8)	<5	20 (17.9)
chronic pain, n (%)	157 (69.5)	469 (0.8)	<5	7 (8.5)	157 (69.5)	477 (0.8)	<5	19 (17.0)
depression, n (%)	67 (29.6)	1,807 (3.2)	9 (100)	6 (7.3)	67 (29.6)	1,831 (3.0)	10 (100)	8 (7.1)
epilepsy, n (%)	10 (4.4)	457 (0.8)	0	<5	10 (4.4)	458 (0.8)	0	5 (4.5)
migraine, n (%)	<5	628 (1.1)	<5	<5	<5	632 (1.0)	<5	<5
none, n (%)	0	344 (0.6)	0	45 (54.9)	0	429 (0.7)	0	51 (45.5)
not in observation, n (%)	0	0	0	0	0	0 (0)	0	0
post-traumatic stress disorder, n (%)	0	151 (0.3)	0	0	0	153 (0.3)	0	0
unknown, n (%)	<5	40,195 (70.2)	0	17 (20.7)	<5	42,853 (70.3)	0	21 (18.8)
Procedures								
none, n (%)	120 (53.1)	4,241 (7.4)	8 (88.9)	82 (100)	120 (53.1)	4,540 (7.5)	9 (90.0)	111 (99.1)
not in observation, n (%)	0	0	0	0	0	0	0	0
sedation anaesthesia, n (%)	0	49,938 (87.2)	0	0	0	52,974 (86.9)	0	0
surgical procedure, n (%)	0	39,989 (69.8)	0	0	0	42,192 (69.2)	0	<5
unknown, n (%)	105 (46.5)	2,764 (4.8)	<5	0	105 (46.5)	3,063 (5.0)	<5	0

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; CPRD GOLD = Clinical Practice Research Datalink GOLD; IQVIA DA Germany = IQVIA Disease Analyzer Germany; DK-DHR = Danish Data Health Registries; FinOMOP-HUS = Hospital District of Helsinki and Uusimaa; IMASIS = Institut Municipal Assistència Sanitària Information System. Number of records is displayed per medication per data source. Data sources without any records for the respective medication are omitted from the table. The frequency of the conditions assessed within one year prior to the index and the frequency of the procedures assessed in a window of 2 days before and 2 days after the index date is displayed. *Indicates whether the criterion of at least one year of data visibility prior to the prescription date is applied or not.

12.2.3.2 Comorbidities

Tables 12A–12B present the frequency of top recorded diagnoses among individuals prescribed ketamine and esketamine. These were individual diagnosis codes rather than aggregated lists of codes for a specific pre-specified condition of interest. The results presented in the report reflect diagnoses recorded within one year window prior to the index date (the time of first prescription of each new treatment episode). The results are presented by drug, data source, and for the sensitivity analysis. The results from the time window "at index date" are presented in the "shiny app" (EUPAS1000000436).

The prevalence of comorbidities varied between ketamine and esketamine and across the data sources. Commonly observed conditions among new users of ketamine included pain, essential hypertension, and recurrent major depression, irrespective of the criterion of one year of prior data visibility. Commonly observed conditions among new users of esketamine included essential hypertension, recurrent major depression, and pain, irrespective of the criterion of one year of prior data visibility. For both medicines, there was some variation in the frequency of recorded diagnoses depending on the data source.

12.2.3.3 Concomitant medication

Tables 13A–13B present the top 10 of the most frequently recorded medications among individuals prescribed ketamine and esketamine within a one year window prior to the index date (the time of incident prescription of the selected medicinal products). The results are presented by drug, data source, and for the sensitivity analysis. The results from the time window "at index date" are presented in the "shiny app" (EUPAS1000000436).

The pattern of recorded medication use varied between ketamine and esketamine and across the data sources. The common pattern included medication related to pain management and electrolyte balance. Additionally, there was evidence of medication related to anaesthesia and managing gastrointestinal health, anxiety, and sleep disorders. The criterion of one year of prior data visibility did not impact the pattern. For both medicines, there was some variation in the frequency of recorded medication depending on the data source.

Table 12A. Frequency of top 10 comorbidities in individuals being prescribed ketamine in a window prior index date (one year before index date), presented by drug, data source, and prior observation criterion.

Prior observation required*					No prior observation required*				
CDW Bordeaux (n = 3,254)	CPRD GOLD (n = 475)	FinOMOP-HUS (n =543)	IMASIS (n = 3,739)	IQVIA DA Germany (n = 62)	CDW Bordeaux (n = 5,666)	CPRD GOLD (n = 513)	FinOMOP-HUS (n = 562)	IMASIS (n = 4,225)	IQVIA DA Germany (n = 109)
Essential hypertension, 1118 (34%)	Pain, 81 (17%)	Severe recurrent major depression without psychotic features, 215 (40%)	Essential hypertension, 1,303 (35%)	Illness, 9 (15%)	Essential hypertension , 1,874 (33%)	Pain, 84 (16%)	Severe recurrent major depression without psychotic features, 216 (39%)	Essential hypertension, 1,382 (33%)	Essential hypertension, 10 (9%)
Tobacco dependence in remission, 785 (24%)	Constipation, 77 (16%)	Severe major depression, single episode, without psychotic features, 116 (21%)	Hyperlipidemia , 826 (22%)	Seborrheic dermatitis of scalp, 7 (11%)	Tobacco dependence in remission, 1,289 (23%)	Constipation, 80 (16%)	Severe major depression, single episode, without psychotic features, 117 (21%)	Hyperlipidemia, 877 (21%)	Chronic intractable pain, 10 (9%)
Hyperkalemia, 781 (24%)	Backache, 58 (12%)	Recurrent depression with current moderate episode, 85 (16%)	COVID-19, 566 (15%)	Constipation, 5 (8%)	Hyperkalemia, 1,253 (22%)	Allergic reaction to drug, 61 (12%)	Recurrent depression with current moderate episode, 85 (15%)	COVID-19, 621 (15%)	Illness, 10 (9%)
Hypo-osmolality and/or hyponatremia, 769 (24%)	Allergic reaction to drug, 53 (11%)	Anxiety disorder, 75 (14%)	Type 2 diabetes mellitus without complication, 555 (15%)	Acute upper respiratory infection, 5 (8%)	Hyponatremia with decreased serum osmolality, 1,226 (22%)	Backache, 60 (12%)	Anxiety disorder, 75 (13%)	Type 2 diabetes mellitus without complication, 584 (14%)	Seborrheic dermatitis of scalp, 9 (8%)
Hyponatremia with decreased serum osmolality, 769 (24%)	Abdominal pain, 41 (9%)	Poisoning by anti-infective agent, 64 (12%)	Obesity, 451 (12%)	Superficial injury, 5 (8%)	Hypo-osmolality and/or hyponatremia, 1,226 (22%)	Abdominal pain, 41 (8%)	Poisoning by anti-infective agent, 64 (11%)	Obesity, 474 (11%)	Primary malignant neoplasm of respiratory tract, 9 (8%)

Prior observation required*					No prior observation required*				
CDW Bordeaux (n = 3,254)	**CPRD GOLD (n = 475)**	**FinOMOP-HUS (n =543)**	**IMASIS (n = 3,739)**	**IQVIA DA Germany (n = 62)**	**CDW Bordeaux (n = 5,666)**	**CPRD GOLD (n = 513)**	**FinOMOP-HUS (n = 562)**	**IMASIS (n = 4,225)**	**IQVIA DA Germany (n = 109)**
Nausea and vomiting, 750 (23%)	Urinary tract infectious disease, 32 (7%)	Recurrent major depression, 62 (11%)	Cataract, 388 (10%)	Bodily distress disorder, 5 (8%)	Nausea and vomiting, 1,196 (21%)	Cough, 34 (7%)	Recurrent major depression, 63 (11%)	Acute posthemorrhagic anemia, 427 (10%)	Primary malignant neoplasm of breast, 8 (7%)
Hypokalemia, 628 (19%)	Cough, 32 (7%)	Emotionally unstable personality disorder, 60 (11%)	Acute posthemorrhagic anemia, 384 (10%)		Hypokalemia, 995 (18%)	Urinary tract infectious disease, 32 (6%)	Emotionally unstable personality disorder, 60 (11%)	Cataract, 411 (10%)	Chronic ischemic heart disease, 7 (6%)
Constipation, 603 (19%)	Pain in lower limb, 30 (6%)	Intentional self poisoning, 49 (9%)	Nicotine dependence, 375 (10%)		Constipation, 977 (17%)	Pain in lower limb, 32 (6%)	Severe recurrent major depression with psychotic features, mood-congruent, 49 (9%)	Nicotine dependence, 407 (10%)	Type 2 diabetes mellitus without complication, 7 (6%)
Fatigue, 600 (18%)	Low back pain, 29 (6%)	Severe recurrent major depression with psychotic features, mood-congruent, 48 (9%)	Chronic obstructive lung disease, 286 (8%)		Obesity, 942 (17%)	Low back pain, 30 (6%)	Intentional self poisoning, 49 (9%)	Chronic obstructive lung disease, 295 (7%)	Constipation, 6 (6%)
Obesity, 560 (17%)	Chest pain, 27 (6%)	Injury whilst engaged in leisure activity, 46 (8%)	Acute kidney injury, 265 (7%)		Pleural effusion, 927 (16%)	Chest pain, 29 (6%)	Injury whilst engaged in leisure activity, 46 (8%)	Acute kidney injury, 283 (7%)	Pruritic rash, 6 (6%)

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; CPRD GOLD = Clinical Practice Research Datalink GOLD; IQVIA DA Germany = IQVIA Disease Analyzer Germany; DK-DHR = Danish Data Health Registries; FinOMOP-HUS = Hospital District of Helsinki and Uusimaa; IMASIS = Institut Municipal Assistència Sanitària Information System. Number of records is displayed per medication per data source. Data sources without any records for the respective medication are omitted from the table. The frequency of the conditions assessed within one year prior to the index is displayed. Conditions with counts <5 are omitted from the table, resulting in empty cells in the table. *Indicates whether the prerequisite of at least one year of data visibility prior to the prescription date is applied or not.

Table 12B. Frequency of top 10 comorbidities in individuals being prescribed esketamine in a window prior index date (one year before index date), presented by drug, data source, and prior observation criterion.

Prior observation required*				No prior observation required*			
DK-DHR (n = 226)	FinOMOP-HUS (n = 57,276)	IMASIS (n = 9)	IQVIA DA Germany (n = 82)	DK-DHR (n = 226)	FinOMOP-HUS (n = 60,933)	IMASIS (n = 10)	IQVIA DA Germany (n = 112)
Severe pain, 219 (97%)	Essential hypertension, 8,445 (15%)	Severe recurrent major depression without psychotic features, 7 (78%)	Nausea and vomiting, 9 (11%)	Severe pain, 219 (97%)	Essential hypertension, 8,530 (14%)	Severe recurrent major depression without psychotic features, 8 (80%)	Chronic pain, 15 (13%)
Pain, 219 (97%)	Injury whilst engaged in leisure activity, 5,599 (10%)	Recurrent major depression, 6 (67%)	Illness, 8 (10%)	Pain, 219 (97%)	Injury whilst engaged in leisure activity, 5,917 (10%)	Recurrent major depression, 6 (60%)	Illness, 12 (11%)
Constipation, 192 (85%)	Osteoarthritis of knee, 3,520 (6%)		Essential hypertension, 7 (9%)	Constipation, 192 (85%)	Osteoarthritis of knee, 3,538 (6%)		Hypothyroidism, 11 (10%)
Adrenal cortical hypofunction, 176 (78%)	Sleep apnea, 3,085 (5%)		Chronic pain, 7 (9%)	Adrenal cortical hypofunction, 176 (78%)	Sleep apnea, 3,100 (5%)		Nausea and vomiting, 10 (9%)
Chronic intractable pain, 147 (65%)	Hypercholesterolemia, 3,050 (5%)		Heart failure, 6 (7%)	Chronic intractable pain, 147 (65%)	Hypercholesterolemia, 3,078 (5%)		Metastatic malignant neoplasm, 9 (8%)
Nausea, 143 (63%)	Nerve root disorder, 2,982 (5%)		Constipation, 5 (6%)	Nausea, 143 (63%)	Nerve root disorder, 3,076 (5%)		Essential hypertension, 9 (8%)
Insomnia, 94 (42%)	Primary malignant neoplasm of prostate, 2,435 (4%)		Chronic ischemic heart disease, 5 (6%)	Insomnia, 94 (42%)	Primary malignant neoplasm of prostate, 2,588 (4%)		Polyneuropathy, 8 (7%)
Esophageal reflux finding, 93 (41%)	Osteoarthritis of hip, 2,391 (4%)		Nerve root disorder, 5 (6%)	Esophageal reflux finding, 93 (41%)	Osteoarthritis of hip, 2,417 (4%)		Constipation, 8 (7%)
Infectious disease, 88 (39%)	Type 2 diabetes mellitus without complication, 2,362 (4%)			Infectious disease, 88 (39%)	Type 2 diabetes mellitus without complication, 2,396 (4%)		Chronic ischemic heart disease, 7 (6%)

Prior observation required*				No prior observation required*			
DK-DHR (n = 226)	FinOMOP-HUS (n = 57,276)	IMASIS (n = 9)	IQVIA DA Germany (n = 82)	DK-DHR (n = 226)	FinOMOP-HUS (n = 60,933)	IMASIS (n = 10)	IQVIA DA Germany (n = 112)
Neuropathic pain, 84 (37%)	Spinal stenosis, 2,224 (4%)			Neuropathic pain, 84 (37%)	Spinal stenosis, 2,261 (4%)		Heart failure, 6 (5%)

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; CPRD GOLD = Clinical Practice Research Datalink GOLD; IQVIA DA Germany = IQVIA Disease Analyzer Germany; DK-DHR = Danish Data Health Registries; FinOMOP-HUS = Hospital District of Helsinki and Uusimaa; IMASIS = Institut Municipal Assistència Sanitària Information System. Number of records is displayed per medication per data source. Data sources without any records for the respective medication are omitted from the table. The frequency of the conditions assessed within one year prior to the index is displayed. Conditions with counts <5 were not reported, resulting in empty cells in the table. *Indicates whether the prerequisite of at least one year of data visibility prior to the prescription date is applied or not.

Table 13A. Frequency of top 10 recorded medication in individuals being prescribed ketamine in a window prior to the index date (one year prior to the index date), presented by drug, data source, and prior observation criterion.

Prior observation required*					No prior observation required*				
CDW Bordeaux (n = 3,254)	CPRD GOLD (n = 475)	FinOMOP-HUS (n = 543)	IMASIS (n = 3,739)	IQVIA DA Germany (n = 62)	CDW Bordeaux (n = 5,666)	CPRD GOLD (n = 513)	FinOMOP-HUS (n = 562)	IMASIS (n = 4,225)	IQVIA DA Germany (n = 109)
sodium, 2,559 (79%)	acetaminophen, 419 (88%)	acetaminophen, 340 (63%)	propofol, 3,333 (89%)	sodium, 28 (45%)	sodium, 4352 (77%)	acetaminophen, 443 (86%)	acetaminophen, 353 (63%)	propofol, 3,732 (88%)	midazolam, 47 (43%)
sodium 9 MG/ML Injectable Solution, 2,554 (78%)	morphine, 335 (71%)	ibuprofen, 232 (43%)	acetaminophen, 3,158 (84%)	dipyrone, 25 (40%)	sodium 9 MG/ML Injectable Solution, 4,345 (77%)	morphine, 351 (68%)	ibuprofen, 237 (42%)	acetaminophen, 3,560 (84%)	sodium, 38 (35%)
acetaminophen, 2,390 (73%)	omeprazole, 322 (68%)	quetiapine, 229 (42%)	100 ML Acetaminophen 10 MG/ML Injection [PARACETAMOL B BRAUN] Box of 10 by B.Braun, 3,022 (81%)	epinephrine, 24 (39%)	acetaminophen, 4,154 (73%)	omeprazole, 336 (66%)	quetiapine, 232 (41%)	100 ML Acetaminophen 10 MG/ML Injection [PARACETAMOL B BRAUN] Box of 10 by B.Braun, 3,404 (81%)	dipyrone, 35 (32%)
acetaminophen 10 MG/ML Injection, 2,000 (61%)	acetaminophen 500 MG Oral Tablet, 307 (65%)	oxazepam, 201 (37%)	20 ML Propofol 10 MG/ML Injectable Suspension Box of 5 by Baxter, 2,759 (74%)	diazepam, 23 (37%)	acetaminophen 10 MG/ML Injection, 3,521 (62%)	acetaminophen 500 MG Oral Tablet, 323 (63%)	oxazepam, 203 (36%)	20 ML Propofol 10 MG/ML Injectable Suspension Box of 5 by Baxter, 3,087 (73%)	morphine, 31 (28%)
glucose, 1,974 (61%)	omeprazole 20 MG Delayed Release Oral Capsule, 306 (64%)	propofol, 181 (33%)	sodium chloride, 2,678 (72%)	prednisolone, 23 (37%)	glucose, 3,494 (62%)	oxycodone, 322 (63%)	propofol, 186 (33%)	sodium chloride, 3,003 (71%)	dexamethasone, 29 (27%)

Prior observation required*					No prior observation required*				
CDW Bordeaux (n = 3,254)	CPRD GOLD (n = 475)	FinOMOP-HUS (n = 543)	IMASIS (n = 3,739)	IQVIA DA Germany (n = 62)	CDW Bordeaux (n = 5,666)	CPRD GOLD (n = 513)	FinOMOP-HUS (n = 562)	IMASIS (n = 4,225)	IQVIA DA Germany (n = 109)
potassium chloride, 1,916 (59%)	oxycodone, 301 (63%)	diazepam, 157 (29%)	omeprazole, 2,650 (71%)	midazolam, 20 (32%)	potassium chloride, 3,403 (60%)	omeprazole 20 MG Delayed Release Oral Capsule, 317 (62%)	ondansetron, 164 (29%)	omeprazole, 2,965 (70%)	metoclopramide, 27 (25%)
sodium chloride, 1,864 (57%)	pregabalin, 263 (55%)	ondansetron, 153 (28%)	potassium chloride, 2,398 (64%)	dimenhydrinate, 20 (32%)	sodium chloride, 3,323 (59%)	pregabalin, 273 (53%)	diazepam, 161 (29%)	midazolam, 2,725 (65%)	epinephrine, 26 (24%)
glucose 100 MG/ML / Potassium Chloride 2 MG/ML / Sodium Chloride 4 MG/ML Prefilled Syringe, 1,727 (53%)	potassium, 258 (54%)	pantoprazole, 147 (27%)	midazolam, 2,393 (64%)	dexamethasone, 19 (31%)	glucose 100 MG/ML / Potassium Chloride 2 MG/ML / Sodium Chloride 4 MG/ML Prefilled Syringe, 3,137 (55%)	potassium, 266 (52%)	pantoprazole, 150 (27%)	potassium chloride, 2,685 (64%)	prednisolone, 26 (24%)
nefopam, 1,485 (46%)	polyethylene glycol 3350, 252 (53%)	oxycodone, 144 (27%)	5 ML Midazolam 1 MG/ML Injectable Solution Box of 50, 2,328 (62%)	glucose, 19 (31%)	nefopam, 2,644 (47%)	dexamethasone, 263 (51%)	oxycodone, 150 (27%)	5 ML Midazolam 1 MG/ML Injectable Solution Box of 50, 2,653 (63%)	diazepam, 25 (23%)
nefopam 10 MG/ML Injectable Solution, 1,485 (46%)	sodium, 252 (53%)	temazepam, 143 (26%)	fentanyl, 2,282 (61%)	metoclopramide, 18 (29%)	nefopam 10 MG/ML Injectable Solution, 2,644 (47%)	polyethylene glycol 3350, 260 (51%)	temazepam, 145 (26%)	dexketoprofen, 2,590 (61%)	lorazepam, 24 (22%)

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Table 13B. Frequency of top 10 recorded medication in individuals being prescribed esketamine in a window prior to the index date (one year prior to the index date), presented by drug, data source, and prior observation criterion.

Prior observation required*				No prior observation required*			
DK-DHR (n = 226)	FinOMOP-HUS (n = 57,276)	IMASIS (n = 9)	IQVIA DA Germany (n = 82)	DK-DHR (n = 226)	FinOMOP-HUS (n = 60,933)	IMASIS (n = 10)	IQVIA DA Germany (n = 112)
acetaminophen 500 MG Oral Tablet, 185 (82%)	acetaminophen, 54,377 (95%)	quetiapine, 7 (78%)	diazepam, 50 (61%)	acetaminophen 500 MG Oral Tablet, 185 (82%)	oxycodone, 57,653 (95%)	quetiapine, 8 (80%)	sodium, 66 (59%)
prednisolone 25 MG Oral Tablet, 165 (73%)	oxycodone, 54,255 (95%)	lormetazepam, 6 (67%)	sodium, 50 (61%)	prednisolone 25 MG Oral Tablet, 165 (73%)	ondansetron, 51,869 (85%)	lormetazepam, 6 (60%)	diazepam, 55 (49%)
midazolam 5 MG/ML Injectable Solution, 148 (65%)	ondansetron, 48,950 (85%)	mirtazapine, 5 (56%)	prednisolone, 47 (57%)	midazolam 5 MG/ML Injectable Solution, 148 (65%)	propofol, 44,196 (73%)	mirtazapine, 6 (60%)	dimenhydrinate, 53 (47%)
pantoprazole 40 MG Delayed Release Oral Tablet, 143 (63%)	propofol, 41,992 (73%)	clonazepam, 5 (56%)	dimenhydrinate, 46 (56%)	pantoprazole 40 MG Delayed Release Oral Tablet, 143 (63%)	cefuroxime, 43,220 (71%)	clonazepam, 5 (50%)	prednisolone, 52 (46%)
POLYETHYLENE GLYCOL 3350 13100 MG / Potassium Chloride 50 MG / Sodium Bicarbonate 179 MG / Sodium Chloride 351 MG Powder for Oral Solution, 142 (63%)	cefuroxime, 40,888 (71%)	quetiapine, 5 (56%)	Epinephrine, 45 (55%)	POLYETHYLENE GLYCOL 3350 13100 MG / Potassium Chloride 50 MG / Sodium Bicarbonate 179 MG / Sodium Chloride 351 MG Powder for Oral Solution, 142 (63%)	fentanyl, 39,862 (65%)	quetiapine, 5 (50%)	dexamethasone, 51 (46%)
morphine sulfate 10 MG Oral Tablet, 140 (62%)	fentanyl, 37,685 (66%)	quetiapine 100 MG Oral Tablet, 5 (56%)	aspirin, 41 (50%)	morphine sulfate 10 MG Oral Tablet, 140 (62%)	lidocaine, 35,602 (58%)	quetiapine 100 MG Oral Tablet, 5 (50%)	epinephrine, 47 (42%)

Prior observation required*				No prior observation required*			
DK-DHR (n = 226)	FinOMOP-HUS (n = 57,276)	IMASIS (n = 9)	IQVIA DA Germany (n = 82)	DK-DHR (n = 226)	FinOMOP-HUS (n = 60,933)	IMASIS (n = 10)	IQVIA DA Germany (n = 112)
oxycodone hydrochloride 10 MG/ML Injectable Solution, 109 (48%)	lidocaine, 33,772 (59%)	clonazepam 2.5 MG/ML Oral Solution, 5 (56%)	dexamethasone, 41 (50%)	oxycodone hydrochloride 10 MG/ML Injectable Solution, 109 (48%)	droperidol, 31,890 (52%)	clonazepam 2.5 MG/ML Oral Solution, 5 (50%)	dipyrone, 47 (42%)
morphine sulfate 10 MG Extended Release Oral Tablet, 103 (46%)	droperidol, 30,201 (53%)		dimethindene, 39 (48%)	morphine sulfate 10 MG Extended Release Oral Tablet, 103 (46%)	ibuprofen, 30,652 (50%)		aspirin, 44 (39%)
methadone hydrochloride 5 MG Oral Tablet, 99 (44%)	ibuprofen, 28,915 (50%)		dipyrone, 37 (45%)	methadone hydrochloride 5 MG Oral Tablet, 99 (44%)	ropivacaine, 27,917 (46%)		dimethindene, 42 (38%)
picosulfate sodium 7.5 MG/ML Oral Solution, 98 (43%)	ropivacaine, 26,500 (46%)		urapidil, 35 (43%)	picosulfate sodium 7.5 MG/ML Oral Solution, 98 (43%)	rocuronium, 27,532 (45%)		midazolam, 41 (37%)

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; CPRD GOLD = Clinical Practice Research Datalink GOLD; IQVIA DA Germany = IQVIA Disease Analyzer Germany; DK-DHR = Danish Data Health Registries; FinOMOP-HUS = Hospital District of Helsinki and Uusimaa; IMASIS = Institut Municipal Assistència Sanitària Information System. Number of records is displayed per medication per data source. Data sources without any records for the respective medication are omitted from the table. The frequency of comedication assessed within one year prior to the index is displayed. Medications with counts <5 are omitted from the table, resulting in empty cells in the table. *Indicates whether the prerequisite of at least one year of data visibility prior to the prescription date is applied or not.

12.2.3.4 Dose and treatment duration

Information on the initial dose at treatment initiation, treatment duration of the first drug era, and cumulative duration of ketamine and esketamine use across the different data sources is provided in **Tables 14A–14B.** The results are stratified by medicine and data source, with sensitivity analysis findings reported separately.

For ketamine, the initial median dose varied from 16.7 milligrams in IQVIA DA Germany to 200 milligrams in CPRD GOLD irrespective of the one year of prior data visibility criterion. There are no records of the initial daily dose of ketamine in CDW Bordeaux and FinOMOP-HUS. The median duration of the first drug era ranged from 0 days in CDW Bordeaux and IMASIS to 29 days in IQVIA DA Germany irrespective of the one year of prior data visibility criterion. The median cumulative duration of ketamine use ranged from 1 day in CDW Bordeaux and IMASIS to 30 days in IQVIA DA Germany irrespective of the one year of prior data visibility criterion.

For esketamine, the initial median dose varied from 8 milligrams in IQVIA DA Germany to 33 milligrams in DK-DHR if the criterion of one year of prior data visibility was applied. Without this criterion, the initial dose varied from 7 milligrams in IMASIS to 33 milligrams in DK-DHR. There are no records of the initial daily dose of esketamine in FinOMOP-HUS. The median duration of the first drug era ranged from 1 day in FinOMOP-HUS to 29 days in DK-DHR, IMASIS, and IQVIA DA Germany irrespective of the one year of prior data visibility criterion. The median cumulative duration of esketamine ranged from 1 day in FinOMOP-HUS to 212 days in IMASIS if the criterion of one year of prior data visibility was applied. Without this criterion, the median cumulative duration of esketamine ranged from 1 day in FinOMOP-HUS to 224 days in IMASIS.

If elements that are needed for calculating the treatment duration are missing, the dates were imputed into the OMOP CDM based on standard conventions, therefore, the median treatment duration for ketamine and esketamine in IQVIA DA Germany may not represent the actual treatment duration.

Table 14A. Initial dose at treatment initiation, treatment duration of the first drug era, and cumulative duration of ketamine prescriptions, presented by drug, data source, and prior observation criterion.

	Prior observation required*					No prior observation required*				
	CDW Bordeaux (n = 3,254)	CPRD GOLD (n = 475)	FinOMOP-HUS (n = 543)	IMASIS (n = 3,739)	IQVIA DA Germany (n = 62)	CDW Bordeaux (n = 5,666)	CPRD GOLD (n = 513)	FinOMOP-HUS (n = 562)	IMASIS (n = 4,225)	IQVIA DA Germany (n = 109)
Initial daily dose (mg), median (IQR)	-	200 (80–2,000)	-	30 (15–40)	16.7 (14.9–33.3)	-	200 (80–1,500)	-	30 (15–40)	16.7 (16.7–33.3)
Initial exposure duration (days), median (IQR)	0 (0–0)	13 (0–24)	1 (1–1)	0 (0–0)	29 (29–29)	0 (0–0)	13 (0–24)	1 (1–1)	0 (0–0)	29 (29–29)
Cumulative exposure duration (days), median (IQR)	1 (1–2)	25 (9–68)	26 (6–50)	1 (1–1)	30 (30–30)	1 (1–2)	25 (8–69)	22 (4–50)	1 (1–1)	30 (30–30)

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; CPRD GOLD = Clinical Practice Research Datalink GOLD; IQVIA DA Germany = Disease Analyzer; DK-DHR = Danish Data Health Registries; FinOMOP-HUS = Hospital District of Helsinki and Uusimaa; IMASIS = Institut Municipal Assistència Sanitària Information System. Number of records is displayed per medication per data source. Data sources without any records for the respective medication are omitted from the table. The median and interquartile range of initial daily dose, initial exposure duration and cumulative exposure duration is displayed. *Indicates whether the prerequisite of at least one year of data visibility prior to the prescription date is applied or not.

Table 14B. Initial dose at treatment initiation, treatment duration of the first drug era, and cumulative duration of esketamine prescriptions, presented by drug, data source, and prior observation criterion.

	Prior observation required*				No prior observation required*			
	DK-DHR (n = 226)	FinOMOP-HUS (n = 57,276)	IMASIS (n = 9)	IQVIA DA Germany (n = 82)	DK-DHR (n = 226)	FinOMOP-HUS (n = 60,933)	IMASIS (n = 10)	IQVIA DA Germany (n = 112)
Initial daily dose (mg), median (IQR)	33 (16–50)	-	13 (0–112)	8 (1.7–8.3)	33 (16–50)	-	7 (0–112)	8 (1.7–8.3)
Initial exposure duration (days), median (IQR)	29 (29–29)	1 (1–2)	29 (0–29)	29 (29–29)	29 (29–29)	1 (1–2)	29 (0–29)	29 (29–29)
Cumulative exposure duration (days), median (IQR)	30 (13–49)	1 (1–3)	212 (175–316)	30 (30–30)	30 (13–49)	1 (1–3)	224 (181–360)	30 (30–30)

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; CPRD GOLD = Clinical Practice Research Datalink GOLD; IQVIA DA Germany = Disease Analyzer; DK-DHR = Danish Data Health Registries; FinOMOP-HUS = Hospital District of Helsinki and Uusimaa; IMASIS = Institut Municipal Assistència Sanitària Information System. Number of records is displayed per medication per data source. Data sources without any records for the respective medication are omitted from the table. The median and interquartile range of initial daily dose, initial exposure duration and cumulative exposure duration is displayed. *Indicates whether the prerequisite of at least one year of data visibility prior to the prescription date is applied or not.

13. DISCUSSION

13.1. Key results

Incidence rates and prevalence of ketamine and esketamine prescriptions – Population-level utilisation

This multi-data source drug utilisation study assessed the population-level incidence rates and prevalence of ketamine and esketamine use across six European data sources from 2014 to 2023. Ketamine prescriptions were identified in five out of six data sources, namely CDW Bordeaux, CPRD GOLD, FinOMOP-HUS, IMASIS, and IQVIA DA Germany, whereas esketamine prescriptions were observed in four data sources: DK-DHR, FinOMOP-HUS, IMASIS, and IQVIA DA Germany.

Incidence rates of ketamine use in general displayed marked differences between primary care and hospital-based data sources. In primary care data sources such as CPRD GOLD and IQVIA DA Germany, monthly and annual incidence rates of ketamine use remained consistently low over time, staying below 1 per 1,000 PYs throughout the study period. In contrast, hospital-based sources such as CDW Bordeaux and IMASIS exhibited an upward trend starting around 2021. In IMASIS, monthly incidence rates increased from 0.35 per 1,000 PYs in 2014 to 4.8 per 1,000 PYs by 2023. Similarly, in CDW Bordeaux, the monthly incidence rates rose from 0.35 per 1,000 PYs in 2014 to 2.13 per 1,000 PYs in 2023. In FinOMOP-HUS, ketamine prescriptions were recorded only at very low levels prior to 2020, followed by a slight increase, with monthly incidence rates reaching 0.11 per 1,000 PYs by 2023. Esketamine prescriptions were rare across all data sources, with monthly and annual incidence rates consistently below 0.02 per 1,000 PYs, except in FinOMOP-HUS, where incidence rates ranged from 0.3 per 1,000 PYs in 2014 to approximately 11 per 1,000 PYs by 2023. The sensitivity analyses yielded results consistent with those of the primary analysis.

Age-stratified analyses revealed that patterns of ketamine use were consistent between the broader adult group (15–64 years) and young adults (15–34 years) across all data sources. However, more granular stratification indicated higher incidence rates among individuals aged 55 years and older, particularly in hospital-based data sources. In primary care settings, ketamine and esketamine use remained very low across all age groups, with no notable age-related differences.

Analysis by sex showed that ketamine use was generally comparable between males and females across most data sources, including CPRD GOLD, IQVIA DA Germany, FinOMOP-HUS, and IMASIS. However, in CDW Bordeaux, incidence rates remained similar between sexes until 2020, after which higher rates were consistently observed among males. For esketamine, incidence rates were broadly comparable between sexes, although slightly higher incidence rates were observed among males in FinOMOP-HUS.

Stratification by route of administration demonstrated that parenteral use accounted for the highest incidence rates of ketamine, particularly in hospital-based settings. In IMASIS, the monthly incidence rate for parenteral ketamine increased from 0.35 per 1,000 PYs in 2014 to 4.83 per 1,000 PYs in 2023, while in CDW Bordeaux, it rose from 0.34 per 1,000 PYs to 2.29 per 1,000 PYs over the same period. In FinOMOP-HUS, prescription records with an unknown route of administration showed slightly higher incidence rates towards the end of the observation period compared with other routes. For esketamine, monthly incidence rates did not differ by route of administration in DK-DHR, IQVIA DA Germany, and IMASIS. In FinOMOP-HUS, the highest incidence rates were observed for unknown route of administration. These patterns were consistently observed across sensitivity analyses.

The trends in prevalence closely mirrored those observed for incidence. In primary care data sources, the prevalence of ketamine use remained very low and stable over time, consistently below 0.01%. In hospital-based data sources, prevalence increased slightly from 2021 onwards. In IMASIS, monthly prevalence rose from below 0.01% in 2014 to 0.04% in 2023, in FinOMOP-HUS from 0.0004% in 2016 to 0.004% in 2023, and in CDW Bordeaux, from < 0.01% in 2014 to 0.02% in 2023. Annual prevalence estimates showed a similar

pattern, increasing from approximately 0.06% in 2014 to 0.29% in 2023 in IMASIS, 0.001% in 2016 to 0.01% in 2023 in FinOMOP-HUS, and 0.05% in 2014 to 0.15% in 2023 in CDW Bordeaux. Prevalence estimates stratified by age group mirrored incidence patterns, with higher prevalence rates observed among individuals aged 55 years and older, particularly within hospital data sources, and uniformly low prevalence across all age groups in primary care settings. Prevalence analyses stratified by sex showed that ketamine use was comparable between males and females across most data sources, although a slight male predominance was again noted in CDW Bordeaux after 2020. For esketamine, prevalence estimates were broadly comparable across sexes, with slightly higher counts among males observed in FinOMOP-HUS. Finally, when stratified by route of administration, parenteral use was again the predominant form for ketamine, particularly within hospital data sources CDW Bordeaux and IMASIS, and unknown form in FinOMOP-HUS for esketamine. The sensitivity analyses, based on a larger sample size, consistently supported the primary findings and provided additional evidence, further strengthening the main observation.

Characterisation of new users of ketamine or esketamine – Patient-level utilisation

The number of individuals prescribed ketamine ranged from 48 individuals in IQVIA DA Germany to 3,646 individuals in IMASIS if one year of prior data visibility was required. Without this criterion, the number of individuals prescribed ketamine ranged from 92 individuals in IQVIA DA Germany to 5,529 individuals in CDW Bordeaux. The number of individuals prescribed esketamine ranged from 9 individuals in IMASIS and 51 individuals in IQVIA DA Germany to 53,657 individuals in FinOMOP-HUS if one year of prior data visibility was required. Without this criterion, the number of individuals prescribed esketamine ranged from 10 individuals in IMASIS and 80 individuals in IQVIA DA Germany to 58,404 individuals in FinOMOP-HUS. If one year of prior data visibility was required, the median age of individuals at the time of their new ketamine prescription ranged between 34 and 66 years, while the median age of new users of esketamine ranged from 47 years to 60 years across different data sources. Without this criterion, the median age of individuals at the time of their new ketamine prescription ranged between 36 and 65 years, and the median age of new users of esketamine ranged from 47 years to 60 years across different data sources. Males were predominant new users of ketamine in CDW Bordeaux and IQVIA DA Germany, comparable in CPRD GOLD, while females were predominant in FinOMOP-HUS and IMASIS. Considering new users of esketamine, males predominated in DK-DHR and IQVIA DA Germany, while the majority were female in IMASIS, and sex distribution was balanced in FinOMOP-HUS. The majority of ketamine and esketamine prescriptions were prescribed in a non-ICU setting, irrespective of the prior data visibility criterion.

The most common pre-specified conditions reported in the year prior to new ketamine prescriptions among individuals with at least one year of prior data visibility were anxiety, cancer, and depression. Notably, many ketamine users had an unknown condition, ranging from 15.7% in FinOMOP-HUS to 56.5% in IMASIS. The sensitivity analysis confirmed these results.

Among ketamine users with a minimum of one year of prior data visibility, there were no records of sedation or anaesthesia procedures in the primary care data sources CPRD GOLD and IQVIA DA Germany, while in hospital data sources, frequency ranged from 0.1% in IMASIS to 9.0% in FinOMOP-HUS around the time of their ketamine prescription. For surgical procedures, the frequencies ranged from 5.2% in FinOMOP-HUS to 75.8% in IMASIS. The sensitivity analyses confirmed the robustness of these findings. Depression, hypertension, and pain were the most common conditions among ketamine users in the year prior to their treatment initiation, irrespective of the prior data visibility criterion. Medication related to pain management, electrolyte balance, anaesthesia and managing gastrointestinal health, anxiety and sleep disorders was most commonly prescribed among ketamine users in the year prior to their ketamine prescription, irrespective of the prior data visibility criterion.

The most common pre-specified conditions among new users of esketamine in the year prior to the prescription were cancer, chronic pain, and depression, irrespective of the prior data visibility criterion. Notably, many esketamine users in IQVIA DA Germany and FinOMOP-HUS had an unknown condition,

representing 20.7% and 70.2% of esketamine users, respectively. Among esketamine users with a minimum of one year of prior data visibility, sedation or anaesthesia procedures were only recorded in FinOMOP-HUS (87.2%), while 69.8% of the individuals prescribed esketamine had a record of surgical procedures in FinOMOP-HUS. The sensitivity analyses confirmed the robustness of these findings. Depression, pain, and essential hypertension were the most common conditions recorded among esketamine users in the year prior to treatment initiation, irrespective of the prior data visibility criterion. Medications related to pain management, electrolyte balance, anaesthesia and managing gastrointestinal health, anxiety and sleep disorders were the most commonly prescribed medicines among esketamine users in the year prior to their esketamine prescription, irrespective of the prior data visibility criterion.

Treatment characteristics of ketamine or esketamine – Patient-level drug utilisation

The recorded median initial daily dose of ketamine ranged between 16.7 milligrams in IQVIA DA Germany and 200 milligrams in CPRD GOLD, while the recorded median initial daily dose of esketamine ranged between 8 milligrams in IQVIA DA Germany and 33 milligrams in DK-DHR, irrespective of the prior data visibility criterion. The median duration that individuals were exposed to ketamine ranged from 0 days in CDW Bordeaux and IMASIS to 29 days in IQVIA DA Germany, while the median total number of days exposed to ketamine ranged from 1 day in CDW Bordeaux and IMASIS to 30 days in IQVIA DA Germany, irrespective of the prior data visibility criterion. The median duration that individuals were exposed to esketamine ranged from 1 day in FinOMOP-HUS to 29 days in DK-DHR, IMASIS, and IQVIA DA Germany, while the median total number of days exposed to esketamine ranged from 1 day in FinOMOP-HUS to 212 days in IMASIS among new users with at least one year of prior data visibility and from 1 day in FinOMOP-HUS to 224 days in IMASIS without the prior data visibility criterion.

13.2. Limitations of the research methods

The study was conducted using routinely collected healthcare data, and it is important to consider several factors that may influence the interpretation of the results.

General limitations:

Data sources/setting: this study utilised data from six sources: CDW Bordeaux, CPRD GOLD, DK-DHR, IMASIS, FinOMOP-HUS, and IQVIA DA Germany. The results derived from these data sources may not be representative of prescriptions in other countries or data sources. Variations in results were expected across different countries and healthcare settings. Specifically, ketamine, as an anaesthetic drug, may not be well captured in primary care data sources, potentially leading to an underestimation of its use, particularly in data sources like CPRD GOLD. Additionally, discrepancies may arise due to differences in how observation periods are handled across data sources. For instance, IMASIS and IQVIA DA Germany use the last interaction with the healthcare system to define the end of the observation period. As a result, infrequent users may have shorter follow-up periods, decreasing the time at risk (i.e., the denominator) for incidence rate calculations. This could lead to an overestimation of incidence rates in the final months of the study period, as users are fully captured by the end of the study.

Drug prescriptions: a recorded prescription does not necessarily indicate that the patient actually took the drug. Therefore, assumptions of actual use were made.

If elements that are needed for calculating the treatment duration are missing, the dates are imputed into the OMOP CDM based on standard conventions (https://ohdsi.github.io/Themis/drug_end_date_not_in_data.html). Therefore, the treatment duration may not represent the actual treatment duration.

Characterisation/indication: the accuracy and consistency of pre-defined conditions, which is crucial for patient characterisation and identification of the potential indication may vary across the data sources included in the study. The actual indication for prescribing the drug of interest is not directly recorded as

such in the data sources. Instead, we assessed indication through proxies by analysing pre-defined conditions recorded around the date of therapy initiation. Consequently, the estimation of potential indications may be incomplete, given that the actual indications were not directly linked to prescriptions or dispensing records of the drugs of interest.

Study-specific limitations:

Unaccounted prescriptions of ketamine or esketamine: CDW Bordeaux does not have information on medications administered during surgery. Furthermore, data on drug administration in the ICU is only available starting from 2022, with data consolidation beginning in 2023. This may lead to an underestimation of the incidence rates and prevalence of ketamine and esketamine use in this data source. Additionally, the actual indication for prescribing ketamine and esketamine is not directly recorded as such and may be incomplete. The indication was assessed though proxies.

Dose information: CDW Bordeaux data on drug administration in the ICU is only available starting from 2022, with data consolidation beginning in 2023. As a result, the quality and completeness of dose information may be limited in some cases. This may lead to an underestimation of dose in CDW Bordeaux.

13.3. Interpretation

The results of this study confirm that the prescription rates of ketamine and esketamine between 2014 and 2023 have remained consistently low across all data sources, which is in line with existing literature. However, distinct differences were observed in the trends of ketamine use across primary care and hospital-based settings. In primary care data sources, the incidence rates of ketamine prescriptions remained very low and stable over time. In contrast, hospital-based data sources showed a noticeable upward trend starting in 2021.

Hospital-based data sources, such as IMASIS and CDW Bordeaux, show a modest increase in the use of ketamine over time, with parenteral formulations (primarily intravenous or intramuscular) being the predominant mode of administration. This supports the notion that hospitals play a central role in the administration of ketamine, typically for indications like anaesthesia, acute pain management, or emerging psychiatric applications. As for esketamine, the overall prescription rates remain limited across these data sources. Despite its availability in various formulations—intravenous, intramuscular, and intranasal—its uptake in hospital settings has been slow.

The FinOMOP-HUS data source offered additional insights into these patterns. Ketamine prescription rates remain low during the study period, consistent with trends seen in other hospital-based data sources like IMASIS and CDW Bordeaux, likely reflecting historical prescribing practices and clinical context. Until esketamine became available, parenteral racemic ketamine was reserved for emergency care and operating theatres, primarily in patients with severe hypotension where opioids and other sedatives were contraindicated. This restricted use explains the limited ketamine exposure captured in the data source. In contrast, esketamine use has increased markedly over the study period, with incidence rising from 0.3 per 1,000 PYs in 2014 to 11 per 1,000 PYs in 2023. Several factors contributed to this trend: inclusion of intranasal esketamine in national depression treatment guidelines in 2021, expanded availability of oral formulations since 2015, expanding its use beyond special care to the entire hospital, and evolving clinical practice for managing severe pain and opioid tolerance. Esketamine has been used alongside opioids for patients with opioid misuse or tolerance and for treatment-resistant depression, including infusion therapy. These changes in guidelines, drug availability, and treatment strategies likely explain the substantial increase in esketamine prescribing observed in FinOMOP-HUS. At the moment, it is not possible to distinguish between type of formulations, as the mapping of the drugs has been done at the ingredient level. This explains the high proportion of unknown route of administration in FinOMOP-HUS.

The high frequency of anxiety, cancer, and depression among individuals prescribed ketamine is consistent with literature. Ketamine is authorised for managing treatment-resistant depression [1]. Anxiety disorders

are often comorbid with treatment-resistant major depressive disorder and ketamine can reduce anxiety in people with treatment-resistant depression [10], potentially explaining the large number of anxiety records among ketamine users. Literature shows that ketamine has analgesic effects in both acute and chronic pain, including cancer pain [11, 12], potentially explaining the large number of records related to pain and cancer. Essential hypertension is also common among ketamine users, while ketamine can cause significant blood pressure increases, especially in older and hypertensive patients [13]. Medication related to pain management, electrolyte balance, anaesthesia and managing gastrointestinal health, anxiety and sleep disorders was often prescribed, suggesting that ketamine is often used in addition to other anaesthetic and analgesic agents [11]. The high prevalence of sodium to manage electrolyte balance is likely administered during surgical procedures [14], as part of the individuals who received ketamine also had records of surgical procedures, anaesthesia or sedation, or other procedures around the date of their ketamine prescription. The frequent use of omeprazole highlights the need for gastrointestinal protection, likely due to the concurrent use of NSAIDs like aspirin and ibuprofen. New users of esketamine with a minimum prior data visibility of one year commonly had records of cancer, chronic pain, and depression in the year prior to the prescription date. Medication related to pain management, electrolyte balance, anaesthesia, and managing gastrointestinal health, anxiety, and sleep disorders were most commonly prescribed. These findings are consistent with literature, as esketamine is also authorised as an anaesthetic agent as well as for managing treatment-resistant depression and has been shown to have analgesic effects [1, 15]. Like ketamine, esketamine also seems to be used in addition to other anaesthetic and analgesic agents. The high prevalence of sodium likely reflects surgical procedures undertaken by several new users of esketamine. Similarly, the frequent recording of surgical and anaesthesia procedures among esketamine initiators likely reflects hospital-based administration contexts rather than indication per se, and these findings should be interpreted cautiously due to coding practices and windowing. The observed short treatment durations most likely correspond to use during surgical procedures, anaesthesia, or sedation, whereas longer durations may represent other applications such as management of treatment-resistant depression or chronic pain, or in hospital-based data sources long-term sedation.

13.4. Generalisability

While our study comprised data from 6 data sources (5 EU countries and the United Kingdom) and covered primary care, outpatient specialists, inpatient care, ICU settings, and registries, findings from this study are not to be generalised to other countries or data sources but only reflect the situation in the specific region and setting covered by the respective data source.

14. CONCLUSION

This multi-data source drug utilisation study provides an overview of ketamine and esketamine prescription patterns across six European healthcare data sources between 2014 and 2023. The study reveals distinct patterns of use for ketamine and esketamine across different healthcare settings. Ketamine prescriptions were consistently infrequent in primary care settings, with little variation over time. In contrast, hospital-based data sources showed a gradual increase in ketamine prescribing since 2021. Esketamine prescriptions remained rare across all data sources, except in FinOMOP-HUS with a gradual increase over time.

Ketamine and esketamine are often prescribed among individuals with a record of depression or pain or individuals that undergo surgical procedures or have a record of anaesthesia or sedation. These findings provide important baseline information for ongoing monitoring of ketamine and esketamine utilisation in clinical practice.

15. REFERENCES

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16. ANNEXES

ANNEX I: List of concept definitions

List of pre-selected drugs of interest

Concept id	Concept Code	Concept Name	Descendants
785649	6130	ketamine	Yes
1366610	2119365	esketamine	Yes

List of pre-specified conditions

Depression

Concept id	Concept Code	Concept Name	Descendants	Exclude
44805550	764711000000106	Single major depressive episode, in remission	Yes	Yes
44813499	764701000000109	Recurrent major depressive episodes, in remission	Yes	Yes
44782943	698957003	Depressive disorder in remission	Yes	Yes
440383	35489007	Depressive disorder	Yes	

Bipolar disorder

Concept id	Concept Code	Concept Name	Descendants
436665	13746004	Bipolar disorder	Yes

Anxiety

Concept id	Concept Code	Concept Name	Descendants
441542	48694002	Anxiety	Yes

Post-traumatic stress disorder

Concept id	Concept Code	Concept Name	Descendants
436676	47505003	Posttraumatic stress disorder	Yes

Cancer

Concept id	Concept Code	Concept Name	Descendants
443392	363346000	Malignant neoplastic disease	Yes

Acute pain

Concept id	Concept Code	Concept Name	Descendants
433456	274663001	Acute pain	Yes

Chronic pain

Concept id	Concept Code	Concept Name	Descendants
43530624	115491000119105	Psychosocial dysfunction due to chronic pain	Yes
436096	82423001	Chronic pain	Yes

Migraine

Concept id	Concept Code	Concept Name	Descendants
318736	37796009	Migraine	Yes

Epilepsy

Concept id	Concept Code	Concept Name	Descendants
36714067	719155005	X-linked intellectual disability and epilepsy with progressive joint contracture and facial dysmorphism syndrome	Yes
4123240	234639001	Triple X syndrome, epilepsy, and hypogammaglobulinemia	Yes
37398922	715428003	Skeletal dysplasia with epilepsy and short stature syndrome	Yes
4029498	128613002	Seizure disorder	Yes
44782474	699328003	Myoclonic epilepsy myopathy sensory ataxia	Yes
36715461	721146009	Intellectual disability, epilepsy, bulbous nose syndrome	Yes
37204209	782721009	Autosomal recessive cerebellar ataxia, epilepsy, intellectual disability syndrome due to RUBCN deficiency	Yes
36715349	720980004	Alopecia, psychomotor epilepsy, periodontal pyorrhea, intellectual disability syndrome	Yes

List of pre-specified procedures

Surgical procedures

Concept id	Concept Code	Concept Name	Descendants
4301351	387713003	Surgical procedure	Yes

Sedation and anaesthesia

Concept id	Concept Code	Concept Name	Descendants
4249997	410011004	Administration of anesthesia AND/OR sedation	Yes

ANNEX II: Supplementary Tables

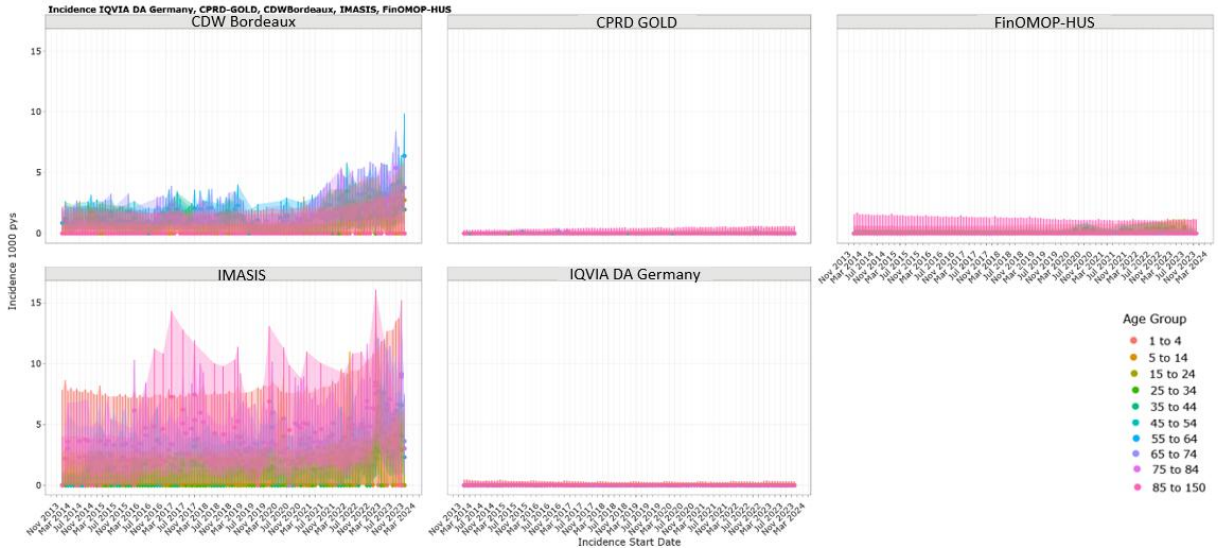
Table 1. Specification of the setting in which ketamine or esketamine were prescribed, presented by drug, data source, and prior observation criterion.

Setting	Prior observation required***						No prior observation required****					
	Ketamine				Esketamine		Ketamine				Esketamine	
	CDW Bordeaux		IMASIS		IMASIS		CDW Bordeaux		IMASIS		IMASIS	
	Number of records*	Number of subjects**	Number of records*	Number of subjects**	Number of records*	Number of subjects**	Number of records*	Number of subjects**	Number of records*	Number of subjects**	Number of records*	Number of subjects**
Unspecified	7,089	3,187	5,959	3,653	215	9	10,379	5,526	6,681	4,131	253	10
Hospitalisation	7,050	3,154	4,299	2,607	66	4	10,314	5,470	4,834	2,942	66	4
ICU	1,946	1,392	506	84	0	0	3,379	2,466	547	102	0	0

The 'unspecified' setting represents the total number of records or subjects, including inpatient settings, outpatient setting, and prescriptions for which the setting is not specified. CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; CPRD GOLD = Clinical Practice Research Datalink GOLD; IQVIA DA Germany = IQVIA Disease Analyzer Germany; DK-DHR = Danish Data Health Registries; FinOMOP-HUS = Hospital District of Helsinki and Uusimaa; IMASIS = Institut Municipal Assistència Sanitària Information System; *Number of records = number of prescriptions; **Number of individuals = number of unique individuals; ***Indicates whether the criterion of at least one year of data visibility prior to the prescription date is applied or not.

ANNEX III: Supplementary Figures

A



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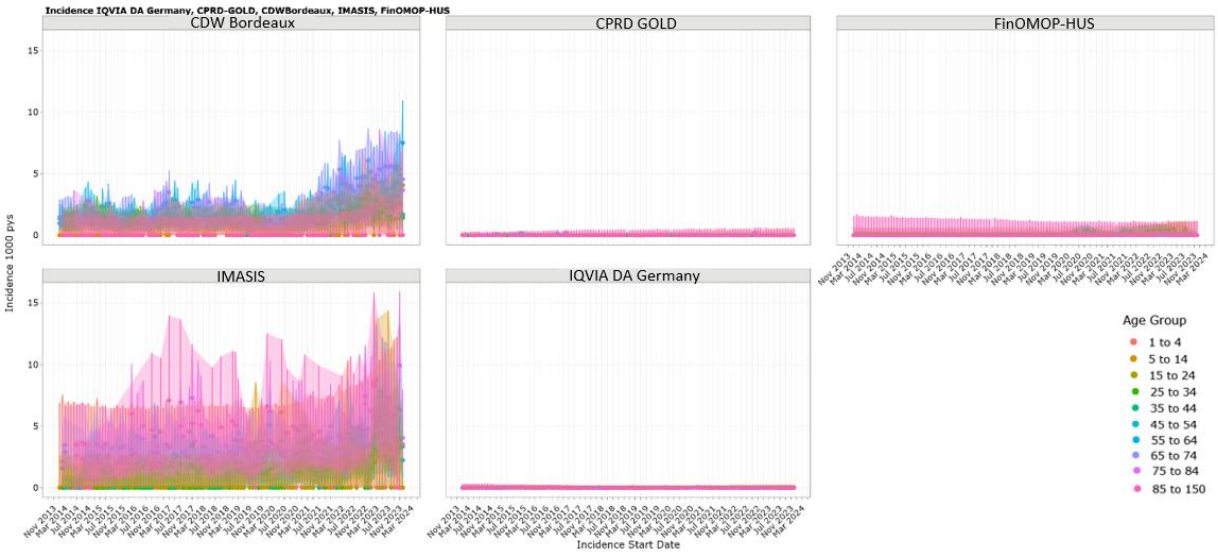
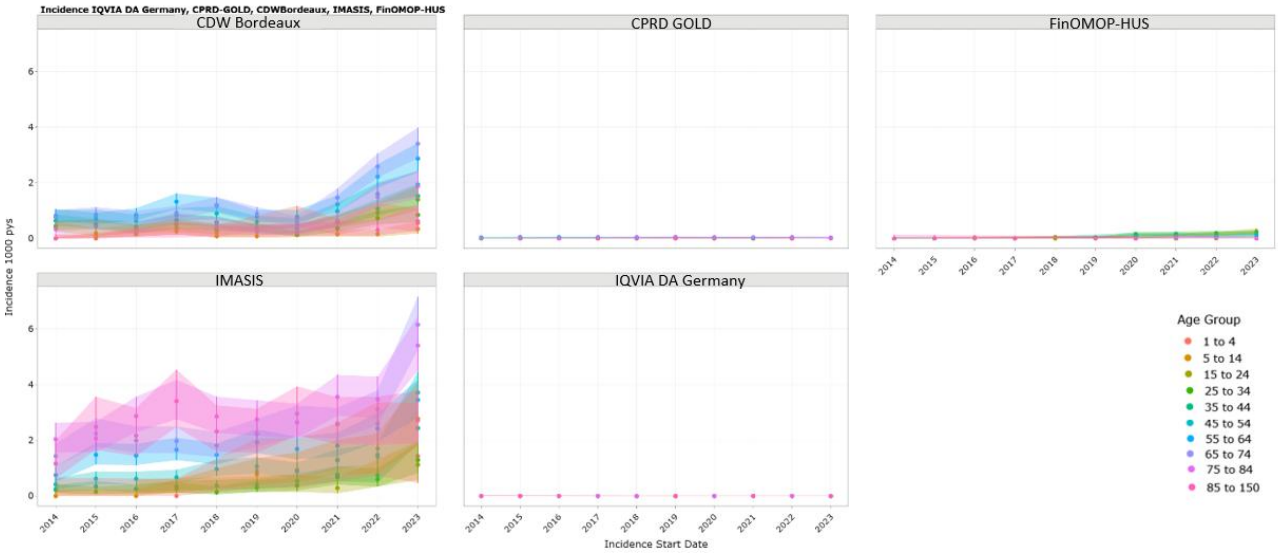


Figure 1. Monthly incidence rates of ketamine prescriptions across data sources during the study period stratified by age groups. Panel A shows incidence rates restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



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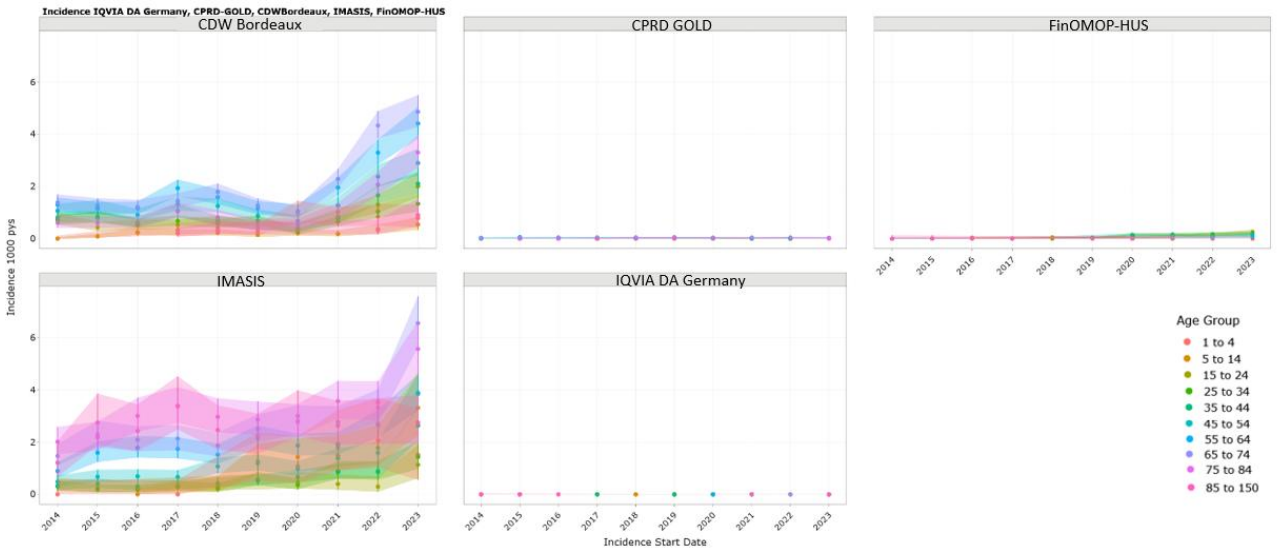

Figure 2. Annual incidence rates of ketamine prescriptions across data sources during the study period stratified by age groups. Panel A shows incidence rates restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

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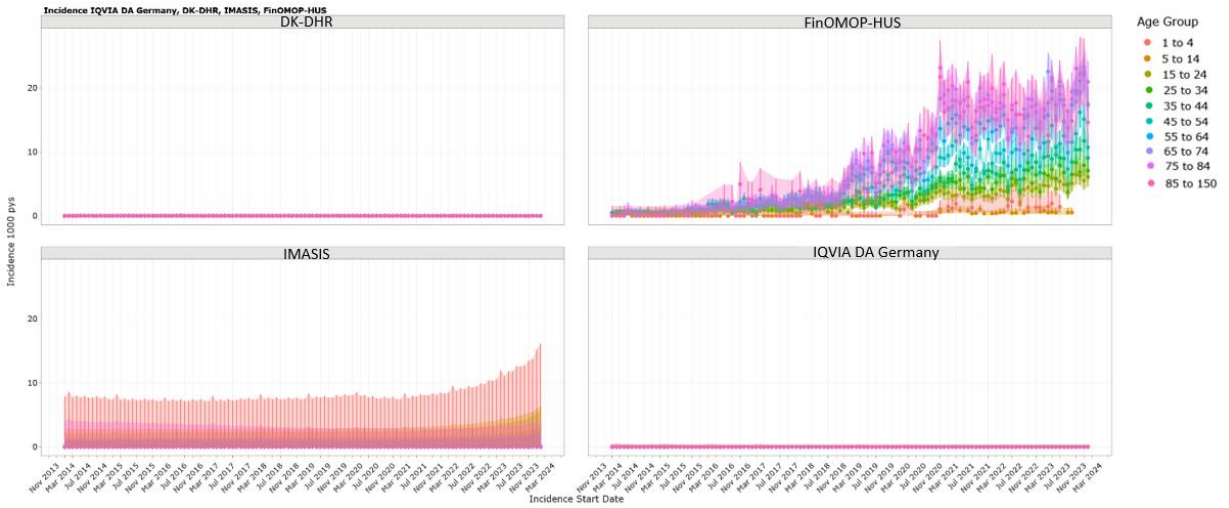

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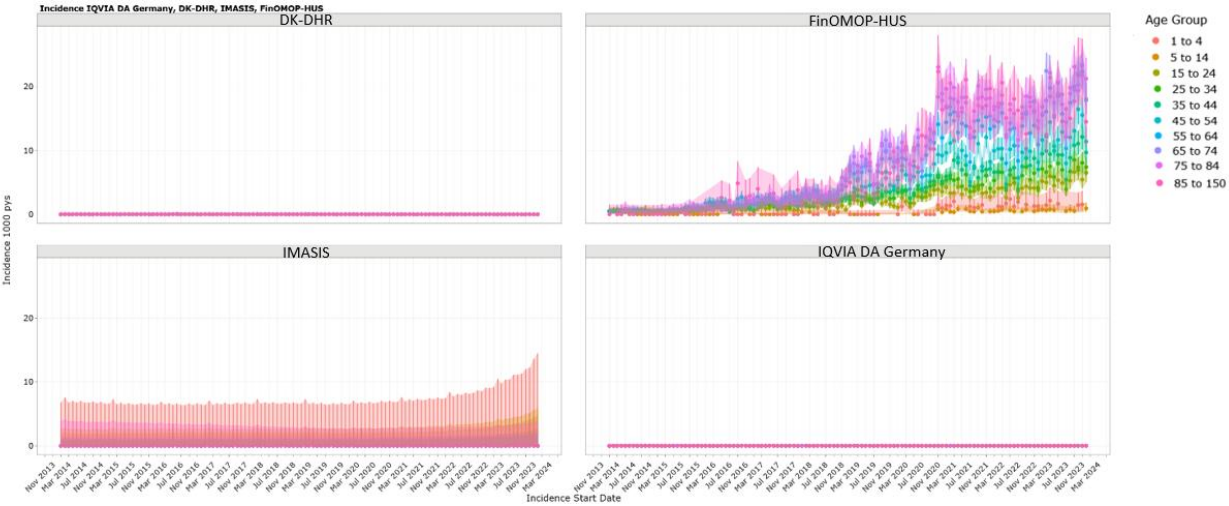

Figure 3. Monthly incidence rates of esketamine prescriptions across data sources during the study period stratified by age groups. Panel A shows incidence rates restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

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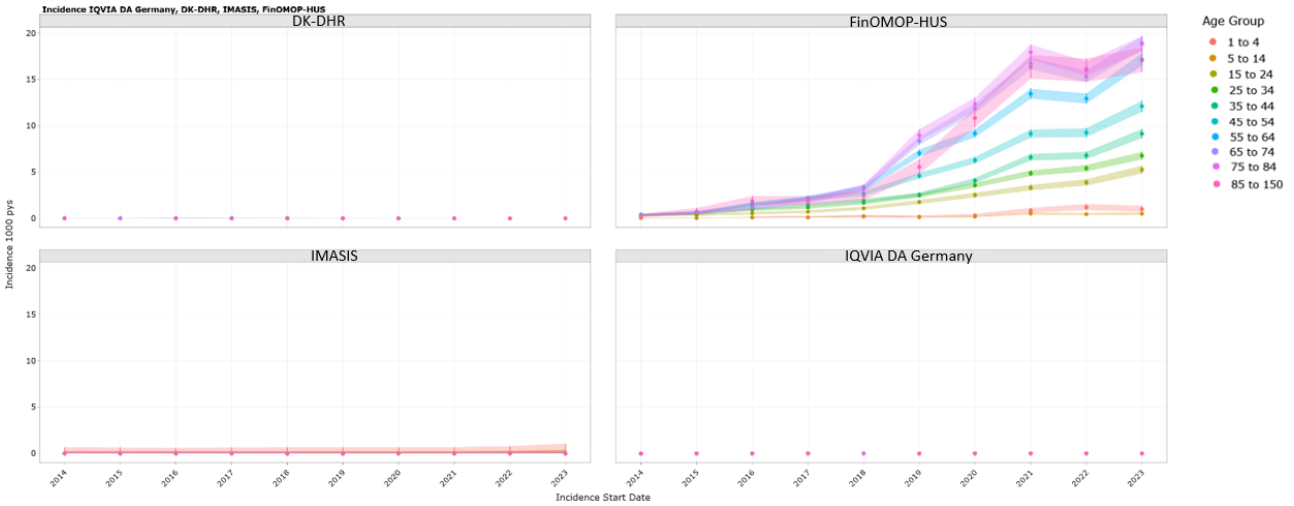

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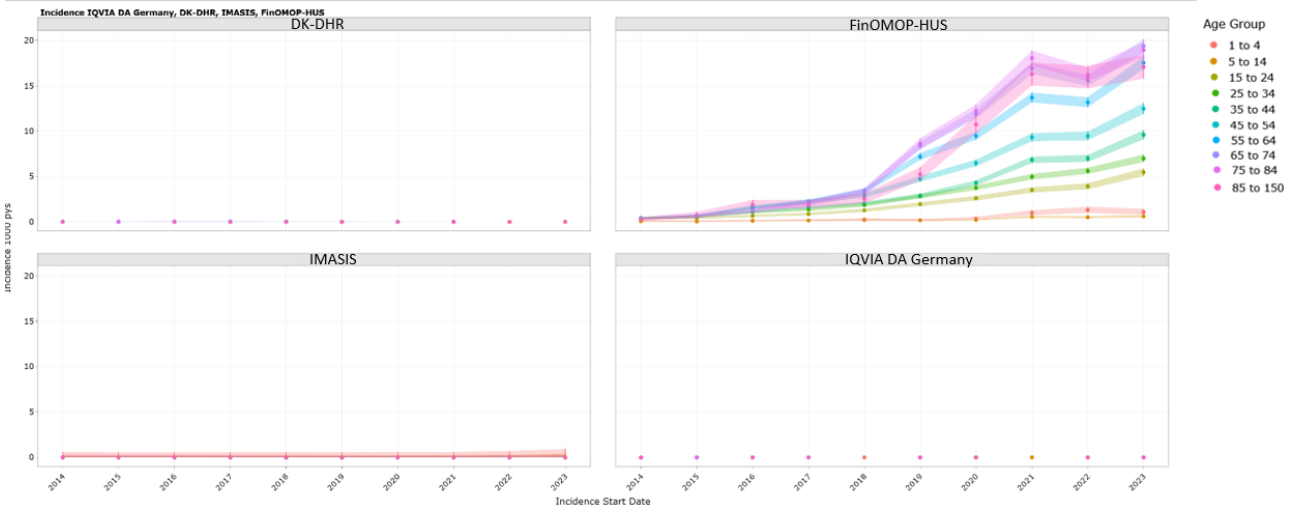

Figure 4. Annual incidence rates of esketamine prescriptions across data sources during the study period stratified by age groups. Panel A shows incidence rates restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

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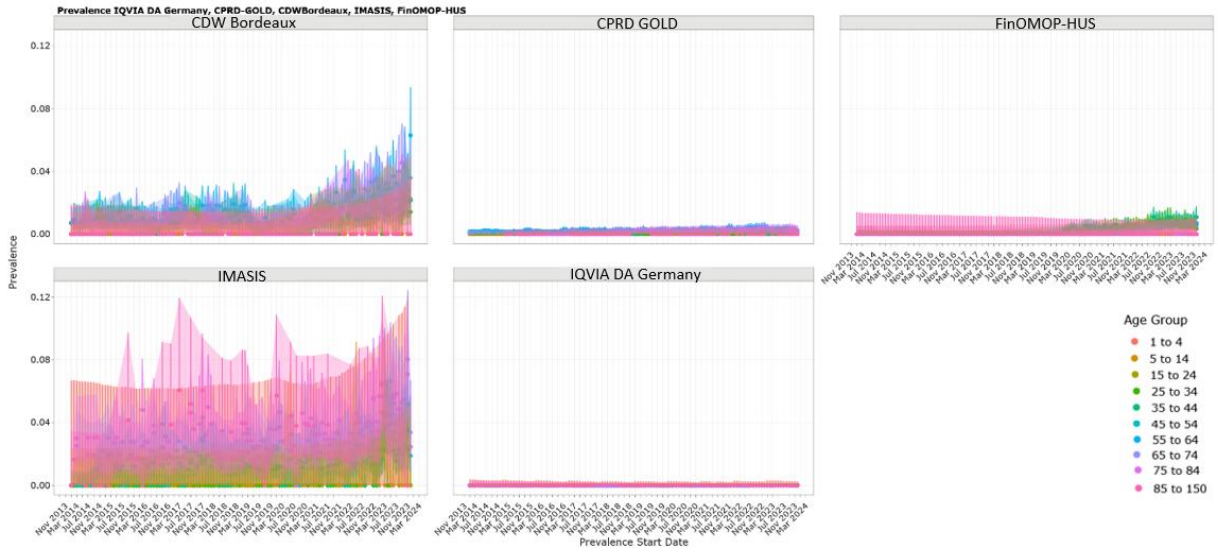

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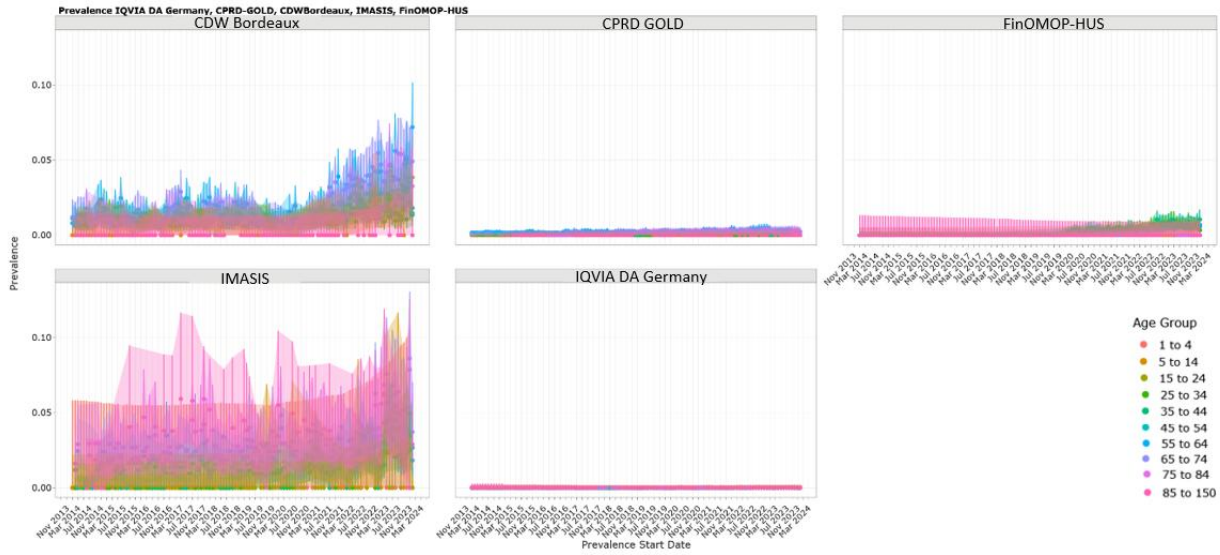
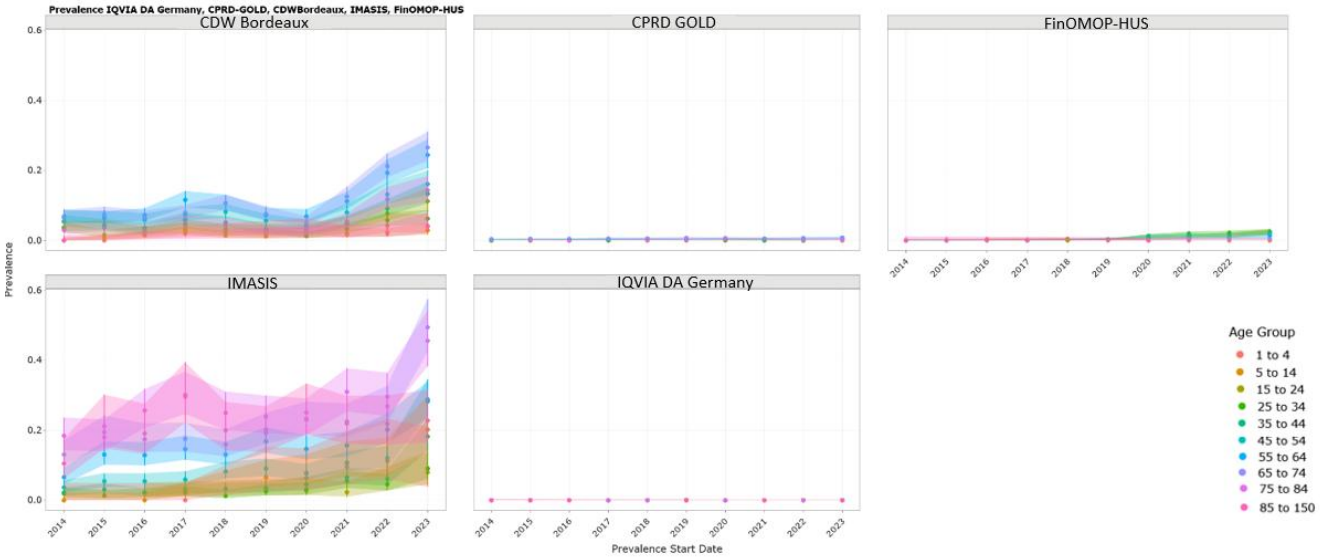


Figure 5. Monthly prevalence of ketamine prescriptions across data sources during the study period stratified by age groups. Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



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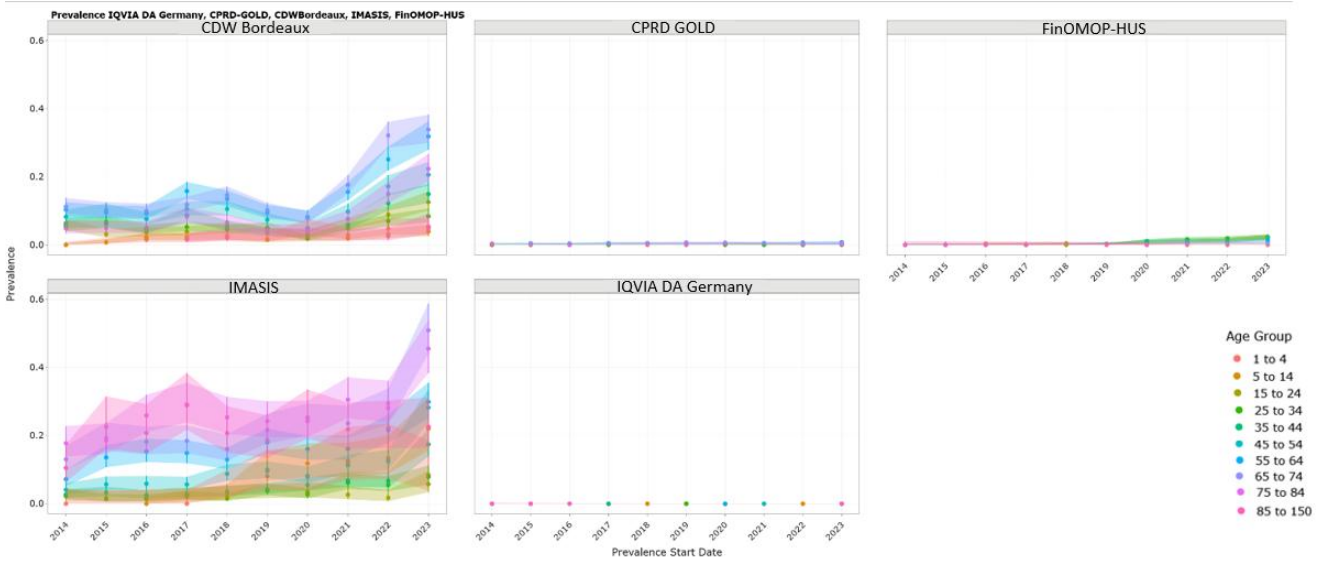

Figure 6. Annual prevalence of ketamine prescriptions across data sources during the study period stratified by age groups. Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

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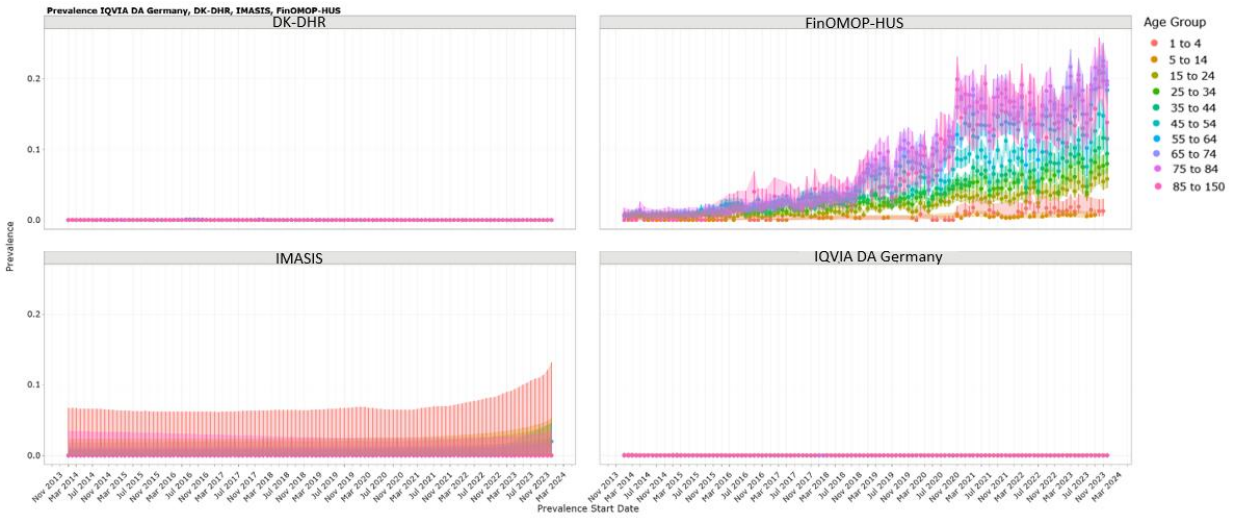

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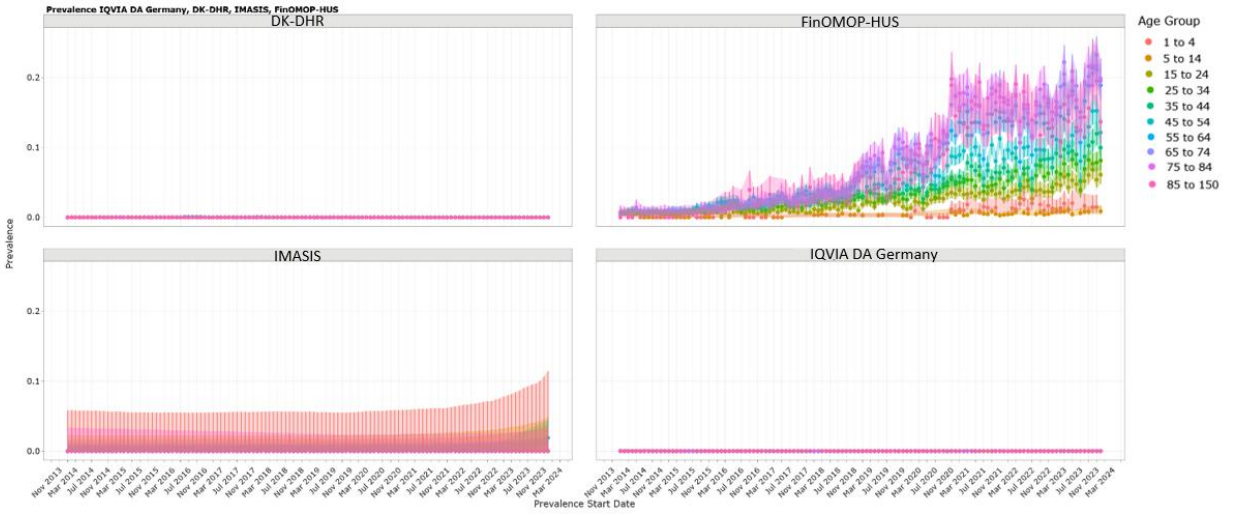
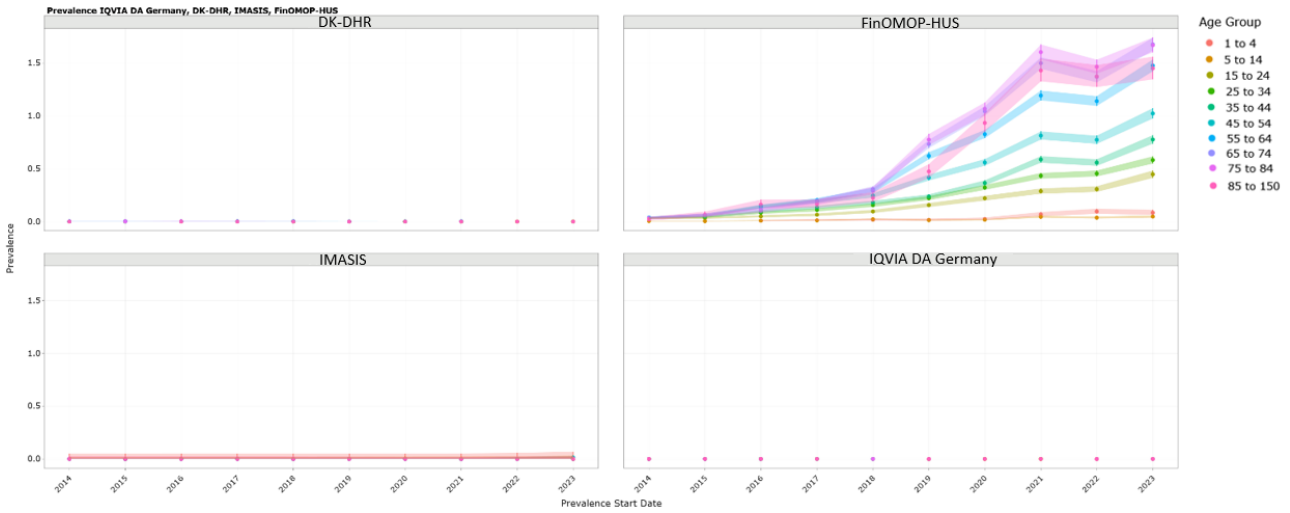


Figure 7. Monthly prevalence of esketamine prescriptions across data sources during the study period stratified by age groups. Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.

A



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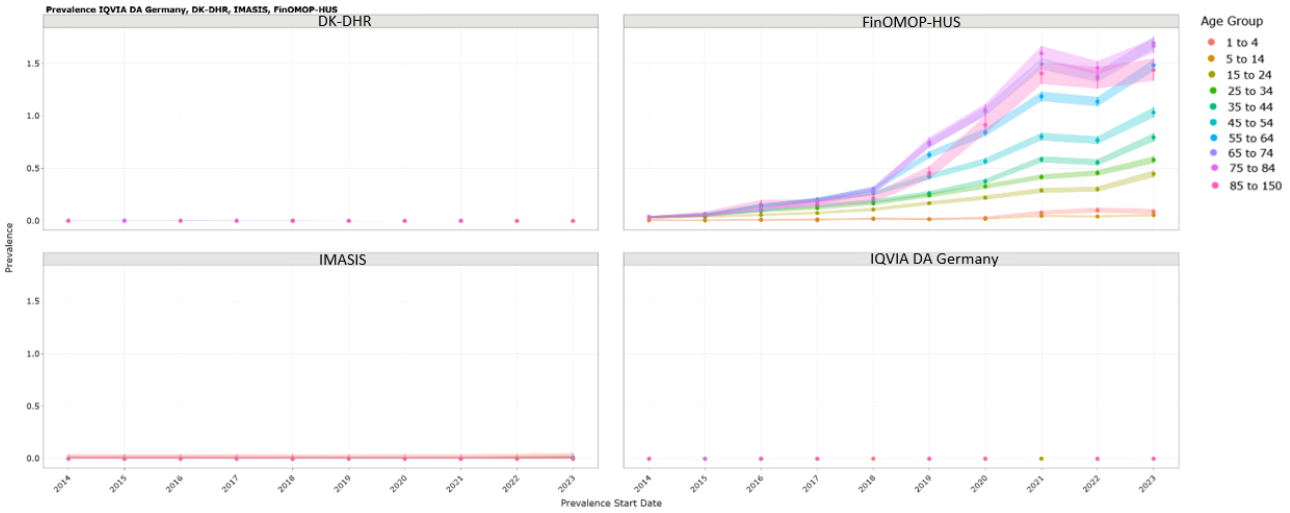

Figure 8. Annual prevalence of esketamine prescriptions across data sources during the study period stratified by age groups. Panel A shows prevalence restricted to individuals with at least one year of prior data visibility. Panel B includes those without this requirement.