Study Report
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DARWIN EU® - Clozapine and the incidence of agranulocytosis over time

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Country(-ies) of study	Finland, Denmark, Croatia, Germany, and Spain
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TITLE

DARWIN EU® - Clozapine and the incidence of agranulocytosis over time

1. DESCRIPTION OF STUDY TEAM

Study team role(s)	Name(s)	Organisation(s)
Principal Investigator	Ellen Gerritsen Dina Vojinovic	IQVIA
Data Scientist	Akram Mendez Isabella Kaczmarczyk	IQVIA
Study Manager	Natasha Yefimenko	Erasmus MC
Data partner name*	**Data Partner member name(s)**	**Organisation(s)**
DK-DHR	Claus Møldrup Elvira Bräuner Susanne Bruun	Danish Medicines Agency
FinOMOP-HILMO	Tuomo Nieminen Tiina Wahlfors	Finnish Care Register for Health Care
IQVIA DA Germany	Gargi Jadhav James Brash	IQVIA
NAJS	Ivan Pristaš Marko Čavlina Antea Jezidžić Jakov Vuković Anamaria Jurčević	Croatian Institute for Public Health
SIDIAP	Talita Duarte Salles Elena Roel Agustina Giuliodori Picco	Institute for Primary Health Care Research Jordi Gol i Gurina

*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

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

1. Danish Data Health Registries (DK-DHR), Denmark
2. Finnish Care Register for Health Care (FinOMOP-HILMO), Finland
3. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
4. Croatian National Public Health Information System (NAJS), Croatia
5. The Information System for Research in Primary Care (SIDIAP), Spain

Detailed information on data sources is described below.

Country	Name of database	Health care setting	Type of data	Total number of subjects	Number of active subjects	Calendar period covered by each data source
Denmark	DK-DHR	Registry	Registry	8.6 million	6.0 million	01/01/1995 until 07/11/2024
Finland	FinOMOP-HILMO	Primary care, outpatient specialist care and inpatient care	EHR and registries	6.6 million	5.7 million	01/01/2011 until 09/10/2024
Germany	IQVIA DA Germany	Primary care and outpatient specialist care	EHR	45.7 million	4.6 million	01/01/1992 until 31/12/2024
Croatia	NAJS	Primary care, outpatient specialist care and inpatient care	EHR and registries	5.2 million	4.3 million	12/05/1978 until 07/06/2024
Spain	SIDIAP	Primary care with link to hospital data	EHR	8.6 million	6.0 million	01/01/2006 until 30/06/2023

DA = Disease Analyzer; DK-DHR = Danish Data Health Registries; EHR = Electronic Health Record; FinOMOP-HILMO = Finnish Care Register for Health Care; NAJS = Croatian National Public Health Information System; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

3. ABSTRACT

Title

DARWIN EU® – Clozapine and the incidence of agranulocytosis over time

Rationale and background

Clozapine is an effective treatment for treatment-resistant schizophrenia and Parkinson's disease psychosis, but it carries a risk of severe haematological complications, including neutropenia and agranulocytosis. Emerging evidence suggests that the risk is highest in the initial months of treatment, yet stringent haematological monitoring requirements remain in place throughout long-term use. These requirements may hinder clinical practice, leading to underuse, early treatment discontinuation, or reluctance to initiate therapy. This study aims to provide epidemiological evidence on the incidence and timing of clozapine-associated neutropenia and agranulocytosis across Europe.

Research question and objectives

Research question

What is the incidence of agranulocytosis and neutropenia over time in new users of clozapine?

Study objectives

1. To estimate the incidence rates of agranulocytosis and neutropenia in consecutive weekly and monthly intervals following the initiation of clozapine treatment, overall and stratified by age and sex.
2. To characterise the timing of agranulocytosis and neutropenia events during clozapine treatment using Kaplan-Meier curves, overall and stratified by age and sex.
3. To characterise individuals initiating clozapine treatment in terms of demographics and pre-specified conditions related to the indication for clozapine use.
4. To determine the treatment duration for clozapine use.

Methods

Study design

This retrospective cohort study aimed to describe the epidemiology of agranulocytosis and neutropenia in new clozapine users at a population level (objective 1), characterise the time to onset of these conditions during clozapine treatment (objective 2), and analyse drug utilisation patterns, including demographics, pre-specified conditions related to clozapine indication and treatment duration in new users (objective 3 and 4).

Population

This study included all new users of clozapine registered in the respective databases between 1st of January 2010 and 31st of December 2024 (or latest data available). Eligible individuals were required to have at least 1 year of data visibility prior to becoming eligible for study inclusion and no history of clozapine use. Additionally, to ensure sufficient follow-up, only individuals who initiated clozapine treatment at least 1 year before the end of the available data in the respective data source were included. Children <1 year of age were excluded.

Variables

Drug of interest: Clozapine.

Outcomes of interest: A combined outcome of neutropenia and agranulocytosis (broad definition) following the initiation of clozapine treatment. Cohort diagnostics showed that coding limitations and inconsistent SNOMED mappings prevented reliable distinction between neutropenia and agranulocytosis. To reduce misclassification and ensure consistency, the outcome was defined as a composite of both conditions.

To ensure that only incident cases were captured, individuals with a prior history of agranulocytosis or neutropenia were excluded.

Data source

1. Danish Data Health Registries (DK-DHR), Denmark
2. Finnish Care Register for Health Care (FinOMOP-HILMO), Finland
3. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
4. Croatian National Public Health Information System (NAJS), Croatia
5. The Information System for Research in Primary Care (SIDIAP), Spain

Statistical analysis

Population-level descriptive epidemiology: Incidence rates of newly diagnosed agranulocytosis and neutropenia were estimated following clozapine treatment initiation (objective 1). These rates are expressed as the number of individuals with the newly diagnosed outcome of interest following clozapine initiation per 1,000 person-years of individuals fulfilling inclusion criteria. Incidence rates were calculated for consecutive weekly (0-7 days, 8-14 days, 15-21 days etc.) and monthly intervals (0-30 days, 31-60 days, 61-90 days etc.) since the initiation of clozapine treatment (index date), with a maximum follow-up period of 24 months for reporting both weekly and monthly estimates. The statistical analysis was performed based on OMOP-CDM mapped data using the "*IncidencePrevalence*" R package. The results are reported overall and stratified by age and sex.

Patient-level characterisation: The timing of agranulocytosis and neutropenia events during clozapine treatment was characterised using Kaplan-Meier curves (objective 2). This analysis was conducted using the "*CohortSurvival*" R package based on OMOP-CDM mapped data. The results were stratified by age and sex.

Patient-level utilisation of clozapine: Characterisation including age and sex was assessed at the date of new (incident) prescription of clozapine (index date) (objective 3). The frequency of pre-specified conditions related to clozapine initiation was assessed at any time prior to 1 day before index date, 365 days prior to 1 day before index date and at the index date (objective 3). Duration of treatment was calculated and summarised providing the minimum, quartiles and maximum, where available (objective 4). Statistical analyses were conducted using the "*CohortCharacteristics*" and "*DrugUtilisation*" R packages based on OMOP-CDM mapped data.

Sensitivity analysis: To evaluate the robustness of incidence rate calculations and treatment duration estimates, sensitivity analyses were conducted in selected data sources (DK-DHR, FinOMOP-HILMO, and IQVIA DA Germany). These analyses included: 1) removing the clozapine treatment end date as a censoring criterion in estimation of incidence rates and time-to-event analyses (objectives 1 and 2), and 2) extending the permissible gap between consecutive prescriptions used to define continuous clozapine treatment episodes from 30 to 90 days (objective 4).

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

Results

Incidence rates of agranulocytosis and neutropenia among new users of clozapine

This multi-database study identified a total of 40,956 individuals who initiated clozapine treatment between 2010 and 2024 across five European countries (DK-DHR: 4,253, FinOMOP-HILMO: 14,944, IQVIA DA Germany: 4,029, NAJS: 13,382, SIDIAP: 4,348). FinOMOP-HILMO and NAJS contributed the largest proportion of individuals initiating clozapine treatment, accounting for 36.5% and 32.7% of the cohort, respectively.

The proportion of individuals diagnosed with agranulocytosis or neutropenia among new users of clozapine was generally low across the data sources (FinOMOP-HILMO: 0.4%, IQVIA DA Germany: 0.1%, NAJS: 0.04%, and SIDIAP: 0.8%). In DK-DHR, due to fewer than five cases, the proportion could not be calculated.

Overall, incidence rates of agranulocytosis and neutropenia (broad definition) were very low and showed distinct trends across various data sources. In FinOMOP-HILMO, the monthly incidence rate peaked at 31.4 per 1,000 person-years (PY) during the second month after clozapine initiation, followed by a decline. In SIDIAP, we observed a peak of 18.7 per 1,000 PY in the second month. In all databases, many intervals either showed no events or had small cell counts (<5).

In DK-DHR, FinOMOP-HILMO, and IQVIA DA Germany, the sensitivity analyses led to identification of additional weekly and monthly events, primarily corresponding to intervals with low event counts (<5 events).

Age- and sex-stratified analyses indicated no meaningful differences in incidence rates across age groups or sex due to low numbers. Sex-stratified incidence rates were only reportable in FinOMOP-HILMO during the first three months of follow-up, where rates were higher among females than males. For other intervals and databases, incidence estimates were either zero or had small cell counts (<5 events).

Time of onset of agranulocytosis and neutropenia during clozapine treatment

The timing of these adverse events showed a reduced risk across the study period, with the probability of not developing agranulocytosis or neutropenia being close to 1.00 in most data sources. However, there were slight variations, particularly in FinOMOP-HILMO and SIDIAP, where the probability declined more noticeably over time. Similar trends were observed in a sensitivity analysis where individuals were not censored at the end of clozapine treatment. The median time to diagnosis of agranulocytosis or neutropenia ranged from 53 days in FinOMOP-HILMO to 278 days in IQVIA DA Germany after clozapine initiation. In the sensitivity analysis that removed the censoring at the end of clozapine treatment, the median time to diagnosis increased: 874 days in DK-DHR, 852 days in FinOMOP-HILMO, and 487 days in IQVIA DA Germany.

Age- and sex-stratified analyses indicated that the probability of not developing agranulocytosis and neutropenia remained above 0.90 across all age groups and above 0.97 for both sexes.

Characterisation of new users of clozapine

The median age at clozapine initiation varied across databases, ranging from 39 years in DK-DHR to 63 years in IQVIA DA Germany. The majority of clozapine users were male, although the NAJS database had a balanced male-to-female ratio.

Treatment-resistant schizophrenia was the most common condition in the year prior to the first clozapine prescription across all databases, with frequencies ranging from 5.1% in IQVIA DA Germany to 43.0% in DK-DHR during this time window. For most individuals, the indication could not have been identified (52.8% in DK-DHR to 80.2% in NAJS).

The duration of clozapine treatment varied across data sources, with median treatment duration ranging from 42 days in NAJS to 428 days in SIDIAP. As part of the sensitivity analysis conducted in DK-DHR,

FinOMOP-HILMO, and IQVIA DA Germany, extending the permissible gap between prescriptions to 90 days resulted in an increase in the estimated median clozapine treatment duration.

Discussion

This multi-database cohort study provides evidence on incidence and timing of agranulocytosis and neutropenia following clozapine treatment initiation across different European countries. The findings reaffirm that these adverse events are rare and typically occur early in treatment, consistent with prior evidence. This underscores the importance of close monitoring during the initial treatment period, aligning with existing clinical guidance.

However, several methodological limitations should be considered when interpreting these findings. Specifically, it was not feasible to reliably differentiate between agranulocytosis and neutropenia, nor to assess the severity of individual events. Furthermore, challenges in accurately capturing treatment duration of clozapine may have affected estimates of both event timing and frequency, although overall incidence rates remained low.

Despite these limitations, the consistently low incidence of events observed beyond the early months following clozapine initiation raises important questions about the necessity of prolonged intensive haematological monitoring. This highlights a potential opportunity to revisit and refine existing monitoring guidelines to balance safety with improved treatment accessibility and patient adherence.

4. LIST OF ABBREVIATIONS

Acronyms/term	Description
ATC	Anatomical Therapeutic Chemical classification system
CDM	Common Data Model
CHI	Catalan Health Institute
CIPH	Croatian Institute of Public Health
CM	Clinical Modification
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
DRE	Digital Research Environment
DUS	Drug Utilisation Study
ED	Emergency Department
EEA	European Economic Area
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
FinOMOP-HILMO	Finnish Care Register for Health Care
GP	General Practitioner
GDPR	General Data Protection Regulation
ICD	International Classification of Diseases
ICU	Intensive Care Unit
ID	Index date
IP	Inpatient
MA	Marketing Authorisation
NA	Not applicable
NAJS	Croatian National Public Health Information System
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
OT	Other
PDP	Parkinson's disease psychosis
RCT	Randomised Controlled Trial
SD	Standard deviation
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SNOMED	Systematized Nomenclature of Medicine
WHO	World Health Organisation

5. AMENDMENTS AND UPDATES

Number	Date	Section of studyprotocol	Amendment or update	Reason
1	April 2025	Results, discussion, conclusion	Exclusion of results for agranulocytosis (narrow definition) and neutropenia (narrow definition) and use of broad definition only.	Based on the results of cohort diagnostics, data sources lacked sufficient coding granularity to reliably distinguish between agranulocytosis and neutropenia.
2	June 2025	Methods, results, discussion	Addition of sensitivity analyses: 1) removal of clozapine treatment end date as a censoring criterion; 2) extension of maximum allowed gap between consecutive clozapine prescriptions to 90 days.	Some data sources showed limitations in reliably capturing clozapine treatment duration. Sensitivity analyses were added to test the robustness of results.

6. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Draft Study Protocol	19th March 2025	18th March 2025
Final Study Protocol	15th April 2025	18th April 2025
Creation of Analytical code	March/April 2025	March/April 2025
Execution of Analytical Code on the data	April 2025	April/May 2025
Draft Study Report	13th May 2025	13th May 2025
Final Study Report	20th June 2025	11th July 2025
Draft Manuscript (if agreed on)	TBC	
Final Manuscript (if agreed on)	TBC	

7. RATIONALE AND BACKGROUND

Clozapine is an atypical antipsychotic widely regarded as the most effective treatment for individuals with treatment-resistant schizophrenia, and it is also indicated for Parkinson's disease psychosis (PDP), with occasional off-label use for other neuropsychiatric conditions. Despite its efficacy, clozapine is associated with severe haematological complications, such as neutropenia and agranulocytosis.[1] Neutropenia, characterised by an abnormally low neutrophil count, increases susceptibility to life-threatening infections.[2, 3] Agranulocytosis is a more severe form of neutropenia often necessitating immediate medical intervention. To mitigate these risks, stringent haematological monitoring protocols have been established, requiring frequent blood testing.[1]

Emerging evidence suggests that the highest risk for these adverse events occurs in the initial months of treatment, yet stringent haematological monitoring remains required throughout long-term use. This

stringent monitoring is burdensome for patients and clinical practice, and potentially limits clinical practice, leading to under-prescription, early discontinuation, or reluctance to initiate clozapine treatment.[2, 3]

Given these considerations, a comprehensive understanding of the incidence and timing of clozapine-associated neutropenia and agranulocytosis is essential for informing clinical guidelines, optimising monitoring strategies and improving patient outcomes. This study aims to generate epidemiological evidence on the temporal patterns of these haematological adverse events in individuals initiating clozapine across Europe.

8. RESEARCH QUESTION AND OBJECTIVES

Research question

What is the incidence of agranulocytosis and neutropenia over time in new users of clozapine?

Study objectives

1. To estimate the incidence rates of agranulocytosis and neutropenia in consecutive weekly and monthly intervals following the initiation of clozapine treatment, overall and stratified by age, and sex.
2. To characterise the timing of agranulocytosis and neutropenia events during clozapine treatment using Kaplan-Meier curves, overall and stratified by age and sex.
3. To characterise individuals initiating clozapine treatment in terms of demographics and pre-specified conditions related to the indication for clozapine use.
4. To determine the treatment duration for clozapine use.

Description of the proposed objectives to be achieved in the study is displayed in **Table 1**.

Table 1. Primary and secondary research questions and objectives.

A. Study objectives 1 and 2.

Objective:	**Objective 1:** To estimate the incidence rates of agranulocytosis and neutropenia in consecutive weekly and monthly intervals following the initiation of clozapine treatment, overall and stratified by age and sex. **Objective 2:** To characterise the timing of agranulocytosis and neutropenia events during clozapine treatment using Kaplan-Meier curves, overall and stratified by age and sex.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	All new users of clozapine registered in the respective databases between 1st of January 2010 and 31st of December 2024 (or latest date available). Eligible individuals needed to have at least 1 year of data visibility prior to becoming eligible for study inclusion and no history of clozapine use. Additionally, to ensure sufficient follow-up, the individuals initiating clozapine treatment between 1st of January 2010 and one year before the end of available data in the respective database were included. Children <1 year of age were excluded.
Exposure:	Clozapine
Comparator:	None

Outcome:	Agranulocytosis and neutropenia (broad definition) following the initiation of clozapine treatment.
Time *(when follow up begins and ends):*	Follow-up started when study participants fulfilled inclusion criteria (i.e. first prescription of clozapine between 1st of January 2010 and 31st of December 2024, with at least 1 year of data visibility prior to becoming eligible for study inclusion and no history of clozapine use). End of follow-up was defined as earliest of following: 1) end of clozapine treatment, 2) first outcome of interest, 3) loss to follow-up, 4) end of data availability, 5) date of death or 6) end of study period (31st of December 2024).
Setting:	Primary care, registry, outpatient specialist care and inpatient care setting using data from the following 5 data sources: DK-DHR, FinOMOP-HILMO, IQVIA DA Germany, NAJS and SIDIAP.
Main measure of effect:	Weekly and monthly incidence rates of newly diagnosed agranulocytosis and neutropenia following clozapine treatment initiation (expressed as the number of individuals with the newly diagnosed outcome of interest following clozapine initiation per 1,000 person-years), overall and stratified by age and sex. Kaplan-Meier curves for the timing of agranulocytosis and neutropenia events during clozapine treatment, overall and stratified by age and sex.

B. Study objectives 3 and 4.

Objective:	**Objective 3**: To characterise individuals initiating clozapine treatment in terms of demographics and pre-specified conditions related to the indication for clozapine use. **Objective 4:** To determine the treatment duration for clozapine use.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	All new users of clozapine registered in the respective databases between 1st of January 2010 and 31st of December 2024. Eligible individuals needed to have at least 1 year of data visibility and no history of clozapine use. To ensure sufficient follow-up, only individuals who initiated clozapine treatment at least 1 year before the end of the available data were included. Children <1 year of age were excluded.
Exposure:	Not applicable
Comparator:	None
Outcome:	Clozapine
Time *(when follow up begins and ends):*	Follow-up started when study participants fulfilled inclusion criteria (i.e. first prescription of clozapine between 1st of January 2010 and 31st of December 2024, with at least 1 year of data visibility prior to becoming eligible for study inclusion and no history of clozapine use). End of follow-up was defined as earliest of following: 1) end of clozapine treatment, 2) loss to follow-up, 3) end of data availability, 4) date of death or 5) end of study period (31st of December 2024).
Setting:	Primary care, registry, outpatient specialist care and inpatient care setting using data from the following 5 data sources: DK-DHR, FinOMOP-HILMO, IQVIA DA Germany, NAJS and SIDIAP.
Main measure of effect:	Age and sex for new (incident) users of clozapine.

	Frequency of pre-specified conditions related to clozapine initiation. Treatment duration for clozapine use using descriptive statistics.

9. RESEARCH METHODS

9.1 Study type and study design

The study types with related study designs are described in **Table 2** and were selected from the Draft Catalogue of Data analytics.

A cohort study was conducted using routinely collected health data from 5 data sources. The study comprised three consecutive parts:

- Population-level cohort study (Objective 1, Population-level descriptive epidemiology of agranulocytosis and neutropenia in new users of clozapine).
- Cohort analysis (Objective 2, Patient-level characterisation to the time of onset of agranulocytosis and neutropenia during clozapine treatment).
- New drug user cohort (Objective 3 and 4, Patient-level drug utilisation regarding demographics, pre-specified conditions related to clozapine indication and treatment duration).

Table 2. Description of study types and related study designs.

Study type	Study design	Study classification
Population-level descriptive epidemiology	Population-level cohort	Off the shelf
Patient-level characterisation	Cohort analysis	Off the shelf
Patient-level drug utilisation study (DUS)	New drug/s user cohort	Off the shelf

9.2 Study setting and data sources

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

1. Danish Data Health Registries (DK-DHR), Denmark
2. Finnish Care Register for Health Care (FinOMOP-HILMO), Finland
3. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
4. Croatian National Public Health Information System (NAJS), Croatia
5. The Information System for Research in Primary Care (SIDIAP), Spain

For this study, we selected 5 databases that were considered fit for purpose from the databases available in the DARWIN EU® Database Catalogue. The selection process was based on several key criteria. Firstly, the number of individuals prescribed clozapine, and the number of individuals diagnosed with agranulocytosis and neutropenia within each data source were evaluated to guarantee sufficient data for analysis. Secondly, the geographical distribution of the data sources was considered to ensure a diverse and representative sample. Additionally, we selected databases which cover the relevant setting for this particular outcome and exposure (hospital, primary care linked with hospital data, registry, and primary care including specialist data). The experience gained from databases that had previously participated in similar DARWIN EU® studies was considered, leveraging their proven reliability and data quality. Lastly, only databases that could deliver timely (within 4 months) were considered.

Information on data sources used with a justification for their choice in terms of ability to capture the relevant data is described in **Table 3**.

When it came to assessing the 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 characterises the data and presents it in a dashboard format that is 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, more general-purpose diagnostic tools, "*CohortDiagnostics"* (https://github.com/darwin-eu-dev/CohortDiagnostics) and "*DrugExposureDiagnostics"* (https://darwin-eu.github.io/DrugExposureDiagnostics/), were developed. The "*CohortDiagnostic"* 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. The "*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 a clear understanding of the time-period covered by each released database, 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 getting insights when data collection started, when new sources of data were added, and until when data was included.

Table 3. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of individuals	Data lock for the last update
Denmark	DK-DHR	Database covers healthcare setting where prescriptions for clozapine and diagnoses of agranulocytosis and/or neutropenia may be recorded	Registry	Registry	8.6 million	18/01/2025
Finland	FinOMOP-HILMO	The database includes healthcare settings where prescriptions for clozapine and diagnoses of agranulocytosis and/or neutropenia may be recorded	Primary care, outpatient specialist care and inpatient care	EHR and registries	6.6 million	01/10/2024
Germany	IQVIA DA Germany	The database includes healthcare settings where prescriptions for clozapine and diagnoses of agranulocytosis and/or neutropenia may be recorded	Primary care and outpatient specialist care	EHR	45.7 million	10/04/2025
Croatia	NAJS	The database includes healthcare settings where prescriptions for clozapine and diagnoses of agranulocytosis and/or neutropenia may be recorded	Primary care, outpatient specialist care and inpatient care	EHR and registries	5.2 million	17/11/2023
Spain	SIDIAP	The database includes healthcare settings where prescriptions for clozapine and diagnoses of agranulocytosis and/or neutropenia may be recorded	Primary care with link to hospital data	EHR	8.6 million	30/08/2023

DA = Disease Analyzer; DK-DHR = Danish Data Health Registries; EHR = Electronic Health Record; FinOMOP-HILMO = Finnish Care Register for Health Care; NAJS = Croatian National Public Health Information System; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

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, the Laboratory Database (including coronavirus disease 2019 test results), and the Vaccination Registry (including COVID-19 vaccinations).

FinOMOP-HILMO, Finland

This database covers both public and private, primary and specialised inpatient and outpatient health care encounters in Finland starting from 2011. The entire public sector and private inpatient encounters have been included since 2011, while private outpatient encounters, including occupational care, are included since 2020. The main content of the THL CDM is The Finnish Care Register for Health Care, which is a continuation of the former Hospital Discharge Register, which originally gathered data on patients discharged from hospitals. The Care Register has comprehensive data on the use of services and service users from Finnish public inpatient and outpatient primary and specialised care nationwide. Since 1998, the register has covered both public outpatient and inpatient specialised care and private inpatient care (TerveysHilmo). From 2011 the register has covered public primary care (AvoHilmo). From 2020 the register has covered private outpatient care and occupational care. In addition, the CDM also contains the vaccination data from the Finnish National Vaccination Register, the vaccination data from the Finnish National Vaccination Register, and COVID-19 test results from the Finnish National Infectious Diseases Register, which is maintained by THL. The CDM includes all the above-mentioned data sources and is limited to observation periods commencing after 1.1.2011. The National Population is used to form the base population. This ensures up-to-date location (municipality of residence) of patients and complete death occurrences (although not the cause of death). Using the complete population as a basis for the person table also facilitates calculations on a population level, e.g. incidence rates. The current CDM population comprises all persons having been alive and residing in Finland since the beginning of 2011.

IQVIA Disease Analyser (DA) Germany, Germany

IQVIA Disease Analyzer (DA) Germany is a database of de-identified electronic medical records from specialised and general primary practices (GP) in Germany since 1992.[4] This dataset encompasses approximately 3% of all outpatient practices within Germany, ensuring a substantial representation of the national healthcare landscape. The sampling methods used for practice selection, taking into account physician's demographics, specialty focus, community size category, and federal state location, were instrumental in constructing a database that accurately mirrors the diverse spectrum of healthcare providers in the country. Consequently, data within the IQVIA DA Germany database has been demonstrated to be representative of general and specialised practices throughout Germany.

The database contains demographics records, basic medical data, disease diagnoses according to the International Classification of Diseases, 10th revision (ICD-10), and prescription records. While the database 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.[5, 6]

National Public Health Information System (NAJS), Croatia

The National Public Health Information System (Nacionalni javnozdravstveni informacijski sustav - NAJS) is an organised system of information services by the Croatian Institute of Public Health (CIPH). This database was established in 1998, with nationwide coverage, representing approximately 5.4 million inhabitants. Settings covered include public primary, secondary/outpatient, and inpatient care. Data is retrieved primarily from EHR and holds information on demographics, inpatient and outpatient visits, conditions and procedures, drugs (outpatient and inpatient prescriptions), measurements, and inpatient and outpatient dates of death. NAJS provides linkage between medical and public health data collected and stored in health registries and other health data collections, including cancer registry, mortality, work injuries, occupational diseases, communicable and non-communicable diseases, health events, disabilities, psychosis and suicide, diabetes, drug abuse, and others. The CDM population comprises all publicly insured persons residing in Croatia starting in 2015. NAJS will provide data from 2017 onwards only, as prior data might include information on duplicated patients.

Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain

The Information System for Research in Primary Care (SIDIAP) is a clinical database of anonymized patient records in Catalonia, Spain. The Spanish public healthcare system covers more than 98% of the population, and more than two thirds of the Catalan population see their GP at least once a year. The computerisation of the primary care patient records of the Catalan Health Institute (CHI) was complete in 2005. SIDIAP was designed to provide a valid and reliable database of information from clinical records of patients registered in primary care centres for use in biomedical research. SIDIAP contains data of anonymized patients' healthcare records for nearly six million people (approximately 80% of the Catalan population) registered in 287 primary care practices throughout Catalonia since 2005. It includes data collected by health professionals during routine visits in primary care, including anthropometric measurements, clinical diagnoses (International Classification of Diseases 10th revision ICD-10), laboratory tests, prescribed and dispensed drugs, hospital referrals, demographic and lifestyle information. It was previously shown that SIDIAP population is highly representative of the entire Catalan region in terms of geographic, age, and sex distributions. The high quality of these data has been previously documented, and SIDIAP has been successfully applied to epidemiological studies of key exposures and outcomes. Quality checks to identify duplicate patient IDs are performed centrally at each SIDIAP database update. Checks for logical values and data harmonisation are performed. For biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed.

9.3 Study period

The study period spanned from 1st of January 2010 until the earliest of 31st of December 2024 or the date of the last database update for each respective database (please see **Table 3** for more details on the last update for each database).

9.4 Follow-up

Follow-up for all objectives started when study participants fulfilled inclusion criteria. Eligibility requirements were a first prescription of clozapine between 1st of January 2010 and 31st of December 2024, with at least 1 year of data visibility prior to becoming eligible for study inclusion and no history of clozapine use. To ensure sufficient follow-up, only the individuals initiating clozapine treatment between 1st of January 2010 and one year before the end of available data in the respective database were included. End of follow-up was defined as the earliest of following: 1) end of clozapine treatment, 2) loss to follow-up, 3) end of data availability, 4) date of death, or 5) end of study period (31st of December 2024). For the incidence analysis, patients were also censored when they experienced the first outcome of interest. Additionally, incidence rates were estimated in the pre-defined consecutive weekly (0-7 days, 8-14 days, 15-21 days, etc.) and monthly intervals (0-30 days, 31-60 days, 61-90 days, etc.) since the initiation of clozapine treatment (post-index date), with a maximum follow-up period of 24 months for reporting both weekly and monthly estimates. Therefore, the study participants were censored at the end of each time window if they did not experience the outcome of interest.

The operational definition of the index date and other primary time anchors are presented by means of **Table 4**.

9.5 Study population with in- and exclusion criteria

The study population included all new users of clozapine registered in the respective data sources between 1st of January 2010 and 31st of December 2024 (or latest date available). “New use” refers to a first prescription of clozapine within the study period with no clozapine prescription in the medical history.

Eligibility Criteria: At least 1 year of data visibility before starting clozapine treatment.

Additional eligibility criteria: To ensure sufficient follow-up, only individuals who initiated clozapine treatment at least one year before the end of the available data in the respective data source were included.

The operational definitions of inclusion criteria are presented by means of **Table 5.**

Table 4. 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	Incident with respect to…
New users of clozapine	Date of first prescription of clozapine	Single entry	Incident	[-Inf, -1]	IP, OP, OT	RxNorm	Use of clozapine

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

Table 5. Operational definitions of inclusion criteria.

Criterion	Details	Order of application *	Assessment window	Care Settings[1]	Code Type	Applied to study populations:
New clozapine users	Individuals initiating clozapine treatment	n/a	[-Inf, -1]	IP, OP, OT	RxNorm	All study populations
Prior database history	Study participants were required to have 365 days of prior history observed before contributing observation time	Prior	[-365, 0]	IP, OP, OT	n/a	Individuals initiating clozapine treatment
Washout period	Individuals who initiated clozapine treatment were required to have not used clozapine ever in the past.	Prior	[-Inf, -1]	IP, OP, OT	RxNorm	Individuals initiating clozapine treatment
Observational period in the data source during the period 01/01/2010-31/12/2024 (or the latest date available)	All individuals present in the data source in the period 2010-2024 (or the latest date available)	After	n/a	IP, OP, OT	n/a	Individuals initiating clozapine treatment
Minimum potential follow-up (objective 1, 2, 3 and 4)	Potential follow-up time	After	n/a	IP, OP, OT	n/a	Individuals initiating clozapine treatment

*Order of application specifies whether the eligibility criterion is applied before or after selection of the study entry date. For example, selecting “before” means that all possible study entry dates are identified, and then one or more is chosen. 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. If the patient does not meet the criterion, then the patient drops out; [1] IP = inpatient; OP = outpatient; OT = other; n/a = not applicable; [2] Specifies whether a diagnosis code is required to be in the primary position (main reason for encounter).

9.6 Variables

9.6.1 Exposure

For this study, the exposure of interest is use of clozapine (during the study period). A preliminary code list is provided in **Appendix I**. The operational definition of exposure is described by means of **Table 6.**

9.6.2 Outcomes

For this study, the outcome of interest is a combined outcome of neutropenia and agranulocytosis (broad definition). The definition was specified through a set of concept codes as outlined in **Appendix I**. The broad definition used a combined set of condition concept codes covering both agranulocytosis and neutropenia. The phenotype of agranulocytosis and neutropenia was determined following input from EMA.

To ensure that only incident cases were captured, individuals with a prior history of agranulocytosis or neutropenia were excluded. The operational definition of the outcomes is presented in **Table 7**.

Table 6. Operational definition of exposure.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Diagnosis position[2]	Applied to study populations	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Clozapine	Preliminary code list provided in Appendix I	[-Inf, -1]	Weekly and monthly intervals post index date	IP, OP, OT	RxNorm	n/a	All individuals present in the database	Previous use of clozapine	n/a	n/a

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

Table 7. 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
Agranulocytosis and neutropenia (broad definition)	Preliminary code list provided in Appendix I	Yes	Binary	[-Inf, 0]	IP, OP, OT	SNOMED	n/a	All eligible individuals within the data source (objective 1 and 2)	n/a	n/a

[1] IP = inpatient; OP = outpatient; OT = other; n/a = not applicable.
[2] Specifies 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 descriptive epidemiology (incidence rates of agranulocytosis and neutropenia following initiation of clozapine treatment)

Covariates for stratification in population-level descriptive epidemiology (objective 1) included:

- Weekly intervals post-index
- Monthly intervals post-index
- Age groups: overall, young (≤ 34 years), middle-age (35 - 64 years), and older adults (≥ 65 years)
- Sex: both, males and females

Patient-level characterisation (time to onset of agranulocytosis and neutropenia during clozapine treatment)

Covariates for stratification of patient-level characterisation (objective 2) included:

- Age groups: overall, young (≤ 34 years), middle-age (35 - 64 years), and older adults (≥ 65 years)
- Sex: both, males and females

Patient-level utilisation of new users of clozapine (characterisation of new (incident) clozapine users)

Additional variables for the characterisation of new clozapine users (objective 3) included age, sex and a pre-specified list of conditions related to clozapine indication. These conditions encompass both authorised and non-authorised indications for clozapine use including:

- Treatment-resistant schizophrenia
- Psychotic disorders in Parkinson's disease
- Delirium in Parkinson's disease
- Suicidal or aggressive behaviour in patients with schizophrenia
- Unknown
- None

The “unknown" indication category included individuals that were not present in the indication cohort but had records of other conditions in the condition occurrence table. The “none" category was assigned to individuals that were neither in an indication cohort nor the condition occurrence table, they were considered as having no observed indication.

The frequency of these conditions was assessed at three time points: 1) any time prior to 1 day before the index date, 2) 365 days prior to 1 day before the index date, and 3) at the index date.

The operational definition of the covariates is described in **Table 8**. The list of concepts for the prespecified conditions of interest is provided in **Appendix I**.

Table 8. 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
Demographics (age, sex)	Characterisation in terms of age and sex	Counts	At ID	IP, OP, OT	SNOMED	n/a	All new users of clozapine eligible for the study	n/a	n/a
Indication for prescribing	Check for pre-specified conditions of interest related to use of clozapine	Counts	At ID, in window around ID [-365, -1] and any time prior to ID [-Inf, -1]	IP, OP, OT	SNOMED	n/a	All new users of clozapine eligible for the study	n/a	n/a

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

9.7 Study size

No formal sample size calculation was conducted for this descriptive study, as the primary objective was to describe the incidence of agranulocytosis and neutropenia over time in individuals following initiation of clozapine, irrespective of sample size. Based on a preliminary feasibility assessment, the expected counts for agranulocytosis differed across databases and ranged from a 300 in FinOMOP-HILMO to a 42,900 person count in IQVIA DA Germany. For neutropenia, the person count varied from 11,300 in FinOMOP-HILMO to a 13,500 person count in SIDIAP.

9.8 Data transformation

Analyses were conducted separately for each database. 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

9.9.1 Patient privacy protection

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

9.9.2 Main statistical methods

The type of analysis by study type was fixed and can be observed from **Table 9**.

Table 9. Description of study types and type of analysis.

Study type	Study classification	Type of analysis
Population-level descriptive epidemiology	Off-the-shelf	- Incidence rates of agranulocytosis and neutropenia following treatment initiation of clozapine
Patient-level characterisation	Off-the-shelf	- Prognosis / progression to a pre-specified outcome (diagnosis of agranulocytosis or neutropenia)
Patient Level DUS	Off-the-shelf	- Characterisation of patient-level features (age, sex) - Frequency of pre-specified conditions related to clozapine treatment initiation - Estimation of minimum, p25, median, p75 and maximum treatment duration for clozapine.

R-packages

We used the R package "*IncidencePrevalence*" (https://github.com/darwin-eu/IncidencePrevalence) for population-level descriptive epidemiology to estimate incidence rates of agranulocytosis and neutropenia following new initiation clozapine treatment. For patient-level characterisation, we used "*CohortSurvival*" (https://github.com/darwin-eu/CohortSurvival) to generate the Kaplan-Meier's curves for the timing of

agranulocytosis and neutropenia events during clozapine treatment. Additionally, "*CohortCharacteristics*" (https://github.com/darwin-eu/CohortCharacteristics) and "*DrugUtilisation*" (https://github.com/darwin-eu/DrugUtilisation) were used to characterise new users of clozapine and to calculate treatment duration of clozapine.

Population-level descriptive epidemiology – incidence calculation

Incidence rates of newly diagnosed agranulocytosis and neutropenia following clozapine treatment initiation were estimated. These rates are expressed as the number of individuals with the outcome of interest following clozapine initiation divided by the sum of person-years contributed by the population at risk of the outcome during the follow-up period.

Study participants in the denominator population began contributing person time from the point they fulfilled inclusion criteria, defined as the first prescription of clozapine between 1st of January 2010 and 31st of December 2024, with at least 1 year of data visibility prior to becoming eligible for study inclusion, and no history of clozapine use. Follow-up was censored as the earliest occurrence of the following: end of clozapine treatment, diagnosis of the first outcome of interest, loss to follow-up, death, or end of study period (31st of December 2024) or data availability.

Incidence rates were calculated for consecutive weekly (0-7 days, 8-14 days, 15-21 days, etc.) and monthly intervals (0-30 days, 31-60 days, 61-90 days, etc.) since the initiation of clozapine treatment (index date), with a maximum follow-up period of 24 months for reporting both weekly and monthly estimates. The incidence rates are expressed per 1,000 person-years and reported alongside 95% Poisson confidence intervals.

Incidence rates are stratified by age and sex. Age-specific cohorts were defined based on age-boundary eligibility criteria and sex-specific cohorts were defined based on sex eligibility criteria.

Patient-level characterisation: the time to onset of agranulocytosis and neutropenia in clozapine initiators

The timing of agranulocytosis and neutropenia events during clozapine treatment was characterised using Kaplan-Meier survival analysis. Results are presented as Kaplan-Meier curves, alongside estimated probabilities of agranulocytosis and neutropenia following treatment initiation. Individuals were censored at the earliest occurrence of any of the following: end of clozapine treatment, diagnosis of the first outcome of interest, loss to follow-up, death, or end of study period (31st of December 2024) or end of data availability.

Patient-level drug utilisation

New users were selected based on their recorded prescription of clozapine within the study period. For each patient, at least 1 year of data visibility was required prior to a prescription. To ensure incident use, individuals were required to have at least one year of data availability before treatment initiation and no prior exposure to clozapine. If the start date of a prescription did not fulfil the exposure washout criteria, 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 related to the indication for clozapine use, and treatment duration. Demographics (age and sex) are described at the index date, while the frequency of pre-specified conditions was assessed at any time prior to 1 day before the index date, 365 days prior to 1 day before the index date, and at the index date.

Drug exposure calculations

Drug eras were defined as follows: exposure started at the date of the first prescription after an indefinite washout period. 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 prescriptions were merged into one continuous drug era if the distance in days between end of the first era and start of the second era was ≤ 30 days. The time between the two joined eras was considered as exposed by the first era, as shown in **Figure 1**, first row.

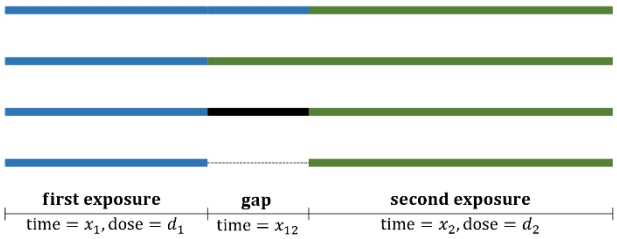
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"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

Figure 1. Gap era joint mode.

Treatment duration

Treatment duration was summarised providing the mean, median, minimum, quartiles, and maximum duration of treatment era. For databases where duration could not be calculated, due to e.g. missing information on quantity or dosing, treatment duration is not provided.

Treatment duration was assessed using two definitions: *days exposed* and *days prescribed*. *Days exposed* refers to the total number of days an individual was continuously exposed to clozapine, allowing treatment gaps of up to 30 days between prescriptions. Exposure periods are constructed by merging prescription records that are separated by gaps shorter than the specified threshold, with the duration calculated from the start of the first prescription to the end of the last in the merged sequence. *Days prescribed* refers to the sum of the days' supply for all individual prescriptions. This metric reflects the total number of days for which clozapine was prescribed. When the allowed gap between prescriptions is increased, more records are merged, leading to a higher total days' supply.

9.9.3 Missing values

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

9.9.4 Sensitivity analysis

Some of the data sources included in this study may have limitations in reliably determining the duration of clozapine treatment. To assess the robustness of the results, additional sensitivity analyses were conducted. Specifically: 1) removal of clozapine treatment end date as a censoring criterion in calculation of incidence rates and time-to-event analyses (Kaplan-Meier curves), 2) extension of the allowed gap between two clozapine prescriptions from 30 to 90 days, allowing prescriptions separated by ≤90 days to be treated as part of a continuous treatment episode (i.e. merged into one drug era). These sensitivity analyses were performed only on data from DK-DHR, FinOMOP-HILMO, and IQVIA DA Germany.

9.9.5 Evidence synthesis

Results from analyses described in section 9.9.2 Main statistical methods were presented separately for each database and no meta-analysis of results was conducted.

9.9.6 Deviations from the protocol

Cohort diagnostics indicated that data sources lacked sufficient coding granularity to reliably distinguish between agranulocytosis and neutropenia. This limitation stemmed from the underlying source coding systems or inconsistencies in how source codes were mapped to standardised SNOMED condition concept IDs. In some instances, source codes representing agranulocytosis were mapped to neutropenia concept IDs, resulting in outcome misclassification. Due to these inconsistencies, it was not feasible to apply narrow outcome definitions consistently across data sources. To address this, we focused on a broad outcome definition encompassing both agranulocytosis and neutropenia. This approach helped mitigate misclassification risk and enabled harmonised outcome identification across data sources.

Furthermore, some data sources showed limitations in reliably capturing clozapine treatment duration. Therefore, sensitivity analyses were added to test the robustness of results (see section 9.9.4 Sensitivity analysis).

10. DATA MANAGEMENT

10.1 Data management

All databases are mapped to the OMOP CDM. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org.

The analytic code for this study is written in R. Each data partner executed the study code against their database containing patient-level data and then returned the results set which only contains aggregated data. The results from each of the contributing data sites is combined in tables and figures for the study report.

10.2 Data storage and protection

For this study, participants from various EU member states processed 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 databases used in this study are already used for pharmacoepidemiological 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 database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it is expected that data partners will have run the OHDSI Data Quality Dashboard tool

(https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

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 allows the user to define a search strategy and using this will then query 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 databases contributing to the study.

The study code is based on four R packages, namely the "*CohortCharacteristics*", "*CohortSurvival*", "*IncidencePrevalence*", and "*DrugUtilisation*" packages. These packages include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package is 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 https://data.darwin-eu.org/P4-C1-001-Clozapine-Agranulocytosis/.

Note: Cohort diagnostics revealed that limitations in source coding and inconsistencies in SNOMED concept mappings precluded reliable differentiation between neutropenia and agranulocytosis across data sources. To mitigate potential misclassification and ensure analytical consistency, the primary outcome was defined as a composite of both conditions (see **AMENDMENTS AND UPDATES**).

12.1 Participants

A total of 40,956 individuals met all inclusion criteria and were retained in the final study population (DK-DHR: 4,253, FinOMOP-HILMO: 14,944, IQVIA DA Germany: 4,029, NAJS: 13,382, SIDIAP: 4,348). FinOMOP-HILMO and NAJS contributed the largest proportion of individuals initiating clozapine treatment, accounting for 36.5% and 32.7%, respectively (**Table 10**)**.**

Among the new users of clozapine, the proportion of individuals ever diagnosed with agranulocytosis or neutropenia (broad definition) during follow-up was low across all data sources (FinOMOP-HILMO: 0.44%, IQVIA DA Germany: 0.15%, NAJS: 0.04%, and SIDIAP: 0.83%). In DK-DHR, fewer than five individuals experienced either outcome and therefore, the proportion could not be calculated due to suppressed counts (**Table 11**). The sensitivity analysis removing the end of clozapine treatment as a censoring criterion yielded higher proportions (DK-DHR: 0.28%, FinOMOP-HILMO: 1.54%, IQVIA DA Germany: 0.30%) (**Table 1** in **Appendix II**).

Table 10. Study attrition of participants based on prescribing of clozapine and relevant inclusion criteria, presented by data source.

Criteria	DK-DHR (n)*	FinOMOP-HILMO (n)*	IQVIA DA Germany (n)*	NAJS (n)*	SIDIAP (n)*
Initial qualifying clozapine prescription	12,035	17,901	11,379	29,115	6,383
Collapse records separated by 30 or less days	12,035	17,901	11,379	29,115	6,383
Require prior observation of 365 days	9,901	15,258	5,215	17,481	5,663
Require cohort_start_date between 2010-01-01 to 2024-12-31	4,484	15,258	4,330	14,199	4,731
Potential 1 year follow up	4,253	14,964	4,041	13,394	4,374
Aged 1 year or older	4,253	14,964	4,041	13,394	4,374
At least 1 observation	4,253	14,964	4,041	13,394	4,374
No prevalent agranulocytosis or neutropenia	4,253	14,944	4,029	13,382	4,348

*n = number of individuals; DA = Disease Analyzer; DK-DHR = Danish Data Health Registries; FinOMOP-HILMO = Finnish Care Register for Health Care; NAJS = Croatian National Public Health Information System; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

Table 11. Proportion of individuals diagnosed with agranulocytosis or neutropenia (broad definition) among new users of clozapine during the study period, per data source.

	Number of individuals	Number of events
DK-DHR	4,207	<5
FinOMOP-HILMO	14,942	66
IQVIA DA Germany	4,008	6
NAJS	13,368	6
SIDIAP	4,346	36

DA = Disease Analyzer; DK-DHR = Danish Data Health Registries; FinOMOP-HILMO = Finnish Care Register for Health Care; NAJS = Croatian National Public Health Information System; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària. Counts <5 are obscured.

12.2 Incidence rates of agranulocytosis and neutropenia following initiation of clozapine treatment

Incidence rates of agranulocytosis and neutropenia among new users of clozapine between 2010 and 2024, showed distinct trends across various data sources (**Figures 2 - 3**).

In FinOMOP-HILMO, the weekly incidence rates started at 24.5 per 1,000 PY during the first week following clozapine treatment initiation, peaked at 58.7 per 1,000 PY in the ninth week, and subsequently decreased to 46.3 per 1,000 PY in the tenth week. From week eleven onwards, most weekly intervals showed either zero (no observed outcome events) or low event counts (<5 events). A similar trend was observed for monthly intervals, with incidence rates of 17.7, 31.4 and 22.9 per 1,000 PY in the first, second and third month, respectively, followed by subsequent months showing either zero or low event counts (<5 events).

In SIDIAP, weekly incidence rates were low and relatively stable across the follow-up period. Most weekly intervals had low event counts (<5), while others showed zero event counts. Monthly incidence rates showed a similar pattern, peaking in the second month at 18.7 per 1,000 PY, with the remaining months reflecting zero or low counts (<5 events).

In DK-DHR, IQVIA DA Germany, and NAJS, incidence rates of agranulocytosis and neutropenia remained low but sporadic over time across both weekly and monthly intervals. Most intervals reported zero events, while others had small event counts (< 5 events).

In DK-DHR, FinOMOP-HILMO, and IQVIA DA Germany, the sensitivity analysis resulted in additional weekly and monthly events, mostly corresponding to intervals with low event counts (<5 events) (**Figures 1-2** in **Appendix III**).

As the number of individuals with agranulocytosis and neutropenia following clozapine initiation was generally low across all data sources, no meaningful differences in incidence rates by sex or age could be determined (**Figures 3 - 6** in **Appendix III**). Sex-stratified incidence rates were only reportable in FinOMOP-HILMO during the first three months of follow-up, where rates were higher among females than males (**Figure 6** in **Appendix III**).

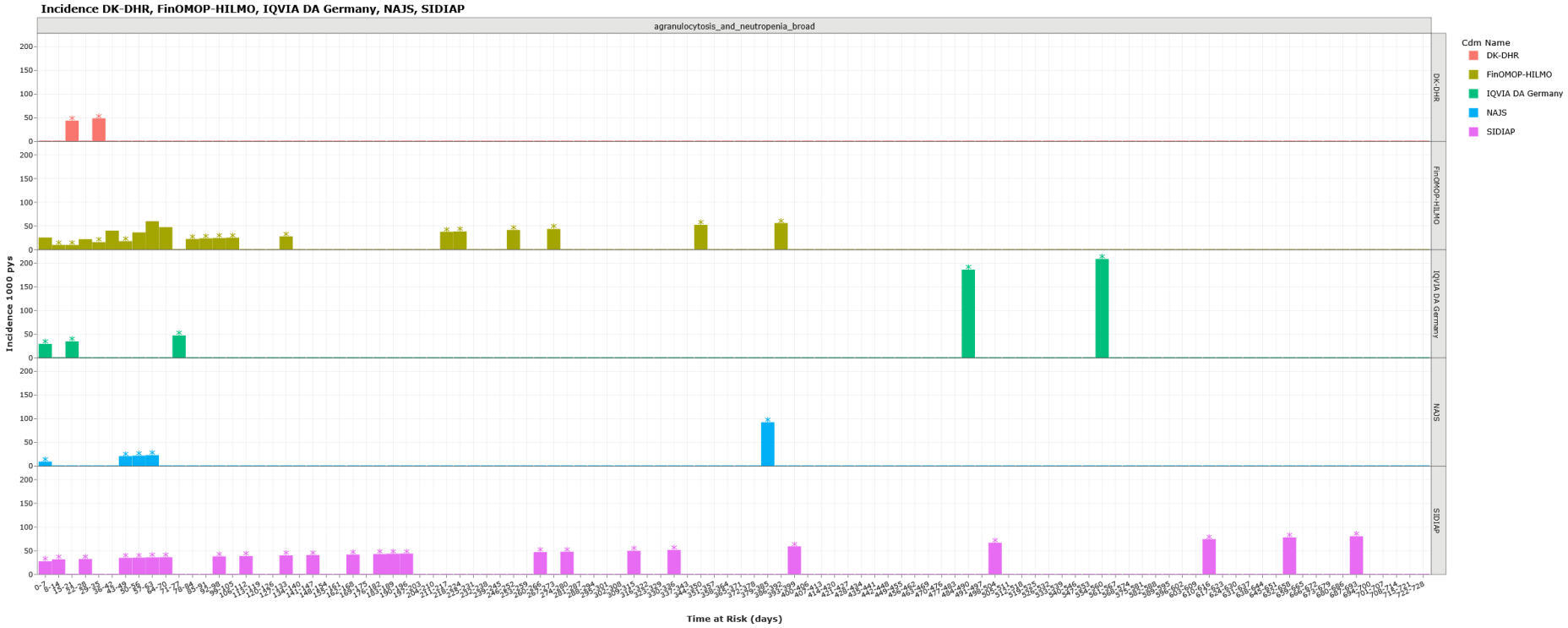


Figure 2. Incidence rates of agranulocytosis and neutropenia (broad definition) following initiation of clozapine treatment by consecut ive weekly intervals for each data source, from 2010 to 2024.

For intervals with fewer than 5 individuals diagnosed with agranulocytosis and neutropenia, a value of 2.5 was used to estimate the incidence rate, reflecting the midpoint of the possible range (from a minimum of 1 to a maximum of 4 events). These estimates are indicated with an asterisk (*) to denote that they are based on imputed rather than actual event counts due to data privacy restrictions.

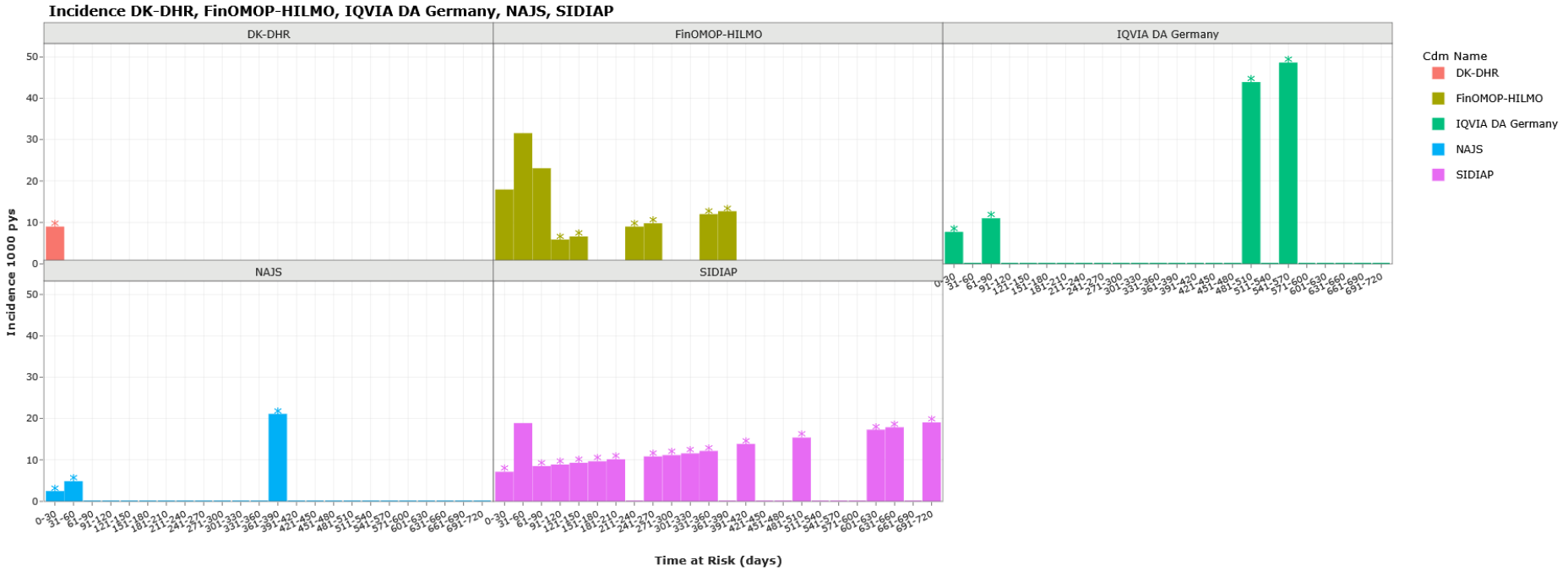


Figure 3. Incidence rates of agranulocytosis and neutropenia (broad definition) following initiation of clozapine treatment by consecutive monthly intervals for each data source, from 2010 to 2024.

For intervals with fewer than 5 individuals diagnosed with agranulocytosis and neutropenia, a value of 2.5 was used to estimate the incidence rate, reflecting the midpoint of the possible range (from a minimum of 1 to a maximum of 4 events). These estimates are indicated with an asterisk (*) to denote that they are based on imputed rather than actual event counts due to data privacy restrictions.

12.3 Timing of agranulocytosis and during clozapine treatment

The probability of not developing agranulocytosis and neutropenia (broad definition) among the patients initiating clozapine treatment remains close to 1.00 in all data sources, indicating a generally low risk of these adverse events. However, differences are observed across the data sources. Notably, the probability drops more noticeably over time in FinOMOP-HILMO and SIDIAP (**Figure 4**). In both FinOMOP-HILMO and SIDIAP, the number of individuals diagnosed with agranulocytosis or neutropenia did not exceed four in any 30-day interval beyond the initial 120 days of follow-up (**Table 2** in **Appendix II**). Similar trends were observed in a sensitivity analysis where individuals were not censored at the end of clozapine treatment (**Figure 7** in **Appendix III**). Cumulative incidence plots (**Figure 8** in **Appendix III**) further illustrate the consistently low incidence of developing agranulocytosis or neutropenia among clozapine users.

Age- and sex-stratified analyses (**Figures 9 - 10** in **Appendix III**) indicated that the probability of not developing agranulocytosis or neutropenia (broad definition) remained above 0.90 across all age groups and above 0.97 in both males and females throughout the study period. No notable differences were identified between strata. However, the overall number of observed events was low, particularly in later follow-up intervals, which limits the robustness of stratified comparisons. The cumulative incidence curves (**Figures 11 - 12** in **Appendix III**) provide additional context.

The median number of days to a diagnosis of agranulocytosis or neutropenia from clozapine initiation ranged from 53 days in FinOMOP-HILMO and 56 days in NAJS to 231 days in SIDIAP and 278 days in IQVIA DA Germany. In DK-DHR, the timing to the diagnosis could not be reported due to low counts (**Table 12**). In the sensitivity analysis that removed the censoring at the end of clozapine treatment, the median time to diagnosis increased: 874 days in DK-DHR, 852 days in FinOMOP-HILMO, and 487 days in IQVIA DA Germany (**Table 3 in Appendix II**).

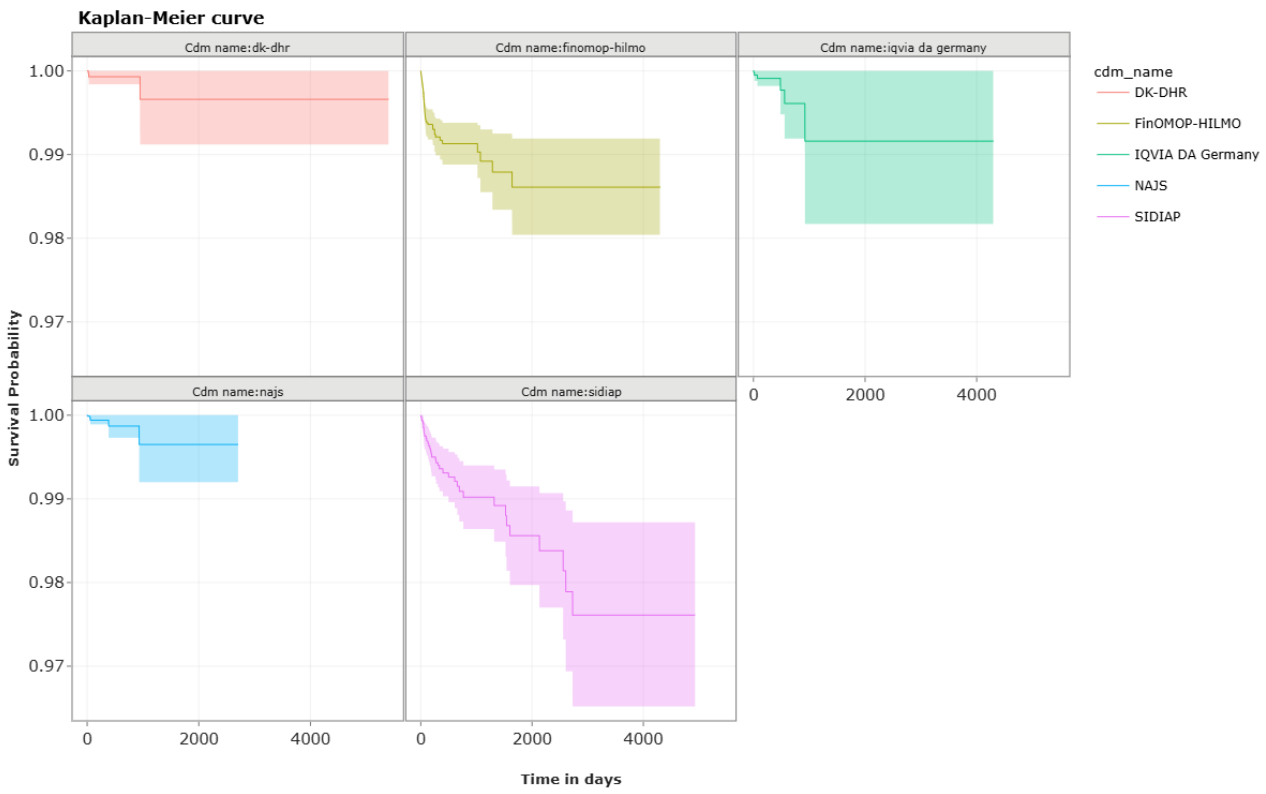


Figure 4. Kaplan-Meier plots of time to agranulocytosis or neutropenia (broad definition) following clozapine treatment initiation by data source.

Table 12. Timing to the diagnosis of agranulocytosis or neutropenia (broad definition) among new users of clozapine who developed either condition of interest.

	DK-DHR	FinOMOP-HILMO	IQVIA DA Germany	NAJS	SIDIAP
Number of individuals	<5	66	6	6	36
Time to event (days)					
Mean (SD)	-	142.58 (301.57)	343.67 (372.98)	246.5 (363.48)	623.19 (814.27)
Median (Q25-Q75)	-	53 (26.25 - 79.50)	278 (31.50 - 540.25)	56 (47.3 - 303.3)	231 (65.5 - 711.3)
Range (min to max)	-	2 to 1641	6 to 923	5 to 932	4 to 2729

DA = Disease Analyzer; DK-DHR = Danish Data Health Registries; FinOMOP-HILMO = Finnish Care Register for Health Care; NAJS = Croatian National Public Health Information System; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària. Counts <5 are obscured.

12.4 Patient characterisation

12.4.1 Demographics

The median age at clozapine initiation varied substantially across the data sources, ranging from 39 years in the DK-DHR to 63 years in the IQVIA DA Germany database. The proportion of males was higher across most data sources and varied from 52.5% in NAJS to 64.9% in SIDIAP. The sex distribution in NAJS was nearly balanced, with 50.1% male and 49.9% female users (**Table 13**).

Table 13. Demographic characteristics of individuals who are newly prescribed clozapine at the time of their first prescription, presented by database.

Variable	DK-DHR	FinOMOP-HILMO	IQVIA DA Germany	NAJS	SIDIAP
Number subjects (N)	4,253	14,944	4,029	13,382	4,348
Age at index (years)					
Median [Q25 - Q75]	39 [26 - 58]	41 [29 - 55]	63 [47 - 75]	55 [37 - 72]	40 [31 - 49]
Mean (SD)	43.11 (19.19)	42.65 (16.67)	60.04 (17.96)	54.21 (20.40)	40.65 (14.16)
Range	13 to 95	4 to 98	9 to 96	9 to 105	11 to 96
Sex, N (%)					
Female	1,906 (44.82%)	6,507 (43.54%)	1,911 (47.43%)	6,674 (49.87%)	1,527 (35.12%)
Male	2,347 (55.18%)	8,437 (56.46%)	2,117 (52.54%)	6,708 (50.13%)	2,821 (64.88%)
None	-	-	<5	-	-

DA = Disease Analyzer; DK-DHR = Danish Data Health Registries; FinOMOP-HILMO = Finnish Care Register for Health Care; NAJS = Croatian National Public Health Information System; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària. Counts below 5 (<5) were obscured.

12.4.2 Pre-specified conditions

Across all data sources, treatment-resistant schizophrenia was the most frequently recorded pre-specified condition in the year before clozapine initiation, ranging from 5.1% in IQVIA DA Germany to 43.0% in DK-DHR. Diagnoses of suicidal or aggressive behaviour in patients with schizophrenia were rare, with frequencies below 1% in all databases. Delirium in Parkinson's disease was recorded in 0.3% in FinOMOP-HILMO to 1.9% of patients in DK-DHR, while psychotic disorders in Parkinson's disease ranged from 0.2% in SIDIAP to 4.6% in DK-DHR. A substantial proportion of individuals had unknown conditions, defined as a recorded diagnosis other than the pre-specified conditions, ranging from 52.8% in DK-DHR to 80.2% in NAJS. It is not excluded that these are alternative indications. Additionally, a subset of individuals had no recorded conditions in the year before clozapine initiation, ranging from 0.5% in DK-DHR and NAJS to 27.4% in SIDIAP (**Table 14**).

When expanding the time window to any time prior to one day before the index date, frequencies of all pre-specified conditions increased across databases.

Table 14. Frequency of pre-specified conditions of interest in individuals being prescribed clozapine recorded any time prior and one year prior to one day before the index date, presented by database.

Condition	DK-DHR (n = 4,253)		FinOMOP-HILMO (n = 14,944)		IQVIA DA Germany (n = 4,029)		NAJS (n = 13,382)		SIDIAP (n = 4,348)	
	-inf to -1	-365 to -1	-inf to -1	-365 to -1	-inf to -1	-365 to -1	-inf to -1	-365 to -1	-inf to -1	-365 to -1
Treatment-resistant schizophrenia, N (%)	2,450 (57.61%)	1,830 (43.03%)	2,553 (17.08%)	1,901 (12.72%)	433 (10.75%)	205 (5.09%)	2,958 (22.10%)	2,378 (17.77%)	1,379 (31.72%)	264 (6.07%)
Delirium in Parkinson's disease, N (%)	107 (2.52%)	82 (1.93%)	55 (0.37%)	43 (0.29%)	42 (1.04%)	24 (0.60%)	68 (0.51%)	61 (0.46%)	35 (0.80%)	14 (0.32%)
Psychotic disorders in Parkinson's disease, N (%)	220 (5.17%)	196 (4.61%)	186 (1.24%)	161 (1.08%)	197 (4.89%)	127 (3.15%)	193 (1.44%)	174 (1.30%)	18 (0.41%)	10 (0.23%)
Suicidal or aggressive behaviour in patients with schizophrenia, N (%)	<5	<5	34 (0.23%)	24 (0.16%)	0	0	178 (1.33%)	113 (0.84%)	72 (1.66%)	34 (0.78%)
Unknown, N (%)	1,644 (38.66%)	2,246 (52.81%)	11,364 (76.04%)	11,211 (75.02%)	3,322 (82.45%)	2,608 (64.73%)	10,194 (76.18%)	10,728 (80.17%)	2,831 (65.11%)	2,849 (65.52%)
None, N (%)	0	23 (0.54%)	834 (5.58%)	1,660 (11.11%)	67 (1.66%)	1,082 (26.86%)	14 (0.10%)	69 (0.52%)	73 (1.68%)	1,193 (27.44%)

'Unknown' includes individuals who had a record of a condition other than the pre-specified conditions, while 'None' includes individuals that have no recorded condition. DA = Disease Analyzer; DK-DHR = Danish Data Health Registries; FinOMOP-HILMO = Finnish Care Register for Health Care; NAJS = Croatian National Public Health Information System; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; -inf to -1 = time window 'any time to one day prior to the index date'; -365 to -1 = time window 'one year to one day prior to the index date'. Counts below 5 (<5) were obscured.

12.4.3 Measurements

The frequency of recorded clinical and laboratory measurements was assessed among individuals newly prescribed clozapine across five-time windows: from one year to 31 days before the index date, 30 days to 1 day before the index date, on the index date, 1 to 30 days after the index date, and 31 to 365 days after the index date.

In the first 30 days after treatment initiation (**Table 15**), the most commonly recorded measurements varied across data sources. However, blood cell counts, including leukocytes, neutrophils, and platelets, were consistently among the top recorded tests in DK-DHR, IQVIA DA Germany, and SIDIAP. For instance, leukocyte counts were assessed in 64.0% of the new users of clozapine in DK-DHR and in 10.6% in IQVIA DA Germany. Additionally, red blood cell indices (e.g. mean corpuscular volume (MCV), haematocrit, haemoglobin) and biochemical markers such as creatinine, cholesterol, and glucose levels were commonly assessed. Enzyme markers, including gamma-glutamyl transferase and alanine aminotransferase, were among the top measurements in IQVIA DA Germany and SIDIAP. In SIDIAP, kidney function was frequently evaluated via estimated glomerular filtration rate (eGFR). Measurements of vital signs, including weight and blood pressure, were prominent in FinOMOP-HILMO, while NAJS recorded high frequencies of screening procedures and laboratory tests.

In the 31 to 365 days post-initiation window (

Table 16), the overall pattern of measurement frequencies remained consistent with the earlier period. The most frequently recorded tests included blood cell counts, red blood cell indices, kidney function markers, liver enzymes, metabolic parameters (e.g., glucose, cholesterol), and vital signs.

Table 15. Frequency of top 10 measurements in individuals being prescribed clozapine in a window after the index date (one day until 30 days after the index date), presented by database.

DK-DHR (n = 4,253)		FinOMOP-HILMO (n = 14,944)		IQVIA DA Germany (n = 4,029)		NAJS (n = 13,382)		SIDIAP (n = 4,348)	
Measurement	**N (%)**	**Measurement**	**N (%)**	**Measurement**	**N (%)**	**Measurement**	**N (%)**	**Measurement**	**N (%)**
Leukocytes [#/volume] in Blood	2,722 (64.02%)	Body weight	391 (2.62%)	MCV [Entitic volume]	441 (10.95%)	Screening for disorder	195 (1.46%)	Platelets [#/volume] in Blood	1,769 (40.70%)
Platelets [#/volume] in Blood	2,715 (63.85%)	Body height	256 (1.71%)	Platelets [#/volume] in Body fluid by Automated count	424 (10.52%)	Laboratory test	78 (0.58%)	Glomerular filtration rate/1.73 sq M.predicted [Volume Rate/Area] in Serum, Plasma or Blood by Creatinine-based formula (CKD-EPI)	874 (20.11%)
Neutrophils [#/volume] in Blood	2,681 (63.05%)	Systolic blood pressure	85 (0.57%)	Leukocytes [#/volume] in Body fluid	413 (10.25%)			Glomerular filtration rate/1.73 sq M.predicted [Volume Rate/Area] in Serum, Plasma or Blood by Creatinine-based formula (MDRD)	859 (19.77%)
Lymphocytes [#/volume] in Blood	2,629 (61.83%)	Diastolic blood pressure	84 (0.56%)	Erythrocytes [#/volume] in Body fluid	407 (10.10%)			Cholesterol [Mass/volume] in Serum or Plasma	858 (19.74%)
Eosinophils [#/volume] in Blood	2,622 (61.67%)			Haemoglobin [Mass/volume] in Body fluid	377 (9.36%)			Alanine aminotransferase [Enzymatic activity/volume] in Serum or Plasma	809 (18.61%)
Monocytes [#/volume] in Blood	2,621 (61.64%)			MCH [Entitic mass]	365 (9.06%)			Glucose [Mass/volume] in Serum or Plasma	664 (15.28%)
Basophils [#/volume] in Blood	2,621 (61.64%)			Creatinine [Mass/volume] in Body fluid	351 (8.71%)			Gamma glutamyl transferase [Enzymatic activity/volume] in Serum or Plasma	555 (12.77%)
Myelocytes [#/volume] in Blood	2,222 (52.26%)			Haematocrit [Volume Fraction] of Body fluid	322 (7.99%)			MCV [Entitic volume]	483 (11.11%)

DK-DHR (n = 4,253)		FinOMOP-HILMO (n = 14,944)		IQVIA DA Germany (n = 4,029)		NAJS (n = 13,382)		SIDIAP (n = 4,348)	
Measurement	**N (%)**	**Measurement**	**N (%)**	**Measurement**	**N (%)**	**Measurement**	**N (%)**	**Measurement**	**N (%)**
Metamyelocytes [#/volume] in Blood	2,221 (52.23%)			Gamma glutamyl transferase [Enzymatic activity/volume] in Body fluid	312 (7.74%)			Cholesterol in HDL [Presence] in Serum or Plasma	417 (9.60%)
Promyelocytes [#/volume] in Blood	2,220 (52.21%)			Alanine aminotransferase [Enzymatic activity/volume] in Body fluid	218 (5.41%)			Cholesterol in LDL [Mass/volume] in Serum or Plasma	417 (9.60%)

DA = Disease Analyzer; DK-DHR = Danish Data Health Registries; FinOMOP-HILMO = Finnish Care Register for Health Care; NAJS = Croatian National Public Health Information System; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària. Measurements with counts <5 are not reported, resulting in empty cells in the table.

Table 16. Frequency of top 10 measurements in individuals being prescribed clozapine in a window after the index date (31 days until 365 days after the index date), presented by database.

DK-DHR (n = 4,253)		FinOMOP-HILMO (n = 14,944)		IQVIA DA Germany (n = 4,029)		NAJS (n = 13,382)		SIDIAP (n = 4,348)	
Measurement	**N (%)**	**Measurement**	**N (%)**	**Measurement**	**N (%)**	**Measurement**	**N (%)**	**Measurement**	**N (%)**
Platelets [#/volume] in Blood	3,551 (83.99%)	Body weight	1,637 (10.98%)	Creatinine [Mass/volume] in Body fluid	1,065 (26.58%)	Screening for disorder	1,079 (8.34%)	Platelets [#/volume] in Blood	2,904 (67.05%)
Leukocytes [#/volume] in Blood	3,500 (82.78%)	Body height	1,117 (7.49%)	MCV [Entitic volume]	1,006 (25.11%)	Screening for cardiovascular system disease	516 (3.99%)	Glomerular filtration rate/1.73 sq M.predicted [Volume Rate/Area] in Serum, Plasma or Blood by Creatinine-based formula (CKD-EPI)	2,558 (59.06%)
Neutrophils [#/volume] in Blood	3,428 (81.08%)	Diastolic blood pressure	366 (2.45%)	Platelets [#/volume] in Body fluid by Automated count	959 (23.93%)	Laboratory test	189 (1.46%)	Cholesterol [Mass/volume] in Serum or Plasma	2,532 (58.46%)
Eosinophils [#/volume] in Blood	3,403 (80.49%)	Systolic blood pressure	362 (2.43%)	Leukocytes [#/volume] in Body fluid	951 (23.73%)	Screening for malignant neoplasm of cervix	125 (0.97%)	Glomerular filtration rate/1.73 sq M.predicted [Volume Rate/Area] in Serum, Plasma or Blood by Creatinine-based formula (MDRD)	2,519 (58.16%)
Monocytes [#/volume] in Blood	3,402 (80.46%)	SARS-CoV-2 (COVID-19) RNA [Presence] in Specimen by NAA with probe detection	140 (0.94%)	Erythrocytes [#/volume] in Body fluid	941 (23.48%)	Diabetes mellitus screening	70 (0.54%)	Alanine aminotransferase [Enzymatic activity/volume] in Serum or Plasma	2,262 (52.23%)
Basophils [#/volume] in Blood	3,402 (80.46%)			Gamma glutamyl transferase [Enzymatic activity/volume] in Body fluid	906 (22.61%)			Glucose [Mass/volume] in Serum or Plasma	1,964 (45.35%)
Lymphocytes [#/volume] in Blood	3,402 (80.46%)			Haemoglobin [Mass/volume] in Body fluid	892 (22.26%)			Gamma glutamyl transferase [Enzymatic activity/volume] in Serum or Plasma	1,861 (42.97%)

DK-DHR (n = 4,253)		FinOMOP-HILMO (n = 14,944)		IQVIA DA Germany (n = 4,029)		NAJS (n = 13,382)		SIDIAP (n = 4,348)	
Measurement	**N (%)**	**Measurement**	**N (%)**	**Measurement**	**N (%)**	**Measurement**	**N (%)**	**Measurement**	**N (%)**
Haemoglobin [Moles/volume] in Blood	3,197 (75.61%)			MCH [Entitic mass]	877 (21.89%)			Cholesterol in HDL [Presence] in Serum or Plasma	1,753 (40.48%)
Creatinine [Moles/volume] in Serum or Plasma	3,119 (73.77%)			Cholesterol [Mass/volume] in Body fluid	732 (18.27%)			Cholesterol in LDL [Mass/volume] in Serum or Plasma	1,752 (40.45%)
Sodium [Moles/volume] in Serum or Plasma	3,100 (73.32%)			Glucose [Mass/volume] in Body fluid	693 (17.29%)			Diastolic blood pressure	1,737 (40.11%)

DA = Disease Analyzer; DK-DHR = Danish Data Health Registries; FinOMOP-HILMO = Finnish Care Register for Health Care; NAJS = Croatian National Public Health Information System; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària. Measurements with counts <5 are not reported, resulting in empty cells in the table.

12.4.4 Treatment duration

Table 17 presents the treatment duration of clozapine across the included data sources. Treatment duration was assessed using two definitions: days exposed and days prescribed (see the Main statistical methods section on treatment duration for details). Briefly, days exposed refers to the total number of days an individual was continuously exposed to clozapine, allowing treatment gaps of up to 30 days between prescriptions. Days prescribed refers to the sum of the days' supply for all individual prescriptions.

The median duration of exposure ranged from 42 days in NAJS, 53 days in FinOMOP-HILMO, 66 days in DK-DHR, and 100 days in IQVIA DA Germany to 428 days in SIDIAP. In comparison, the median treatment duration based on prescribed days ranged from 60 days in NAJS, 66 days in DK-DHR, 87 days in FinOMOP-HILMO, and 100 days in IQVIA DA Germany to 570 days in SIDIAP.

Extending the allowed gap between prescriptions to 90 days, as part of the sensitivity analysis in DK-DHR, FinOMOP-HILMO, and IQVIA DA Germany, increased both the days exposed and days prescribed. The median duration of exposure increased to 230 days in DK-DHR, 188 days in FinOMOP-HILMO, and 139 days in IQVIA DA Germany. Similarly, the median treatment duration based on prescribed days increased to 165 days in DK-DHR, 210 days in FinOMOP-HILMO, and 180 days in IQVIA DA Germany to (**Table 4** in **Appendix II**).

Table 17. Treatment duration of clozapine prescriptions, presented by database.

		DK-DHR (n = 4,253)	FinOMOP-HILMO (n= 14,944)	IQVIA DA Germany (n = 4,029)	NAJS (n = 13,382)	SIDIAP (n = 4,348)
days exposed*	Mean (SD)	315.17 (702.21)	262.06 (559.02)	266.19 (404.42)	164.19 (315.29)	843.97 (964.67)
	Median (Q25 - Q75)	66 (8 - 236)	53 (30 - 201)	100 (50 - 300)	42 (30 - 145)	428 (154 - 1,166)
	Min	1	2	1	1	1
	Max	5,398	4,299	4,295	2,705	4,929
days prescribed**	Mean (SD)	452.08 (1,192.57)	385.74 (939.48)	410.78 (852.86)	183.46 (414.27)	1,183.73 (1,538.45)
	Median (Q25 - Q75)	66 (8 - 271)	87 (30 - 300)	100 (50 - 400)	60 (30 - 150)	570 (180 - 1,568)
	Min	1	2	1	1	1
	Max	13,432	35,730	14,018	6,620	13,974

* = the number of days that an individual is in a continuous exposure episode, including allowed treatment gaps. ** = the sum of the number of days for each prescription that contributes to the analysis. DA = Disease Analyzer; DK-DHR = Danish Data Health Registries; FinOMOP-HILMO = Finnish Care Register for Health Care; NAJS = Croatian National Public Health Information System; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

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

14. DISCUSSION

14.1 Key results

Incidence rates of agranulocytosis and neutropenia among new users of clozapine

This multi-database study identified a total of 40,956 individuals who initiated clozapine treatment between 2010 and 2024 across five European countries. FinOMOP-HILMO and NAJS combined contributed almost 70% of the included individuals.

The proportion of individuals diagnosed with agranulocytosis or neutropenia (broad definition) among new users of clozapine was generally low across the data sources (FinOMOP-HILMO: 0.44%, NAJS: 0.04%, IQVIA DA Germany: 0.15%, and SIDIAP: 0.83%). In DK-DHR, due to fewer than five cases, the proportion could not be calculated. The sensitivity analyses removing the end of clozapine treatment as a censoring criterion yielded higher proportions (DK-DHR: 0.28%, FinOMOP-HILMO: 1.54%, IQVIA DA Germany: 0.30%) (**Table 1** in **Appendix II**).

Overall, incidence rates of agranulocytosis and neutropenia were very low and showed distinct trends across various data sources. In FinOMOP-HILMO, the weekly incidence rate peaked at 58.7 per 1,000 PY during the ninth week after clozapine initiation, followed by a decline. Subsequently, many intervals either showed no events or had a low event count (<5). In SIDIAP, incidence rates were low and relatively stable across the follow-up period with either zero or a low event count (<5), except for a peak of 18.7 per 1,000 PY in the second month. In databases like DK-DHR, IQVIA DA Germany, and NAJS, incidence rates were low but sporadic over time.

In DK-DHR, FinOMOP-HILMO, and IQVIA DA Germany, the sensitivity analysis, removing the end of clozapine treatment as a censoring criterion, resulted in additional weekly and monthly events, mostly corresponding to intervals with low event counts (<5 events).

Due to generally low numbers of agranulocytosis and neutropenia cases following clozapine initiation across all data sources, no meaningful differences in incidence rates by sex or age were observed. Sex-stratified incidence rates were only available from FinOMOP-HILMO for the first three months, showing higher rates in females compared to males.

Time of onset of agranulocytosis and neutropenia during clozapine treatment

The probability of not developing agranulocytosis or neutropenia remains close to 1.00 in most data sources. However, there were slight variations, particularly in FinOMOP-HILMO and SIDIAP, where the probability declined more noticeably over time. A similar trend was observed in the sensitivity analysis, without censoring at the clozapine treatment end. The median time to first neutropenia/agranulocytosis

diagnosis ranged from 53 days in FinOMOP-HILMO to 278 days in IQVIA DA Germany. In DK-DHR, results for the timing of diagnosis were not reported due to low event counts. Removing the censoring at the end of clozapine treatment extended the median time to diagnosis to 852 days in FinOMOP-HILMO and 487 days in IQVIA DA Germany.

The probability of not developing agranulocytosis or neutropenia remained above 0.90 across all age groups and above 0.97 in both males and females throughout the study period. No notable differences were identified between strata.

Characterisation of new users of clozapine

The median age at clozapine initiation varied across databases, ranging from 39 years in DK-DHR to 63 years in IQVIA DA Germany. The majority of clozapine users were male, although the NAJS database had a balanced male-to-female ratio.

Treatment-resistant schizophrenia was the most common condition in the year prior to the first clozapine prescription across all databases, with frequencies ranging from 5.1% in IQVIA DA Germany to 43.0% in DK-DHR during this time window. Notably, conditions like suicidal or aggressive behaviours in schizophrenia and psychotic disorders in Parkinson's disease were rare, with most individuals having other unknown or unspecified diagnoses before clozapine initiation. The pattern of pre-specified conditions remained consistent when the time window was expanded to include any period before the day of clozapine initiation, with frequencies of all pre-specified conditions increasing across all databases.

The duration of clozapine treatment also varied. The median exposure duration ranged from 42 days in NAJS, 53 days in FinOMOP-HILMO, 66 days in DK-DHR, and 100 days in IQVIA DA Germany to 428 days in SIDIAP. When the maximum allowed gap between prescriptions was extended from 30 to 90 days, the median exposure duration increased to 188 days in FinOMOP-HILMO, 230 days in DK-DHR, and 139 days in IQVIA DA Germany.

14.2 Limitations of the research methods

The study was informed by routinely collected healthcare data, and it is important to consider several factors that may have influenced the interpretation of the results.

Data sources/setting: this study utilised data from five sources: DK-DHR, FinOMOP-HILMO, IQVIA DA Germany, NAJS, and SIDIAP. The results derived from these databases may not be representative of prescriptions in other countries or data sources. Variations in results are expected across different countries and healthcare settings.

Differences in how observation periods are handled across data sources may also introduce discrepancies. For instance, IQVIA DA Germany uses 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.

Regarding the study period, NAJS contributed data from 2017 onwards, as earlier data may have included duplicate patients and were therefore excluded.

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

Outcome capture: Low counts of agranulocytosis and neutropenia events raise concerns about potential under capture. Variability in coding practices and completeness of outcome data across sources may have contributed to missed or unrecorded events, possibly leading to underestimation of true incidence rates.

Phenotype of agranulocytosis and neutropenia: Outcomes of interest were defined based on standard concept IDS without incorporating laboratory measurements. Diagnostic codes may not capture subclinical or transient cases, lack granularity in disease severity, and vary across healthcare settings, potentially underestimating incidence. In DK-DHR, there is a lack of granularity in neutropenia and agranulocytosis classification. The available codes do not distinguish between neutropenia and agranulocytosis. Additionally, there is incomplete capture of specific conditions, such as secondary agranulocytosis and chronic idiopathic neutropenia, a coding gap for rare disorders (e.g. Kostmann syndrome) and a lack of unique codes for combination conditions such as agranulocytosis with AIDS or HIV infection. These gaps may potentially have led to misclassification.

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 databases. 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 recorded in the data.

Treatment duration: Some data sources included in this study may have faced challenges in reliably determining treatment duration. Variations in care settings and transitions between inpatient and outpatient care can affect the completeness of medication data. Documentation gaps during these transitions may lead to underestimation of treatment duration or misclassification of treatment episodes. Due to the observational nature and incomplete data capture, end-of-treatment dates may not always be available or reliable. When treatment duration could not be directly observed, imputation methods using fixed duration assumptions (aligned with OMOP conventions) were applied to approximate continuous treatment episodes. While this promotes consistency, it may not fully capture true treatment variability and should be interpreted with caution.

14.3 Interpretation

This multi-database study provides an overview of the occurrence and timing of agranulocytosis and neutropenia following clozapine initiation across diverse European populations. The overall incidence of these haematological adverse outcomes was low across all data sources, with the highest incidence rates generally observed within the first two to three months of treatment initiation.

The results of this study are consistent with prior work indicating that the risk of agranulocytosis and neutropenia is highest during the early phase of clozapine therapy. For example, Australian and New Zealand data showed a 1.4% cumulative incidence of serious neutropenia, with no fatal cases and markedly reduced risk after 24 months. Similarly, Finnish national data showed a cumulative incidence of agranulocytosis for 1.37% of individuals diagnosed with schizophrenia or schizoaffective disorder using clozapine. The timing and magnitude of the risk observed in our study reflect these broader patterns, reinforcing the need for early but not indefinite monitoring.[2, 3]

Time-to-event analysis revealed that agranulocytosis and neutropenia typically occurred early in the treatment course. Median time to diagnosis ranged between just over one month to two months in three databases to nearly eight months in another database. The early clustering of events aligns with known pharmacovigilance data, supporting the rationale for intensive haematological monitoring in the first few months after clozapine initiation. The observed variability in timing between data sources may be driven by differences in surveillance intensity, coding lag, or clinical thresholds for diagnostic labelling. These findings reinforce the value of a time-based risk stratification approach to guide the duration and intensity of blood monitoring protocols.

Sensitivity analyses conducted across selected databases, which extended follow-up beyond the end of recorded clozapine treatment, showed an increase in the number of agranulocytosis and neutropenia

events and a shift towards later median time to diagnosis. While the incidence rates remained highest in the early treatment phase, a substantial number of additional events emerged later, resulting in longer median times to diagnosis. However, it remains unknown if these events occurred during actual treatment or after treatment discontinuation and whether late events are directly related to clozapine use. These later events may instead reflect background rates of haematological abnormalities related to underlying comorbidities common in the study population (e.g. infections, concomitant medications, or chronic conditions) not fully captured in the data sources. Furthermore, potential misclassification of treatment status, particularly among early discontinuers or individuals classified as non-users, could contribute to these late-occurring events. Therefore, later events warrant cautious interpretation, highlighting the need for careful consideration of alternative explanations when assessing adverse event timing and attribution.

Extending the maximum allowed gap between two consecutive prescriptions from 30 days to 90 days resulted in an increased median treatment duration. This occurs because a longer permissible gap enables the grouping of prescriptions separated by extended intervals into a single continuous treatment episode. In contrast, a shorter gap definition may fragment treatment episodes and underestimate the true duration of clozapine treatment. This underestimation may be further exacerbated by inconsistent recordings of treatment end dates in real-world data. Therefore, the choice of gap length used to define continuous exposure has an influence on estimated treatment duration and must be interpreted considering data limitations.

Additionally, potential incompleteness of rare adverse events such as agranulocytosis or neutropenia may have impacted the findings. These events may be under-recorded in routine healthcare databases, particularly if they are managed in care settings not fully captured by the data. Outcomes of interest were defined using standard concept IDS without incorporating laboratory measurements, limiting detection of subclinical, transient or milder cases, and preventing differentiation by disease severity. Diagnostic codes also vary across the data sources and may lack granularity for classifying rare haematological conditions. Despite these limitations, findings were generally consistent across multiple data sources, supporting the robustness of the observed patterns. Additionally, the early clustering of events following clozapine initiation aligns with existing pharmacovigilance data and known clinical profiles.

A further limitation encountered in this study was the inability to reliably differentiate between neutropenia and agranulocytosis across databases due to limitations in diagnostic coding systems and inconsistent mapping to SNOMED condition concepts. As a result, a broad composite definition was employed, encompassing both diagnoses and the whole spectrum of severity. While this approach improves sensitivity, it sacrifices specificity, limiting conclusions about the incidence of each condition separately.

Our results on indications for clozapine use are consistent with clinical expectations, with treatment-resistant schizophrenia being the predominant diagnosis across data sources. Nevertheless, a notable proportion of patients had non-specific or missing diagnoses.

Importantly, this study also reviewed the availability of laboratory measurements (e.g., blood cell counts) following clozapine initiation. Although these measurements were not analysed in depth, their observed frequency across databases demonstrates their feasibility as a data source. If consistently captured and paired with actual test values, particularly absolute neutrophil counts, future studies could potentially use this information to distinguish more accurately between agranulocytosis and neutropenia. This could enable more specific outcome definitions and improve the diagnostic precision of narrow definitions.

14.4 Generalisability

While our study comprised data from 5 data sources across the European Union, and covered primary care, registry, outpatient specialist care, and inpatient care, findings from this study are not to be generalised to other countries or databases but only reflect the situation in the specific region and setting covered by the respective database.

15. CONCLUSION

This multi-database cohort study provides evidence on incidence and timing of agranulocytosis and neutropenia following clozapine initiation across different European countries. The findings reaffirm that these adverse events are rare and typically occur early in treatment, consistent with prior evidence. This underscores the importance of close monitoring during the initial treatment period, aligning with existing clinical guidance.

However, the low incidence observed beyond the early months raises important questions about the necessity of prolonged intensive haematological monitoring. This highlights a potential opportunity to revisit and refine existing monitoring guidelines to balance safety with improved treatment accessibility and patient adherence.

16. REFERENCES

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17. ANNEXES

17.1 Appendix I: Final lists with concept definitions

List of concept definition for drug of interest

Concept id	Concept Code	Concept Name	Descendants
800878	2626	clozapine	Yes

List of concept definitions for outcomes of interest

The primary outcome of interest is broad phenotype including agranulocytosis or neutropenia. This broad phenotype included a combined set of concept codes covering agranulocytosis and neutropenia (please refer to the "narrow definition" columns in the tables below). The narrow definition was based on a distinct set of concept codes, specified separately for agranulocytosis and neutropenia. These outcomes of interest occur after the initiation of clozapine and were considered part of the narrow definition.

Additionally, individuals with a record from a list of prevalent concept ids for agranulocytosis and neutropenia, defined as those already present before clozapine treatment initiation, prior to the index date, were excluded (please refer to the "prevalent" column in the tables below).

The final phenotype definitions were determined based on input from the EMA.

Agranulocytosis

Concept id	Concept Code	Concept Name	Descendants	Exclude	Narrow definition	Prevalent
440689	17182001	Agranulocytosis	-	-	Yes	Yes
4224553	421312009	Agranulocytosis associated with AIDS	-	Yes	-	Yes
37017282	713530002	Agranulocytosis co-occurrent with human immunodeficiency virus infection	-	Yes	-	Yes
601107	350691000119103	Agranulocytosis due to and following administration of antineoplastic agent	-	Yes	-	Yes
606394	1144929002	Secondary agranulocytosis	-	-	Yes	Yes

Neutropenia

Concept id	Concept Code	Concept Name	Descendants	Exclude	Narrow definition	Prevalent
604243	1156296001	Acquired neutropenia	-	-	Yes	Yes
4101126	191345000	Acquired neutropenia in newborn	-	Yes	-	Yes
37205095	784392009	Adult chronic idiopathic neutropenia	-	Yes	-	Yes
4030703	14333004	Alloimmune neonatal neutropenia	-	Yes	-	Yes
4125635	234425008	Autoimmune neutropenia	-	Yes	-	Yes
36674950	770947009	Autosomal dominant severe congenital neutropenia	-	Yes	-	Yes

37204524	783201001	Autosomal recessive severe congenital neutropenia due to CSF3R deficiency	-	Yes	-	Yes
37204523	783200000	Autosomal recessive severe congenital neutropenia due to CXCR2 deficiency	-	Yes	-	Yes
37204406	783058007	Autosomal recessive severe congenital neutropenia due to G6PC3 deficiency	-	Yes	-	Yes
37203832	783199003	Autosomal recessive severe congenital neutropenia due to JAGN1 deficiency	-	Yes	-	Yes
604245	1156300000	Benign ethnic neutropenia	-	Yes	-	Yes
4174297	276628009	Chloramphenicol-induced neutropenia	-	Yes	-	Yes
4122939	234423001	Chronic benign neutropenia	-	Yes	-	Yes
4030442	129641006	Chronic benign neutropenia of childhood	-	Yes	-	Yes
4125805	234576008	Chronic familial neutropenia	-	Yes	-	Yes
4030443	129643009	Chronic hypoplastic neutropenia	-	Yes	-	Yes
4032353	129642004	Chronic idiopathic immunoneutropenia in adult	-	Yes	-	Yes
4095623	248693006	Chronic idiopathic neutropenia	-	Yes	-	Yes
434895	89655007	Congenital neutropenia	-	Yes	-	Yes
36678497	775909002	Congenital neutropenia, myelofibrosis, nephromegaly syndrome	-	Yes	-	Yes
432297	191347008	Cyclical neutropenia	-	Yes	-	Yes
4232037	350353007	De Vaal's syndrome	-	Yes	-	Yes
4211401	56918001	Dose-related drug-induced neutropenia	-	-	Yes	Yes
432289	47318007	Drug-induced neutropenia	-	-	Yes	Yes
1340411	OMOP5166066	Exacerbation of neutropenia	-	-	Yes	Yes
4085181	247860002	Familial neutropenia	-	Yes	-	Yes
4250734	409089005	Febrile neutropenia	-	-	Yes	Yes
4276649	65623009	Immune neutropenia	-	Yes	-	Yes
4300659	78378009	Isoimmune neutropenia	-	Yes	-	Yes
36674945	770942003	Kostmann syndrome	-	Yes	-	Yes
4197402	80255009	Maternal transfer neutropenia	-	Yes	-	Yes
4121120	234424007	Metabolic neutropenia	-	Yes	-	Yes
4093513	24974008	Myelokathexis	-	Yes	-	Yes
42514077	9991/3-NULL	Neoplasm defined only by histology: Refractory neutropenia	-	Yes	-	Yes
320073	165517008	Neutropenia	-	-	Yes	Yes
4211956	416729007	Neutropenia associated with AIDS	-	Yes	-	Yes
4008700	111585004	Neutropenia associated with autoimmune disease	-	Yes	-	Yes

432589	46359005	Neutropenia associated with infectious disease	-	-	Yes	Yes
35624757	767658000	Neutropenia due to and following chemotherapy	-	Yes	-	Yes
4143354	267540007	Neutropenia due to irradiation	-	Yes	-	Yes
4171104	276576000	Neutropenia of the small for gestational age baby	-	Yes	-	Yes
42596532	312901000009100	Neutropenia with degenerative left shift	-	Yes	-	Yes
4219985	41814009	Neutropenia with dysgranulopoiesis	-	Yes	-	Yes
37117238	725137007	Neutropenia, monocytopenia, deafness syndrome	-	Yes	-	Yes
4119158	303011007	Neutropenic disorder	-	-	Yes	Yes
40484176	443980004	Neutropenic sepsis	-	-	Yes	Yes
4190716	3902000	Non dose-related drug-induced neutropenia	-	-	Yes	Yes
604592	1003381002	Onycho-tricho-dysplasia neutropenia syndrome	-	Yes	-	Yes
45766061	703148008	Periodontitis associated with chronic familial neutropenia	-	Yes	-	Yes
46273778	709608008	Periodontitis co-occurrent with acquired neutropenia	-	Yes	-	Yes
46272545	710927004	Periodontitis co-occurrent with cyclical neutropenia	-	Yes	-	Yes
46272544	710926008	Periodontitis co-occurrent with familial neutropenia	-	Yes	-	Yes
46273559	709535007	Periodontitis co-occurrent with infantile genetic agranulocytosis	-	Yes	-	Yes
36675666	772126000	Poikiloderma with neutropenia	-	Yes	-	Yes
4101125	191338000	Primary splenic neutropenia	-	Yes	-	Yes
36715585	721303001	Refractory neutropenia	-	-	Yes	Yes
4006469	111584000	Reticular dysgenesis	-	Yes	-	Yes
4230679	351287008	Reticular dysgenesis with congenital aleukocytosis	-	Yes	-	Yes
4097998	190996002	Severe combined immunodeficiency with reticular dysgenesis	-	Yes	-	Yes
4232178	89454001	Schwachman syndrome	-	Yes	-	Yes
4135712	32092008	Toxic neutropenia	-	-	Yes	Yes
439149	55444004	Transient neonatal neutropenia	-	Yes	-	Yes
36716753	722925004	Transient neonatal neutropenia due to congenital viral infection	-	Yes	-	Yes
36716754	722926003	Transient neonatal neutropenia due to neonatal bacterial sepsis	-	Yes	-	Yes

37204236	782759001	X-linked dyserythropoietic anaemia with abnormal platelets and neutropenia	-	Yes	-	Yes
4120603	234416002	X-linked hypogammaglobulinemia	-	Yes	-	Yes
36714068	719156006	X-linked intellectual disability with hypogammaglobulinemia and progressive neurological deterioration syndrome	-	Yes	-	Yes
36713881	718882006	X-linked severe congenital neutropenia	-	Yes	-	Yes

In DK-DHR, there was no specific code to the combination conditions including agranulocytosis associated with AIDS and agranulocytosis co-occurrent with human immunodeficiency virus infection. Additionally, no specific code was observed for agranulocytosis due to and following administration of antineoplastic agent. Therefore, cohort definition specified that individuals with a record of agranulocytosis or neutropenia were only included in the agranulocytosis and neutropenia cohort if they had no records of HIV (Concept IDs: 439727, 4078242, 4013105, 4276586, 37017660, 3200792) on the date of agranulocytosis or neutropenia diagnosis and no records of antineoplastic drugs (definition based on 349 Concept IDs) in a window 7 days prior and 7 days after the date of agranulocytosis or neutropenia diagnosis.

List of concept definitions for pre-specified conditions related to clozapine use

Treatment-resistant schizophrenia

It was defined as patients with schizophrenia with prior use of ≥2 non-clozapine antipsychotics before starting clozapine. In terms of concepts:

Concept id	Concept Code	Concept Name	Exclude	Descendants
Condition				
4213979	39610001	Undifferentiated schizophrenia in remission	Yes	-
435219	4926007	Schizophrenia in remission	Yes	-
435783	58214004	Schizophrenia	-	Yes
434321	191574005	Schizoaffective schizophrenia in remission	Yes	-
440686	51133006	Residual schizophrenia in remission	Yes	-
435217	63181006	Paranoid schizophrenia in remission	Yes	-
432300	191565008	Latent schizophrenia in remission	Yes	-
436947	31373002	Disorganized schizophrenia in remission	Yes	-
434332	111483008	Catatonic schizophrenia in remission	Yes	-
Medication				
36269455	OMOP3120330	Zuclopenthixol Topical Solution	Yes	Yes
19010886	114176	zuclopenthixol	-	Yes
19102109	40003	zotepine	-	Yes
712615	115698	ziprasidone	-	Yes
19043327	39468	veralipride	-	Yes
19005104	10805	triflupromazine	-	Yes

19005101	10804	trifluperidol	-	Yes
704984	10800	trifluoperazine	-	Yes
36259222	OMOP3110097	Tiapride Topical Solution	Yes	Yes
19008012	10588	tiapride	-	Yes
700465	10510	thiothixene	-	Yes
700299	10502	thioridazine	-	Yes
19000305	10498	thioproperazine	-	Yes
19041817	38133	thiopropazate	-	Yes
19100431	37416	sultopride	-	Yes
19136626	10239	sulpiride	-	Yes
19050633	41996	sertindole	-	Yes
37498033	2265727	Secuado Topical Product	Yes	Yes
735979	35636	risperidone	-	Yes
19035226	35350	remoxipride	-	Yes
35862962	OMOP5019401	quetiapine Topical Ointment	Yes	Yes
766814	51272	quetiapine	-	Yes
19115044	55244	prothipendyl	-	Yes
19052903	8742	promazine	-	Yes
752061	8704	prochlorperazine	-	Yes
19133992	8348	pipothiazine	-	Yes
36277114	OMOP3127989	pipamperone Topical Solution	Yes	Yes
19093225	33739	pipamperone	-	Yes
745790	8331	pimozide	-	Yes
42628962	1791685	pimavanserin	-	Yes
733008	8076	perphenazine	-	Yes
19053565	8766	periciazine	-	Yes
19131663	8042	perazine	-	Yes
19028044	7974	penfluridol	-	Yes
703244	679314	paliperidone	-	Yes
19025922	7815	oxypertine	-	Yes
785788	61381	olanzapine	-	Yes
36848724	OMOP5166339	MOSAPRAMINE	-	Yes
40798964	OMOP2721313	Moperone	-	Yes
709699	7019	molindone	-	Yes
19072088	29961	metylperon	-	Yes
19005147	6852	methotrimeprazine	-	Yes
703083	6779	mesoridazine	-	Yes
40230761	1040028	lurasidone	-	Yes

37498659	2275602	lumateperone	-	Yes
792263	6475	loxapine	-	Yes
43025924	OMOP4841020	Lithium Topical Gel	Yes	Yes
40986332	OMOP2184294	Lithium / Zinc Sulfate Topical Ointment	Yes	Yes
40986331	OMOP2184293	Lithium / Oxygen / Sodium Topical Gel	Yes	Yes
40892851	OMOP2090813	Lithium / Oxygen / SEA SALT Topical Gel	Yes	Yes
36421456	OMOP4763738	Lithium / Minerals Homeopathic Topical Gel	Yes	Yes
19124477	6448	lithium	-	Yes
43009023	OMOP4700449	levosulpiride	-	Yes
19017241	73178	iloperidone	-	Yes
40861705	OMOP2059667	Hypochlorite / Lithium Topical Gel	Yes	Yes
40923962	OMOP2121924	Hypochlorite / Lithium / Sodium Topical Gel	Yes	Yes
41298341	OMOP2496303	Hypochlorite / Lithium / SEA SALT Topical Gel	Yes	Yes
36266912	OMOP3117787	Haloperidol Topical Solution	Yes	Yes
766529	5093	haloperidol	-	Yes
19056465	4507	fluspirilene	-	Yes
756018	4496	fluphenazine	-	Yes
19055982	4495	flupenthixol	-	Yes
40798823	OMOP2721176	Fluanisone	-	Yes
739323	3648	droperidol	-	Yes
40798772	OMOP2721133	Dixyrazine	-	Yes
19051234	21877	cyamemazine	-	Yes
800878	2626	clozapine	Yes	Yes
19100363	2620	clothiapine	-	Yes
36848877	OMOP5166493	CLOPENTHIXOL	-	Yes
19095002	2406	chlorprothixene	-	Yes
794852	2403	chlorpromazine	-	Yes
19122262	59860	chlorproethazine	-	Yes
35603277	1667655	cariprazine	-	Yes
40798666	OMOP2721030	Butaperazine	-	Yes
36277136	OMOP3128011	bromperidol Topical Solution	Yes	Yes
19039227	19777	bromperidol	-	Yes
46275300	1658314	brexpiprazole	-	Yes
19016440	1373	benperidol	-	Yes
37497568	2261738	asenapine Topical Product	Yes	Yes
40164052	784649	asenapine	-	Yes
757688	89013	aripiprazole	-	Yes
19057607	46303	amisulpride	-	Yes

19029555	16735	acetophenazine	-	Yes
19018226	155	acepromazine	-	Yes
36215883	1152504	4-cymene / chlorproethazine Topical Product	Yes	Yes
40001867	447121	4-cymene / chlorproethazine Topical Ointment	Yes	Yes

Psychotic disorders in Parkinson's disease (PD)

Individuals with PD diagnosis were identified and checked for a co-occurring diagnosis of psychotic symptoms or schizophrenia within the observation period. In terms of concepts:

Concept id	Concept Code	Concept Name	Exclude	Descendants
36714473	719717006	Psychosis co-occurrent and due to Parkinson's disease	-	Yes
381270	49049000	Parkinson's disease	-	Yes
4155336	28368009	Psychoactive substance-induced organic hallucinosis	Yes	Yes
440987	191486006	Hallucinosis caused by drug	Yes	Yes
433031	7011001	Hallucinations	-	Yes
444401	2073000	Delusions	-	Yes
4214950	417633001	Alcohol induced hallucinations	Yes	Yes
372607	7052005	Alcohol hallucinosis	Yes	Yes
4213979	39610001	Undifferentiated schizophrenia in remission	Yes	-
435219	4926007	Schizophrenia in remission	Yes	-
435783	58214004	Schizophrenia	-	Yes
434321	191574005	Schizoaffective schizophrenia in remission	Yes	-
440686	51133006	Residual schizophrenia in remission	Yes	-
435217	63181006	Paranoid schizophrenia in remission	Yes	-
432300	191565008	Latent schizophrenia in remission	Yes	-
436947	31373002	Disorganized schizophrenia in remission	Yes	-
434332	111483008	Catatonic schizophrenia in remission	Yes	-

Delirium in Parkinson's disease (PD)

Individuals with PD diagnosis were identified and checked for a co-occurring diagnosis of delirium within the observation period. In terms of concepts:

Concept id	Concept Code	Concept Name	Exclude	Descendants
36714473	719717006	Psychosis co-occurrent and due to Parkinson's disease	-	Yes
381270	49049000	Parkinson's disease	-	Yes
44782944	698958008	Delirium in remission	Yes	-
373995	2776000	Delirium	-	Yes

Suicidal or aggressive behaviour in patients with schizophrenia

Individuals with schizophrenia diagnosis were identified and checked for a suicidal or aggressive behaviour code within the observation period. In terms of concepts:

Concept id	Concept Code	Concept Name	Exclude	Descendants
36714069	719157002	X-linked intellectual disability and hypotonia with facial dysmorphism and aggressive behaviour syndrome	-	Yes
4113020	284607007	Finding relating to aggressive behaviour	Yes	-
4266361	61372001	Aggressive behaviour	-	Yes
213979	39610001	Undifferentiated schizophrenia in remission	Yes	-
435219	4926007	Schizophrenia in remission	Yes	-
435783	58214004	Schizophrenia	-	Yes
434321	191574005	Schizoaffective schizophrenia in remission	Yes	-
440686	51133006	Residual schizophrenia in remission	Yes	-
435217	63181006	Paranoid schizophrenia in remission	Yes	-
432300	191565008	Latent schizophrenia in remission	Yes	-
436947	31373002	Disorganized schizophrenia in remission	Yes	-
434332	111483008	Catatonic schizophrenia in remission	Yes	-
4216115	41501003	Threatening suicide	-	Yes
37399733	3161000175102	Suicide risk	-	Yes
600767	8521000175109	Suicide plan	-	Yes
4219484	82313006	Suicide attempt	-	Yes
440925	44301001	Suicide	-	Yes
444362	86849004	Suicidal deliberate poisoning	-	Yes
42596336	310991000009108	Self-mutilation of tail	Yes	Yes
4181216	363293009	Self-administered poisoning	-	Yes
4206010	53754001	Self-administered accidental poisoning	Yes	Yes
439235	276853009	Self inflicted injury	-	Yes
608248	1157096002	Self destructive behaviour	-	Yes
602870	1144845004	Risk of suicide decreased	Yes	Yes
42536693	735642007	Non suicidal self inflicted injury	Yes	-
4190444	394687007	Low suicide risk	Yes	Yes
435446	219174008	Late effect of self inflicted injury	-	-
4303690	418420002	Intentionally harming self	-	Yes
607149	1149224003	Intentional overdose	-	Yes
4257906	440144004	Injury due to suicide attempt	-	-
4037303	162314006	Harmful thoughts	-	Yes
4021339	225457007	Feeling suicidal	-	-
42573140	354511000009109	Feather plucking	Yes	-

42573949	308291000009100	Biting at flank	Yes	Yes
4021336	225444004	At risk for suicide	-	Yes

17.2 Appendix II: Supplementary Tables

Table 1. Proportion of individuals diagnosed with agranulocytosis or neutropenia (broad definition) among new users of clozapine during the study period, without censoring at clozapine treatment end (sensitivity analysis), per data source.

	Number of individuals	Number of events
DK-DHR	4,252	12
FinOMOP-HILMO	14,942	230
IQVIA DA Germany	4,027	12

DA = Disease Analyzer; DK-DHR = Danish Data Health Registries; FinOMOP-HILMO = Finnish Care Register for Health Care. Counts <5 are obscured.

Table 2. Timing to the diagnosis of agranulocytosis or neutropenia (broad definition) among new users of clozapine who developed either condition of interest.

Time (days)	DK-DHR			FinOMOP-HILMO			IQVIA DA Germany			NAJS			SIDIAP		
	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored
0	4,207	0	0	14,942	0	0	4,008	0	0	13,368	0	0	4,346	0	0
30	2,988	<5	1,219	8,409	20	6,563	3,738	<5	269	6,913	<5	6,485	4,125	<5	298
60	2,198	0	800	7,096	20	1,28	2,901	0	837	5,911	<5	1,007	3,778	6	274
90	1,846	0	348	5,747	12	1,332	2,744	<5	159	4,5	0	1,389	3,588	<5	187
120	1,601	0	242	5,052	<5	698	1,732	0	1,016	3,865	0	655	3,419	<5	160
150	1,415	0	190	4,439	<5	584	1,585	0	144	3,269	0	570	3,268	<5	146
180	1,254	0	153	3,971	0	466	1,444	0	139	2,858	0	413	3,134	<5	142
210	1,15	0	104	3,621	0	356	1,241	0	201	2,507	0	357	3,003	<5	120
240	1,049	0	103	3,329	<5	292	1,156	0	90	2,217	0	278	2,911	0	95
270	991	0	56	3,064	<5	254	1,084	0	67	2,004	0	213	2,82	<5	88
300	931	0	62	2,864	0	197	994	0	93	1,811	0	192	2,726	<5	94

Time (days)	DK-DHR			FinOMOP-HILMO			IQVIA DA Germany			NAJS			SIDIAP		
	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored
330	873	0	57	2,665	0	205	932	0	59	1,669	0	144	2,61	<5	116
360	834	0	38	2,501	<5	154	876	0	55	1,523	0	142	2,471	<5	139
390	789	0	46	2,371	<5	131	836	0	41	1,404	<5	115	2,27	0	197
420	744	0	45	2,246	0	123	779	0	59	1,292	0	113	2,184	<5	85
450	714	0	29	2,139	0	106	739	0	38	1,193	0	98	2,103	0	81
480	680	0	34	2,041	0	99	713	0	26	1,11	0	83	2,034	0	68
510	646	0	35	1,964	0	80	679	<5	32	1,046	0	68	1,974	<5	61
540	617	0	28	1,876	0	91	645	0	37	968	0	76	1,905	0	67
570	596	0	20	1,793	0	79	613	<5	28	881	0	85	1,856	0	48
600	574	0	22	1,7	0	93	409	0	204	819	0	63	1,808	0	49
630	542	0	32	1,624	0	79	381	0	28	768	0	51	1,751	<5	57
660	517	0	25	1,558	0	60	364	0	17	720	0	47	1,697	<5	54
690	495	0	23	1,506	0	53	342	0	25	674	0	49	1,65	0	46
720	474	0	20	1,449	0	56	324	0	15	640	0	30	1,582	<5	65
750	457	0	17	1,405	0	46	306	0	18	610	0	31	1,533	0	52
780	449	0	9	1,336	0	70	289	0	17	574	0	36	1,49	<5	39
810	433	0	15	1,286	0	47	269	0	20	554	0	20	1,453	0	38
840	411	0	22	1,246	0	41	251	0	19	529	0	27	1,409	0	44
870	401	0	10	1,207	0	40	240	0	10	498	0	30	1,374	0	35
900	385	0	16	1,172	0	34	230	0	11	473	0	23	1,331	0	43
930	376	0	10	1,13	0	41	215	<5	14	454	0	19	1,305	0	26
960	362	<5	12	1,089	0	45	206	0	8	431	<5	22	1,272	0	34

Time (days)	DK-DHR			FinOMOP-HILMO			IQVIA DA Germany			NAJS			SIDIAP		
	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored
990	353	0	11	1,041	0	46	194	0	12	412	0	19	1,233	0	39
1020	344	0	8	991	<5	50	184	0	10	393	0	19	1,203	0	29
1050	337	0	7	956	0	34	174	0	10	376	0	18	1,174	0	31
1080	323	0	14	924	<5	31	167	0	7	358	0	18	1,144	0	27
1110	315	0	8	895	0	28	157	0	10	346	0	14	1,118	0	26
1140	301	0	13	865	0	29	148	0	9	331	0	12	1,095	0	23
1170	296	0	5	840	0	25	136	0	12	317	0	15	1,079	0	16
1200	293	0	<5	817	0	23	127	0	9	306	0	11	1,059	0	20
1230	284	0	9	802	0	15	125	0	<5	296	0	10	1,034	0	26
1260	280	0	5	779	0	27	117	0	6	282	0	13	1,005	0	29
1290	273	0	6	754	<5	20	111	0	6	264	0	18	979	0	26
1320	267	0	6	728	0	26	108	0	<5	255	0	9	951	<5	27
1350	261	0	6	714	0	14	105	0	<5	246	0	9	932	0	18
1380	255	0	6	694	0	22	100	0	5	238	0	11	919	0	14
1410	247	0	9	666	0	26	98	0	<5	226	0	10	895	0	24
1440	238	0	8	642	0	26	93	0	5	219	0	6	884	0	10
1470	235	0	<5	630	0	13	87	0	6	211	0	8	869	0	16
1500	231	0	<5	604	0	23	83	0	<5	208	0	<5	855	0	14
1530	227	0	<5	588	0	17	80	0	<5	196	0	13	832	<5	21
1560	222	0	5	577	0	11	75	0	<5	187	0	8	815	<5	16
1590	220	0	<5	562	0	15	74	0	<5	182	0	6	799	0	17
1620	217	0	<5	551	0	10	73	0	<5	174	0	7	783	<5	14

Time (days)	DK-DHR			FinOMOP-HILMO			IQVIA DA Germany			NAJS			SIDIAP		
	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored
1650	214	0	<5	539	<5	12	70	0	<5	169	0	6	773	0	10
1680	209	0	5	533	0	6	68	0	<5	164	0	<5	751	0	23
1710	203	0	6	515	0	18	67	0	<5	160	0	<5	738	0	13
1740	194	0	9	500	0	14	64	0	<5	154	0	6	730	0	7
1770	188	0	6	491	0	9	62	0	<5	146	0	8	718	0	12
1800	183	0	5	475	0	16	57	0	5	139	0	8	706	0	12
1830	179	0	<5	458	0	17	55	0	<5	135	0	<5	689	0	19
1860	179	0	0	447	0	12	52	0	<5	130	0	6	675	0	12
1890	177	0	<5	431	0	16	50	0	<5	123	0	6	666	0	10
1920	172	0	5	416	0	15	48	0	<5	119	0	<5	654	0	15
1950	170	0	<5	404	0	12	48	0	0	113	0	6	639	0	11
1980	167	0	<5	395	0	8	48	0	<5	106	0	7	625	0	15
2010	163	0	<5	381	0	14	44	0	<5	101	0	5	607	0	18
2040	162	0	<5	368	0	13	44	0	0	93	0	8	596	0	11
2070	157	0	5	357	0	11	42	0	<5	88	0	6	586	0	9
2100	153	0	<5	348	0	9	40	0	<5	79	0	9	577	0	9
2130	150	0	<5	339	0	9	37	0	<5	73	0	5	564	0	13
2160	148	0	<5	327	0	12	35	0	<5	67	0	6	546	<5	17
2190	146	0	<5	317	0	10	32	0	<5	57	0	10	536	0	11
2220	144	0	<5	310	0	7	31	0	<5	52	0	5	512	0	27
2250	142	0	<5	300	0	10	30	0	<5	48	0	<5	495	0	13
2280	140	0	<5	292	0	8	29	0	<5	43	0	5	488	0	7

Time (days)	DK-DHR			FinOMOP-HILMO			IQVIA DA Germany			NAJS			SIDIAP		
	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored
2310	137	0	5	282	0	10	28	0	<5	42	0	<5	479	0	9
2340	130	0	5	274	0	9	24	0	<5	37	0	5	472	0	7
2370	130	0	0	266	0	8	23	0	<5	34	0	<5	457	0	15
2400	128	0	<5	256	0	9	23	0	0	31	0	<5	449	0	8
2430	125	0	<5	253	0	<5	22	0	<5	25	0	7	442	0	7
2460	124	0	<5	249	0	<5	22	0	<5	23	0	<5	437	0	5
2490	122	0	<5	243	0	7	21	0	0	19	0	<5	433	0	<5
2520	119	0	<5	237	0	5	20	0	<5	17	0	<5	426	0	7
2550	118	0	<5	231	0	6	20	0	0	15	0	<5	416	0	11
2580	114	0	<5	226	0	5	19	0	<5	15	0	0	402	<5	13
2610	111	0	<5	224	0	<5	18	0	<5	12	0	<5	389	<5	11
2640	108	0	<5	217	0	7	17	0	<5	10	0	<5	382	0	7
2670	106	0	<5	211	0	6	17	0	0	8	0	<5	373	0	9
2700	105	0	<5	203	0	8	17	0	0	<5	0	5	365	0	8
2730	101	0	<5	196	0	7	16	0	<5	-	-	-	352	<5	12
2760	100	0	<5	195	0	<5	16	0	0	-	-	-	345	0	7
2790	97	0	<5	191	0	<5	15	0	<5	-	-	-	334	0	11
2820	95	0	<5	184	0	7	13	0	<5	-	-	-	322	0	12
2850	90	0	<5	183	0	<5	13	0	0	-	-	-	313	0	9
2880	89	0	<5	178	0	5	12	0	<5	-	-	-	303	0	10
2910	88	0	<5	175	0	<5	12	0	0	-	-	-	294	0	11
2940	86	0	<5	168	0	7	12	0	0	-	-	-	277	0	16

Time (days)	DK-DHR			FinOMOP-HILMO			IQVIA DA Germany			NAJS			SIDIAP		
	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored
2970	83	0	<5	162	0	6	12	0	0	-	-	-	268	0	8
3000	82	0	<5	159	0	<5	12	0	0	-	-	-	261	0	7
3030	80	0	<5	158	0	<5	11	0	<5	-	-	-	249	0	13
3060	80	0	0	151	0	7	11	0	<5	-	-	-	237	0	11
3090	79	0	<5	148	0	<5	10	0	0	-	-	-	223	0	14
3120	77	0	<5	143	0	<5	10	0	0	-	-	-	196	0	27
3150	76	0	<5	141	0	<5	10	0	0	-	-	-	181	0	15
3180	73	0	<5	140	0	<5	10	0	0	-	-	-	164	0	20
3210	69	0	<5	138	0	<5	10	0	0	-	-	-	145	0	17
3240	68	0	<5	135	0	<5	10	0	0	-	-	-	134	0	10
3270	65	0	<5	131	0	<5	10	0	0	-	-	-	118	0	16
3300	65	0	0	129	0	<5	10	0	0	-	-	-	112	0	7
3330	64	0	<5	127	0	<5	10	0	0	-	-	-	108	0	<5
3360	63	0	<5	126	0	<5	10	0	0	-	-	-	97	0	11
3390	63	0	0	124	0	<5	10	0	0	-	-	-	85	0	13
3420	62	0	<5	122	0	<5	10	0	0	-	-	-	72	0	12
3450	62	0	0	117	0	<5	9	0	<5	-	-	-	68	0	<5
3480	62	0	0	114	0	<5	9	0	0	-	-	-	67	0	<5
3510	59	0	<5	113	0	<5	8	0	<5	-	-	-	66	0	<5
3540	57	0	<5	111	0	<5	8	0	0	-	-	-	60	0	6
3570	56	0	<5	111	0	0	8	0	0	-	-	-	56	0	<5
3600	55	0	<5	109	0	<5	7	0	<5	-	-	-	49	0	7

Time (days)	DK-DHR			FinOMOP-HILMO			IQVIA DA Germany			NAJS			SIDIAP		
	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored
3630	55	0	0	107	0	<5	6	0	<5	-	-	-	47	0	<5
3660	52	0	<5	103	0	<5	6	0	0	-	-	-	46	0	0
3690	52	0	0	103	0	0	6	0	0	-	-	-	44	0	<5
3720	51	0	<5	99	0	<5	5	0	<5	-	-	-	41	0	<5
3750	49	0	<5	98	0	<5	5	0	0	-	-	-	39	0	<5
3780	47	0	<5	96	0	<5	5	0	0	-	-	-	37	0	<5
3810	44	0	<5	93	0	<5	5	0	0	-	-	-	34	0	<5
3840	43	0	<5	91	0	<5	<5	0	<5	-	-	-	34	0	0
3870	43	0	0	88	0	<5	<5	0	0	-	-	-	33	0	<5
3900	43	0	0	86	0	<5	<5	0	0	-	-	-	33	0	0
3930	43	0	0	82	0	<5	<5	0	0	-	-	-	31	0	<5
3960	41	0	<5	77	0	5	<5	0	0	-	-	-	31	0	0
3990	39	0	<5	72	0	5	<5	0	0	-	-	-	30	0	<5
4020	39	0	0	67	0	5	<5	0	0	-	-	-	28	0	<5
4050	38	0	<5	59	0	9	<5	0	0	-	-	-	28	0	0
4080	37	0	<5	32	0	26	<5	0	0	-	-	-	27	0	<5
4110	36	0	<5	23	0	9	<5	0	<5	-	-	-	25	0	<5
4140	36	0	0	18	0	5	<5	0	0	-	-	-	24	0	<5
4170	35	0	<5	16	0	<5	<5	0	0	-	-	-	23	0	<5
4200	35	0	<5	13	0	<5	<5	0	0	-	-	-	21	0	<5
4230	34	0	0	12	0	<5	<5	0	0	-	-	-	20	0	<5
4260	31	0	<5	5	0	7	<5	0	0	-	-	-	19	0	<5

Time (days)	DK-DHR			FinOMOP-HILMO			IQVIA DA Germany			NAJS			SIDIAP		
	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored
4290	31	0	<5	<5	0	<5	<5	0	<5	-	-	-	18	0	<5
4320	30	0	0	-	-	-	-	-	-	-	-	-	18	0	0
4350	30	0	0	-	-	-	-	-	-	-	-	-	17	0	<5
4380	30	0	0	-	-	-	-	-	-	-	-	-	17	0	0
4410	28	0	<5	-	-	-	-	-	-	-	-	-	15	0	<5
4440	27	0	<5	-	-	-	-	-	-	-	-	-	15	0	0
4470	26	0	<5	-	-	-	-	-	-	-	-	-	15	0	0
4500	25	0	<5	-	-	-	-	-	-	-	-	-	15	0	0
4530	25	0	0	-	-	-	-	-	-	-	-	-	15	0	0
4560	25	0	0	-	-	-	-	-	-	-	-	-	13	0	<5
4590	25	0	0	-	-	-	-	-	-	-	-	-	10	0	<5
4620	24	0	<5	-	-	-	-	-	-	-	-	-	9	0	<5
4650	22	0	<5	-	-	-	-	-	-	-	-	-	7	0	<5
4680	20	0	<5	-	-	-	-	-	-	-	-	-	7	0	0
4710	20	0	0	-	-	-	-	-	-	-	-	-	6	0	<5
4740	19	0	<5	-	-	-	-	-	-	-	-	-	6	0	<5
4770	18	0	<5	-	-	-	-	-	-	-	-	-	<5	0	<5
4800	17	0	<5	-	-	-	-	-	-	-	-	-	<5	0	<5
4830	17	0	0	-	-	-	-	-	-	-	-	-	<5	0	<5
4860	16	0	<5	-	-	-	-	-	-	-	-	-	<5	0	0
4890	15	0	<5	-	-	-	-	-	-	-	-	-	<5	0	0
4920	13	0	<5	-	-	-	-	-	-	-	-	-	<5	0	0

Time (days)	DK-DHR			FinOMOP-HILMO			IQVIA DA Germany			NAJS			SIDIAP		
	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored	Number at risk	Number events	Number censored
4950	12	0	<5	-	-	-	-	-	-	-	-	-	-	-	-
4980	12	0	0	-	-	-	-	-	-	-	-	-	-	-	-
5010	11	0	<5	-	-	-	-	-	-	-	-	-	-	-	-
5040	10	0	0	-	-	-	-	-	-	-	-	-	-	-	-
5070	10	0	0	-	-	-	-	-	-	-	-	-	-	-	-
5100	10	0	0	-	-	-	-	-	-	-	-	-	-	-	-
5130	8	0	<5	-	-	-	-	-	-	-	-	-	-	-	-
5160	7	0	<5	-	-	-	-	-	-	-	-	-	-	-	-
5190	<5	0	<5	-	-	-	-	-	-	-	-	-	-	-	-
5220	<5	0	0	-	-	-	-	-	-	-	-	-	-	-	-
5250	<5	0	0	-	-	-	-	-	-	-	-	-	-	-	-
5280	<5	0	0	-	-	-	-	-	-	-	-	-	-	-	-
5310	<5	0	<5	-	-	-	-	-	-	-	-	-	-	-	-
5340	<5	0	0	-	-	-	-	-	-	-	-	-	-	-	-
5370	<5	0	<5	-	-	-	-	-	-	-	-	-	-	-	-

Number at risk represents the total number of unique individuals at risk of developing agranulocytosis or neutropenia per 30 days interval (Time), Number events represents the number of individuals who developed agranulocytosis or neutropenia during that time window, and Number events represents the number of individuals who are censored at that time window. DA = Disease Analyzer; DK-DHR = Danish Data Health Registries; FinOMOP-HILMO = Finnish Care Register for Health Care; NAJS = Croatian National Public Health Information System; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària. Counts <5 are obscured

Table 3. Timing to the diagnosis of agranulocytosis or neutropenia (broad definition) among new users of clozapine who developed either condition of interest, without censoring at clozapine treatment end (sensitivity analysis).

	DK-DHR	FinOMOP-HILMO	IQVIA DA Germany
Number of individuals	12	230	12
Time to event (days)			
Mean (SD)	1,077.67 (1,032.47)	1,152.12 (1,162.22)	468.67 (508.78)
Median (Q25 - Q75)	874.00 [70.25 - 1,931.00]	851.50 [85.50 - 1,907.00]	487.00 [63.50 - 585.25]
Range (min to max)	21.00 to 2,829.00	2.00 to 4,307.00	6.00 to 1,768.00

DA = Disease Analyzer; DK-DHR = Danish Data Health Registries; FinOMOP-HILMO = Finnish Care Register for Health Care; SD = standard deviation; Q25 - Q75 interquartile range.

Table 4. Treatment duration of clozapine prescriptions, presented by database, allowing a 90 day gap between prescriptions (sensitivity analysis).

		DK-DHR (n = 4,253)	FinOMOP-HILMO (n = 14,944)	IQVIA DA Germany (n = 4,029)
days exposed*	Mean (SD)	740.38 (1,127.52)	917.57 (1,319.20)	428.25 (667.43)
	Median (Q25 - Q75)	230 (33 - 879)	188 (30 - 1,297)	139 (68 - 568)
	min	1	2	1
	max	5,411	4,585	5,354
days prescribed**	Mean (SD)	884.79 (1,651.47)	1,048.97 (1,612.32)	595.51 (1,138.48)
	Median (Q25 - Q75)	165 (33 - 869)	210 (58 - 1,469)	180 (80 - 600)
	min	1	2	1
	max	13,432	35,730	16,123

This table shows the results of the sensitivity analysis in which the allowed gap between two clozapine prescriptions is extended from 30 to 90 days. The results from the original analysis can be observed in **Table 17**. * = the number of days that an individual is in a continuous exposure episode, including allowed treatment gaps. ** = the sum of the number of days for each prescription that contributes to the analysis. DA = Disease Analyzer; DK-DHR = Danish Data Health Registries; FinOMOP-HILMO = Finnish Care Register for Health Care; SD = standard deviation; Q25 - Q75 interquartile range.

17.3 Appendix III: Supplementary Figures

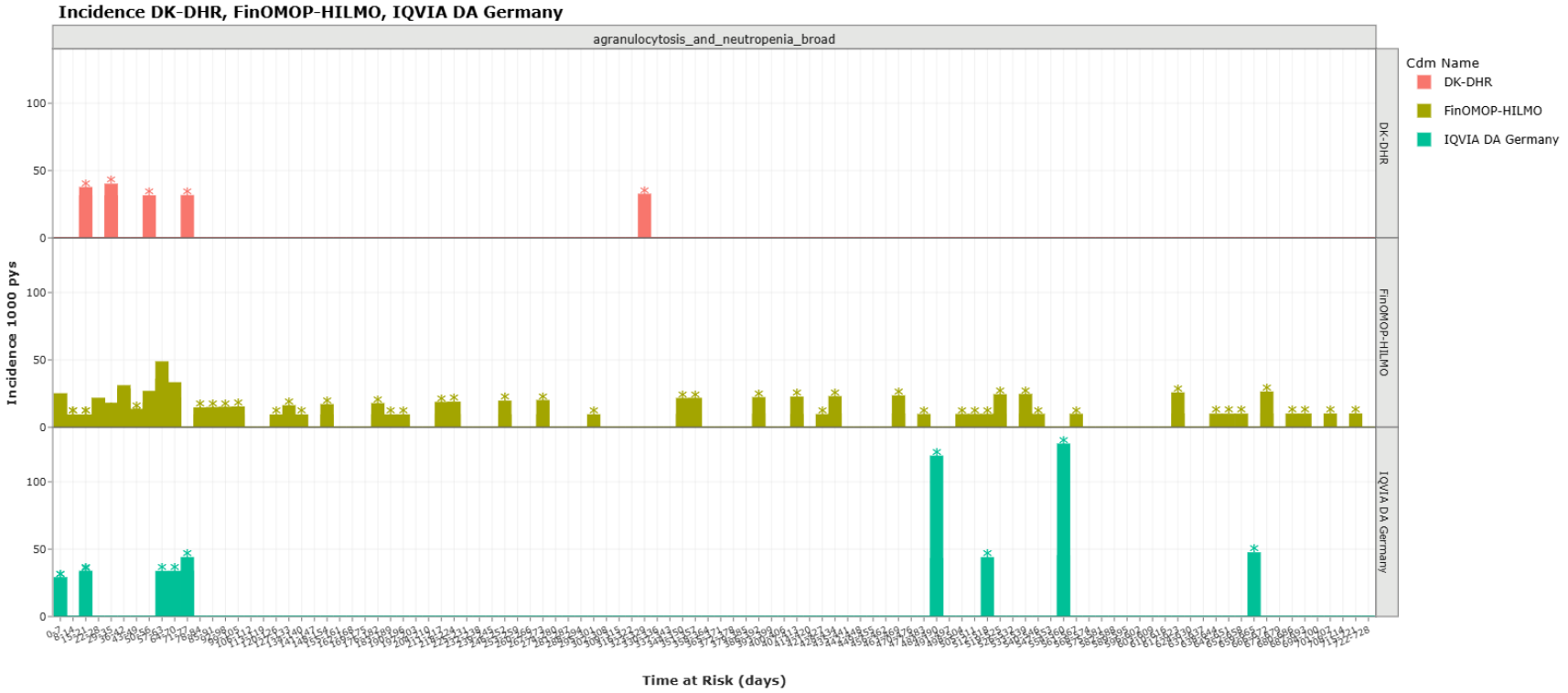

Figure 1. Incidence rates of agranulocytosis and neutropenia (broad definition) following initiation of clozapine treatment (2010 - 2024) by consecutive weekly intervals for each data source, without censoring at clozapine treatment end (sensitivity analysis).

For intervals with fewer than 5 individuals diagnosed with agranulocytosis and neutropenia, a value of 2.5 was used to estimate the incidence rate, reflecting the midpoint of the possible range (from a minimum of 1 to a maximum of 4 events). These estimates are indicated with an asterisk (*) to denote that they are based on imputed rather than actual event counts due to data privacy restrictions.

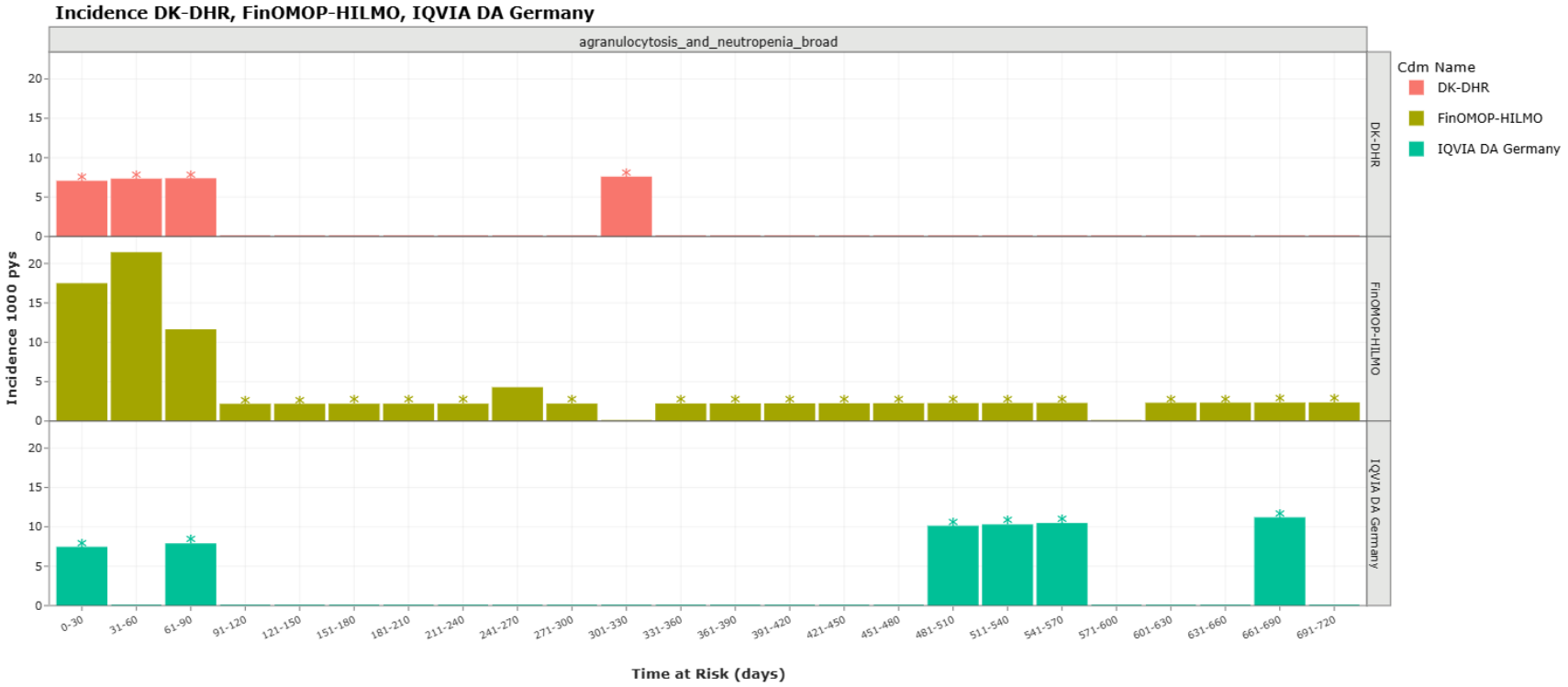

Figure 2. Incidence rates of agranulocytosis and neutropenia (broad definition) following initiation of clozapine treatment (2010 – 2024) by consecutive monthly intervals for each data source, without censoring at clozapine treatment end (sensitivity analysis).

For intervals with fewer than 5 individuals diagnosed with agranulocytosis and neutropenia, a value of 2.5 was used to estimate the incidence rate, reflecting the midpoint of the possible range (from a minimum of 1 to a maximum of 4 events). These estimates are indicated with an asterisk (*) to denote that they are based on imputed rather than actual event counts due to data privacy restrictions.

Figure 3. Incidence rates of agranulocytosis and neutropenia (broad definition) following initiation of clozapine treatment by consecutive weekly intervals for each data source, from 2010 to 2024, by age.

For intervals with fewer than 5 individuals diagnosed with agranulocytosis and neutropenia, a value of 2.5 was used to estimate the incidence rate, reflecting the midpoint of the possible range (from a minimum of 1 to a maximum of 4 events). These estimates are indicated with an asterisk (*) to denote that they are based on imputed rather than actual event counts due to data privacy restrictions.

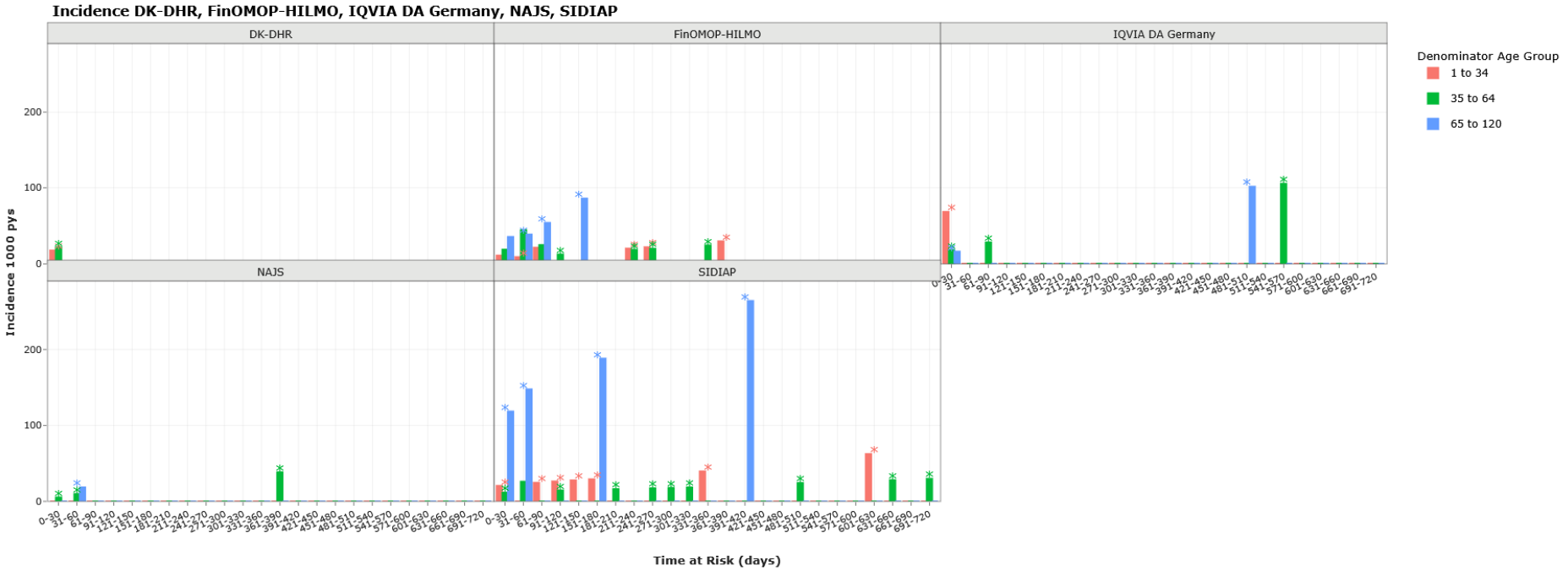

Figure 4. Incidence rates of agranulocytosis and neutropenia (broad definition) following initiation of clozapine treatment by consecutive monthly intervals for each data source, from 2010 to 2024, by age.

For intervals with fewer than 5 individuals diagnosed with agranulocytosis and neutropenia, a value of 2.5 was used to estimate the incidence rate, reflecting the midpoint of the possible range (from a minimum of 1 to a maximum of 4 events). These estimates are indicated with an asterisk (*) to denote that they are based on imputed rather than actual event counts due to data privacy restrictions.

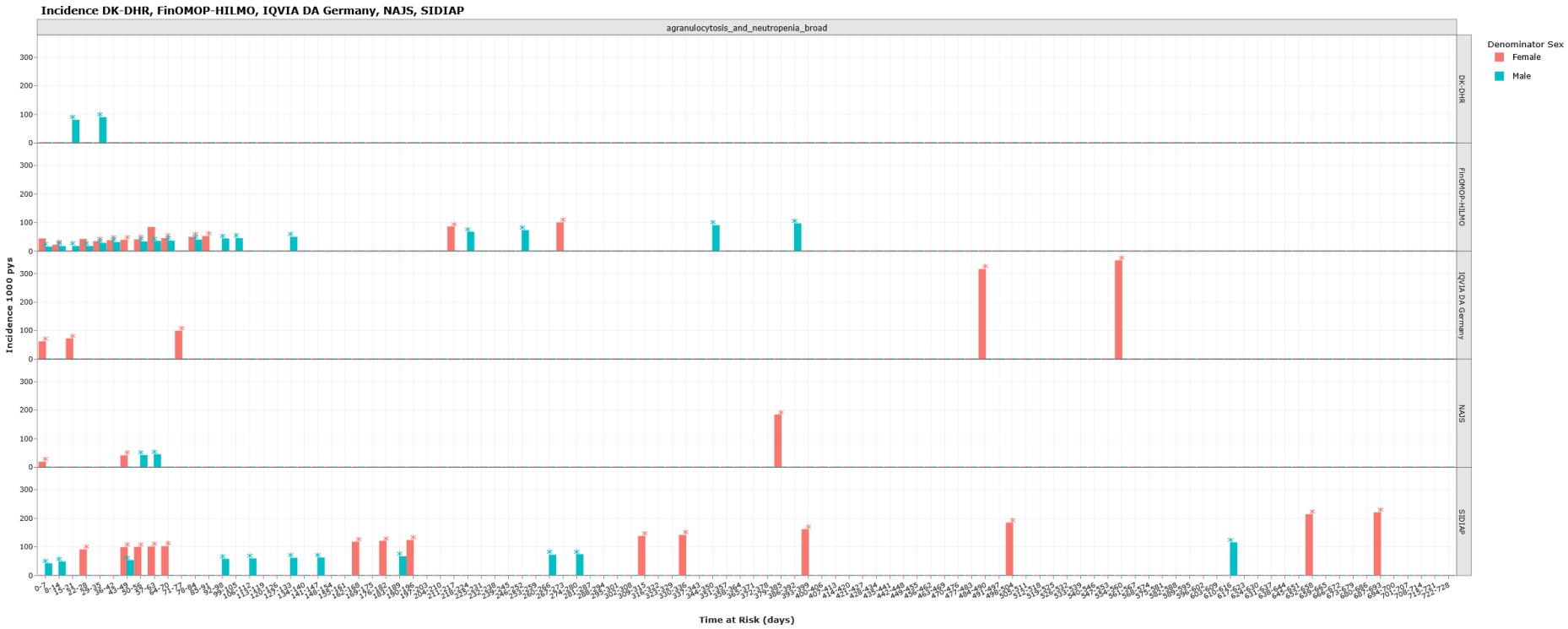

Figure 5. Incidence rates of agranulocytosis and neutropenia (broad definition) following initiation of clozapine treatment by consecutive weekly intervals for each data source, from 2010 to 2024, by sex.

For intervals with fewer than 5 individuals diagnosed with agranulocytosis and neutropenia, a value of 2.5 was used to estimate the incidence rate, reflecting the midpoint of the possible range (from a minimum of 1 to a maximum of 4 events). These estimates are indicated with an asterisk (*) to denote that they are based on imputed rather than actual event counts due to data privacy restrictions.

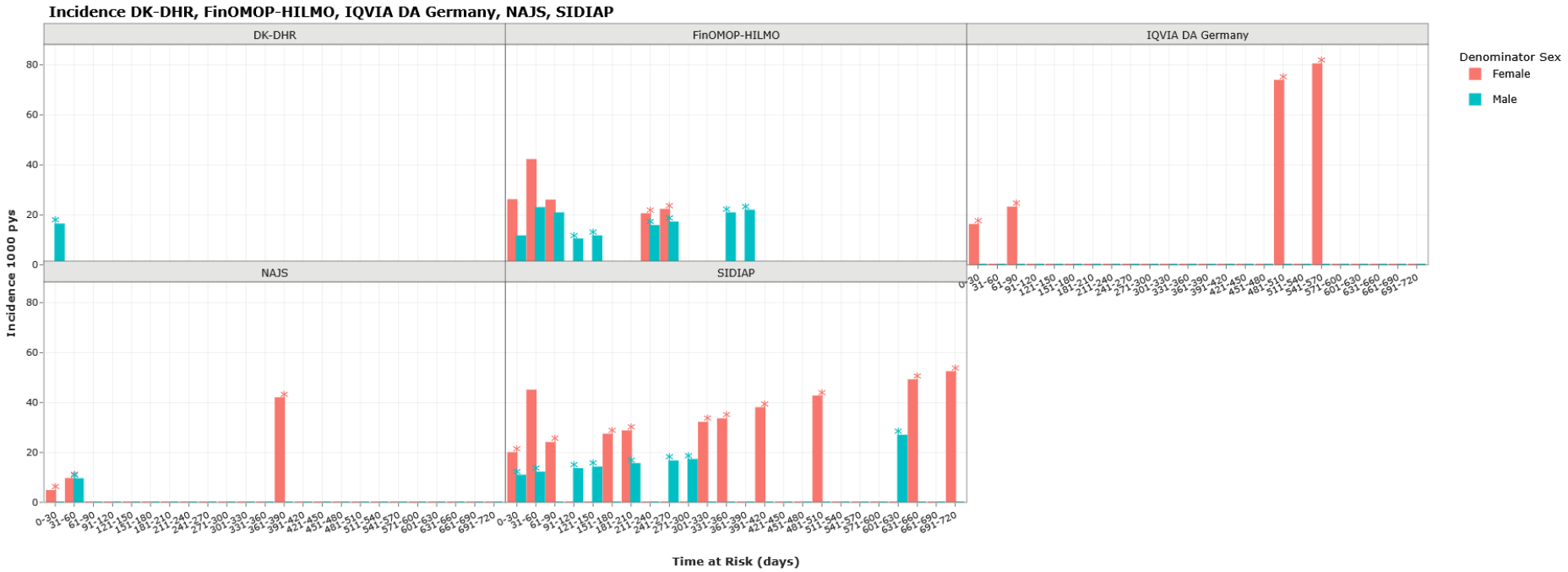

Figure 6. Incidence rates of agranulocytosis and neutropenia (broad definition) following initiation of clozapine treatment by consecutive monthly intervals for each data source, from 2010 to 2024, by sex.

For intervals with fewer than 5 individuals diagnosed with agranulocytosis and neutropenia, a value of 2.5 was used to estimate the incidence rate, reflecting the midpoint of the possible range (from a minimum of 1 to a maximum of 4 events). These estimates are indicated with an asterisk (*) to denote that they are based on imputed rather than actual event counts due to data privacy restrictions.

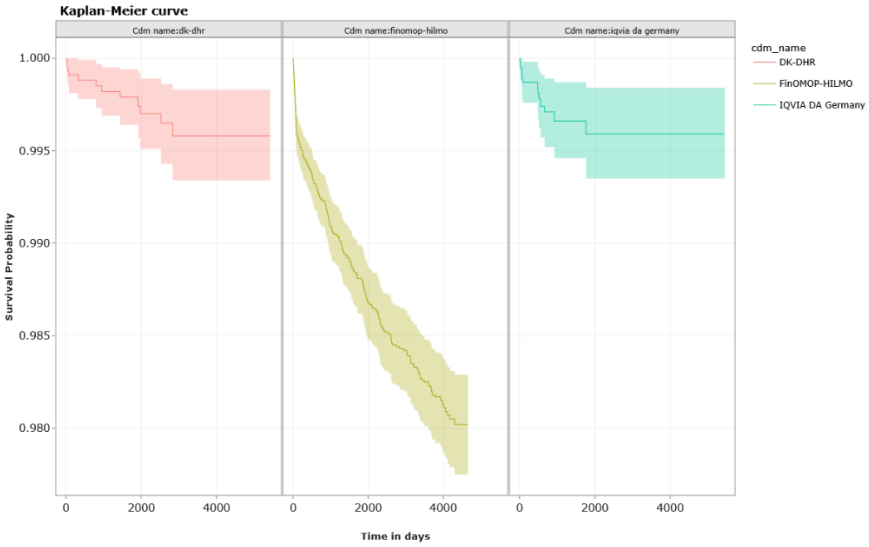

Figure 7. Kaplan-Meier plots of time to agranulocytosis and neutropenia (broad definition) following initiation of clozapine treatment over time by each data source, from 2010 to 2024, without censoring at clozapine treatment end (sensitivity analysis).

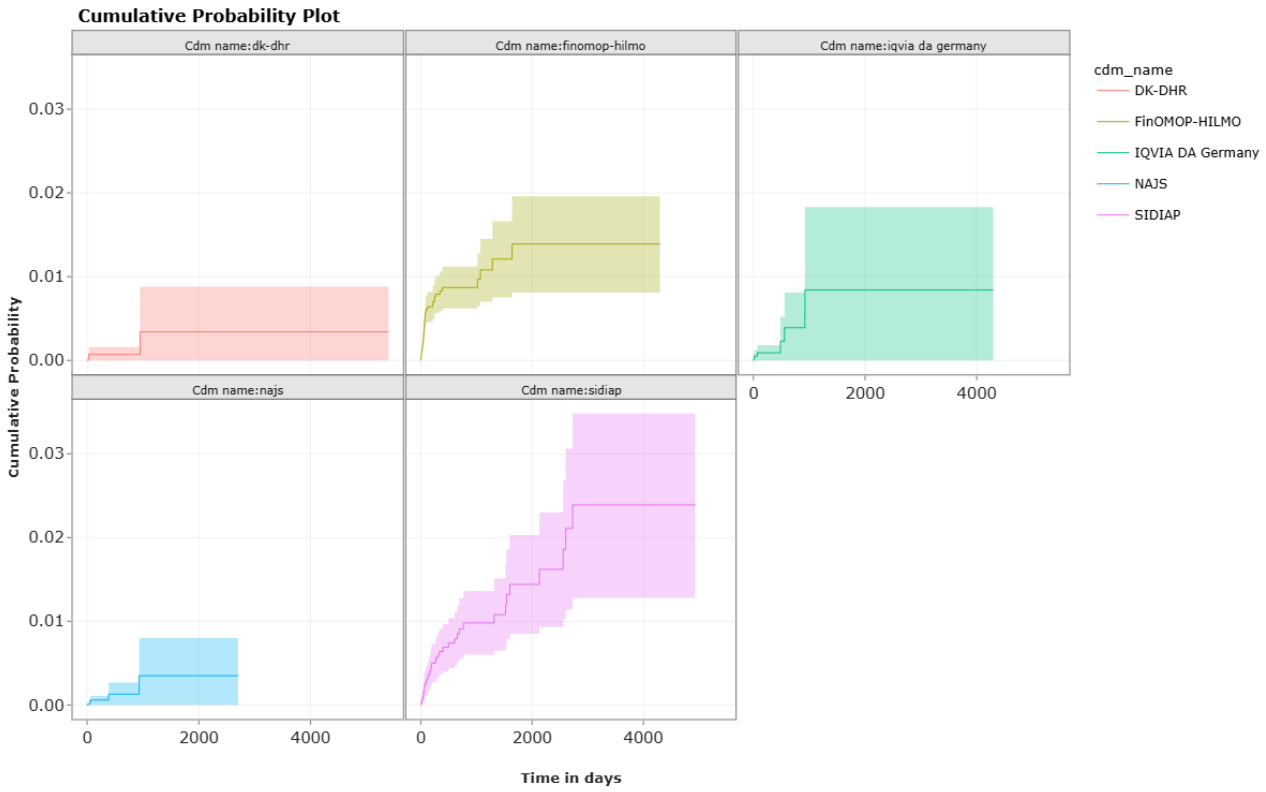

Figure 8. Cumulative risk of agranulocytosis and neutropenia (broad definition) following initiation of clozapine treatment over time by each data source, from 2010 to 2024.

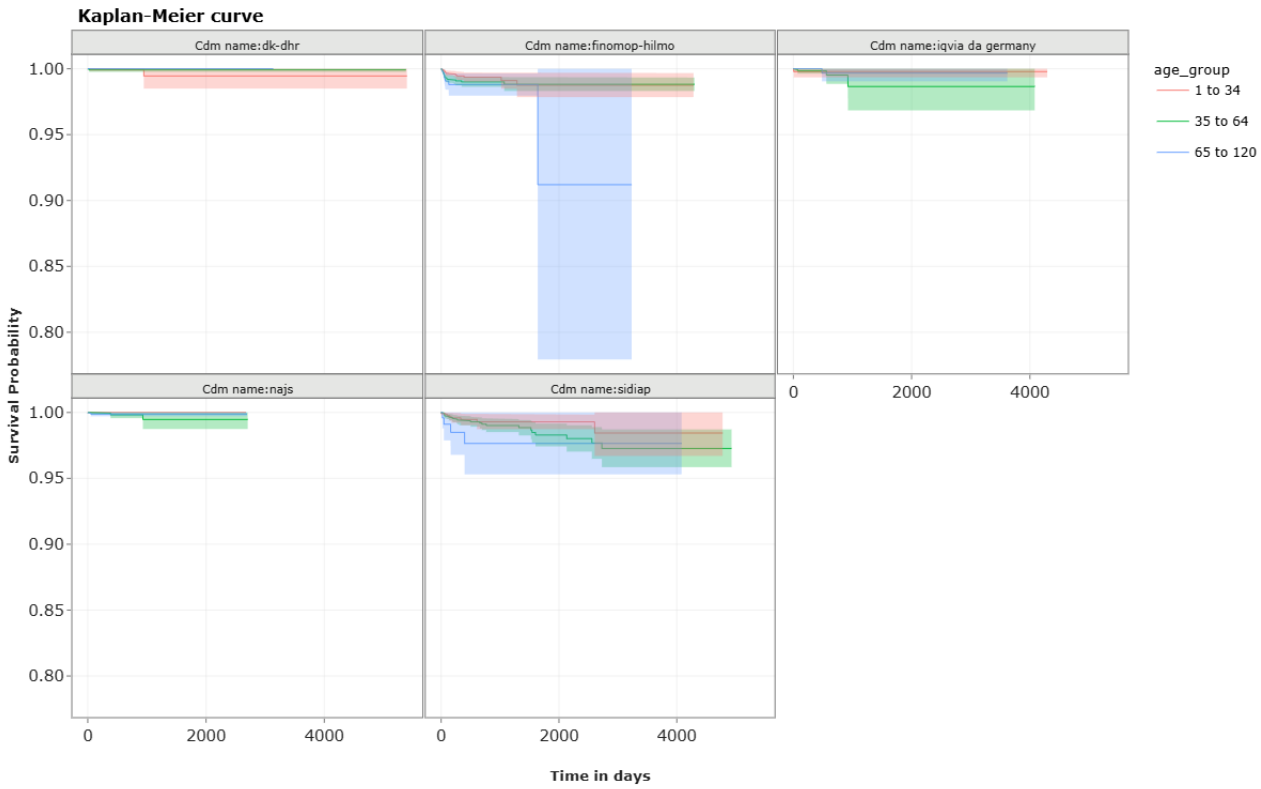

Figure 9. Kaplan-Meier plots of time to agranulocytosis or neutropenia (broad definition) following clozapine treatment initiation, by age group.

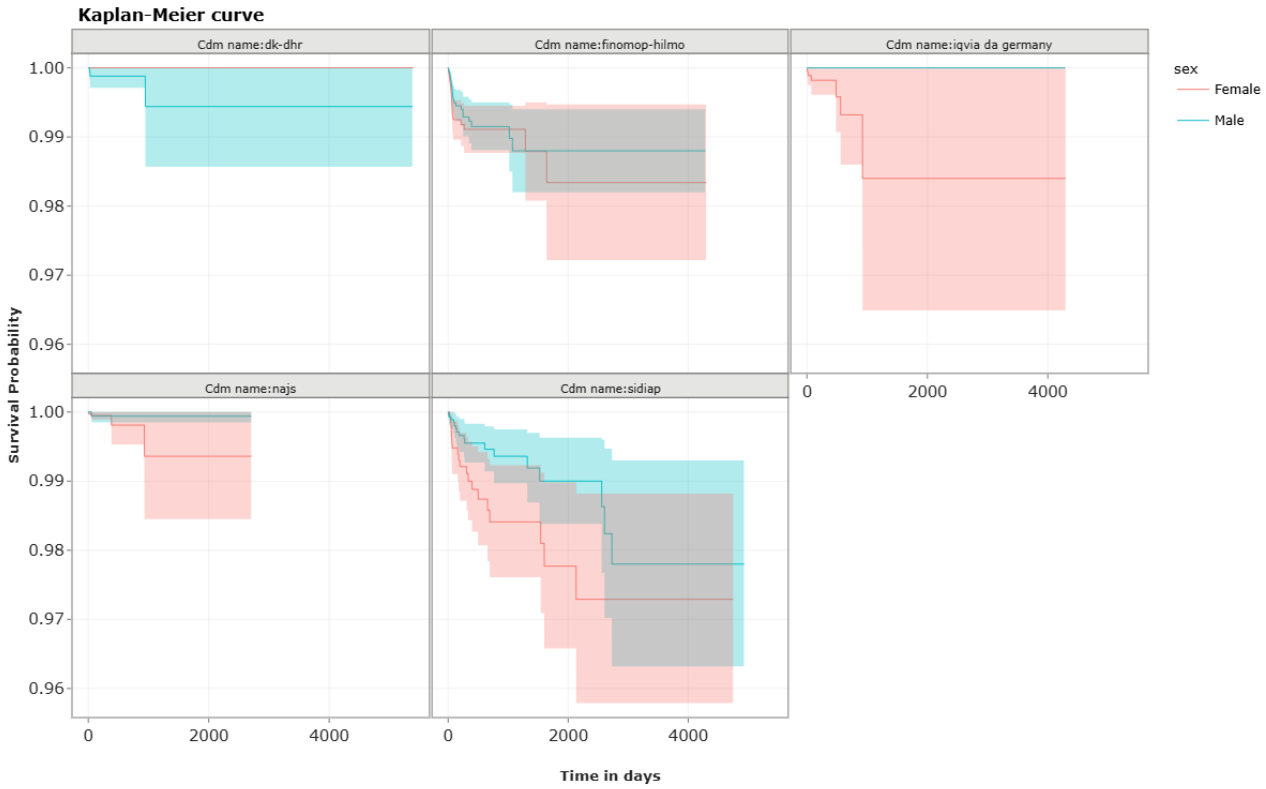

Figure 10. Kaplan-Meier plots of time to agranulocytosis or neutropenia (broad definition) following clozapine treatment initiation, by sex.

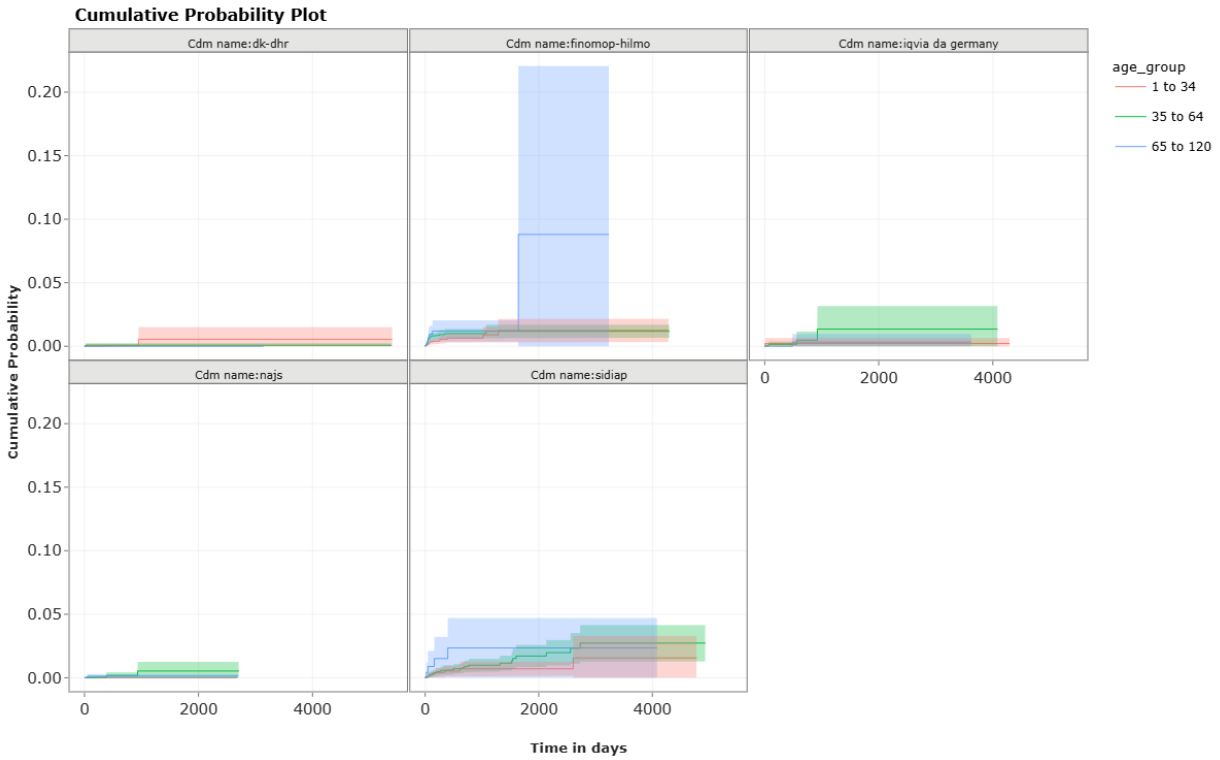

Figure 11. Cumulative risk of agranulocytosis and neutropenia (broad definition) following initiation of clozapine treatment over time by each data source, from 2010 to 2024, by age group.

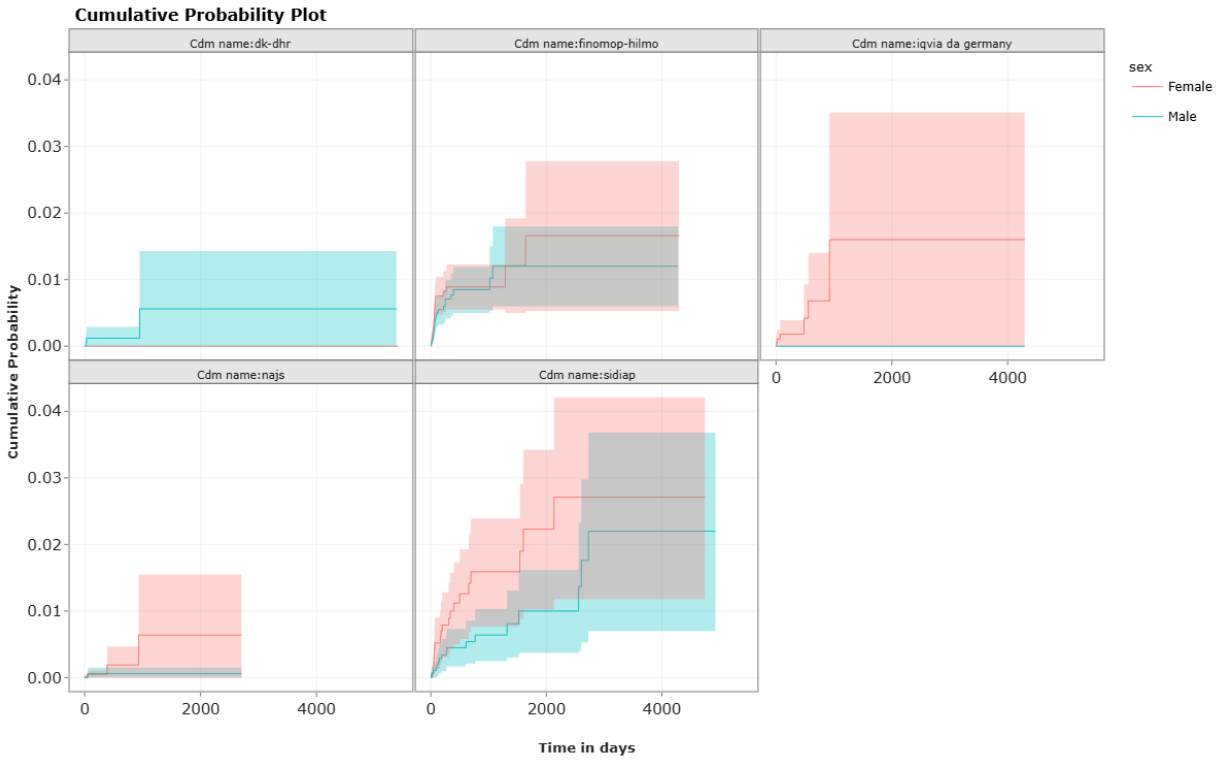

Figure 12. Cumulative risk of agranulocytosis and neutropenia (broad definition) following initiation of clozapine treatment over time by each data source, from 2010 to 2024, by sex.