Study Report

P3-C1-012

DARWIN EU® - Antipsychotic prescribing in the general population in Europe: a descriptive analysis of trends and patient characteristics

25/02/2025

Version 3.0

Contents

Study title	DARWIN EU® - Antipsychotic prescribing in the general population in Europe: a descriptive analysis of trends and patient characteristics
Study report version	V3.0
Date	25/02/2025
EU PAS number	EUPAS1000000330
Active substance	**Drug of interest** Common antipsychotics (ATC: N05A) Substances included: • Sulpiride • Quetiapine • Risperidone • Olanzapine • Haloperidol • Aripiprazole • Pipamperone • Prothipendyl • Prochlorperazine • Chlorprothixene • Promazine • Paliperidone • Zuclopenthixol • Clozapine • Fluspirilene • Amisulpride • Fluphenazine • Perphenazine • Pimozide • Ziprasidone
Medicinal product	Not applicable
Research question and objectives	Study Objectives: 1. To characterise the general population with a first use of common antipsychotics in terms of age, gender and

	comorbidities/indication 2. To measure trends in the incidence of first use of common antipsychotic prescribing overall, by typical/atypical grouping and by the top 20 most common drug substances. Results would be stratified by database, calendar year, age and sex. 3. To characterise first time users of common antipsychotic drug therapy after initiation by drug substance (in terms of initial dose and duration). Results would be stratified by drug route, age and sex. 4. To measure overall survival in the general population with a first use of common antipsychotic overall, for typical/atypical grouping and for top 20 most common drug substances.
Countries of study	Spain, Netherlands, Denmark, Germany, Belgium, Croatia
Authors	W. Wang, M. Pineda-Moncusí

TITLE

DARWIN EU® - Antipsychotic prescribing in the general population in Europe: a descriptive analysis of trends and patient characteristics

1. DESCRIPTION OF STUDY TEAM

Study team role	Names	Organisation
Study Project Manager/Principal Investigator	Marta Pineda Moncusí Edward Burn	University of Oxford
Data Scientist	Mike Du Edward Burn	University of Oxford
Epidemiologist	Wanning Wang Daniel Prieto Alhambra	University of Oxford University of Oxford/Erasmus MC University
Clinical Domain Expert	Danielle Newby	University of Oxford
Data Analyst	Mike Du	University of Oxford
Data Partner*	**Names**	**Organisation**
Local Study Coordinator/Data Analyst	Talita Duarte	SIDIAP
	Anna Palomar	
	Irene López Sánchez	
	Agustina Giuliodori	
	Katia Verhamme	IPCI
	Claus Møldrup Elvira Bräuner Susanne Bruun	DK-DHR
	Dina Vojinovic	IQVIA DA Germany, IQVIA LPD Belgium
	Isabella Kaczmarczyk	
	James Brash	
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	Akram Mendez	
	Hanne van Ballegooijen	
	Pero Ivanko	NAJS
	Marko Čavlina	
	Antea Jezidžić	
	Emanuel Brađašević	
	Lucija Raič	

*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

Country	Name of Database	Health Care setting	Type of Data	Number of active subjects	Calendar period covered by each data source.
Spain	SIDIAP	Primary care records	EHR	8.5M	01/07/2013 to 01/06/2023
Netherlands	IPCI	Primary care records	EHR	2.9M	01/01/2013 to 31/12/2023
Germany	IQVIA DA Germany	Outpatient: primary care and specialist records	EHR	43M	01/01/2013 to 31/12/2023
Belgium	IQVIA LPD Belgium	Outpatient: primary care and specialist records	EHR	1.1M	01/01/2015 to 31/01/2024
Denmark	DK-DHR	Primary and hospital in-patient care settings	EHR, registries	5.8M	01/01/2013 to 31/12/2023
Croatia	NAJS	Primary and hospital in-patient care settings	Registry	3M	01/01/2015 to 17/11/2023

3. ABSTRACT

Title

DARWIN EU® - Antipsychotic prescribing in the general population in Europe: a descriptive analysis of trends and patient characteristics

Rationale and background

Antipsychotic drugs have been associated with several adverse drug reactions, particularly in the elderly. Somnolence, hypotension, extrapyramidal side effects and gait abnormalities are well-recognised side effects that may in turn contribute to the risk of falls and fracture in elderly persons.(1) Similarly, cardiovascular adverse effects, falls and injuries may increase mortality.

Antipsychotic drugs are indicated for the management of schizophrenia and bipolar disorder. Antipsychotics are also used to manage behavioural and psychological symptoms of dementia (BPSD) and recommendations over their use suggest they should be discontinued after BPSD symptoms resolve. Safety concerns have previously led to regulatory warnings and risk communications over their use.(2,3)

Antipsychotic drugs can be classified into typical and atypical antipsychotics with different recommendations for their use. For example, guidelines recommend the preferential use of atypical antipsychotics when required for the management of BPSD.(4)

The rationale of the study was to provide an overview of common antipsychotic prescribing in Europe, and to describe the characteristics of patients initiating antipsychotics. This may help to contextualise information contained in future antipsychotic periodic safety update reports.

Research question and objectives

1. To characterise the general population with a first use of common antipsychotics in terms of age, gender and comorbidities/indication.

2. To measure trends in the incidence of first use of common antipsychotic prescribing overall, by typical/atypical grouping and by the top 20 most common drug substances. Results would be stratified by database, calendar year, age and sex.

3. To characterise first time users of common antipsychotic drug therapy after initiation by drug substance (in terms of initial dose and duration). Results would be stratified by drug route, age and sex.

4. To measure overall survival in the general population with a first use of common antipsychotic overall, for typical/atypical grouping and for top 20 most common drug substances.

Methods

Study design

- New user cohort study (Objective 1 and 4, Patient-level antipsychotic utilisation)
- Population level cohort study (Objective 2, Population-level antipsychotic drug utilisation)
- New user cohort study (Objective 3, Patient-level characterisation)

Population

Population-level antipsychotic utilisation: All individuals between 01/01/2013 and 31/12/2023, with at least 365 days of prior history before the day they become eligible for study inclusion. For incidence, anyone with prior use of antipsychotic/s of interest was excluded from the analysis.

Patient-level antipsychotic drug utilisation and patient-level characterisation: New users of antipsychotic drugs in the period between 01/01/2013 and 31/12/2023 (or latest date available), with at least 365 days of visibility prior to the date of their first antipsychotic prescription and no prior use of the respective antipsychotic drug/s.

Variables

Drugs of interest: Sulpiride, Quetiapine, Risperidone, Olanzapine, Haloperidol, Aripiprazole, Pipamperone, Prothipendyl, Prochlorperazine, Chlorprothixene, Promazine, Paliperidone, Zuclopenthixol, Clozapine, Fluspirilene, Amisulpride, Fluphenazine, Perphenazine, Pimozide, and Ziprasidone

Data sources

- SIDIAP (Spain, Primary Care Database) [Objective 1 to 4]
- IPCI (Netherlands, Primary Care Database) [Objective 1 to 4]
- DK-DHR (Denmark, National Registry) [Objective 1 to 4]
- IQVIA DA Germany (Primary and Secondary care database) [Objective 1 to 3]
- IQVIA LPD Belgium (Primary and Secondary care database) [Objective 1 to 3]
- NAJS (Croatia, National Registry) [Objective 1 and 2]

Statistical analysis

Population-level antipsychotic utilisation, patient-level antipsychotic drug utilisation, and patient-level characterisation were conducted in databases based on data availability.

Population-level antipsychotic utilisation: annual incidence rates of antipsychotic use per 100,000 person-years were estimated overall, by typical/atypical grouping and by top 20 individual drug substances. Results were stratified by database, calendar year, age and sex.

Patient-level antipsychotic drug utilisation: patient-level characterisation of new antipsychotic users was conducted at index date (date of first prescription of the antipsychotic of interest), including patient demographics. Records of dementia, schizophrenia, bipolar disorder, depression and insomnia in the

week/month or any time before antipsychotic initiation were used as a proxy for indication and were reported as proportions.

Initial and cumulative dose and treatment duration were estimated for the first treatment era and the median [IQR] were provided. Results were stratified by drug route (restricting to antipsychotic with systemic routes).

Survival analyses using Kaplan-Meier curves for 1 year mortality was conducted to estimate the probability of overall survival in new users of antipsychotic drugs overall, by typical/atypical grouping and by top 20 individual drug substances.

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

Results

Across the databases of IPCI, SIDIAP, IQVIA DA Germany, IQVIA LPD Belgium, DK-DHR and NAJS, atypical antipsychotic initiation (ranged from 62% to 97% of overall antipsychotic initiators was higher than typical antipsychotic initiation (ranged from 14% to 49% of overall antipsychotic initiators). The most commonly prescribed antipsychotics across databases are the typical antipsychotic haloperidol and atypical antipsychotics of quetiapine, risperidone, sulpiride, and olanzapine.

Objective 1

In terms of patient characteristics, median age ranged from 53 to 68 years across the databases. There were large differences in age distribution of atypical and typical antipsychotic incident use within the IPCI, SIDIAP, NAJS and DK-DHR databases, where atypical antipsychotics were mainly used in younger populations whilst typical antipsychotics were predominantly used in older. IQVIA DA Germany and IQVIA LPD Belgium age distributions remained relatively stable. Sex distributions varied with database but were relatively consistent across types of antipsychotics.

When comorbidities were taken any time prior to index date, results were similar to what was expected from the general population, with obesity (ranged between 6% to 34% in the overall antipsychotic populations), type 2 diabetes (ranged between 10% to 20%) and hypertension (ranged between 21% to 58%) having the highest proportions. In IPCI, SIDIAP, DK-DHR, NAJS, IQVIA LPD Belgium and IQVIA DA Germany, typical antipsychotic new users had higher percentages of all comorbidities.

The most common indications for antipsychotic use any time prior to index date appeared to be insomnia and other sleep disorders, depression and dementia across most databases. Indications differed between atypical and typical antipsychotic users.

Objective 2

For overall antipsychotic incidence rates (IRs) in IPCI, values remained relatively stable throughout the study period at around 400 cases per 100,000 person-years. In SIDIAP, all antipsychotic use remained relatively stable at around 850 per 100,000 person-years, with dips in 2013 and 2020 (IR [95% CI]: 721 [714 - 728] and 797 [790 - 805] cases per 100,000 person-years, respectively). In IQVIA DA Germany, incident use increased from 2013 to 2018 (IR [95% CI] per 100,000 person-years: from 155 [152 - 158] to 438 [432 - 445], respectively).

The incident use of atypical compared to typical antipsychotic use differed across the databases. In IPCI and IQVIA DA Germany, atypical and typical antipsychotic use was relatively similar . In IPCI atypical use rates surpassed typical rates from 2017 onwards. In IQVIA DA Germany atypical use were consistently higher than typical use. In IQVIA LPD Belgium, DK-DHR, NAJS and SIDIAP, atypical use closely followed the trends

for all antipsychotic rates while typical use was considerably lower and remained stable throughout 2013 (2016 in NAJS) to 2023.

Amongst all databases and types of antipsychotics, the oldest age group (the ≥85-year-olds) had the highest IRs, followed by the 75 to 84 group, 65 to 74, and ≤64. Additionally, we observed increasing trends in the IRs among the ≥85 years old age group in SIDIAP, IQVIA DA Germany and DK-DHR.

There were no differences between sexes for IRs of all, atypical and typical antipsychotic use in IPCI, DK-DHR or IQVIA DA Germany. For SIDIAP, there were higher IR of atypical antipsychotic use among females compared to males. In IQVIA LPD Belgium and NAJS, there were higher IRs for female antipsychotic use in all antipsychotics and atypical cohorts. Antipsychotic IRs in the typical user's cohort were consistent between sexes.

Objective 3

We observed different treatment durations across the databases of the study, but also across the drug types. In the overall population, duration of antipsychotic use ranged from 3 to 192 days. Additionally, there were differences in the initial daily dose between those 0 to 64 years of age compared to ≥ 65 years of age, for quetiapine in SIDIAP, IQVIA DA Germany, IQVIA LPD Belgium.

Objective 4

Across the databases of IPCI, SIDIAP and DK-DHR, the typical antipsychotic cohort had lower survival probabilities compared to the atypical antipsychotic cohort. For IPCI, SIDIAP and DK-DHR, across all and the specific types of antipsychotics, those in the ≥65-year-old age group showed lower probabilities of survival compared to the overall and the 0 to 64 age groups. There were no strong differences in one-year survival based on sex across the databases. Males had slightly lower probabilities of survival compared to females except for typical antipsychotics in DK-DHR.

The typical antipsychotic, haloperidol, had the lowest one-year survival in IPCI (44%, with a median survival of 152 days), SIDIAP (62% one- year survival) and DK-DHR (16% surviving past the one-year and a median survival of 14 days).

Conclusion

Our study observed higher atypical antipsychotic initiation than typical use with the most common antipsychotics being quetiapine, risperidone, sulpiride and olanzapine. Compared to those initiating atypical antipsychotics, new users of typical antipsychotics had higher proportions of comorbidities, with type 2 diabetes, obesity and hypertension being the most common.

Depression, insomnia and other sleep disorders, and dementia appeared to be the most common indications for both types of antipsychotics. Incident use of antipsychotics was higher in those over 85 years of age compared to other age groups for all databases, with an increasing trend among this age group in SIDIAP, IQVIA DA Germany and DK-DHR databases. Survival was lowest among those taking the typical antipsychotic haloperidol in IPCI, SIDIAP and DK-DHR.

4. LIST OF ABBREVIATIONS

Acronyms/terms	Description
BPSD	Behavioural and Psychological Symptoms of Dementia
CHI	Catalan Health Institute
CDM	Common Data Model
DA	Disease Analyzer
DARWIN EU	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
DUS	Drug Utilisation Study
EHR	Electronic Health Records
EMA	European Medicines Agency
GP	General Practitioner
ID	Index Date
IPCI	Integrated Primary Care Information Project
IQR	Interquartile Range
LPD	Longitudinal Patient Database
NAJS	Croatian National Public Health Information System
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	22/01/2025	Sections 9.6.3.1 and 11	Addition of broader definitions for chronic kidney disease and insomnia, into renal impairment and sleep disorders respectively.	Low counts observed during diagnostics in some databases.

6. MILESTONES

Study deliverable	Timeline (planned)	Timelines (actual)
Draft Study Protocol	26/08/2024	26/08/2024
Final Study Protocol	September 2024	01/10/2024
Creation of Analytical code	October 2024	01/11/2024
Execution of Analytical Code on the data	October 2024	11/11/2024
Draft Study Report	November	06/12/2024
Final Study Report	January	22/01/2025

7. RATIONALE AND BACKGROUND

Antipsychotic drugs have been associated with several adverse drug reactions, particularly in the elderly. Somnolence, hypotension, extrapyramidal side effects and gait abnormalities are well-recognised side effects that may in turn contribute to the risk of falls and fracture in elderly persons.(1) Similarly, cardiovascular adverse effects, falls and injuries may increase mortality.

Antipsychotic drugs are indicated for the management of schizophrenia and bipolar disorder. Antipsychotics are also used to manage behavioural and psychological symptoms of dementia (BPSD) and recommendations over their use suggest they should be discontinued after BPSD symptoms resolve. Safety concerns have previously led to regulatory warnings and risk communications over their use.(2,3)

Antipsychotic drugs can be classified into typical and atypical antipsychotics with different recommendations for their use. For example, guidelines recommend the preferential use of atypical antipsychotics when required for the management of BPSD.(4)

The rationale of the study was to provide an overview of common antipsychotic prescribing in Europe, and to describe the characteristics of patients initiating antipsychotics. This may help to contextualise information contained in future antipsychotic periodic safety update reports.

8. RESEARCH QUESTION AND OBJECTIVES

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

Table 1. Research questions and objectives.

A. Objective 1.

Objective:	To characterise the general population with a first use of common antipsychotics in terms of age, gender and comorbidities/indication
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	New users were defined as having prescription of an antipsychotic (overall or typical/atypical antipsychotic use) in the period between 01/01/2013 and 31/12/2023 with 1 year of prior data availability and no prior use of the respective antipsychotic drug/s.
Exposure:	Common antipsychotics (Sulpiride, Quetiapine, Risperidone, Olanzapine, Haloperidol, Aripiprazole, Pipamperone, Prothipendyl, Prochlorperazine, Chlorprothixene, Promazine, Paliperidone, Zuclopenthixol, Clozapine, Fluspirilene, Amisulpride, Fluphenazine, Perphenazine, Pimozide, and Ziprasidone)
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Follow-up started on the date of incident antipsychotic prescription and/or dispensation (index date). End of follow-up was defined as the earliest of loss to follow-up, end of data availability or death, or end of study period (31st December 2023).
Setting:	Inpatient and outpatient setting using data from the following 6 data sources: IQVIA DA Germany [Germany], IQVIA LBD Belgium [Belgium], SIDIAP [Spain], IPCI [The Netherlands], DK-DHR [Denmark], NAJS [Croatia]
Main measure of effect:	We described demographic characteristics including age, sex, comorbidities, and assessed the proportion of new users with a record of dementia, schizophrenia, bipolar disorder, depression and insomnia in the week, month or any time before index date as a proxy for indication.

B. Objective 2.

Objective:	To measure trends in the incidence of first use of common antipsychotic prescribing overall, by typical/atypical grouping and by the top 20 most common drug substances. Results would be stratified by database, calendar year, age and sex.

Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	New users of antipsychotics in the period between 01/01/2013 and 31/12/2023), with at least 1 year of data availability, and no prior use of the respective antipsychotic drug/s, were included for incidence rate calculations.
Exposure:	Common antipsychotics (Sulpiride, Quetiapine, Risperidone, Olanzapine, Haloperidol, Aripiprazole, Pipamperone, Prothipendyl, Prochlorperazine, Chlorprothixene, Promazine, Paliperidone, Zuclopenthixol, Clozapine, Fluspirilene, Amisulpride, Fluphenazine, Perphenazine, Pimozide, and Ziprasidone)
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Follow-up started on a pre-specified calendar time point, namely 1st of January for each calendar year between 2013-2023 for the calculation of annual incidence rates. End of follow-up was defined as the earliest of loss to follow-up, end of data availability, death, or end of study period (e.g. 31st December 2023).
Setting:	Inpatient and outpatient setting using data from the following 6 data sources: IQVIA DA Germany [Germany], IQVIA LBD Belgium [Belgium], SIDIAP [Spain], IPCI [The Netherlands], DK-DHR [Denmark], NAJS[Croatia]
Main measure of effect:	Incidence of antipsychotic drug use

C. Objective 3.

Objective:	To characterise first time users of common antipsychotic drug therapy after initiation by drug substance (in terms of initial dose and duration). Results would be stratified by drug route, age and sex.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	New users of antipsychotics in the period between 01/01/2013 and 31/12/2023 with at least 1 year of data availability, and no prior use of the respective antipsychotic drug/s, were included.
Exposure:	Common antipsychotics (Sulpiride, Quetiapine, Risperidone, Olanzapine, Haloperidol, Aripiprazole, Pipamperone, Prothipendyl, Prochlorperazine, Chlorprothixene, Promazine, Paliperidone, Zuclopenthixol, Clozapine, Fluspirilene, Amisulpride, Fluphenazine, Perphenazine, Pimozide, and Ziprasidone)
Comparator:	None
Outcome:	None

Time *(when follow up begins and ends):*	Follow-up started on the date of incident antipsychotic prescription and/or dispensation (index date). End of follow-up was defined as the earliest of loss to follow-up, end of data availability or death, or end of study period (31st December 2023).
Setting:	Inpatient and outpatient setting using data from the following 5 data sources: IQVIA DA Germany [Germany], IQVIA LBD Belgium [Belgium], SIDIAP [Spain], IPCI [The Netherlands], DK-DHR [Denmark]
Main measure of effect:	Duration of antipsychotic use (first treatment era) expressed as median [IQR] Antipsychotics dose (cumulative and initial) expressed as median [IQR]

D. Objective 4.

Objective:	To measure overall survival in the general population with a first use of common antipsychotic overall, for typical/atypical grouping and for top 20 most common drug substances.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	New users of antipsychotics in the period between 01/01/2013 and 31/12/2023 (or latest date available, whatever comes first), with at least 1 year of data availability, and no prior use of the respective antipsychotic drug/s, were included.
Exposure:	Common antipsychotics (Sulpiride, Quetiapine, Risperidone, Olanzapine, Haloperidol, Aripiprazole, Pipamperone, Prothipendyl, Prochlorperazine, Chlorprothixene, Promazine, Paliperidone, Zuclopenthixol, Clozapine, Fluspirilene, Amisulpride, Fluphenazine, Perphenazine, Pimozide, and Ziprasidone)
Comparator:	None
Outcome:	Death
Time *(when follow up begins and ends):*	Follow-up started on the date of incident antipsychotic prescription and/or dispensation (index date). End of follow-up was defined as the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2023).
Setting:	Inpatient and outpatient setting using data from the following 3 data sources: SIDIAP [Spain], IPCI [The Netherlands], DK-DHR [Denmark]

Main measure of effect:	Kaplan Meier curves estimated 1 year probability of overall survival

9. RESEARCH METHODS

9.1 Study type and study design

Retrospective cohort studies were conducted using routinely collected health data from 6 databases. **Table 2** describes the study types and related study designs. The study comprised of four consecutive parts:

1. A new user cohort study was conducted to characterise patient-level antipsychotic utilisation.

2. A population level cohort study was used to assess incidence rates of antipsychotic use.

3. A new users cohort analyses was used to describe patient level characterisation of antipsychotic use.

4. A new users cohort study was used to assess overall survival.

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

Study type	Study design	Study classification
Population Level DUS	Population Level Cohort	Off the shelf
Patient Level DUS	New drug/s user cohort	Off the shelf
Patient-level characterisation	Cohort analysis	Off the shelf

9.2 Study setting and data sources

This study was conducted using routinely collected data from 6 databases from 6 European countries. All databases were previously mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

1. SIDIAP (Spain, Primary Care Database) [Objective 1 to 4]
2. IPCI (Netherlands, Primary Care Database) [Objective 1 to 4]
3. DK-DHR (Denmark, National Registry) [Objective 1 to 4]
4. IQVIA DA Germany (Primary Care database) [Objective 1 to 3]
5. IQVIA LPD Belgium (Primary Care database) [Objective 1 to 3]
6. NAJS (Croatia, National Registry) [Objective 1 and 2]

Data sources contributed to objectives based on the available requisite data. IQVIA DA Germany, IQVIA LPD Belgium and NAJS did not contribute to Objective 4 (Survival analyses) as death records were not captured in these databases. Additionally, NAJS did not have drug utilisation details such as duration and amount/dose/strength reliably recorded and did not contribute to Objective 3.

Data sources were chosen for their wide geographical coverage as each database represents a different country. Since antipsychotics are commonly prescribed in both the inpatient and outpatient settings, the databases we chose reflect the broad prescription patterns for antipsychotics. The DK-DHR and NAJS are

national registries that contain records on both in-patient hospital visits as well as primary care visits. IQVIA DA Germany contains data from primary care and specialists practicing in ambulatory care settings, whilst SIDIAP, IPCI and IQVIA LPD Belgium are primary care databases that covers wide geographic region of Europe.

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**.

Table 3. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Feasibility count of exposure (range for top 5 most commonly prescribed antipsychotics)	Data lock for the last update
Spain	SIDIAP	Database covers primary care setting where antipsychotics prescriptions are issued.	Primary Care	EHR	5.8 million	136,700 to 472,220 records	30/06/2023
Netherlands	IPCI	Database covers primary care setting where antipsychotics prescriptions are issued.	Primary Care	EHR	2.9 million	5,400 to 30,500 people	30/04/2024
Denmark	DK-DHR	Database covers primary and hospital in-patient care settings where antipsychotics prescriptions are issued.	Secondary Care and Hospital in-patient care	EHR, registries	5.8 million	146,200 to 1,163,500 records	21/5/2024
Germany	IQVIA Germany	Database covers primary and secondary care settings where antipsychotics prescriptions are issued.	Primary & Secondary Care	EHR	43.1 million	38,700 to 149,100 people	30/09/2023
Belgium	IQVIA Belgium	Database covers primary care setting where antipsychotics prescriptions are issued.	Primary Care	EHR	8.5 million	3,000 to 10,800 people	31/12/2023
Croatia	NAJS	Database covers primary and hospital in-patient care settings where antipsychotics prescriptions are issued.	Primary, Secondary Care and Hospital in-patient care	Registry	3 million	48,200 to 114,400 people	17/11/2023

1) Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària [SIDIAP] (Spain, Primary Care Database)

The Information System for Research in Primary Care (SIDIAP) is a clinical database of anonymised 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 anonymised 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.

2) Integrated Primary Care Information [IPCI] (Netherlands, Primary Care Database)

The Integrated Primary Care Information (IPCI) database is a longitudinal observational database containing routinely collected data from computer-based patient records of a selected group of GPs throughout the Netherlands (N=723). IPCI was started in 1992 by the department of Medical Informatics of the Erasmus University Medical Center in Rotterdam with the objective to enable better post marketing surveillance of drugs. The current database includes patient records from 2006 on, when the size of the database started to increase significantly. In 2016, IPCI was certified as Regional Data Center. Since 2019 the data is also standardised to the Observational Medical Outcomes Partnership common data model (OMOP CDM), enabling collaborative research in a large network of databases within the Observational Health Data Sciences and Informatics (OHDSI) community. The primary goal of IPCI is to enable medical research. In addition, reports are generated to inform GPs and their organisations about the provided care. Contributing GPs are encouraged to use this information for their internal quality evaluation. The IPCI database is registered on the EMA-HMA Catalogue of RWD sources (https://catalogues.ema.europa.eu/catalogue-rwd-sources).

3) Danish Data Health Registries [DK-DHR] (Denmark, National Registry)

Danish health data is collected, stored and managed in national health registers at the Danish Health Data Authority and covers the entire population which makes it possible to study the development of diseases and their treatment over time. There are no gaps in terms of gender, age and geography in Danish health data due to mandatory reporting on all patients from cradle to grave, in all hospitals and medical clinics. Personal identification numbers enable linking of data across registers, so we have data on all Danes throughout their lives, regardless of whether they have moved around the country. High data quality due to standardisation, digitisation and documentation means that Danish health data is not based on interpretation. The Danish Health Data Authority is responsible for the national health registers and for maintaining and developing standards and classifications in the Danish healthcare system. Legislation ensures balance between personal data protection and use.

In the present data base, we have access to the following registries for the entire Danish population of 5.9 million persons from 1.1.1995: The central Person Registry, The National Patient Registry, The Register of

Pharmaceutical Sales, The National Cancer Register, The Cause of Death registry, The Clinical Laboratory Information Register, COVID-19 test and vaccination Registries, The complete Vaccination registry. All data registered from 1.1.1995 will be included.

4) IQVIA Disease Analyzer Germany [IQVIA DA Germany] (Primary Care database)

Germany DA is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings. Data coverage includes 39.6 M cumulative person. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilisation studies.

5) IQVIA Longitudinal Patient Database Belgium [IQIVIA LPD Belgium] (Primary Care Database)

Belgium Longitudinal patient data (LPD) is collected from GP prescribing systems and contains patient records on all signs and symptoms, diagnoses and prescribed medications. The information recorded allows patients and doctors to be monitored longitudinally. Data are recorded directly in the LPD from doctors' surgeries in real-time during patient consultations via a practice management software system. It is used in studies to provide various market insights such as treatment trends, patient pathway analysis and treatment compliance. The panel of contributing physicians (a stable 300 GPs) is maintained as a representative sample of the primary care physician population in Belgium according to three criteria known to influence prescribing: age, sex and geographical distribution. Currently, the database is covering 1.1 M cumulative patients and covers from 2012 through to the present. The panel consists of a stable 300 GPs that are geographically well spread. The total number of active GPs in Belgium is 15.602. The regional geographical spread of physicians in the LPD data is also representative of the distribution across the country: 57% GPs in the North (compared to 54% nationally), 31% in the South (33% nationally) and 12% in Brussels (13%). The provider of the data has more than 2.250 GPs under contract so in case of a drop out a replacement is easily found. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilisation studies.

6) Croatian National Public Health Information System [NAJS] (Croatia, Registry)

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

9.3 Study period

The study period was from the 1st of January 2013 until the earliest of either 31st December 2023 or the latest date of data availability of the respective databases. For the population-level analyses for incidence, individuals contributed person-time from the date they have reached at least 365 days of data availability.

9.4 Follow-up

For patient-level antipsychotic drug utilisation, follow-up started at first prescription of the antipsychotic of interest, and patients were followed until loss to follow-up, lack of data availability, death or end of study period, whichever came first. The operational definition of follow-up is reported in **Table 4.**

For survival analyses, first time users who had 365 days of prior history were followed from the first prescription of antipsychotics until the earliest of death, lack of data availability, 1 year follow-up or end of the study period occurred.

To estimate the incidence rates, we required the appropriate population and their contributed observation time to first be identified. Thus, follow-up started from the date they had reached at least 365 days of data availability. Study participants in the denominator population began contributing person time on the respective date of the latest of the following: 1) study start date, 2) date at which the observation period starts, 3) date at which the observation period has reached sufficient prior history. Participants stopped contributing person time at the earliest date of the following: 1) end of available data in each of the data sources or 2) date at which the observation period of the specific person ends.

An example of entry and exit into the denominator population for incidence rates is shown in **Figure 1**. In this example, person ID 1, and 3 were included as denominators after the study start date as all were observed in the database from a prior date. Person ID 2 and 4 entered the study after the study start date, when they reached sufficient prior history of 365 days. Person ID 1, 2 and 4 were followed until the study end date (end of available data in each of the data sources) whilst Person ID 3 left when exiting the database (the end of observation period). Lastly, person ID 5 had two observation periods in the database. The first period contributed time from study start until end of observation period, the second started contributing time again on the date of their second observation period started and exited at study end date.

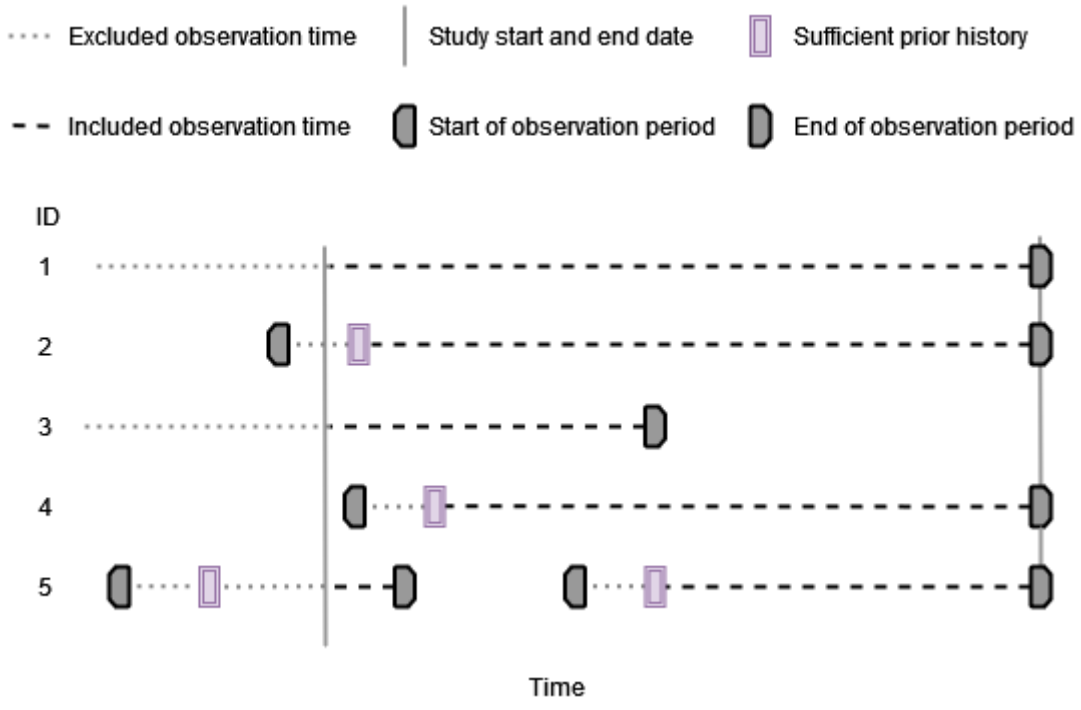


Figure 1. Included observation time for denominator population of incidence calculations.

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	Code Type	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
All patients with incident use of medicines of interest	Patient present in the database during the study period (2013-2023) and with at least 365 days of valid database history.	Multiple	incident	[-Inf, -1]	PC, SC	n/a	n/a	Specific medicine of interest	n/a	n/a
Survival of patients with incident use of medicines of interest	Patient present in the database during the study period (2013-2023)	Multiple	incident	None	PC, SC	n/a	Death	Specific medicine of interest	n/a	n/a

PC = Primary Care, SC = Secondary Care, n/a = not applicable

9.5 Study population with in and exclusion criteria

Population included in objectives 1 to 4:

The study cohort comprised all individuals on 1st of January of each year in the period 2013-2023 (or the latest available), with at least 365 days of data availability before the day they became eligible for study inclusion. Additional eligibility criteria were applied for the identification of new users:

When overall, no prior use of any antipsychotics was required. In other words, users with prior use of any of the antipsychotics of interest was excluded from the analysis.

When stratified by specific antipsychotic drug, no prior use of the specific antipsychotic was required. In other words, users with prior use of the same antipsychotic were excluded from the analysis. The operational definitions of the inclusion criteria are presented in **Table 5**.

Table 5. Operational definitions of inclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
All individuals on the 1st of January of each year in the period between 2013 and 2023	See under inclusion criterion	After	N/A	PC, SC	N/A	N/A	All adults within selected databases	N/A	N/A
Prior database history of 365 days	Study participants were required to have a year of prior history observed before contributing observation time in incidence calculations, and for characterisation of new users	After	[-365, -1]	PC, SC	N/A	N/A	New users of the drugs of interest within selected databases	N/A	N/A
Washout period	New users were required to not have used antipsychotics/the specific antipsychotic before	After	[-Inf, -1]	PC, SC	N/A	N/A	New users of the drugs of interest	N/A	N/A

[1] PC = Primary Care, SC = Secondary Care

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

n/a = not applicable

9.6 Variables

9.6.1 Exposure/s

The exposure of interest for this study was common antipsychotics (**Table 6**). Substances were included at ingredient level including combinations of the respective ingredient. The list of 20 substances accounts for around 95% of antipsychotic use across the data sources. Details of exposure are described in **Table 7**. Only the top 5 substances for each database were included in the report, the rest were presented in the Shiny App.

For Objective 1 (Summary characterisation of new users), new users were grouped by use of:

1) Overall use of antipsychotics
2) Typical/atypical antipsychotics

For Objective 2 (annual incidence rates) and Objective 4 (Survival analyses), exposure was grouped by:

1) Overall use of antipsychotics
2) Typical/atypical antipsychotics
3) 20 most common individual substances per database (only the top 5 substances for each database will be included in report)

Objective 3 (drug utilisation studies) was grouped by the top 20 prescribed antipsychotics (only the top 5 substances for each database was included in report).

Table 6. List of common antipsychotics included in the study and their categorisation and use in database.

Substance Name	Typical/Atypical
Sulpiride	Atypical
Quetiapine	Atypical
Risperidone	Atypical
Olanzapine	Atypical
Haloperidol	Typical
Aripiprazole	Atypical
Pipamperone	Typical
Prothipendyl	Typical
Prochlorperazine	Typical
Chlorprothixene	Typical
Promazine	Typical
Paliperidone	Atypical
Zuclopenthixol	Typical
Clozapine	Atypical
Fluspirilene	Typical
Amisulpride	Atypical
Fluphenazine	Typical
Perphenazine	Typical
Pimozide	Typical
Ziprasidone	Atypical

Table 7. Operational definitions of exposure.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Diagnosis position	Applied to study populations	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Common Antipsychotics	Preliminary code lists provided in Appendix 1	[-Inf, -1]	Calendar Year	PC, SC	RxNorm	N/A	All individuals who have had a prescription of the medicine of interest present in the respective databases during the study period (2013-2023)	Previous antipsychotic use	N/A	N/A

[1] PC = Primary Care, SC = Secondary Care
n/a = not applicable

9.6.2 Outcomes

The survival analyses reporting Kaplan Meier curves utilised death as an outcome to evaluate 1 year survival probabilities for new users of antipsychotic drugs. Patients were censored if they were lost to follow-up, lacked data availability, or the study period had ended. The operational definition of the outcomes is presented in the **Table 8**.

Table 8. Operational definitions of outcome.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings	Code Type	Diagnosis Position	Applied to study populations	Measurement characteristics/ validation	Source of algorithm
Death	1 year mortality, Kaplan-Meier curves	Yes	Time-to-event	N/A	Primary and secondary care	n/a	n/a	New users of antipsychotics	n/a	n/a

n/a = not applicable

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

9.6.3.1 Objective 1:

Demographic characteristics (among new users, and by typical/atypical antipsychotics) included:

- Age
- Sex
- Indication of use: Proportion of new users with record of dementia, schizophrenia, bipolar disorder, depression, insomnia and sleep disorders in the week/month or any time before antipsychotic-treatment initiation
- Comorbidities: chronic kidney disease, renal impairment, heart failure, hypertension, myocardial infarction, stroke, type 2 diabetes, obesity

9.6.3.2 Objective 2:

Incidence rates were stratified by calendar year. Additionally, they were stratified by:

- Age group: <65, 65-74, 75-84, ≥85 years old
- Sex
- Typical/atypical antipsychotics
- 20 most common individual substances

9.6.3.3 Objective 3:

Drug utilisation analysis from new users of antipsychotics included:

- Initial and cumulative dose
- Duration of use of first continuous treatment era (gap of ≤30 days between repeated prescriptions)

These were stratified by:

- Systemic drug routes: parenteral (including "injectable" and “implant”), oral.
- Age groups: <65 years, ≥65 years
- Sex

9.6.3.4 Objective 4:

Survival analyses among new users of antipsychotics were analysed overall and then stratified:

- Overall
- Typical/atypical antipsychotics
- Top 20 most common individual substances
- Age groups: <65 years, ≥65 years
- Sex

9.7 Study size

No sample size had been calculated. Incidence of antipsychotic use among the study population was estimated as part of Objective 2.

9.8 Statistical methods

9.8.1 Main statistical methods

This section describes the details of the analysis approach and rationale for the choice of analysis, with reference to the D1.3.8.1 Draft Catalogue of Data Analysis which describes the type of analysis in function of the study type. Description of type of analysis based on study type is provided in **Table 9**.

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

Study type	Study classification	Type of analysis
Population Level DUS	Off-the-shelf	- Population-based incidence rates
Patient Level DUS	Off-the-shelf	- Characterisation of patient-level features for new users of antipsychotic users - Frequency and % of indication/s - Estimation of median [IQR], initially prescribed or dispensed initial and cumulative dose of antipsychotics - Estimation of median [IQR] treatment duration for new users of antipsychotics
Patient-level characterisation	Off-the-shelf	- Patient-level characteristics - Survival analyses (time-to-death)

9.8.2 Federated network analyses

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on a subset of the data sources or on a simulated set of patients and quality control checks were performed. Once all the tests are 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 before returning them to the Coordination Centre. Sometimes multiple execution iterations were performed, and additional fine tuning of the code base was needed. A service desk was available during the study execution for support.

The study results of all data sources were checked after which they were made available to the team in the Digital Research Environment and the Dissemination Phase could start. All results were locked and timestamped for reproducibility and transparency.

9.8.3 Patient privacy protection

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

9.8.4 Statistical model specification and assumptions of the analytical approach considered

R-packages

We used the R package "DrugUtilization" for the patient-level drug utilisation analyses including patient-level characterisation, "IncidencePrevalence" package for the population-level estimation of drug utilisation and "CohortSurvival" for survival analyses.

Drug exposure calculations

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

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

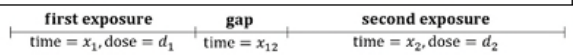


Figure 2. Gap era joint mode.

If two eras overlapped, the overlap time was considered exposed by the first era (**Figure 3**). No time was added at the end of the combined drug era to account for the overlap.

Overlap mode	Schematics	Dose overlap
"first"		d_1
"second"		d_2
"both"		$d_1 + d_2$
"maximum"		$\max(d_1, d_2)$

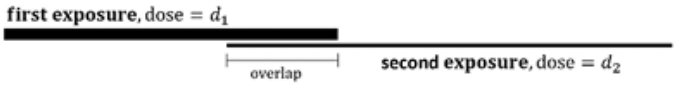


Figure 3. Gap era overlap mode.

New user cohorts

New users were selected based on their first prescription of the respective drug of interest after the start of the study and/or in a pre-defined time window. For each patient, at least 365 days of data visibility was required prior to that prescription. New users were required to not have been exposed to the drug of

interest any time prior the current prescription. If the index day did not fulfil the exposure washout criteria the whole exposure was eliminated.

9.8.5 Methods to derive parameters of interest

Calendar time

Calendar time was based on the calendar year of the index prescription.

Age

Age at index date was calculated using January 1st of the year of birth as proxy for the actual birthday. The following age groups were used for stratification: <65, 65-74, 75-84, ≥85 years old.

Indications

Indications were determined based on recordings of 5 pre-defined conditions, namely dementia, schizophrenia, bipolar disorder, depression, and insomnia and other sleep disorders, one week/month or any time before the first prescription of the respective drug (index date).

Characterisation of patient-level features (comorbidities)

Patient-level characterisation was conducted. Covariates was extracted for the following time intervals 30 days before index date and any time prior to index date.

Survival Analyses

To obtain Kaplan-Meier plots, patients were followed for 1 year from their initial antipsychotic prescription to evaluate probability of survival. Deaths were obtained from the relevant databases using OMOP CDM codes. Patients were censored if before reaching 1 year of follow-up, they were lost to follow-up, lacked data availability or the study period ended.

9.8.6 Methods planned to obtain point estimates with confidence intervals of measures of occurrence

Population-level drug utilisation study

Incidence rates were calculated for antipsychotic treatment overall, by typical/atypical and by the 5 most common drug substances for each database.

Annual incidence rates for antipsychotic use were calculated as the number of new users per 100,000 person-years of the population at risk of getting exposed during the period for each calendar year. Any study participants with use of the medication of interest prior to the date at which they would have otherwise satisfied the criteria to enter the denominator population (as described above) was excluded. Those study participants who entered the denominator population then contributed time at risk up to their first prescription (e.g. antipsychotic use) during the study period. Or if they did not have a drug exposure, they contributed time at risk, as described above in section 8.4 (study end, end of observation period, or the last day of maximum age). An illustration of the calculation of incidence of antipsychotic use is shown below in **Figure 4**.

Patient ID 1 and 4 contributed time at risk up to the point at which they became incident users of antipsychotics. Patient ID 2 and 5 were not seen to use antipsychotics and so contributed time at risk but no incident outcomes. Meanwhile, patient ID 3 was excluded from the analysis as they were seen to have had the outcome before the study start date.

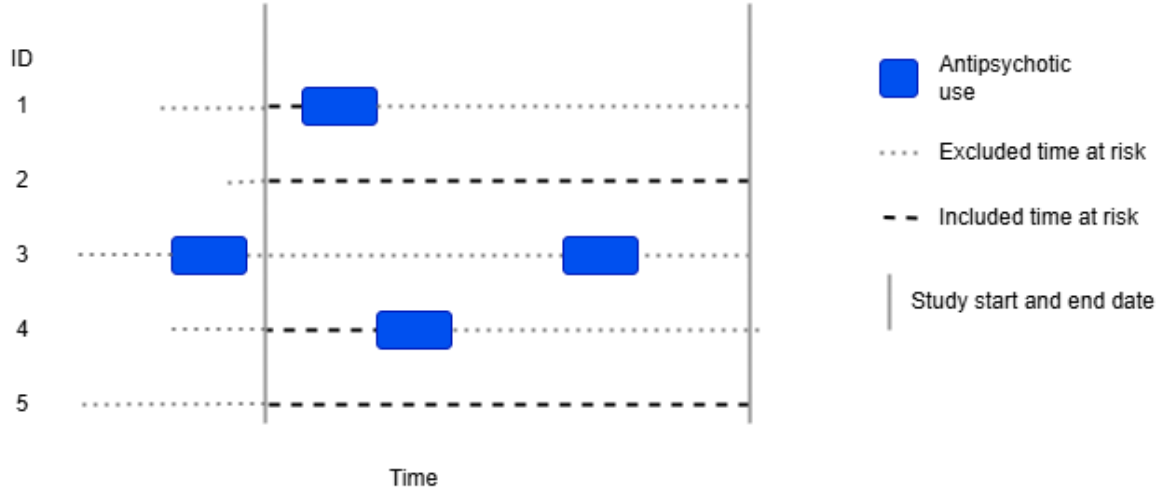


Figure 4. Illustration of incidence calculations.

Patient-level drug utilisation study

New drug user patient-level characteristics on/before index date

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

Indications and comorbidities

The number of persons (N, %) with a record of the respective indication (i.e. dementia, schizophrenia, bipolar disorder, depression, and insomnia and other sleep disorders) and comorbidities was provided. If a person had a record of more than one specific indication/comorbidity, that person was included in both specific indication groups separately.

Initially prescribed or dispensed dose

For each prescription at index date, the prescribed dose was retrieved from the drug_exposure tables, where the quantity and units were available.

The quality of recording of drug dose might be of varying quality for different databases. Therefore, data quality checks were conducted to evaluate the quality of the recording of units, dosage (OMOP drug_exposure tables) for antipsychotics in the databases this study was conducted in.

From this, the initial dose in the cohort was characterised by median [IQR].

Treatment duration

Treatment duration was calculated as the duration of the first continuous exposure episode, with less than a 30-day gap between prescriptions. Estimates of treatment duration was summarised providing the median [IQR] treatment duration. For databases, where duration could not be calculated due to e.g. missing information on quantity or dosing, treatment duration was not provided.

Survival Analyses

Kaplan-Meier curves for 1-year all-cause mortality was calculated for any new antipsychotic users and then stratified by typical/atypical antipsychotics and the 5 most common substances per database. Kaplan-Meier curves were used to estimate the probability of 1-year survival starting from day of treatment initiation.

9.8.7 Methods to control for potential sources of bias

None.

9.8.8 Methods to deal with missing data

None.

9.8.10 Evidence synthesis

Results from analyses described in Section 8.8 were presented separately for each database and no meta-analysis of results was conducted.

10. DATA MANAGEMENT

10.1 Data management

All databases were mapped to the OMOP common data model. 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 was written in R. Each data partner executed the study code against their database containing patient-level data and returned the results set which only contained aggregated data. The results from each of the contributing data sites was then combined in tables and figures for this study report.

10.2 Data storage and protection

For this study, participants from various EU member states processed personal data from individuals which was 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 were already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control were adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses was run, which generated non-identifiable aggregate summary results. The output files were stored in the DARWIN Remote Research Environment. These output files do not contain any data that allowed identification of subjects included in the study. The RRE implements further security measures in order to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

11. QUALITY CONTROL

General database quality control

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

(https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality was solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories 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 drug cohorts, non-systemic products were excluded from the list of included codes summarised on the ingredient level. A pharmacist reviewed the codes of the drugs of interest. When defining cohorts for indications, a systematic search of possible codes for inclusion was identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). This software allowed us to define a search strategy that sent a query to the vocabulary tables of the OMOP common data model to find potentially relevant codes. In addition, the necessary diagnostic tools were run to assess the use of different codes across the databases contributing to the study and to identify any codes potentially omitted in error:

The diagnostics to review drug codes included the overall counts in the population of interest, the routes, types, source concepts duration, days' supply, quantity, strength, daily dose, missingness and period covered. The diagnostics to review the conditions of interest included counts in the population of interest, attrition, cohort timing, specific code counts, counts of potential missing codes related to the condition of interest, distribution of index date, age and time; cohort overlap between different conditions of interest (including different flavours for the same condition), incidence and prevalence, and a large scale characterisation of the individuals with the condition of interest including a comparison with random sample from the general population matched by age and sex (the large scale characterisation allows us to see how different is the cohort we identified from population of same age and sex).

Deviations from the protocol

Upon reviewing diagnostic results from the databases, counts for the phenotypes of chronic kidney disease and insomnia were lower than expected as some codes were mapped to more broader definitions for IPCI, IQVIA DA Germany, IQVIA LPD Belgium, DK-DHR and NAJS. Taken this into account, we broadened our definition of chronic kidney disease to include renal impairment, and we included sleep disorders for our insomnia definition as two additional phenotypes.

12. RESULTS

All results for each individual drug and database are available in the shiny app at:
P3-C1-012_antipsychotics_general_population - DARWIN EU®

The shiny app contains seven tabs:

- Background: brief description of the study
- Snapshot: description of databases included in the study
- Cohort details:
  - Cohort code Use: lists of concepts (i.e. clinical codes) that were used to create each cohort
  - Cohort attrition: breakdown of cohort composition based on the inclusion criteria

  - Cohort characteristics: table describing characteristics of interest such as age, sex, length of follow up, indications and comorbidities.
- Drug Utilisation: summary of exposed time (duration of treatment), cumulative dose, and initial daily dose
- Incidence: annual incidence for antipsychotics of interest
- Survival: One year survival for antipsychotics of interest

12.1 Participants

Complete flow-charts showing the attrition of the different cohorts in each of the study databases and their respective plots were included in the study shiny app under the "Cohort details - Cohort attrition" tab.

The number of individuals composing the overall, typical and atypical populations for antipsychotic use is shown in **Table 10.** Note that individuals can be included in both categories of typical and atypical antipsychotics.

Among the overall antipsychotic initiators, the proportion of individuals using atypical antipsychotics was higher than the proportion of individuals using typical antipsychotics (ranged between 62% to 97% for atypical, vs 14% to 49% for typical).

Table 10. Number of individuals in the overall, typical and atypical drug cohorts.

Number of individuals (n)	IPCI	IQVIA LPD Belgium	IQVIA DA Germany	NAJS	SIDIAP	DKR
Overall	46,446	20,223	170,076	573,433	497,978	169,217
Typical antipsychotics N (%)	22,967 (49%)	3,405 (17%)	81,211 (48%)	191,504 (33%)	71,060 (14%)	65,365 (39%)
Atypical antipsychotics N (%)	28,838 (62%)	18,608 (92%)	125,779 (74%)	494,828 (86%)	480,796 (97%)	138,594 (95%)

In **Table 11**, the top 5 antipsychotics are listed for each database. The most commonly prescribed antipsychotics across databases are the typical antipsychotic haloperidol, atypical antipsychotics of quetiapine, risperidone, sulpiride, and olanzapine.

Table 11. Counts for the top 5 antipsychotics in each database

Data base	IPCI		SIDIAP		IQVIA DA Germany		IQVIA LPD Belgium		DK-DHR		NAJS	
Ran-king	Top 5 Anti-psychotics	N (%)	Top 5 Anti-psychotics	N (%)	Top 5 Anti-psychotics	(N%)	Top 5 Anti-psychotics	N (%)	Top 5 Antipsychotics	N (%)	Top 5 Anti-psychotics	N (%)
1	Haloperidol	20,512 (44%)	Quetiapine	226,158 (45%)	Quetiapine	68,064 (40%)	Sulpiride	6,844 (34%)	Quetiapine	114,039 (67%)	Sulpiride	448,218 (78%)
2	Quetiapine	17,504 (38%)	Sulpiride	204,635 (41%)	Risperidone	50,971 (30%)	Quetiapine	6,680 (33%)	Haloperidol	44,097 (26%)	Perphenazine	101,053 (18%)
3	Risperidone	6,321 (14%)	Risperidone	114,019 (23%)	Pipamperone	49,470 (29%)	Risperidone	2,688 (13%)	Risperidone	29,721 (18%)	Promazine	79,554 (14%)
4	Olanzapine	6,262 (13%)	Olanzapine	65,865 (13%)	Olanzapine	13,918 (8%)	Olanzapine	2,566 (13%)	Olanzapine	26,556 (16%)	Quetiapine	64,140 (11%)
5	Aripiprazole	3,382 (7%)	Haloperidol	63,942 (13%)	Prothipendyl	13,305 (8%)	Prothipendyl	2,348 (12%)	Chlorprothixene	23,482 (14%)	Haloperidol	49,562 (9%)

12.2 Main results

12.2.1 Objective 1: Patient-level characteristics of new users

Characteristics of patients at the time of their first prescription of antipsychotics (i.e., incident users) are summarised in **Table 12**, and correspond to the "Cohort Details - Cohort Characteristics" tab displayed in the shiny app. For all antipsychotic use, median age [IQR] was consistent for IPCI and SIDIAP at around 63-64 years [41,82], with approximately 51% of the population less than 65 years of age among both databases. IQVIA DA Germany had an older median age of 68 years [50,82]. IQVIA LPD Belgium (overall median age: 54 years [39,71]) and DK-DHR's populations (53 years [30,76]) was younger. For NAJS, the overall median age was 59 [45,73].

There were large differences in the age distribution of atypical and typical antipsychotic incident use within the IPCI, SIDIAP, NAJS and DK-DHR databases, while IQVIA DA Germany and IQVIA LPD Belgium age distributions were relatively similar In IPCI, SIDIAP, DK-DHR, atypical antipsychotics were predominantly used in younger populations whilst typical antipsychotics were predominantly used in older populations, whereas NJAS presented similar trends, though the difference was less pronounced: median age [IQR] of new users of atypical antipsychotics vs new users of typical antipsychotics were 49 years [32,66] vs 79 years [65,87] in IPCI (73% vs 24% of the population were under 65 years of age, respectively); 63 years [43,81] vs 82 years [67,89] in SIDIAP (51% vs 23% under 65 years, respectively); 58 years [44,70] vs 66 [50,80] in NAJS (64% vs 48% under 65 years, respectively) and 46 years [28,69] vs 71 years [46,83] in DK-DHR (71% vs 40% under 65 years, respectively).

Sex distributions varied with database but were relatively consistent across types of antipsychotics. In IPCI and DK-DHR, 52% of all antipsychotic users were female and this was consistent in the atypical and typical incident antipsychotic new users' populations. In SIDIAP and NAJS, there was a larger proportion of females with 59% - 66% females in all antipsychotic users and typical users cohorts; there was 56% females in the atypical antipsychotic user cohort. Similarly, in IQVIA DA Germany, there was a higher percentage of females with 57% in all antipsychotic populations, which was consistent across atypical and typical users. The proportion of females in the typical antipsychotic new user's population for IQVIA LPD Belgium was lower at 54%, while females accounted for around 58% of all antipsychotics and atypical populations.

Comorbidities recorded any time before the first antipsychotic use were similar to what was expected from the general population, with obesity (ranged between 6% to 34% in the overall antipsychotic populations), type 2 diabetes (ranged between 10% to 20%) and hypertension (ranged between 21% to 58%) having the highest proportions. In IPCI, SIDIAP, DK-DHR, NAJS, IQVIA LPD Belgium and IQVIA DA Germany, typical antipsychotic new users had higher percentages of all comorbidities. In IPCI, 30% of the typical antipsychotic users had hypertension whereas 21% of all antipsychotic users and 15% of atypical antipsychotic users were diagnosed with hypertension prior to index date.

The most common indications for antipsychotic use any time prior to index date was insomnia and other sleep disorders, depression and dementia across most databases. About 19% of all antipsychotic new users had a record of depression in IPCI, SIDIAP and DKR. Insomnia and other sleep disorders were present in around 20% of all antipsychotic new users in IPCI and SIDIAP, and 5% in DK-DHR. A recording of dementia was present in 8 to 12% of all antipsychotic new users in IPCI, SIDIAP and DK-DHR. Among all antipsychotic new users in QVIA DA Germany 52% had an indication of depression, 24% with insomnia and other sleep disorders, and 23% with dementia. For IQVIA LPD Belgium, the proportions of depression, insomnia and other sleep disorders and dementia were 48%, 49% and 6% respectively. In NAJS the proportion of depression, insomnia and other sleep disorders and dementia were 33%, 16% and 5% respectively.

Indications differed between atypical and typical antipsychotic new users. For IPCI, the most common indications for the atypical population were 26% for depression and 23% for insomnia and other sleep disorders. Whereas in the typical population for IPCI, the most common indications were insomnia and other sleep disorders (19%), followed by dementia (17%). Similarly, in SIDIAP the indication of dementia was more common in the typical population (28%). For both databases, indications for bipolar disorder and schizophrenia were relatively low ranging from less than 1% to around 3%. For DK-DHR, the most common indication in the atypical and typical populations was depression (24% and 16%, respectively). In the typical population there were higher levels of insomnia sleep disorder (7%), and dementia (12%) compared to the atypical population (4%, 8% respectively). For IQVIA DA Germany, indications were relatively similar between typical and atypical users and all antipsychotic users, with the most notable difference being insomnia and other sleep disorders where 29% of the typical users vs 22% of atypical users had an indication. In IQVIA LPD Belgium and NAJS, typical users had higher proportion of insomnia and other sleep disorders, depression, schizophrenia and bipolar disorder indications than atypical users. The most common indications for atypical users were depression at 49% (IQVIA LPD Belgium) and 36% (NAJS), insomnia and other sleep disorders at 47% (IQVIA LPD Belgium) and 16% (NAJS), and dementia at 7% (IQVIA LPD Belgium) and 4% (NAJS). For typical users the most common indications were insomnia sleep disorders at 76% (IQVIA LPD Belgium) and 23% (NAJS), depression at 59% (IQVIA LPD Belgium) and 35% (NAJS), and bipolar disorder at 8% (IQVIA LPD Belgium) and 13% (NAJS).

Table 12. Patient characteristics for antipsychotics new users and by type of antipsychotics

			Cohort name		
Variable name	**Variable level**	**Estimate name**	**All antipsychotics**	**Atypical**	**Typical**
IQVIA DA Germany					
Age	-	Median [Q25 - Q75]	68.00 [50.00 - 82.00]	68.00 [49.00 - 82.00]	68.00 [51.00 - 82.00]
Age group	0-64	N (%)	78,265 (46.02%)	58,398 (46.43%)	36,849 (45.37%)
	65-74	N (%)	21,225 (12.48%)	15,191 (12.08%)	10,188 (12.55%)
	75-84	N (%)	40,095 (23.57%)	29,918 (23.79%)	18,698 (23.02%)
	85+	N (%)	30,491 (17.93%)	22,272 (17.71%)	15,476 (19.06%)
Sex	Female	N (%)	97,027 (57.05%)	70,293 (55.89%)	47,857 (58.93%)
Comorbidities (anytime prior)	Chronic kidney disease	N (%)	11,757 (6.91%)	8,023 (6.38%)	6,185 (7.62%)
	Chronic kidney disease- renal impairment	N (%)	17,530 (10.31%)	12,064 (9.59%)	9,189 (11.31%)
	Heart failure	N (%)	20,248 (11.91%)	13,904 (11.05%)	10,768 (13.26%)
	Hypertension	N (%)	71,303 (41.92%)	49,292 (39.19%)	35,641 (43.89%)

			Cohort name		
Variable name	**Variable level**	**Estimate name**	**All antipsychotics**	**Atypical**	**Typical**
	Myocardial infarction	N (%)	4,222 (2.48%)	2,881 (2.29%)	2,214 (2.73%)
	Obesity	N (%)	21,867 (12.86%)	15,141 (12.04%)	10,926 (13.45%)
	Stroke	N (%)	13,096 (7.70%)	9,575 (7.61%)	6,427 (7.91%)
	Type 2 diabetes	N (%)	34,684 (20.39%)	24,273 (19.30%)	17,304 (21.31%)
Indications (anytime prior)	Bipolar disorder	N (%)	4,255 (2.50%)	4,079 (3.24%)	1,963 (2.42%)
	Dementia	N (%)	38,374 (22.56%)	30,903 (24.57%)	19,396 (23.88%)
	Depression	N (%)	89,164 (52.43%)	66,610 (52.96%)	44,206 (54.43%)
	Insomnia	N (%)	2,360 (1.39%)	1,694 (1.35%)	1,305 (1.61%)
	Insomnia- sleep disorder	N (%)	41,420 (24.35%)	28,096 (22.34%)	23,250 (28.63%)
	Schizophrenia	N (%)	8,008 (4.71%)	7,997 (6.36%)	4,510 (5.55%)
IQVIA LPD Belgium					
Age	-	Median [Q25 - Q75]	54.00 [39.00 - 71.00]	54.00 [38.00 - 71.00]	55.00 [42.00 - 69.00]
Age group	0-64	N (%)	13,344 (65.98%)	12,334 (66.28%)	2,355 (69.16%)
	65-74	N (%)	2,653 (13.12%)	2,395 (12.87%)	441 (12.95%)
	75-84	N (%)	2,435 (12.04%)	2,251 (12.10%)	323 (9.49%)
	85+	N (%)	1,791 (8.86%)	1,628 (8.75%)	286 (8.40%)
Sex	Female	N (%)	11,619 (57.45%)	10,725 (57.64%)	1,812 (53.22%)
Comorbidities (anytime prior)	Chronic kidney disease	N (%)	235 (1.16%)	209 (1.12%)	52 (1.53%)
	Chronic kidney disease- renal impairment	N (%)	266 (1.32%)	238 (1.28%)	58 (1.70%)
	Heart failure	N (%)	966 (4.78%)	840 (4.51%)	217 (6.37%)
	Hypertension	N (%)	7,359 (36.39%)	6,662 (35.80%)	1,358 (39.88%)

			Cohort name		
Variable name	**Variable level**	**Estimate name**	**All antipsychotics**	**Atypical**	**Typical**
	Myocardial infarction	N (%)	224 (1.11%)	204 (1.10%)	40 (1.17%)
	Obesity	N (%)	1,204 (5.95%)	1,098 (5.90%)	263 (7.72%)
	Stroke	N (%)	472 (2.33%)	435 (2.34%)	74 (2.17%)
	Type 2 diabetes	N (%)	2,299 (11.37%)	2,033 (10.93%)	527 (15.48%)
Indications (anytime prior)	Bipolar disorder	N (%)	992 (4.91%)	995 (5.35%)	261 (7.67%)
	Dementia	N (%)	1,270 (6.28%)	1,218 (6.55%)	169 (4.96%)
	Depression	N (%)	9,803 (48.47%)	9,052 (48.65%)	2,011 (59.06%)
	Insomnia	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Insomnia- sleep disorder	N (%)	9,841 (48.66%)	8,649 (46.48%)	2,581 (75.80%)
	Schizophrenia	N (%)	503 (2.49%)	486 (2.61%)	219 (6.43%)
DK-DHR					
Age	-	Median [Q25 - Q75]	53 [30 - 76]	46 [28 - 69]	71 [46 - 83]
Age group	0-64	N (%)	103,189 (60.98%)	98,817 (71.30%)	26,419 (40.42%)
	65-74	N (%)	19,475 (11.51%)	13,466 (9.72%)	10,120 (15.48%)
	75-84	N (%)	24,708 (14.60%)	15,161 (10.94%)	14,289 (21.86%)
	85+	N (%)	21,845 (12.91%)	11,150 (8.05%)	14,537 (22.24%)
Sex	Female	N (%)	88,055 (52.04%)	72,407 (52.24%)	33,281 (50.92%)
Comorbidities (anytime prior)	Chronic kidney disease	N (%)	4,078 (2.41%)	2,060 (1.49%)	2,814 (4.31%)
	Chronic kidney disease- renal impairment	N (%)	5,685 (3.36%)	2,918 (2.11%)	3,905 (5.97%)
	Heart failure	N (%)	8,835 (5.22%)	4,642 (3.35%)	5,862 (8.97%)
	Hypertension	N (%)	35,867 (21.20%)	22,756 (16.42%)	20,448 (31.28%)

			Cohort name		
Variable name	**Variable level**	**Estimate name**	**All antipsychotics**	**Atypical**	**Typical**
	Myocardial infarction	N (%)	6,927 (4.09%)	4,137 (2.98%)	4,131 (6.32%)
	Obesity	N (%)	13,014 (7.69%)	11,464 (8.27%)	4,866 (7.44%)
	Stroke	N (%)	5,611 (3.32%)	3,367 (2.43%)	3,479 (5.32%)
	Type 2 diabetes	N (%)	17,331 (10.24%)	11,666 (8.42%)	9,557 (14.62%)
Indications (anytime prior)	Bipolar disorder	N (%)	3,589 (2.12%)	4,260 (3.07%)	1,092 (1.67%)
	Dementia	N (%)	14,130 (8.35%)	10,798 (7.79%)	7,517 (11.50%)
	Depression	N (%)	32,311 (19.09%)	32,831 (23.69%)	10,385 (15.89%)
	Insomnia	N (%)	489 (0.29%)	489 (0.35%)	148 (0.23%)
	Insomnia- sleep disorder	N (%)	8,892 (5.25%)	6,277 (4.53%)	5,043 (7.72%)
	Schizophrenia	N (%)	3,163 (1.87%)	3,741 (2.70%)	1,748 (2.67%)
IPCI					
Age	-	Median [Q25 - Q75]	63 [41 - 81]	49 [32 - 66]	79 [65 - 87]
Age group	0-64	N (%)	23,919 (51.50%)	21,123 (73.25%)	5,585 (24.32%)
	65-74	N (%)	5,728 (12.33%)	2,885 (10.00%)	3,503 (15.25%)
	75-84	N (%)	8,362 (18.00%)	3,048 (10.57%)	6,357 (27.68%)
	85+	N (%)	8,437 (18.17%)	1,782 (6.18%)	7,522 (32.75%)
Sex	Female	N (%)	24,045 (51.77%)	15,083 (52.30%)	11,724 (51.05%)
Comorbidities (anytime prior)	Chronic kidney disease	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Chronic kidney disease- renal impairment	N (%)	4,093 (8.81%)	1,195 (4.14%)	3,389 (14.76%)
	Heart failure	N (%)	3,532 (7.60%)	794 (2.75%)	3,112 (13.55%)
	Hypertension	N (%)	10,193 (21.95%)	4,379 (15.18%)	6,959 (30.30%)

			Cohort name		
Variable name	**Variable level**	**Estimate name**	**All antipsychotics**	**Atypical**	**Typical**
	Myocardial infarction	N (%)	1,606 (3.46%)	614 (2.13%)	1,177 (5.12%)
	Obesity	N (%)	6,228 (13.41%)	3,609 (12.51%)	3,489 (15.19%)
	Type 2 diabetes	N (%)	6,813 (14.67%)	2,784 (9.65%)	4,909 (21.37%)
	Stroke	N (%)	2,717 (5.85%)	927 (3.21%)	2,131 (9.28%)
Indications (anytime prior)	Bipolar disorder	N (%)	659 (1.42%)	650 (2.25%)	201 (0.88%)
	Dementia	N (%)	5,034 (10.84%)	2,128 (7.38%)	3,927 (17.10%)
	Depression	N (%)	8,674 (18.68%)	7,504 (26.02%)	2,309 (10.05%)
	Insomnia	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Insomnia-sleep disorder	N (%)	9,742 (20.97%)	6,550 (22.71%)	4,375 (19.05%)
	Schizophrenia	N (%)	850 (1.83%)	816 (2.83%)	358 (1.56%)
NAJS					
Age	-	Median [Q25 - Q75]	59 [45 - 73]	58 [44 - 70]	66 [50 - 80]
Age group	0-64	N (%)	347,689 (60.63%)	316,220 (63.91%)	92,027 (48.05%)
	65-74	N (%)	99,133 (17.29%)	85,762 (17.33%)	31,174 (16.28%)
	75-84	N (%)	86,241 (15.04%)	67,483 (13.64%)	40,110 (20.94%)
	85+	N (%)	40,370 (7.04%)	25,363 (5.13%)	28,193 (14.72%)
Sex	Female	N (%)	365,376 (63.72%)	324,252 (65.53%)	106,126 (55.42%)
Comorbidities (anytime prior)	Chronic kidney disease	N (%)	15,793 (2.75%)	11,588 (2.34%)	9,044 (4.72%)
	Chronic kidney disease- renal impairment	N (%)	19,854 (3.46%)	14,642 (2.96%)	11,504 (6.01%)
	Heart failure	N (%)	29,292 (5.11%)	21,252 (4.29%)	17,052 (8.90%)
	Hypertension	N (%)	332,268 (57.94%)	279,134 (56.41%)	124,077 (64.79%)

			Cohort name		
Variable name	**Variable level**	**Estimate name**	**All antipsychotics**	**Atypical**	**Typical**
	Myocardial infarction	N (%)	15,141 (2.64%)	11,994 (2.42%)	6,952 (3.63%)
	Obesity	N (%)	34,258 (5.97%)	30,046 (6.07%)	12,658 (6.61%)
	Stroke	N (%)	24,956 (4.35%)	17,757 (3.59%)	15,575 (8.13%)
	Type 2 diabetes	N (%)	89,004 (15.52%)	73,351 (14.82%)	37,694 (19.68%)
Indications (anytime prior)	Bipolar disorder	N (%)	3,283 (0.57%)	3,391 (0.69%)	3,487 (1.82%)
	Dementia	N (%)	29,167 (5.09%)	21,031 (4.25%)	24,744 (12.92%)
	Depression	N (%)	188,675 (32.90%)	177,261 (35.82%)	67,956 (35.49%)
	Insomnia	N (%)	21,253 (3.71%)	18,253 (3.69%)	10,057 (5.25%)
	Insomnia- sleep disorder	N (%)	90,580 (15.80%)	77,532 (15.67%)	41,959 (21.91%)
	Schizophrenia	N (%)	7,576 (1.32%)	9,178 (1.85%)	10,544 (5.51%)
SIDIAP					
Age	-	Median [Q25 - Q75]	64 [43 - 82]	63 [43 - 81]	82 [67 - 89]
Age group	0-64	N (%)	252,446 (50.69%)	249,353 (51.86%)	16,407 (23.09%)
	65-74	N (%)	61,295 (12.31%)	59,108 (12.29%)	6,810 (9.58%)
	75-84	N (%)	88,573 (17.79%)	84,103 (17.49%)	17,318 (24.37%)
	85+	N (%)	95,664 (19.21%)	88,232 (18.35%)	30,525 (42.96%)
Sex	Female	N (%)	292,935 (58.82%)	284,278 (59.13%)	39,787 (55.99%)
Comorbidities (anytime prior)	Chronic kidney disease	N (%)	57,875 (11.62%)	54,068 (11.25%)	15,118 (21.27%)
	Chronic kidney disease- renal impairment	N (%)	60,060 (12.06%)	56,089 (11.67%)	15,695 (22.09%)
	Heart failure	N (%)	29,869 (6.00%)	27,465 (5.71%)	8,622 (12.13%)
	Hypertension	N (%)	117,379 (23.57%)	112,191 (23.33%)	20,893 (29.40%)

			Cohort name		
Variable name	Variable level	Estimate name	All antipsychotics	Atypical	Typical
	Myocardial infarction	N (%)	8,427 (1.69%)	7,920 (1.65%)	1,860 (2.62%)
	Obesity	N (%)	170,155 (34.17%)	164,041 (34.12%)	27,901 (39.26%)
	Stroke	N (%)	27,549 (5.53%)	25,989 (5.41%)	7,021 (9.88%)
	Type 2 diabetes	N (%)	96,898 (19.46%)	91,730 (19.08%)	20,274 (28.53%)
Indications (anytime prior)	Bipolar disorder	N (%)	4,186 (0.84%)	4,300 (0.89%)	1,152 (1.62%)
	Dementia	N (%)	60,241 (12.10%)	59,557 (12.39%)	19,905 (28.01%)
	Depression	N (%)	96,956 (19.47%)	94,975 (19.75%)	14,650 (20.62%)
	Insomnia	N (%)	82,471 (16.56%)	79,718 (16.58%)	15,421 (21.70%)
	Insomnia-sleep disorder	N (%)	95,198 (19.12%)	92,063 (19.15%)	17,035 (23.97%)
	Schizophrenia	N (%)	3,411 (0.68%)	3,800 (0.79%)	2,112 (2.97%)

12.2.2 Objective 2: Incidence rates

Incidence rates (IRs) of overall, typical and atypical antipsychotics from 2013 to 2023 are depicted in **Figure 5**.

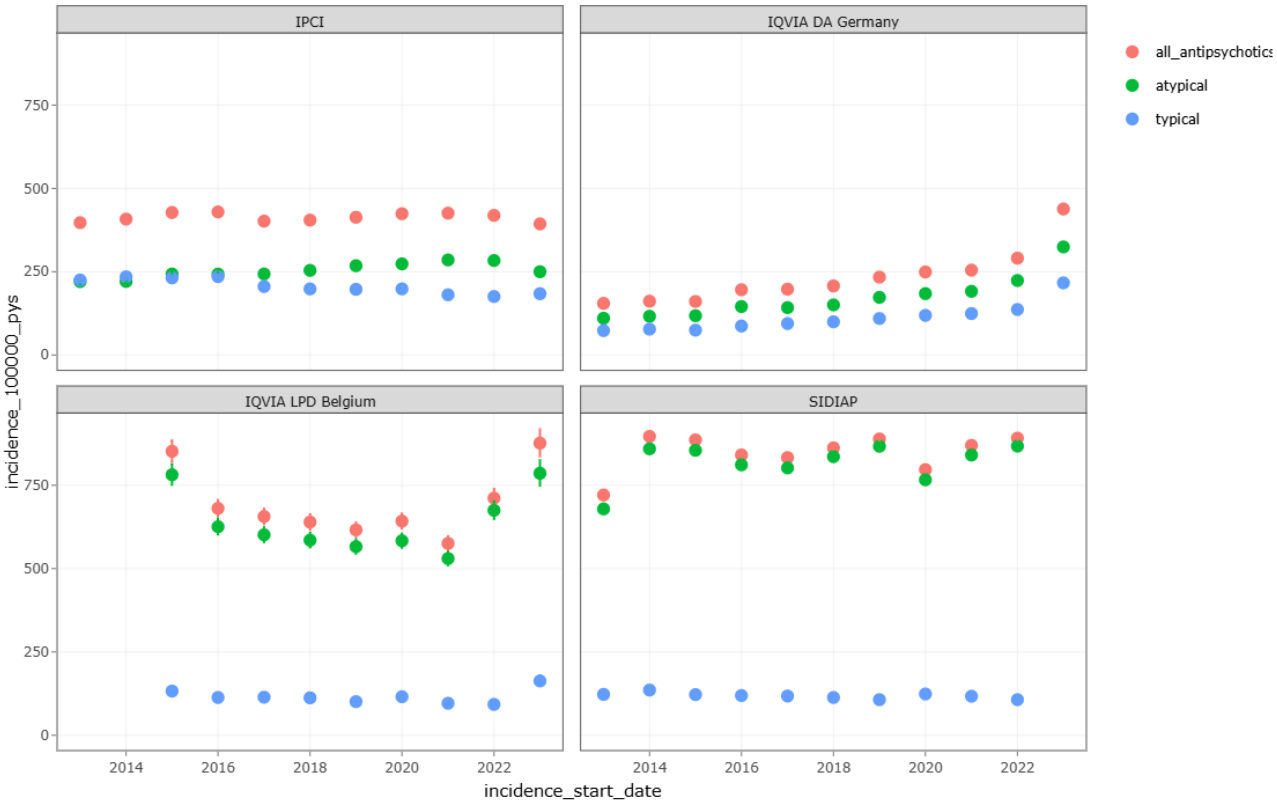
12.2.2.1 Overall use of antipsychotics

In IPCI, IR values remained relatively stable throughout the study period at around 400 cases per 100,000 person-years. In IQVIA DA Germany, incident use increased from 2013 to 2018 (IR [95% CI] per 100,000 person-years: from 155 [152 - 158] to 438 [432 - 445], respectively). In IQVIA LPD Belgium, incident use (IR [95% CI] cases per 100,000 person-years) decreased from 2015 to 2021 (from 852 [818 - 887] to 576 [551 - 601], respectively) and then proceeded to increase from 2021 to 2023 (from 576 [551 - 601] to 877 [834 - 921], respectively). In SIDIAP, all antipsychotic use remained relatively stable at around 850 per 100,000 person-years, with dips in 2013 and 2020 (IR [95% CI]: 721 [714 - 728] and 797 [790 - 805] cases per 100,000 person-years, respectively). IR [95% CI] in DK-DHR remained relatively stable between 250 [243 - 252] to 284 [280 - 288] cases per 100,000 person-years between 2013 to 2020 and has slowly increased in trend from 2020 to 2023 (with an IR [95% CI] of 312 [308 – 317] cases per 100,000 person-years in 2023). In NAJS IR [95% CI] ranged between 2250 [2,233-2,266] cases per 100,000 person-years in 2016 and 980 [970-990] cases per 100,000 person-years in 2020, with an outlier in 2017 of 4,244 [4,223 – 4,265] cases per 100,000 person-years.

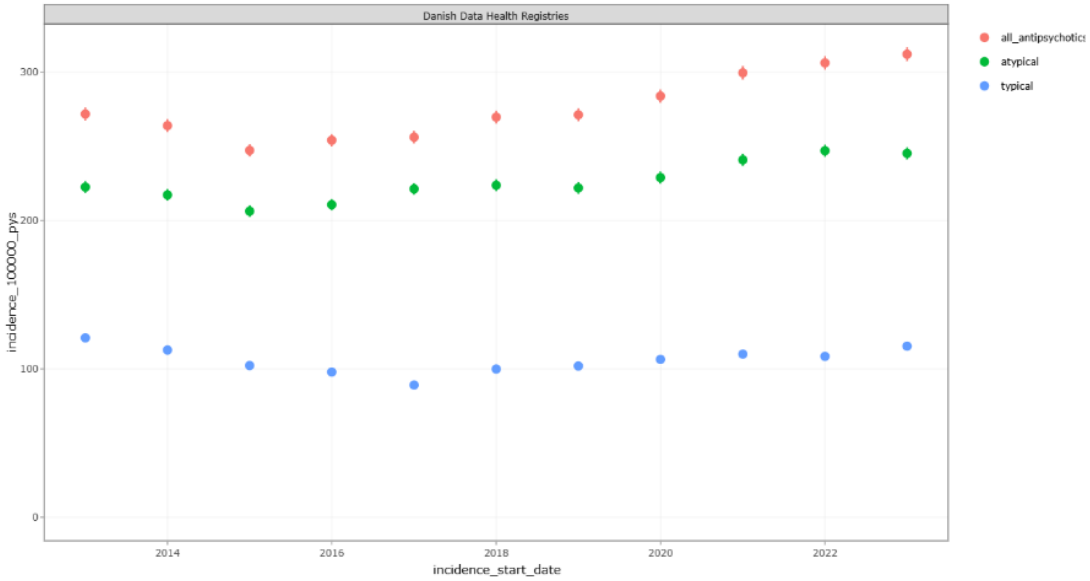
12.2.2.2 Use of atypical vs typical antipsychotics

The incidence use of atypical compared to typical antipsychotic use differed across databases. In IPCI and IQVIA DA Germany, atypical and typical antipsychotic use was evenly distributed. In IPCI atypical use rates surpassed typical rates from 2017 onwards. In IQVIA DA Germany atypical use were consistently higher than typical use. In IQVIA LPD Belgium, DK-DHR, NAJS and SIDIAP, atypical use closely followed the trends for all antipsychotic rates while typical use was considerably lower and remained stable throughout 2013 (2016 in NAJS) to 2023.

A) IPCI, IQVIA DA Germany, IQVIA LPD Belgium and SIDIAP:



B) DK-DHR



C) NAJS

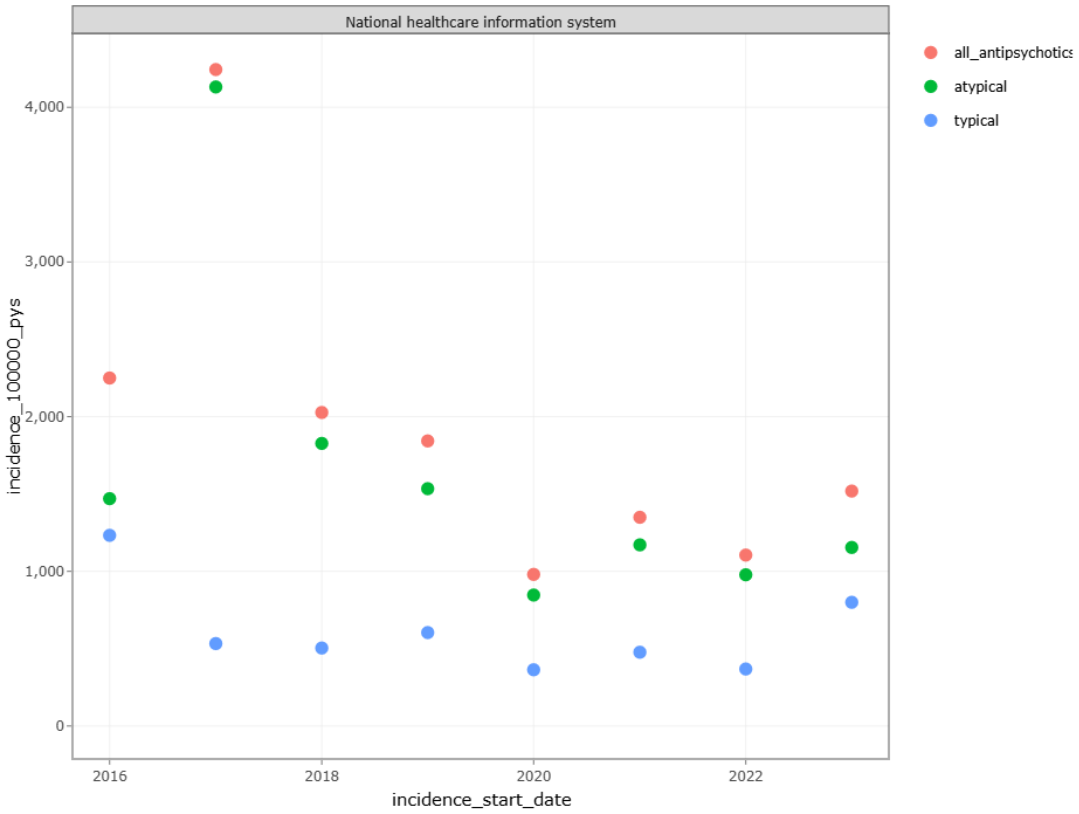


Figure 5. Incidence rates for all antipsychotic use, typical and atypical, for A) IPCI, IQVIA DA Germany, IQVIA LPD Belgium and SIDIAP, and B) for DK-DHR and C) NAJS

12.2.2.3 Age stratification

Amongst all databases and types of antipsychotics there were higher IRs of antipsychotic use among the ≥85 years old age group, followed by the 75 to 84, 65 to 74, and ≤64 age groups.

In IPCI, IR [95% CI cases per 100,000 person-years] in the ≥85 age group were considerably higher in the all-antipsychotic users and typical antipsychotic users, where IR values ranged between 2,823 [2,617 - 3,040] and 4,242 [3,965 - 4,534], and both cohorts presented an increasing trend from 2013 to 2016 and a moderate decrease from 2016 to 2023. IRs in the second highest age group, the 75 to 84 years, all antipsychotic users and typical antipsychotic users had values between 1,368 [1,276 - 1,465] and 711 [655 - 771], respectively. For atypical use, while the ≥85 age group had the highest rates, these were always below 1,000 cases per 100,000 person-years (**Figure 6**).

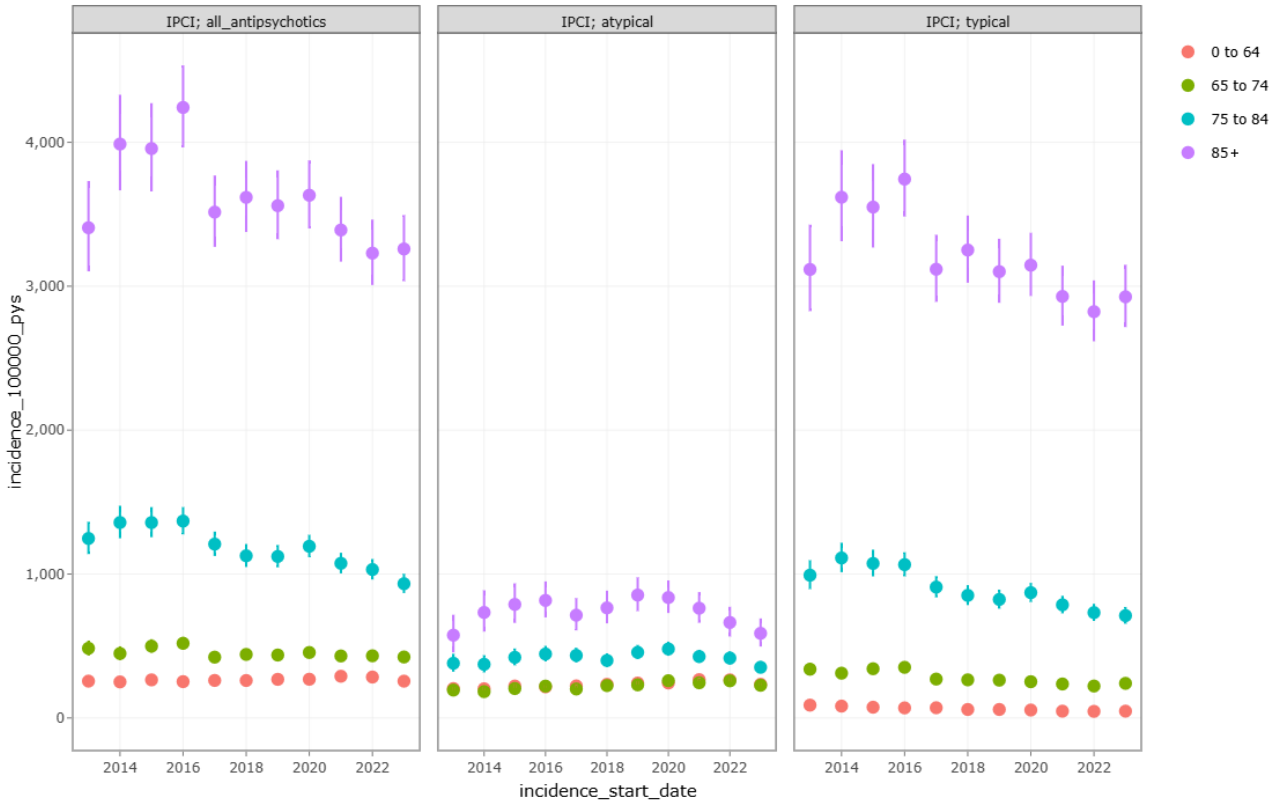


Figure 6. Incidence rates for all antipsychotic use, typical and atypical, stratified by age groups in IPCI

Due to the larger proportion of atypical antipsychotic users in SIDIAP, trends in atypical users reflect the trends in all antipsychotic incidence rates. In the ≥85 age group there was a consistent increase in IRs of atypical use from 2013 to 2023 from 3,900 people to 6,000 people per 100,000 person-years. Use of typical in all age groups, and in the other age groups for the atypical antipsychotic use remained relatively stable during the study period. For instance, IR in incident users of atypical antipsychotic among the 75 to 84 age group varied between 2,043 [1,997 - 2,089] and 2,537 [2,484 - 2,590] cases per 100,000 person-years (**Figure 7**).

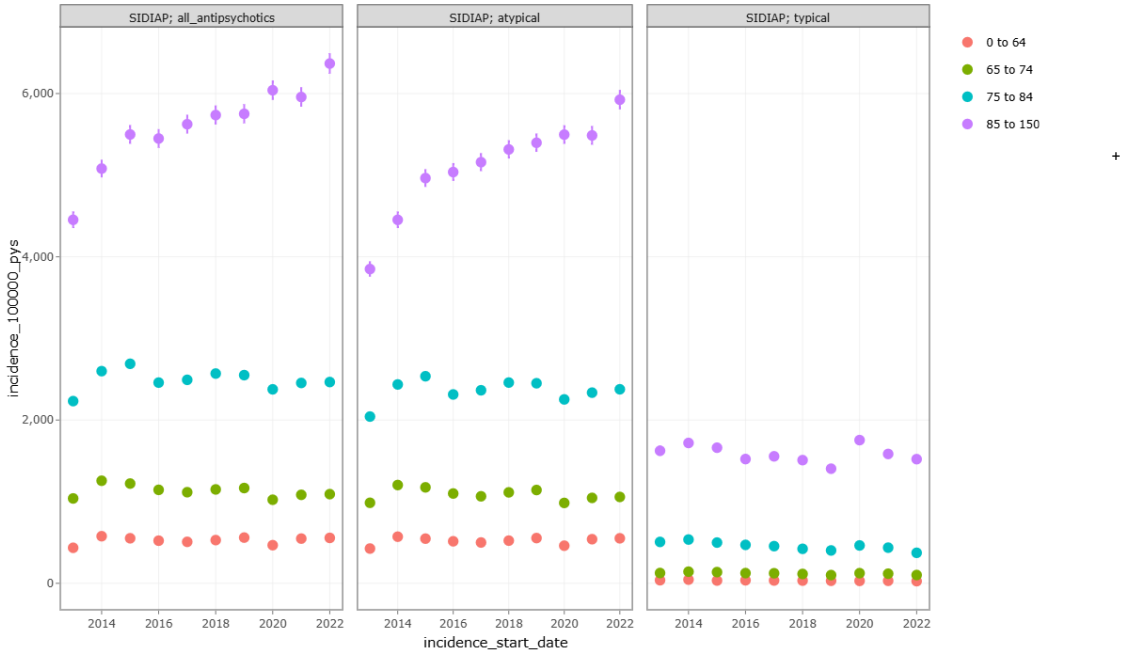


Figure 7. Incidence rates for all antipsychotic use, typical and atypical, stratified by age groups in SIDIAP

In IQVIA DA Germany, age trends were consistent between all, typical and atypical antipsychotic cohorts. For all three cohorts, the ≥85 age group had higher IRs compared to the other age groups, also showing an increasing trend from 2015 to 2023 (e.g., IR [95% CI] of overall use per 100,000 person-years in the ≥85 age group ranged from 976 [919 - 1,037] in 2014 to 1,886 [1,827 - 1,947] in 2023). The other age groups also had increasing rates but were less pronounced (**Figure 8**).

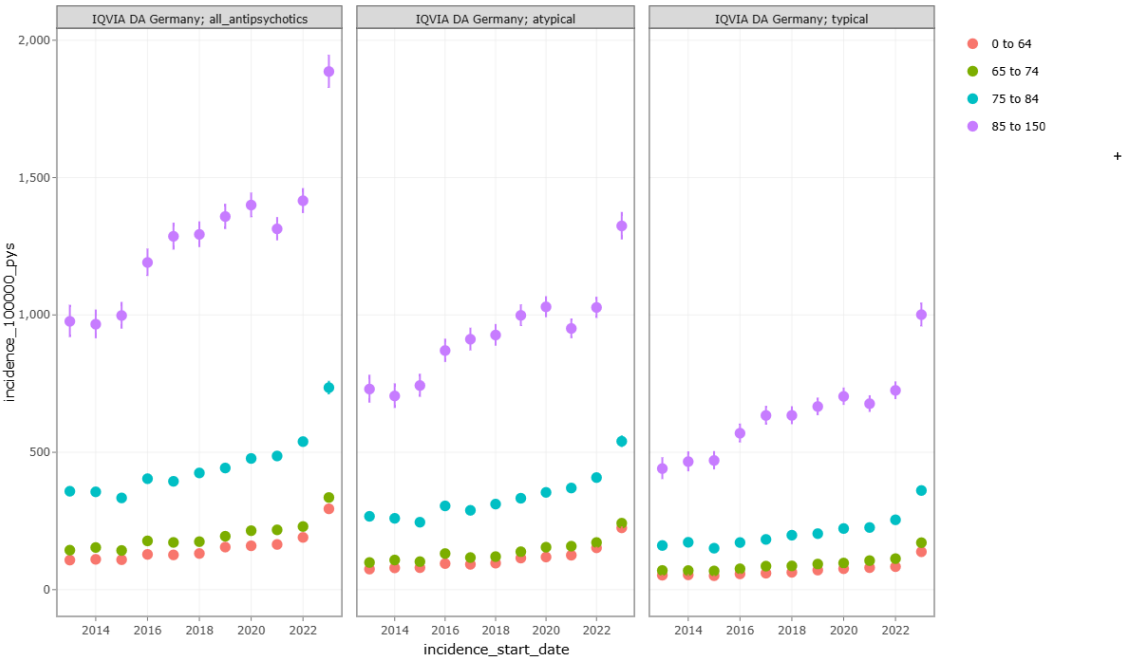


Figure 8. Incidence rates for all antipsychotic use, typical and atypical, stratified by age groups in IQVIA DA Germany

Due to a smaller sample size, IR estimates for IQVIA LPD Belgium had wider confidence intervals. IRs for all antipsychotic use was heavily influenced by atypical antipsychotic use. Both cohorts had a slight increase in the ≥85 age group from 2016 to 2023 (e.g., IR [95% CI] per 100,000 person-years of all antipsychotic use in 2016 was 1,494 [1,275 - 1,740] vs in 2023 that was 1,929 [1,653 - 2,239]). IRs for typical users were low and relatively stable for all age groups (**Figure 9**).

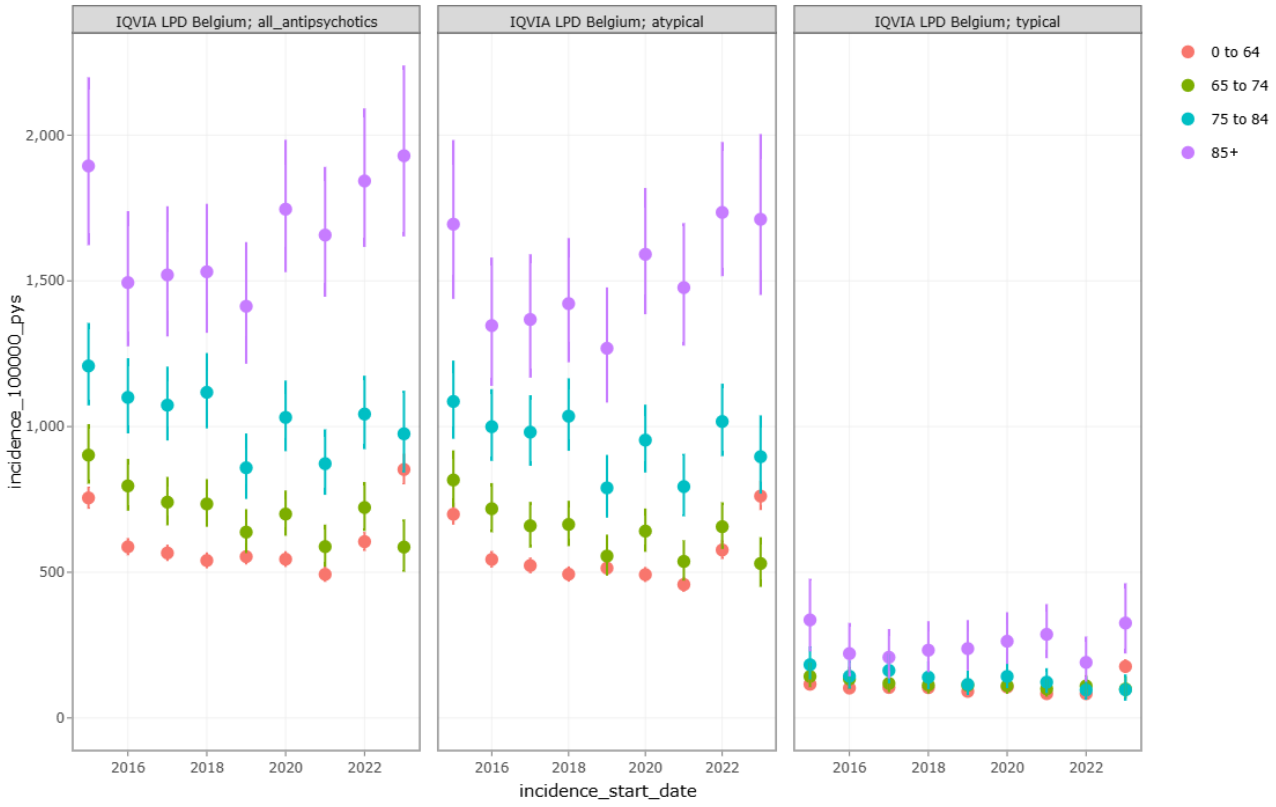


Figure 9. Incidence rates for all antipsychotic use, typical and atypical, stratified by age groups in IQVIA LPD Belgium

In the DK-DHR, age trends in the typical antipsychotic users were reflected in the overall population. There had been a sharp and consistent increase in antipsychotic use (IR [95% CI] cases per 100,00 person-years) among the ≥85 age group from 2013 (overall: 1,208 [1,145 - 1,274]; typical: 605 [561 - 652]) to 2023 (overall: 2,027 [1,952 - 2,105]; typical: 1574 [1,508 - 1,642]). IRs remained relatively stable for atypical antipsychotic use (**Figure 10**).

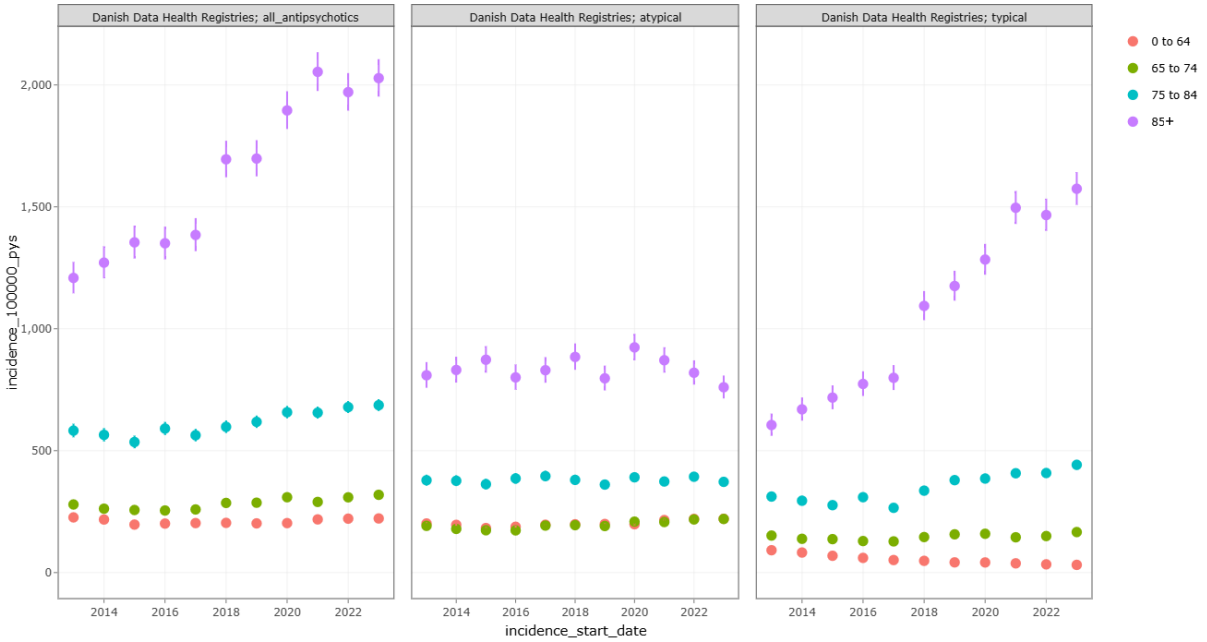


Figure 10. Incidence rates for all antipsychotic use, typical and atypical, stratified by age groups in DK-DHR

In NAJS, there was high antipsychotic use in the ≥85 age group for all antipsychotic use and typical users. The outlier in 2017 for all antipsychotic users ≥85 age group (IR [95% CI] 10,500 [10,200 – 10,700]) cases per 100,000 person-years, was consistent with the outlier in atypical antipsychotics for all age groups. The general trend of a gradual decrease in antipsychotic use in the older population was reflected in all antipsychotic users and those in the typical group (e.g. in the ≥85 age group for all antipsychotic users in 2016 the IR was 5,732.26 [5,558.33 - 5,910.24] and in 2023 was 3,566.64 [3,445.75 - 3,690.70] cases per 100,000 person-years) (**Figure 11**).

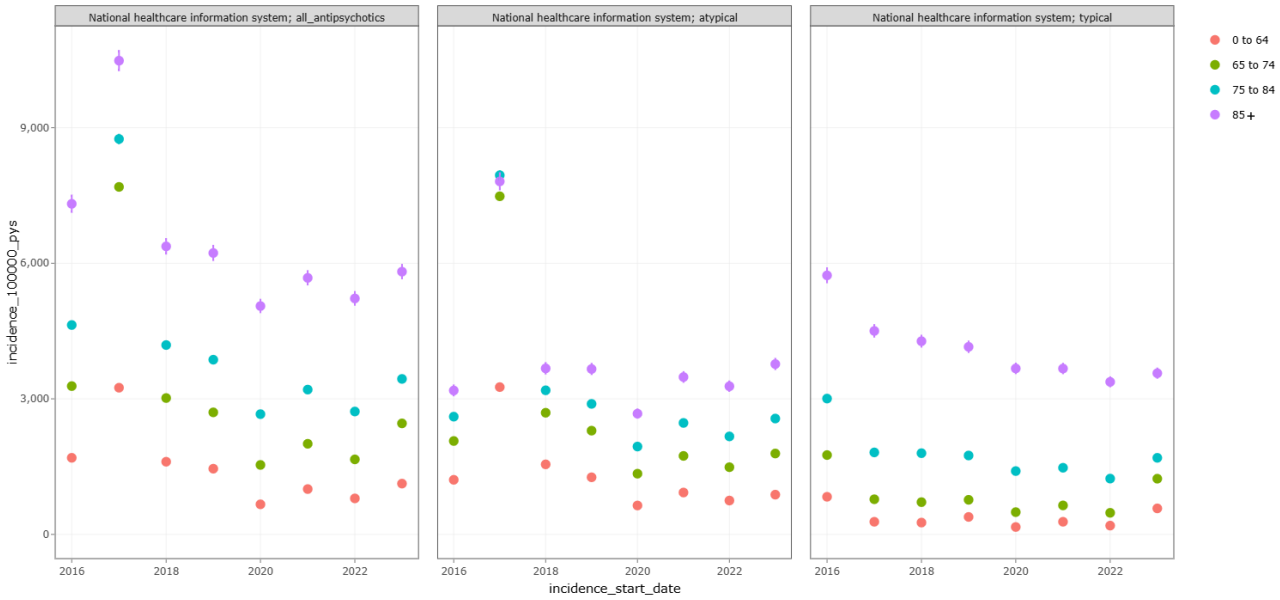


Figure 11. Incidence rates for all antipsychotic use, typical and atypical, stratified by age groups in NAJS

12.2.2.4 Sex stratification

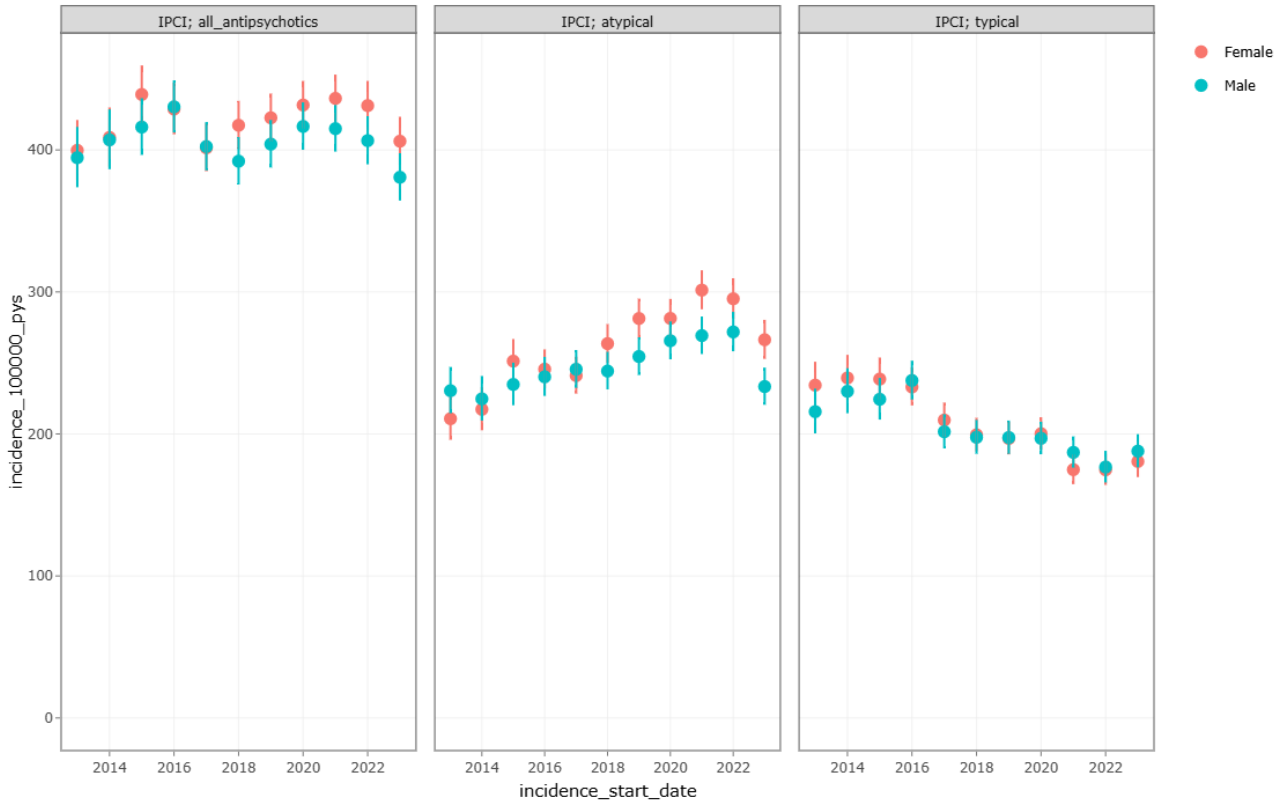
As shown in **Figure 12 A-C**, there were no differences between sexes for IRs of all, atypical and typical antipsychotic use in IPCI, DK-DHR or IQVIA DA Germany.

For SIDIAP, there were higher IRs of atypical antipsychotic use among females compared to males. These trends were not evident in the typical user's cohort (**Figure 12D**).

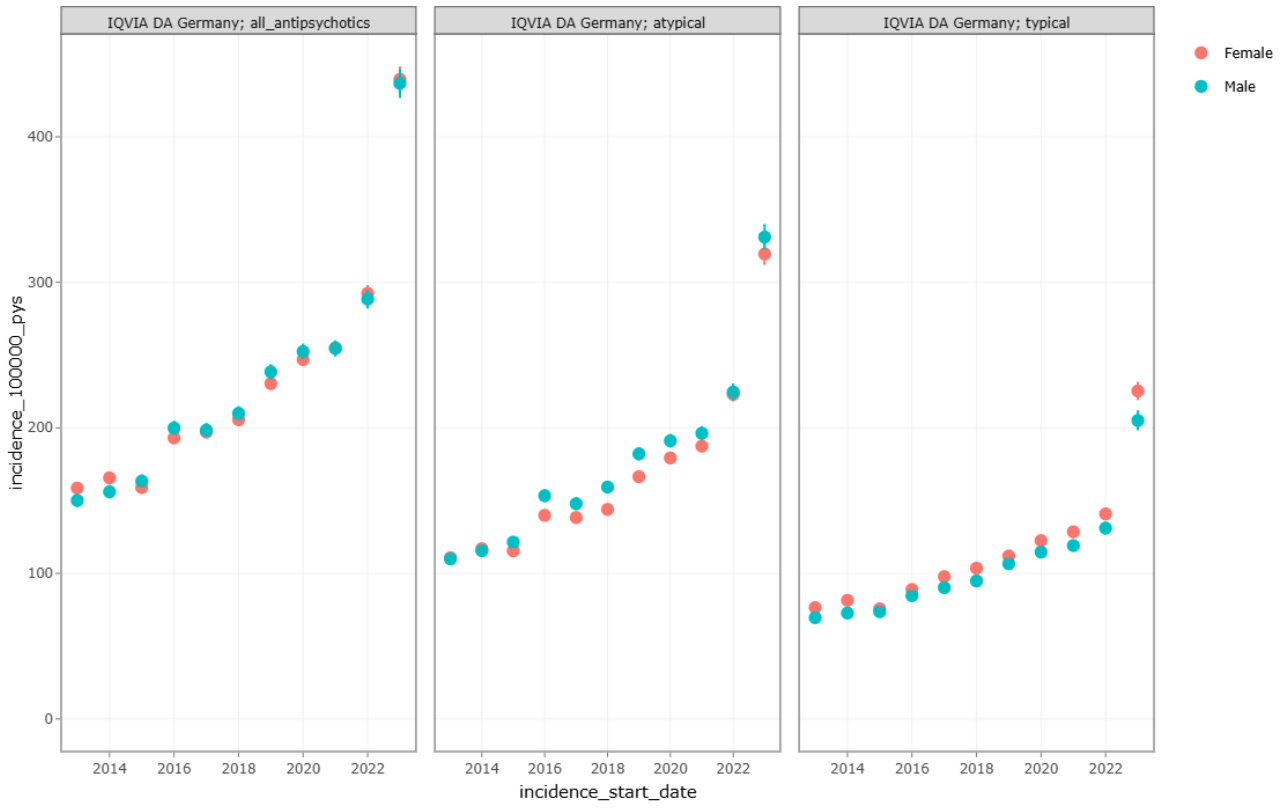
In IQVIA LPD Belgium, there were some sex differences in IRs for the atypical antipsychotic cohort. Typical users' cohort did not have the same trends (**Figure 12E**).

In NAJS, there were higher IRs for female antipsychotic use in all antipsychotics and atypical cohorts. Antipsychotic IRs in the typical user's cohort were consistent between sexes (**Figure 12F**).

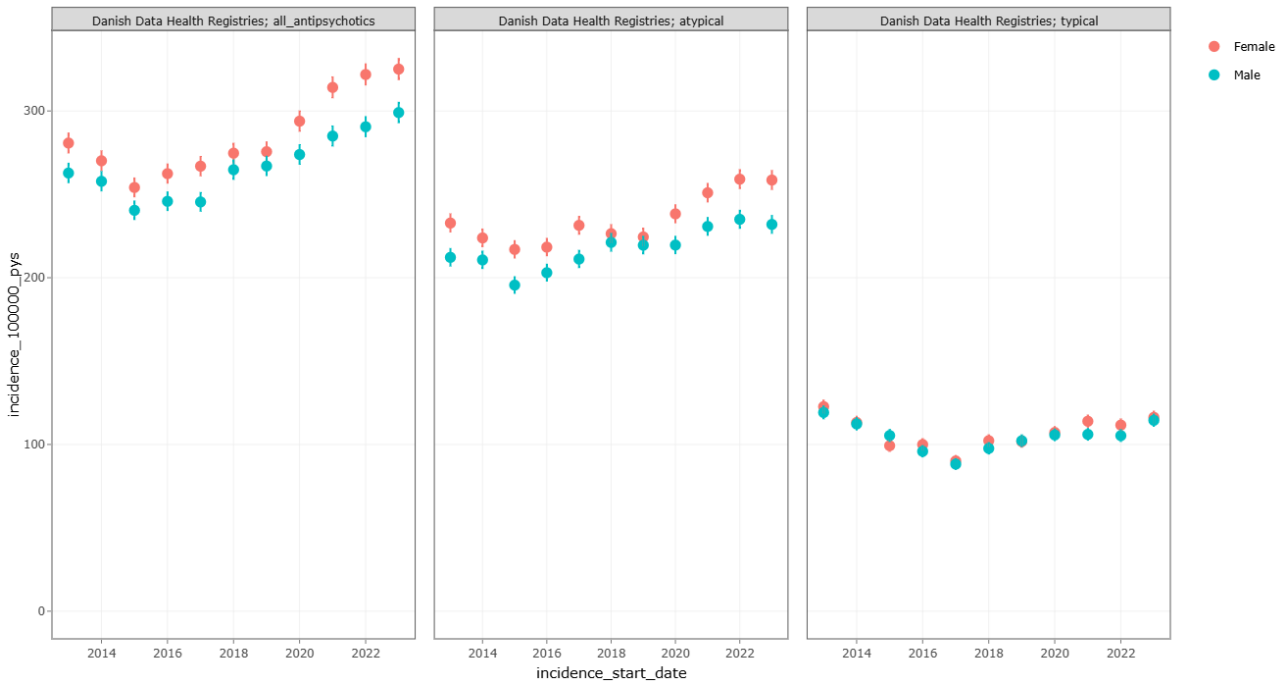
A) IPCI



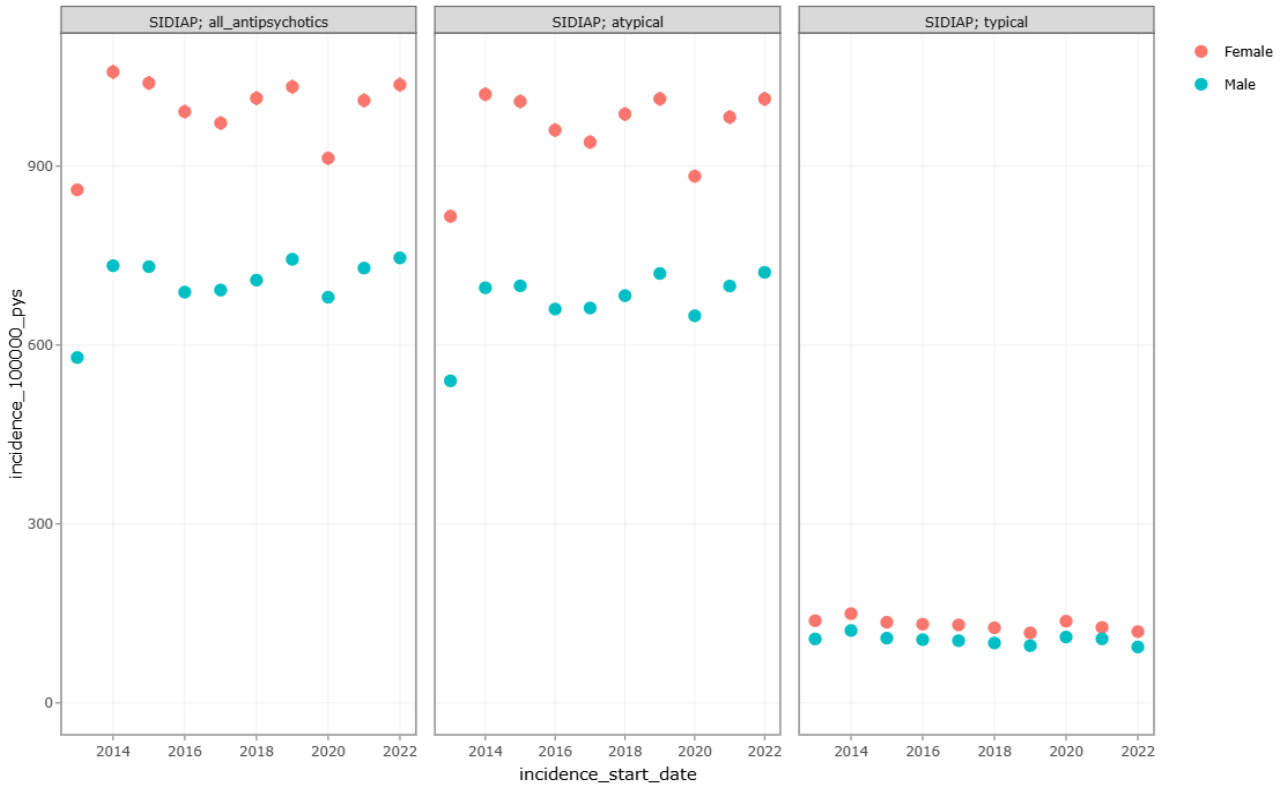
B) IQVIA DA Germany



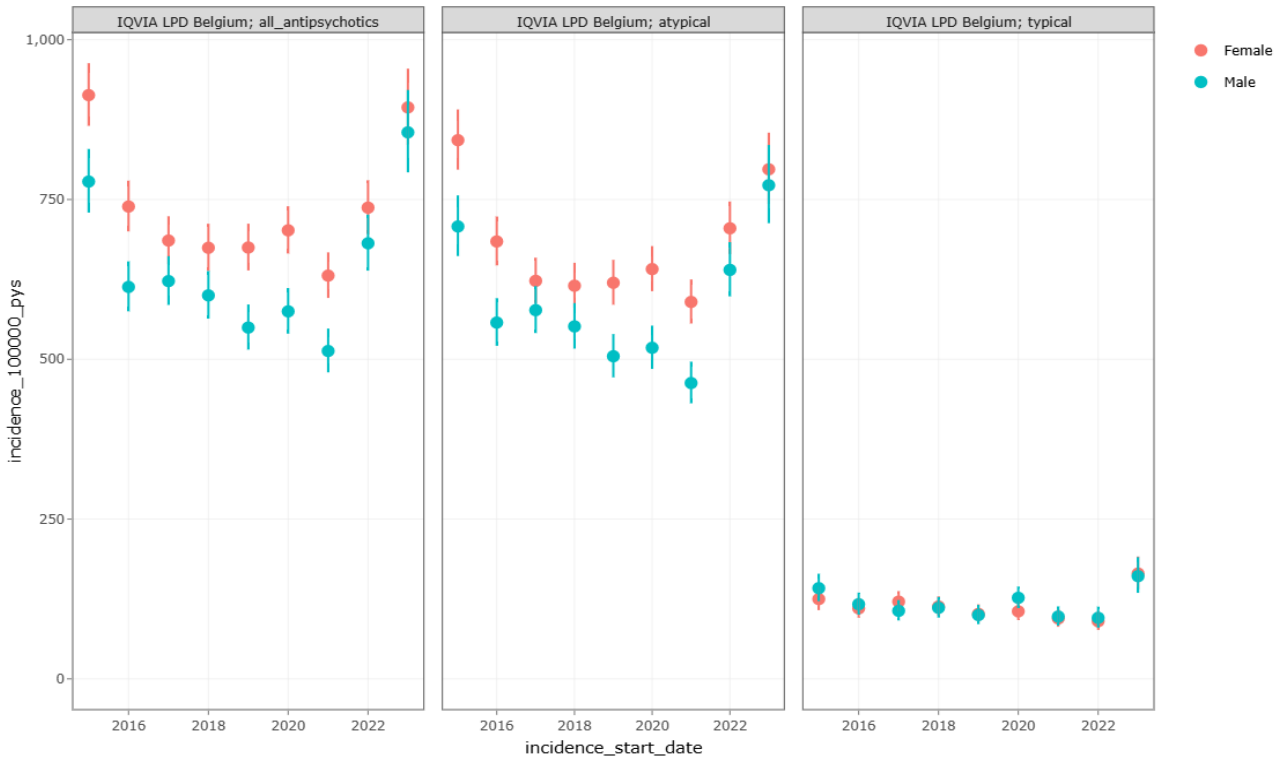
C) DK-DHR



D) SIDIAP



E) IQVIA LPD Belgium



F) NAJS

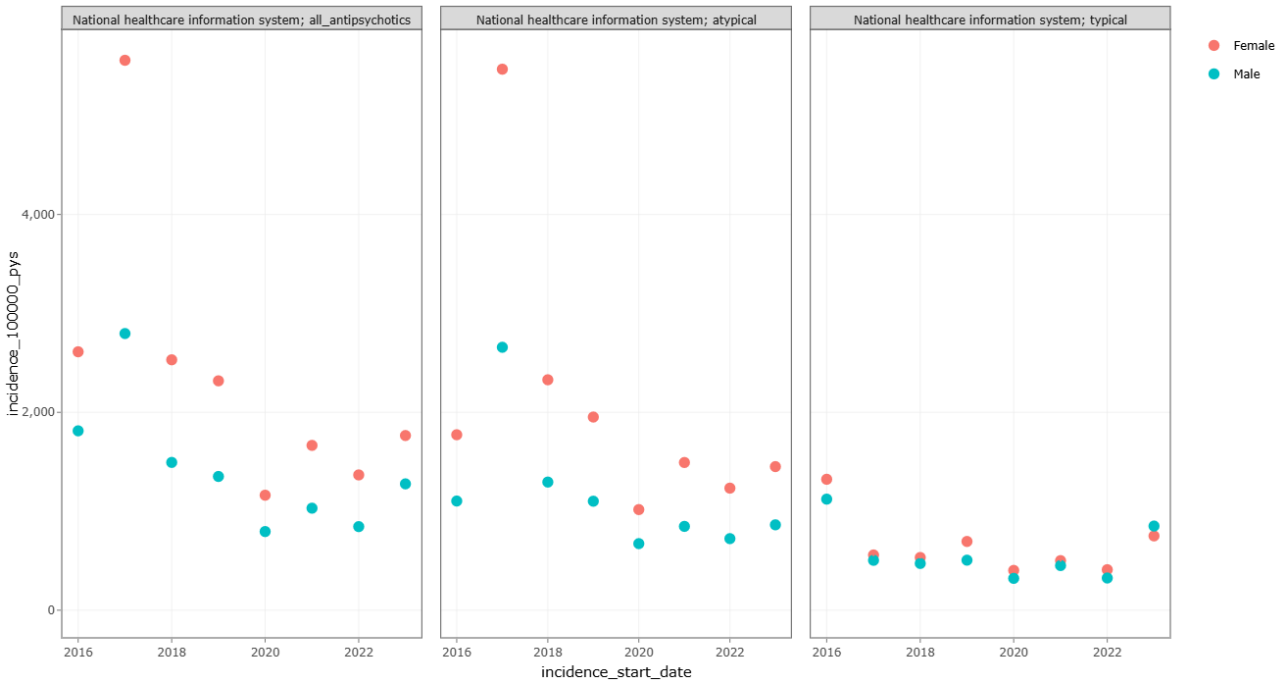


Figure 12. Incidence rates for all antipsychotic use, typical and atypical, stratified by sex in A) IPCI, B) IQVIA DA Germany, C) DK-DHR, D) SIDIAP, E) IQVIA LPD Belgium, and F) NAJS

12.2.2.5 Top 5 most common antipsychotics per database

IPCI

For IRs of the top 5 antipsychotics in IPCI, haloperidol and quetiapine had the highest rates (IRs ranged between 164-209 and 122-187 cases per 100,000 person-years, respectively). Haloperidol use increased from 2013 to 2016 (to the 209 [95% CI: 200 - 218] peak), and then decreased from 2016 to 2023 (IR in 2023 was 170 [95% CI: 163 - 178]). Quetiapine use increased from 2013 to 2021 (to the 187 [95% CI: 180 - 195] peak) and showed a decline from 2021 to 2023 (to 157 [95% CI: 149 – 164]). Other drugs remained relatively stable (**Figure 13**).

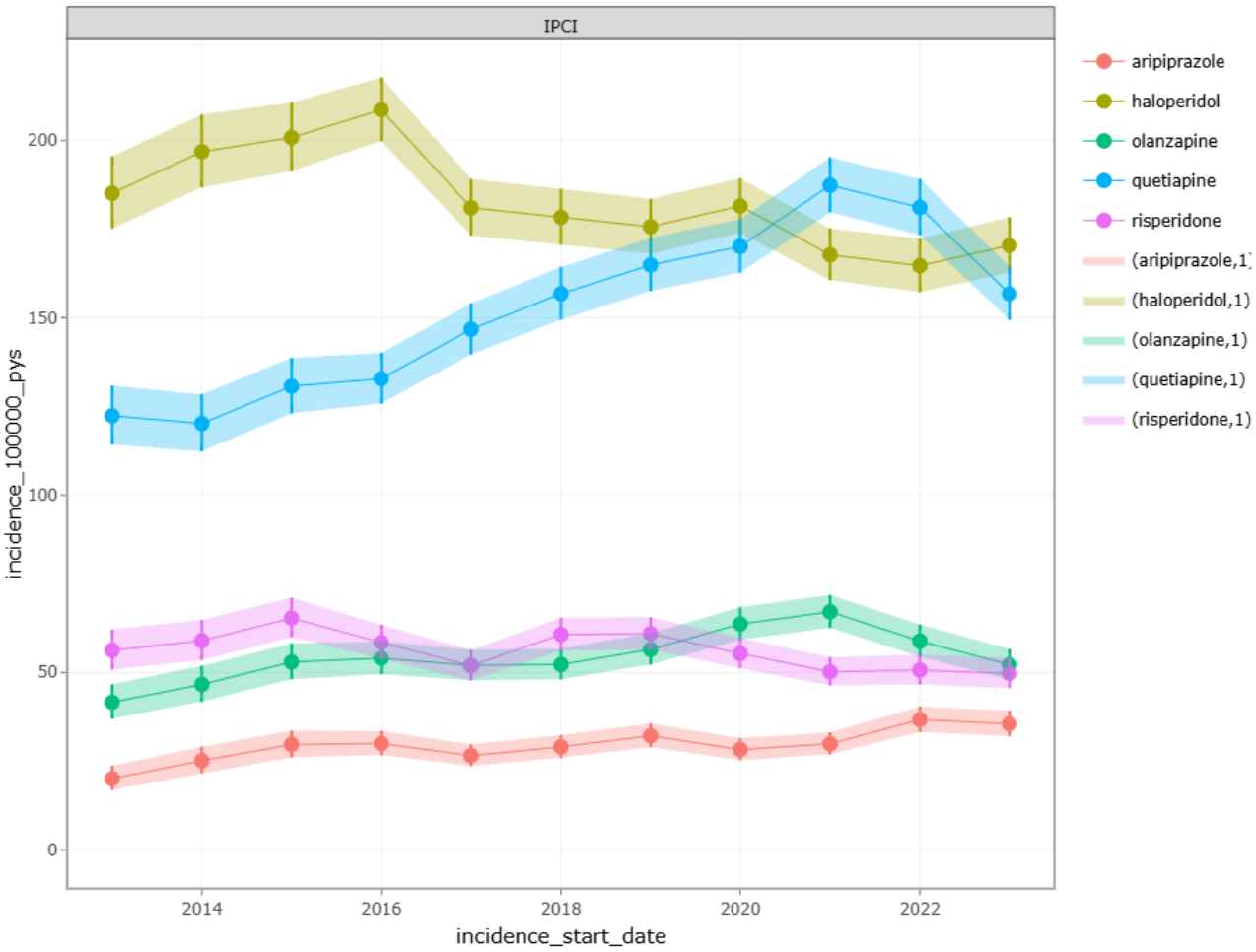


Figure 13. Incidence rates of use of the top 5 most common antipsychotics in IPCI

SIDIAP

The most common antipsychotics in SIDIAP were sulpiride and quetiapine. Quetiapine use had been steadily increasing from 2013 to 2023 from 247 [95% CI: 243 - 251] to 458 [95% CI: 452 - 463] cases per 100,000 person-years. Sulpiride use showed some sharp increases and decreases between 2013 to 2023 but remained within the range of 300 and 400 cases per 100,000 person-years during this time. Risperidone, haloperidol and olanzapine had lower IRs of use and remained relatively stable (**Figure 14**).

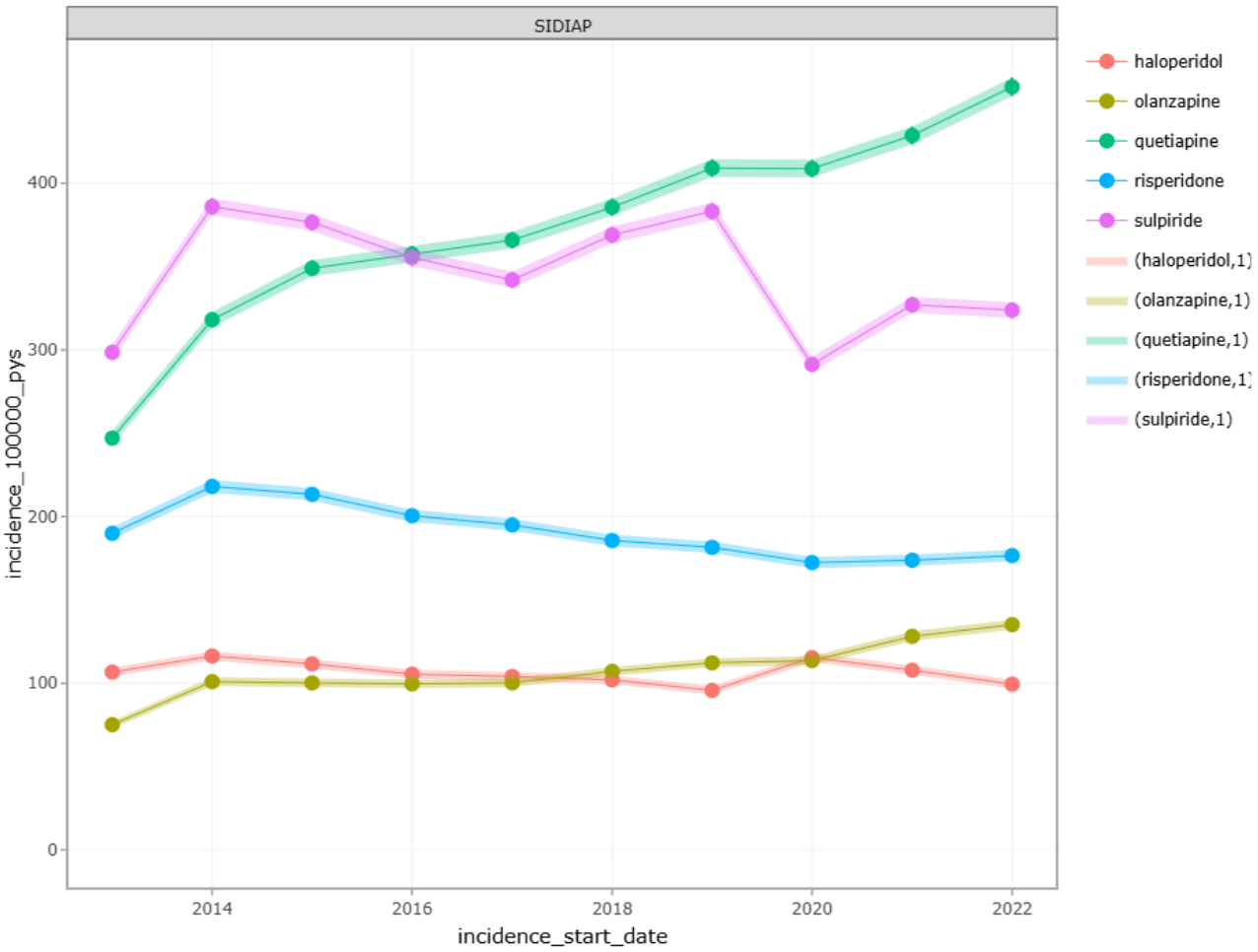


Figure 14. Incidence rates of use of the top 5 most common antipsychotics in SIDAP

IQVIA DA Germany

The most common antipsychotics in IQVIA DA Germany were quetiapine, pipamperone and risperidone, which all showed an increasing trend in use from 2013 to 2023 (from IR values between 28-52 cases per 100,000 person-years to values between 133-192 cases per 100,000 person-years, respectively). IRs for olanzapine and prothipendyl use remained relatively stable and saw similar numbers (**Figure 15**).

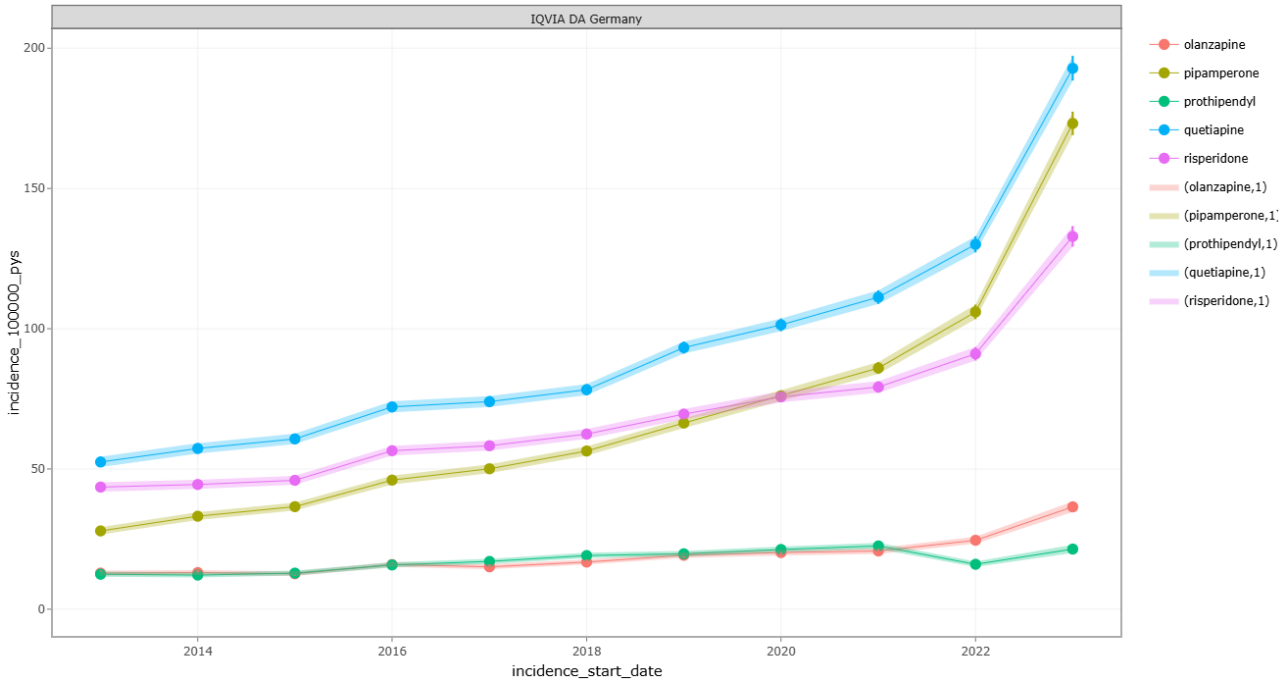


Figure 15. Incidence rates of use of the top 5 most common antipsychotics in IQVIA DA Germany.

IQVIA LPD Belgium

In the IQVIA LPD Belgium database, quetiapine and sulpiride had the highest IRs ([95% CI] cases per 100,000 person-years) throughout the study period compared to olanzapine, prothipendyl and risperidone. Quetiapine showed an increase from 2018 to 2023 (from 186 [172 - 201] to 326 [301 - 353]) whereas sulpiride showed a decreasing trend between 2015 to 2021 (from 340 [318 - 362] to 167 [154 - 181]), followed by a slight recovery towards 2023 (209 [189 - 231]). (**Figure 16**)

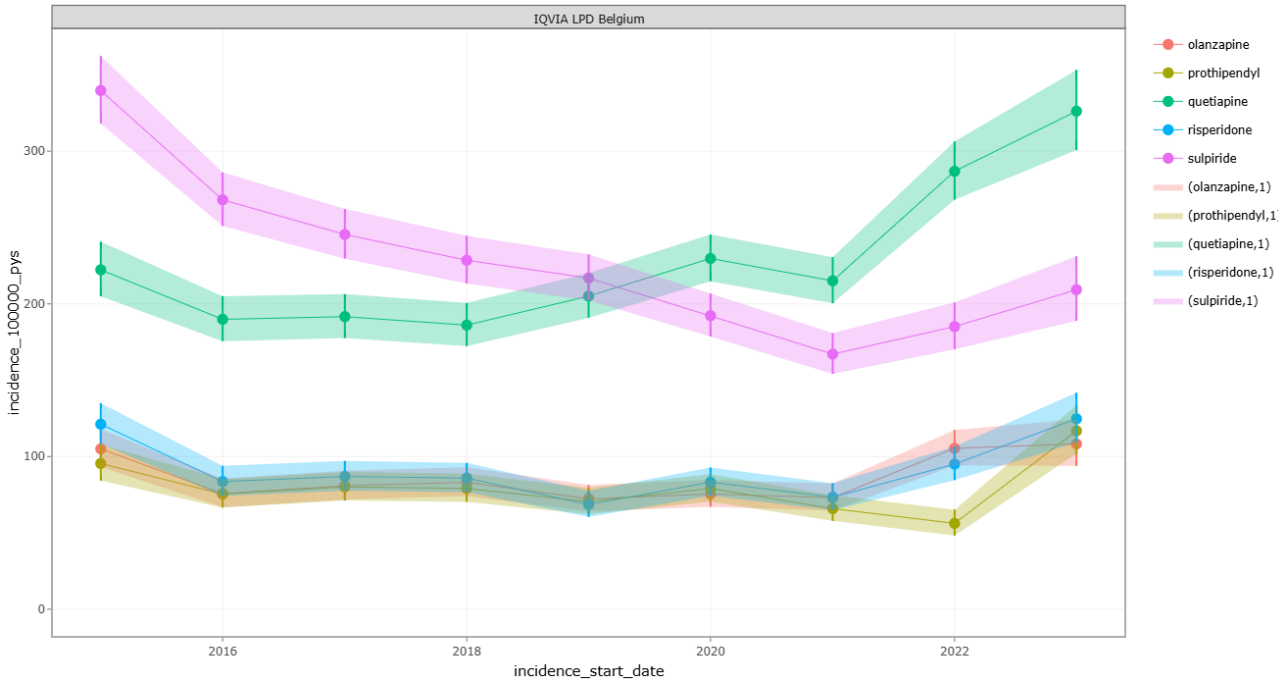


Figure 16. Incidence rates of use of the top 5 most common antipsychotics in IQVIA LPD Belgium

DK-DHR

In DK-DHR, quetiapine was the most commonly prescribed antipsychotic and had a high and stable IR of around 200 cases per 100,000 person-years. There was an increase in use of haloperidol from 2017 to 2023 (IR [95% CI] from 47 [51 - 55] to 103 [101 - 106] cases per 100,000 person-years), whereas incidence use of chlorprothixene decreased from 2013 to 2023 (IR [95% CI] from 75 [73 - 76] to 17 [16- 18] cases per 100,000 person-years). Use of risperidone and olanzapine remained stable (**Figure 17**).

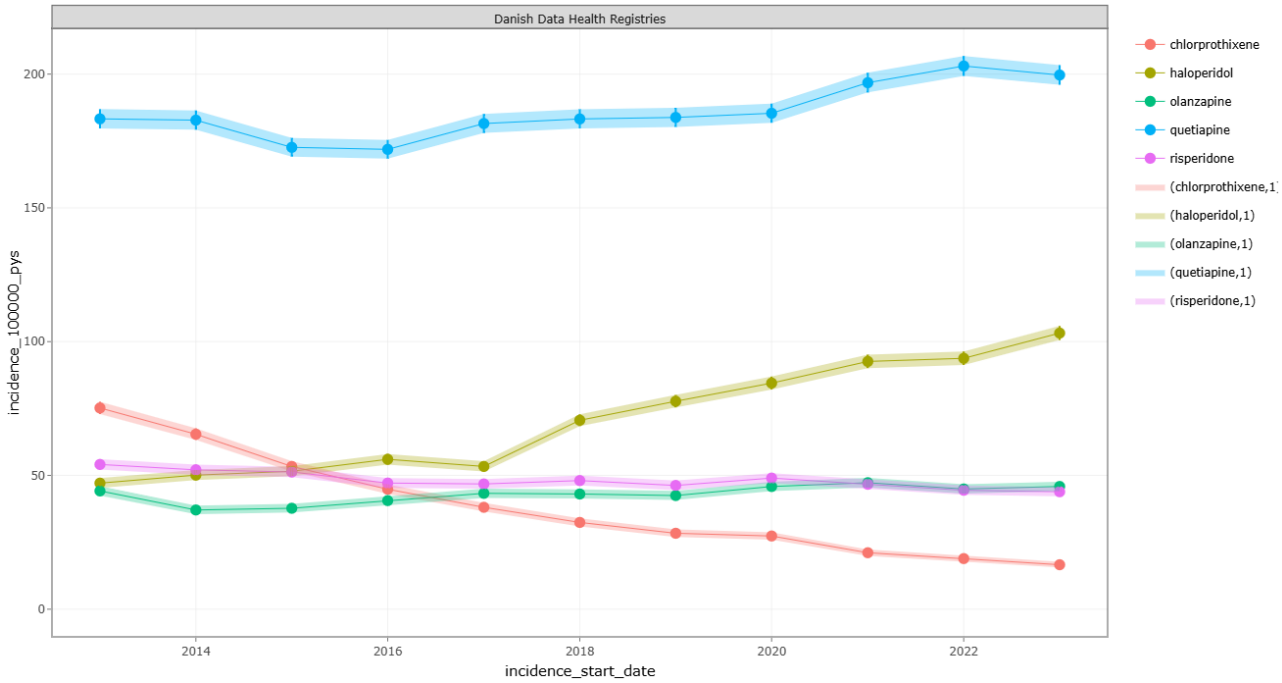


Figure 17. Incidence rates of use of the top 5 most common antipsychotics in DK-HR

NAJS

In NAJS, there was an outlier in sulpiride use in 2017 (IR [95% CI] cases per 100,000 person-years, 2016: 1,255 [1,243 - 1,268]; 2017: 4,040 [4,020 - 4,061]; 2018: 1,682 [1,669 - 1,695] and remained relatively stable after 2017. IR of use of antipsychotics of haloperidol, perphenazine, promazine and quetiapine were low and remained stable from 2016 to 2023 (**Figure 18**).

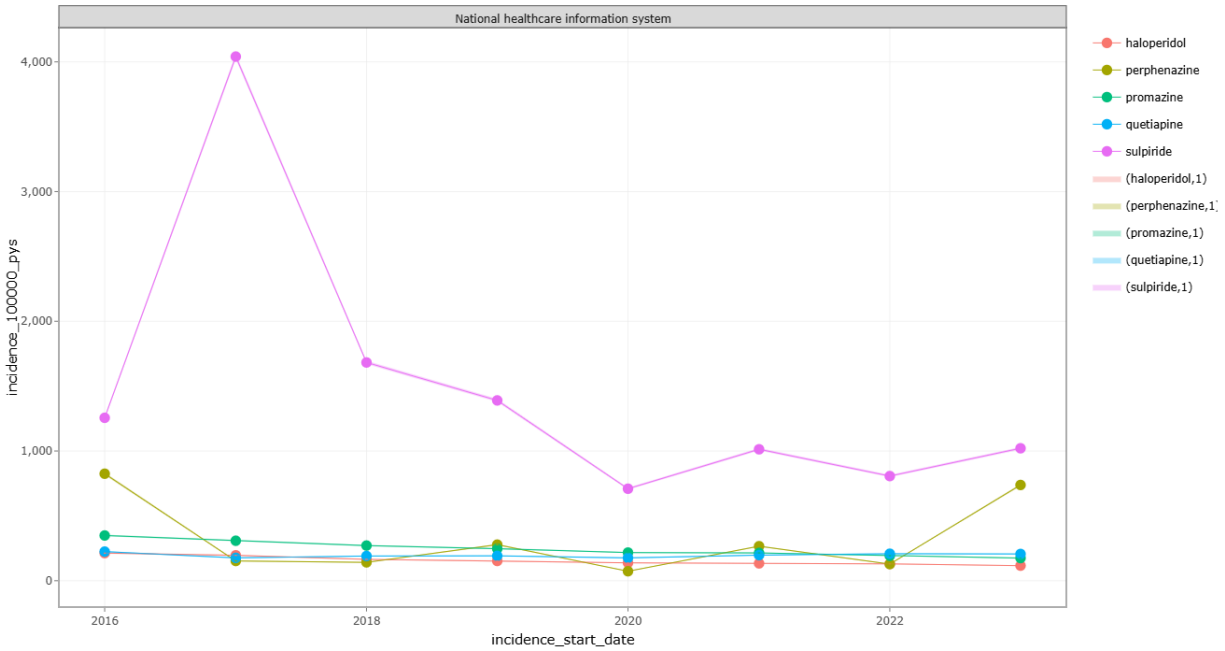


Figure 18. Incidence rates of use of the top 5 most common antipsychotics in NAJS.

12.2.3 Objective 3: Drug utilisation

Drug utilisation was described for the most common drug route per drug (when the drug route composed more than 80% of the drug use in the specific database). The top two most common drugs for each database are reported in **Table 13**. There were no missing data for any of the drugs reported. In the overall population, duration of antipsychotic use ranged from 3 days to 192 days based on drug type and database. There were differences in initial daily dose between those 0 to 64 compared to ≥ 65 years of age, for quetiapine in SIDIAP, IQVIA DA Germany, IQVIA LPD Belgium.

Table 13. Drug utilisation of top 2 antipsychotics for each database for most common drug route stratified by age and sex.

A) IPCI

		Cohort name									
		haloperidol oral					quetiapine oral				
		Age group									
		0 to 64	≥65	overall			0 to 64	≥65	overall		
		Sex									
Variable	Estimate name	overall	overall	overall	Female	Male	overall	overall	overall	Female	Male
Number records	N	3,560	16,102	19,662	10,195	9,467	13,788	3,716	17,504	9,806	7,698
Exposed time (days)	Median (Q25 - Q75)	30 (14 - 67)	25 (13 - 49)	26 (13 - 53)	28 (14 - 60)	22 (11 - 46)	43 (15 - 140)	35 (15 - 122)	42 (15 - 137)	42 (15 - 143)	41 (15 - 129)
Cumulative dose (mg)	Median (Q25 - Q75)	40.00 (18.00 - 120.00)	33.00 (14.00 - 55.72)	36.00 (14.33 - 63.31)	40.00 (15.00 - 72.00)	32.00 (13.91 - 60.00)	1,500.00 (375.00 - 6,000.00)	1,075.00 (375.00 - 4,500.00)	1,500.00 (375.00 - 5,625.00)	1,312.50 (375.00 - 5,600.00)	1,500.00 (375.00 - 5,625.00)
Initial daily dose (mg)	Median (Q25 - Q75)	1.33 (1.00 - 2.50)	1.00 (0.67 - 2.00)	1.00 (0.67 - 2.00)	1.00 (0.67 - 2.00)	1.00 (0.67 - 2.00)	25.00 (25.00 - 50.00)	25.00 (12.50 - 35.71)	25.00 (25.00 - 50.00)	25.00 (25.00 - 50.00)	25.00 (25.00 - 50.00)

B) SIDIAP

		Cohort name									
		quetiapine oral					sulpiride oral				
		Age group									
		0 to 64	≥65	overall			0 to 64	≥65	overall		
		Sex									
Variable	Estimate name	overall	overall	overall	Female	Male	overall	overall	overall	Female	Male
Number records	N	84,078	142,080	226,158	130,058	96,100	124,500	73,362	197,862	133,182	64,680
Exposed time (days)	Median (Q25 - Q75)	181 (61 - 477)	206 (61 - 641)	192 (61 - 579)	211 (61 - 630)	181 (61 - 513)	10 (6 - 16)	11 (7 - 30)	11 (6 - 16)	11 (6 - 16)	11 (6 - 16)
Cumulative dose (mg)	Median (Q25 - Q75)	8,375.00 (2,100.00 - 32,925.00)	7,629.04 (1,500.00 - 31,290.22)	7,904.92 (1,675.00 - 31,804.93)	8,225.00 (1,700.00 - 33,247.40)	7,525.00 (1,625.00 - 29,855.17)	1,500.00 (750.00 - 1,800.00)	1,500.00 (750.00 - 2,800.00)	1,500.00 (750.00 - 2,100.00)	1,500.00 (750.00 - 2,150.00)	1,500.00 (750.00 - 2,100.00)
Initial daily dose (mg)	Median (Q25 - Q75)	37.50 (24.59 - 74.78)	24.76 (24.07 - 48.00)	24.86 (24.22 - 49.55)	24.86 (24.19 - 49.24)	24.91 (24.29 - 49.81)	131.25 (112.50 - 136.36)	128.57 (93.75 - 136.36)	131.25 (98.78 - 136.36)	131.25 (98.36 - 136.36)	131.25 (99.58 - 136.36)

C) IQVIA DA Germany

		Cohort name									
		quetiapine oral					risperidone oral				
		Age group									
		0 to 64	≥65	overall			0 to 64	≥65	overall		
		Sex									
Variable	Estimate name	overall	overall	overall	Female	Male	overall	overall	overall	Female	Male
Number records	N	37,356	30,708	68,064	37,894	30,120	14,543	36,318	50,861	27,958	22,847
Exposed time (Days)	Median (Q25 - Q75)	100.00 (50.00 - 166.00)	100.00 (50.00 - 212.00)	100.00 (50.00 - 191.00)	100.00 (50.00 - 194.00)	100.00 (50.00 - 187.00)	50.00 (50.00 - 126.00)	68.00 (50.00 - 145.00)	67.00 (50.00 - 139.00)	67.00 (50.00 - 146.00)	61.00 (50.00 - 130.00)
Cumulative dose (mg)	Median (Q25 - Q75)	5,000.00 (2,500.00 - 15,000.00)	5,000.00 (2,500.00 - 12,500.00)	5,000.00 (2,500.00 - 13,750.00)	5,000.00 (2,500.00 - 12,500.00)	5,000.00 (2,500.00 - 15,000.00)	100.00 (50.00 - 250.00)	73.00 (28.00 - 150.00)	100.00 (40.00 - 200.00)	87.25 (37.50 - 200.00)	100.00 (50.00 - 200.00)
Initial daily dose (mg)	Median (Q25 - Q75)	50.00 (25.00 - 100.00)	25.00 (25.00 - 50.00)	25.00 (25.00 - 50.00)	25.00 (25.00 - 50.00)	25.00 (25.00 - 73.53)	1.00 (1.00 - 2.00)	1.00 (0.50 - 1.00)	1.00 (0.50 - 1.25)	1.00 (0.50 - 1.00)	1.00 (0.50 - 2.00)

D) IQVIA LPD Belgium

		Cohort name									
		quetiapine oral					sulpiride oral				
		Age group									
		0 to 64	≥65	overall			0 to 64	≥65	overall		
		Sex									
Variable	Estimate name	overall	overall	overall	Female	Male	overall	overall	overall	Female	Male
Number records	N	4,275	2,388	6,663	3,677	2,986	4,753	2,059	6,812	4,456	2,356
Exposed time (Days)	Median (Q25 - Q75)	60.00 (30.00 - 120.00)	65.00 (30.00 - 120.25)	60.00 (30.00 - 120.00)	60.00 (30.00 - 120.00)	63.50 (30.00 - 122.00)	24.00 (12.00 - 48.00)	24.00 (12.00 - 48.00)	24.00 (12.00 - 48.00)	24.00 (12.00 - 48.00)	24.00 (12.00 - 48.00)
Cumulative dose (mg)	Median (Q25 - Q75)	4,500.00 (1,500.00 - 20,000.00)	3,000.00 (1,500.00 - 8,125.00)	3,000.00 (1,500.00 - 13,000.00)	3,000.00 (1,500.00 - 12,000.00)	3,250.00 (1,500.00 - 18,000.00)	7,200.00 (2,400.00 - 7,200.00)	7,200.00 (2,400.00 - 7,200.00)	7,200.00 (2,400.00 - 7,200.00)	7,200.00 (2,400.00 - 7,200.00)	7,200.00 (2,400.00 - 7,200.00)
Initial daily dose (mg)	Median (Q25 - Q75)	75.00 (25.00 - 200.00)	50.00 (25.00 - 100.00)	50.00 (25.00 - 200.00)	50.00 (25.00 - 150.00)	50.00 (25.00 - 200.00)	150.00 (150.00 - 300.00)	150.00 (122.03 - 300.00)	150.00 (126.32 - 300.00)	150.00 (126.32 - 300.00)	200.00 (150.00 - 300.00)

E) DK-DHR: quetiapine oral drug route

		Cohort name				
		quetiapine oral				
		Age group				
		0 to 64	≥65	overall		
		Sex				
Variable	Estimate name	overall	overall	overall	Female	Male
Number subjects	N	90,225	23,680	113,905	60,000	53,905
Exposed time (day)	Median (Q25 - Q75)	6 (6 - 7)	6 (6 - 7)	6 (6 - 7)	6 (6 - 6)	6 (6 - 7)
Cumulative dose (mg)	Median (Q25 - Q75)	5,000.00 (2,500.00 - 7,500.00)	5,000.00 (2,500.00 - 7,500.00)	5,000.00 (2,500.00 - 7,500.00)	5,000.00 (2,500.00 - 6,000.00)	5,000.00 (2,500.00 - 7,500.00)
Initial daily dose (mg)	Median (Q25 - Q75)	833.33 (416.67 - 833.33)	833.33 (416.67 - 833.33)	833.33 (416.67 - 833.33)	833.33 (416.67 - 833.33)	833.33 (416.67 - 833.33)

F) DK-DHR: haloperidol routes

		Cohort name									
		haloperidol oral					haloperidol parenteral				
		Age group									
		0 to 64	≥65	overall			0 to 64	≥65	overall		
		Sex									
Variable	Estimate name	overall	overall	overall	Female	Male	overall	overall	overall	Female	Male
Number subjects	N	3,480	13,620	17,100	8,445	8,655	3,935	28,046	31,981	16,786	15,195
Exposed time (Day)	Median (Q25 - Q75)	54 (25 - 62)	25 (19 - 62)	25 (22 - 62)	25 (25 - 62)	25 (18 - 62)	3 (3 - 8)	3 (3 - 4)	3 (3 - 5)	3 (3 - 5)	3 (3 - 4)
Cumulative dose (mg)	Median (Q25 - Q75)	500.00 (275.67 - 1,000.00)	400.00 (200.00 - 800.00)	416.67 (200.00 - 904.10)	450.00 (200.00 - 967.74)	400.00 (200.00 - 873.39)	50.00 (32.87 - 100.00)	50.00 (25.00 - 75.00)	50.00 (25.00 - 75.00)	50.00 (25.00 - 75.00)	50.00 (25.00 - 75.00)
Initial daily dose (mg)	Median (Q25 - Q75)	16.00 (8.06 - 16.13)	16.00 (8.06 - 16.13)	16.00 (8.06 - 16.13)	16.00 (8.06 - 16.13)	16.00 (8.06 - 16.13)	16.67 (8.33 - 16.67)	16.67 (8.33 - 16.67)	16.67 (8.33 - 16.67)	16.67 (8.33 - 16.67)	16.67 (8.33 - 16.67)

12.2.4 Objective 4: Survival Analyses

This section reports the Kaplan-Meier curves of one-year survival of incident users of antipsychotics. These results are unadjusted and therefore only represents the trends of survival without accounting for any confounding. The percentages included in this section represent the proportion of users alive at the end of one year (i.e., the survival probability). In the shiny app (Survival – Formatted tab), cases where median survival is presented as NA meant one-year survival probability did not decrease to a value equal or below 50%.

12.2.4.1 Overall and age stratification

Figure 19 depicts one-year survival curves overall and stratified by age in IPCI, SIDIAP and DK-DHR.

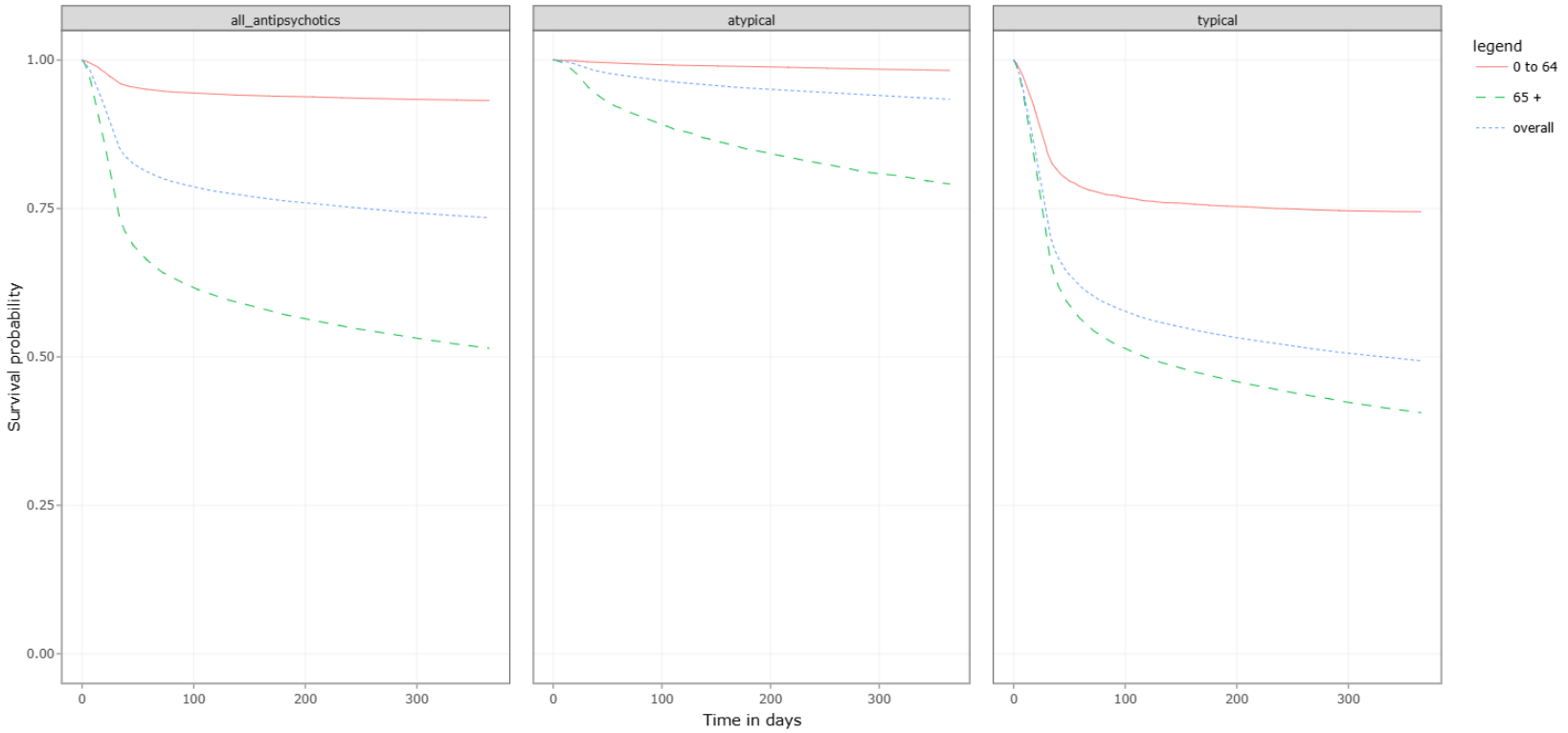
Across the databases IPCI, SIDIAP and DK-DHR, the typical antipsychotic cohort had lower survival probabilities compared to the atypical antipsychotic cohort. For IPCI, SIDIAP and DK-DHR, across all and the specific types of antipsychotics, those in the ≥65 age group showed lower probabilities of survival compared to the overall and the 0 to 64 age groups.

The survival percentages IPCI are as follows: in the 0 to 64 age group, all antipsychotics (93%), atypical antipsychotics (98%), typical antipsychotics (75%); in the ≥65 age group, all antipsychotics (51%), atypical antipsychotics (79%), typical antipsychotics (41%).

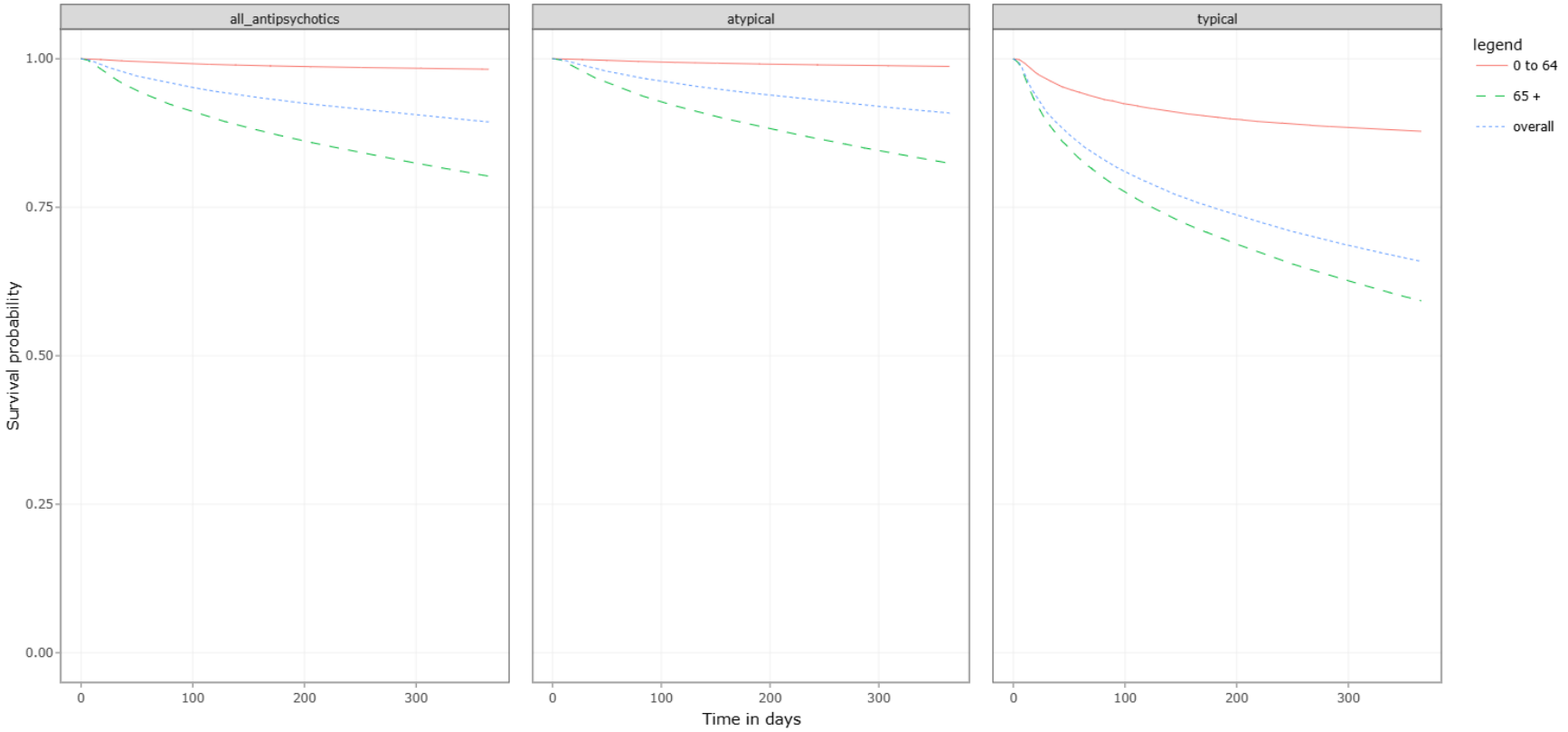
For SIDIAP: in the 0 to 64 age group, all antipsychotics (98%), atypical antipsychotics (99%), typical antipsychotics (88%); in the ≥65 age group, all antipsychotics (80%), atypical antipsychotics (83%), typical antipsychotics (59%).

DK-DHR had the largest age difference in survival, particularly among the typical cohort in the 0 to 64 age group, all antipsychotics (95%), atypical antipsychotics (98%), typical antipsychotics (83%); in the ≥65 age group, all antipsychotics (44%), atypical antipsychotics (67%), typical antipsychotics (20%). Among the 65 and older age group median survival for all antipsychotics use was 192 days (95% CI: 184, 201), and typical antipsychotics use was 16 days (95% CI: 16, 17).

A) IPCI


all_antipsychotics
atypical
typical
legend
0 to 64
65 +
overall
Survival probability
1.00
0.75
0.50
0.25
0.00
0
100
200
300
Time in days

B) SIDIAP


all_antipsychotics
atypical
typical
legend
0 to 64
65 +
overall
Survival probability
1.00
0.75
0.50
0.25
0.00
0
100
200
300
Time in days

C) DK-DHR

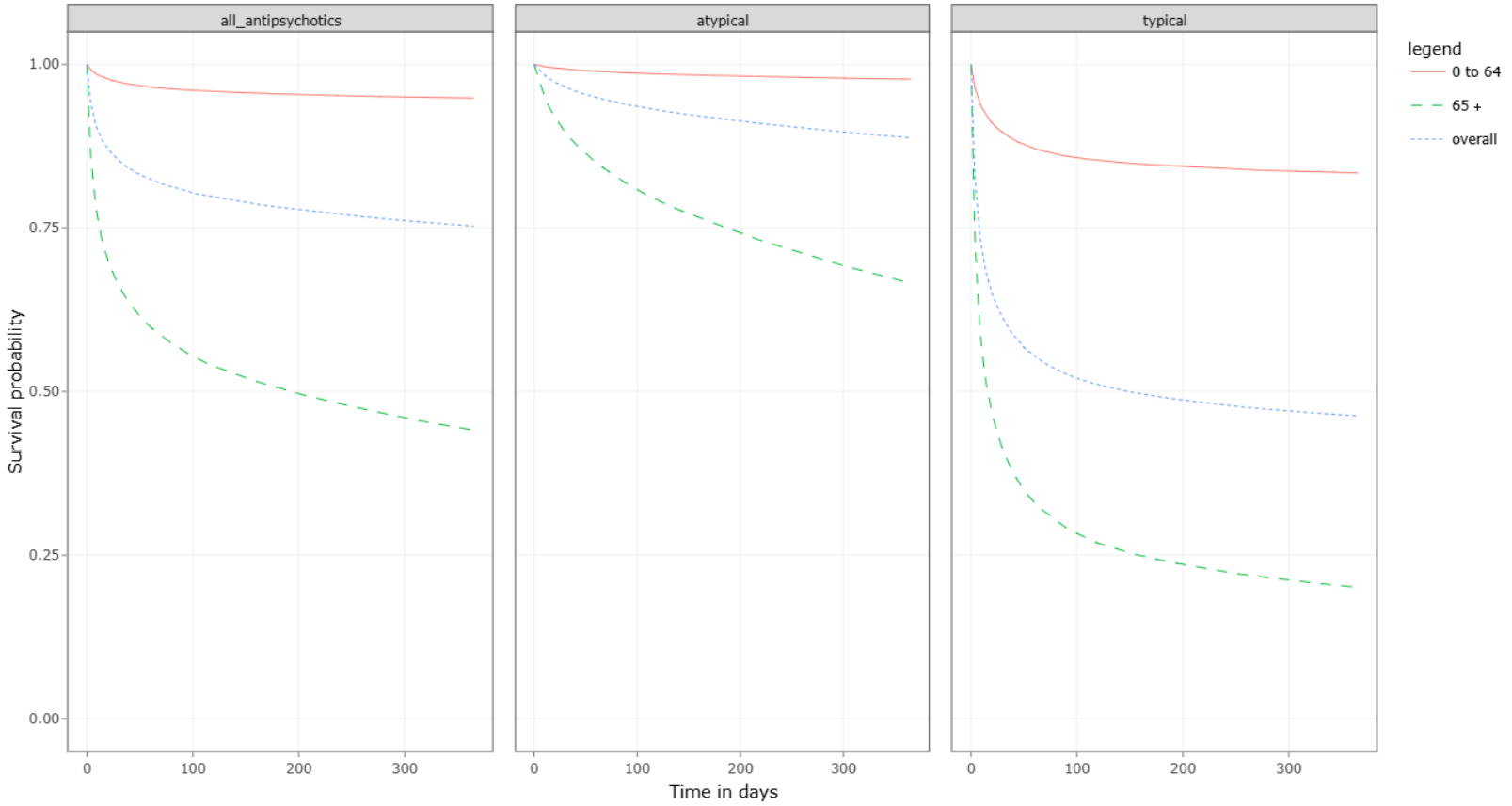
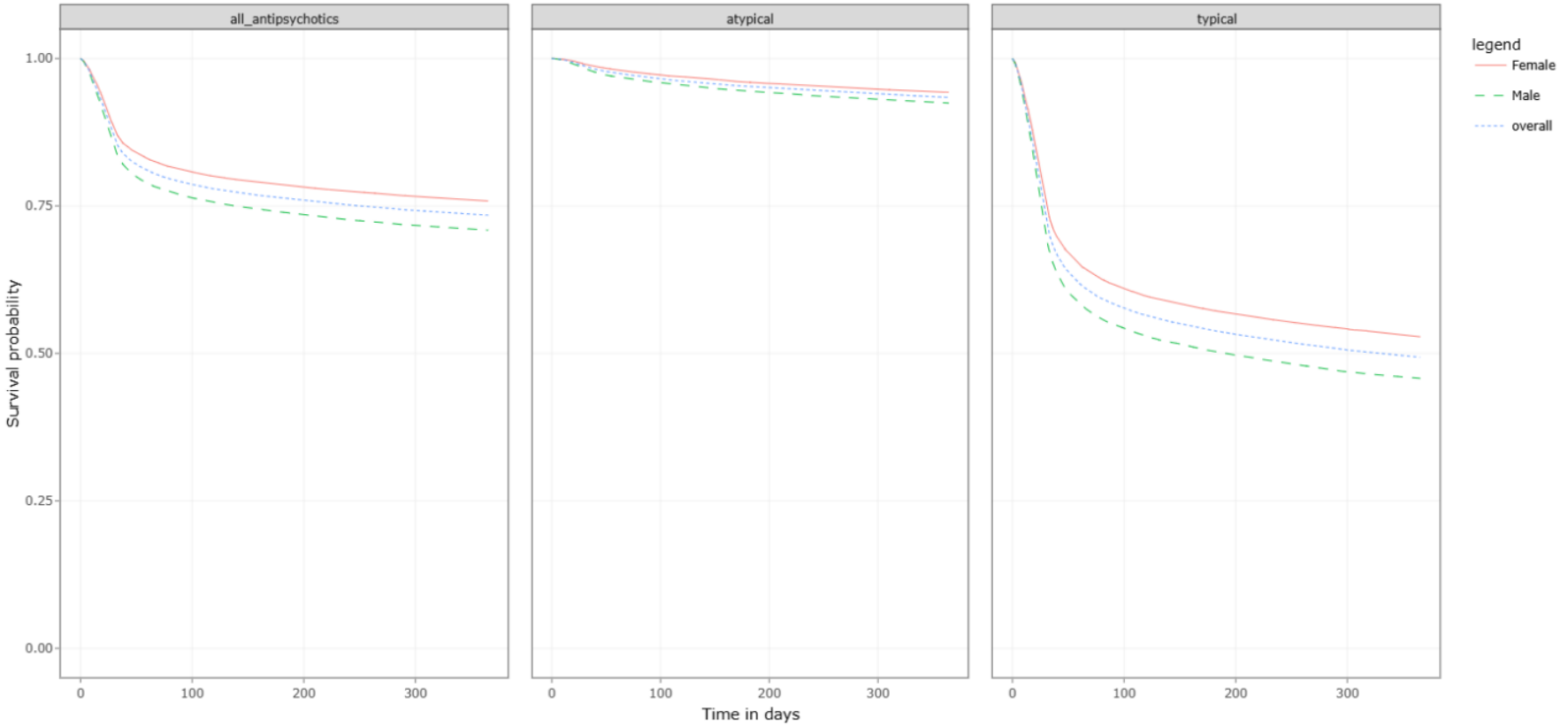


Figure 19. Kaplan-Meier curves illustrating the crude 1–year survival rates in all antipsychotics and typical and atypical for A) IPCI, B) SIDIAP and C) DK-DHR.

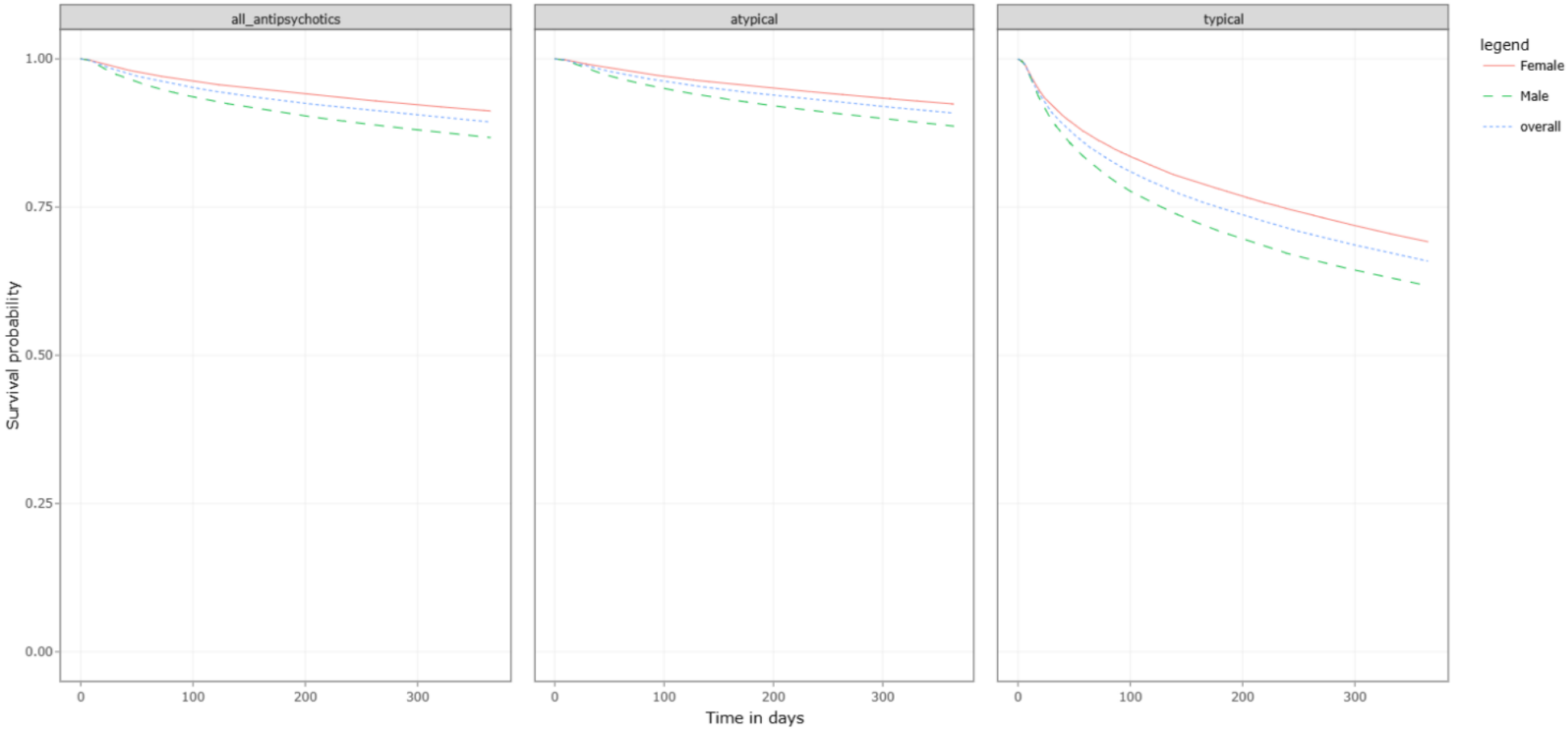
12.2.4.2 Sex stratification

There were no strong differences in one-year survival based on sex across the databases. Males had slightly lower probabilities of survival compared to females except for typical antipsychotics in DK-DHR, where the lines overlapped (**Figure 20**).

A) IPCI



B) SIDIAP


all_antipsychotics
atypical
typical
legend
Female
Male
overall
Survival probability
1.00
0.75
0.50
0.25
0.00
0
100
200
300
Time in days

C) DK-DHR

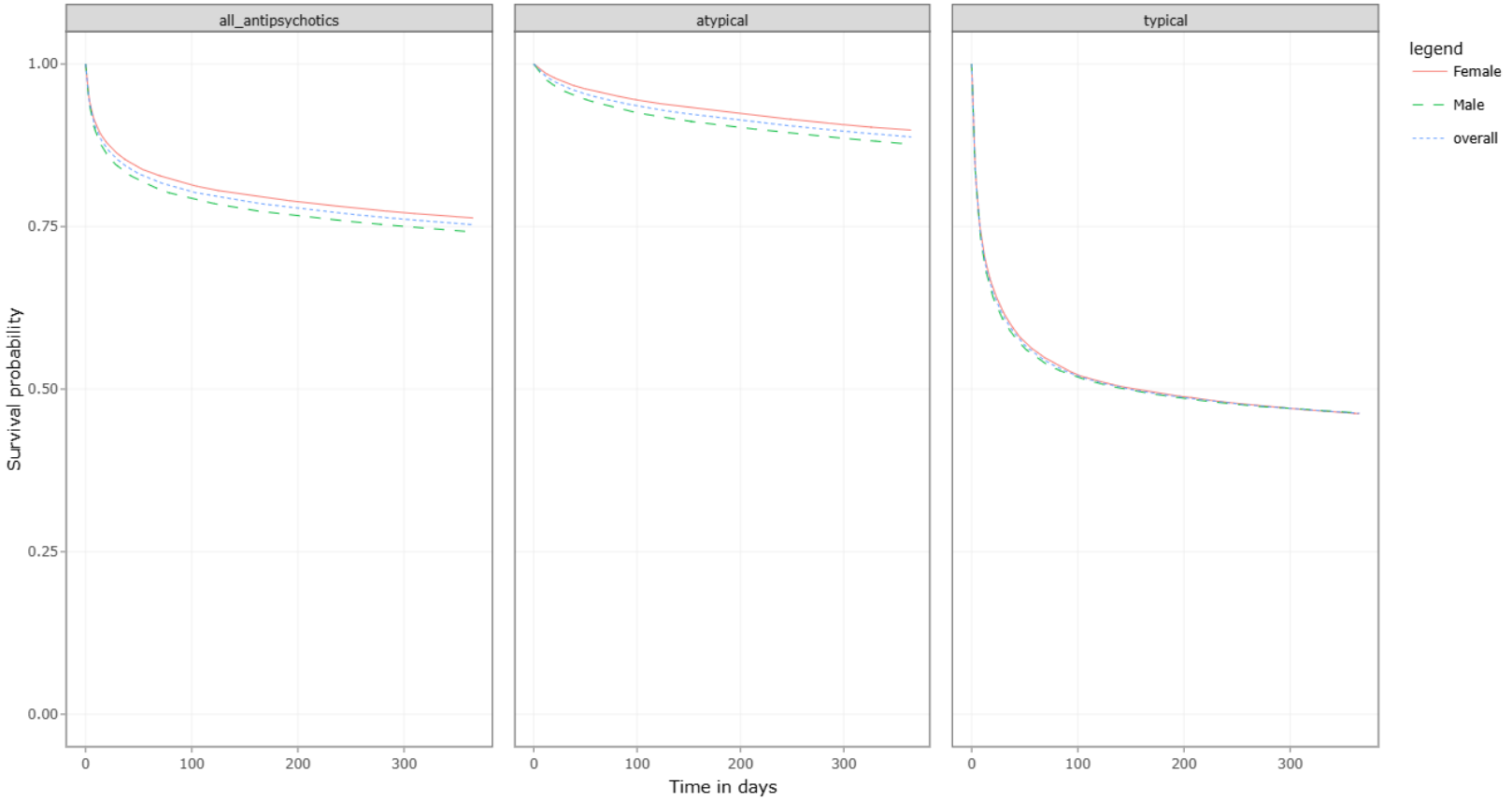


Figure 20. Kaplan-Meier curves illustrating the crude 1–year survival rates in all antipsychotics and typical and atypical stratified by sex for A) IPCI, B) SIDIAP and C) DK-DHR

12.2.4.3 Top 5 most common antipsychotics per database

For the top 5 antipsychotics for IPCI, the typical antipsychotic, haloperidol, had the lowest one-year survival (63% in the 0 to 64 age group, 39% in the ≥ 65 age group), with a median survival in the ≥ 65 age group of 100 (95% CI: 91, 109-) days. For the other antipsychotics, the proportion who survived for one-year was greater than half, aripiprazole (0 to 64 age group: 99%, ≥ 65 age group: 93%), olanzapine (0 to 64 age group: 96%, ≥ 65 age group: 80%), quetiapine 0 to 64 age group: 99%, ≥ 65 age group: 84%) and risperidone (0 to 64 age group: 99%, ≥ 65 age group: 73%)(**Figure 21**).

Similarly, for the top 5 antipsychotics in the SIDIAP database, the typical antipsychotic haloperidol had the lowest one-year survival (0 to 64 age group: 81%, ≥ 65 age group: 59%). For the other antipsychotics, the proportion who survived for one-year was greater, olanzapine (0 to 64 age group: 98%, ≥ 65 age group: 80%), quetiapine (0 to 64 age group: 97%, ≥ 65 age group: 77%), risperidone (0 to 64 age group: 98%, ≥ 65 age group: 71%) and sulpiride (0 to 64 age group: 100%, ≥ 65 age group: 97%)(**Figure 22**).

In DK-DHR, haloperidol had the lowest one-year survival among the other top 5 antipsychotics and compared to the other databases, among the 0 to 64 age group 29% survived past the one-year and a median survival of 39 days (95% CI: 36, 42), among the ≥ 65 age group, survival percentage was 14% and median survival was 12 days (95 % CI: 12,13) . Other antipsychotics had higher survival percentages, chlorprothixene (0 to 64 age group: 99% , ≥ 65 age group: 88%), olanzapine (0 to 64 age group: 90%, ≥ 65 age group: 50%), quetiapine (0 to 64 age group: 99%, ≥ 65 age group: 78%) and risperidone (0 to 64 age group: 98%, ≥ 65 age group: 62%) (**Figure 23**).

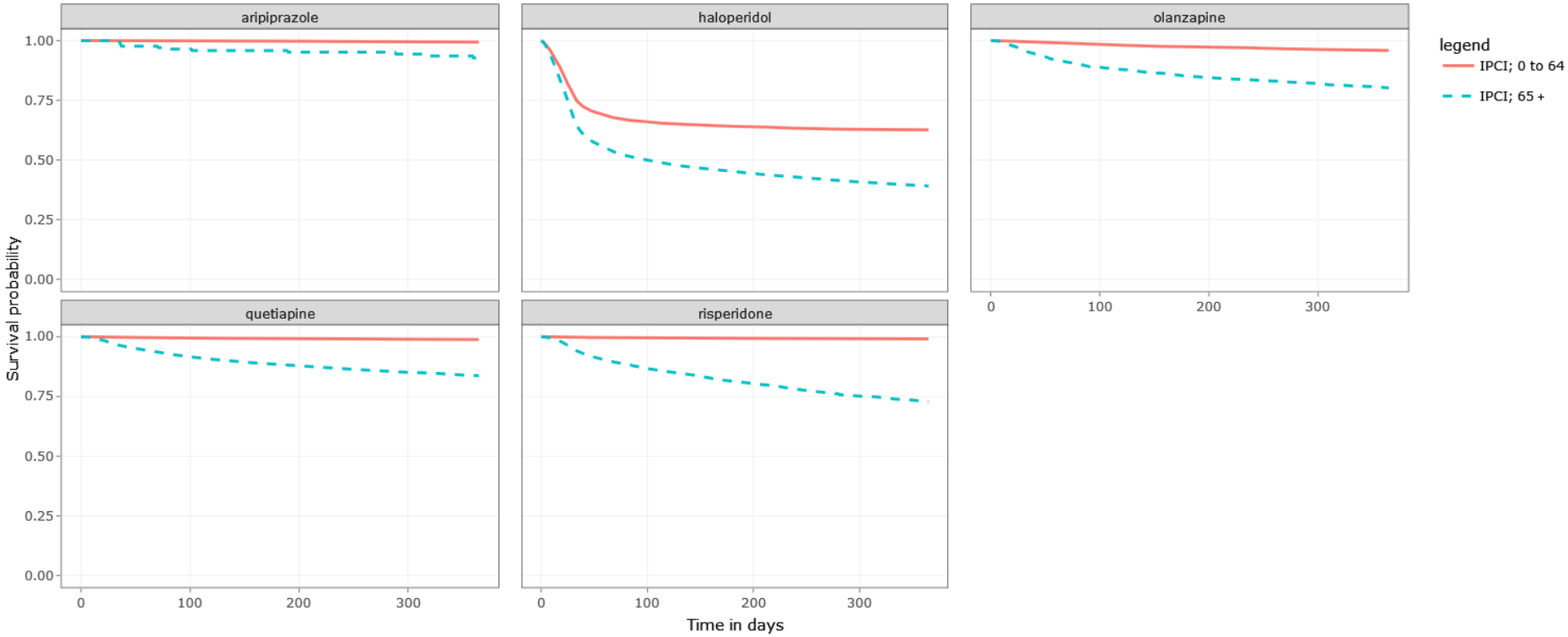


Figure 21. Kaplan-Meier curves illustrating the crude 1–year survival rates in the top 5 most common antipsychotics in IPCI stratified by age

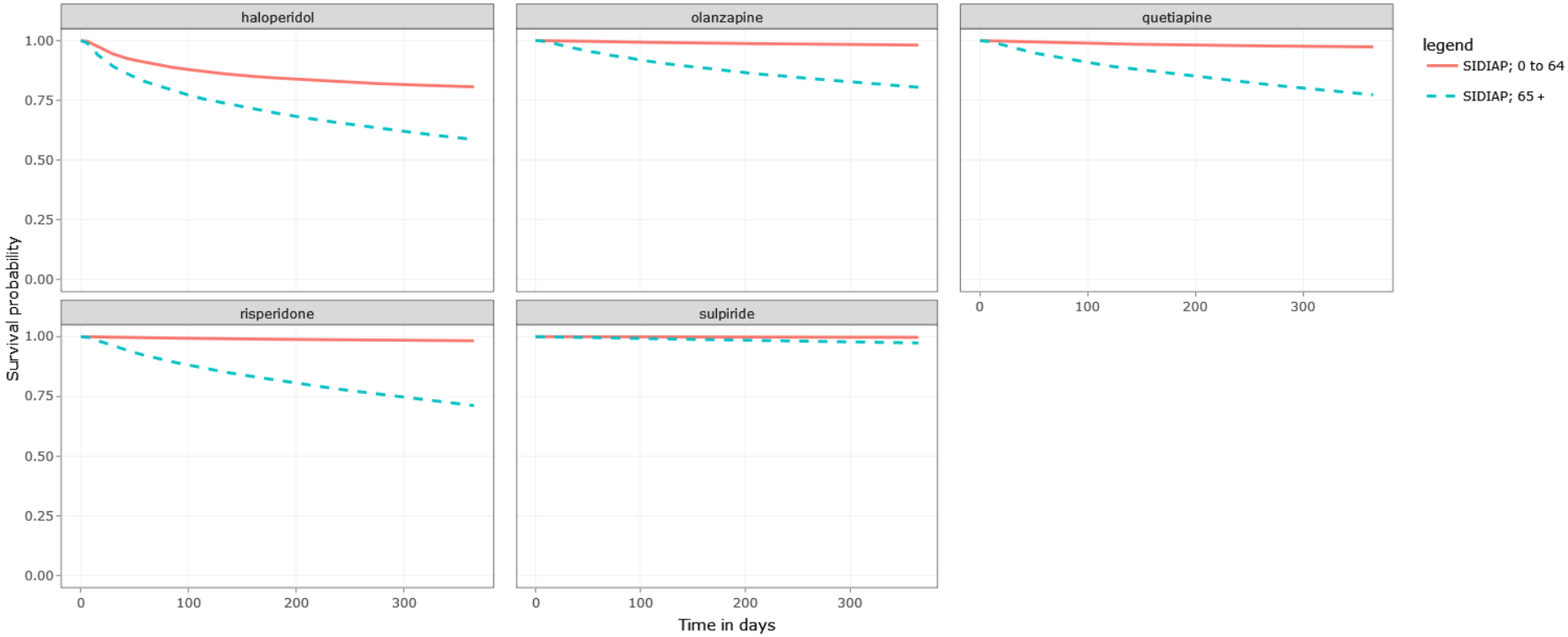


Figure 22. Kaplan-Meier curves illustrating the crude 1–year survival rates in the top 5 most common antipsychotics in SIDIAP stratified by age

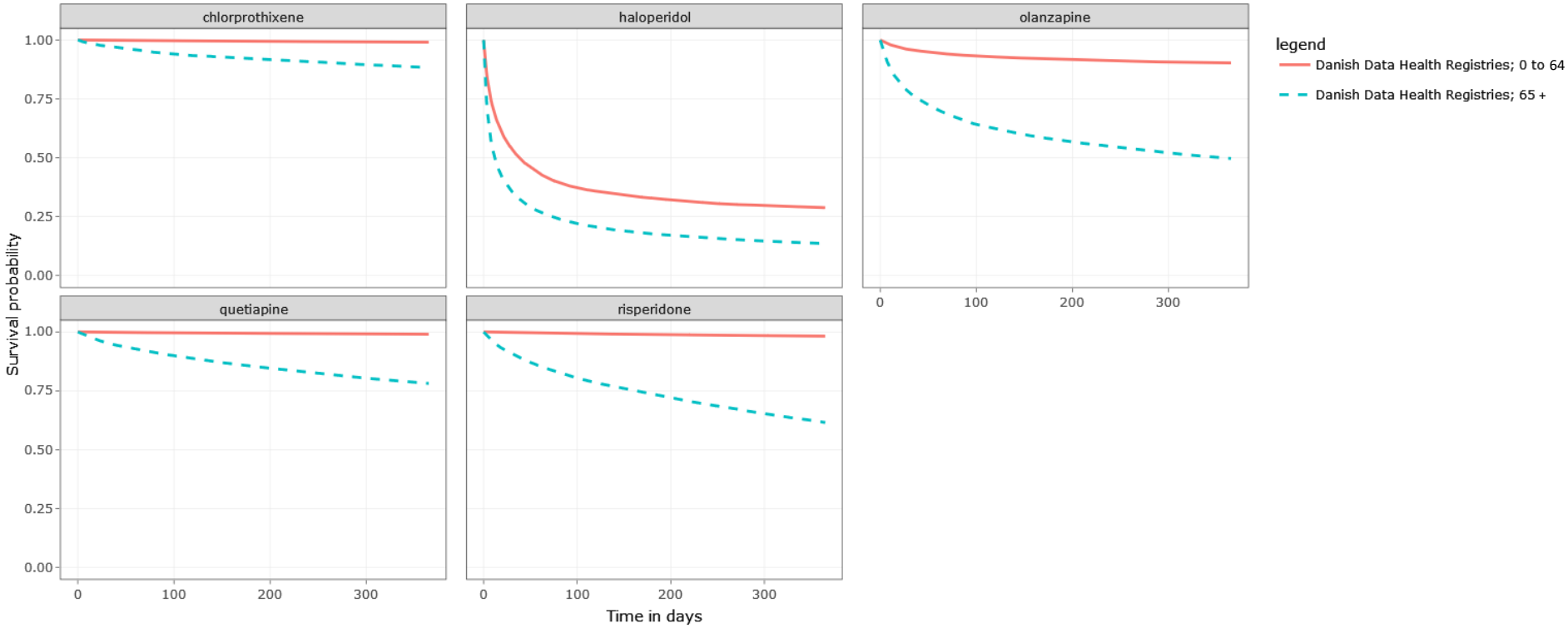


Figure 23. Kaplan-Meier curves illustrating the crude 1–year survival rates in the top 5 most common antipsychotics in DK-DHR stratified by age

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

Our study aimed to describe the antipsychotic usage among new users of antipsychotics in the general population, with special interest on older adults, of six European databases from Spain (SIDIAP), Netherlands (IPCI), Denmark (DK-DHR), Germany (IQVIA DA Germany), Belgium (IQVIA LPD Belgium) and Croatia (NAJS).

When characterising new users of antipsychotics, we observed higher counts for atypical antipsychotics users than typical antipsychotic users in all databases. The most prescribed atypical antipsychotics across databases were quetiapine, risperidone, sulpiride and olanzapine; whilst the most prescribed typical antipsychotic was haloperidol. The overall median age of participants ranged between 53 and 68 years old across the six data sources. In IPCI, SIDIAP and DK-DHR, differences in age between new users of typical and atypical antipsychotic were wide. Typical antipsychotic users were older on average with median ages between 70 and 80 years of age, whereas atypical users were generally younger, where median age ranged between 40 and 60 years of age. In NAJS, median age for typical antipsychotic users was 66 years old while for atypical users median age was younger at 58 years old. IQVIA DA Germany and IQVIA LPD Belgium had similar median ages between types of antipsychotics. Across all data sources, a larger proportion of typical antipsychotic users had pre-existing comorbidities, with the most common being hypertension (ranged 21-58%), type 2 diabetes (ranged 10-20%) and obesity (ranged 6-34%). The most common indications for antipsychotic initiation were depression, insomnia and other sleep disorders, and dementia. The distribution of indications varied for typical and atypical antipsychotic new users across data sources. For instance, dementia was an indication more frequent in typical antipsychotics users than atypical in SIDIAP (28% vs 12%), IPCI (17% vs 7%) and DK-DHR (12% vs 8%, respectively).

General trends for annual IRs from 2013 to 2023 of overall antipsychotics use was relatively stable for IPCI, SIDIAP and DK-DHR, with some upward trends for IQVIA DA Germany and IQVIA LPD Belgium. In IQVIA LPD Belgium, SIDIAP and DK-DHR, IRs of atypical antipsychotic use were considerably higher than typical antipsychotic use during the study period. Notably, the oldest age group of ≥85-year-olds had the highest IRs across all databases and types of antipsychotic use. In IPCI and DK-DHR, IRs of typical antipsychotic use among the ≥85 age group was higher than atypical antipsychotics during the entire study period, with a pronounced increasing trend in the DK-DHR population. Conversely, SIDIAP and IQVIA LPD Belgium had higher IRs for atypical antipsychotic use in the same age group (i.e., ≥85-year-olds), with an increasing trend in the SIDIAP population. There was an increasing trend of antipsychotic use among both atypical and typical antipsychotics in the oldest age group in IQVIA DA Germany. The age group of 75 to 84 years old had

the seconds highest IRs with trends similar to those of the ≥85-year-olds age group. The 65 to 74 age and the <65 years old age groups had relatively low and stable IRs, with the lowest IRs amongst the <65 years old age group. There were no sex differences in IRs for most databases except SIDIAP and IQVIA LPD Belgium which had higher IRs for females in the atypical antipsychotic populations. In NAJS, apart from an outlier in 2017, IRs were relatively stable with higher antipsychotic use among ≥85 age group.

One-year Kaplan Meier survival curves were estimated for IPCI, SIDIAP and DK-DHR. Survival probabilities were lowest among the typical antipsychotic users compared to atypical antipsychotics across all three databases. Among all three databases and different types of antipsychotics, those aged 65 and older had lower one-year survival. There were no clear sex differences in survival probabilities. When examining the most common antipsychotics for each database, haloperidol consistently had the lowest one-year survival: in particular, survival for haloperidol was low in DK-DHR with a 16% surviving rate at one-year and a median survival of 14 days.

14.2 Limitations of the research methods

The study was conducted in routinely collected health care databases and so data quality issues must be considered. In particular, a recording of a prescription or dispensation does not mean that the patient actually took the drug. In addition, assumptions were made around the duration of drug use: the methodology to calculate initial and cumulative dose in the OMOP-CDM relies on the data availability of the drug strength, which is not always captured. Additionally, the strength can be stored differently depending on the dose form (e.g., number of tablets for pills or number of millilitres for liquids), and the record of different units for the same ingredient produces results separately for each unit. Different levels of granularity may also impact the calculation of dose and duration. However, the methodology developed to calculate dose and duration in OMOP-CDM was applicable to >85% of drugs records and its testing included IPCI and both IQVIA databases.(5)

The actual reason for prescription of the drug (i.e., the indication) was not recorded in any of the databases. We have assessed indication via a proxy based on pre-defined conditions recorded on the date of therapy initiation. In addition, recordings of indications were not mutually exclusive, with the potential of patients having more than one indication. However, not all recordings of indications were captured in the study, which is suggested by the low frequencies of indications in DK-DHR, IPCI and NAJS, where the sum of the different indication only would cover around half the population (disregarding indications were not mutually exclusive). In addition, the completeness of recordings of co-morbidities used for patient characterisation varied across databases. For example, even upon utilising a broader definition of chronic kidney disease that included renal impairment, frequencies were lower than in the general population (global prevalence of 10%)(6) in IQVIA DA Germany, IQVIA LPD Belgium, DK-DHR, and NAJS.

In addition, we captured antipsychotics used at primary care settings, but antipsychotics may be prescribed for acute hospital settings, which are not captured in the databases of the study. Similarly, the databases of the study did not contain prescriptions at nursing home settings unless such prescriptions were given by a GP.

Database-specific limitations:

In IQVIA LPD Belgium and IQVIA DA Germany, the observation period of the patients in these databases was calculated based on the last visit, observation or interaction of the patient with the health care system. This methodology impacts the individuals considered “at risk” for the different drugs of interest of the study (i.e., the individuals included in the denominator populations) during the latest months of available data from the latest data lock, where healthy and/or non-frequent users of the health care system will not be considered active. Consequently, the denominators used to calculate the incident use of drugs in the last

year of the observation period might present an artefactual decrease whilst the incident users would have remained constant, incrementing the incidence ratios. Thus, the presence of these artefacts may had skewed the 2023 estimates in both IQVIA databases.

In NAJS, the number of recorded patients in the database before 2015 was low, leading to unstable estimates for the denominator population of incidence rates during this period. To obtain accurate estimates, we only reported incidence rates starting from 2016. In addition, NAJS did not contain detailed recordings of dose/duration, as was not included for the drug utilisation analyses.

Due to the limited availability of data from 3 databases, we could not produce estimates for Objective 4 in IQVIA LPD Belgium and IQVIA DA Germany, and for Objectives 3 and 4 for NAJS: IQVIA LPD Belgium, IQVIA DA Germany and NAJS databases did not have mortality records available and therefore they were excluded from the survival analyses.

DK-DHR presented drug records where drug exposure end date was incomplete and thus such records were removed. The impact of these invalid records in the whole database was less than 5% and in the overall users of antipsychotics was 1.6%, hence we considered the effect of eliminating them negligible.

14.3 Interpretation

Trends in increased atypical antipsychotic use in our study are consistent with worldwide prescribing trends. Across all six databases, more than half of antipsychotic prescriptions were for atypical antipsychotics. Similarly, in a study conducted by Hálfdánarson et al. across 16 countries in Europe, Asia, Oceania and North America using administrative databases in 2014, the majority of the prescriptions for all but one country were for atypical antipsychotics.(7) These results were also consistent in Australia hospital databases and UK primary care settings.(8,9) Previous studies reported quetiapine, risperidone and olanzapine as the most commonly prescribed antipsychotics: these three antipsychotics were commonly prescribed in most of the databases in our study.(7,9) Consistent with our findings, Marston et al. also found that haloperidol was the most commonly prescribed typical antipsychotic.(9)

Large proportions of off-label use of antipsychotics have been documented. In our study, across all antipsychotic use, the most frequent indications were for depression, insomnia and other sleep disorders, and dementia. Across all databases, less than 10% of the population had an indication for bipolar disorder or schizophrenia. In a review of 77 studies, Carton et al. estimated that 40-75% of all antipsychotic prescriptions were off-label, primarily for mood disorders, anxiety disorders, insomnia and agitation.(10) In the Marston et al. study conducted in the UK, more than half of antipsychotic users did not have a record of a psychotic or bipolar disorder; most common conditions were anxiety, depression and sleep disorders.(9) According to the European Sleep Research Society, guidelines from 2017 do not recommend antipsychotics for insomnia treatment due to insufficient evidence and the risk of side effects.(11) There are few guidelines for clinicians on depression management in Europe (12); as of June 2022, the UK's National Institute for Health and Care Excellence (NICE), listed treatment of depression as an off-label use of antipsychotics with recommendations for close monitoring of the patient's physical health.(13) The United States Food and Drug Administration (USFDA) has approved the use of aripiprazole, olanzapine, fluoxetine and slow-release quetiapine for adjunctive medication in the treatment of depressive disorders.(14) Quetiapine is the only atypical antipsychotics approved in Europe as an adjunctive treatment for depression.(14,15)

Among all databases and types of antipsychotics in our study, older adults had higher incidence rates for antipsychotic use. Marston et al. found that individuals aged 80 years and older were two times more likely to receive antipsychotics compared with those aged 40-49 years.(9) In our study, among those 85 and older, IPCI and DK-DHR had higher incidence rates of typical antipsychotics, specifically haloperidol.

Previous studies conducted in the UK reported almost one-third of people receiving haloperidol had a record of dementia.(9) In the 2017 European Medicines Agency (EMA) review of haloperidol, the drug received a licensed indication for treatment for persistent aggression and psychotic symptoms in patients with moderate to severe Alzheimer's and vascular dementia when there is a risk of harm to the patient or others, as well as for acute treatment of delirium.(16) The severity of disease among older patients taking haloperidol at end of life can contribute to the lower survival curves for the drug in both IPCI and DK-DHR in our study, where in DK-DHR the median survival was 14 days.

Currently risperidone and haloperidol are the only EU and UK approved drugs indicated for dementia, though many are taken off-label.(17) Given the increased initiation of antipsychotics among older adults and the high frequency of records of dementia found in our study, the safety risks should be considered. For example, Mok et al. recently reported that in people with dementia the use of antipsychotics compared to non-use increased risks of pneumonia, acute kidney injury, venous thromboembolism, stroke, fracture, myocardial infarction and heart failure.(18) The Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) considers inappropriate antipsychotic prescribing in: 1) behavioural and psychological symptoms of dementia (BPSD), unless symptoms are severe and other non-pharmacological treatments have failed (increased risk of stroke) and 2) for use as a hypnotic, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extrapyramidal side-effects, and falls), among other reasons.(19) Thus, the use and potential misuse of antipsychotic prescribing among older adults should be closely monitored.

14.4 Generalisability

The study comprised all individuals using antipsychotics of interest present in six databases from six different European countries in a primary care setting. While we consider the results representative for the study population in the respective regions, the results should not be generalised to other countries or databases but only reflect the situation in the specific region and setting covered by the respective database as documented by the differing patterns for some medicines.

15. CONCLUSION

Broadly, our study aimed to characterise antipsychotic use across six primary care databases in Spain, Belgium, Germany, Croatia, Denmark and Netherlands. We observed higher atypical antipsychotic initiation than typical initiation with the most common antipsychotics being quetiapine, sulpiride, risperidone and olanzapine. Compared to new users of atypical antipsychotics, new users of typical antipsychotics had higher proportions of comorbidities, with type 2 diabetes, obesity and hypertension being the most common.

Depression, insomnia and other sleep disorders, and dementia appeared to be the most common indications for both types of antipsychotics based upon our definition. Incident use of antipsychotics was higher in those over 85 years of age compared to other age groups for all databases, with an increasing trend among this age group in SIDIAP, IQVIA DA Germany and DK-DHR databases. Among the most prescribed antipsychotics, one-year survival was lower among those in the ≥65-year-old age group compared to the 0 to 64 age group. Survival was lowest among those taking the typical antipsychotic haloperidol in IPCI, SIDIAP and DK-DHR.

Taken together, our results suggest that off-label use of antipsychotics observed in the databases and countries studied is common

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17. ANNEXES

Appendix I: Concept List for Antipsychotic substances.

ATC Code	Substance Name	Typical/Atypical	Concept ID Ingredient
N05AL01	Sulpiride	Atypical	19136626
N05AH04	Quetiapine	Atypical	766814
N05AX08	Risperidone	Atypical	735979
N05AH03	Olanzapine	Atypical	785788
N05AD01	Haloperidol	Typical	766529
N05AX12	Aripiprazole	Atypical	757688
N05AD05	Pipamperone	Typical	19093225
N05AX07	Prothipendyl	Typical	19115044
N05AB04	Prochlorperazine	Typical	752061
N05AF03	Chlorprothixene	Typical	19095002
N05AA03	Promazine	Typical	19052903
N05AX13	Paliperidone	Atypical	703244
N05AF05	Zuclopenthixol	Typical	19010886
N05AH02	Clozapine	Atypical	800878
N05AG01	Fluspirilene	Typical	19056465
N05AL05	Amisulpride	Atypical	19057607
N05AB02	Fluphenazine	Typical	756018
N05AB03	Perphenazine	Typical	733008
N05AG02	Pimozide	Typical	745790
N05AE04	Ziprasidone	Atypical	712615