Study Report

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DARWIN EU® - Antipsychotic prescribing in people with dementia in Europe: a descriptive analysis of trends and patient characteristics

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CONTENTS

Study title	DARWIN EU® - Antipsychotic prescribing in people with dementia in Europe: a descriptive analysis of trends and patient characteristics
Study report version	V3.0
Date	06/11/2025
EU PAS number	EUPAS1000000382
Active substance	**Drug of interest** Common antipsychotics (ATC: N05A) Substances included: • Sulpiride • Quetiapine • Risperidone • Olanzapine • Haloperidol • Aripiprazole • Piamperone • 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 people with dementia (overall, vascular dementia, and Alzheimer's disease) with a first use of common antipsychotics in terms of age, gender, comorbidities, and indication 2. To measure trends in the incidence of first use of common antipsychotic prescribing among people with dementia (overall, vascular dementia, and Alzheimer's disease) overall, by

	typical/atypical grouping, and by the top 20 most commonly prescribed drug substances. Results were stratified by database, calendar year, age, and sex. 3. To characterise first time users of common antipsychotic drug therapy in people with dementia (overall, vascular dementia, and Alzheimer's disease) by drug substance (in terms of dose and duration). Results were stratified by drug route, age, and sex. 4. To measure overall survival in people with dementia (overall, vascular dementia, and Alzheimer's disease) with a first use of common antipsychotic drugs overall, for typical/atypical grouping, and for the top 20 most common drug substances.
Countries of study	Spain, Netherlands, Denmark, Germany, Belgium, Croatia
Authors	W. Wang M. Pineda-Moncusi

1. TITLE

DARWIN EU® - Antipsychotic prescribing in people with dementia in Europe: a descriptive analysis of trends and patient characteristics

2. 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 Anna Palomar Irene López Sánchez Agustina Giuliodori	SIDIAP
	Katia Verhamme	IPCI
	Claus Møldrup Elvira Bräuner Susanne Bruun	DK-DHR
	Dina Vojinovic Isabella Kaczmarczyk James Brash Gargi Jadhav Akram Mendez Hanne van Ballegooijen	IQVIA DA Germany, IQVIA LPD Belgium

	Pero Ivanko Marko Čavlina Antea Jezidžić Emanuel Brađašević Lucija Raič	NAJS

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

3. 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 31/12/2023

4. ABSTRACT

Title

DARWIN EU® - Antipsychotic prescribing in people with dementia 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 is to provide an overview of common antipsychotic prescribing in Europe among people with dementia, and to describe the characteristics of patients initiating antipsychotics. This may help to contextualize information contained in future antipsychotic periodic safety update reports.

Research question and objectives

1. To characterise people with dementia (overall, vascular dementia, and Alzheimer's disease) with first use of common antipsychotics in terms of age, gender, indication, and comorbidities.
2. To measure trends in the incidence of first use of common antipsychotic prescribing among people with dementia (overall, vascular dementia, and Alzheimer's disease) overall, by typical/atypical grouping, and by top 20 most common drug substances. Results were stratified by database, calendar year, age, and sex.
3. To characterise first time users of common antipsychotic drug therapy in people with dementia (overall, vascular dementia, and Alzheimer's disease) by drug substance (in terms of initial dose and duration). Results were stratified by drug route, age, and sex.
4. To measure overall survival in people with dementia (overall, vascular dementia, and Alzheimer's disease) with first use of common antipsychotics 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 a diagnosis of dementia up to first antipsychotic prescription (index date) and at least 365 days of prior

history before the day they became 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, a prior diagnosis of the condition of dementia, and no prior use of the respective antipsychotic drug/s.

Variables

Drugs of interest: Sulpiride, Quetiapine, Risperidone, Olanzapine, Haloperidol, Aripiprazole, Piamperone, 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 (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 antipsychotic use incidence rates [IR] per 100 person years were estimated overall, by typical/atypical grouping, and by the 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 schizophrenia, bipolar disorder, depression, and insomnia in the week/month or any time before antipsychotic initiation was used as a proxy for indication and was reported as proportions.

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

Survival analyses using Kaplan-Meier curves for 1 year mortality were 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 SIDIAP, IQVIA DA Germany, IQVIA LPD Belgium, DK-DHR, and NAJS, atypical antipsychotic initiation (ranged from 42% to 99% of the dementia population) was higher than typical antipsychotic initiation (ranged from 13% to 72% of the dementia population). In IPCI, typical antipsychotic initiation was higher than atypical antipsychotic initiation (typical: 78% of the dementia population vs

atypical: 42%). The most commonly prescribed antipsychotics in people with dementia across databases were the typical antipsychotic haloperidol, and atypical antipsychotics quetiapine and risperidone.

Proportions of the total dementia population taking any antipsychotics ranged between 17% (DK-DHR) and 78% (SIDIAP).

General patient characteristics, trends in IR, and crude survival curves were similar between all dementia patients, and the subtypes of vascular and Alzheimer's dementia.

Objective 1

In terms of dementia patient characteristics, median age ranged from 82 to 84 years across the databases, with a higher proportion of females in all data sources. Across all data sources, pre-existing comorbidities in people with dementia were consistent between atypical and typical antipsychotic users, with the most common being hypertension (ranged 33-85%), type 2 diabetes (ranged 18-31%), and obesity (ranged 4-40%). Among other potential indications observed in addition to dementia, the most common were depression, and insomnia and other sleep disorders; these were consistent between atypical and typical antipsychotic users across all databases.

Objective 2

Incidence of all antipsychotic use (IR [95% CI] per 100 person-years) remained relatively stable throughout the study period in IPCI (IR values ranged between 9 [8-10] and 11 [10-12] cases per 100 person-years), DK-DHR (3.6 [3.4-3.8] and 4.6 [4.4-4.8]), and IQVIA LPD Belgium (6.6 [5.5-7.9]). IRs were increasing in IQVIA DA Germany from 5 [4.8- 5.3] cases per 100 person-years in 2013 to 7.7 [7.5-8] in 2023 and increased in SIDIAP from 18 [17.7-18.6] in 2013 to 24 [23.6-24.9] in 2022. IRs in NAJS decreased from 33.1 [32.0 - 34.2] in 2016 to 16.8 [16.3 - 17.3] in 2023.

When stratifying by sex, men showed higher IRs in IPCI, DK-DHR, IQVIA LPD Belgium, and SIDIAP, whereas there were no observed sex differences in IQVIA DA Germany and NAJS.

The incidence of atypical antipsychotic use was higher than the typical use in all databases, except IPCI and NAJS. IRs were higher among the oldest age group of ≥85-year-olds of dementia patients for most databases, which was consistent when stratifying between atypical and typical antipsychotics. Most commonly prescribed atypical antipsychotics were risperidone and quetiapine, whilst the most commonly prescribed typical antipsychotic was haloperidol.

Objective 3

In the overall dementia population, duration of first antipsychotic use ranged from 3 days to 310 days based on drug type and database. There were no strong differences in initial daily dose between age groups or sex for the different drugs of interest.

Objective 4

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

The typical antipsychotic haloperidol had the lowest one-year crude survival in IPCI (60%), SIDIAP (67%), and DK-DHR (22% surviving past the one-year and a median survival of 17 days).

Conclusion

Our study aimed to characterise antipsychotic use among patients with dementia across six primary care databases in Europe. The proportion of patients with dementia taking antipsychotics ranged between 17% (DK-DHR) to 78% (SIDIAP). We observed atypical antipsychotic initiation of risperidone and quetiapine, and typical antipsychotic use of haloperidol as the most commonly prescribed antipsychotics. Patients with dementia taking antipsychotics had high prevalence of comorbidities, were more frequently female, and among other potential indications observed in addition to dementia, the most common were depression, insomnia and other sleep disorders.

Incident use of antipsychotics among patients diagnosed with dementia between the study period was higher in those over 85 years of age compared to other age groups for most databases, and typical antipsychotic rates were higher than atypical antipsychotic rates in IPCI and NAJS. Use in men was consistently higher than women for most databases. Among the most prescribed antipsychotics, one-year survival was high. Crude survival was lowest among those taking the typical antipsychotic haloperidol in IPCI, SIDIAP, and DK-DHR.

These results were consistent between subgroups of vascular and Alzheimer's dementia.

5. LIST OF ABBREVIATIONS

Acronyms/term	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 Utilization 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

6. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	19/12/2024	Table 5: Assessment window of Diagnosis of dementia	Time window for dementia as [-Inf,0]	Time 0 instead of time -1 to capture dementia diagnosis the same day as first antipsychotic use

7. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE (planned)	TIMELINES (actual)
Draft Study Protocol	08/10/2024	08/10/2024
Final Study Protocol	October 2024	29/11/2024
Creation of Analytical code	October 2024	27/11/2024
Execution of Analytical Code on the data	November 2024	04/12/2024
Draft Study Report	November 2024	10/12/2024
Final Study Report	Beginning of December 2024	17/02/2025

8. 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 is to provide an overview of common antipsychotic prescribing in Europe, and to describe the characteristics of patients initiating antipsychotics. This may help to contextualize information contained in future antipsychotic periodic safety update reports.

9. RESEARCH QUESTION AND OBJECTIVES

Table 1. Primary and secondary research questions and objective.

A. Objective 1.

Objective:	To characterise people with dementia (overall, vascular dementia, and Alzheimer's disease) with a first use of common antipsychotics in terms of age, gender, comorbidities, and 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 1/1/2013 and 31/12/2023 with 1 year of prior data availability, and no prior use of the respective antipsychotic drug/s, and a diagnosis for dementia prior to index date (date of first prescription). Based on the diagnosis for dementia, two subpopulations were created: vascular dementia and Alzheimer's dementia.
Exposure:	Common antipsychotics (Sulpiride, Quetiapine, Risperidone, Olanzapine, Haloperidol, Aripiprazole, Piamperone, 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, and comorbidities, and assessed the proportion of new users with a record of 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 among people with dementia overall, by typical/atypical grouping, and by the top 20 most commonly prescribed drug substances. Results were stratified by database, calendar year, age group (<65, 65-74, 75-84, ≥85 years), and sex.
Hypothesis:	Not applicable

Population *(mention key inclusion-exclusion criteria):*	New users of antipsychotics in the period between 1/1/2013 and 31/12/2023, with at least 1 year of data availability, diagnosed with dementia, and no prior use of the respective antipsychotic drug/s, were included for incidence rate calculations. Based on the diagnosis for dementia, two subpopulations were created: vascular dementia and Alzheimer's disease
Exposure:	Common antipsychotics (Sulpiride, Quetiapine, Risperidone, Olanzapine, Haloperidol, Aripiprazole, Piamperone, 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 in people with dementia by drug substance (in terms of dose and duration). Results were stratified by drug route, age, and sex.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	New users of antipsychotics in the period between 1/1/2013 and 31/12/2023 with at least 1 year of data availability, prior diagnosis of dementia, and no prior use of the respective antipsychotic drug/s, were included. Based on the diagnosis for dementia, two subpopulations were created: vascular dementia and Alzheimer's disease.
Exposure:	Common antipsychotics (Sulpiride, Quetiapine, Risperidone, Olanzapine, Haloperidol, Aripiprazole, Piamperone, 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 people with dementia with a first use of common antipsychotic overall, for typical/atypical grouping, and for the top 20 most common drug substances.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	New users of antipsychotics in the period between 1/1/2013 and 31/12/2023 (or latest date available, whichever comes first), with at least 1 year of data availability, prior diagnosis of dementia, and no prior use of the respective antipsychotic drug/s, were included. Based on the diagnosis for dementia, two subpopulations were created: vascular dementia and Alzheimer's disease.
Exposure:	Common antipsychotics (Sulpiride, Quetiapine, Risperidone, Olanzapine, Haloperidol, Aripiprazole, Piamperone, 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.

10. RESEARCH METHODS

10.1. 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 conducted to assess incidence rates of antipsychotic use.
3. A new users cohort analyses was conducted to describe patient level characterisation of antipsychotic use.
4. A new users cohort study was conducted 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

10.2. 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 OMOP 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 were chosen to reflect the broad prescription patterns for antipsychotics. 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 cover a wide geographic region of Europe.

Information on the 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	08/02/2025

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 anonymized patients' healthcare records for nearly six million people (approximately 80% of the Catalan population) registered in 287 primary care practices throughout Catalonia since 2005. It includes data collected by health professionals during routine visits in primary care, including anthropometric measurements, clinical diagnoses (International Classification of Diseases 10th revision ICD-10), laboratory tests, prescribed and dispensed drugs, hospital referrals, demographic, and lifestyle information. It was previously shown that SIDIAP population is highly representative of the entire Catalan region in terms of geographic, age, and sex distributions. The high quality of these data has been previously documented, and SIDIAP has been successfully applied to epidemiological studies of key exposures and outcomes. Quality checks to identify duplicate patient IDs are performed centrally at each SIDIAP database update. Checks for logical values and data harmonisation are performed. For biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed.

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 standardized 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 organizations about the provided care. Contributing GPs are encouraged to use this information for their internal quality evaluation. The IPCI database is registered on the European Medicines Agency (EMA) ENCePP resources database (http://www.encepp.eu).

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 birth to death, 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.

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 utilization studies.

IQVIA Longitudinal Patient Database Belgium [IQVIA 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 utilization studies.

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.

10.3. 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.

10.4. 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.

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, or 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.

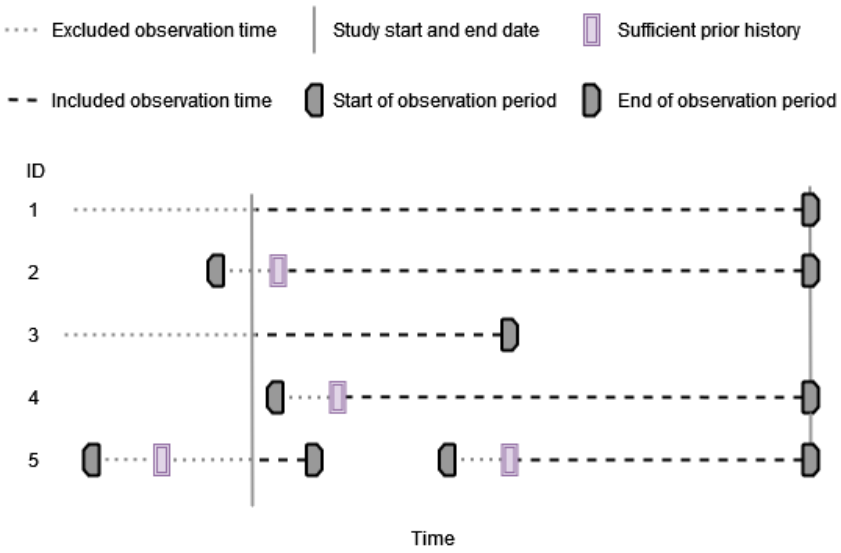


Figure 1. Included observation time for denominator population of incidence calculations.

Table 4. Operational definition of time 0 (index date) and other primary time anchors.

Study population names	Time Anchor Description	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

10.5. 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 and a diagnosis of dementia. Two subpopulations were made based on the specific diagnosis of vascular dementia and Alzheimer's dementia. Results from the overall dementia population was included in the report, whereas results from the two subpopulations are available in the Shiny App. The phenotype for dementia was constructed with the input of clinicians. Additional eligibility criteria were applied for the identification of new users:

- When overall, no prior use of any of the common antipsychotics was required. In other words, users with prior use of any of the antipsychotics of interest were 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	N/A	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
Diagnosis of dementia	Study participants were required to have a prior diagnosis for the indication of dementia to be included in the study	After	[-Inf, 0]	PC, SC	N/A	N/A	All adults within selected databases	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

10.6. Variables

10.6.1. 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 are 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 were included in report)

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

Complete data can be found in the Shiny App.

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	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

10.6.2. 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 are lost to follow-up, lack data availability, or the study period has 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

10.6.3. Other covariates, including confounders, effect modifiers, and other variables

Objective 1:

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

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

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

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

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

10.7. Study size

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

10.8. Statistical methods

10.8.1. 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)

10.8.2. 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 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.

10.8.3. Patient privacy protection

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

10.8.4. 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 is 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 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	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

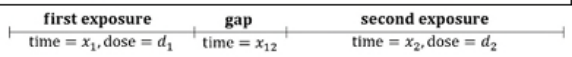


Figure 2. Gap era joint mode.

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"		$\max(d_1, d_2)$

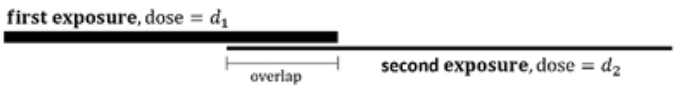


Figure 3. Gap era overlap mode.

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.

10.8.5. 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 schizophrenia, bipolar disorder, depression, insomnia, and insomnia and other sleep disorder, 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 were 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.

10.8.6. 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 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 enter the denominator population then contributed time at risk up to their first prescription (e.g., antipsychotic use) during the study period. Or if they do not have a drug exposure, they contributed time at risk, as described above in **Section 10.4** (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 is excluded from the analysis as they were seen to have had the outcome before the study start date.

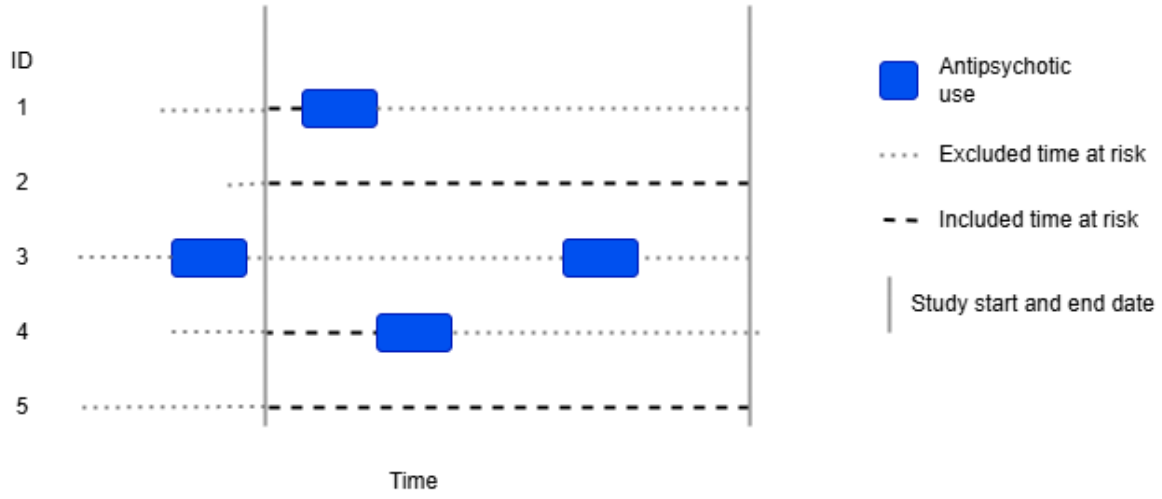


Figure 4. Illustration of incidence calculations.

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., schizophrenia, bipolar disorder, depression, and insomnia) 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 summarized providing the median [IQR] treatment duration. For databases, where duration cannot 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.

10.8.7. Methods to control for potential sources of bias

None.

10.8.8. Methods to deal with missing data

None.

10.8.9. Evidence synthesis

Results from analyses described in **Section 10.8** were presented separately for each database and no meta-analysis of results was conducted.

11. DATA MANAGEMENT

11.1. 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.

11.2. 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 EU® 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.

12. 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).

13. RESULTS

All results for each individual drug and database are available in the shiny app at:
EUPAS1000000382

The shiny 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

13.1. 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 with a prior diagnosis of dementia 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. Proportions of the total dementia population taking any antipsychotics ranged between 17% (DK-DHR) and 78% (SIDIAP).

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

Number of individuals	IPCI	IQVIA LPD Belgium	IQVIA DA Germany	NAJS	SIDIAP	DK-DHR
Total individuals with dementia captured within the study period with no prior use of antipsychotics	19,169	3,166	142,635	83,213	77,410	82,941
Overall antipsychotic users N (% out of total dementia population)	5,034 (26%)	1,270 (40%)	38,374 (27%)	33,419 (40%)	60,241 (78%)	14,129 (17%)
Typical antipsychotics N (% out of overall antipsychotic users)	3,927 (78%)	169 (13%)	19,396 (51%)	21,205 (63%)	19,905 (33%)	7,516 (53%)
Atypical antipsychotics N (% out of overall antipsychotic users)	2,128 (42%)	1,218 (96%)	30,903 (81%)	25,495 (76%)	59,557 (99%)	10,797 (76%)

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

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

Database	IPCI		SIDIAP		IQVIA DA Germany		IQVIA LPD Belgium		DK-DHR		NAJS	
Ranking	Top 5 Antipsychotics	N (%)	Top 5 Antipsychotics	N (%)	Top 5 Antipsychotics	(N%)	Top 5 Antipsychotics	N (%)	Top 5 Antipsychotics	N (%)	Top 5 Antipsychotics	N (%)
1	Haloperidol	3,684 (73%)	Quetiapine	54,512 (90%)	Risperidone	22,175 (58%)	Quetiapine	643 (51%)	Haloperidol	7,571 (54%)	Promazine	17,420 (52%)
2	Risperidone	1,286 (26%)	Risperidone	35,050 (58%)	Pipamperone	15,395 (40%)	Risperidone	504 (40%)	Risperidone	6,305 (45%)	Haloperidol	14,799 (44%)
3	Quetiapine	699 (14%)	Haloperidol	19,840 (33%)	Quetiapine	12,854 (33%)	Olanzapine	218 (17%)	Quetiapine	5,875 (42%)	Quetiapine	14,723 (44%)
4	Pipamperone	401 (8%)	Olanzapine	3,601 (6%)	Haloperidol	4,030 (11%)	Prothipendyl	79 (6%)	Olanzapine	2,292 (16%)	Risperidone	6,990 (21%)
5	Clozapine	281 (6%)	Sulpiride	2,494 (4%)	Prothipendyl	1,495 (4%)	Amisulpride	72 (6%)	Aripiprazole	594 (4%)	Olanzapine	3,130 (23%)

13.2. Main results

13.2.1. Objective 1: Patient-level characteristics of new users

Characteristics of patients with dementia 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 across all databases of IPCI, SIDIAP, IQVIA DA Germany, IQVIA LPD Belgium, DK-DHR, and NAJS, median age [IQR] was consistent around 82 [77-87] (NAJS) to 84 [79-88] (SIDIAP) years of age. Age distribution of atypical and typical antipsychotic incident use within all databases remained stable across databases and type of antipsychotic, with median age [IQR] ranging from 81 [75-87] (DK-DHR; atypical) to 86 years [81,90] (SIDIAP; typical).

There were higher proportion of females for all data sources compared to males among patients with dementia taking antipsychotics, with trends persisting between typical and atypical antipsychotic incident use. For example, IPCI had the lowest proportion of females compared to other data sources with 55% of all antipsychotic users, 53% of atypical antipsychotic users, and 56% of typical antipsychotic users being female. The highest percentage of females with dementia was NAJS with 67% of all antipsychotic users, 67% of atypical antipsychotic users, and 67% of typical antipsychotic users.

When comorbidities were measured any time prior to index date, frequencies were higher than expected from the general population given the advanced age of the population, with obesity (ranged between 4% to 40% in the overall antipsychotic populations among patients with dementia), heart failure (ranged between 9% to 21%), type 2 diabetes (ranged between 18% to 31%), and hypertension (ranged between 33% to 87%) having the highest proportions. Comorbidities between atypical and typical antipsychotic new users were mostly consistent across all databases.

The most common indications for antipsychotic use any time prior to index date was insomnia and other sleep disorders, and depression across most databases. Depression ranged between 8% (IPCI) to 43% (IQVIA LPD Belgium) and insomnia and other sleep disorders ranged between 3% (DK-DHR) to 49% (IQVIA LPD Belgium). Across all databases bipolar disorder or schizophrenia accounted for less than 5% of indications for all antipsychotic use. Indications remained consistent between atypical and typical antipsychotic users across all databases.

Table 12. Patient characteristics for antipsychotics users and by type of antipsychotics for patients with dementia.

Variable name	Variable level	Cohort name Estimate name	All antipsychotics	Atypical	Typical
IQVIA DA Germany					
Age	-	Median [Q25 - Q75]	83.00 [78.00 - 88.00]	83.00 [78.00 - 87.00]	84.00 [79.00 - 88.00]
Age group	0-64	N (%)	1,440 (3.75%)	1,212 (3.92%)	727 (3.75%)
	65-74	N (%)	3,744 (9.76%)	3,110 (10.06%)	1,799 (9.28%)
	75-84	N (%)	16,980 (44.25%)	13,876 (44.90%)	8,261 (42.59%)
	85+	N (%)	16,210 (42.24%)	12,705 (41.11%)	8,609 (44.39%)
Sex	Female	N (%)	23,099 (60.19%)	18,520 (59.93%)	11,872 (61.21%)

Variable name	Variable level	Estimate name	Cohort name: All antipsychotics	Atypical	Typical
Comorbidities (any time prior)	Chronic kidney disease	N (%)	4,884 (12.73%)	3,705 (11.99%)	2,622 (13.52%)
	Chronic kidney disease- renal impairment	N (%)	7,024 (18.30%)	5,395 (17.46%)	3,758 (19.38%)
	Heart failure	N (%)	8,379 (21.84%)	6,400 (20.71%)	4,550 (23.46%)
	Hypertension	N (%)	23,018 (59.98%)	17,979 (58.18%)	11,864 (61.17%)
	Myocardial infarction	N (%)	1,432 (3.73%)	1,120 (3.62%)	780 (4.02%)
	Obesity	N (%)	4,775 (12.44%)	3,710 (12.01%)	2,519 (12.99%)
	Stroke	N (%)	5,052 (13.17%)	3,982 (12.89%)	2,615 (13.48%)
	Type 2 diabetes	N (%)	11,159 (29.08%)	8,650 (27.99%)	5,850 (30.16%)
Indications in addition to diagnosis of dementia (any time prior)	Bipolar disorder	N (%)	331 (0.86%)	325 (1.05%)	224 (1.15%)
	Depression	N (%)	14,959 (38.98%)	12,349 (39.96%)	7,934 (40.91%)
	Insomnia	N (%)	335 (0.87%)	243 (0.79%)	217 (1.12%)
	Insomnia- sleep disorder	N (%)	8,769 (22.85%)	6,842 (22.14%)	5,200 (26.81%)
	Schizophrenia	N (%)	800 (2.08%)	818 (2.65%)	527 (2.72%)
IQVIA LPD Belgium					
Age	-	Median [Q25 - Q75]	83.00 [77.00 - 87.00]	83.00 [77.00 - 87.00]	84.00 [76.00 - 88.00]
Age group	0-64	N (%)	72 (5.67%)	71 (5.83%)	16 (9.47%)
	65-74	N (%)	145 (11.42%)	142 (11.66%)	17 (10.06%)
	75-84	N (%)	546 (42.99%)	521 (42.78%)	64 (37.87%)
	85+	N (%)	507 (39.92%)	484 (39.74%)	72 (42.60%)
Sex	Female	N (%)	756 (59.53%)	718 (58.95%)	107 (63.31%)
Comorbidities (any time prior)	Chronic kidney disease	N (%)	51 (4.02%)	45 (3.69%)	15 (8.88%)
	Chronic kidney disease- renal impairment	N (%)	56 (4.41%)	50 (4.11%)	16 (9.47%)
	Heart failure	N (%)	173 (13.62%)	158 (12.97%)	37 (21.89%)
	Hypertension	N (%)	820 (64.57%)	782 (64.20%)	110 (65.09%)
	Myocardial infarction	N (%)	41 (3.23%)	39 (3.20%)	<5 (<5%)
	Obesity	N (%)	52 (4.09%)	50 (4.11%)	6 (3.55%)
	Stroke	N (%)	105 (8.27%)	99 (8.13%)	14 (8.28%)

Variable name	Variable level	Estimate name	Cohort name: All antipsychotics	Atypical	Typical
	Type 2 diabetes	N (%)	231 (18.19%)	214 (17.57%)	41 (24.26%)
Indications in addition to diagnosis of dementia (any time prior)	Bipolar disorder	N (%)	18 (1.42%)	19 (1.56%)	<5 (<5%)
	Depression	N (%)	545 (42.91%)	532 (43.68%)	71 (42.01%)
	Insomnia	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Insomnia-sleep disorder	N (%)	621 (48.90%)	596 (48.93%)	115 (68.05%)
	Schizophrenia	N (%)	8 (0.63%)	9 (0.74%)	<5 (<5%)
DK-DHR (Danish Data Health Registries)					
Age	-	Median [Q25 - Q75]	83 [77 - 88]	81 [75 - 87]	84 [78 - 89]
Age group	0-64	N (%)	573 (4.06%)	579 (5.36%)	242 (3.22%)
	65-74	N (%)	2,104 (14.89%)	1,866 (17.28%)	868 (11.55%)
	75-84	N (%)	5,643 (39.94%)	4,550 (42.14%)	2,758 (36.70%)
	85+	N (%)	5,809 (41.11%)	3,802 (35.21%)	3,648 (48.54%)
Sex	Female	N (%)	7,979 (56.47%)	6,008 (55.65%)	4,285 (57.01%)
Comorbidities (any time prior)	Chronic kidney disease	N (%)	527 (3.73%)	341 (3.16%)	356 (4.74%)
	Chronic kidney disease-renal impairment	N (%)	746 (5.28%)	468 (4.33%)	510 (6.79%)
	Heart failure	N (%)	1,326 (9.38%)	885 (8.20%)	849 (11.30%)
	Hypertension	N (%)	6,667 (47.19%)	4,847 (44.89%)	3,770 (50.16%)
	Myocardial infarction	N (%)	1,057 (7.48%)	783 (7.25%)	626 (8.33%)
	Obesity	N (%)	622 (4.40%)	483 (4.47%)	340 (4.52%)
	Stroke	N (%)	1,171 (8.29%)	841 (7.79%)	741 (9.86%)
	Type 2 diabetes	N (%)	2,225 (15.75%)	1,633 (15.12%)	1,245 (16.56%)
Indications in addition to diagnosis of dementia (any time prior)	Bipolar disorder	N (%)	73 (0.52%)	87 (0.81%)	65 (0.86%)
	Depression	N (%)	2,046 (14.48%)	1,739 (16.11%)	1,211 (16.11%)
	Insomnia- sleep disorder	N (%)	378 (2.68%)	296 (2.74%)	220 (2.93%)
	Insomnia	N (%)	19 (0.13%)	15 (0.14%)	13 (0.17%)
	Schizophrenia	N (%)	25 (0.18%)	42 (0.39%)	26 (0.35%)
IPCI					

Variable name	Variable level	Estimate name	Cohort name: All antipsychotics	Cohort name: Atypical	Cohort name: Typical
Age	-	Median [Q25 - Q75]	83 [78 - 88]	81 [76 - 86]	84 [79 - 89]
Age group	0-64	N (%)	105 (2.09%)	70 (3.29%)	59 (1.50%)
	65-74	N (%)	586 (11.64%)	344 (16.17%)	380 (9.68%)
	75-84	N (%)	2,117 (42.05%)	982 (46.15%)	1,594 (40.59%)
	85+	N (%)	2,226 (44.22%)	732 (34.40%)	1,894 (48.23%)
Sex	Female	N (%)	2,781 (55.24%)	1,121 (52.68%)	2,212 (56.33%)
Comorbidities (any time prior)	Chronic kidney disease	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Chronic kidney disease-renal impairment	N (%)	879 (17.46%)	336 (15.79%)	725 (18.46%)
	Heart failure	N (%)	592 (11.76%)	213 (10.01%)	502 (12.78%)
	Hypertension	N (%)	1,917 (38.08%)	809 (38.02%)	1,490 (37.94%)
	Myocardial infarction	N (%)	292 (5.80%)	119 (5.59%)	227 (5.78%)
	Obesity	N (%)	716 (14.22%)	304 (14.29%)	567 (14.44%)
	Stroke	N (%)	560 (11.12%)	245 (11.51%)	446 (11.36%)
	Type 2 diabetes	N (%)	1,111 (22.07%)	458 (21.52%)	885 (22.54%)
Indications in addition to diagnosis of dementia (any time prior)	Bipolar disorder	N (%)	5 (0.10%)	<5 (<5%)	6 (0.15%)
	Depression	N (%)	404 (8.03%)	213 (10.01%)	296 (7.54%)
	Insomnia	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Insomnia sleep disorder	N (%)	917 (18.22%)	454 (21.33%)	700 (17.83%)
	Schizophrenia	N (%)	<5 (<5%)	0 (0.00%)	<5 (<5%)
SIDIAP					
Age	-	Median [Q25 - Q75]	84 [79 - 88]	84 [79 - 88]	86 [81 - 90]
Age group	0-64	N (%)	1,136 (1.89%)	1,129 (1.90%)	298 (1.50%)
	65-74	N (%)	5,522 (9.17%)	5,442 (9.14%)	1,412 (7.09%)
	75-84	N (%)	24,320 (40.37%)	23,991 (40.28%)	6,982 (35.08%)
	85+	N (%)	29,263 (48.58%)	28,995 (48.68%)	11,213 (56.33%)
Sex	Female	N (%)	38,761 (64.34%)	38,347 (64.39%)	12,818 (64.40%)
Comorbidities (any time prior)	Chronic kidney disease	N (%)	14,272 (23.69%)	14,171 (23.79%)	5,060 (25.42%)

Variable name	Variable level	Estimate name	Cohort name: All antipsychotics	Atypical	Typical
	Chronic kidney disease-renal impairment	N (%)	14,683 (24.37%)	14,587 (24.49%)	5,213 (26.19%)
	Heart failure	N (%)	6,337 (10.52%)	6,293 (10.57%)	2,440 (12.26%)
	Hypertension	N (%)	20,137 (33.43%)	19,920 (33.45%)	6,751 (33.92%)
	Myocardial infarction	N (%)	1,475 (2.45%)	1,448 (2.43%)	513 (2.58%)
	Obesity	N (%)	23,821 (39.54%)	23,619 (39.66%)	8,024 (40.31%)
	Stroke	N (%)	6,500 (10.79%)	6,441 (10.81%)	2,424 (12.18%)
	Type 2 diabetes	N (%)	18,995 (31.53%)	18,799 (31.56%)	6,246 (31.38%)
Indications in addition to diagnosis of dementia (any time prior)	Bipolar disorder	N (%)	72 (0.12%)	79 (0.13%)	76 (0.38%)
	Schizophrenia	N (%)	58 (0.10%)	70 (0.12%)	84 (0.42%)
	Depression	N (%)	12,324 (20.46%)	12,315 (20.68%)	4,584 (23.03%)
	Insomnia sleep disorder	N (%)	13,262 (22.01%)	13,360 (22.43%)	5,063 (25.44%)
	Insomnia	N (%)	11,857 (19.68%)	11,962 (20.08%)	4,680 (23.51%)
NAJS (National healthcare information system)					
Age	-	Median [Q25 - Q75]	82 [77 - 87]	81 [76 - 86]	83 [78 - 87]
Age group	0-64	N (%)	1,076 (3.22%)	946 (4.46%)	738 (2.89%)
	65-74	N (%)	4,422 (13.23%)	3,380 (15.94%)	3,062 (12.01%)
	75-84	N (%)	15,302 (45.79%)	10,037 (47.33%)	11,408 (44.75%)
	85+	N (%)	12,619 (37.76%)	6,842 (32.27%)	10,287 (40.35%)
Sex	Female	N (%)	22,288 (66.69%)	14,214 (67.03%)	17,121 (67.15%)
Comorbidities (any time prior)	Chronic kidney disease	N (%)	2,777 (8.31%)	1,705 (8.04%)	2,179 (8.55%)
	Chronic kidney disease-renal impairment	N (%)	3,497 (10.46%)	2,173 (10.25%)	2,751 (10.79%)
	Heart failure	N (%)	5,184 (15.51%)	3,081 (14.53%)	4,197 (16.46%)
	Hypertension	N (%)	28,926 (86.56%)	18,370 (86.63%)	22,010 (86.33%)
	Myocardial infarction	N (%)	1,446 (4.33%)	880 (4.15%)	1,147 (4.50%)

Variable name	Variable level	Estimate name	Cohort name: All antipsychotics	Cohort name: Atypical	Cohort name: Typical
	Obesity	N (%)	1,588 (4.75%)	1,063 (5.01%)	1,234 (4.84%)
	Stroke	N (%)	4,316 (12.91%)	2,808 (13.24%)	3,417 (13.40%)
	Type 2 diabetes	N (%)	8,863 (26.52%)	5,703 (26.89%)	6,724 (26.37%)
Indications in addition to diagnosis of dementia (any time prior)	Bipolar disorder	N (%)	132 (0.39%)	129 (0.61%)	161 (0.63%)
	Depression	N (%)	10,787 (32.28%)	8,041 (37.92%)	8,330 (32.67%)
	Insomnia	N (%)	2,218 (6.64%)	1,500 (7.07%)	1,756 (6.89%)
	Insomnia- sleep disorder	N (%)	9,103 (27.24%)	6,120 (28.86%)	7,217 (28.31%)
	Schizophrenia	N (%)	546 (1.63%)	712 (3.36%)	575 (2.26%)

13.2.2. Objective 2: Incidence rates

Incidence rates (IRs) of overall, typical, and atypical antipsychotics in people diagnosed with dementia between 2013 to 2023 are depicted in **Figure 5**.

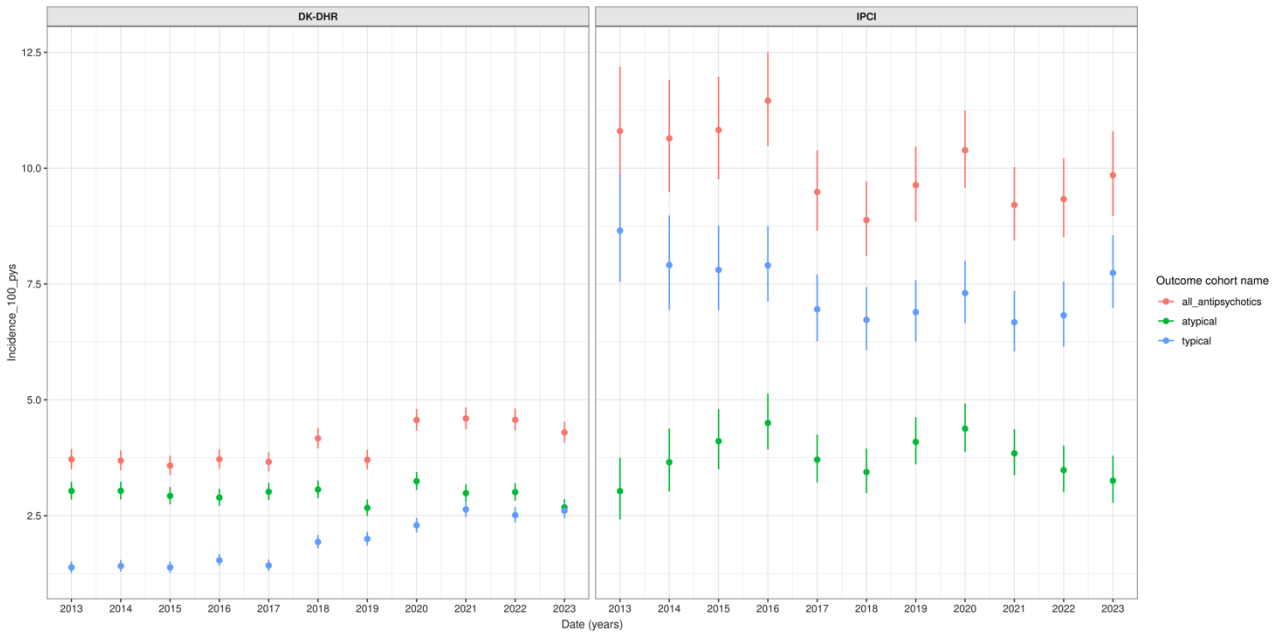
13.2.2.1. Overall use of antipsychotics in people with dementia

Incidence of all antipsychotic use (IR [95% CI] per 100 person-years) remained relatively stable throughout the study period in IPCI (IR values ranged between 9 [8-10] and 11 [10-12] cases per 100 person-years), DK-DHR (3.6 [3.4-3.8] and 4.6 [4.4-4.8]), and IQVIA LPD Belgium (6.6 [5.5-7.9]). IRs were increasing in IQVIA DA Germany from 5 [4.8- 5.3] cases per 100 person-years in 2013 to 7.7 [7.5-8] in 2023 and increased in SIDIAP from 18 [17.7-18.6] in 2013 to 24 [23.6-24.9] in 2022. IRs in NAJS decreased from 33.1 [32.0 - 34.2] in 2016 to 16.8 [16.3 - 17.3] in 2023.

13.2.2.2. Use of atypical vs typical antipsychotics in people with dementia

The incidence of atypical antipsychotic use was higher than the typical use in all databases, except for IPCI during its full observation period, and NAJS between 2016 to 2021.

A) DK-DHR and IPCI:



B) IQVIA DA Germany, IQVIA LPD Belgium and SIDIAP:

C) NAJS:

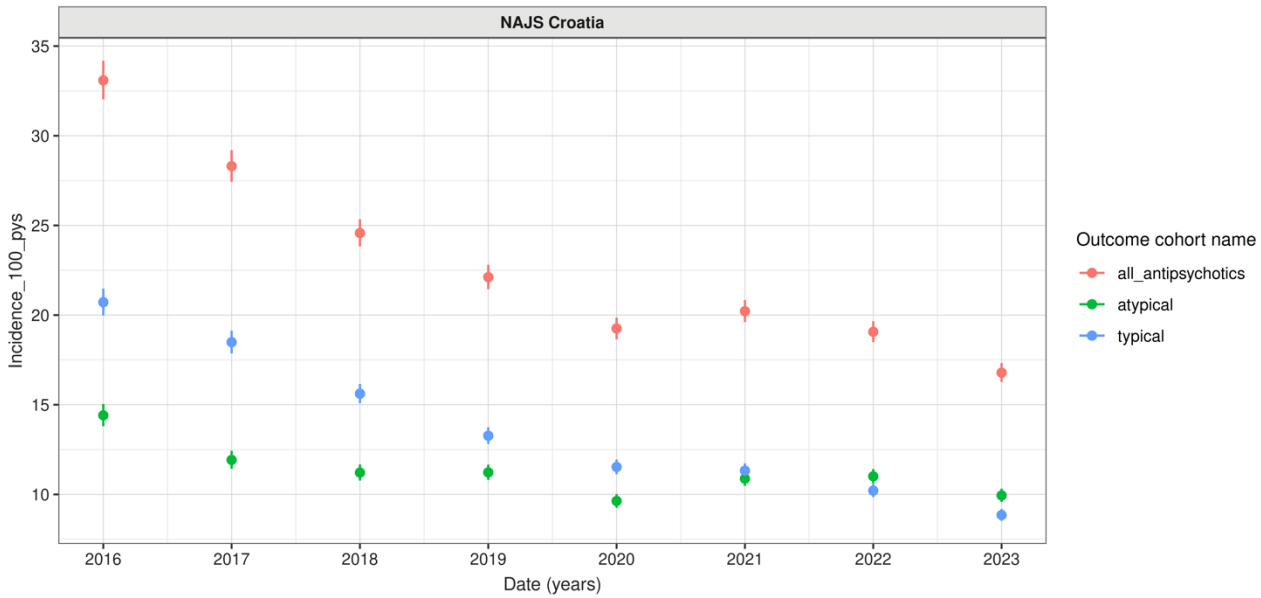


Figure 5. Incidence rates for all antipsychotic use, typical, and atypical, for A) DK-DHR and IPCI, B) IQVIA DA Germany, IQVIA LPD Belgium, and SIDIAP and C) NAJS among patients with dementia.

Reported follow-up time for each database: DK-DHR (01/01/2013 to 31/12/2023), IPCI (01/01/2013 to 31/12/2023), IQVIA DA Germany (01/01/2013 to 31/12/2023), IQVIA LPD Belgium (01/01/2015 to 31/01/2024), SIDIAP (01/07/2013 to 01/06/2023), NAJS (01/01/2016 to 17/11/2023).

13.2.2.3. Age stratification

Incidence of overall antipsychotics use (i.e., all antipsychotics) were higher among the ≥85 age group, followed by the 75 to 84, 65 to 74, and ≤64 age groups in all databases, except IQVIA LPD Belgium (where confidence intervals overlapped). Similar trends were observed when stratified by type of antipsychotic, except for atypical antipsychotic use in IPCI and DK-DHR (IRs overlapped), and NAJS (age group with higher IR fluctuated: 75 to 84 group had the highest IR between 2016 to 2020, whilst ≥85 group had it from 2021 until 2023).

In IPCI, IR [95% CI] cases per 100 person-years in the ≥85 age group were higher in the all-antipsychotic users and typical antipsychotic users, where IR values ranged between 8.8 [7.6-10.2] and 15 [12.7-17.7], and both cohorts presented a moderated decrease over the study period. IRs in the other three age groups had overlapping confidence intervals, for these two populations. For atypical use, confidence intervals overlapped between age groups, with IR values ranged between 2.6 [1-5.7] to 6.4 [3.1-11.8] (**Figure 6**).

Due to the larger proportion of atypical antipsychotic users in SIDIAP, trends in atypical users reflect the trends in all antipsychotic incidence rates. There was a general increasing trend among all age groups for all antipsychotic use and atypical antipsychotic use. For the ≥85 age group, IRs increased in all antipsychotic cohort from 21.7 [20.9-22.5] cases per 100 person-years in 2013 to 27.8 [26.8-28.9] in 2022 and in the atypical cohort from 18.4 [17.7-19.1] in 2013 to 25.6 [24.7-26.6] in 2022 with a decreasing trend from 2015 to 2017 in both cohorts. The 75- to 84-year-old age group followed a similar trend (all antipsychotic cohort: 17.3 [16.6-18.0] in 2013 to 23.1 [22.1-24.1] in 2022; atypical cohort: 15.6 [15.0-16.2] in 2013 to 22.3 [21.3-23.3] in 2022). This was followed by an increasing trend in IRs in the 65 to 74 year old age group and then 0- to 64-year-old age group with a stable trend over time. IRs of typical IRs were relatively stable and low for all age groups with IRs ranging from 5.0 [4.7-5.3] to 1.5 [0.93 -2.2]. (**Figure 7**)

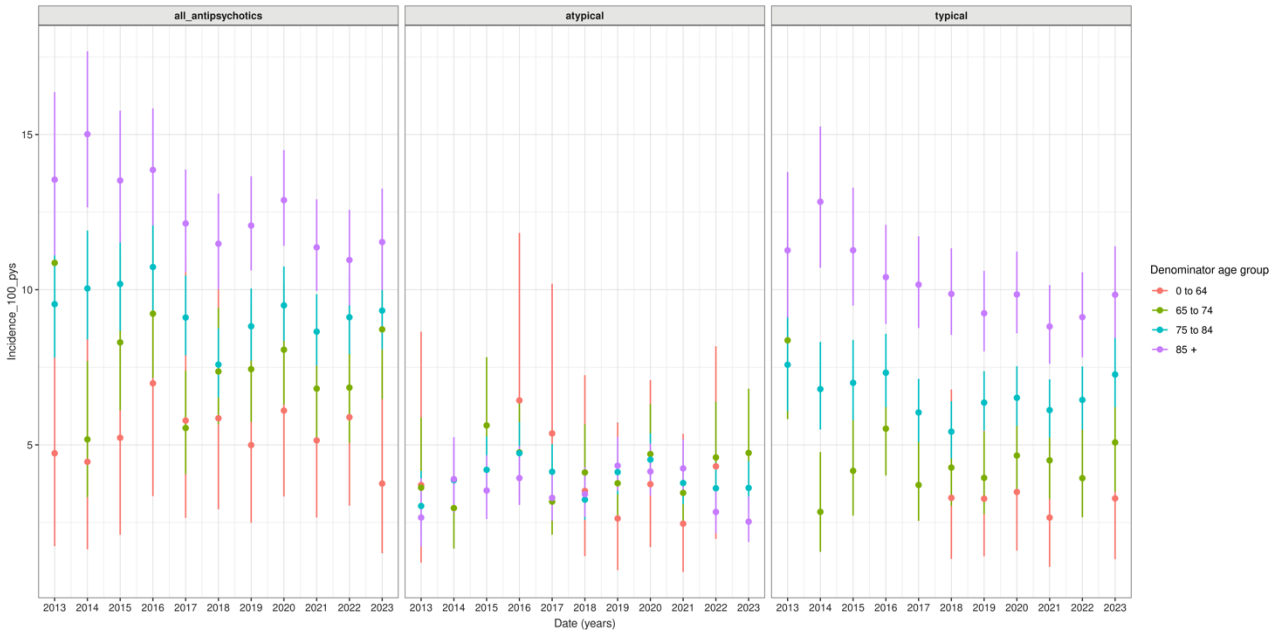


Figure 6. Incidence rates for all antipsychotic use, typical, and atypical, stratified by age groups in IPCI among patients with dementia.

Reported follow-up in IPCI was 01/01/2013 to 31/12/2023.

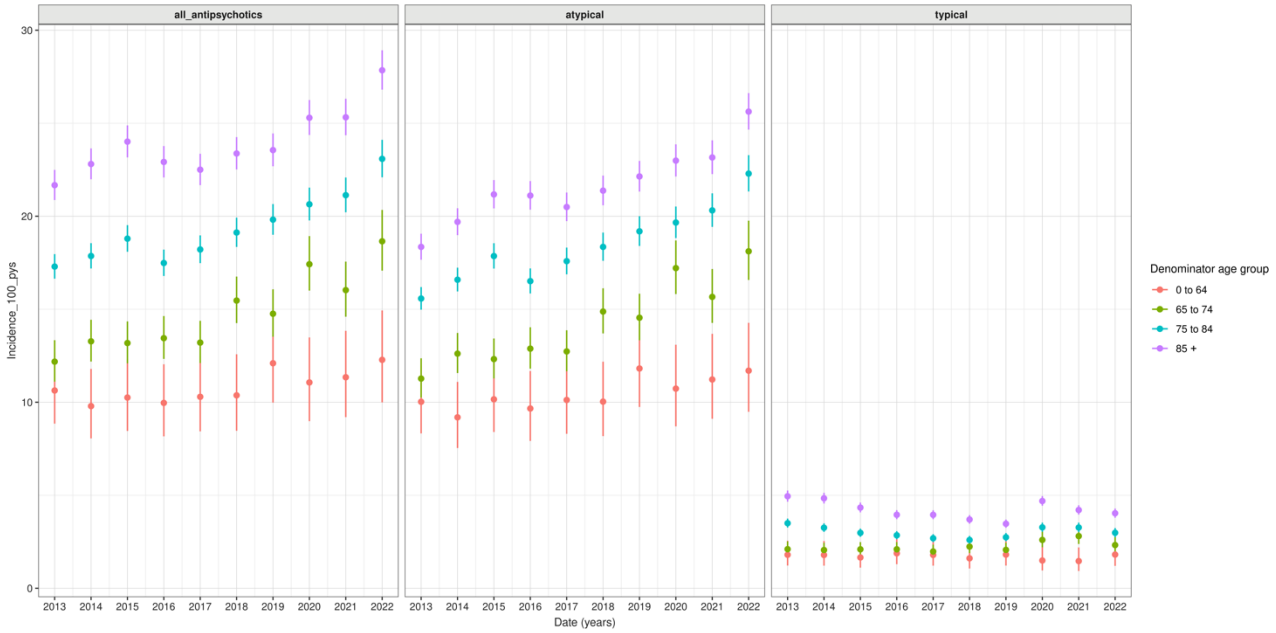


Figure 7. Incidence rates for all antipsychotic use, typical and atypical, stratified by age groups in SIDIAP among patients with dementia.

Reported follow-up in SIDIAP was 01/07/2013 to 01/06/2023.

In IQVIA DA Germany, general increasing age trends were consistent between all, typical, and atypical antipsychotic cohorts. The ≥85 age group had higher IRs ([95% CI] cases per 100 person-years) compared to the other age groups during the whole study period, with an increasing trend from 2014 to 2023 (e.g., all

antipsychotic use in ≥85 age group increased from 6.6 [6.1-7.1-] to 9.4 [9.0-9.8-]). IRs in the other age groups followed a similar trend. (**Figure 8**)

Due to a smaller sample size, IR estimates for IQVIA LPD Belgium had wider confidence intervals, which show stable trends (confidence intervals for the different IR in each age group overlap). IRs for all antipsychotic use was heavily influenced by atypical antipsychotic use (e.g., IRs in the ≥85 age group for all and atypical antipsychotic use were mainly between 7 to 11 cases per 100 person-years, whilst in the typical use it was lower than 5 cases per 100 person-years) (**Figure 9**).

In DK-DHR, there were overlapping CIs between the ≥85 age group, 75 to 84 age group, and 65 to 74 age group for all, typical, and atypical antipsychotic use. In the all antipsychotic and typical antipsychotic groups there were higher IRs in the ≥85 age group from 2018 to 2023 (with a decrease in all antipsychotic use IR in 2019). In the ≥85 age group for all antipsychotic use IRs ranged from 4.0 [3.6-4.3] to 5.8 [5.3-6.2]. (**Figure 10**).

In NAJS, there was a decrease in atypical and typical antipsychotic use in most age groups. However, atypical use for ≥85 age group presented a spike in use 2021 and 2022 (IR of 12.7 [12.0-13.5] and 13.0 [12.3-13.8], respectively), followed by a decrease in 2023 (IR of 11.4 [10.7-12.2]). Incidence in the ≥85 age group was higher in typical antipsychotic use than for age ≥85, specially in 2016 (e.g., IR [95% CI] cases per 100 person-years was 31.3 [29.5-33.1] for typical use whereas it was 14.2 [13.1-15.4] in atypical use). Incidence of typical antipsychotic use in the 75 to 84 age group was higher between 2016 and 2020 (ranged between 12 and 22 cases per 100 person-years), but atypical antipsychotic use became higher between 2021 and 2023 (ranged between 11 and 13 cases per 100 person-years). Conversely, use across the other age groups between all, typical and atypical was comparable (**Figure 11**).

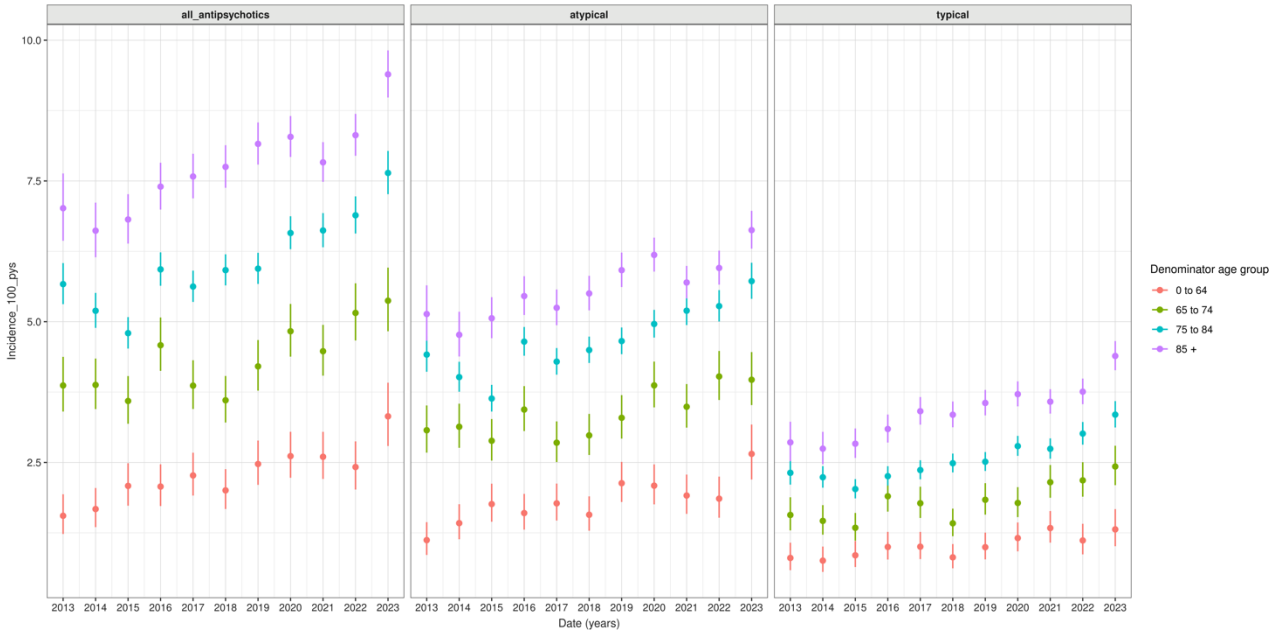


Figure 8. Incidence rates for all antipsychotic use, typical, and atypical, stratified by age groups in IQVIA DA Germany among patients with dementia.

Reported follow-up in IQVIA DA Germany was 01/01/2013 to 31/12/2023.

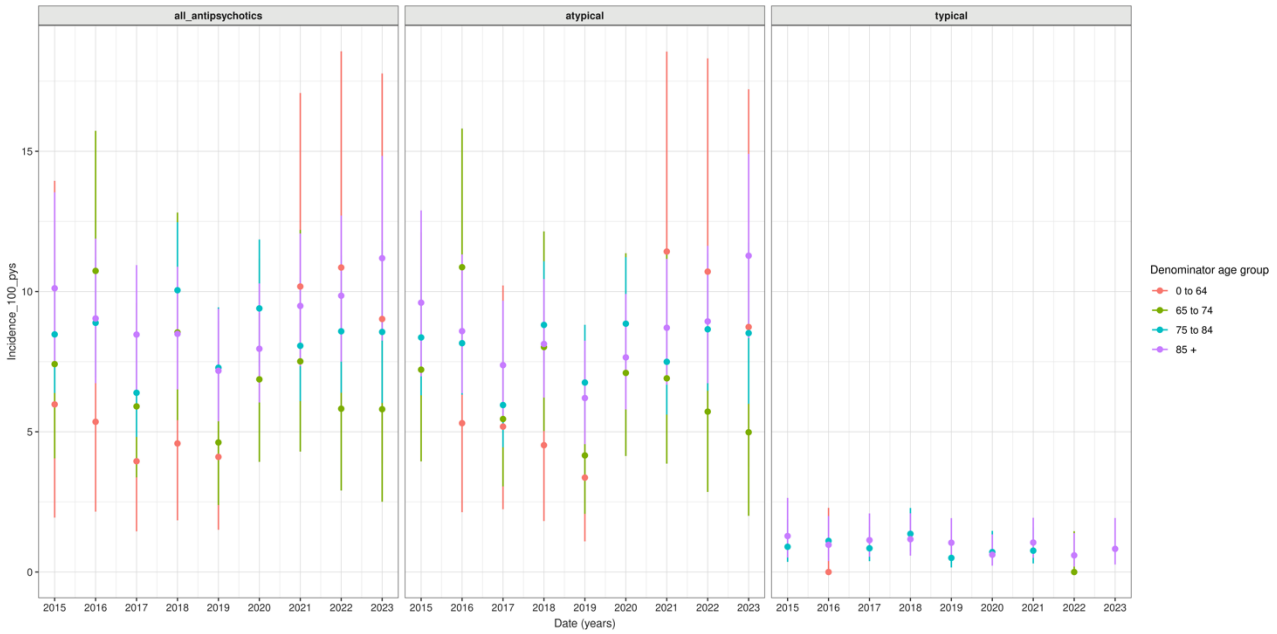


Figure 9. Incidence rates for all antipsychotic use, typical, and atypical, stratified by age groups in IQVIA LPD Belgium among patients with dementia.

Reported follow-up in IQVIA LPD Belgium was 01/01/2015 to 31/01/2024.

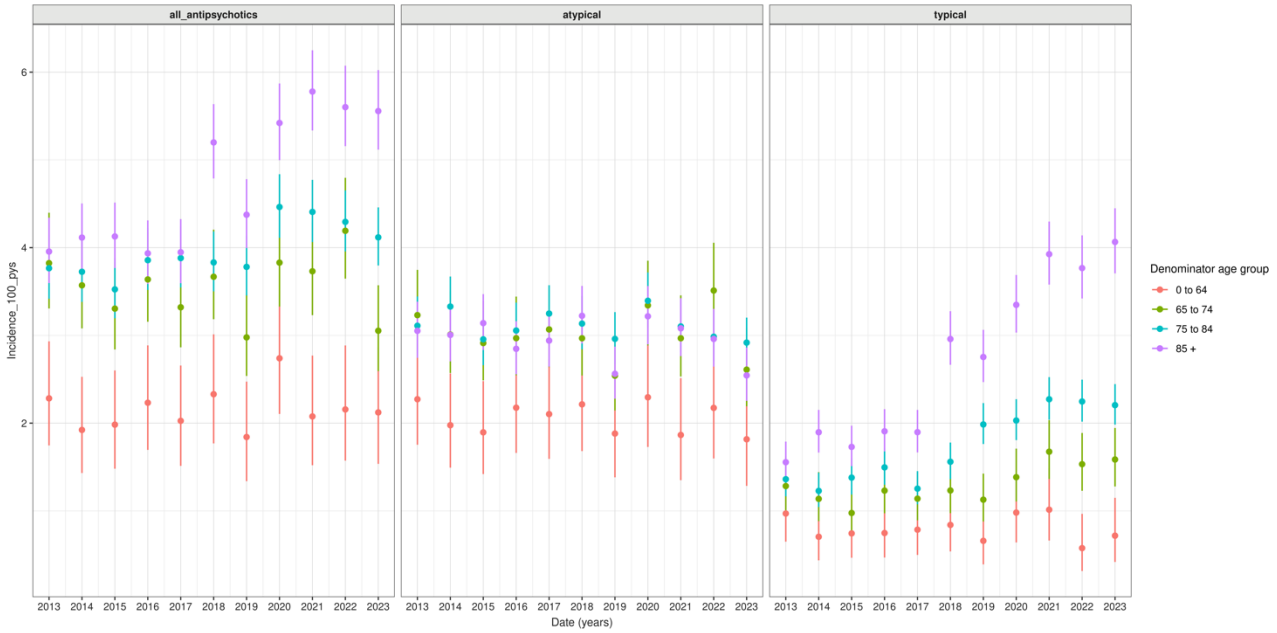


Figure 10. Incidence rates for all antipsychotic use, typical, and atypical, stratified by age groups in DK-DHR among patients with dementia.

Reported follow-up in DK-DHR was 01/01/2013 to 31/12/2023.

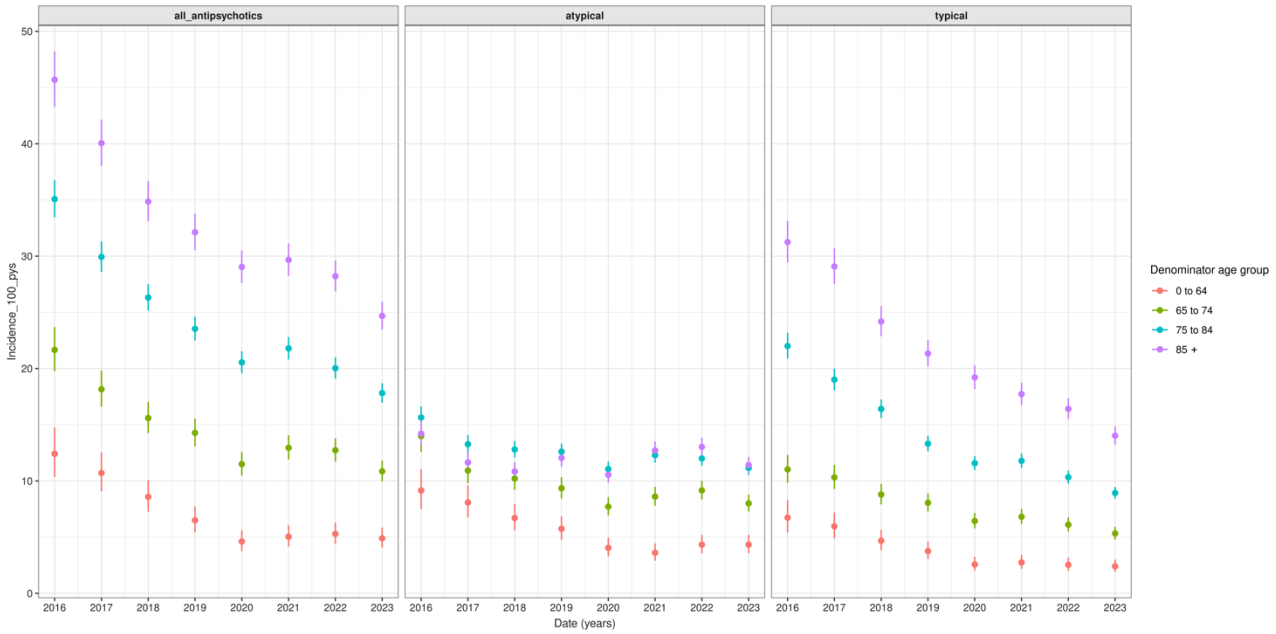


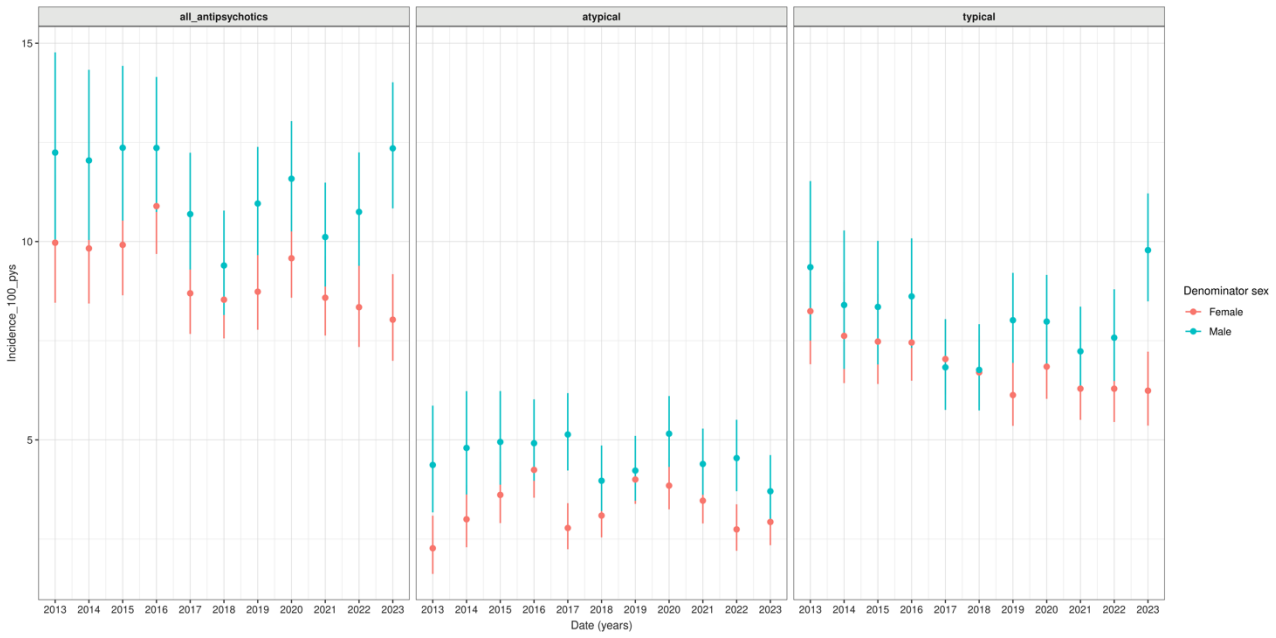
Figure 11. Incidence rates for all antipsychotic use, typical and atypical, stratified by age groups in NAJS among patients with dementia.

Reported follow-up in NAJS was 01/01/2016 to 17/11/2023.

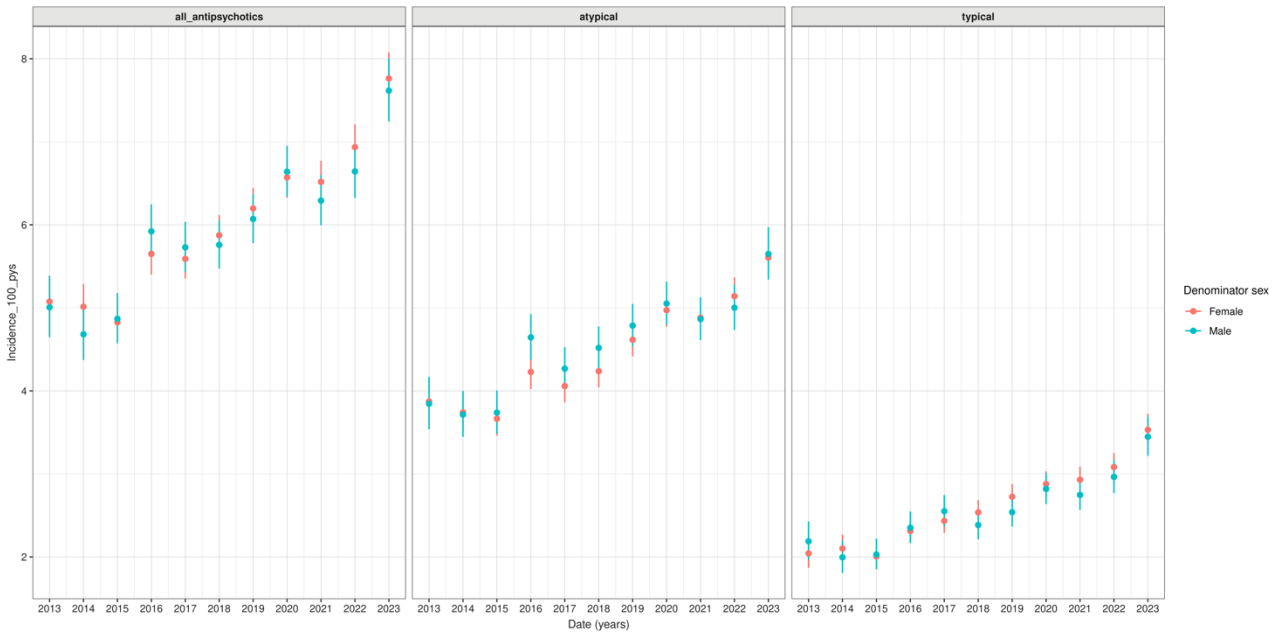
13.2.2.4 Sex stratification

As shown in **Figure 12**, use in men was higher among patients with dementia in SIDIAP, with similar trends but overlapping CIs in IPCI, DK-DHR (in all and atypical antipsychotics males were higher from 2013 to 2017 and then overlapping CIs since then), and IQVIA LPD Belgium (all and atypical users had some sex differences). No differences between sexes were observed in IQVIA DA Germany and NAJS.

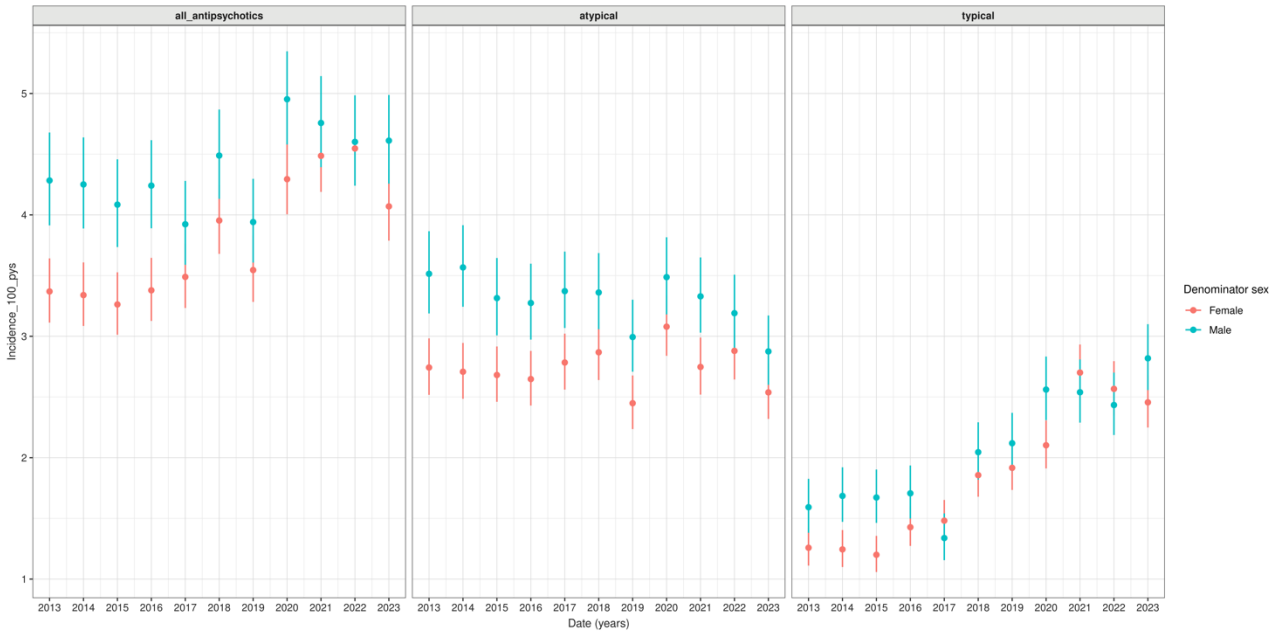
A) IPCI



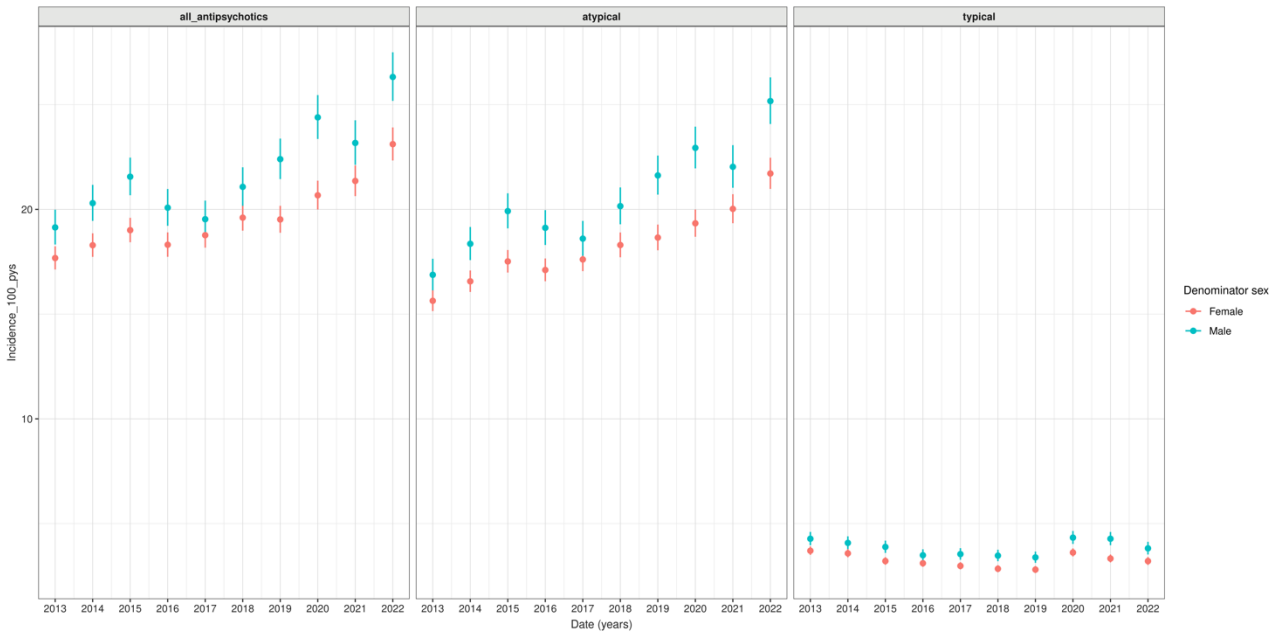
B) IQVIA DA Germany



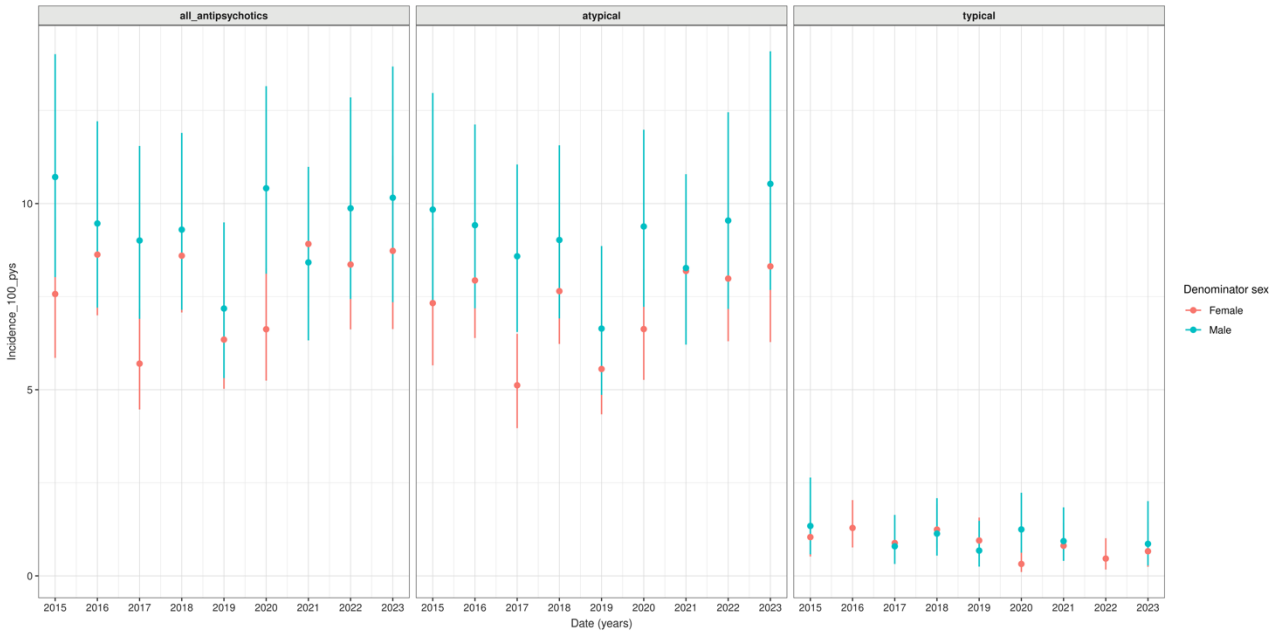
C) DK-DHR



D) SIDIAP



E) IQVIA LPD Belgium



F) NAJS

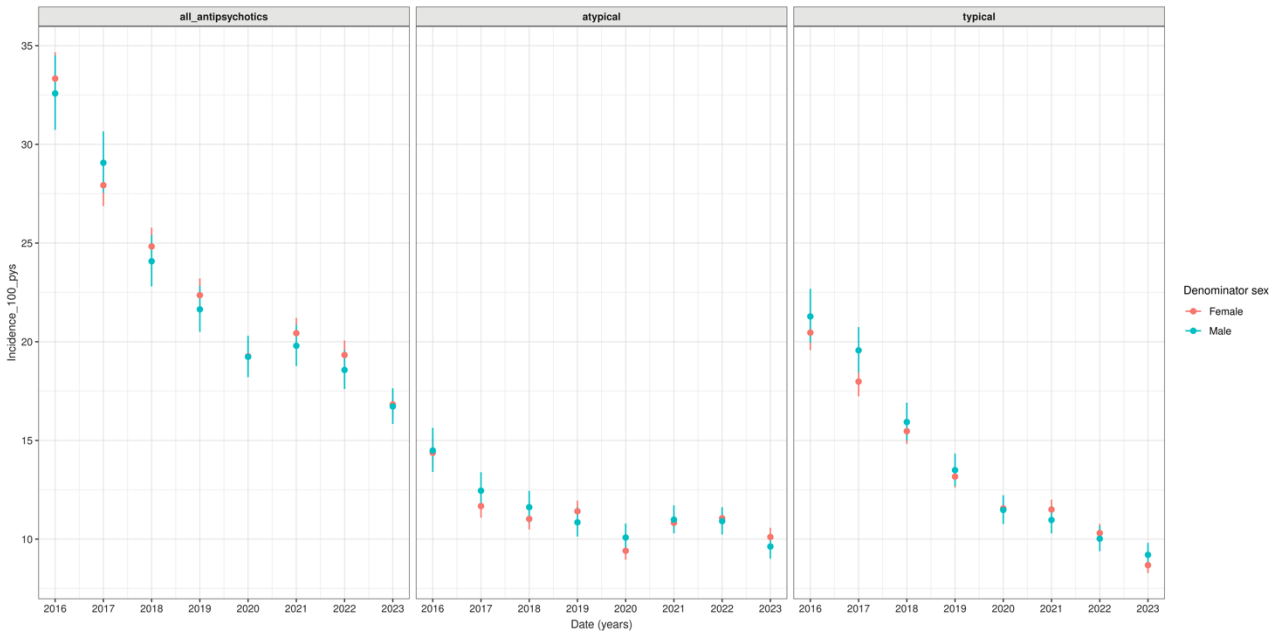


Figure 12. Incidence rates for all antipsychotic use, typical. and atypical, stratified by sex in A) IPCI, B) IQVIA DA Germany, C) DK-DHR, D) SIDIAP, E) IQVIA LPD Belgium, and F) NAJS among patients with dementia.

Reported follow-up time for each database: DK-DHR (01/01/2013 to 31/12/2023), IPCI (01/01/2013 to 31/12/2023), IQVIA DA Germany (01/01/2013 to 31/12/2023), IQVIA LPD Belgium (01/01/2015 to 31/01/2024), SIDIAP (01/07/2013 to 01/06/2023), NAJS (01/01/2016 to 17/11/2023).

13.2.2.4. Top 5 most common antipsychotics per database

IPCI

The most common antipsychotic in IPCI was haloperidol, which showed a stable trend from 2013 to 2023 with peaks in 2016 (IR [95% CI]: 7.5 [6.7-8.3]) and 2020 (7.0 [6.3-7.6]). The following most used antipsychotic was risperidone, where use ranged between 1.6 to 3 cases per 100 person-years over the study period. IRs for quetiapine, clozapine, and sulpiride, use remained relatively stable and saw similar numbers after 2016 (**Figure 13**).

SIDIAP

The most common antipsychotics in SIDIAP were quetiapine (IR [95% CI] cases per 100 person-years increased from 8.3 [8.0 – 8.6] in 2013 to 16.4 [16.0 – 16.9] in 2022,), followed by risperidone (IR decreased from 8.0 [7.8 – 8.3] in 2013 to 6.7 [6.4 – 6.9] in 2022), and haloperidol (IR ranged between 2.9 and 3.8 cases per 100 person-years). IRs for olanzapine and pipamperone, use remained relatively stable and saw low numbers (**Figure 14**).

IQVIA DA Germany

The most common antipsychotics in IQVIA DA Germany were risperidone, pipamperone, and quetiapine. Use of these three antipsychotics increased from 2015 to 2023 (e.g., IR [95% CI] of risperidone use changed from 2.4 [2.3 – 2.5] in 2015 to 3.6 [3.5 – 3.8] cases per 100 person-years). IRs for haloperidol and prothipendyl use remained relatively stable and saw similar numbers (**Figure 15**).

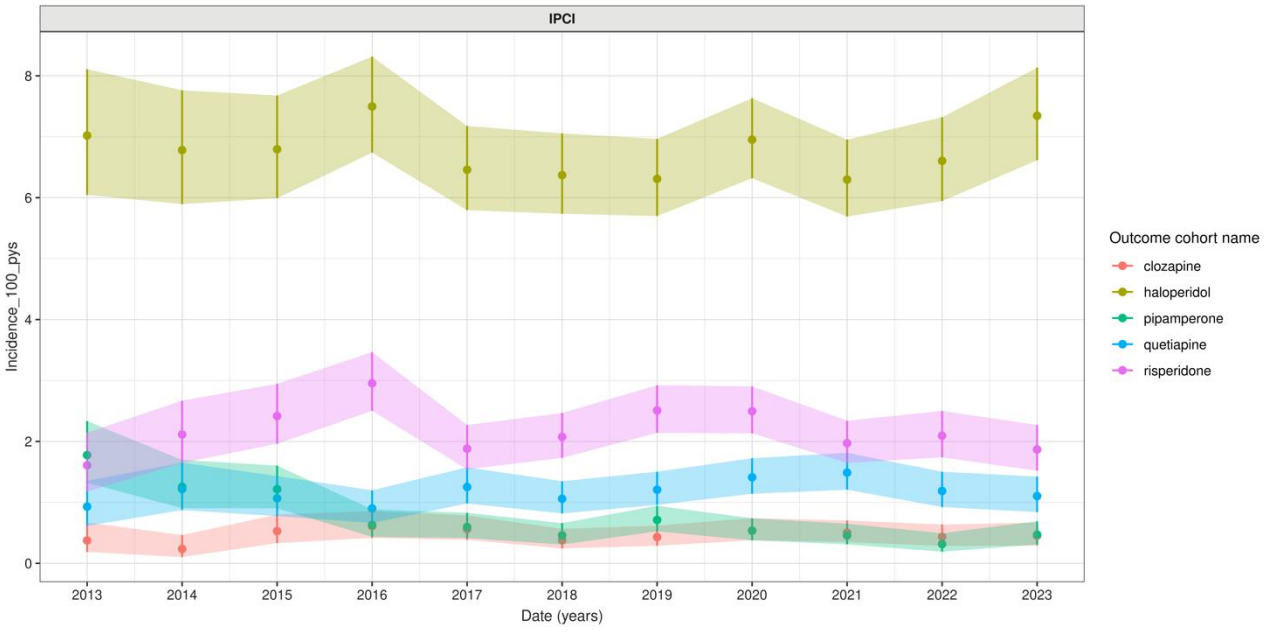


Figure 13. Incidence rates of use of the top 5 most common antipsychotics in IPCI among patients with dementia.

Reported follow-up in IPCI was 01/01/2013 to 31/12/2023.

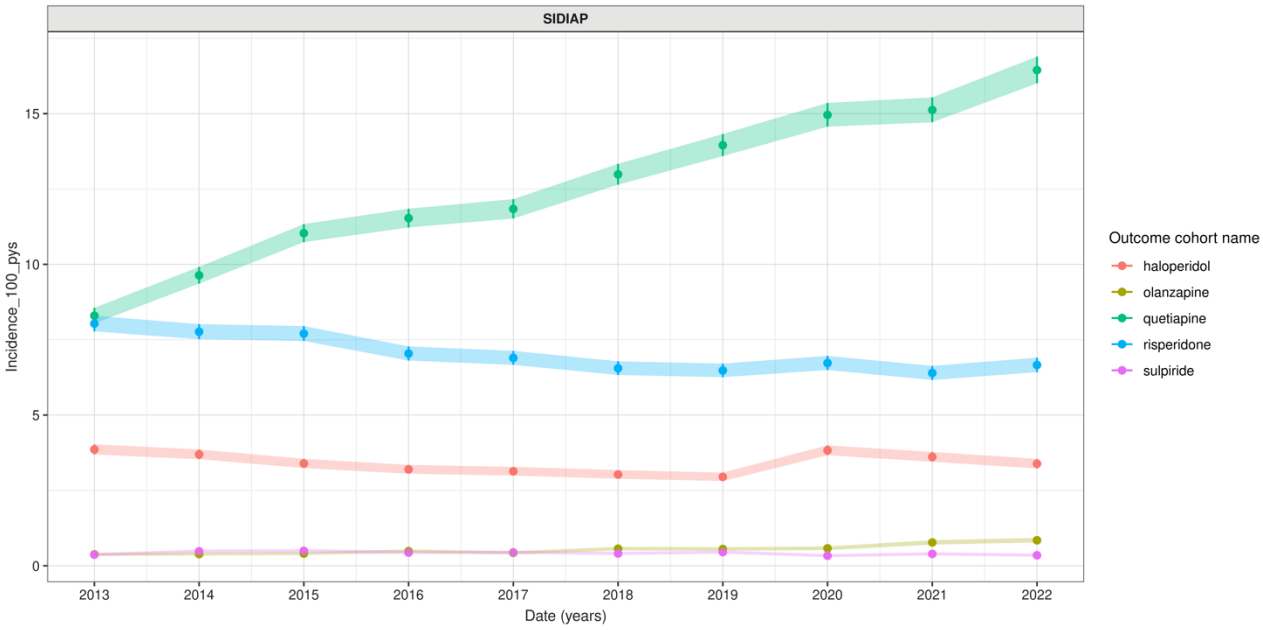


Figure 14. Incidence rates of use of the top 5 most common antipsychotics in SIDIAP among patients with dementia.

Reported follow-up in SIDIAP was 01/07/2013 to 01/06/2023.

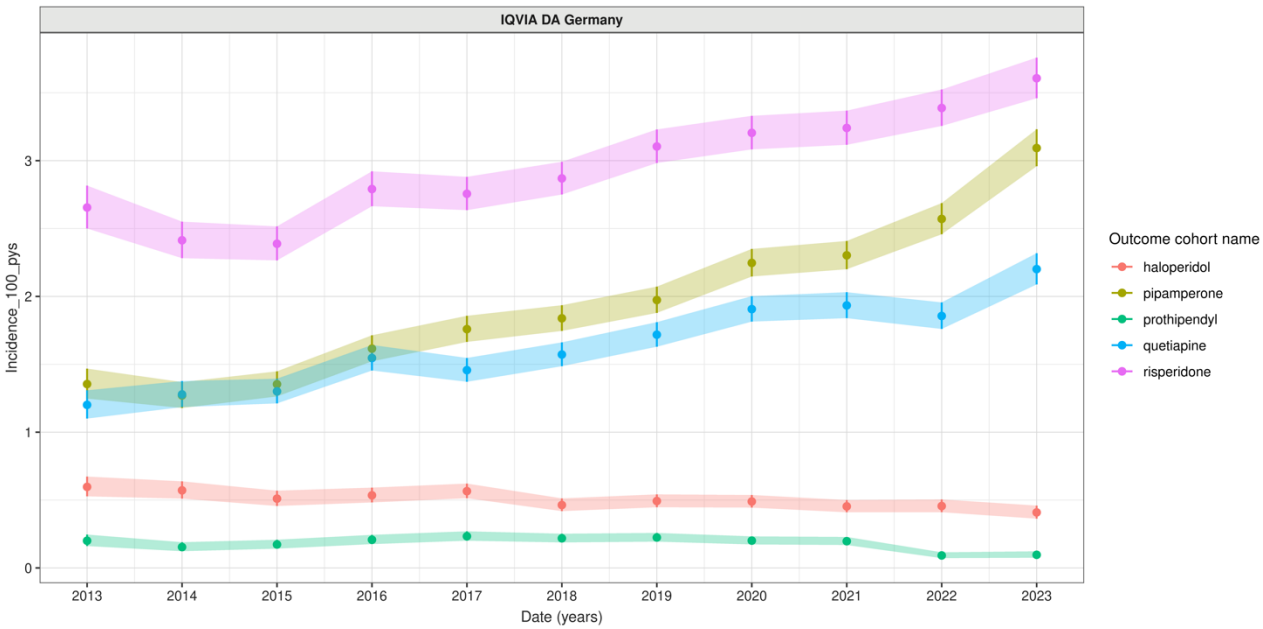


Figure 15. Incidence rates of use of the top 5 most common antipsychotics in IQVIA DA Germany among patients with dementia.

Reported follow-up in IQVIA DA Germany was 01/01/2013 to 31/12/2023.

IQVIA LPD Belgium

In the IQVIA LPD Belgium database, quetiapine (IR [95% CI] cases per 100,000 person-years ranged from 2.7 [2.1 – 3.4] in 2019 to 4.7 [3.6 - 6] in 2023) and risperidone (ranged from 1.8 [2 - 4]in 2021 to 3.6 [2.8 – 4.7] in 2015) had the highest throughout the study period, followed by olanzapine (IR ranged between 1.0 and 1.4 cases per 100 person-years). Use of prothipendyl and amisulpride remained low. (**Figure 16**)

DK-DHR

In DK-DHR, the most used antipsychotics from 2013 to 2021 were quetiapine, risperidone, haloperidol, olanzapine, and aripiprazole. Then use of quetiapine and risperidone decreased, whilst haloperidol increased since 2017 and became the most used antipsychotic in 2023 (IR [95% CI] from 1.3 [1.2-1.47] to 2.6 [2.4-2.8] cases per 100 person-years in 2017 and 2023, respectively). Use of olanzapine and aripiprazole remained generally stable over the study period. (**Figure 17**)

NAJS

In NAJS, use of promazine and haloperidol (the first and second most used antipsychotics in 2016 respectively) declined, whilst quetiapine use was stable between 2017 to 2023 and became the most frequently used in 2022 (with an IR of 6.8 [95% CI: 6.5-7.0] cases per 100 person-years). Risperidone use fluctuated with values between 2.7 and 3.3 cases per 100 person-years. Olanzapine use decreased between 2016 and 2023 (from 2.1 [1.89-2.3] of to 0.9 [0.8 – 0.95], respectively) (**Figure 18**).

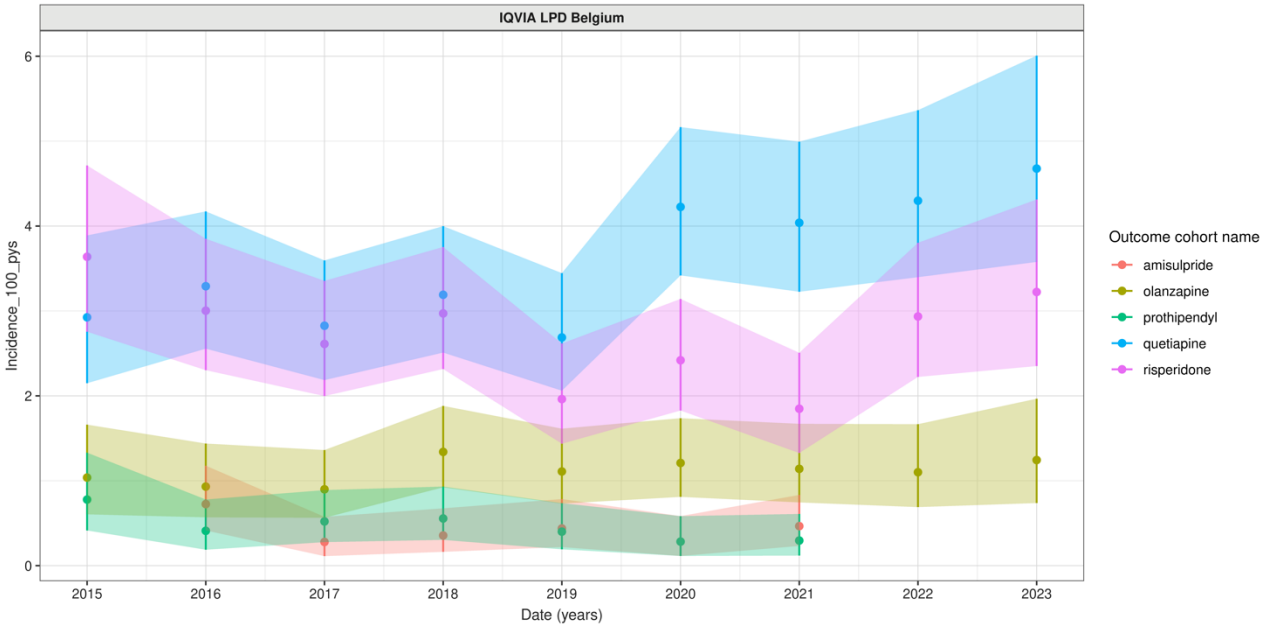


Figure 16. Incidence rates of use of the top 5 most common antipsychotics in IQVIA LPD Belgium among patients with dementia.

Reported follow in IQVIA LPD Belgium was 01/01/2015 to 31/01/2024.

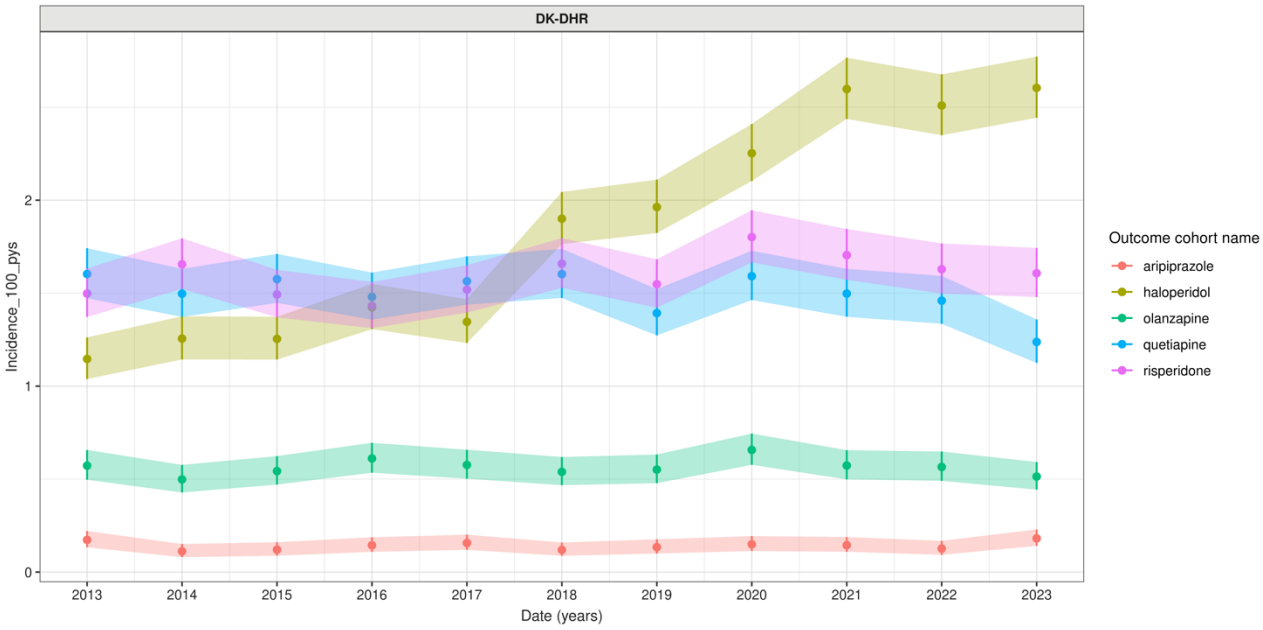


Figure 17. Incidence rates of use of the top 5 most common antipsychotics in DK-DHR among patients with dementia.

Reported follow in DK-DHR was 01/01/2013 to 31/12/2023.

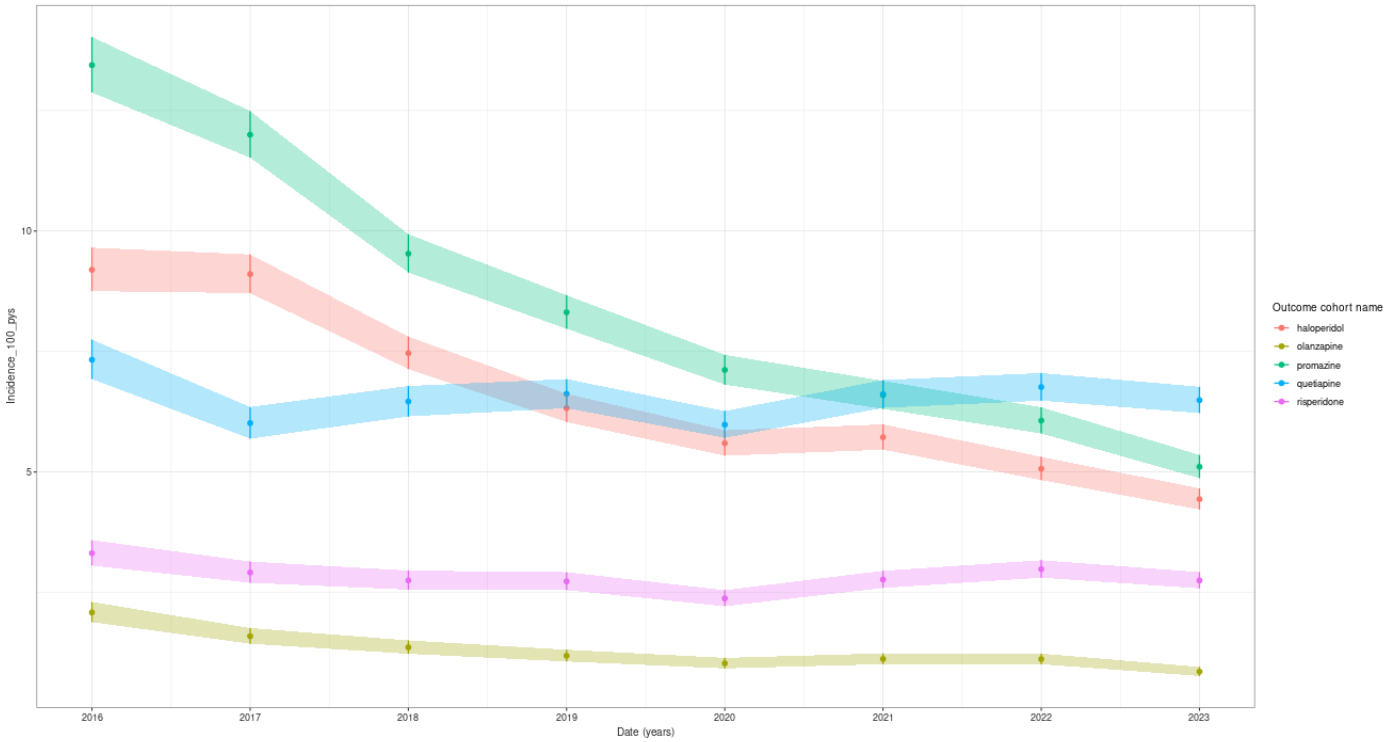


Figure 18. Incidence rates of use of the top 5 most common antipsychotics in NAJS among patients with dementia.

Reported follow in NAJS was 01/01/2016 to 17/11/2023.

13.2.3. 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 was no missing data for any of the drugs reported. In the overall population, duration of antipsychotic use ranged from 3 days to 310 days based on drug type and database. There were no strong differences in initial daily dose between age groups or sex for the different drugs of interest.

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

A) IPCI

		Cohort name									
		haloperidol_oral					risperidone_oral				
		Age group					Age group				
		0 to 64	≥65	overall			0 to 64	≥ 65	overall		
					Sex					Sex	
Variable	Estimate name	overall	overall	overall	Female	Male	overall	overall	overall	Female	Male
Number subjects	N	51	3,585	3,636	2,060	1,576	36	1,250	1,286	724	562
Exposed time (Day)	Median (Q25 - Q75)	46 (16 - 72)	36 (15 - 78)	36 (15 - 78)	40 (15 - 84)	31 (15 - 70)	66 (30 - 142)	46 (15 - 126)	46 (15 - 127)	52 (18 - 132)	42 (15 - 117)
Cumulative dose (mg)	Median (Q25 - Q75)	40.00 (30.00 - 76.58)	40.00 (16.00 - 80.00)	40.00 (16.00 - 80.00)	40.00 (19.12 - 88.25)	40.00 (15.00 - 80.00)	67.70 (15.00 - 145.38)	43.00 (15.00 - 120.00)	44.00 (15.00 - 120.75)	46.00 (15.00 - 138.62)	34.75 (15.00 - 105.00)
Initial daily dose (mg)	Median (Q25 - Q75)	1.00 (0.67 - 1.77)	1.00 (0.50 - 1.43)	1.00 (0.50 - 1.43)	1.00 (0.50 - 1.35)	1.00 (0.67 - 1.48)	0.72 (0.50 - 1.00)	0.50 (0.50 - 1.00)	0.50 (0.50 - 1.00)	0.50 (0.50 - 1.00)	0.50 (0.50 - 1.00)

B) SIDIAP

Variable	Estimate name	Cohort name: quetiapine_oral					Cohort name: risperidone_oral				
		Age group			Sex		Age group			Sex	
		0 to 64	≥ 65	overall			0 to 64	≥65	overall		
		overall	overall	overall	Female	Male	overall	overall	overall	Female	Male
Number subjects	N	1,037	53,475	54,512	35,207	19,305	607	34,444	35,051	23,007	12,044
Exposed time (day)	Median (Q25 - Q75)	383 (95 - 969)	309 (80 - 801)	310 (80 - 804)	338 (86 - 868)	268 (68 - 702)	196 (61 - 568)	156 (53 - 437)	157 (53 - 438)	171 (57 - 477)	133 (46 - 375)
Cumulative dose (mg)	Median (Q25 - Q75)	22,168.99 (4,600.00 - 82,693.08)	12,650.00 (2,521.53 - 45,552.39)	12,775.00 (2,550.00 - 46,050.00)	13,762.30 (2,775.00 - 49,500.00)	11,186.61 (2,250.00 - 39,575.14)	203.73 (51.25 - 823.75)	125.50 (30.00 - 411.94)	126.50 (30.00 - 416.03)	135.50 (31.50 - 448.53)	112.76 (30.00 - 366.46)
Initial daily dose (mg)	Median (Q25 - Q75)	36.06 (24.56 - 73.58)	24.84 (24.19 - 48.91)	24.84 (24.19 - 48.98)	24.84 (24.19 - 48.84)	24.84 (24.19 - 49.15)	0.98 (0.49 - 1.50)	0.50 (0.48 - 0.99)	0.50 (0.48 - 0.99)	0.50 (0.48 - 0.99)	0.73 (0.48 - 0.99)

C) IQVIA DA Germany

		Cohort name									
		pipamperone_oral					risperidone_oral				
		Age group					Age group				
		0 to 64	≥ 65	overall	Sex		0 to 64	≥ 65	overall	Sex	
Variable	Estimate name	overall	overall	overall	Female	Male	overall	overall	overall	Female	Male
Number subjects	N	515	14,880	15,395	9,439	5,931	629	21,540	22,169	13,492	8,646
Exposed time (day)	Median (Q25 - Q75)	84.00 (22.00 - 150.00)	50.00 (14.00 - 111.00)	50.00 (15.00 - 113.00)	50.00 (15.00 - 115.50)	50.00 (15.00 - 107.00)	77.00 (50.00 - 153.00)	75.00 (50.00 - 152.00)	75.00 (50.00 - 152.00)	81.00 (50.00 - 161.00)	68.00 (50.00 - 140.00)
Cumulative dose (mg)	Median (Q25 - Q75)	4,000.00 (1,440.00 - 8,000.00)	2,000.00 (960.00 - 4,785.00)	2,000.00 (960.00 - 4,800.00)	2,000.00 (960.00 - 4,800.00)	2,000.00 (960.00 - 4,320.00)	100.00 (50.00 - 226.00)	75.00 (30.00 - 150.00)	75.00 (30.00 - 150.00)	75.00 (30.00 - 150.00)	75.00 (30.00 - 150.00)
Initial daily dose (mg)	Median (Q25 - Q75)	40.00 (40.00 - 40.00)	40.00 (24.00 - 59.70)	40.00 (24.00 - 59.70)	40.00 (24.00 - 59.70)	40.00 (28.24 - 59.70)	1.00 (0.50 - 2.00)	1.00 (0.50 - 1.00)	1.00 (0.50 - 1.00)	1.00 (0.50 - 1.00)	1.00 (0.50 - 1.00)

D) IQVIA LPD Belgium

Variable	Estimate name	Cohort name									
		quetiapine_oral					risperidone_oral				
		Age group					Age group				
		0 to 64	≥ 65	overall	Sex		0 to 64	≥ 65	overall	Sex	
		overall	overall	overall	Female	Male	overall	overall	overall	Female	Male
Number subjects	N	31	609	640	359	281	22	477	499	302	197
Exposed time (day)	Median (Q25 - Q75)	63.00 (30.00 - 134.00)	93.00 (31.00 - 132.00)	90.00 (30.75 - 132.25)	60.00 (30.00 - 120.00)	100.00 (55.00 - 160.00)	60.00 (20.00 - 100.00)	60.00 (28.00 - 120.00)	60.00 (28.00 - 120.00)	60.00 (26.50 - 120.00)	60.00 (30.00 - 120.00)
Cumulative dose (mg)	Median (Q25 - Q75)	4,000.00 (2,500.00 - 12,150.00)	3,000.00 (1,500.00 - 7,500.00)	3,000.00 (1,500.00 - 7,500.00)	2,500.00 (1,500.00 - 6,325.00)	3,000.00 (2,500.00 - 9,000.00)	80.00 (20.00 - 115.00)	60.00 (0.00 - 100.00)	60.00 (0.00 - 100.00)	60.00 (0.00 - 100.00)	60.00 (6.00 - 100.00)
Initial daily dose (mg)	Median (Q25 - Q75)	50.00 (50.00 - 175.00)	50.00 (25.00 - 73.53)	50.00 (25.00 - 75.00)	50.00 (25.00 - 75.76)	50.00 (25.00 - 50.00)	1.00 (1.00 - 3.50)	1.00 (0.00 - 1.00)	1.00 (0.00 - 1.00)	0.50 (0.00 - 1.00)	1.00 (0.50 - 1.00)

E) DK-DHR: haloperidol routes

Variable	Estimate name	Cohort name: haloperidol_oral					Cohort name: haloperidol_parenteral				
		Age group			Sex		Age group			Sex	
		0 to 64	≥ 65	overall	Female	Male	0 to 64	≥ 65	overall	Female	Male
		overall	overall	overall			overall	overall	overall		
Number subjects	N	137	3,110	3,247	1,696	1,551	114	5,109	5,223	3,137	2,086
Exposed time (day)	Median (Q25 - Q75)	62 (25 - 62)	26 (25 - 62)	27 (25 - 62)	25 (25 - 62)	31 (25 - 62)	3 (3 - 6)	3 (3 - 3)	3 (3 - 3)	3 (3 - 3)	3 (3 - 3)
Cumulative dose (mg)	Median (Q25 - Q75)	564.52 (377.00 - 1,000.00)	496.59 (200.00 - 1,000.00)	500.00 (200.00 - 1,000.00)	500.00 (212.90 - 1,000.00)	500.00 (200.00 - 1,000.00)	50.00 (25.00 - 100.00)	50.00 (25.00 - 50.00)	50.00 (25.00 - 50.00)	50.00 (25.00 - 50.00)	50.00 (25.00 - 50.00)
Initial daily dose (mg)	Median (Q25 - Q75)	8.06 (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)

F) DK-DHR: Risperidone oral drug route

Cohort name						
		risperidone_oral				
		Age group				
		0 to 64	≥ 65	overall		
				Sex		
Variable	Estimate name	overall	overall	overall	Female	Male
Number subjects	N	321	5,983	6,304	3,604	2,700
Exposed time (day)	Median (Q25 - Q75)	33 (12 - 78)	22 (4 - 56)	22 (4 - 57)	23 (5 - 58)	21 (4 - 55)
Cumulative dose (mg)	Median (Q25 - Q75)	120.00 (50.00 - 320.00)	70.00 (30.00 - 160.00)	70.00 (30.00 - 170.00)	80.00 (30.00 - 170.00)	70.00 (30.00 - 173.25)
Initial daily dose (mg)	Median (Q25 - Q75)	10.00 (5.00 - 10.00)	10.00 (5.00 - 10.00)	10.00 (5.00 - 10.00)	10.00 (5.00 - 10.00)	10.00 (5.00 - 10.00)

13.2.4. Objective 4: Survival Analyses

This section reports the Kaplan-Meier curves of one-year survival of incident users of antipsychotics among patients diagnosed with dementia. These results are unadjusted and therefore only represent 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%.

Overall and age stratification among patients with dementia

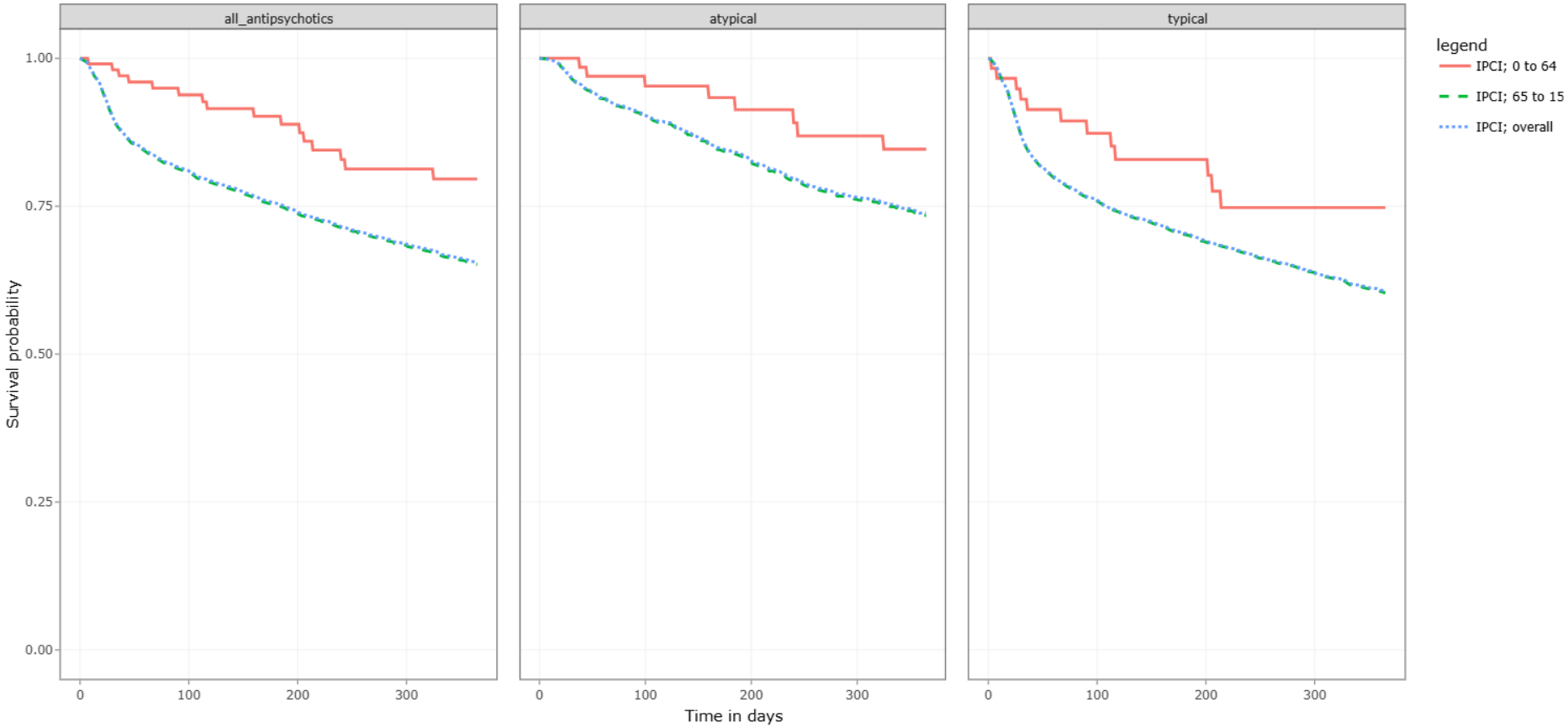
Figure 19 depict one-year survival curves overall and stratified by age in IPCI, SIDIAP, and DK-DHR.

Across the databases of IPCI, SIDIAP, and DK-DHR, the typical antipsychotic cohort had lower survival probabilities compared to the atypical antipsychotic cohort. The survival percentages in IPCI are as follows: all antipsychotics (65%), atypical antipsychotics (74%), typical antipsychotics (61%). For SIDIAP: all antipsychotics (80%), atypical (80%), typical (67%). DK-DHR had the largest age difference in survival, particularly among the typical cohort: all antipsychotics (51%), atypical (64%), typical (26%).

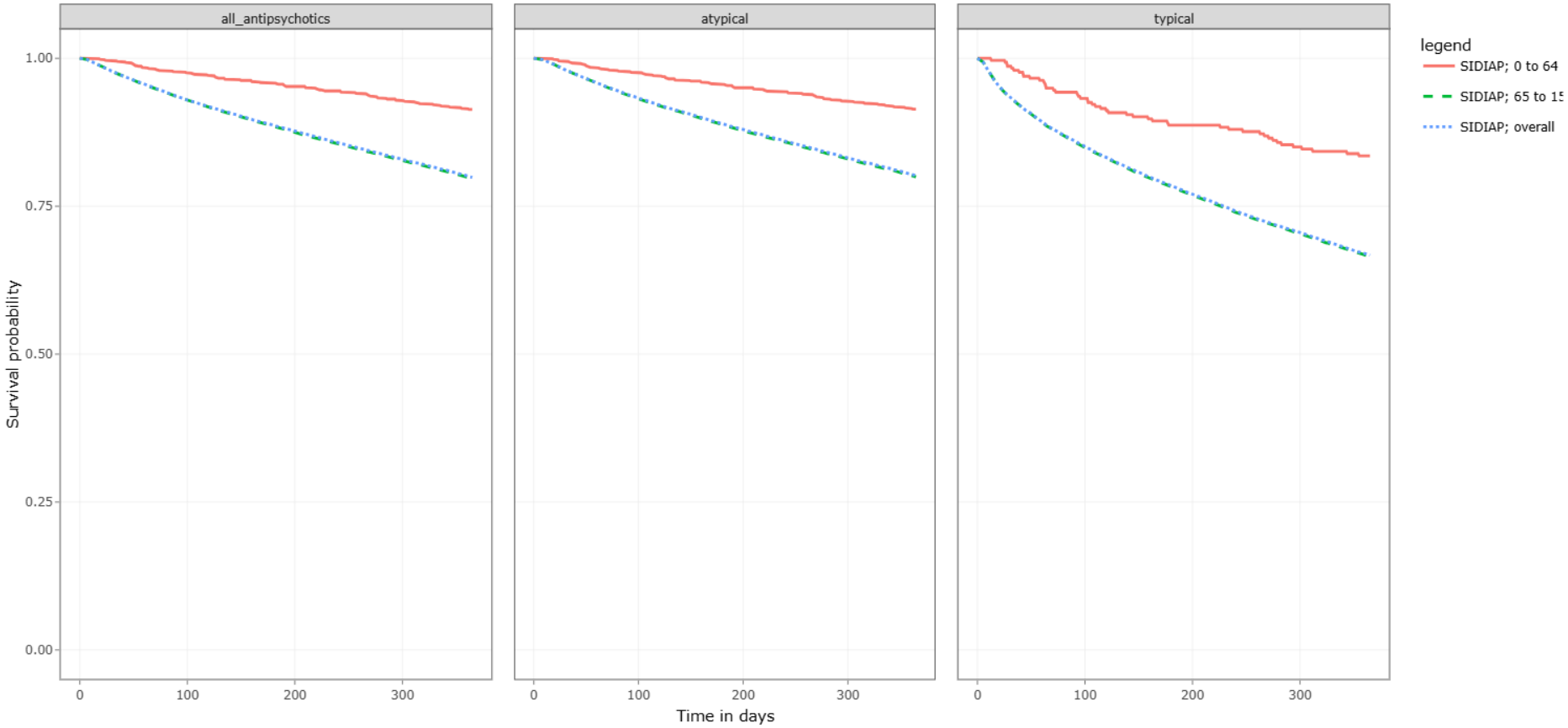
DK-DHR had the lowest survival among the three databases, with the typical antipsychotics users having a median survival of 24 days (95% CI: 21 - 27).

For IPCI, SIDIAP, and DK-DHR, across all and the specific types of antipsychotics, those in the ≥65-year-old age group showed similar probabilities of survival to the overall. The 0 to 64 age groups had higher survival probabilities.

A) IPCI


all_antipsychotics
atypical
typical
1.00
0.75
0.50
0.25
0.00
Survival probability
0
100
200
300
Time in days
legend
IPCI; 0 to 64
IPCI; 65 to 15
IPCI; overall

B) SIDIAP


all_antipsychotics
atypical
typical
1.00
0.75
0.50
0.25
0.00
Survival probability
0
100
200
300
Time in days
legend
SIDIAP; 0 to 64
SIDIAP; 65 to 15
SIDIAP; overall

C) DK-DHR

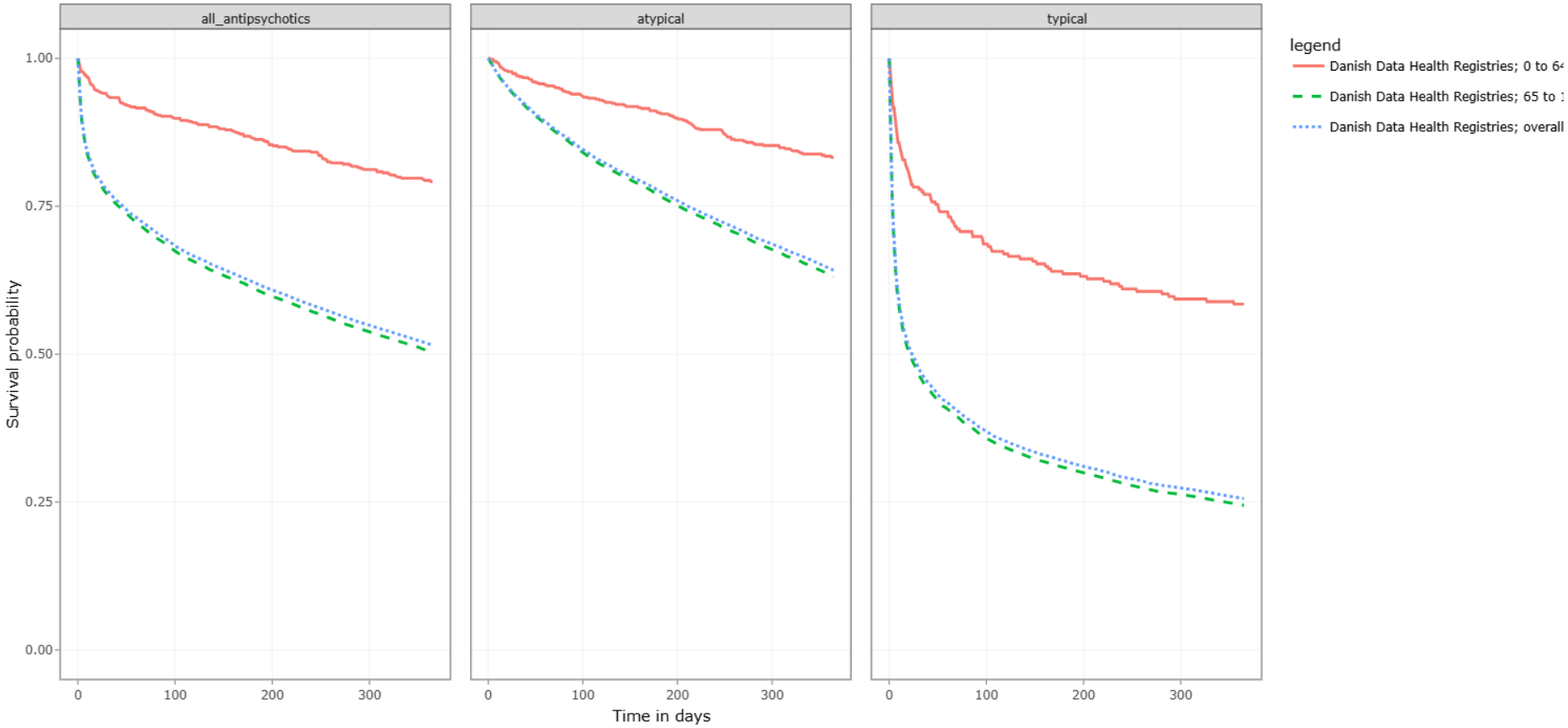
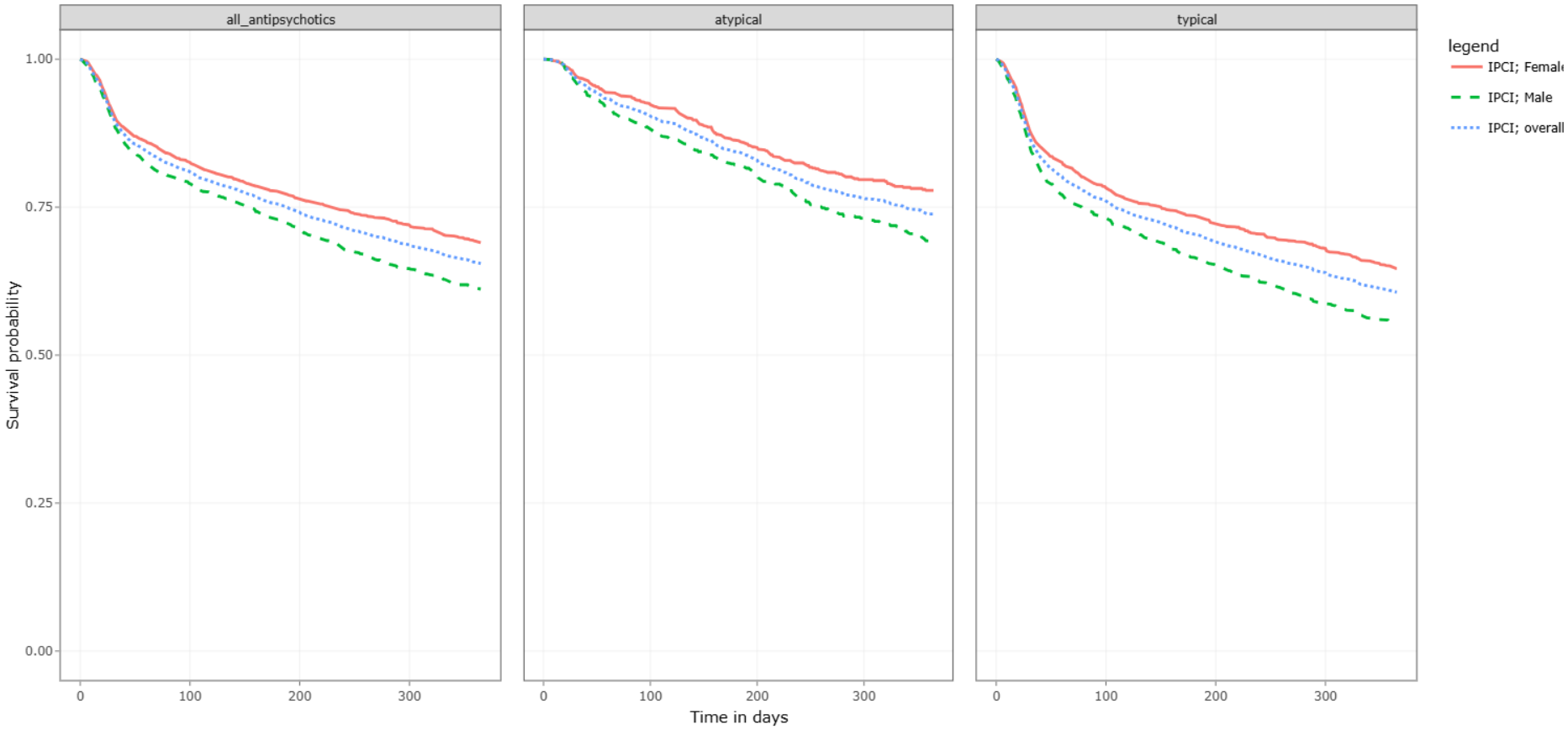


Figure 19. Kaplan-Meier curves illustrating the crude 1–year survival rates in all antipsychotics and typical and atypical for A) IPCI, B) SIDIAP, and C) DK-DHR among patients with dementia.

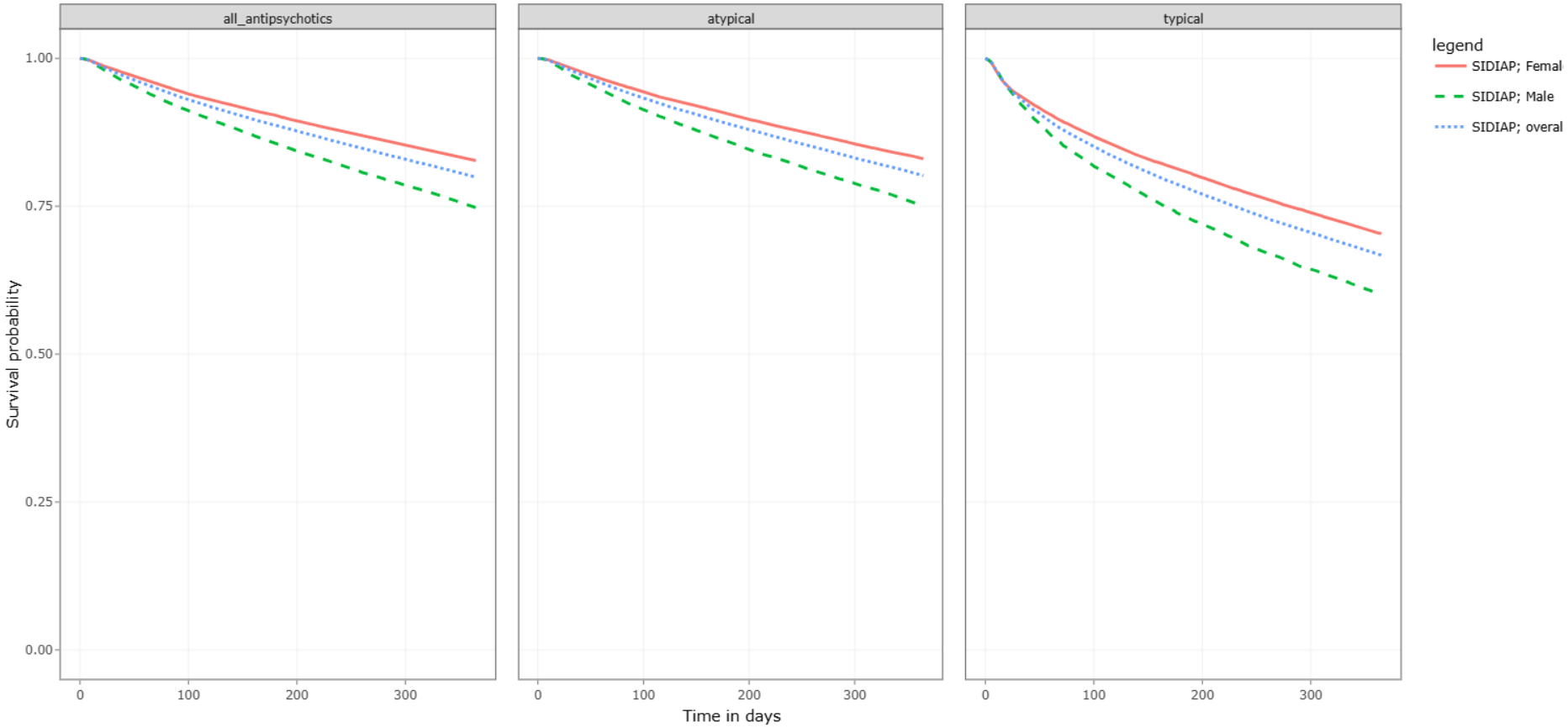
13.2.4.1. Sex stratification

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
1.00
0.75
0.50
0.25
0.00
Survival probability
0
100
200
300
Time in days
legend
SIDIAP; Femal
SIDIAP; Male
SIDIAP; overal

C) DK-DHR

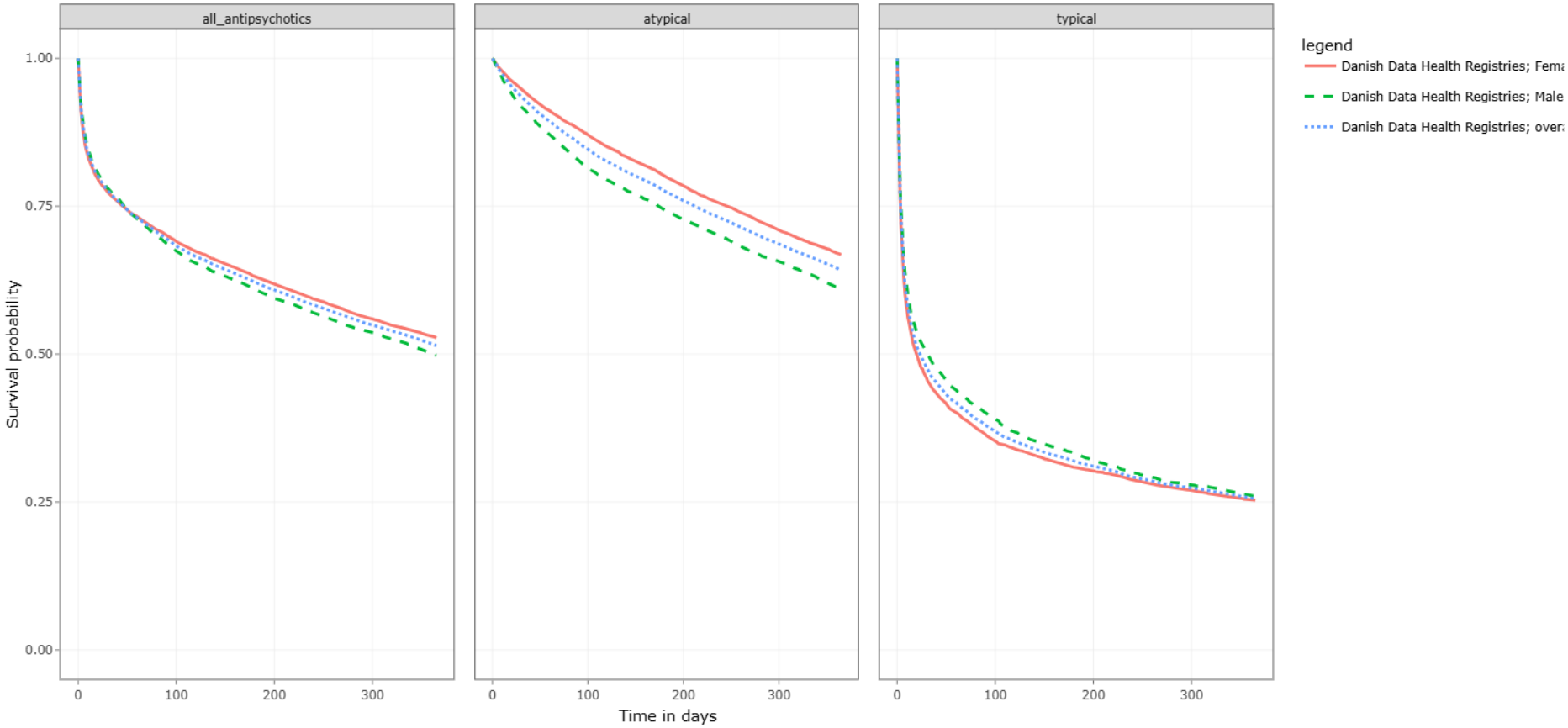


Figure 20. Kaplan-Meier curves illustrating the crude 1–year survival rates in all antipsychotics and typical and atypical stratified by sex for A) IPCI, B) SIDIAP, and C) DK-DHR among patients with dementia.

13.2.4.2. Top 5 most common antipsychotics per database

For the top 5 antipsychotics for IPCI, the typical antipsychotic, haloperidol, had the lowest one-year survival (60%). The other antipsychotics had higher survival probabilities, clozapine (76%), pipamperone (67%), quetiapine (78%), and risperidone (71%) (**Figure 21**).

Similarly, for the top 5 antipsychotics in the SIDIAP database, the typical antipsychotic haloperidol had the lowest one-year survival, with 67% surviving past the one-year. For the other antipsychotics, the proportion who survived for one-year was greater, olanzapine (72%), quetiapine (81%), risperidone (74%), and sulpiride (93%) (**Figure 22**).

In DK-DHR, haloperidol had the lowest one-year survival among the other top 5 antipsychotics and compared to the other databases, with 22% surviving past the one-year and a median survival of 17 days (95% CI: 16 - 19). Other antipsychotics had higher survival percentages, clozapine (75%), pipamperone (63%), quetiapine (69%), and risperidone (62%) (**Figure 23**).

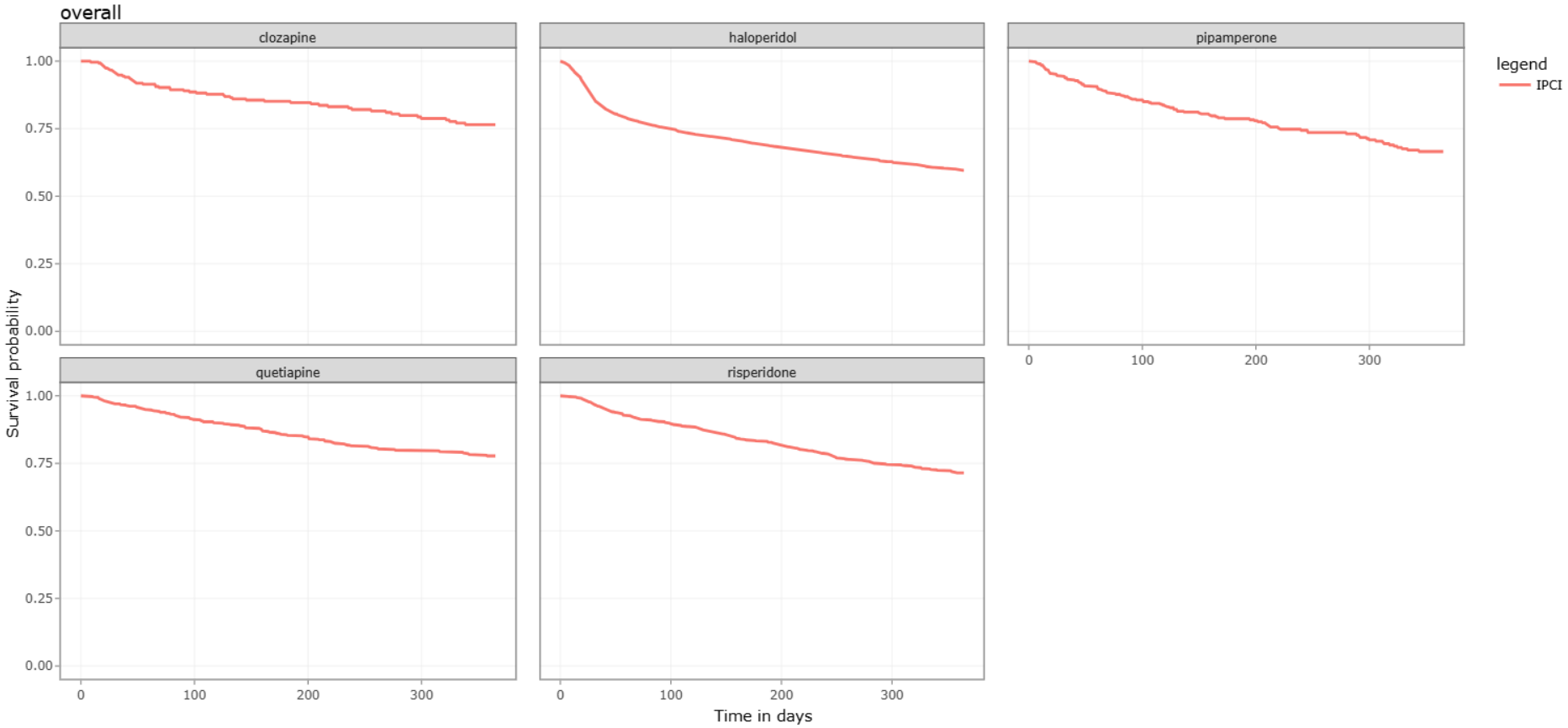


Figure 21. Kaplan-Meier curves illustrating the crude 1–year survival rates in the top 5 most common antipsychotics in IPCI among patients with dementia.

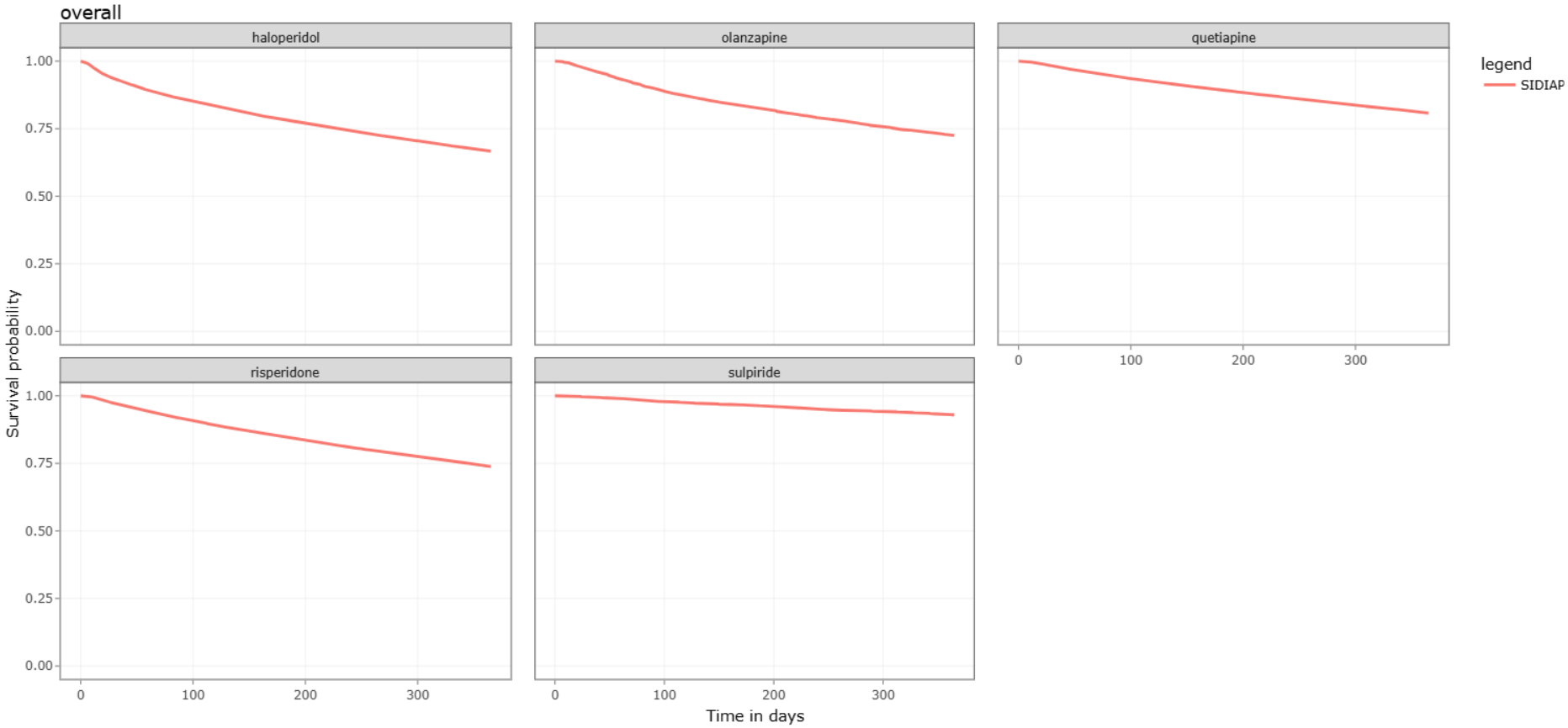


Figure 22. Kaplan-Meier curves illustrating the crude 1–year survival rates in the top 5 most common antipsychotics in SIDIAP among patients with dementia.

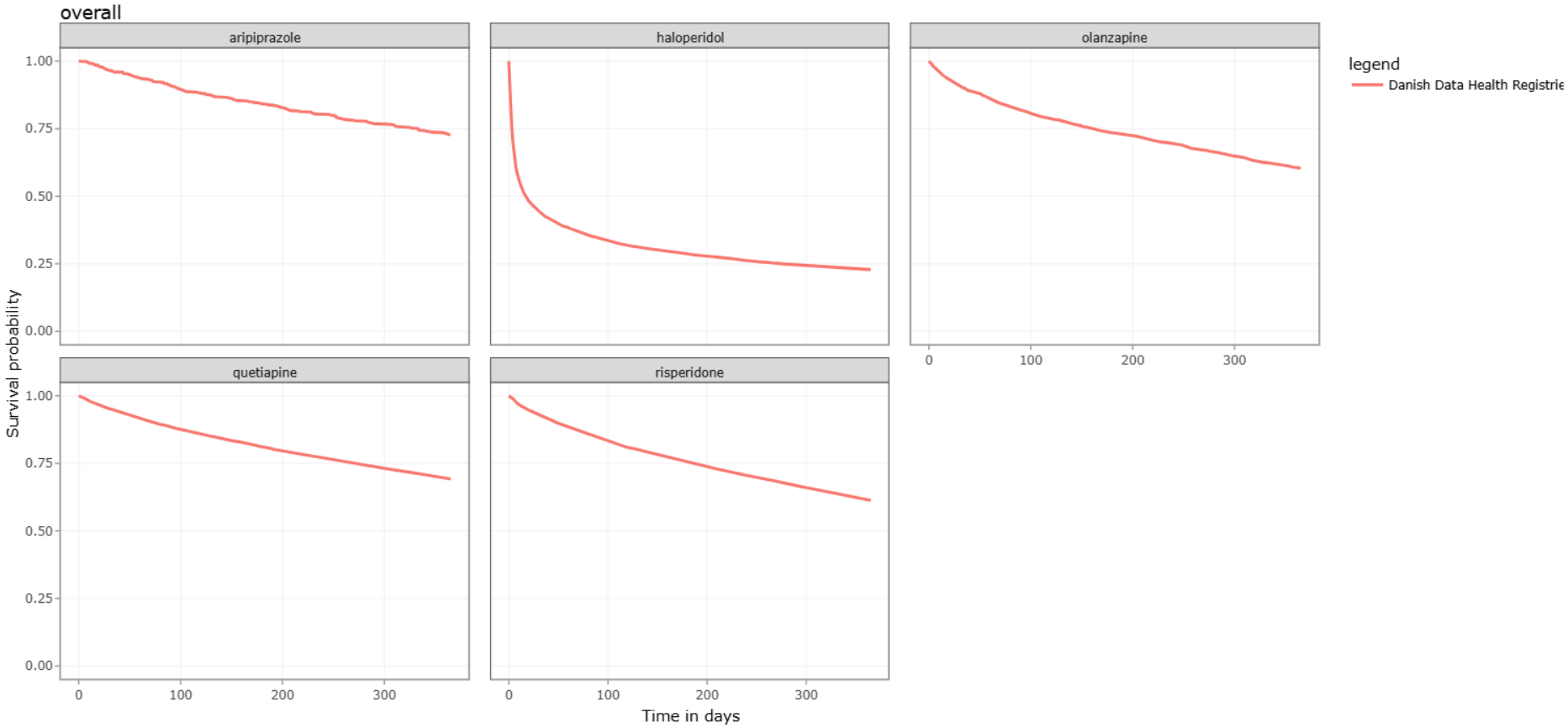


Figure 23. Kaplan-Meier curves illustrating the crude 1–year survival rates in the top 5 most common antipsychotics in DK-DHR among patients with dementia.

13.3. Sub-populations

Results from sub-group analyses among patients with vascular and Alzheimer's dementia can be found in the Shiny App. **Table 14** summarises the proportions of individuals from our overall dementia population that are in each of the sub-groups. In brief, patient characteristics and drug utilisation were similar to the overall dementia population. Incidence rate and crude survival curve trends were also consistent with the overall dementia population.

Table 14. Number of individuals in the Alzheimer's and vascular dementia subgroups across databases

Number of individuals	IPCI	IQVIA LPD Belgium	IQVIA DA Germany	NAJS	SIDIAP	DK-DHR
Overall dementia new antipsychotic users	5,034	1,270	38,374	33,419	60,241	14,129
Alzheimer's dementia new antipsychotic users	1,927 (38%)	610 (48%)	14,382 (37%)	8,304 (25%)	29,332 (49%)	8,915 (63%)
Vascular dementia new antipsychotic users	541 (11%)	84 (7%)	7,679 (20%)	10,216 (31%)	7,170 (12%)	1,697 (12%)

14. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

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

15. DISCUSSION

15.1. Key results

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

We found that the proportion of patients with dementia taking antipsychotics ranged between 17% (DK-DHR) to 78% (SIDIAP). When characterising new users of antipsychotics among patients with dementia, we observed higher counts for atypical antipsychotics users than typical antipsychotics in all databases, except IPCI. The most prescribed atypical antipsychotics across databases in patients with dementia were quetiapine and risperidone, which appeared in all databases, whilst the most prescribed typical antipsychotic was haloperidol. The overall median age of participants with dementia ranged between 82 to 84 years of age across the six data sources. The proportion of females was higher than males in all of them. The most common comorbidities were hypertension (ranged 33-87%), type 2 diabetes (ranged 18-31%), and obesity (ranged 4-40%). Among other potential indications observed in addition to dementia, the most

common indications for antipsychotic initiation were depression, and insomnia and other sleep disorders: in the overall population of patients with dementia, depression ranged between 8% (IPCI) to 43% (IQVIA LPD Belgium) and insomnia and other sleep disorders ranged between 3% (DK-DHR) to 49% (IQVIA LPD Belgium). The observed median age, sex distribution, pre-existing conditions, and indications where were consistent when stratified by atypical and typical antipsychotic user cohorts.

General trends for annual IRs from 2013 to 2023 of overall antipsychotics use were relatively stable for IPCI, DK-DHR, and IQVIA LPD Belgium. There was a decreasing trend in NAJS. In SIDIAP and IQVIA DA Germany there were increasing trends. Incident use of atypical antipsychotics was higher for all databases, except IPCI and NAJS. When stratified by age, those in the ≥85-year-old age group had the highest IRs among most databases, except IQVIA LPD Belgium. This trend stayed consistent when stratified by atypical and typical antipsychotics for most databases, except atypical antipsychotic use in IPCI, DK-DHR, and NAJS. Incident use in men was higher in IPCI, DK-DHR, IQVIA LPD Belgium, and SIDIAP, whereas there no differences between sexes were observed in IQVIA DA Germany and NAJS. Additionally, the most commonly prescribed atypical antipsychotics were risperidone and quetiapine, whilst the most commonly prescribed typical antipsychotic was haloperidol. 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 younger than 65 years of age had better 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 poor in DK-DHR with a 22% surviving rate at one-year and a median survival of 17 days.

15.2. Limitations of the research methods

The study was conducted in routinely collected health care databases and so, data quality issues must be considered. 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. Therefore, recording of potential indication may be incomplete and may lead to potential misclassification. In addition, the completeness of recordings of co-morbidities used for patient characterisation may vary across databases.

Furthermore, 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, 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.

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 and therefore they were excluded from the survival analyses. NAJS did not contained information on dose and therefore was not included in the drug utilisation 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.

15.3. Interpretation

The proportion of antipsychotic use among patients with dementia observed during our study period of 2013 to 2023 ranged between 17 to 78%. From a meta-analysis of 43 studies across North America and Europe conducted in 2014, primarily in long-term care settings the pooled prevalence of use was 27.5% [95% CI 25.7% to 29.3%] (6). In our study, the proportion of antipsychotic use among patients with dementia in SIDIAP, IQVIA LPD Belgium, and Croatia was of 40% or higher, indicating higher than expected proportions of use in these countries.

Type and ingredient of antipsychotic usage across databases among patients with dementia differed to the general population. A related DARWIN EU® study of the antipsychotic use in the general population (using the same data sources) observed increased use of atypical antipsychotics when compared to typical, and the most common antipsychotics were quetiapine, sulpiride, risperidone and olanzapine [https://catalogues.ema.europa.eu/node/4231/methodological-aspects]. In contrast, patients with dementia had larger proportion of typical antipsychotic use in IPCI and DK-DHR. In addition, there were higher proportions of the population with dementia taking the atypical antipsychotic risperidone and the typical antipsychotic haloperidol across most databases. Other studies conducted among populations with dementia in a community-dwelling cohort in Canada between 1997 to 2003 showed three quarters of their population taking risperidone and 60% on haloperidol. The breakdown was also similar in the long-term care cohort (7). These results are consistent with commercial use, as risperidone and haloperidol are currently the only EU and UK approved drugs indicated for dementia, though many are taken off-label (8).

Our study found that among patients with dementia the population was older in age, had increased comorbidities, and higher proportion of females compared to the general population. Indications that were common among the general population such as depression and insomnia and other sleep disorders were seen at lower rates. Thus, assumptions could be made that those without other indications may be prescribed antipsychotics for their dementia. However, antipsychotic prescription for dementia is not well supported by current evidence and guidelines. For example, the European Academy of Neurology recommends, with low levels of evidence, atypical antipsychotics prescription for dementia only after all non-pharmacological measures have been proven to be without benefit or in the case of severe self-harm or harm to others (4).

Trends in IRs among patients with dementia were stable for IPCI, DK-DHR, and IQVIA LPD Belgium, with decreasing trends in NAJS and increasing trends in SIDIAP and IQVIA DA Germany. Previous studies

examined trends in prevalence over time saw decreasing trends from the 2000s to 2010s in both Denmark and the UK (9,10). Efforts have been made to curb prescribing of antipsychotics to patients with dementia. For example, in 2008 the EMA issued safety warnings regarding the use of all antipsychotics for patients with dementia (4), the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) specifies only certain specific cases where prescribing antipsychotics may be appropriate (11). Whether these trends and the stable incident use observed in our study were due to safety warnings by the EMA from 2008 remains unclear. For example, a study using data from IPCI from 2008 to 2013 saw a decrease in prevalence in antipsychotic use in elderly dementia patients after the 2009 EMA warnings (2). However, in France, among patients with dementia there was an observed reduction of 14.2% in 2004 to 10.2% in 2011 which was unaffected by warnings (12).

In our study, curves of mortality among the population with dementia was lower overall than the general population, which could be attributed to the advanced age and severity of comorbidities. When comparing survival across different antipsychotics, haloperidol saw lowest survival probabilities in both the general population and among those with dementia. Other studies conducted in a nursing home setting found that compared to risperidone, users of haloperidol had an increased rate of mortality (13), and that haloperidol had highest 180-day crude mortality relative to nonusers at 21% (14). Thus, concerns of lower mortality with haloperidol have been well documented and supported by our results. The use of antipsychotics in elderly and patients with dementia is associated with an increased risk of severe morbidity and mortality (15–18). Mok et al. recently reported that among 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 (19).

15.4. Generalisability

The study comprised all individuals with dementia 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.

16. CONCLUSION

Our study aimed to characterise antipsychotic use among patients with dementia across six primary care databases in Europe. The proportion of patients with dementia taking antipsychotics ranged between 17% (DK-DHR) to 78% (SIDIAP). We observed atypical antipsychotic initiation of risperidone and quetiapine, and typical antipsychotic use of haloperidol as the most commonly prescribed antipsychotics. Patients with dementia taking antipsychotics had high proportions of comorbidities, were more frequently female, and among other potential indications observed in addition to dementia, the most common were depression, insomnia and other sleep disorders.

Trends in IRs among patients with dementia were stable for IPCI, DK-DHR, and IQVIA LPD Belgium, with decreasing trends in NAJS and increasing trends in SIDIAP and IQVIA DA Germany. Incident use of antipsychotics among patients with dementia was higher in those over 85 years of age compared to other age groups for most databases, and typical antipsychotic rates were higher than atypical antipsychotic rates in IPCI and NAJS. Use in men was consistently higher than women for most databases. Among the most prescribed antipsychotics, one-year survival was high. Survival was lowest among those taking the typical antipsychotic haloperidol in IPCI, SIDIAP, and DK-DHR.

These results were consistent between different types of dementia of vascular and Alzheimer’s dementia.

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18. ANNEXES

Appendix I: Concept List for Antipsychotic substances.

ATC Code	Substance Name	Typical/Atypical	ConceptID 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

Concept List for dementia

Concept ID	Concept Name
4167839	Primary degenerative dementia of the Alzheimer type, senile onset, with delirium
4204688	Primary degenerative dementia of the Alzheimer type, senile onset, with delusions
4097384	Primary degenerative dementia of the Alzheimer type, senile onset, with depression
36674472	PRKAR1B-related neurodegenerative dementia with intermediate filaments
4043379	Progressive aphasia in Alzheimer's disease
37311890	Psychological symptom due to dementia
37109635	Rapidly progressive dementia
37395572	Alzheimer's disease co-occurrent with delirium
36717455	Familial Alzheimer-like prion disease
4046091	Semantic dementia
4048875	Senile dementia
4236297	GDS level 7 - very severe cognitive decline
4196433	Senile dementia of the Lewy body type
37312036	Aggression due to dementia
376946	Senile dementia with delirium
45765477	GRN-related frontotemporal dementia
380986	Senile dementia with delusion
44782726	Delusions in Alzheimer's disease
379778	Multi-infarct dementia
379784	Senile dementia with depression
37109222	Hallucinations co-occurrent and due to late onset dementia
37312035	Agitation due to dementia
4043243	Familial Alzheimer's disease of late onset
4043377	Focal Alzheimer's disease
4182210	Dementia
4043378	Frontotemporal dementia
44784643	Altered behavior in Alzheimer's disease
45765480	Frontotemporal dementia with parkinsonism-17
4101137	Senile dementia with depressive or paranoid features
4228133	Dementia associated with AIDS
4100250	Senile dementia with paranoia
4159643	Senile dementia with psychosis
44784620	Altered behavior in Huntington's dementia

Concept ID	Concept Name
3654598	Amyotrophic lateral sclerosis, parkinsonism, dementia complex
765653	Severe dementia
42538857	Subcortical dementia
37395562	Multi-infarct dementia due to atherosclerosis
45766396	Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia
4250118	GDS level 4 - moderate cognitive decline
377254	Multi-infarct dementia, uncomplicated
762704	Moderate dementia
4233045	GDS level 5 - moderately severe cognitive decline
378419	Alzheimer's disease
374888	Dementia associated with another disease
4236296	GDS level 6 - severe cognitive decline
4043244	Non-familial Alzheimer's disease of late onset
444091	Multi-infarct dementia with delirium
4044415	Language disorder of dementia
4224860	Organic dementia associated with AIDS
37312031	Anxiety due to dementia
37312030	Apathetic behavior due to dementia
37117145	Behavioral disturbance co-occurrent and due to late onset Alzheimer dementia
44784472	Dementia associated with cerebral lipidosis
44784474	Dementia associated with multiple sclerosis
376094	Arteriosclerotic dementia with delirium
374326	Arteriosclerotic dementia with depression
44782763	Lewy body dementia with behavioral disturbance
443790	Multi-infarct dementia with delusions
37110513	Dementia due to disorder of central nervous system
4100252	Arteriosclerotic dementia with paranoia
4047748	Patchy dementia
443864	Multi-infarct dementia with depression
37399020	Behavioral variant of frontotemporal dementia
35610098	Predominantly cortical dementia
4314734	Dementia associated with Parkinson's Disease
762497	Mild dementia
40483103	Dementia due to Huntington chorea

Concept ID	Concept Name
36716796	Dementia due to metabolic abnormality
44782559	Dementia due to multiple sclerosis with altered behavior
35608576	Behavioral and psychological symptoms of dementia
4092747	Cerebral degeneration presenting primarily with dementia
36716558	Non-amnestic Alzheimer disease
35610099	Predominantly cortical vascular dementia
44782422	Dementia due to Parkinson's disease
4046090	Mixed cortical and subcortical vascular dementia
37017549	Dementia co-occurrent with human immunodeficiency virus infection
378125	Presenile dementia
45771254	CHMP2B-related frontotemporal dementia
44782710	Dementia due to Pick's disease
4224240	Presenile dementia associated with AIDS
37017247	Presenile dementia co-occurrent with human immunodeficiency virus infection
36717248	Ischemic vascular dementia
381832	Presenile dementia with delirium
4043242	Non-familial Alzheimer's disease of early onset
44782771	Presenile dementia with delusions
441002	Dementia of frontal lobe type
43021816	Mixed dementia
44782727	Depressed mood in Alzheimer's disease
3654434	Cortical vascular dementia
377527	Presenile dementia with depression
4098163	Presenile dementia with paranoia
37111242	Delirium co-occurrent with dementia
4218017	Primary degenerative dementia of the Alzheimer type, presenile onset
43530664	Dementia of the Alzheimer type with behavioral disturbance
380701	Diffuse Lewy body disease
35610096	Presenile dementia with psychosis
43530666	Dementia with behavioral disturbance
43020444	Primary degenerative dementia
4277444	Primary degenerative dementia of the Alzheimer type, presenile onset, uncomplicated
37311665	Disinhibited behavior due to dementia
44782432	Early onset Alzheimer's disease with behavioral disturbance

Concept ID	Concept Name
37110677	Epilepsy co-occurrent and due to dementia
4277746	Primary degenerative dementia of the Alzheimer type, presenile onset, with delirium
4182539	Primary degenerative dementia of the Alzheimer type, presenile onset, with delusions
4019705	Primary degenerative dementia of the Alzheimer type, presenile onset, with depression
4220313	Primary degenerative dementia of the Alzheimer type, senile onset
4278830	Primary degenerative dementia of the Alzheimer type, senile onset, uncomplicated
762578	Primary degenerative dementia of the Alzheimer type, senile onset, with behavioral disturbance
4047747	Subcortical vascular dementia
439276	Uncomplicated arteriosclerotic dementia
376085	Uncomplicated presenile dementia
375791	Uncomplicated senile dementia
443605	Vascular dementia
4046089	Vascular dementia of acute onset
37018688	Vascular dementia with behavioral disturbance
37109056	Vascular dementia without behavioral disturbance
37312577	Wandering due to dementia
4043241	Familial Alzheimer's disease of early onset
37018608	Epileptic dementia with behavioral disturbance
4244346	Dialysis dementia
37116469	Dementia with Down syndrome
43020422	Dementia due to Rett's syndrome
42538609	Dementia due to prion disease
378726	Dementia associated with alcoholism
4041685	Amyotrophic lateral sclerosis with dementia
36716797	Dementia due to chromosomal anomaly
44784607	Dementia associated with cerebral anoxia
37396063	Parkinsonism with dementia of Guadeloupe
4180284	Dementia due to Creutzfeldt Jakob disease