Study Report

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DARWIN EU® - Treatment characterisation and post-diagnosis outcomes in individuals with Alzheimer's disease

18/06/2026

Version 4.0

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Public

CONTENTS

Study title	DARWIN EU® - Treatment characterisation and post-diagnosis outcomes in individuals with Alzheimer's disease
Study report version	V4.0
Date	18/06/2026
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Active substance	• Acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) • Memantine • Antipsychotics
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Objectives	Research objectives The aim of this study is to describe pharmacological treatment patterns, clinical and care-related events, and survival of patients with Alzheimer's disease (AD) in the 5 years after diagnosis. The specific objectives of this study are: 1. To describe the demographic characteristics and clinical profile of individuals who initiate AD treatment within 5 years after the diagnosis of AD. 2. To describe the prevalence of pharmacological treatments recorded post-diagnosis of AD, overall and by treatment class. 3. To describe timing and sequences of pharmacological treatments following AD diagnosis, in terms of: a. Time from diagnosis to first treatment initiation, overall and by pharmacological treatment class. b. Sequencing of treatments of interest up to 5 years following diagnosis, by pharmacological treatment class. 4. To describe the timing and frequency of relevant clinical and care-related events following AD diagnosis, in terms of: a. Number of hospitalisations b. Number of outpatient visits c. Time to first record of caregiver support d. Prevalence of at least one recorded caregiver support. 5. To describe survival in terms of: a. 5-year overall survival from AD diagnosis. b. 5-year overall survival from first AD treatment initiation following AD diagnosis.
Countries of study	Croatia, Denmark, Germany, The Netherlands
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LIST OF ABBREVIATIONS

Acronyms/terms	Description
AD	Alzheimer's disease
ApoE ε4	Apolipoprotein E ε4
ARIA	Amyloid-related imaging abnormalities
ATC	Anatomical Therapeutic Chemical
CC	Coordination centre
CI	Confidence interval
CDM	Common Data Model
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DE	Germany
DK	Denmark
DK-DHR	Danish Data Health Registries
DRE	Digital Research Environment
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUPAS	EU Post-Authorisation Studies Register
GDPR	General Data Protection Regulation
HR	Croatia
ICD	International Classification of Diseases
IgG1	Immunoglubulin G1
InGef RDB	InGef Research Database
IPCI	The Integrated Primary Care Information
IQR	Interquartile range
IQVIA DA Germany	IQVIA Disease Analyser Germany
IRB	Institutional Review Board
KM	Kaplan-Meier
MCI	Mild Cognitive Impairment
MRI	Magnetic Resonance Imaging
NAJS	National Public Health Information System
NL	The Netherlands
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
RxNorm	Medical prescription normalized
SD	Standard deviation

Acronyms/terms	Description
SNOMED	Systematized Nomenclature of Medicine
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Treatment characterisation and post-diagnosis outcomes in individuals with Alzheimer's disease

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Melissa Leung Guido van Leeuwen	Erasmus MC
Co-Principal Investigator	Talita Duarte-Salles	Erasmus MC
Data Scientist	Ger Inberg Adam Black	Erasmus MC
Clinical Domain Expert	Guido van Leeuwen	Erasmus MC
Study Manager	Natasha Yefimenko	Erasmus MC
Data source	**Names**	**Data Partner Organisation***
NAJS	Antea Jezidžić Marko Čavlina Karlo Pintaric Anamaria Jurcevic Jakov Vukovic	Croatian Institute of Public Health
DK-DHR	Elvira Bräuner Susanne Bruun	Danish Medicines Agency
InGef RDB	Josephine Jacob Raeleesha Norris Alexander Harms Annika Vivirito	Institute for Applied Health Research Berlin GmbH
IQVIA DA Germany	Dina Vojinovic Akram Sharim Mendez Rangel Ellen Gerritsen Gargi Jadhav Hugo Vernooij Isabella Kaczmarczyk	IQVIA
IPCI	Katia Verhamme	Erasmus MC

*Data partners do not have an investigator role. Data partners execute code at their data source, review, and approve their results.

3. ABSTRACT

Title

DARWIN EU® - Treatment characterisation and post-diagnosis outcomes in individuals with Alzheimer's disease

Rationale and background

Alzheimer's disease (AD) is the most common cause of dementia, characterised by progressive cognitive decline and increasing loss of independence. Its burden is rising globally due to population ageing, with substantial implications for healthcare systems and society. Recent therapeutic advances, such as the approval of anti-amyloid monoclonal antibodies, are reshaping AD management, but also highlight the need for updated real-world evidence on the epidemiology and characteristics of affected populations.

Objectives

To describe pharmacological treatment patterns, clinical and care-related events, and survival of patients with AD in the 5 years after diagnosis.

The specific objectives of this study were:

1. To describe the demographic characteristics and clinical profile of individuals who initiate AD treatment within 5 years after the diagnosis of AD.
2. To describe the prevalence of pharmacological treatments recorded post-diagnosis of AD, overall and by treatment class.
3. To describe timing and sequences of pharmacological treatments following AD diagnosis, in terms of a) time from diagnosis to first treatment initiation, overall and by pharmacological treatment class, and b) sequencing of treatments of interest up to 5 years following diagnosis, by pharmacological treatment class.
4. To describe the timing and frequency of relevant clinical and care-related events following AD diagnosis, in terms of a) number of hospitalisations, b) number of outpatient visits, c) time to first record of caregiver support, and d) prevalence of at least one recorded caregiver support.
5. To describe survival in terms of a) 5-year overall survival from AD diagnosis, and b) 5-year overall survival from first AD treatment initiation following AD diagnosis.

Methods

Study design

Cohort study. Four cohorts were created: (1) objectives 1 and 5b; (2) objectives 2, 3b, 4a–b, 4d, and 5a; (3) objective 3a; and (4) objective 4c. The index date, i.e. date of cohort entry, was the date of treatment initiation for AD after the first AD diagnosis (objectives 1 and 5b) and the date of the first AD diagnosis (objectives 2–5a). In all cohorts, individuals were followed up until the earliest of: 5 years of follow-up, end of data availability, end of the study period (31/12/2024), or death.

Population

The study population for objectives 1 and 5b included individuals with incident AD and with AD treatment initiation between 01/01/2014 and 31/12/2023. The study population for objectives 2, 3b, 4a–b, 4d, and 5a included individuals in the data source with incident AD, defined as a first diagnosis of AD between 01/01/2014 and 31/12/2023 with at least 365 days of database history prior to the date of the first diagnosis of AD (index date) and aged ≥18 years at index date.

Outcome

The outcomes of interest were: prescription of pharmacological treatments for AD (objectives 2 and 3), occurrence of clinical and care-related events (objective 4), and overall survival (objective 5). The pharmacological treatments of interest were acetylcholinesterase inhibitors (*donepezil, rivastigmine, and galantamine*), memantine, and antipsychotics. The clinical and care-related events of interest were hospitalisation, outpatient visit, and caregiver support.

Data source

1. Croatia: Croatian National Public Health Information System (NAJS)
2. Denmark: Danish Data Health Registries (DK-DHR)
3. Germany: InGef Research Database (InGef RDB)
4. Germany: IQVIA Disease Analyzer Germany (IQVIA DA Germany)
5. The Netherlands: Integrated Primary Care Information (IPCI)

Statistical analysis

Analyses were conducted separately for each data source and carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data. A minimum cell count of 5 was used when reporting results, with any smaller count reported as "<5" and a cell count of zero as "0".

Objective 1: Age was reported as mean (standard deviation) and median (interquartile range (IQR)). Age group, sex, pre-specified comorbidities, concomitant medications, and prior cognitive diagnosis were reported as counts and proportions.

Objective 2: The number and percentage of individuals receiving each of a pre-specified list of AD treatments and treatment classes (see **Annex V**) was described within 1, 3, and 5 years after index date. The results were reported overall and stratified by age and sex.

Objective 3: Time from AD diagnosis to first treatment initiation was reported as median, 5th, 25th, 75th, and 95th percentiles, with 95% confidence interval (CI) around each estimate. Treatment sequence was reported as the number of individuals and percentage of the study population with each sequence. Additionally, sunburst plots were used to describe treatment sequences over time from 0 days to 5 years post index date. The results were reported overall and stratified by age and sex.

Objective 4: Frequency of hospitalisations and outpatient visits was reported as mean (Standard deviation (SD)) and median (IQR, min–max range) within 1, 3, and 5 years after index date. Time from AD diagnosis to first caregiver support was reported as median, 5th, 25th, 75th, and 95th percentiles, with 95% CI around each estimate. The number and percentage of individuals receiving caregiver support was described within 1, 3 and 5 years after index date. The results were reported overall and stratified by age and sex.

Objective 5: Overall survival up to 5 years from AD diagnosis (objective 5a) and from treatment initiation following AD diagnosis (objective 5b) was calculated using the Kaplan-Meier (KM) method. Results were reported as plots of the estimated survival curves, as well as the estimated median survival and the estimated 5-year survival probability. In addition, overall survival was estimated after every 6 months post-diagnosis of AD. The results were reported overall and stratified by age and sex.

All objectives: For the analyses of objectives 2–5, the number and percentage of individuals with the outcome (except for hospitalisations and outpatient visits) was reported. All analyses were reported by country/data source, overall and restricted to the subgroup of the study population with history of mild cognitive impairment (MCI) prior to diagnosis of AD. The analyses for objectives 2–5 were additionally reported stratified by sex and age (categorised into categorised into 18–55; 56–65; 66–75; 76–85; and ≥86 years).

Results

The number of individuals with a first record of AD diagnosis (i.e. incident AD) and a first treatment prescription for AD included in this study was 9,909 in NAJS, 49,200 in DK-DHR, 25,546 in InGef RDB, 10,648 in IQVIA DA Germany, and 1,185 in IPCI, with a median age ranging from 77 years in IPCI to 81 years in IQVIA DA Germany and with the proportion of females ranging from 54.4% in InGef RDB to 65.8% in NAJS. The most prescribed medications during the year prior to index date were antihypertensives and lipid-lowering drugs. The most common comorbidities were hypertension and diabetes. Among individuals with a first treatment prescription for AD, the prevalence of a diagnosis of MCI prior to the diagnosis of AD ranged from 5.6% in DK-DHR to 14.2% in IQVIA DA Germany.

Across most data sources, more than 50% of the individuals with incident AD were prescribed a pharmacological treatment (i.e. acetylcholinesterase inhibitors, memantine, or antipsychotics) during the first year after AD diagnosis. IPCI was an exception, where only a quarter of individuals were prescribed any of these treatments. The prevalence of acetylcholinesterase inhibitor prescriptions was highest in DK-DHR (75.1%), while it ranged from 14.9% in IPCI to 34.0% in InGef RDB in the other data sources. The prevalence of memantine prescriptions was lowest in IPCI (0.7%) and ranged from 12.2% in IQVIA DA Germany to 43.3% in NAJS in the other data sources. The prevalence of antipsychotic prescriptions ranged from 13.6% in DK-DHR to 45.4% in NAJS.

Twenty-five percent of the individuals initiated a pharmacological treatment for AD on the day of AD diagnosis in NAJS and DK-DHR, within 37 days [95% CI: 36–38] after AD diagnosis in InGef RDB, within 15 days [95% CI: 12–20] after AD diagnosis in IQVIA DA Germany, and within 471 days [95% CI: 435–507] after AD diagnosis in IPCI.

Monotherapy was more frequently prescribed than combination therapy as the initial treatment after AD diagnosis. The prevalence of prescription of acetylcholinesterase inhibitors and antipsychotics as the first treatment after diagnosis was similar in InGef RDB (approximately 30%), IQVIA DA Germany (approximately 20%), and IPCI (approximately 17%). The most common first treatments after diagnosis were acetylcholinesterase inhibitors in DK-DHR (prescribed to 73.0%) and memantine in NAJS (prescribed to 31.5%). Treatment sequences were uncommon in the population with incident AD: the prevalence of the most common sequence of prescriptions for two different treatments ranged from 1.5% (IPCI) to 14.8% (DK-DHR).

The median [IQR] number of hospitalisations per individual within five years after diagnosis of AD was 1 [0–3] in NAJS, 1 [0–2] in DK-DHR, and 2 [1–3] in InGef RDB. The median [IQR] number of outpatient visits per individual approximately doubled from one year after diagnosis of AD (ranging from 5 [3–9] in DK-DHR to 30 [17–44] in NAJS) to five years after (ranging from 9 [5–17] in DK-DHR to 65 [26–123] in NAJS). Five percent of the individuals received caregiver support within 44 days [95% CI: 31–57] after AD diagnosis in NAJS and within 860 days [95% CI: 789–915] in IQVIA DA Germany. Less than five percent of the individuals in DK-DHR received caregiver support within five years after diagnosis, which is largely because data on caregiver support was not fully recorded in DK-DHR.

The 5-year survival probability from AD diagnosis ranged from 37.4% [95% CI: 36.6%–38.3%] in NAJS to 71.1% [95% CI: 70.6%–71.6%] in InGef RDB. The 5-year survival probability from the first treatment prescription for AD ranged from 40.4% [95% CI: 39.2%–41.6%] in NAJS to 75.7% [95% CI: 75.0%–76.5%] in InGef RDB.

Discussion

This study included a representative sample of individuals with incident AD from five data sources in four European countries. The treatment patterns, frequency of clinical and care-related events, and mortality after diagnosis of AD varied between data sources. This could be due to heterogeneity in individuals in the stage of the AD continuum at the time of diagnosis, but also due to differences between healthcare

systems and settings, and the way in which data are captured and coded. More complete recording in routinely collected healthcare data of the stages of the AD continuum, including MCI and diagnostic criteria, could enhance treatment characterisation and description of outcomes post-diagnosis of AD in the future. Follow-up studies may include additional data sources with more detailed information on demographic characteristics, diagnostic procedures, and the clinical profile of individuals with newly diagnosed AD.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Final Study Protocol	3 December 2025	12 December 2025
Creation of Analytical code	December 2025	November 2025 – January 2026
Execution of Analytical Code on the data	January 2026	February 2026
Draft Study Report	February 2026	27 February 2026
Final Study Report	April 2026	15 April 2026

6. RATIONALE AND BACKGROUND

Alzheimer's disease (AD) is a disorder that causes degeneration of the cells in the brain. AD is the main cause of dementia, which is characterised by a decline in thinking and dependence in personal daily activities.[1] AD is considered a multifactorial disease associated with several risk factors, such as increasing age, genetic factors, head injuries, vascular diseases, infections, and environmental factors.[1]

The diagnosis of AD was initially based solely on clinical symptoms.[2] Biomarkers were first included as supportive features in new diagnostic criteria in 2004, to identify AD in the prodromal phase (defined by mild cognitive impairment (MCI) and biomarkers that represent the brain signature of AD). Biomarkers became more important in the diagnosis of AD; in 2012, the diagnostic criteria of the pathophysiological process of AD were separated from the clinical phases of AD. This led to the description of three stages of AD: preclinical (defined by neuropathological changes without clinical symptoms), MCI due to the pathophysiological process of AD, and dementia due to the pathophysiological process of AD. Since 2018, the diagnosis of AD is based solely on biomarkers. Clinical symptoms now define the disease severity, from normal cognition to severe dementia, but they are no longer necessary for the diagnosis.

Acetylcholinesterase inhibitors were first approved in 1996 to treat cognitive impairment in mild to moderate Alzheimer's dementia. Memantine was first approved in 2003 to treat moderate-to-severe Alzheimer's dementia. These drugs can also be used in combination. 30–40% of people with AD develop psychosis,[3] which may be treated with antipsychotics. In a recent systematic review and meta-analysis,[4] the probability of nursing home admission was 13% within one year after diagnosis of dementia, 35% within three years, and 57% within five years. The median survival after diagnosis of AD at the age of 60 years was 9 years among women and 6.5 years among men. After diagnosis at the age of 85 years, the median survival was 4.5 years among women and 2.2 years among men.

However, the clinical management of AD is evolving due to new treatments targeting the amyloid-related pathology of AD. Lecanemab (Leqembi) was authorised for the EU market in April 2025 [5] and Donanemab (Kisunla) in September 2025.[6] Both are indicated for the treatment of adults with a clinical diagnosis of mild cognitive impairment and mild dementia due to early AD who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes with confirmed amyloid pathology.[5,7] These immunoglobulin G1 (IgG1) monoclonal antibodies reduce Aβ plaques, although some differences exist in the mechanism of action of the two treatments. According to the label, these treatments should be discontinued once the user progresses to moderate Alzheimer's disease dementia.

Anti-amyloid antibodies can cause amyloid-related imaging abnormalities (ARIA), characterised as ARIA-E, which is observed on Magnetic Resonance Imaging (MRI) as brain oedema or sulcal effusions, and ARIA-H,

which includes microhaemorrhage and superficial siderosis. In addition, intracerebral haemorrhages greater than 1 cm in diameter have occurred in patients treated with anti-amyloid treatments. As a condition to the marketing authorisation of Leqembi and Kisunla, the European Medicines Agency's Committee for Medicinal Products for Human Use requires a controlled access programme to ensure appropriate use in routine clinical practice, and a study to further characterise known adverse reactions, assess drug utilisation, and the effectiveness of the risk minimisation measures.

Such future research requires a comprehensive overview of contemporary patterns of treatments of AD, as well as disease progression and survival in European countries. Given the changes in diagnostic criteria over the last three decades, it may be expected that individuals have been diagnosed at an increasingly earlier stage of AD and with less severe symptoms. Moreover, future research of the new antiamyloid therapies will mostly include individuals with less severe AD than those who have been treated with acetylcholinesterase inhibitors or memantine. Although it will thus be challenging to compare treatment outcomes between the older and newer therapies, this DARWIN EU® study is proposed to provide key insights into the treatment and post-diagnosis outcomes of individuals with AD in European countries in the last decade.

7. RESEARCH QUESTION AND OBJECTIVES

Research objectives

The aim of this study is to describe pharmacological treatment patterns, clinical and care-related events, and survival of patients with AD in the 5 years after diagnosis.

The specific objectives of this study are:

1. To describe the demographic characteristics and clinical profile of individuals who initiate AD treatment within 5 years after the diagnosis of AD.
2. To describe the prevalence of pharmacological treatments recorded post-diagnosis of AD, overall and by treatment class.
3. To describe timing and sequences of pharmacological treatments following AD diagnosis, in terms of:
    a. Time from diagnosis to first treatment initiation, overall and by pharmacological treatment class.
    b. Sequencing of treatments of interest up to 5 years following diagnosis, by pharmacological treatment class.
4. To describe the timing and frequency of relevant clinical and care-related events following AD diagnosis, in terms of:
    a. Number of hospitalisations.
    b. Number of outpatient visits.
    c. Time to first record of caregiver support.
    d. Prevalence of at least one recorded caregiver support.
5. To describe survival in terms of:
    a. 5-year overall survival from AD diagnosis.
    b. 5-year overall survival from first AD treatment initiation following AD diagnosis.

8. RESEARCH METHODS

8.1. Study design

This was a retrospective cohort study, comprising four cohorts: one each for (1) objectives 1 and 5b; (2) objectives 2, 3b, 4a–b, 4d, and 5a; (3) objective 3a; and (4) objective 4c. The index date, i.e. date of cohort entry, was the date of treatment initiation (objectives 1 and 5b) and the date of the AD diagnosis (objectives 2–5a). The latest possible index date was 31/12/2023 to allow for sufficient follow-up before the end of the study period on 31/12/2024.

The study design is visualised in **Figures 1 and 2**.

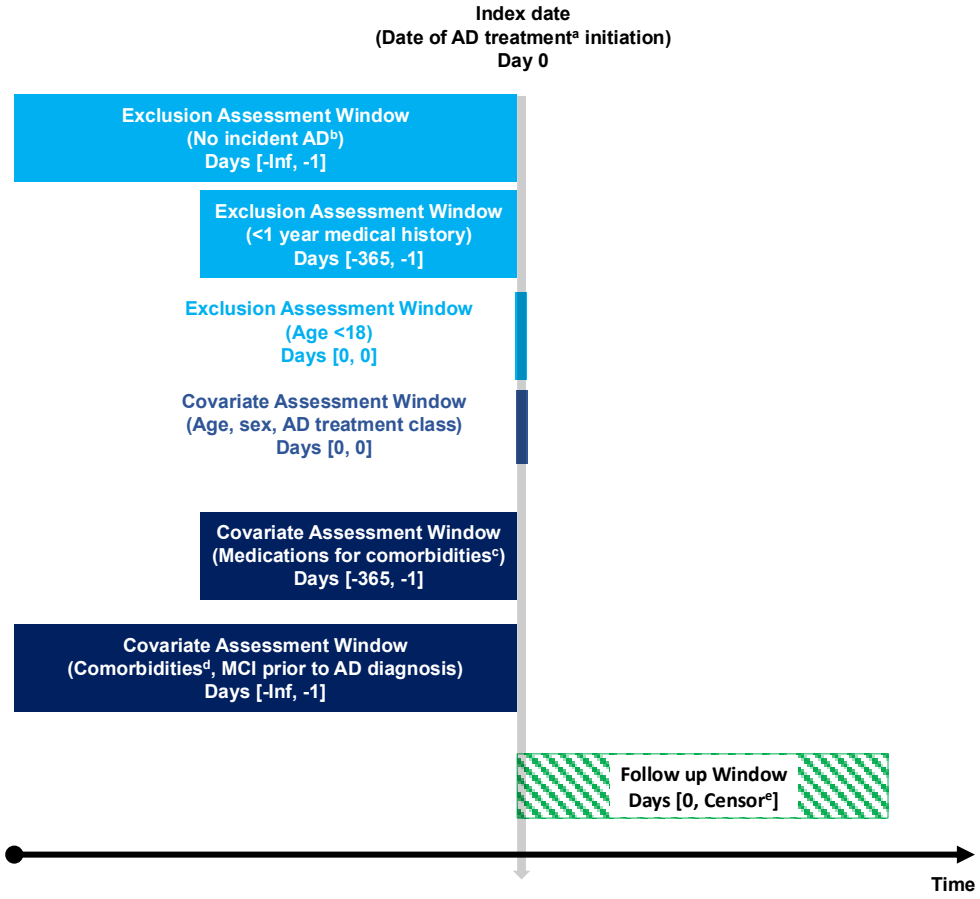

Figure 1. Graphical depiction of the study design (objectives 1 and 5b).

a. AD treatment classes of interest: acetylcholinesterase inhibitors and memantine.
b. Incident AD is defined as diagnosis of AD between 01/01/2014 and 31/12/2023, after at least 365 days of available medical history.
c. Medications for predefined comorbidities: antiplatelets, anticoagulants/antithrombotic agents, glucose-lowering therapies (insulin and oral agents), antihypertensives, antiarrhythmics/rhythm control drugs, and lipid-lowering drugs.
d. Predefined comorbidities: Down's syndrome, stroke, atrial fibrillation, myocardial infarction, heart failure, hypertension, diabetes, hypercholesterolemia, and hypertriglyceridemia.
e. Earliest of: death, end of observation period, 5 years of follow-up, or end of study period.

AD=Alzheimer's disease; MCI=mild cognitive impairment.

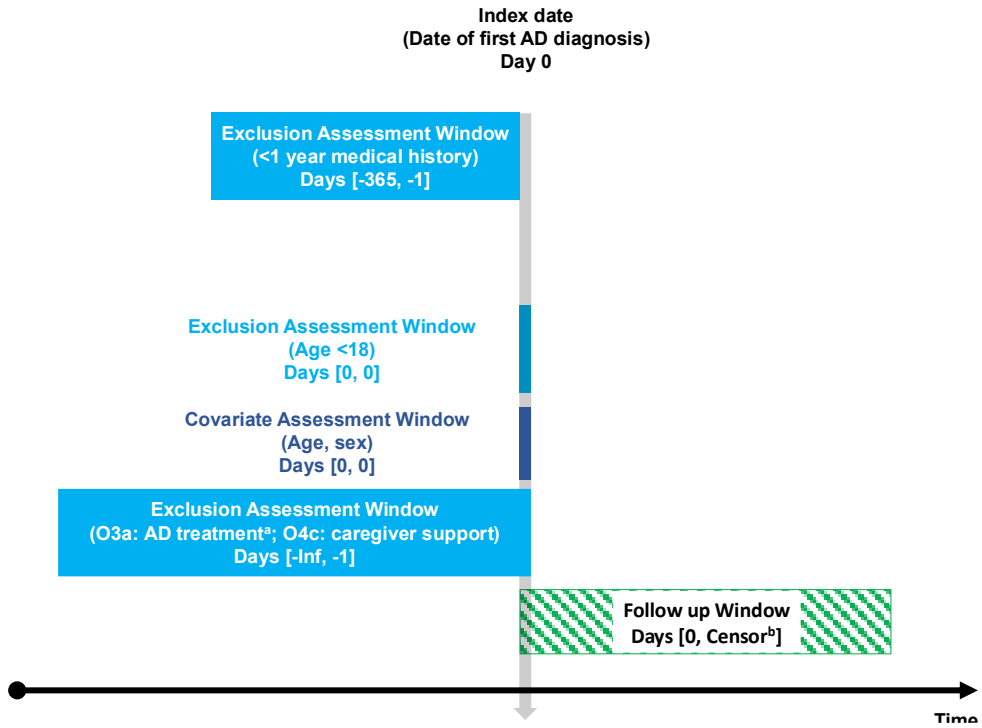

Figure 2. Graphical depiction of the study design (objectives 2–5a).

a. AD treatment classes of interest: acetylcholinesterase inhibitors, memantine, and antipsychotics.
b. Earliest of: death, end of observation period, 5 years of follow-up, or end of study period.

AD=Alzheimer's disease; O3a=objective 3a; O4c=objective 4c.

8.2. Follow-up

Objectives 1 and 5b

Follow-up started on the date of treatment initiation for AD following the first diagnosis of AD.

Objectives 2–5a

Follow-up started on the date of the first AD diagnosis.

All objectives

The follow-up for each objective is described in **Table 1**. An example of entry and exit into the denominator population is shown in **Annex III**.

Table 1. Definition of numerator, denominator, study population, and follow-up per objective.

Objective	Numerator	Denominator	Study population	Follow-up
1. To describe the demographic characteristics and clinical profile of individuals who initiate AD treatment within 5 years after the diagnosis of AD	Number of individuals within each category group (when applicable) for each demographic and clinical characteristic described	Number of individuals with diagnosis of AD and subsequent treatment initiation with a predefined AD treatment class.	Individuals with diagnosis of AD and subsequent treatment initiation with a predefined AD treatment class	Not applicable
2. To describe the prevalence of pharmacological treatments recorded	Number of individuals with diagnosis of AD and treated with a predefined AD	Number of individuals with diagnosis of AD	Individuals with diagnosis of AD	From date of AD diagnosis until the earliest of: end of follow-up (1, 3, or 5

Objective	Numerator	Denominator	Study population	Follow-up
post-diagnosis of AD, overall and by treatment class	treatment class (overall and per class)			years), end of data availability, date of death, or end of the study period.
3a. To describe the time from diagnosis of AD to first treatment initiation, overall and by pharmacological treatment class	Not applicable	Not applicable	Individuals with diagnosis of AD	From date of AD diagnosis until the earliest of: end of follow-up (5 years), treatment initiation with a predefined AD treatment class, end of data availability, date of death, or end of the study period.
3b. To describe the sequencing of treatments of interest up to 5 years following diagnosis of AD, by pharmacological treatment class	Number of individuals with diagnosis of AD and treated with a predefined AD treatment class	Number of individuals with diagnosis of AD	Individuals with diagnosis of AD	From date of AD diagnosis until the earliest of: end of follow-up (5 years), end of data availability, date of death, or end of the study period.
4a. To describe the number of hospitalisations following diagnosis of AD	Not applicable	Not applicable	Individuals with diagnosis of AD	From date of AD diagnosis until the earliest of: end of follow-up (1, 3, or 5 years), end of data availability, date of death, or end of the study period.
4b. To describe the number of outpatient visits following diagnosis of AD	Not applicable	Not applicable	Individuals with diagnosis of AD	From date of AD diagnosis until the earliest of: end of follow-up (1, 3, or 5 years), end of data availability, date of death, or end of the study period.
4c. To describe the time to first record of caregiver support following diagnosis of AD	Not applicable	Not applicable	Individuals with diagnosis of AD	From date of AD diagnosis until the earliest of: end of follow-up (5 years), record of caregiver support, end of data availability, date of death, or end of the study period.
4d. To describe the prevalence of at least one recorded caregiver support following diagnosis of AD	Number of individuals with diagnosis of AD and with caregiver support	Number of individuals with diagnosis of AD	Individuals with diagnosis of AD	From date of AD diagnosis until the earliest of: end of follow-up (1, 3, or 5 years), end of data availability, date of death, or end of the study period.

Objective	Numerator	Denominator	Study population	Follow-up
5a. To describe 5-year overall survival from diagnosis of AD	Not applicable	Not applicable	Individuals with diagnosis of AD	From date of AD diagnosis until the earliest of: end of follow-up (5 years), end of data availability, date of death, or end of the study period.
5b. To describe 5-year overall survival from first AD treatment initiation following AD diagnosis	Not applicable	Not applicable	Individuals with diagnosis of AD and subsequent treatment initiation with an acetylcholinesterase inhibitor or memantine	From date of treatment initiation for AD until the earliest of: end of follow-up (5 years), end of data availability, date of death, or end of the study period.

AD=Alzheimer's disease

8.3. Study population with inclusion and exclusion criteria

Objectives 1 and 5b

Inclusion criteria:

- AD diagnosis between 01/01/2014 and 31/12/2023
- Minimum 365 days of available history before AD diagnosis
- First prescription or dispensing recorded of an acetylcholinesterase inhibitor or memantine on or after the date of the first diagnosis of AD and between 01/01/2014 and 31/12/2023. The preliminary concept sets used for the identification of records of acetylcholinesterase inhibitor or memantine are described in **Annex V**. These codes were refined during the study execution following the DARWIN EU® phenotyping standard processes, which involve the review of code lists by clinical experts and the review of phenotypes after their execution in the participating data sources.
- Minimum 365 days of available history before index date (date of first treatment for AD)
- Age ≥18 years at index date

Exclusion criterion for the analyses stratified by sex:

- Unknown sex at index date

Objectives 2, 3b, 4a–b, 4d, and 5a

Inclusion criteria:

- AD diagnosis between 01/01/2014 and 31/12/2023
- Minimum 365 days of available history before index date (date of AD diagnosis)
- Age ≥18 years at index date

Exclusion criterion for the analyses stratified by sex:

- Unknown sex at index date

Objective 3a

Inclusion criteria:

- AD diagnosis between 01/01/2014 and 31/12/2023
- Minimum 365 days of available history before index date (date of AD diagnosis)
- Age ≥18 years at index date

Exclusion criterion:

- For the analyses stratified by sex: unknown sex at index date
- History of AD treatment ever before index date

Objective 4c

Inclusion criteria:

- AD diagnosis between 01/01/2014 and 31/12/2023
- Minimum 365 days of available history before index date (date of AD diagnosis)
- Age ≥18 years at index date

Exclusion criterion:

- For the analyses stratified by sex: unknown sex at index date
- History of caregiver support ever before index date

For the definition of AD, diagnostic codes explicitly referring to AD or primary degenerative dementia of the Alzheimer type (including presenile/senile onset, uncomplicated, or with depression, delirium, delusions, or behavioural disturbance) were included. The definition of AD did not include biomarkers. The concept sets used for the identification of individuals with AD are described in **Annex V**. These codes were refined during the study execution following the DARWIN EU® phenotyping standard processes,[8] which involve the review of code lists by clinical experts and the review of phenotypes after their execution in the participating data sources.

8.4. Study setting and data sources

This study was conducted using routinely collected data from five primary/secondary care data sources in the DARWIN EU® network of data partners from four European countries (**Table 2**). All data were a priori mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM).

Table 2. Data sources.

Country	Name of Data source	Health Care setting	Type of Data	Number of active individuals	Calendar period covered by each data source	Contributing to objectives*
Croatia	NAJS	Primary and secondary care	Registry	4.3M	2017–2025	All
Denmark	DK-DHR	Secondary care	Registry	5.98M	1995–2025	All
Germany	InGef RDB	Primary and secondary care	Claims	7.67M	2015–2025	All except 4c–d
Germany	IQVIA DA Germany	Primary care	EHR	4.48M	1992–2025	1–3, and 4b–d
The Netherlands	IPCI	Primary care	EHR	1.33M	2006–2025	1–3, 4b, and 5a

*Results from *CohortDiagnostics*[8] in the study implementation phase will further inform the availability of records of clinical and care-related events in each data source for objective 3.
Data sources: NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; InGef RDB=InGef Research Database; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=The Integrated Primary Care Information.
Types of data: EHR=electronic health record
Number of active subjects: M=millions

Data sources selection

These data sources fulfil the criteria required in terms of data quality, completeness, timeliness, and representativeness for this population-level cohort study while covering different regions of Europe (**Annex II**).

8.5. Study period

The study period was from 01/01/2014 to 31/12/2024 or the most recent data available for each contributing data source. It should be noted that in the NAJS data source, hospital data are available starting from 01/01/2017, which is often used as the start of data collection. In InGef RDB, data are available starting from 01/01/2015. Therefore, to meet the 365 days prior history requirement, the study period for NAJS started on 01/01/2018; and for InGef RDB on 01/01/2016.

8.6. Variables

8.6.1. Outcome

Objective 1

Not applicable.

Objectives 2 and 3

The outcome was a record of prescription (all data sources)/dispensing (DK-DHR and InGef RDB) of monotherapy of pharmacological treatments for AD, categorised into three classes:

- Acetylcholinesterase inhibitors
    - Donepezil
    - Rivastigmine
    - Galantamine
- Memantine

- Antipsychotics

The assessment windows for objective 2 were 0–1 year after index date, 0–3 years after index date, and 0–5 years after index date. The assessment windows for objective 3 were from index date until the end of follow-up, as described in **Section 8.2**.

Objective 4

The outcomes for this objective were records of occurrence/procedure/visit of healthcare utilisation:

- Hospitalisation
- Outpatient visit
- Caregiver support

The assessment windows for objectives 4a–c were 0–1 year after index date, 0–3 years after index date, and 0–5 years after index date. For objective 4c, the assessment window was from index date until the end of follow-up (as described in **Section 8.2**) to assess the time until the first record of caregiver support.

Objective 5

The outcome for this objective was overall survival (time to death) in individuals with incident diagnosis of AD, which was calculated based on the individual's registered date of death. Individuals contributed survival time as per the follow-up described in **Section 8.2**. The assessment windows for objectives 5a–b were from index date (i.e. date of AD diagnosis in objective 5a and date of treatment initiation for AD in objective 5b) until the end of follow-up, as described in **Section 8.2**.

Objectives 2–5

The concept sets used for the identification of outcomes are described in **Annex V**. Condition codes are available in SNOMED, and drug codes are available in RxNorm. These codes were refined during the study execution following the DARWIN EU® phenotyping standard processes, which involve the review of code lists by clinical experts and the review of phenotypes after their execution in the participating data sources.

8.6.2. Covariates, including confounders, effect modifiers, intercurrent events, and other variables

All objectives

Sex (male/female), age, and history of diagnosis of MCI at any time prior to diagnosis of AD were assessed at the respective index date of each cohort. Sex, age, and history of MCI prior to diagnosis of AD (yes/no) were used to describe the study population (objective 1). History of MCI prior to diagnosis of AD was used to conduct a subgroup analysis: all analyses (objectives 1–5) were repeated with the subgroup of the study population with history of MCI. Sex and age were used to stratify analyses (objectives 2–5). Age in years was categorised into 18–55; 56–65; 66–75; 76–85; and ≥86.

Objective 1

The clinical profile of individuals with a first AD treatment was assessed in different time windows:

- At index date:
  - First AD treatment class (acetylcholinesterase inhibitor, memantine, or both)
- Within 365 days prior to index date:
  - Medications for predefined comorbidities: antiplatelets, anticoagulants/antithrombotic agents, glucose-lowering therapies (insulin and oral agents), antihypertensives, antiarrhythmics/rhythm control drugs, and lipid-lowering drugs.
- At any time prior and up to index date:

- Predefined comorbidities of interest:
  - Down's syndrome
  - Stroke
  - Atrial fibrillation
  - Myocardial infarction
  - Heart failure
  - Hypertension
  - Diabetes
  - Hypercholesterolemia
  - Hypertriglyceridemia

The concept sets used for the identification of covariates are described in **ANNEX V**. All codes were refined during the study execution following the DARWIN EU® phenotyping standard processes, which involve the review of code lists by clinical experts and the review of phenotypes after their execution in the participating data sources.

8.7. Study size

No sample size was calculated, as this is a descriptive disease epidemiology study, which did not test a specific hypothesis. The sample size was driven by the availability of data for individuals with AD. Based on a preliminary feasibility assessment, the expected number of persons counts for AD diagnosis in the data sources included in this study ranged from 13,400 (IPCI) to 107,900 (DK-DHR). The number of individuals with record of use of an acetylcholinesterase inhibitor (*donepezil, rivastigmine, or galantamine*) was expected to range from 100 (donepezil in IPCI) to 85,000 (donepezil in DK-DHR), and the number with memantine use from 800 (IPCI) to 50,000 (DK-DHR). These numbers were based on the overall number of condition and exposure registries in each data source, with no filter by study period or inclusion and exclusion criteria.

8.8. Data transformation

Analyses were conducted separately for each data source. Before study initiation, test runs of the analyses were performed on a subset of the data sources and quality control checks were performed. Once all the tests passed (see **Annex IV**), the final study codes package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP CDM in R Studio and reviewed and approved the, by default, aggregated results.

The study results of all data sources were checked, after which they were made available to the team, and the dissemination phase started. All results were locked and timestamped for reproducibility and transparency.

8.9. Statistical methods

8.9.1. Main statistical methods

<u>All objectives</u>

The analysis was conducted on data mapped to the OMOP CDM using the standardised R packages developed for DARWIN EU®, which are described per objective. For the analyses of objectives 2–5, the number and percentage of individuals with the outcome (except for hospitalisations and outpatient visits)

was reported. All analyses were reported by country/data source, overall and restricted to the subgroup of the study population with history of MCI prior to diagnosis of AD. The analyses for objectives 2–5 were additionally reported stratified by age and sex.

In InGef RDB, at least two outpatient diagnoses, at least one inpatient diagnosis, or both, are required as standard methodology. Therefore, an algorithm was used to determine the date of the first diagnosis of AD:

1. If present, the date of the first inpatient diagnosis of AD was selected.
2. If present, the first date of the calendar quarter of the first outpatient diagnosis of AD was selected. The reason for this is that the dates of outpatient diagnosis records are set to the last date of each calendar quarter in InGef RDB.
3. The next step depended on the number of dates that were selected in the steps above and whether they originated from the inpatient records or outpatient records:
    a. If two dates were selected based on the steps above (i.e. one from the inpatient records and one from the outpatient records), the earliest of the two selected dates was selected as the date of the first diagnosis of AD.
    b. If only one date was selected and it originated from the inpatient records, this was selected as the date of the first diagnosis of AD.
    c. If only one date was selected and it originated from the outpatient records, it was assessed whether the outpatient records contained at least one more outpatient diagnosis of AD. If so, the first date of the calendar quarter of the first outpatient diagnosis of AD in InGef RDB was selected.
4. The date of the first diagnosis of AD depended on the number of dates that resulted from step 3:
    a. If only one date was ascertained that date was selected as the date of the first diagnosis of AD.
    b. If multiple dates were ascertained, the earliest of the dates was selected as the date of the first diagnosis of AD.

Objective 1

Descriptive statistics were used to summarise demographic and clinical characteristics at different time windows, as described in **Section 8.6.2**.

Categorical variables (e.g. sex, comorbidities, medication use) were described using counts and percentages.

Continuous variables (e.g. age at index date) were described using means, standard deviations, medians, and interquartile ranges.

Objective 2

The prevalence of pharmacological treatments was assessed using the R package *DrugUtilisation*.[9] The number and percentage of individuals receiving each of a pre-specified list of AD treatments and treatment classes (see **Section 8.6.1** and **Annex V**) was described within 1, 3, and 5 years after index date.

Objective 3a

The timing of pharmacological treatments post-diagnosis of AD was assessed using the R package *CohortSurvival*,[10] which uses the Kaplan-Meier (KM) method. Individuals who were lost to follow-up were censored at the time of loss of follow-up (see **Table 1**). The KM approach implicitly assumed censoring occurs at random. Time from AD diagnosis to first treatment initiation was reported as median, 5th, 25th,

75th, and 95th percentiles with 95% confidence interval (CI) around each estimate, overall and by treatment class (see **Section 8.6.1** and **Annex V**).

Objective 3b

The sequence of pharmacological treatments up to 5 years post-diagnosis of AD was assessed using the R package *TreatmentPatterns*.[11] Treatment sequence was reported as number of individuals and percentage of the study population with each sequence. Additionally, sunburst plots were used to describe treatment sequences within 5 years after index date. The parameters for *TreatmentPatterns* are shown in **Table 3**. The use of each parameter in the analysis is shown in **Figure 3**. The parameters were refined upon review of the results from *DrugExposureDiagnostics*[12] during the study implementation, as treatment duration was recorded differently in different data sources.

Table 3. Parameters for the assessment of treatment sequences.

Individual pathway setting	Description	Value
WindowStart	The start time (number of days) prior to the index date of the target cohort (i.e. cohort of patients newly diagnosed with AD) from which treatments should be included	0 days
WindowEnd	The end time (number of days) after the index date of the target cohort (i.e. cohort of patients newly diagnosed with AD) from which treatments should be included	1825 days
minEraDuration	Minimum time an event era (i.e. span of time an individual is exposed to a specific treatment of interest) should last to be included in the analysis	7 days
eraCollapseSize	Maximum gap within two eras of the same event cohort which would still allow the eras to be collapsed into one era	Main analysis: 7 days Sensitivity analysis 1: 35 days Sensitivity analysis 2: 60 days The sensitivity analyses are described in detail in **Table 4**.
combinationWindow	Time that two event eras need to overlap to be considered a combination treatment	7 days
minPostCombinationDuration	Minimum time that an event era before or after a generated combination treatment should last to be included in the pathway as a separate treatment	7 days
filterTreatments	Select which treatments should be included in pathway first time occurrences of treatments ('First'), remove sequential repeated treatments ('Changes'), all treatments ('All')	Changes
maxPathLength	Maximum number of treatments included in pathway	5

AD=Alzheimer's disease

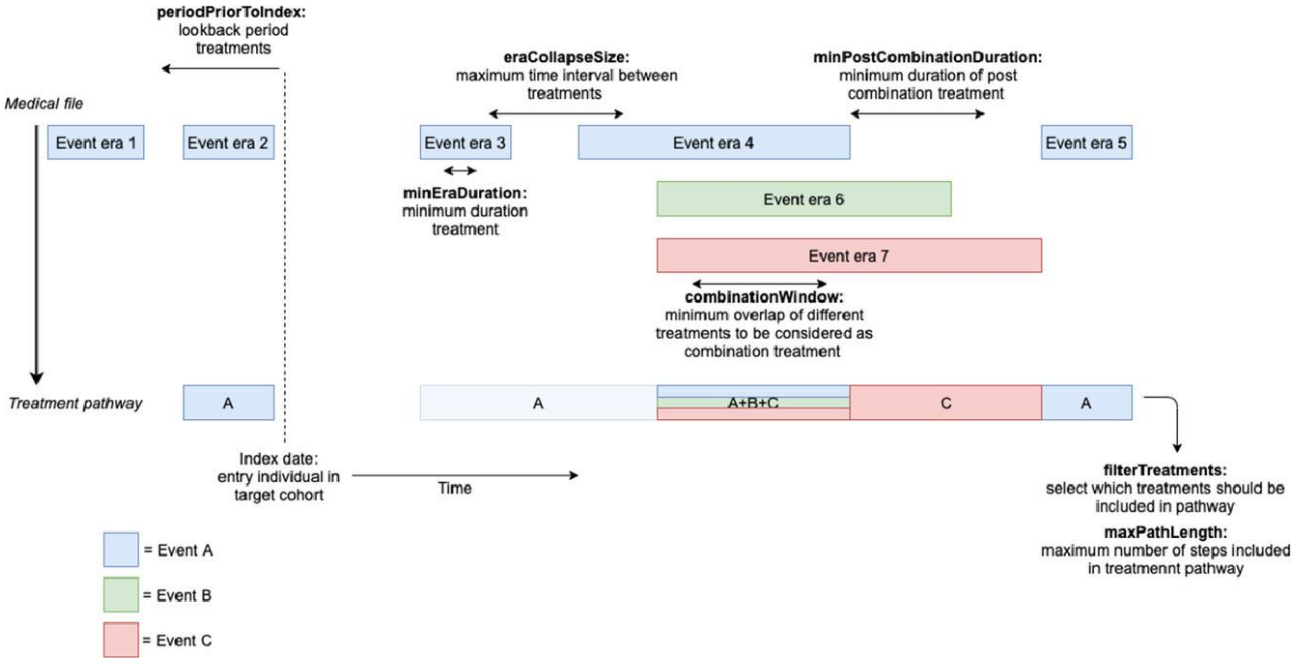

Figure 3. Summary of decisions to construct individual treatment pathways.

This figure is taken from Markus AF et al.[11]. The events A, B, and C refer to the treatments of interest.

Objectives 4a–b and 4d

The frequency of clinical and care-related events was assessed using the R package *PatientProfiles*.[13] Frequency of hospitalisations and outpatient visits was reported as mean (Standard deviation (SD)) and median (interquartile range (IQR), min–max range) within 1, 3, and 5 years after index date. The number and percentage of individuals receiving caregiver support was described within 1, 3, and 5 years after index date.

Objective 4c

The timing of caregiver support was assessed using the R package *CohortSurvival,*[10] which uses the KM method. Individuals who were lost to follow-up were censored at the time of loss of follow-up (see **Table 1**). The KM approach implicitly assumed censoring occurs at random. Time from AD diagnosis to first caregiver support was reported as median, 5^{th}, 25^{th}, 75^{th}, and 95^{th} percentiles with 95% CI around each estimate.

Objective 5

Overall survival up to 5 years from AD diagnosis (objective 5a) and from AD treatment initiation following AD diagnosis (objective 5b) was calculated using data on time-at-risk of death from any cause and the R package *CohortSurvival*, which uses the Kaplan-Meier (KM) method. Individuals who were lost to follow-up were censored at the time of loss of follow-up (see **Table 1**). The KM approach implicitly assumed censoring occurs at random. Results were reported as plots of the estimated survival curves, as well as the estimated median (IQR) survival, and the estimated probability of survival at year 5. In addition, overall survival was estimated after every 6 months post-diagnosis of AD (objective 5a) and post-initiation of AD treatment (objective 5b).

8.9.2. Missing values

Absence of diagnosis codes was interpreted as absence of the conditions themselves, and absence of prescription records was interpreted as absence of the treatments themselves.

8.9.3. Sensitivity analysis

The description of sensitivity analyses is presented in **Table 4**.

Table 4. Sensitivity analyses – rationale, strengths, and limitations.

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Sensitivity analysis 1	The maximum permissible gap between prescriptions of acetylcholinesterase inhibitors, memantine, and antipsychotics will be 35 days, versus 7 days in the main analysis.	The aim of the sensitivity analyses is to investigate the effect of a longer permissible gap on the ascertainment of combined treatment, especially of acetylcholinesterase inhibitors and memantine (objective 3b). The durations of the maximum permissible gap in the sensitivity analysis themselves were based on a cohort study of persistence of use of AD treatments in Europe.[14]	The longer the permissible gap, the more sensitive the ascertainment of combination treatment will be.	The longer the permissible gap, the lower the specificity of the ascertainment of treatment use. In this study, this may be the most concerning for antipsychotics, as true non-exposed time between periods of use will be more likely to be misclassified as continued use. Although the limitation is similar for acetylcholinesterase inhibitors and memantine, these treatments are more likely to be intended for continued use.
Sensitivity analysis 2	The maximum permissible gap between prescriptions of acetylcholinesterase inhibitors, memantine, and antipsychotics will be 60 days, versus 7 days in the main analysis.			

8.10. Deviations from the protocol

None.

9. RESULTS

The main results based on data from the overall study population are presented below. Results stratified by sex and age, as well as results from the subgroup with MCI prior to AD, are described in text in **Annex VI**. The full set of tables and figures for this study is available through an interactive web-application (ShinyApp) at EUPAS1000000827.

9.1. Participants

The number of individuals with a record of AD treatment was 30,149 in NAJS, 122,516 in DK-DHR, 76,418 in InGef RDB, 112,532 in IQVIA DA Germany, and 8,977 in IPCI (**Table S3** in **Annex VI**). Out of these, the number of individuals who met all eligibility criteria and were included in the study population of objectives 1 and 5b was 9,909 in NAJS, 49,200 in DK-DHR, 25,546 in InGef RDB, 10,648 in IQVIA DA Germany, and 1,185 in IPCI.

The number of individuals with a record of AD diagnosis was 33,360 in NAJS, 130,430 in DK-DHR, 109,541 in InGef RDB, 153,321 in IQVIA DA Germany, and 13,923 in IPCI (**Table S4** in **Annex VI**). Out of these, the number of individuals who met all eligibility criteria and were included in the study population of objectives 2, 3b, 4a–b, 4d, and 5a was 20,218 in NAJS, 57,462 in DK-DHR, 72,767 in InGef RDB, 37,182 in IQVIA DA Germany, and 7,379 in IPCI.

Out of the individuals with incident AD who were included in objectives 2, 3b, 4a–b, 4d, and 5a, the number of individuals with no AD treatment ever before the first AD diagnosis, which were included in objective 3a,

was 12,188 in NAJS, 44,853 in DK-HR, 46,967 in InGef RDB, 26,575 in IQVIA DA Germany, and 6,364 in IPCI (**Table S5b in Annex VI**).

Out of the individuals with incident AD who were included in objectives 2, 3b, 4a–b, 4d, and 5a, the number of individuals with no caregiver support ever before the first AD diagnosis, which were included in objective 4c, was 9,154 in NAJS, 56,119 in DK-HR, and 35,367 in IQVIA DA Germany (**Table S5c in Annex VI**).

9.2. Descriptive data (objective 1)

Table 5 presents the baseline demographic characteristics and clinical profile of individuals with incident AD and with a prescription of acetylcholinesterase inhibitor, memantine, or both.

The median age of individuals with a first treatment prescription for AD varied from 77 (IPCI) to 81 years (IQVIA DA Germany), with a higher prevalence of females across all data sources (varying from 54.4% in InGef RDB to 65.8% in NAJS). The largest proportion of individuals initiating AD treatment after diagnosis of AD was in the age group 76–85 years (varying from 47.8% in IPCI to 58.4% in IQVIA DA Germany).

Among the individuals with a first treatment prescription for AD, 32.9% were prescribed acetylcholinesterase in NAJS, 80.9% in DK-DHR, 74.1% in InGef RDB, 70.9% in IQVIA DA Germany, and 96.9% in IPCI. Memantine was prescribed to 65.2% in NAJS, 19.1% in DK-DHR, 25.7% in InGef RDB, 28.5% in IQVIA DA Germany, and 3.0% in IPCI. The proportion who were prescribed both acetylcholinesterase inhibitor and memantine ranged from 0% in IPCI to 2.0% in NAJS.

Among the pre-specified comedications, the most prescribed during the year prior to index date was antihypertensives (prevalence of prescription ranging from 21.5% in IQVIA DA Germany to 58.5% in DK-DHR), followed by lipid-lowering drugs (from 15.0% in IQVIA DA Germany to 42.3% in DK-DHR), and antiplatelets (from 1.5% in NAJS to 33.9% in DK-DHR). The next most frequently prescribed drugs were anticoagulants/antithrombotic agents (from 5.7% in IPCI to 17.5% in DK-DHR), oral glucose-lowering drugs (from 3.0% in IQVIA DA Germany to 7.3% in InGef RDB), and insulin (from 2.6% in IQVIA DA Germany to 7.1% in InGef RDB). The least commonly prescribed medication during the year prior to index date were antiarrhythmics/rhythm control drugs (from 0.5% in IQVIA DA Germany to 3.3% in NAJS).

Among the pre-specified comorbidities, the most commonly recorded any time prior to AD treatment initiation was hypertension (prevalence ranging from 35.4% in IPCI to 86.1% in NAJS), followed by diabetes (from 15.9% in DK-DHR and IPCI to 30.9% in NAJS) and hypercholesterolemia (from 5.7% in NAJS to 54.2% in DK-DHR). The next most common comorbidities were heart failure (from 3.0% in IPCI to 15.9% in InGef RDB), atrial fibrillation (from 5.2% in IQVIA DA Germany to 15.8% in InGef RDB), and myocardial infarction (from 3.7% in IQVIA DA Germany to 7.6% in DK-DHR). The least common comorbidities were hypertriglyceridemia (from 0.1% in DK-DHR to 1.2% in IQVIA DA Germany), Down's syndrome (from 0% in NAJS and InGef RDB to 0.2% in IQVIA DA Germany), and stroke (from 0% in IQVIA DA Germany and IPCI to 0.1% in InGef RDB).

Among individuals initiating AD treatment, the prevalence of a diagnosis of MCI any time prior to the diagnosis of AD ranged from 5.6% in DK-DHR to 14.2% in IQVIA DA Germany. The baseline characteristics of this subgroup were similar to those in the overall population of individuals with AD initiating treatment (see ShinyApp at EUPAS1000000827).

Table 5. Baseline demographic and clinical characteristics of individuals with a first prescription of acetylcholinesterase inhibitor, memantine, or both.

	NAJS	DK-DHR	InGef RDB	IQVIA DA Germany	IPCI
Overall, N	9,909	49,200	25,546	10,648	1,185
• Median age [IQR] at index date	79 [73–83]	80 [75–85]	80 [75–84]	81 [76–84]	77 [72–82]
• Mean age (SD) at index date	77.82 (7.53)	79.71 (7.71)	79.07 (7.56)	79.72 (7.12)	76.36 (7.58)
Age group, N (%)					
• 18–55 years	79 (0.8%)	425 (0.9%)	234 (0.9%)	68 (0.6%)	16 (1.4%)
• 56–65 years	505 (5.1%)	1,729 (3.5%)	1,171 (4.6%)	395 (3.7%)	82 (6.9%)
• 66–75 years	2,825 (28.5%)	10,694 (21.7%)	5,244 (20.5%)	1,923 (18.1%)	406 (34.3%)
• 76–85 years	5,103 (51.5%)	24,943 (50.7%)	14,325 (56.1%)	6,214 (58.4%)	566 (47.8%)
• ≥86 years	1,397 (14.1%)	11,409 (23.2%)	4,572 (17.9%)	2,048 (19.2%)	115 (9.7%)
Sex, N (%)					
• Male	3,387 (34.2%)	19,482 (39.6%)	11,660 (45.6%)	4,380 (41.1%)	517 (43.6%)
• Female	6,522 (65.8%)	29,718 (60.4%)	13,886 (54.4%)	6,259 (58.8%)	668 (56.4%)
First AD treatment class, N (%)					
• Acetylcholinesterase inhibitor	3,257 (32.9%)	39,789 (80.9%)	18,924 (74.1%)	7,551 (70.9%)	1,148 (96.9%)
• Memantine	6,456 (65.2%)	9,383 (19.1%)	6,538 (25.6%)	3,031 (28.5%)	36 (3.0%)
• Acetylcholinesterase inhibitor and memantine	196 (2.0%)	28 (0.1%)	84 (0.3%)	66 (0.6%)	0 (0.0%)
Medications for comorbidities, N (%)					
• Antiplatelets	150 (1.5%)	16,700 (33.9%)	4,585 (17.9%)	1,145 (10.8%)	240 (20.3%)
• Anticoagulants/antithrombotic agents	1,278 (12.9%)	8,616 (17.5%)	3,862 (15.1%)	679 (6.4%)	67 (5.7%)
• Oral glucose-lowering drugs	710 (7.2%)	1,810 (3.7%)	1,856 (7.3%)	322 (3.0%)	50 (4.2%)
• Insulin	469 (4.7%)	1,791 (3.6%)	1,807 (7.1%)	278 (2.6%)	34 (2.9%)
• Antihypertensives	5,346 (54.0%)	28,806 (58.5%)	13,638 (53.4%)	2,288 (21.5%)	523 (44.1%)
• Antiarrhythmics/rhythm control drugs	328 (3.3%)	351 (0.7%)	376 (1.5%)	56 (0.5%)	34 (2.9%)
• Lipid-lowering drugs	3,046 (30.7%)	20,794 (42.3%)	9,787 (38.3%)	1,594 (15.0%)	436 (36.8%)
Comorbidities					
• Down's syndrome	0 (0.0%)	57 (0.1%)	8 (0.0%)	18 (0.2%)	0 (0.0%)
• Stroke	5 (0.1%)	39 (0.1%)	37 (0.1%)	0 (0.0%)	0 (0.0%)
• Atrial fibrillation	539 (5.4%)	3,343 (6.8%)	4,027 (15.8%)	548 (5.1%)	98 (8.3%)
• Myocardial infarction	480 (4.8%)	3,720 (7.6%)	1,420 (5.6%)	395 (3.7%)	49 (4.1%)
• Heart failure	907 (9.2%)	3,963 (8.1%)	4,051 (15.9%)	1,077 (10.1%)	36 (3.0%)
• Hypertension	8,531 (86.1%)	28,254 (57.4%)	14,728 (57.7%)	4,668 (43.8%)	419 (35.4%)

	NAJS	DK-DHR	InGef RDB	IQVIA DA Germany	IPCI
• Diabetes	3,061 (30.9%)	7,832 (15.9%)	4,664 (18.3%)	2,430 (22.8%)	188 (15.9%)
• Hypercholesterolemia	569 (5.7%)	26,662 (54.2%)	2,949 (11.5%)	1,673 (15.7%)	149 (12.6%)
• Hypertriglyceridemia	96 (1.0%)	35 (0.1%)	100 (0.4%)	126 (1.2%)	<5
MCI prior to diagnosis of AD, N(%)	746 (7.5%)	2,769 (5.6%)	1,653 (6.5%)	1,511 (14.2%)	NC

IQR=interquartile range; SD=standard deviation; MCI=mild cognitive impairment; NC=not captured; NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; InGef RDB=InGef Research Database; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=The Integrated Primary Care Information.

Tables S5a–c in **Annex VI** show the number of individuals included in the analyses stratified by sex, by age, and in the subgroup of individuals with MCI prior to AD among the study population with incident AD (**Table S5a**), the study population with no AD treatment prior to the first diagnosis of AD (**Table S5b**), and the study population with no caregiver support prior to the first diagnosis of AD (**Table S5c**).

Across the three study population and the data sources, the age distribution of individuals with AD was consistent, with the age group 76–85 years consistently representing the largest proportion (approximately 48–52%), and very few individuals under 65. Most individuals with AD were women in all data sources and populations, typically accounting for around 59–66% of each population, with NAJS showing the highest female prevalence at roughly 65–66%. The proportion of individuals with a prior MCI diagnosis was low and broadly similar across data sources at around 4–5%. The exception was for IQVIA DA Germany which consistently showed a higher MCI capture rate of approximately 8%, likely reflecting differences in clinical coding practices rather than a true difference in person characteristics.

9.3. Main results

9.3.1. Prevalence of pharmacological treatments post-diagnosis of AD (objective 2)

Table 6 presents the prevalence of pharmacological treatment prescription within 1, 3, and 5 years after the first diagnosis of AD.

Across most data sources, more than 50% of the individuals with incident AD were prescribed a pharmacological treatment for AD (i.e. acetylcholinesterase inhibitors, memantine, or antipsychotics) during the first year after AD diagnosis. IPCI was an exception, where only 27.2% of individuals were prescribed any of these treatments. During the first five years after diagnosis, the prevalence of pharmacological treatment prescriptions for AD remained lower in IPCI (40.1%) than the other data sources (ranging from 59.6% in IQVIA DA Germany to 95.3% in DK-DHR).

The prevalence of acetylcholinesterase inhibitor prescriptions during the first year after diagnosis of AD was highest in DK-DHR (75.1%), while it ranged from 14.9% in IPCI to 34.0% in InGef RDB in the other data sources. The prevalence of acetylcholinesterase inhibitor prescriptions was up to 4% higher across data sources during the first three years after diagnosis than during the first year. The prevalence of acetylcholinesterase inhibitor prescriptions during the first five years after diagnosis was similar to the prevalence during the first three years.

The prevalence of memantine prescriptions during the first year after diagnosis of AD was lowest in IPCI (0.7%) and ranged from 12.2% in IQVIA DA Germany to 43.3% in NAJS in the other data sources. The prevalence of memantine prescriptions in DK-DHR during the first three years after diagnosis of AD was 9.2% higher than during the first year after diagnosis, while the difference in the other data sources was up to 4%. The prevalence of memantine prescriptions in DK-DHR during the first five years was 3.3% higher than during the first three years, while the difference was approximately 0.1% in IPCI and approximately 1% in the other data sources.

The prevalence of antipsychotic prescriptions ranged from 13.6% in DK-DHR to 45.4% in NAJS during the first year after diagnosis. The prevalence of antipsychotic prescriptions was approximately 10% higher across data sources during the first three years after diagnosis than during the first year. The prevalence of antipsychotic prescriptions was approximately 5% higher during the first five years after diagnosis than during the first three years in DK-DHR and InGef RDB, whereas the difference was approximately 3% in the other data sources.

Table 6. Pharmacological treatment prescription within 1, 3, and 5 years post-AD diagnosis.

	NAJS (N=20,218)	DK-DHR (N=57,462)	InGef RDB (N=72,767)	IQVIA DA Germany (N=37,182)	IPCI (N=7,379)
Individuals with any pharmacological treatment prescription 0–1 year post-AD diagnosis, N (%)	15,881 (78.5%)	53,745 (93.5%)	51,560 (70.9%)	18,911 (50.9%)	2,010 (27.2%)
• Acetylcholinesterase inhibitors monotherapy	4,700 (23.2%)	43,173 (75.1%)	24,708 (34.0%)	9,640 (25.9%)	1,102 (14.9%)
• Memantine monotherapy	8,755 (43.3%)	16,217 (28.2%)	10,976 (15.1%)	4,540 (12.2%)	52 (0.7%)
• Antipsychotic	9,184 (45.4%)	7,815 (13.6%)	28,682 (39.4%)	9,323 (25.1%)	1,029 (13.9%)
Individuals with any pharmacological treatment prescription 0–3 years post-AD diagnosis, N (%)	16,500 (81.6%)	54,592 (95.0%)	56,036 (77.0%)	21,383 (57.5%)	2,739 (37.1%)
• Acetylcholinesterase inhibitors monotherapy	5,118 (25.3%)	43,820 (76.3%)	26,481 (36.4%)	10,661 (28.7%)	1,405 (19.0%)
• Memantine monotherapy	9,552 (47.2%)	21,825 (38.0%)	13,379 (18.4%)	5,526 (14.9%)	75 (1.0%)
• Antipsychotic	10,912 (54.0%)	13,041 (22.7%)	37,728 (51.8%)	12,276 (33.0%)	1,638 (22.2%)
Individuals with any pharmacological treatment prescription 0–5 years post-AD diagnosis, N (%)	16,664 (82.4%)	54,740 (95.3%)	57,288 (78.7%)	22,157 (59.6%)	2,957 (40.1%)
• Acetylcholinesterase inhibitors monotherapy	5,210 (25.8%)	43,877 (76.4%)	26,842 (36.9%)	10,950 (29.4%)	1,487 (20.2%)
• Memantine monotherapy	9,767 (48.3%)	23,755 (41.3%)	14,120 (19.4%)	5,831 (15.7%)	83 (1.1%)
• Antipsychotic	11,485 (56.8%)	16,148 (28.1%)	41,412 (56.9%)	13,385 (36.0%)	1,850 (25.1%)

AD=Alzheimer's disease; NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; InGef RDB=InGef Research Database; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=The Integrated Primary Care Information.

9.3.2. Timing and sequences of pharmacological treatments following AD diagnosis (objective 3)

Timing of pharmacological treatments following AD diagnosis (objective 3a)

Table 7 and **Figure 4** present the proportion of the population with incident AD who initiated a pharmacological treatment for AD (i.e. acetylcholinesterase inhibitors, memantine, or antipsychotics) within five years after the date of AD diagnosis. Treatment initiation was defined in this objective as the first treatment prescription.

Twenty-five percent of the individuals initiated any of the three pharmacological treatment classes on the day of AD diagnosis in NAJS and DK-DHR, within 37 days [95% CI: 36–38] after AD diagnosis in InGef RDB, within 15 days [95% CI: 12–20] in IQVIA DA Germany, and within 471 days [95% CI: 435–507] in IPCI. Half of the individuals initiated any of the three pharmacological treatment classes within a range from 2 days [95% CI: 2–2] after AD diagnosis in DK-DHR to 1,685 days [95% CI: 1,533–1,778] in IPCI. Seventy-five percent of the individuals initiated any of the three pharmacological treatment classes within 526 days [95% CI: 461–611] after AD diagnosis in NAJS, 49 days [95% CI: 48–51] in DK-DHR, and 1,102 days [95% CI: 1,056–1,146] in InGef RDB Germany.

Twenty-five percent of the individuals initiated acetylcholinesterase inhibitors on the date of diagnosis in DK-DHR and within a range from 82 days [95% CI: 81–84] (InGef RDB) to 1,418 days [95% CI: 1,282–1,740] (IPCI) after AD diagnosis in the other data sources. Seventy-five percent of the individuals initiated acetylcholinesterase inhibitors within 183 days [95% CI: 173–196] after AD diagnosis in DK-DHR, while less than half of the individuals initiated acetylcholinesterase inhibitors within five years after AD diagnosis in each of the other data sources.

Twenty-five percent of the individuals initiated memantine on the day of AD diagnosis or on the following day in NAJS, compared to 5% in DK-DHR and IQVIA DA Germany. In InGef RDB, five percent of individuals initiated memantine within 51 days [95% CI: 49–53] after AD diagnosis. In IPCI, less than five percent of the individuals initiated memantine within five years after AD diagnosis in IPCI.

Twenty-five percent of the individuals initiated antipsychotics within approximately 1,200–1,300 days after AD diagnosis in DK-DHR and IPCI, compared to 50% of the population in NAJS and InGef RDB. In IQVIA DA Germany, twenty-five percent of the individuals initiated antipsychotics within 784 days [95% CI: 749–811] after AD diagnosis. Less than half of the individuals initiated antipsychotics within five years after diagnosis in DK-DHR, IQVIA DA Germany, and IPCI.

Table 7. Number of days from AD diagnosis to the first treatment prescription for AD.

		Number of individuals with prescription	5th percentile [95% CI]	25th percentile [95% CI]	Median [95% CI]	75th percentile [95% CI]	95th percentile [95% CI]
NAJS (N=12,188)	Any	9,268	0 [0–0]	0 [0–0]	4 [3–5]	526 [461–611]	NI
	Acetylcholinesterase inhibitors	3,174	0 [0–0]	510 [406–643]	NI	NI	NI
	Memantine	5,731	0 [0–0]	0 [0–0]	987 [881–1,148]	NI	NI
	Antipsychotics	5,419	0 [0–0]	156 [138–181]	1,263 [1,192–1,336]	NI	NI
DK-DHR (N=44,853)	Any	42,622	0 [0–0]	0 [0–0]	2 [2–2]	49 [48–51]	530 [485–578]
	Acetylcholinesterase inhibitors	35,030	0 [0–0]	0 [0–0]	9 [8–10]	183 [173–196]	NI
	Memantine	18,180	0 [0–1]	292 [279–307]	NI	NI	NI
	Antipsychotics	9,842	245 [231–258]	1,358 [1,334–1,379]	NI	NI	NI
InGef RDB (N=46,967)	Any	33,876	1 [1–1]	37 [36–38]	106 [103–109]	1,102 1,056–1,146]	NI
	Acetylcholinesterase inhibitors	17,597	8 [7–9]	82 [81–84]	NI	NI	NI
	Memantine	8,494	51	NI	NI	NI	NI

		Number of individuals with prescription	5th percentile [95% CI]	25th percentile [95% CI]	Median [95% CI]	75th percentile [95% CI]	95th percentile [95% CI]
			[49–53]				
	Antipsychotics	22,502	4 [4–5]	269 [258–282]	1,190 [1,166–1,215]	NI	NI
IQVIA DA Germany (N=26,575)	Any	13,245	0 [0–0]	15 [12–20]	714 [671–748]	NI	NI
	Acetylcholinesterase inhibitors	7,106	0 [0–0]	441 [390–490]	NI	NI	NI
	Memantine	3,557	1 [0–7]	NI	NI	NI	NI
	Antipsychotics	6,976	1 [0–2]	784 [749–811]	NI	NI	NI
IPCI (N=6,364)	Any	2,172	30 [21–38]	471 [435–507]	1,685 [1,533–1,778]	NI	NI
	Acetylcholinesterase inhibitors	1,148	83 [73–94]	1,418 [1,282–1,740]	NI	NI	NI
	Memantine	53	NI	NI	NI	NI	NI
	Antipsychotics	1,288	133 [102–164]	1,155 [1,080–1,234]	NI	NI	NI

AD=Alzheimer's disease; NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); InGef RDB=InGef Research Database; IPCI=The Integrated Primary Care Information; CI=confidence interval. Any=acetylcholinesterase inhibitors, memantine, or antipsychotics; NI=treatment not initiated in the proportion of the population required for the time-to-event analysis.

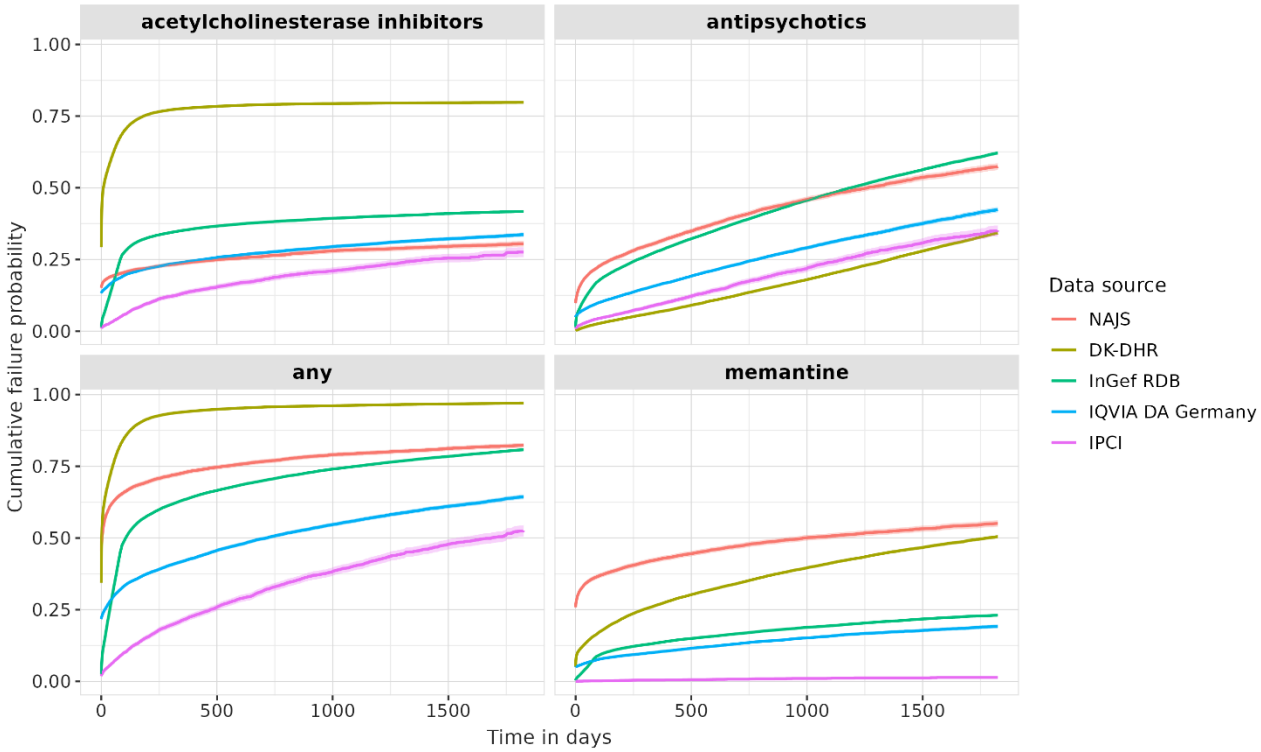

Figure 4. Probability of treatment initiation for AD after AD diagnosis.

NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; InGef RDB=InGef Research Database; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=The Integrated Primary Care Information.

Sequences of pharmacological treatments following AD diagnosis (objective 3b)

Analyses in this section were restricted to individuals with incident AD whose treatment sequence occurred in more than five individuals. This resulted in the inclusion of 7,246 individuals in IPCI, 18,929 individuals in NAJS, 34,462 individuals in IQVIA DA Germany, 56,416 individuals in DK-DHR, and 71,430 individuals in InGef RDB.

Figures 5a–e present the proportion of the population with incident AD who were prescribed a pharmacological treatment sequence, with the first treatment after diagnosis plotted in the inner ring of the sunburst plot and each subsequent treatment in the next ring.

The proportion of individuals who had no treatment prescription for AD within five years after AD diagnosis was 6.7% in DK-DHR, 21.9% in NAJS, 23.0% in InGef RDB, 43.2% in IQVIA DA Germany, and 65.5% in IPCI.

In each data source, monotherapy was more frequently prescribed than combination therapy as the initial treatment after AD diagnosis. The prevalence of prescription of acetylcholinesterase inhibitors and antipsychotics as the first treatment after AD diagnosis was similar in InGef RDB (approximately 30%), IQVIA DA Germany (approximately 20%), and IPCI (approximately 17%). Acetylcholinesterase inhibitors were prescribed as the first treatment after AD diagnosis to 15.7% in NAJS and to 73.0% in DK-DHR. Antipsychotics were prescribed as the first treatment after AD diagnosis to 22.5% in NAJS and to 2.4% in DK-DHR. Memantine was prescribed as the first treatment after AD diagnosis to 31.5 in NAJS, compared to 17.5% in DK-DHR and approximately 10% in InGef RDB and IQVIA DA Germany, but only 0.4% in IPCI.

The most common treatment sequences comprised prescription of acetylcholinesterase inhibitors (in InGef RDB, IPCI, and IQVIA DA Germany) or memantine (in NAJS) as the first treatment after AD diagnosis, followed by antipsychotics, either as a monotherapy or combined with the initially prescribed treatment. In

DK-DHR, the most common sequences comprised prescription of acetylcholinesterase inhibitors as the first treatment after AD diagnosis followed by memantine, either as a monotherapy or combined with acetylcholinesterase inhibitors. The prevalence of the prescription of the most common sequence of two treatments ranged from 1.5% in IPCI to 14.8% in DK-DHR, while the prevalence of the second most common sequence of two treatments ranged from 1.4% in IPCI to 5.6% in DK-DHR.

The most common sequences of three different treatments in InGef RDB, IQVIA DA Germany, and IPCI comprised prescription of acetylcholinesterase inhibitors as the first treatment after AD diagnosis, followed by acetylcholinesterase inhibitors combined with antipsychotics, and followed by either acetylcholinesterase inhibitors or antipsychotics. In NAJS, the most common sequences comprised prescription of memantine as the first treatment after AD diagnosis, followed by memantine combined with antipsychotics, and followed by either memantine or antipsychotics. In DK-DHR, the most common sequences comprised prescription of acetylcholinesterase inhibitors as the first treatment after AD diagnosis, followed by acetylcholinesterase inhibitors combined with memantine, and followed by either acetylcholinesterase inhibitors or memantine. The only deviation from this pattern was in InGef RDB: the second most common treatment sequence comprised prescription of acetylcholinesterase inhibitor as the first treatment after AD diagnosis, followed by antipsychotics, and followed by acetylcholinesterase inhibitors combined with antipsychotics. The prevalence of the prescription of the most common sequence ranged from 0.8% in IPCI to 9.6% in DK-DHR. The prevalence of the prescription of the next most common sequence ranged from 0.4% in IPCI to 4.5% in DK-DHR.

Only one sequence of four treatments was observed in more than 5% of the study population, and only in DK-DHR: prescription of acetylcholinesterase inhibitors as the first treatment after diagnosis followed by acetylcholinesterase inhibitors + memantine, acetylcholinesterase inhibitor monotherapy, and acetylcholinesterase inhibitors + memantine (prescribed to 7.4% of the population with incident AD). Sequences of four or more treatments were prescribed to less than 5% of the population with incident AD up to five years after diagnosis in NAJS, InGef RDB, IQVIA DA Germany, and IPCI.

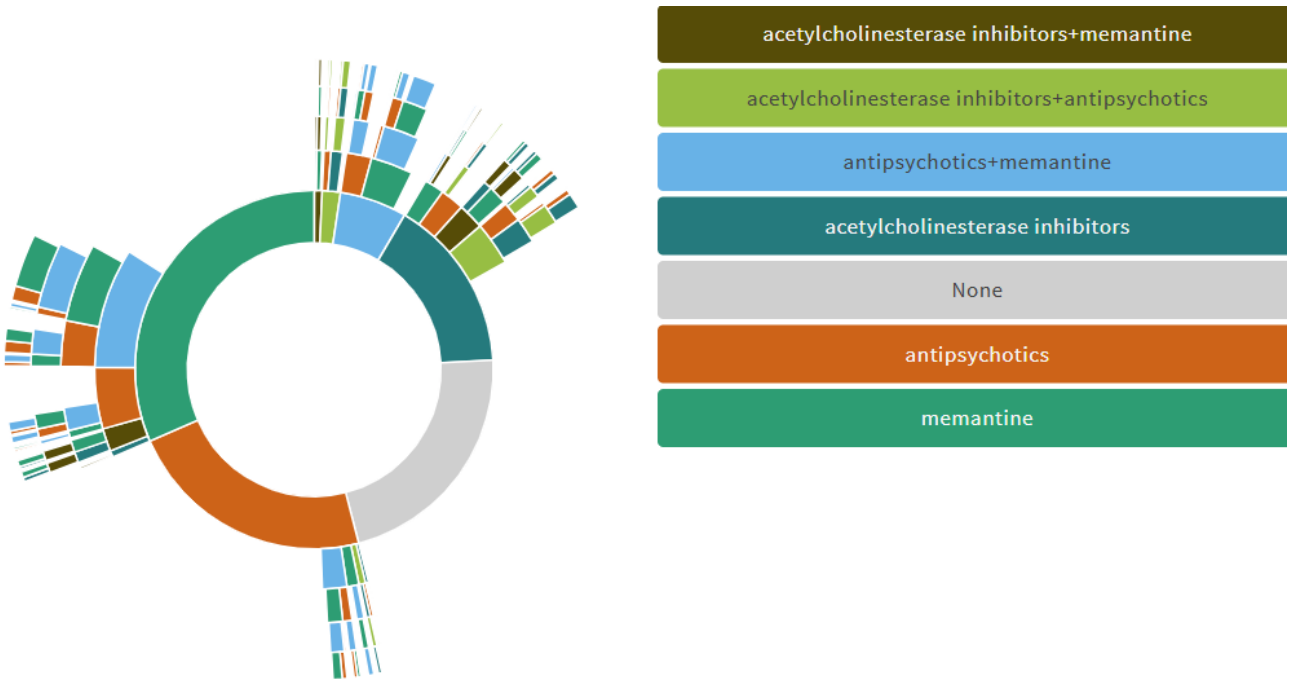

Figure 5a. Sunburst plot of treatment sequence up to 5 years after AD diagnosis in NAJS.

AD=Alzheimer's disease; NAJS=National Public Health Information System.

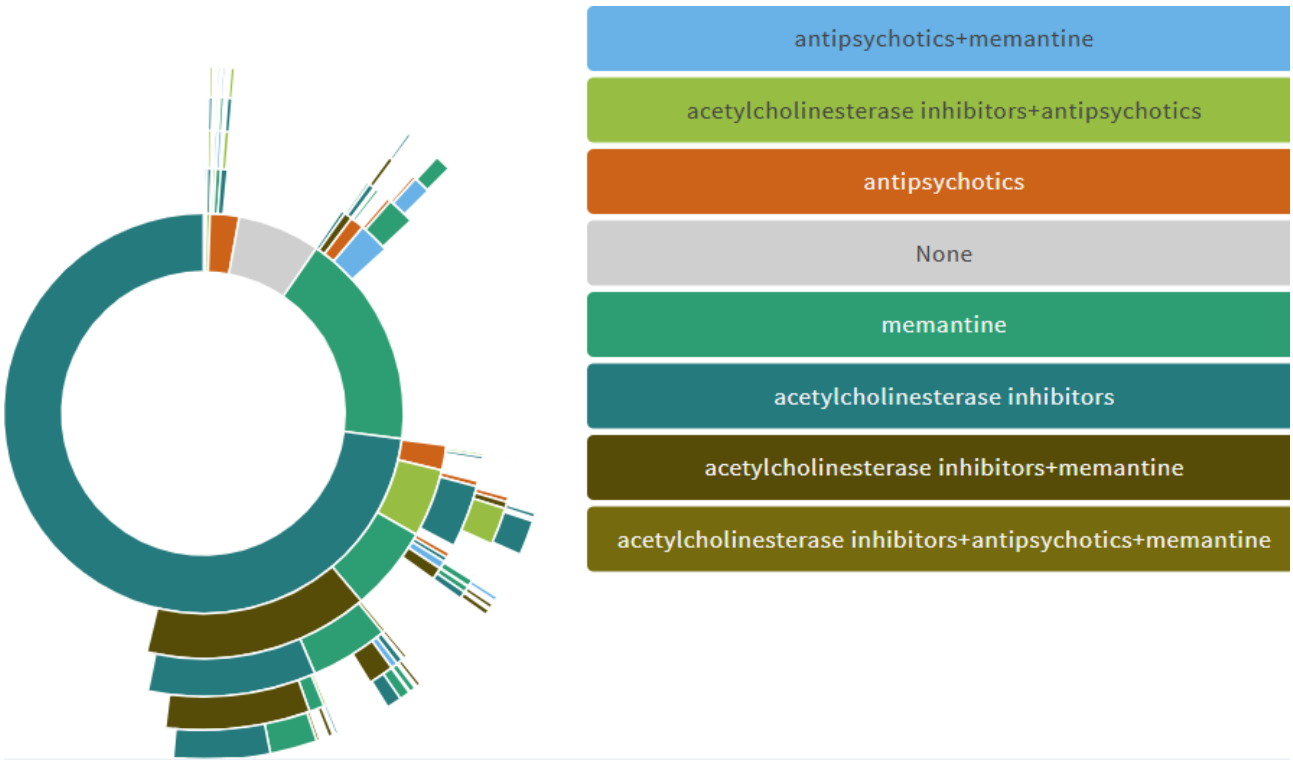

Figure 5b. Sunburst plot of treatment sequence up to 5 years after AD diagnosis in DK-DHR.

AD=Alzheimer's disease; DK-DHR=Danish Data Health Registries.

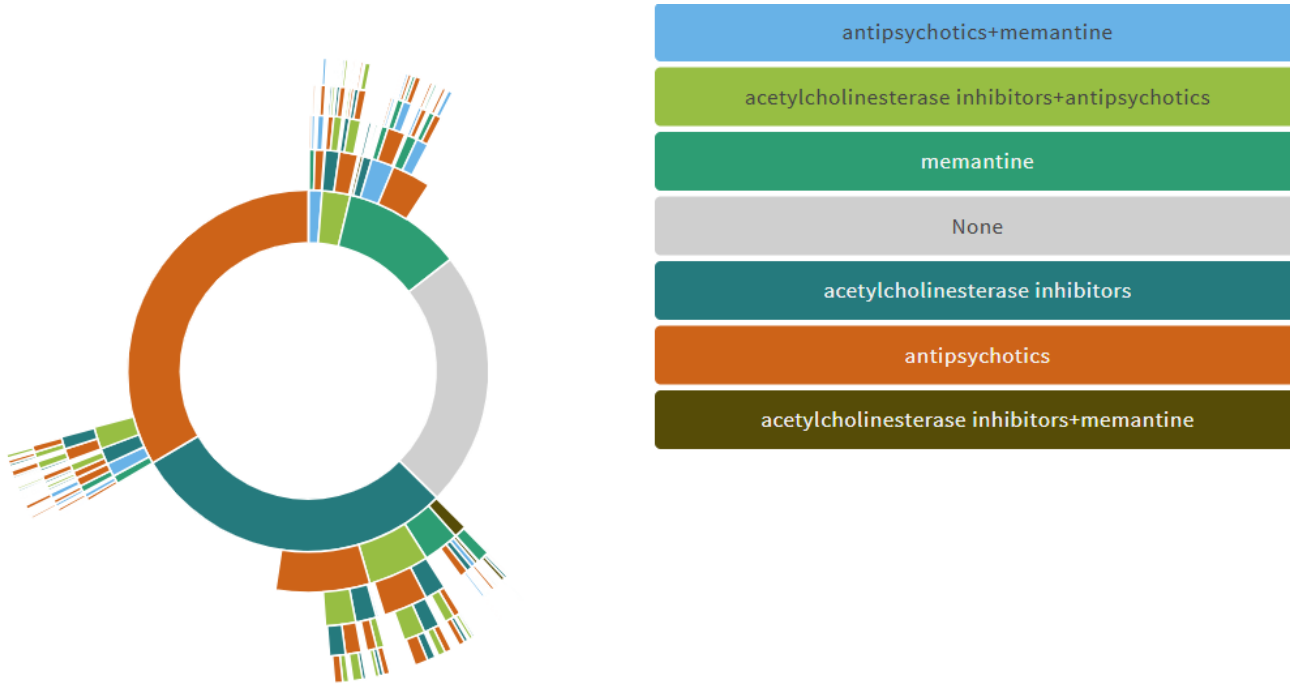

Figure 5c. Sunburst plot of treatment sequence up to 5 years after AD diagnosis in InGef RDB.

AD=Alzheimer's disease; InGef RDB=InGef Research Database.

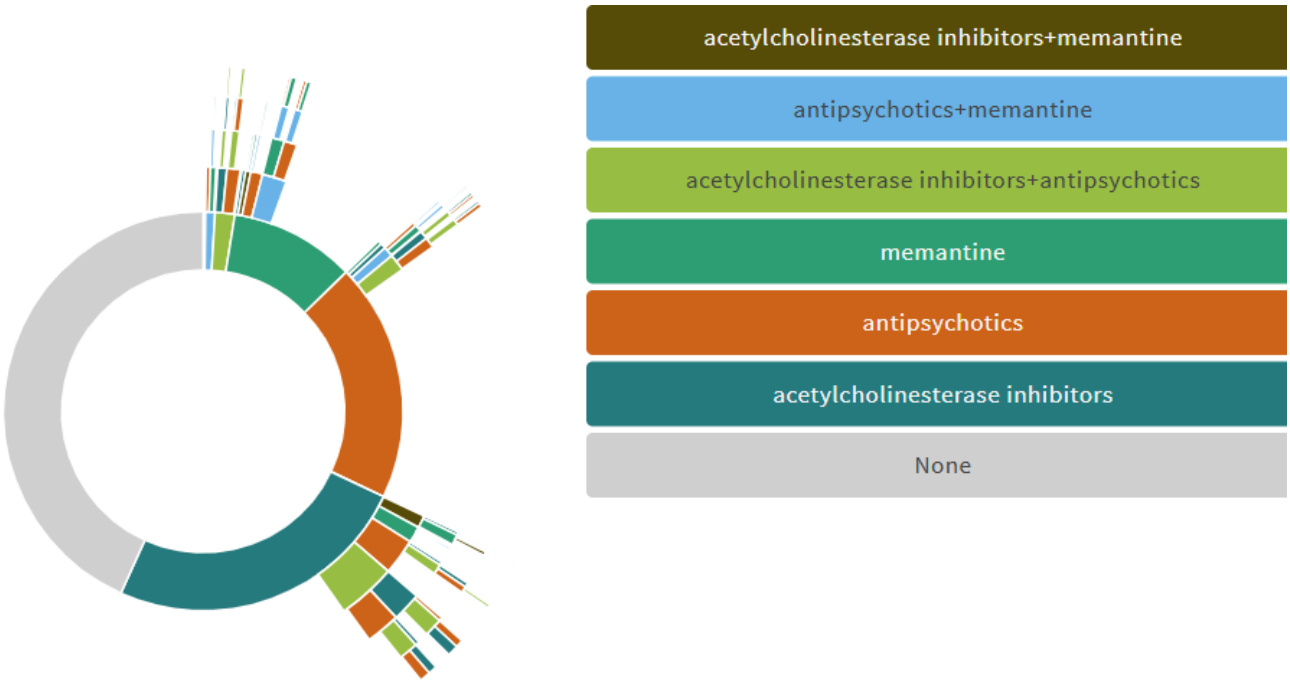

Figure 5d. Sunburst plot of treatment sequence up to 5 years after AD diagnosis in IQVIA DA Germany.

AD=Alzheimer's disease; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany).

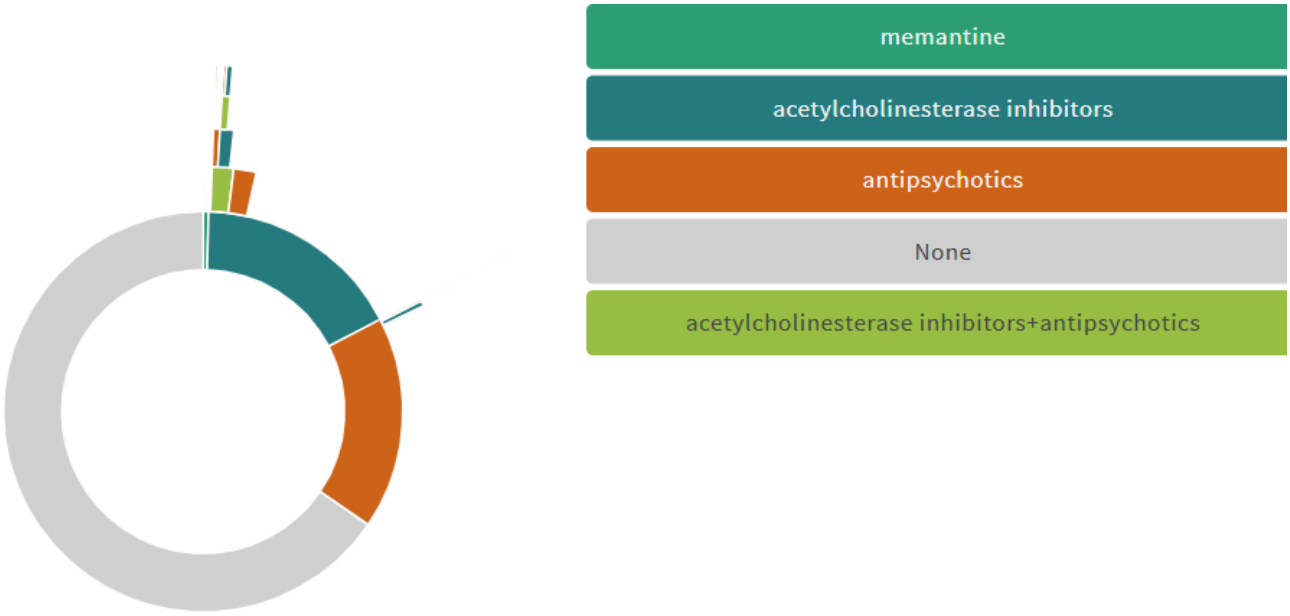

Figure 5e. Sunburst plot of treatment sequence up to 5 years after AD diagnosis in IPCI.

AD=Alzheimer's disease; IPCI=The Integrated Primary Care Information.

9.3.3. Clinical and care-related events following AD diagnosis (objective 4)

Frequency of hospitalisations, outpatient visits, and caregiver support (objectives 4a–c)

Table 8, Table 9, and Table 10 present the frequency of clinical and care-related events within one, three, and five years post-AD diagnosis, respectively.

The median [IQR] number of hospitalisations was consistently low across all time points and data sources. In NAJS, it was 1 [0–2] at one year and 1 [0–3] at both three and five years. In DK-DHR, it was 0 [0–1] at one year and 1 [0–2] at three and five years. In InGef RDB, it was 1 [0–2] at one year and 2 [1–3] at three and five years.

NAJS had higher outpatient visit counts than other data sources: the median [IQR] number was 30 [17–44] at one year, 59 [26–100] at three years, and 65 [26–123] at five years. The other data sources showed lower and more similar counts: in DK-DHR, the median [IQR] number was 5 [3–9], 8 [4–15], and 9 [5–17]; in IQVIA DA Germany, 7 [3–17], 15 [4–38], and 17 [5–45]; and in IPCI, 6 [3–11], 12 [5–21], and 13 [5–25] at one, three, and five years, respectively.

Caregiver support was recorded more frequently in NAJS: among 12,197 individuals (60.3%) at one year, 12,852 (63.6%) at three years, and 13,100 (64.8%) at five years. In DK-DHR, 1,571 (2.7%), 1,827 (3.2%), and 1,937 (3.4%) received support at one, three, and five years, respectively. In IQVIA DA Germany, the corresponding figures were 2,709 (7.3%), 3,307 (8.9%), and 3,539 (9.5%).

Table 8. Number of care-related events within 1 year post-AD diagnosis.

	NAJS (N=20,218)	DK-DHR (N=57,462)	InGef RDB (N=72,767)	IQVIA DA Germany (N=37,182)	IPCI (N=7,379)
Number of hospitalisations per individual					
• Mean (SD)	1.2 (1.9)	0.5 (1.0)	1.1 (1.3)	NC	NC
• Median [IQR]	1 [0–2]	0 [0–1]	1 [0–2]	NC	NC
• Min–max range	0–68	0–27	0–23	NC	NC
Number of outpatient visits per individual					
• Mean (SD)	32.1 (20.6)	7.0 (6.7)	NC	12.0 (12.3)	7.9 (7)
• Median (IQR)	30 [17–44]	5 [3–9]	NC	7 [3–17]	6 [3–11]
• Min–max range	0–216	0–208	NC	1–148	0–65
Individuals with caregiver support, N (%)	12,197 (60.3%)	1,571 (2.7%)	NC	2,709 (7.3%)	NC

AD=Alzheimer's disease; NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); InGef RDB=InGef Research Database; IPCI=The Integrated Primary Care Information; IQR=interquartile range; SD=standard deviation; NC=information not captured in the data source.

Table 9. Number of care-related events within 3 years post-AD diagnosis.

	NAJS (N=20,218)	DK-DHR (N=57,462)	InGef RDB (N=72,767)	IQVIA DA Germany (N=37,182)	IPCI (N=7,379)
Number of hospitalisations per individual					
• Mean (SD)	2.2 (3.6)	1.1 (1.7)	2.0 (2.1)	NC	NC
• Median [IQR]	1 [0–3]	1 [0–2]	2 [1–3]	NC	NC
• Min–max range	0–137	0–49	0–48	NC	NC
Number of outpatient visits per individual					
• Mean (SD)	68.4 (53.3)	11.5 (13.4)	NC	26.1 (30)	15.4 (14.3)
• Median [IQR]	59 [26–100]	8 [4–15]	NC	15 [4–38]	12 [5–21]
• Min–max range	0–580	0–567	NC	1–310	0–155
Individuals with caregiver support, N (%)	12,852 (63.6%)	1,827 (3.2%)	NC	3,307 (8.9%)	NC

AD=Alzheimer's disease; NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; InGef RDB=InGef Research Database; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=The Integrated Primary Care Information. IQR=interquartile range; SD=standard deviation. NC=information not captured in the data source.

Table 10. Number of care-related events within 5 years post-AD diagnosis.

	NAJS (N=20,218)	DK-DHR (N=57,462)	InGef RDB (N=72,767)	IQVIA DA Germany (N=37,182)	IPCI (N=7,379)
Number of hospitalisations per individual					
• Mean (SD)	2.6 (4.42)	1.4 (1.94)	2.4 (2.4)	NC	NC
• Median [IQR]	1 [0–3]	1 [0–2]	2 [1–3]	NC	NC
• Min–max range	0–165	0–51	0–48	NC	NC
Number of outpatient visits per individual					
• Mean (SD)	84.4 (74.83)	13.3 (16.41)	NC	33 (40.98)	18.3 (18.18)
• Median [IQR]	65 [26–123]	9 [5–17]	NC	17 [5–45]	13 [5–25]
• Min–max range	0–833	0–806	NC	1–444	0–232
Individuals with caregiver support, N (%)	13,100 (64.8%)	1,937 (3.4%)	NC	3,539 (9.5%)	NC

AD=Alzheimer's disease; NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; InGef RDB=InGef Research Database; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=The Integrated Primary Care Information. IQR=interquartile range; SD=standard deviation; NC=information not captured in the data source.

Time from AD diagnosis to caregiver support (objective 4d)

Table 11 presents the proportion of the population with incident AD who had a first record of caregiver support (i.e. first received caregiver support) between the date of AD diagnosis and five years after.

Five percent of the individuals received caregiver support within 44 days [95% CI: 31–57] after AD diagnosis in NAJS and within 860 days [95% CI: 789–915] in IQVIA DA Germany, whereas less than five percent received caregiver support within five years after diagnosis in DK-DHR. Twenty-five percent of the individuals received caregiver support within 993 days [95% CI: 927–1,076] after AD diagnosis in NAJS, while less than twenty-five percent of the individuals received caregiver support within five years after AD diagnosis in IQVIA DA Germany.

Table 11. Number of days from AD diagnosis to caregiver support.

	Number of individuals with caregiver support	5th percentile [95% CI]	25th percentile [95% CI]	Median [95% CI]	75th percentile [95% CI]	95th percentile [95% CI]
NAJS (N=9,154)	2,036	44 [31–57]	993 [927–1,076]	NI	NI	NI
DK-DHR (N=56,119)	594	NI	NI	NI	NI	NI
InGef RDB (N=NC)	NC	NC	NC	NC	NC	NC
IQVIA DA Germany (N=35,367)	1,724	860 [789–915]	NI	NI	NI	NI
IPCI (N=NC)	NC	NC	NC	NC	NC	NC

AD=Alzheimer's disease; NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; InGef RDB=InGef Research Database; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=The Integrated Primary Care Information CI=confidence interval; NC=information not captured in the data source; NI=caregiver support not initiated in the proportion of the population required for the time-to-event analysis.

9.3.4. Survival (objective 5)

Overall survival from AD diagnosis (objective 5a)

Figure 6 presents Kaplan–Meier estimates of the overall survival from the date of incident AD diagnosis to five years of follow-up. **Table 12** presents the proportion of the population with incident AD who died within five years since AD diagnosis. **Table 13** presents the survival probability of individuals with incident AD every six months from the date of diagnosis to five years of follow-up.

Twenty-five percent of the individuals died within 325 days [95% CI: 308–340] after AD diagnosis in NAJS, 819 days [95% CI: 809–830] in DK-DHR, 1,552 days [95% CI: 1,552–1,634] in InGef RDB, and 1,243 days [95% CI: 1,171–1,298] in IPCI.

Half of the individuals died within 1,162 days [95% CI: 1,127–1,200] after AD diagnosis in NAJS and 1,517 days [95% CI: 1,502–1,530] in DK-DHR, while less than half of the population with incident AD had a record of death within five years after diagnosis in InGef RDB and IPCI.

The 1-year survival probability after AD diagnosis ranged from 73.5% [95% CI: 72.9%–74.1%] in NAJS to 93.6% [95% CI: 93.5%–93.8%] in InGef RDB. The 3-year survival probability ranged from 51.7% [95% CI: 50.9%–52.4%] in NAJS to 83.2% [95% CI: 82.9%–83.5%] in InGef RDB. The 5-year survival probability ranged from 37.4% [95% CI: 36.6%–38.3%] in NAJS to 71.1% [95% CI: 70.6%–71.6%] in InGef RDB.

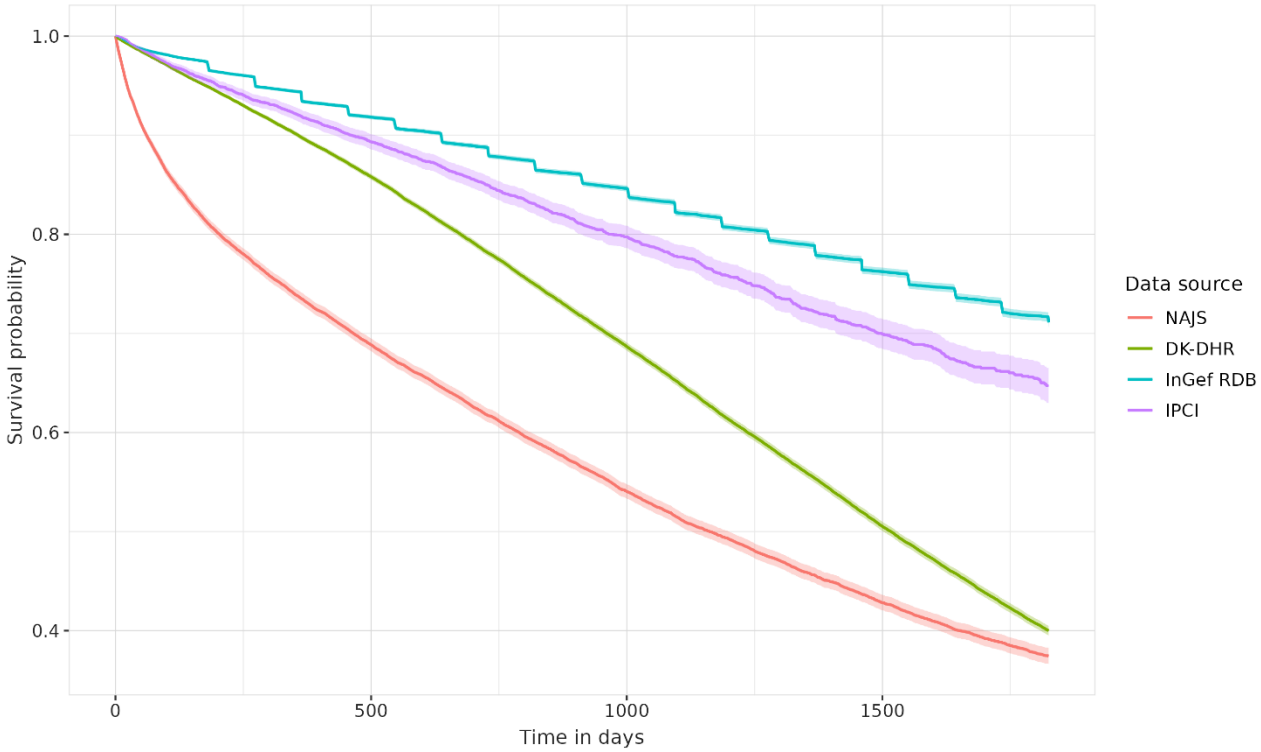

Figure 6. Survival probability after AD diagnosis.

AD=Alzheimer's disease; NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; InGef RDB=InGef Research Database; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=The Integrated Primary Care Information. Shaded area=95% confidence interval.

Table 12. Number of days from AD diagnosis until death.

	Number of individuals with record of death	25th percentile [95% CI]	Median [95% CI]	75th percentile [95% CI]
NAJS (N=20,218)	10,758	325 [308–340]	1,162 [1,127–1,200]	ND
DK-DHR (N=57,462)	27,567	819 [809–830]	1,517 [1,502–1,530]	ND
InGef RDB (N=72,767)	13,048	1,552 [1,552–1,634]	ND	ND
IQVIA DA Germany (N=37,182)	NC	NC	NC	NC
IPCI (N=7,379)	1,437	1,243 [1,171–1,298]	ND	ND

AD=Alzheimer's disease; NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; InGef RDB=InGef Research Database; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=The Integrated Primary Care Information. CI=confidence interval; NC=information not captured in the data source; ND=death not recorded in the proportion of the population required for the time-to-event analysis.

Table 13. Survival probability after AD diagnosis, % [95% confidence interval].

Time (months) since AD diagnosis	NAJS (N=20,218)	DK-DHR (N=57,462)	InGef RDB (N=72,767)	IQVIA DA Germany (N=37,182)	IPCI (N=7,379)
6	81.0 [80.5–81.5]	94.8 94.6–95.0]	96.8 [96.6–96.9]	NC	95.5 [95.0–96.0]
12	73.4 [72.8–74.1]	89.7 [89.5–90.0]	93.6 [93.4–93.8]	NC	91.9 [91.2–92.5]
18	67.2 [66.6–67.9]	84.3 [84.0–84.6]	91.2 [91.0–91.4]	NC	88.5 [87.7–89.3]
24	61.7 [61.0–62.4]	78.1 [77.8–78.4]	88.7 [88.5–89.0]	NC	84.9 [84.0–85.8]
30	56.5 [55.8–57.2]	71.7 [71.4–72.1]	86.0 [85.7–86.2]	NC	81.0 [80.0–82.1]
36	51.6 [50.9–52.3]	65.3 [64.9–65.7]	83.2 [82.9–83.5]	NC	77.8 [76.6–79.0]
42	47.5 [46.8–48.3]	58.7 [58.2–59.1]	80.3 [79.9–80.6]	NC	74.3 [73.0–75.7]
48	43.7 [43.0–44.5]	52.1 [51.6–52.5]	77.4 [77.0–77.8]	NC	70.8 [69.3–72.2]
54	40.1 [39.4–40.9]	45.9 [45.4–46.3]	74.5 [74.1–74.9]	NC	67.4 [65.8–69.0]
60	37.4 [36.6–38.2]	39.9 [39.5–40.4]	71.1 [70.6–71.5]	NC	64.7 [62.9–66.5]

AD=Alzheimer's disease; NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; InGef RDB=InGef Research Database; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=The Integrated Primary Care Information. NC=information not captured in the data source.

Overall survival from the first treatment prescription for AD (objective 5b)

Figure 7 presents Kaplan–Meier estimates of the overall survival from the date of the first treatment prescription for AD to five years of follow-up. **Table 14** presents the proportion of the population with incident AD who died between the date of the first treatment prescription for AD and five years after. **Table 15** presents the survival probability of individuals with incident AD every six months from the date of the first treatment prescription for AD until five years after.

Twenty-five percent of the individuals died within 557 days [95% CI: 537–583] after the first treatment prescription for AD in NAJS, 874 days [95% CI: 864–885] in DK-DHR, and 1,534 days [95% CI: 1,320–1,758] in IPCI, while less than twenty-five percent died within five years after the first treatment prescription for AD in InGef RDB.

Half of the individuals died within 1,387 days [95% CI: 1,337–1,432] after the first treatment prescription for AD in NAJS and 1,557 days [95% CI: 1,541–1,571] in DK-DHR, while less than half of the individuals died within five years after the first treatment prescription for AD in InGef RDB and IPCI.

The 1-year survival probability after the first treatment prescription ranged from 75.4% [95% CI: 74.5%–76.2%] in NAJS to 94.8% [95% CI: 94.5%–95.1%] in InGef RDB. The 3-year survival probability ranged from 57.9% [95% CI: 56.9%–59.0%] in NAJS to 87.4% [95% CI: 87.0%–87.9%] in InGef RDB. The 5-year survival probability ranged from 40.4% [95% CI: 39.2%–41.6%] in NAJS to 75.7% [95% CI: 75.0%–76.5%] in InGef RDB.

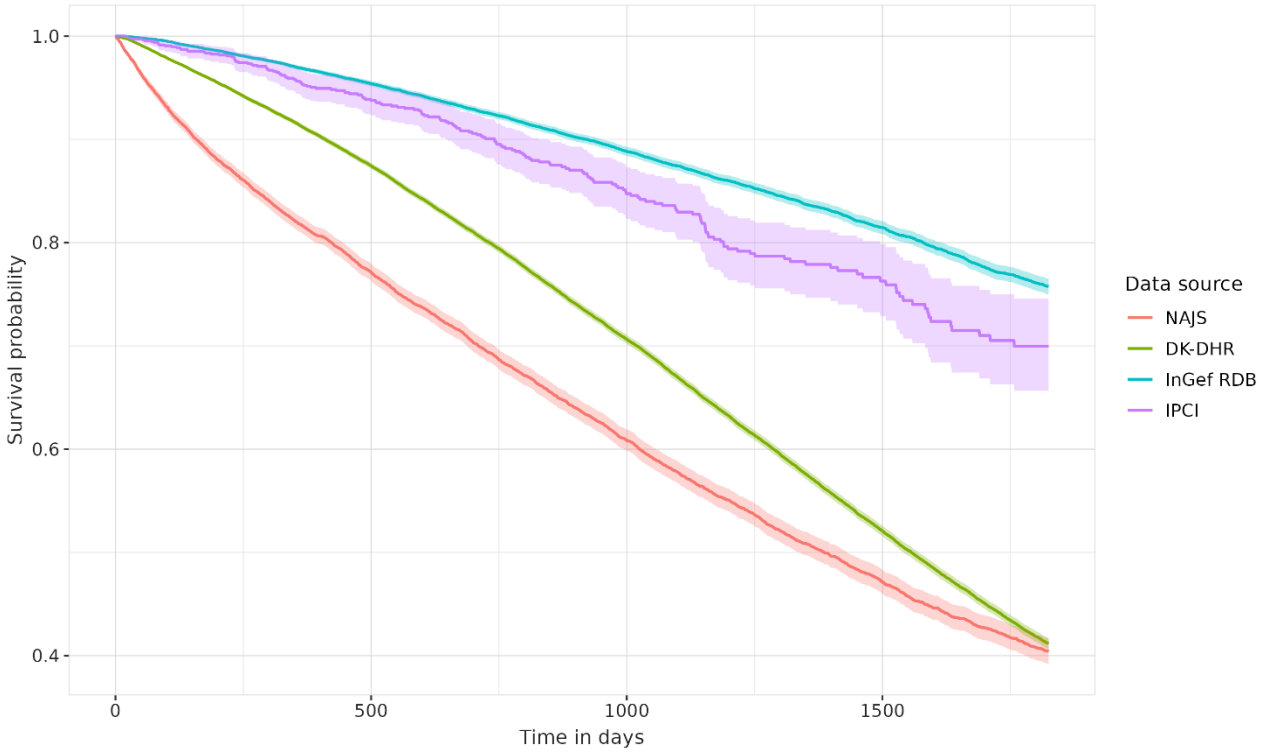

Figure 7. Survival probability after treatment initiation for AD.

AD=Alzheimer's disease; NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; InGef RDB=InGef Research Database; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=The Integrated Primary Care Information. Shaded area=95% confidence interval.

Table 14. Number of days from AD treatment initiation until death.

	Number of individuals with record of death	25th percentile [95% CI]	Median [95% CI]	75th percentile [95% CI]
NAJS (N=9,909)	4,703	557 [537–583]	1,387 [1,337–1,432]	ND
DK-DHR (N=49,200)	22,633	874 [864–885]	1,557 [1,541–1,571]	ND
InGef RDB (N=25,546)	3,684	ND	ND	ND
IQVIA DA Germany (N=10,648)	NC	NC	NC	NC
IPCI (N=1,185)	182	1,534 [1,320–1,758]	ND	ND

AD=Alzheimer's disease; NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; InGef RDB=InGef Research Database; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=The Integrated Primary Care Information. CI=confidence interval; NC=information not captured in the data source; ND=death not recorded in the proportion of the population required for the time-to-event analysis.

Table 15. Survival probability after AD treatment initiation, % [95% confidence interval].

Time (months) since treatment initiation for AD	NAJS (N=9,909)	DK-DHR (N=49,200)	InGef RDB (N=25,546)	IQVIA DA Germany (N=10,648)	IPCI (N=1,185)
6	88.8 [88.2–89.4]	95.9 [95.7–96.1]	98.7 [98.6–98.8]	NC	98.3 [97.6–99.0]
12	81.6 [80.9–82.4]	91.2 [91.0–91.5]	96.8 [96.6–97.1]	NC	95.4 [94.2–96.6]
18	75.4 [74.5–76.2]	85.9 [85.6–86.2]	94.8 [94.5–95.1]	NC	93.2 [91.7–94.7]
24	69.4 [68.4–70.3]	80.1 [79.7–80.4]	92.5 [92.2–92.9]	NC	90.0 [88.1–91.9]
30	63.6 [62.7–64.6]	73.7 [73.3–74.1]	90.1 [89.6–90.5]	NC	87.0 [84.8–89.2]
36	57.9 [56.9–59.0]	67.2 [66.8–67.7]	87.4 [87.0–87.9]	NC	83.5 [81.0–86.2]
42	52.7 [51.6–53.8]	60.5 [60.0–60.9]	84.9 [84.3–85.4]	NC	78.6 [75.5–81.9]
48	48.1 [47.0–49.3]	53.6 [53.1–54.1]	82.0 [81.4–82.6]	NC	76.9 [73.6–80.4]
54	43.7 [42.5–44.9]	47.1 [46.6–47.6]	78.8 [78.2–79.5]	NC	71.4 [67.4–75.8]
60	40.4 [39.2–41.6]	41.1 [40.6–41.6]	75.7 [75.0–76.5]	NC	69.9 [65.6–74.5]

AD=Alzheimer's disease; NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; InGef RDB=InGef Research Database; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=The Integrated Primary Care Information; NC=information not captured in the data source.

9.4. Sensitivity analyses

Two sensitivity analyses were conducted for objective 3, as reported in **Section 8.9.3**.

Compared to the main results, the sequences up to and including the first three treatments were very similar in both sensitivity analyses. Identical to the main analysis, the treatments most prescribed as the initial treatment were monotherapies. The prevalence of prescription of a sequence with combination therapy was only slightly higher in the sensitivity analyses compared to the main analysis. Accordingly, the prevalence of monotherapy prescription was slightly lower. Sequences of four or more treatments were prescribed to <5% of the study population in both sensitivity analyses and in all data sources (see ShinyApp at EUPAS1000000827).

10. DISCUSSION

10.1. Key results

The number of individuals with incident AD (i.e. with a first record of AD diagnosis) included in this study was 20,218 in NAJS, 57,462 in DK-DHR, 72,767 in InGef RDB, 37,182 in IQVIA DA Germany, and 7,379 in IPCI. The number of individuals with incident AD and a first treatment prescription for AD included in this study was 9,909 in NAJS, 49,200 in DK-DHR, 25,546 in InGef RDB, 10,648 in IQVIA DA Germany, and 1,185 in IPCI, with a median age ranging from 77 years (IPCI) to 81 years (IQVIA DA Germany) and with the proportion of females ranging from 54.4% (InGef RDB) to 65.8% (NAJS). The most prescribed medications during the year up to index date were antihypertensives (prevalence of prescription ranging from 21.5% in IQVIA DA Germany to 58.6% in DK-DHR) and lipid-lowering drugs (from 15.0% in IQVIA DA Germany to 42.3% in DK-DHR). The most common comorbidities were hypertension (prevalence ranging from 35.4% in IPCI to 86.1% in NAJS) and diabetes (from 15.9% in DK-DHR and IPCI to 30.9% in NAJS). The prevalence of a diagnosis of MCI prior to the diagnosis of AD ranged from 5.6% (DK-DHR) to 14.2% (IQVIA DA Germany) among individuals initiating AD treatment. The baseline characteristics of individuals with MCI prior to the diagnosis of AD were similar to those in the overall population of individuals with incident AD and a first treatment prescription for AD.

More than 50% of the individuals with incident AD were prescribed a pharmacological treatment (i.e. acetylcholinesterase inhibitors, memantine, or antipsychotics) during the first year after diagnosis across data sources, except in IPCI, where only a quarter were prescribed any of these treatments. The prevalence of acetylcholinesterase inhibitor prescriptions during the first year after diagnosis was 75.1% in DK-DHR, while it ranged between 14.9% (IPCI) and 34.0% (InGef RDB) in the other data sources. The prevalence of memantine prescriptions during the first year after diagnosis was 0.7% in IPCI, while it ranged between 12.2% (IQVIA DA Germany) and 43.3% (NAJS) in the other data sources. The prevalence of antipsychotic prescriptions during the first year after diagnosis ranged from 13.6% in DK-DHR to 45.4% in NAJS. The prevalence of antipsychotic prescriptions during the first five years after diagnosis was approximately 11% higher than during the first year across data sources, whereas the difference was up to approximately 5% each for acetylcholinesterase inhibitors and memantine. The only deviation from this pattern was observed in the prevalence of memantine prescriptions in DK-DHR, which was 13% larger during the first five years after diagnosis than during the first year after diagnosis.

Twenty-five percent of the individuals initiated any of the three pharmacological treatment classes on the day of AD diagnosis in NAJS and DK-DHR, within 37 days [95% CI: 36–38] after in InGef RDB, within 15 days [95% CI: 12–20] in IQVIA DA Germany, and within 471 days [95% CI: 435–507] in IPCI. Seventy-five percent of the individuals initiated acetylcholinesterase inhibitors within 183 days [95% CI: 173–196] after AD diagnosis in DK-DHR, while less than half initiated acetylcholinesterase inhibitors within five years after AD diagnosis in each of the other data sources. Twenty-five percent of the individuals initiated memantine on the day of AD diagnosis or the day after in NAJS, compared to five percent in DK-DHR and IQVIA DA Germany. In contrast, five percent of the individuals initiated memantine within 51 days [95% CI: 49–53] after AD diagnosis in InGef RDB, and less than five percent initiated memantine within five years after AD diagnosis in IPCI. Half of the individuals initiated antipsychotics within approximately 1,300 days after AD diagnosis in NAJS and InGef RDB, while less than half initiated antipsychotics within five years after AD diagnosis in DK-DHR, IQVIA DA Germany, and IPCI.

The proportion of individuals who had no treatment prescription for AD within five years after AD diagnosis was 6.7% in DK-DHR, 21.9% in NAJS, 23.0% in InGef RDB, 43.2% in IQVIA DA Germany, and 65.5% in IPCI. In each data source, monotherapy was more frequently prescribed than combination therapy as the initial treatment after AD diagnosis. The prevalence of prescription of acetylcholinesterase inhibitors and antipsychotics as the first treatment after AD diagnosis was similar in InGef RDB (approximately 30%), IQVIA DA Germany (approximately 20%), and IPCI (approximately 17%). The treatments that were the most

common as the first treatment after diagnosis were acetylcholinesterase inhibitors in DK-DHR (prescribed to 73.0%) and memantine in NAJS (prescribed to 31.5%).

Treatment sequences were uncommon: the prevalence of prescription of the most common sequence of two treatments ranged between 1.5% (IPCI) and 14.8% (DK-DHR). The most common sequences of prescriptions of three different treatments after the diagnosis of AD were similar between InGef RDB, IQVIA DA Germany, and IPCI. In these three data sources, the most common sequences comprised prescription of acetylcholinesterase inhibitors as the first treatment after diagnosis, followed by prescription of acetylcholinesterase inhibitors combined with antipsychotics, and followed by prescription of either acetylcholinesterase inhibitors or antipsychotics. In NAJS, the most common sequences comprised prescription of memantine as the first treatment after diagnosis, followed by prescription of memantine combined with antipsychotics, and followed by prescription of either memantine or antipsychotics. In DK-DHR, the most common sequences comprised prescription of acetylcholinesterase inhibitors as the first treatment after diagnosis, followed by prescription of acetylcholinesterase inhibitors combined with memantine, and followed by prescription of either acetylcholinesterase inhibitors or memantine.

The median [IQR] number of hospitalisations per individual within five years after diagnosis of AD was 1 [0–3] in NAJS, 1 [0–2] in DK-DHR, and 2 [1–3] in InGef RDB. The median [IQR] number of outpatient visits per individual approximately doubled from one year after diagnosis of AD (ranging from 5 [3–9] in DK-DHR to 30 [17–44] in NAJS) to five years after (ranging from 9 [5–17] in DK-DHR to 65 [26–123] in NAJS). The number of individuals with caregiver support within one year after diagnosis of AD was 12,197 (60.3%) in NAJS, 1,571 (2.7%) in DK-DHR, and 2,709 (7.3%) in IQVIA DA Germany, and hardly increased up to five years after diagnosis of AD. Five percent of the individuals received their first caregiver support within 44 days [95% CI: 31–57] after AD diagnosis in NAJS and within 860 days [95% CI: 789–915] in IQVIA DA Germany. Less than five percent of the individuals in DK-DHR had a record of caregiver support within five years after AD diagnosis.

The 5-year survival probability from AD diagnosis ranged from 37.4% [95% CI: 36.6%–38.3%] in NAJS to 71.1% [95% CI: 70.6%–71.6%] in InGef RDB. The 5-year survival probability from the first treatment prescription for AD ranged from 40.4% [95%CI: 39.2%–41.6%] in NAJS to 75.7% [95%CI: 75.0%–76.5%] in InGef RDB.

Key results by sex

The prevalence of pharmacological treatment prescriptions after diagnosis of AD was generally similar between females and males, with similar time from diagnosis of AD until treatment initiation for AD, and similar prevalence of sequences of pharmacological treatment prescriptions. The frequency of care and care-related events was similar between females and males as well. However, the 5-year survival probability from diagnosis of AD and from treatment initiation for AD was up to approximately 5% higher among females than males.

Key results by age

The prevalence of pharmacological treatment prescriptions (i.e. of acetylcholinesterase inhibitors, memantine, and antipsychotics) varied between age groups. The time from AD diagnosis until five percent of the individuals initiated antipsychotics was generally shorter in the older age groups, while the time between diagnosis of AD until five percent of the individuals initiated acetylcholinesterase inhibitors varied between age groups, and the pattern for memantine varied between data sources.

The proportion of individuals who were not prescribed a pharmacological treatment for AD (i.e. acetylcholinesterase inhibitors, memantine, or antipsychotics) within five years after AD diagnosis ranged from 19.6% in DK-DHR to 71.3% in IQVIA DA Germany in the age group 18 to 55 years, from 6.4% in DK-DHR to 60.4% in IQVIA DA Germany in the age group 56 to 65 years, from 4.4% in DK-DHR to 57.7% in IPCI in the

age group 66 to 75 years, from 5.1% in DK-DHR to 65.9% in IPCI in the age group 76 to 85 years, and from 11.2% in DK-DHR to 73.0% in IPC in the age group ≥86 years.

The treatment patterns from the overall cohort with AD were generally similar to the pattern in each age group of each data source. The only exception in the first treatment after AD diagnosis was in the age groups 18–55 years and ≥86 years in NAJS, InGef RDB, and IQVIA DA Germany, in which antipsychotics were the most common as initial treatment. Treatment sequences were uncommon in the age group 18–55 years. In the other age groups, the most common treatment sequences were generally similar between the age groups and compared with the overall cohort.

The frequency of hospitalisations was similar between age groups within five years after diagnosis of AD across data sources. Outpatient visits within five years after AD diagnosis were generally less frequent in the higher age groups. The pattern of the frequency and timing of caregiver support across age groups varied between data sources.

The 5-year survival probability from AD diagnosis was lower in the older age groups. It ranged from 76.6% [95% CI: 72.8%–80.6%] in NAJS to 97.7% [95% CI: 93.4%–100.0%] in IPCI in the age group 18–55 years and from 13.1% [95% CI: 11.7%–14.6%] in NAJS to 52.3% [95% CI: 51.1%–53.5%] in InGef RDB in the age group ≥86 years. Similarly, the 5-year survival probability from the first treatment prescription for AD ranged from 74.0% [95% CI: 69.3%–79.1%] in DK-DHR to 90.8% [95% CI: 86.3%–95.7%] in InGef RDB in the age group 18–55 years (<5 events in IPCI and from 15.1% [95% CI: 12.7%–17.9%] in NAJS to 58.3% [95% CI: 55.9%–60.8%] in InGef RDB in the age group ≥86 years.

Key results among the subgroup with MCI prior to AD

The prevalence of acetylcholinesterase inhibitor prescription after AD diagnosis was higher among those with MCI prior to AD than among the overall cohort with AD, while the prevalence of memantine prescription was similar, and the prevalence of antipsychotic prescription was generally lower. The time from diagnosis until twenty-five percent of the individuals initiated acetylcholinesterase inhibitors was shorter among the subgroup with MCI prior to AD diagnosis than among the overall cohort, while the time from diagnosis until twenty-five percent of the individuals initiated antipsychotics was generally longer, and the pattern for memantine varied between data sources.

The proportion of individuals with incident AD who were not prescribed a pharmacological treatment for AD (i.e. acetylcholinesterase inhibitors, memantine, or antipsychotics) within five years of diagnosis was slightly smaller among the subgroup with AD than among the overall cohort. The prevalence of acetylcholinesterase inhibitor prescription as the first treatment after AD diagnosis was higher among the subgroup with MCI prior to AD diagnosis than among the overall cohort, while the prevalence of antipsychotic prescription as the first treatment was generally lower, and the pattern for memantine varied between data sources. The most common treatment sequences were generally similar between the subgroup with MCI and the overall cohort.

The frequency of hospitalisation within five years after diagnosis of AD was similar between individuals with MCI prior to AD diagnosis and the overall cohort, while the frequency of outpatient visits was slightly higher. The pattern of the frequency and timing of caregiver support among the subgroup with MCI prior to AD diagnosis versus the overall cohort varied between data sources.

The 5-year survival probability from diagnosis of AD onwards and from treatment initiation for AD onwards was higher among the subgroup with MCI prior to AD diagnosis than among the overall cohort. The 5-year survival probability from AD diagnosis among the subgroup with MCI prior to AD diagnosis was 49.1% [95% CI: 45.4%–53.1%] in NAJS, 49.7% [95% CI: 47.4%–52.1%] in DK-DHR, and 74.7% [95% CI: 72.6%–76.9%] in InGef RDB. The 5-year survival probability from the first treatment prescription for AD among individuals with MCI prior to AD diagnosis was 53.3% [95% CI: 48.8%–58.3%] in NAJS, 50.3% [95% CI: 47.9%–52.9%] in DK-DHR, and 81.0% [95% CI: 78.2%–83.8%] in InGef RDB.

10.2. Strengths and limitations of the research methods

One strength of this study is that data from five data sources was used in four European countries, resulting in a comprehensive overview of the treatment and outcomes post-diagnosis of AD. The longitudinal nature of the routinely collected healthcare data allowed for follow-up up to five years with broad population coverage. Another strength of this study is that sensitivity analyses were conducted to investigate the effect of allowing for longer permissible gaps between treatment episodes (to define a treatment era) on the results of the treatment sequencing analysis; the results were robust to longer permissible gaps (up to 60 days from 7 days in the main analysis).

One limitation of this study was that the subgroup of individuals with MCI prior to AD was relatively small: up to 14.2% (IQVIA DA Germany) of those with a first treatment initiation for AD after the diagnosis of AD and up to 8.2% (IQVIA DA Germany) in the population newly diagnosed with AD. This may limit the representativeness of the findings among those with MCI prior to AD. In addition to the missing data on the status of MCI, also biomarkers, the severity of dementia (e.g. by Minimal Mental State Examination), the frequency and type of disease monitoring, and the progression of AD could not be taken into account in this study.

A limitation arising from the routinely collected nature of the data was that not all data sources could participate in all objectives. Moreover, some data source-specific limitations were observed. Firstly, the proportion of individuals who were prescribed memantine was lower in IPCI than in the other data sources (up to five years after AD diagnosis: 1.1% versus more than 15% in the other data sources). Since IPCI is a primary care data source, it is possible that memantine is predominantly prescribed by specialists in geriatric medicine or neurology in the Netherlands, leading to underreporting of memantine prescription in this study. Similarly, IQVIA DA Germany is a primary care data source. This could explain the lower prevalence of prescriptions of acetylcholinesterase inhibitors, memantine, and antipsychotics compared to InGef RDB, which also contains data from Germany, but from both primary and secondary care. Secondly, the survival was higher in InGef RDB and IPCI than in NAJS and DK-DHR. In InGef RDB, survival was likely overestimated due to incomplete death records from the first three quarters of the year 2025, while in IPCI survival was likely overestimated due to the censored deaths of individuals who entered palliative care.

10.3. Interpretation

Descriptive data

Among individuals with incident AD and a first treatment prescription for AD included in this study the median age ranged from 77 years (IPCI) to 81 years (IQVIA DA Germany) and with the proportion of females ranged from 54.4% (InGef RDB) to 65.8% (NAJS). This aligns with results from previous studies, which reported an increase in the incidence of AD between the age of 60 and 80 years[15] and the odds ratio of 1.6 for AD among women versus men.[16]

During the year up to the first treatment prescription for AD, the most prescribed medications were antihypertensives (prevalence of prescription ranging from 21.5% in IQVIA DA Germany to 58.6% in DK-DHR) and lipid-lowering drugs (from 15.0% in IQVIA DA Germany to 42.3% in DK-DHR). The most common comorbidities were hypertension (prevalence ranging from 35.4% in IPCI to 86.1% in NAJS) and diabetes (from 15.9% in DK-DHR and IPCI to 30.9% in NAJS). This is similar to findings in a recent review, in which the reported prevalence of hypertension ranged from 30.2% to 73.9% and the prevalence of diabetes ranged from 6.0% to 24.3% in individuals with MCI due to AD or AD dementia.[17]

The prevalence of a diagnosis of MCI prior to the diagnosis of AD ranged from 5.6% (DK-DHR) to 14.2% (IQVIA DA Germany) among individuals with a first treatment prescription for AD. This is relatively low, which could be because individuals do not yet seek health care at the stage of MCI.

Prevalence, timing, and sequences of pharmacological treatments following AD diagnosis

More than half of individuals with incident AD were prescribed acetylcholinesterase inhibitors, memantine, or antipsychotics within the first year, except in IPCI, where only about 25% were. The prevalence of specific treatment prescriptions varied widely across data sources: from approximately 15% to 75% for acetylcholinesterase inhibitors, from under 1% to over 40% for memantine, and from approximately 14% to 45% for antipsychotics. Over five years, the prevalence of antipsychotic prescriptions increased by roughly 11%, while the prevalence of acetylcholinesterase inhibitors and memantine prescriptions rose more modestly (around 5%), with a larger increase for memantine in one data source.

The higher the prevalence of the prescription of a pharmacological treatment for AD in the data source, the shorter the time was between the diagnosis of AD and the treatment prescription. Twenty-five percent of the individuals initiated a pharmacological treatment on the day of diagnosis in NAJS and DK-DHR, within 37 days [95% CI: 36–38] in InGef RDB, within 15 days [95% CI: 12–20] in IQVIA DA Germany, and within 471 days [95% CI: 435–507] in IPCI. Seventy-five percent of the individuals initiated acetylcholinesterase inhibitors within approximately six months after AD diagnosis in DK-DHR, twenty-five percent of individuals initiated memantine on the day of diagnosis or the day after in NAJS, and half of the individuals initiated antipsychotics within approximately 3.5 years after AD diagnosis in NAJS and InGef RDB.

The percentage of individuals that remained untreated until the end of follow-up up to five years varied between data sources from 6.7% to 65.5%. Memantine was the most commonly prescribed first treatment after diagnosis of AD in NAJS (prescribed to 31.5%), while acetylcholinesterase inhibitors were the most common as the first treatment in DK-DHR (prescribed to 73.0%), and the prevalence of prescription of acetylcholinesterase inhibitors and antipsychotics as the first treatment after AD diagnosis was similar in IPCI (approximately 17%), IQVIA DA Germany (approximately 20%), and InGef RDB (approximately 30%).

Treatment sequences were relatively rare, with the prevalence of the most common sequence of prescriptions for two different treatments ranging from approximately 1.5% to 14.8% of the population with incident AD. Across most data sources, the most common sequences of prescriptions for three different treatments started with acetylcholinesterase inhibitors as the first treatment after AD diagnosis, followed by their combination with antipsychotics, and then continued with either acetylcholinesterase inhibitors or antipsychotics. In NAJS, treatment sequences instead started with prescription of memantine as the first treatment after diagnosis, followed by memantine combined with antipsychotics, and continued with either memantine or antipsychotics. In DK-DHR, treatment sequences started with prescription of acetylcholinesterase inhibitors as the first treatment after AD diagnosis, followed by acetylcholinesterase inhibitors combined with memantine, and continued with either acetylcholinesterase inhibitors or memantine.

The predominance of initial treatment with memantine (approved to treat moderate-to-severe Alzheimer's dementia) in NAJS versus the predominance of initial treatment with acetylcholinesterase inhibitors (approved to treat cognitive impairment in mild to moderate Alzheimer's dementia) in the other data sources could suggest a higher severity of AD at the time of diagnosis in NAJS compared to the other data sources. Moreover, the relatively common combination of acetylcholinesterase inhibitors with memantine following acetylcholinesterase inhibitor monotherapy in DK-DHR could reflect a response to an increase in the severity of AD, as the combination of memantine with donepezil (an acetylcholinesterase inhibitor) is recommended for moderate-to-severe AD.[3]

The large variability in treatment patterns between data sources aligns with the findings of a recent review[18] of real-world use of acetylcholinesterase inhibitors and memantine among individuals with MCI due to AD and mild AD dementia. It was suggested in this review that the variability between countries in the use of treatments for AD could be due to differences in reimbursement, access to treatments, and healthcare funding. Differences in the coverage of healthcare settings and the type of data may have introduced additional variability in the results between data sources in our study. In particular, the

prevalence of prescriptions of any of the three treatment classes was higher in NAJS, DK-DHR, and InGef RDB than in IQVIA DA Germany and IPCI. This could be because IQVIA DA Germany and IPCI are both primary care data sources, in which the first record of AD diagnosis might reflect an earlier or milder stage of AD, and specialist prescriptions may be missing compared to a data source with secondary care data (DK-DHR) or both primary and secondary care data (NAJS and InGef RDB). In the DARWIN EU study EUPAS1000000826, the estimated prevalence of AD between 2018 and 2023 was higher in DK-DHR, InGef RDB, and NAJS than in IQVIA DA Germany and IPCI. Taken together, the results of both studies suggest that not only the records of diagnosis of AD, but also the records of prescriptions for AD may be more complete in secondary care data sources than in primary care data sources.

Although it was not possible to take into account the severity of AD in our study, the observed treatment patterns were broadly similar to the treatment pattern described in the review.[18] The reported percentage of individuals using neither acetylcholinesterase inhibitors nor memantine ranged between 16% and 26% among individuals with mild AD dementia in Europe. The reported user prevalence in Europe of acetylcholinesterase inhibitors was 31% among individuals with MCI due to AD and up to 89% among individuals with mild AD dementia, while the user prevalence of memantine was 8% among individuals with MCI due to AD and ranging between 7% and 21% among individuals with mild dementia. The user prevalence of the combination of acetylcholinesterase inhibitors and memantine ranged between 0.4% and 8% among individuals with mild AD dementia. Moreover, the prevalence of antipsychotic prescriptions in our study aligns with the reported prevalence of psychosis of 30%–40% over the course of AD.[3]

Clinical and care-related events following AD diagnosis

The frequency of hospitalisations after diagnosis of AD was low in all data sources, with a median of up to two hospitalisations per individuals within five years after diagnosis. The median number of outpatient visits per individual approximately doubled in all data sources from one year after diagnosis of AD (varying from 5 to 30) to five years after (varying from 9 to 65). The frequency of caregiver support hardly increased between one and five years after the diagnosis of AD in all data sources, but the frequency and timing varied between data sources: five percent of the individuals received caregiver support within 44 days [95% CI: 31–57] after AD diagnosis in NAJS and within 860 days [95% CI: 789–915] in IQVIA DA Germany, while only 3.4% received caregiver support five years after the diagnosis of AD in DK-DHR.

Caregiver support is not routinely captured in DK-DHR, which may explain the lower prevalence. In contrast, the relatively high prevalence in NAJS may reflect a higher proportion of individuals with moderate to severe dementia at the time of AD diagnosis, as suggested by the observed prescription pattern. More generally, the variability in the frequency and timing of clinical and care-related events following AD diagnosis could be due to the different stages of the AD continuum at which different individuals may receive their first record of AD diagnosis in the different data sources. Another factor could be that information is not uniformly recorded across data sources and that coding practices vary across data sources. Previous studies of clinical and care-related events among individuals with AD were conducted on different populations (e.g. in another country, including prevalent AD, or with dementia not necessarily due to Alzheimer's disease) and with different outcomes (e.g. healthcare costs or nursing home admission) than in our study.[4,19,20]

Survival

The 5-year survival probability from diagnosis of AD was approximately 40% in NAJS and DK-DHR, versus 71.1% in InGef RDB and 64.7% in IPCI. However, the survival was likely overestimated in InGef RDB (due to incomplete death records from the first three quarters of the year 2025) and IPCI (due to censored deaths of individuals who entered palliative care).

In a recent review of time to death in people with dementia, the 5-year survival probability among individuals diagnosed with dementia (due to any cause) at 80 years was 32% among males and 59% among

females.[4] In our study, the age group 76–85 years comprised approximately half of the population with incident AD in NAJS and DK-DHR and the 5-year survival probability was approximately 35% among males and approximately 40% among females. Although the survival estimates for males were similar between our study and the review, the difference for females could be due the different study population in the review, as it included results from populations with different types of dementia. In our study, the 5-year survival probability after diagnosis of AD was approximately 71% in the age group 56–65 years and below 20% in the age group ≥86 years in NAJS and DK-DHR. Similarly, the 5-year survival probability after diagnosis of dementia (due to any cause) in the review was 59% among males and 86% among females who were diagnosed at age 60 years and 18% among males and 45% among females who were diagnosed at age 90 years.

The survival probability five years after the first treatment prescription for AD ranged from 40.4% [95% CI: 39.2%–41.6%] in NAJS to 75.7% [95% CI: 75.0%–76.5%] in InGef RDB. The slightly higher survival probability after the first treatment prescription for AD than after diagnosis of AD was likely due to the lower of age of the study population with a prescription. The effect of different initial treatments for AD on overall survival could be studied in future research, in which additionally the age at death could be compared between individuals with versus without AD.

10.4. Generalisability

Due to feasibility and timelines, only five primary care/secondary care data sources from Croatia, Denmark, Germany, and the Netherlands could be included, which operate under blanket IRB approval or can obtain approval within a month. The heterogeneity of the results suggests that treatment and post-diagnosis outcomes of AD may be highly country-specific, possibly due to differences in healthcare settings and healthcare systems between countries. Follow-up studies may include additional data sources to provide insights into patterns of treatment and post-diagnosis outcomes of AD in different countries. Moreover, inclusion of data sources with more detailed information on demographic characteristics, diagnostic procedures, and the clinical profile of individuals with newly diagnosed AD could enhance the generalisability of the findings to individuals across the continuum from prodromal to severe AD.

11. CONCLUSION

In this study we described pharmacological treatment patterns, clinical and care-related events, and survival of individuals with incident AD in the five years after diagnosis using data from four European countries. In most of the data sources, the most commonly prescribed treatments for AD were acetylcholinesterase inhibitors and antipsychotics, while memantine was less commonly prescribed. Combination therapy was generally uncommon. Hospitalisations up to five years after diagnosis of AD were uncommon, but the number of outpatient visits approximately doubled from one year after diagnosis of AD to five years after. The prevalence of caregiver support and timing from diagnosis of AD until caregiver support varied between countries, which may have been affected by data constraints such as incomplete recording. The 5-year survival probability ranged from approximately 40% to approximately 70% both from diagnosis of AD onwards and from the first treatment prescription for AD onwards. For a deeper understanding of the natural history of AD, a more complete recording in routinely collected healthcare data of the stages of the AD continuum, including MCI and diagnostic criteria, could enhance treatment characterisation and description of outcomes post-diagnosis of AD in the future. Finally, the results of this study can inform the assessment of fit for purpose of the included data sources in future research requiring information on caregiver support, MCI, hospitalisations, and survival outcomes. The variability in data availability and quality across data sources should be carefully considered in the design of future studies.

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13. ANNEXES

ANNEX I. Description of data sources

Croatia, National Public Health Information System (NAJS)

#	Section	Description
1	Database Identification and country	NAJS (Croatian National Public Health Information System) Croatia
2	Data partner information section	Croatian Institute of Public Health Department of Data Science and Analytics
3	Coverage and timespan	Data collection since: 1998 Extent: Nation-wide. Geographic coverage covers whole Croatia, with various levels of resolution for different registries. Current estimates for the population in Croatia will be available at: https://podaci.dzs.hr/hr/podaci/stanovnistvo/procjena-stanovnistva/ for each year.
4	Healthcare setting / type of data	Primary care – GPs, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. For both inpatient and outpatient setting diagnoses, medication, procedures, and measurements are captured. Since 2025, family relationships from the birth registry, histopathological data from the cancer registry, and vital signs from health risk assessment have also been added. The year of availability of information depends on the setting: • 2014 for lab tests • 2015 for general practitioners • 2016 for secondary conciliatory care • 2017 for hospital records • 2020 for vaccination records
5	Data collection process	Inpatient hospital billing systems, and Other. Data is entered by clinicians at healthcare contact, then combined by CIPH into the NAJS database.
6	General representativeness	The data is collected from public health records, as the majority of health care in Croatia is public. Personal details are collected to a better extent for insured individuals compared to uninsured patients.
7	Data content /source coding	Medication prescriptions are recorded with ATC codes, and diagnoses with ICD10 codes.
8	Data Harmonization	Complete Records from 2017 include insured patients with reliable IDs. Uninsured patients do not have reliable IDs. For example, if a patient changed her status from insured to uninsured, or vice versa, she could be counted several times, as could tracking records from before 2017 and after. By using the unique personal identifier for Croatian citizens, it can be checked and verified.
9	Quality control (database specific)	There is a network of registry personnel (leaders, administrators, coders, sources) working on data coverage and other quality dimensions. An analytical team routinely checks for erroneous entries in hospital records, removing double entries, false dates, and overlapping stays. Entries without enough data or with obviously erroneous dates from primary care analysis are being excluded.
10	Linkage	The national death registry is updated monthly and primary care is updated weekly. Specific registries are included in NAJS (e.g. diabetes registry), where inclusion criteria vary across these registries.
11	Vital status	NAJS is linked to the national death registry.

#	Section	Description
12	Limitations	Hospital data is available from 2017 onwards. This is often used as start of data collection, while laboratory and GP data is captured before that (since 2014 and 2015 respectively). The total and active person count in the NAJS data is larger than the current population of Croatia. This explained by a) the person table included deceased and all previously insured people and b) there is no information about insurance ending. It is known that a lot of people migrated (300k-400k) and weren't included in the last population census but still are in the NAJS database. In-hospital administrations are managed via paper drug charts and hospital discharge summaries are currently not captured into NAJS.
13	Main references	No main reference provided
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111155 Website: https://www.hzjz.hr/nacionalni-javnozdravstveni-informacijski-sustav-najs/

Denmark, Danish Data Health Registries (DK-DHR)

#	Section	Description
1	Database Identification and country	DK-DHR (Danish Data Health Registries) Denmark
2	Data partner information section	Danish Medicines Agency (DKMA) Data Analytics Centre (DAC)
3	Coverage and timespan	Data collection since: 1995 Extent: Nation-wide. The data is representative of the entire Danish population.
4	Healthcare setting / type of data	Community pharmacists, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. The following data elements are collected: diagnosis (including rare diseases and pregnancy data), hospital admissions, discharge and ICU data, Cause of death, Drug prescriptions, dispensing, vaccination and contraception, Procedures, Devices, and Sociodemographic information.
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries, and Other. All causes of deaths, all retrieved drug prescriptions, all records of vaccinations, all hospital inpatient and outpatients contacts including disease diagnoses and hospital surgical and non-surgical procedures, cancers, laboratory test results for the entire Danish population from 1/1/1995 onwards.
6	General representativeness	The data is representative of the entire Danish population. Healthcare is free in Denmark, so we do not expect any bias in data collection based on socio-economic status.
7	Data content /source coding	Diagnoses and causes of death are collected using the ICD-10 vocabulary. ATC and RxNorm are used for Drugs. SNOMED codes are used for Procedures.
8	Data Harmonization	Complete No.
9	Quality control (database specific)	The data we have received relating to nationwide Danish Health Data registries offer an opportunity for large-scale, population-based studies with several advantages 1) Their large size improves the precision of estimates and enables the study of rare exposures and outcomes with long-term latency, 2) Inclusion of nearly all individuals in the target population ensures that the data reflect routine clinical care and all clinical segments of the source population, 3) Data are collected independently of each research study, thus minimising certain types of bias, e.g. non-response, and the influence from attention to the research question on the diagnostic process. Before the source data is sent to us, the Danish Health Data Authority does running and comprehensive checks of the registry table data validity of the variables, breaks in data, changes in variable coding, missingness, etc. We perform checks of missingness/completeness in relation to requested variables. In essence, we are receiving a dump of a mirror of the data that is controlled

#	Section	Description
		by the SDS. The documentation performed by SDS is available online, in Danish primarily https://www.esundhed.dk/Dokumentation (all variables), but also in English https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/national_health_registers
10	Linkage	There is no linkage in this data source.
11	Vital status	The Cause of Death registry (DAR) is used, the cause of death is collected using ICD-10 codes.
12	Limitations	There are no clinical measurements in the data.
13	Main references	Schmidt M, Schmidt SAJ,Adelborg K,Sundbøll J,Laugesen K,Ehrenstein V,Sørensen HT "The Danish health care system and epidemiological research: from health care contacts to database records." Clinical epidemiology (2019): 31372058
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111217 Website: https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/healthdatadenmark

Germany, InGef Research Database (InGef RDB)

#	Section	Description
1	Database Identification and country	InGef Research Database (InGef RDB) Germany (DE)
2	Data partner information section	InGef – Institute for Applied Health Research Berlin GmbH InGef is a research service provider within the German statutory health insurance system.
3	Coverage and timespan	The Research Database contains approximately 10.5 million insured persons from 50 of the 94 statutory health insurances in Germany (as of Oct 2025). All individuals in the research database are included in the OMOP CDM. Due to data protection laws for personal data in Germany, only the last 10 years of data are available in the RDB and thus in the OMOP CDM.
4	Healthcare setting / type of data	In general, the data in the RDB reflects most of the health services paid for by statutory health insurances. In the OMOP CDM, the health services are reduced to primary and secondary care. This means that treatments by GPs and specialists (e.g. paediatricians), prescription medicines dispensed by pharmacies, hospital inpatient and outpatient care, as well as information about all insured individuals are included. The following data elements are presented in the OMOP CDM: demographic information, diagnoses, procedures, dispensing drugs and advanced therapy medicinal products, vaccinations, pregnancy data (via diagnoses and procedures) and contraception.
5	Data collection process	In Germany, data exchange between medical service providers and statutory health insurances is organized via central data collection centers. In addition to receiving and forwarding data, these centers also store data and provide access to third parties under strict regulations in data warehouses. The RDB contains selected, condensed and anonymized information from one of these data warehouses. Data sovereignty remains with the individual health insurance companies.
6	General representativeness	The RDB covers about 11% of the German population and is comparable to the German population in terms of the distribution of age and sex. Most health insurances that contribute to the RDB have nationwide coverage, meaning that the database covers all regions of Germany. Since almost all services covered by statutory health insurances are specified in national legislation, healthcare provision all over Germany is well represented in the RDB. Additionally, in Germany it is very common to stay with the same health insurance throughout life, which results in a good longitudinal coverage over the entire period of 10 years.

#	Section	Description
7	Data content /source coding	The coding in the research database complies with national classification and coding rules in Germany. Diagnoses are coded according to ICD-10-GM. Inpatient and outpatient surgeries or procedures are recorded as OPS codes (German classification of Operations and Procedures). The dispensing of drugs in pharmacies is recorded using the PZN (pharmaceutical registration number). For drugs that miss a PZN-to-RxNorm mapping, the ATC code is used instead. In some cases, dispensed drugs can be coded using OPS codes (e.g. in hospitals) or EBM codes (fee schedule for outpatient treatments).
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network.
9	Quality control (database specific)	The data transmitted by healthcare providers complies with the standardized requirements and formats of the Association of Statutory Health Insurances (GKV-SV). Before being imported into the research database, the data elements are checked for data format, completeness and plausibility. After each update of the research database, various counts are compared with the previous update to verify completeness. Due to the anonymity of the database, direct validation of the data (e.g. using medical records as the gold standard) is not possible.
10	Linkage	Due to the anonymization of the source data, linkage is not possible.
11	Vital status	The date of death is recorded as the last day of the quarter in which the death occurred (i.e. 30/31st of Mar/Jun/Sept/Dec) as reported to the health insurance (no linkage to death registry). The cause of death is not available.
12	Limitations	Ambulatory diagnoses and procedures are summarised in the source on a quarterly basis. Both are mapped to the observation table with the date set to the last day of the respective quarter (i.e. 30/31st of Mar/Jun/Sept/Dec) and the concept “History of event within 3 months” (observation_concept_id 1340222), with the actual diagnosis or procedure concept_id recorded in the field “value_as_concept_id”. There is no vocabulary for the German pharmaceutical product codes (PZN). A direct source-to-standard-mapping has been done manually by InGef but is incomplete. The drug exposure duration is unknown. Following OMOP conventions, the end date is always set to dispensing date + 29. Outpatient and inpatient procedures are recorded as OPS codes (German Procedure Classification), for which the vocabulary is incomplete.
13	Main references	Andersohn F, Walker J "Characteristics and external validity of the German Health Risk Institute (HRI) Database." Pharmacoepidemiology and drug safety (2016): PMID 26530279 | doi: 10.1002/pds.3895 Ludwig M, Enders D, Basedow F, Walker J, Jacob J: Sampling strategy, characteristics and representativeness of the InGef research database. Public Health 2022. doi: 10.1016/j.puhe.2022.02.013
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111207 Website: https://www.ingef.de/en/

Germany, IQVIA Disease Analyser (IQVIA DA Germany)

#	Section	Description
1	Database Identification and country	IQVIA DA Germany (IQVIA Disease Analyzer Germany) Germany
2	Data partner information section	IQVIA
3	Coverage and timespan	Data collection since: 1989 Extent: Nation-wide. GP and specialists in Germany using specific patient management software.
4	Healthcare setting / type of data	Primary care – gps, and primary care specialists (e.g. paediatricians). Diagnoses, medication, and procedures from an ambulatory setting. Medications are recorded as prescriptions of marketed products.
5	Data collection process	Outpatient electronic health records. By clinicians at healthcare contact.
6	General representativeness	No specific details on general representativeness given.
7	Data content /source coding	Prescription is on product code level (German PZN), ICD10, NFC, Local lab coding.
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. There can be patients registered under different ID numbers, because there is no linkage between different GPs.
9	Quality control (database specific)	Data is quality checked on plausibility.
10	Linkage	No.
11	Vital status	Death information is derived from medical events.
12	Limitations	No database-specific limitations documented. General limitations of data type applicable.
13	Main references	No main reference provided.
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/104282 Website: https://www.iqvia.com/

The Netherlands, The Integrated Primary Care Information (IPCI)

#	Section	Description
1	Database Identification and country	IPCI (Integrated Primary Care Information) The Netherlands
2	Data partner information section	Erasmus University Medical Center Department of Medical Informatics
3	Coverage and timespan	Data collection since: 2006 Extent: Nation-wide. IPCI is a Dutch database that contains patient records from 2006 onwards.

#	Section	Description
		However, it mainly covers the central part of the country, including the most densely populated area (the 'Randstad') and non-urban areas. IPCI contains information on all patients registered with GPs responsible for non-emergency care and referrals. A patient is registered at birth or at first encounter with the GP.
4	Healthcare setting / type of data	Primary care – gps. Data is collected from primary care EHR. This includes demographic information, complaints and symptoms, diagnoses, laboratory test results, lifestyle factors (in limited amount), and correspondence with secondary care, such as referral and discharge letters.
5	Data collection process	Outpatient electronic health records. Data is entered into the EHR system by the GPs, during or after the visit. Data is aggregated by Erasmus MC data managers and combined in one harmonized database. Several checks are done on this database to ensure correct data processing. Persons are mostly uniquely identified, with the exception of when persons change GP practice (when the same individual can receive several different identifiers).
6	General representativeness	More than 99% of the Dutch population has health insurance, and almost all citizens are registered with a general practitioner. Over 12 months, around 78% of the population has at least one contact with their GP. IPCI included around 350 GP practices out of around 5000 in the country (~ 7%). The demographic composition of the IPCI population mirrors that of the general Dutch population in terms of age and sex.
7	Data content /source coding	Dutch GPs use mainly Dutch standard codes, like ICPC-1 and Diagnostische Bepalingen maintained by NHG. And for therapy the G-Standard is used, maintained by ZIndex.
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Patients can be registered under different IDs. However, in the Netherlands, patients typically have one GP and changing practice is uncommon.
9	Quality control (database specific)	Prior to each data release, extensive quality control steps are performed, e.g. comparison of patient characteristics between practices, and checks to identify abnormal temporal data patterns in practices. For each practice, around 200 quality indicators are obtained. Of these indicators, a quarter refer to population characteristics, e.g. number of birth and mortalities relative to practice size, temporal consistency. The other indicators are based on medical data, e.g. distribution of measurement values, frequencies of diagnoses and procedures relative to age, completeness of data. The indicators are combined in a couple of quality scores for each practice. For these scores, cut-off values for acceptable quality have been defined. Practices with a score below a cut-off are excluded for research. This approach has shown to be very important, for example to check if data from practices that just joined the database are at an acceptable level of quality. The details of the approach, like the cut-off values for acceptance, are based on years of experience. In addition, trends are compared with the previous database release. Extensive quality control steps are performed before each data release. These include comparing patient characteristics between practices and checks to identify abnormal temporal data patterns in practices. Additional checks include over 200 indicators related to population characteristics (e.g. reliability of birth and mortality rates) and medical data (e.g. availability of durations of prescriptions and completeness of laboratory results). Records of low quality are excluded from the database.
10	Linkage	Linkage requires additional approval steps and needs to be assessed on a case-by-case basis. IPCI is not routinely linked with other databases.
11	Vital status	Vital status (death date and cause) is collected based on GP records.
12	Limitations	The main limitation comes with the fact that IPCI is limited to GP records, and although it contains information on referrals and discharge letters, it may not fully capture specific hospital

#	Section	Description
		information. IPCI does not include coded/detailed data about medications/procedures/test results from the hospital or other care-providers.
13	Main references	de Ridder MAJ, de Wilde M,de Ben C,Leyba AR,Mosseveld BMT,Verhamme KMC,van der Lei J,Rijnbeek PR "Data Resource Profile: The Integrated Primary Care Information (IPCI) database, The Netherlands." International journal of epidemiology (2022): 35182143
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/42618 Website: http://www.ipci.nl

ANNEX II. Fitness for use assessment

Croatia, National Public Health Information System (NAJS)

NAJS included primary care, outpatient specialist care, and inpatient care registries providing information on AD occurrence, caregiver support, medications, and relevant comorbidities in the general adult population (≥18 years). The CDM population comprised all publicly insured persons residing in Croatia starting in 2017. The inclusion of NAJS enhanced the geographical diversity of data sources, with adequate data coverage over the study period. A preliminary feasibility assessment estimated approximately 28,900 individuals with AD in NAJS.

Data availability and follow-up were sufficient, with records available from 01/01/1995 and the most recent data extraction on 02/08/2025, fully aligned with the study period. No study-specific limitations were identified for this data source. Furthermore, IRB approval for NAJS was obtained within approximately one month, supporting the feasibility of study execution within the study timelines.

Denmark, Danish Data Health Registries (DK-DHR)

DK-DHR included nationwide registry data, comprising inpatient, outpatient, and emergency care data from hospitals, providing information on AD occurrence, medications, and relevant comorbidities in the general adult population (≥18 years). However, caregiver support was not available. The inclusion of DK-DHR enhanced the geographical diversity of data sources, with adequate data coverage over the study period. A preliminary feasibility assessment estimated approximately 107,900 individuals with AD in DK-DHR. The absence of primary care data meant that chronic comorbidities were not detected during this study if they were treated only in primary care.

Data availability and follow-up were sufficient, with records available from 01/01/1995 and the most recent data extraction on 10/04/2025, fully aligned with the study period. No study-specific limitations were identified for this data source. Furthermore, DK-DHR operated under blanket IRB approval, ensuring feasibility of study execution within the study timelines.

Germany, InGef Research Database (InGef RDB)

InGef RDB included primary care, hospital inpatient care, and secondary outpatient care claims data, providing information on AD occurrence, medications, and relevant comorbidities in the general adult population (≥18 years). However, caregiver support and review of mild cognitive impairment were not available. The CDM population comprised individuals from all regions in Germany who were covered by one of the approximately 50 contributing statutory health insurance companies, ~15% of the German population starting in 2015. The inclusion of InGef RDB enhanced the geographical diversity of data sources, with adequate data coverage over the study period. A preliminary feasibility assessment estimated approximately 27,500 individuals with AD in InGef RDB.

Data availability and follow-up were sufficient, with records available from 01/01/2015 and the most recent data extraction on 18/04/2025, fully aligned with the study period. No study-specific limitations were identified for this data source. Furthermore, InGef RDB operated under blanket IRB approval, ensuring feasibility of study execution within the study timelines.

Germany, IQVIA Disease Analyser (DA)

IQVIA DA Germany included primary and outpatient secondary care electronic health record data, providing information on AD occurrence, caregiver support, medications, and relevant comorbidities in the general adult population (≥18 years). The inclusion of IQVIA DA Germany enhanced the geographical diversity of data sources, with adequate data coverage over the study period. A preliminary feasibility assessment estimated approximately 79,300 individuals with AD in IQVIA DA Germany.

Data availability and follow-up were sufficient, with records available from 01/01/1992 and the most recent data extraction on 10/04/2025, fully aligned with the study period. No study-specific limitations were identified for this data source. Furthermore, IQVIA DA Germany operated under blanket IRB approval, ensuring feasibility of study execution within the study timelines.

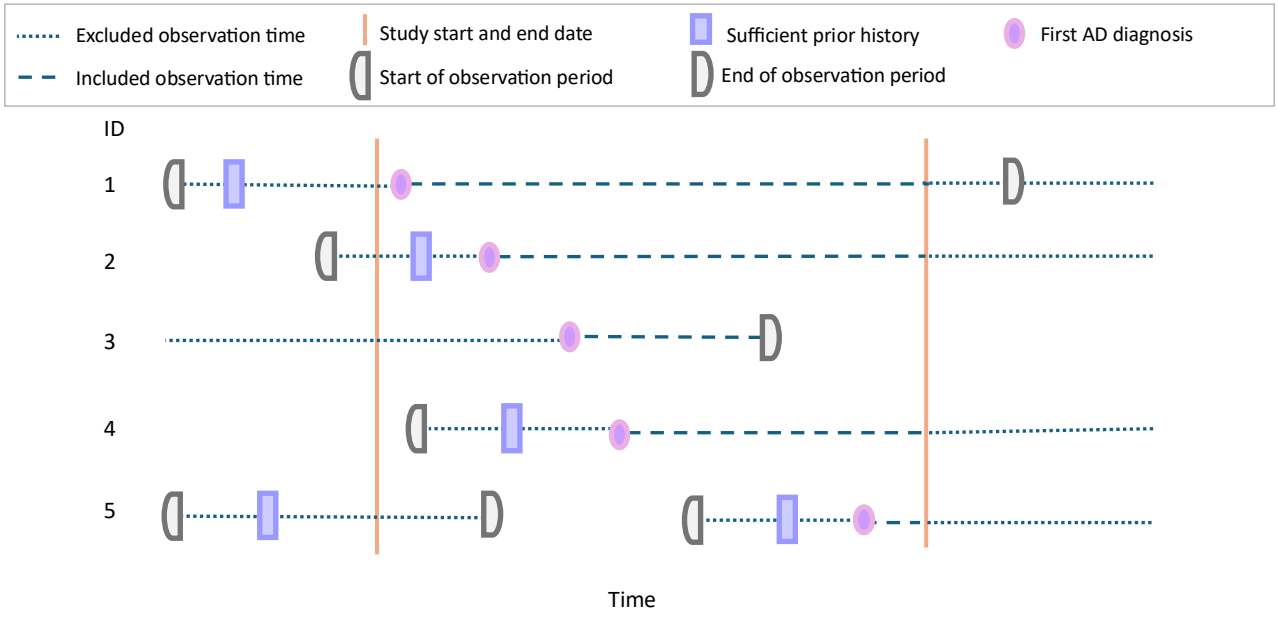
The Netherlands, The Integrated Primary Care Information (IPCI)

IPCI included primary care electronic health records data, providing information on AD occurrence, caregiver support, medications, and relevant comorbidities in the general adult population (≥18 years). The inclusion of IPCI enhanced the geographical diversity of data sources, with adequate data coverage over the study period. A preliminary feasibility assessment estimated approximately 13,400 individuals with AD in IPCI.

Data availability and follow-up were sufficient, with records available from 01/01/2006 and the most recent data extraction on 16/04/2025, fully aligned with the study period. No study-specific limitations were identified for this data source. Furthermore, IRB approval for IPCI was obtained within approximately one month, supporting the feasibility of study execution within the study timelines.

ANNEX III. Included observation time for the denominator population

In this example, person IDs represent individuals with no record of AD diagnosis before (1) they have fulfilled the prior history requirement and (2) the study period start date. Person ID 1 already has sufficient prior history before the study period start date, and the observation period ends after the study period end date, so this person will contribute starting from their first AD diagnosis until the end of the study period. Person IDs 2 and 4 enter the study only when they have sufficient prior history and subsequently their first AD diagnosis. Person ID 3 leaves when exiting the data source (the end of the observation period). Lastly, person ID 5 has two observation periods in the data source. The first period contains no AD diagnosis and thus does not contribute time. The second starts contributing time only when sufficient prior history is reached and the first AD diagnosis is recorded.



AD=Alzheimer's disease

ANNEX IV. Operational and reporting considerations

DATA MANAGEMENT

Data management

All data sources have previously mapped their data to the OMOP common data model. This enabled the use of standardised analytics and using DARWIN EU® tools across the network since the structure of the data and the terminology system was harmonised. The OMOP CDM was 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 and used standardized analytics wherever possible. Each data partner executed the study code against their data source containing individual data and then returned the results (csv files) which only contained aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

Data storage and protection

For this study, personal data from individuals in various EU member states were processed, using information collected from national/regional electronic health record data sources. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All data sources used in this study 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 were run, which generate non-identifiable aggregate summary results.

The output files are stored in the DARWIN EU® Digital Research Environment (DRE). These output files do not contain any data that allow identification of subjects included in the study. The DRE implements further security measures to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

QUALITY CONTROL

Data source quality control

When defining drug cohorts, non-systemic products will be excluded from the list of included codes summarised on the ingredient level.

When defining cohorts for indications, a systematic search of possible codes for inclusion will be identified using the *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This package allows the user to define a search strategy and will use this to query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the *CohortDiagnostics* (https://github.com/OHDSI/CohortDiagnostics) and *DrugExposureDiagnostics* (https://cran.r-project.org/web/packages/DrugExposureDiagnostics/index.html) R packages will be run, if needed, to assess the use of different codes across the data sources contributing to the study and identify any codes potentially omitted in error. The *DrugExposureDiagnostics* package evaluates ingredient-specific attributes and patterns in drug exposure records.

The study code will be based on DARWIN EU® R packages: *DrugUtilisation* to characterise the drug use, and *CohortCharacteristics* to characterise the cohort by indication. These packages will include numerous

automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

ANNEX V. List of stand-alone documents

Table S1. List of conditions definitions.

Phenotype	Concept name	Concept ID (including descendants)	Exclude concept ID	Vocabulary
Alzheimer's disease	Alzheimer's disease	378419	-	SNOMED
	Descendant concepts of Alzheimer's disease: Altered behaviour in Alzheimer's disease, Alzheimer disease with psychosis, Alzheimer's disease co-occurrent with delirium, Alzheimers continuum, Autosomal dominant Alzheimer disease due to mutation of amyloid precursor protein, Autosomal dominant Alzheimer disease due to mutation of presenilin 1, Autosomal dominant Alzheimer disease due to mutation of presenilin 2, Behavioural disturbance co-occurrent and due to late onset Alzheimer dementia, Delusions in Alzheimer's disease, Dementia of the Alzheimer type with behavioural disturbance, Depressed mood in Alzheimer's disease, Early Alzheimers disease, Early onset Alzheimer's disease with behavioural disturbance, Familial Alzheimer's disease of early onset, Familial Alzheimer's disease of late onset, Focal Alzheimer's disease, Frontal variant non-amnestic Alzheimer disease, High level Alzheimers neuropathology changes, Intermediate level Alzheimers neuropathology changes, Logopenic non-amnestic Alzheimer disease, Low level Alzheimers neuropathology changes, Mixed dementia, Non-amnestic Alzheimer disease, Non-familial Alzheimer's disease of early onset, Non-familial Alzheimer's disease of late onset, Primary degenerative dementia of the Alzheimer type, presenile onset, Primary degenerative dementia of the Alzheimer type, presenile onset in remission, Primary degenerative dementia of the Alzheimer type, presenile onset, uncomplicated, Primary degenerative dementia of the Alzheimer type, presenile onset, with delirium, Primary degenerative dementia of the Alzheimer type, presenile onset, with delusions, Primary degenerative dementia of the Alzheimer type, presenile onset, with depression, Primary degenerative dementia of the Alzheimer type, senile onset, Primary degenerative dementia of the Alzheimer type, senile onset in remission, Primary degenerative dementia of the Alzheimer type, senile	Descendant concept IDs: 44784643, 37166126, 37395572, 3170377, 608051, 603149, 608060, 37117145, 44782726, 43530664, 44782727, 3179057, 44782432, 4043241, 4043243, 4043377, 37167060, 3184947, 3176418, 37167043, 3177168, 43021816, 36716558, 4043242, 4043244, 4218017, 44782941, 4277444, 4277746, 4182539, 4019705, 4220313, 44782940, 4278830, 762578, 4167839, 4204688, 4097384, 1340510, 4043379.	-	SNOMED

Phenotype	Concept name	Concept ID (including descendants)	Exclude concept ID	Vocabulary
	onset, uncomplicated, Primary degenerative dementia of the Alzheimer type, senile onset, with behavioural disturbance, Primary degenerative dementia of the Alzheimer type, senile onset, with delirium, Primary degenerative dementia of the Alzheimer type, senile onset, with delusions, Primary degenerative dementia of the Alzheimer type, senile onset, with depression, Progression of Alzheimer's disease, Progressive aphasia in Alzheimer's disease.			
Hospitalisation	Admission by health worker, Admission for care, Admission to department, Admission to high secure unit, Admission to hospice, Admission to inpatient rehabilitation facility, Admission to medium secure unit, Admission to regional secure unit, Admission under the Mental Health Act, Emergency Room and Inpatient Visit, Hospital admission, Inpatient Visit, Involuntary admission, Listed for admission to hospital, Referral to physician, Voluntary admission, Care of intensive care unit patient, Intensive care monitoring	4137737, 4085709, 4137915, 44787815, 4123927, 763992, 44812023, 44811987, 44790848, 262, 8715, 9201, 4046990, 4084992, 4084682, 4047815, 4046295, 4057410	4224134, 38004515, 2110331, 2110332, 2110333, 2110334, 2110335, 2110336, 38004290, 38004288, 38004291	SNOMED
Outpatient visit	First outpatient appointment date, Follow-up in outpatient clinic, Hospital based outpatient care, Outpatient Visit, Outpatient procedure, Seen in hospital outpatient department, Specialist palliative care treatment – outpatient, Consultation, Seen in diabetic nurse consultant clinic	4188014, 4084839, 44792364, 9202, 4155973, 4083412, 4193678, 4014829, 4217373		SNOMED
Atrial fibrillation	Atrial fibrillation	313217		SNOMED
Caregiver support	Caregiver support, Maximum level of support, Minimum level of support, Need for personal care assistance, Patient dependence on care provider, Problem related to life management difficulty, Support	4303295, 44791822, 44791823, 42535090, 4022076, 43020485, 4055254	4254219, 36685469, 35609662, 37170021, 37163172, 37311826, 45769206, 37170022, 37164347, 46273902, 36715096, 37164586, 46272455, 607715, 44792004, 44790457	SNOMED
Diabetes	Complication due to diabetes mellitus, Diabetes mellitus	442793, 201820		SNOMED
Down’s syndrome	Complete trisomy 21 syndrome, Partial trisomy 21 in Down's syndrome	439125, 4110269		SNOMED
Heart failure	Heart failure	316139		SNOMED

Phenotype	Concept name	Concept ID (including descendants)	Exclude concept ID	Vocabulary
Hypercholesterolemia	Hypercholesterolemia, Pure hypercholesterolemia	4029305, 437827		SNOMED
Hypertension	Hypertension secondary to endocrine disorder, Hypertension secondary to kidney transplant, Hypertensive complication, Hypertensive disorder, Hypertensive heart AND renal disease, Hypertensive heart failure, Hypertensive renal disease, Rebound hypertension, Secondary diastolic hypertension, Secondary hypertension, Transient hypertension, Transient hypertension of pregnancy, Transient hypertension of pregnancy - not delivered	4110948, 4178312, 42709887, 316866, 195556, 444101, 201313, 4221991, 4253928, 319826, 4199306, 441922, 136760	42599748, 4071202, 762994, 43021830, 137940, 141639, 4062906	SNOMED
Hypertriglyceridemia	Hypertriglyceridemia	4120314		SNOMED
Mild cognitive impairment	Mild cognitive impairment review, Mild neurocognitive disorder, Minimal cognitive impairment	37398899, 4297400, 439795		SNOMED
Myocardial infarction	Myocardial infarction	4329847		SNOMED
Stroke	Alteration of sensation as late effect of stroke, Autosomal recessive leukoencephalopathy, ischemic stroke, retinitis pigmentosa syndrome, Brainstem stroke syndrome, Cerebellar stroke, Cerebral ischemic stroke due to dissection of artery, Cerebral ischemic stroke due to global hypoperfusion with watershed infarct, Cerebral ischemic stroke due to hypercoagulable state, Cerebral ischemic stroke due to subarachnoid haemorrhage, Chronic central post-stroke pain, Completed stroke, Decreased cardiac stroke volume, Decreased cardiac stroke volume index, Embolic stroke, Haemorrhagic stroke, Heat stroke, Hemiplegia and/or hemiparesis following stroke, Increased cardiac stroke volume, Ischemic stroke, Juvenile myopathy, encephalopathy, lactic acidosis, stroke, Late effects of cerebral ischemic stroke, Neonatal stroke, Nonparalytic stroke, Nonpyogenic cerebral venous thrombosis with stroke, Normal cardiac stroke volume, Occlusion of cerebral artery with stroke, Paralytic stroke, Paralytic syndrome as late effect of stroke, Rapid upstroke pulse, Seizure disorder as sequela of stroke, Sequela of cardioembolic stroke, Sequela of lacunar stroke, Sequela of thrombotic stroke, Spasticity as sequela of stroke, Spinal cord stroke, Stroke co-occurrent with migraine, Stroke in the puerperium, Stroke of uncertain pathology, Stroke test finding, Thrombotic stroke,	43531617, 36675148, 4111710, 36716999, 37312017, 37312015, 37312014, 37312013, 4079008, 4099974, 4243337, 37118679, 4153352, 35609033, 4181404, 44782781, 4338810, 4310996, 4219010, 36716860, 4159152, 4006295, 761790, 4236498, 43531605, 4023571, 372654, 4088120, 43530665, 43530736, 43530732, 43531592, 43531610, 4045755, 37110241, 4168056,	36684840, 3663227, 37110521	SNOMED

Phenotype	Concept name	Concept ID (including descendants)	Exclude concept ID	Vocabulary
	Vertigo as late effect of stroke, Weakness as a late effect of stroke, Weakness of extremities as sequela of stroke, Weakness of face muscles as sequela of stroke	4046363, 4280420, 4159140, 440426, 44782753, 43531595, 43530744		

Table S2. List of medicines definitions.

Substance Name	Concept name	Ingredient Concept ID	Include descendants	Exclude concept ID with all descendants
Memantine	Memantine	701322	Yes	
Acetylcholinesterase inhibitors	Donepezil, rivastigmine, galantamine	715997, 733523, 757627	Yes*	
Antipsychotics	Acepromazine, acetophenazine, amisulpride, aripiprazole, asenapine, benperidol, brexpiprazole, bromperidol, butaperazine, cariprazine, chlorproethazine, chlorpromazine, chlorprothixene, clopenthixol, clothiapine, clozapine, cyamemazine, dixyrazine, droperidol, fluanisone, flupenthixol, fluphenazine, fluspirilene, haloperidol, iloperidone, levosulpiride, lithium, loxapine, lumateperone, lurasidone, mesoridazine, methotrimeprazine, metylperon, molindone, moperone, mosapramine, mosapramine hydrochloride, olanzapine, oxypertine, paliperidone, penfluridol, perazine, periciazine, perphenazine, pimavanserin, pimozide, pipamperone, pipothiazine, prochlorperazine, promazine, prothipendyl, quetiapine, remoxipride, risperidone, sertindole, sulpiride, sultopride, thiopropazate, thioproperazine, thioridazine, thiothixene, tiapride, trifluoperazine, trifluperidol, triflupromazine, veralipride, ziprasidone, zotepine, zuclopenthixol, melperone hydrochloride, lithium carbonate, lithium citrate	19018226, 19029555, 19057607, 757688, 40164052, 19016440, 46275300, 19039227, 40798666, 35603277, 19122262, 794852, 19095002, 36848877, 19100363, 800878, 19051234, 40798772, 739323, 40798823, 19055982, 756018, 19056465, 766529, 19017241, 43009023, 19124477, 792263, 37498659, 40230761, 703083, 19005147, 19072088, 709699, 40798964, 36848724, 35198101, 785788, 19025922, 703244, 19028044, 19131663, 19053565, 733008, 42628962, 745790, 19093225, 19133992, 752061, 19052903, 19115044, 766814, 19035226, 735979, 19050633, 19136626, 19100431, 19041817, 19000305, 700299, 700465, 19008012, 704984, 19005101, 19005104, 19043327, 712615, 19102109, 19010886, 40684643, 751246, 767410	Yes	40001867, 36215883, 37497568, 37497570, 36277136, 36266912, 41298341, 40923962, 40861705, 36421456, 40892851, 40986331, 40986332, 43025924, 36277114, 35862962, 37498033, 36259222, 36269455

Substance Name	Concept name	Ingredient Concept ID	Include descendants	Exclude concept ID with all descendants
Antiarrhythmics/rhythm control drugs	amiodarone, dofetilide, dronedarone, flecainide, propafenone, sotalol	1309944, 1362979, 40163615, 1354860, 1353256, 1370109	Yes	
Anticoagulants/antithrombotic agents	apixaban, bivalirudin, dabigatran etexilate, edoxaban, fondaparinux, heparin, rivaroxaban, warfarin	43013024, 19084670, 40228152, 45892847, 1315865, 1367571, 40241331, 1310149	Yes	
Antihypertensives	amlodipine, atenolol, diltiazem, enalapril, furosemide, hydrochlorothiazide, lisinopril, losartan, metoprolol, spironolactone, valsartan	1332418, 1314002, 1328165, 1341927, 956874, 974166, 1308216, 1367500, 1307046, 970250, 1308842	Yes	
Antiplatelets	aspirin, clopidogrel, prasugrel, ticagrelor	1112807, 1322184, 40163718, 40241186	Yes	
Insulin	INSULINS AND ANALOGUES	21600713	Yes	
Lipid-lowering drugs	alirocumab, atorvastatin, evolocumab, ezetimibe, fenofibrate, gemfibrozil, omega-3 fatty acids, rosuvastatin, simvastatin	46275447, 1545958, 46287466, 1526475, 1551803, 1558242, 19106973, 1510813, 1539403	Yes	
Oral glucose-lowering drugs	biguanide, dapagliflozin, empagliflozin, gliclazide, glipizide, linagliptin, liraglutide, semaglutide, sitagliptin	1593986, 44785829, 45774751, 19059796, 1560171, 40239216, 40170911, 793143, 1580747	Yes	

*Descendant concept IDs of memantine and acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) include combinations of both. However, 0 descendant record counts are present in the DARWIN EU® portal.

ANNEX VI. Supplemental results

Number of individuals included in stratified analyses and subgroup analyses, by subobjectives

Table S5a. Number of individuals included in the analyses stratified by sex, by age, and in the subgroup of individuals with MCI prior to AD, among the study population with incident AD (**objectives 2, 3b, 4a–b, 4d, and 5a**).

	NAJS	DK-DHR	InGef RDB	IQVIA DA Germany	IPCI
Overall, N (100%)	20,218	57,462	72,767	37,182	7,379
Age group (years), N (%)					
• 18–55	483 (2.4%)	582 (1.0%)	863 (1.2%)	811 (2.2%)	50 (0.7%)
• 56–65	1,179 (5.8%)	2,060 (3.6%)	3,001 (4.1%)	1,835 (4.9%)	281 (3.8%)
• 66–75	4,988 (24.7%)	12,528 (21.8%)	12,122 (16.7%)	6,515 (17.5%)	1,508 (20.4%)
• 76–85	9,729 (48.1%)	28,576 (49.7%)	36,111 (49.6%)	19,475 (52.4%)	3,522 (47.7%)
• ≥86	3,839 (19.0%)	13,716 (23.9%)	20,670 (28.4%)	8,546 (23.0%)	2,018 (27.3%)
Sex, N (%)					
• Male	6,798 (33.6%)	23,274 (40.5%)	31,889 (43.8%)	15,120 (40.7%)	2,780 (37.7%)
• Female	13,420 (66.4%)	34,188 (59.5%)	40,878 (56.2%)	22,030 (59.2%)	4,599 (62.3%)
MCI prior to diagnosis of AD, N (%)	1,085 (5.4%)	3,039 (5.3%)	3,537 (4.9%)	3,038 (8.2%)	NC

MCI=mild cognitive impairment; NC=not captured; NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; InGef RDB=InGef Research Database; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=The Integrated Primary Care Information.

Table S5b. Number of individuals included in the analyses stratified by sex, by age, and in the subgroup of individuals with MCI prior to AD, among the study population with **no AD treatment prior to the first diagnosis** of AD (**objective 3a**).

	NAJS	DK-DHR	InGef RDB	IQVIA DA Germany	IPCI
Overall, N (100%)	12,188	44,853	46,967	26,575	6,364
Age group (years), N (%)					
• 18–55	301 (2.5%)	455 (1.0%)	628 (1.3%)	613 (2.3%)	45 (0.7%)
• 56–65	665 (5.5%)	1,578 (3.5%)	2,016 (4.3%)	1,331 (5.0%)	236 (3.7%)
• 66–75	3,006 (24.7%)	9,630 (21.5%)	8,151 (17.4%)	4,821 (18.1%)	1,323 (20.8%)
• 76–85	5,901 (48.4%)	22,528 (50.2%)	23,486 (50.0%)	14,032 (52.8%)	3,019 (47.4%)
• ≥86	2,315 (19.0%)	10,662 (23.8%)	12,686 (27.0%)	5,778 (21.7%)	1,741 (27.4%)
Sex, N (%)					
• Male	4,253 (34.9%)	18,143 (40.4%)	20,827 (44.3%)	10,974 (41.3%)	2,370 (37.2%)

	NAJS	DK-DHR	InGef RDB	IQVIA DA Germany	IPCI
• Female	7,935 (65.1%)	26,710 (59.6%)	26,140 (55.7%)	15,582 (58.6%)	3,994 (62.8%)
MCI prior to diagnosis of AD, N (%)	593 (4.9%)	2,310 (5.2%)	1,860 (4.0%)	2,098 (7.9%)	NC

MCI=mild cognitive impairment; NC=not captured; NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; InGef RDB=InGef Research Database; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=The Integrated Primary Care Information.

Table S5c. Number of individuals included in the analyses stratified by sex, by age, and in the subgroup of individuals with MCI prior to AD, among the study population **with no caregiver support prior to the first diagnosis of AD** (**objective 4c**).

	NAJS	DK-DHR	InGef RDB	IQVIA DA Germany	IPCI
Overall, N (100%)	9,154	56,119	NC	35,367	NC
Age group (years), N (%)					
• 18–55	310 (3.4%)	554 (1.0%)	NC	785 (2.2%)	NC
• 56–65	626 (6.8%)	1,974 (3.5%)	NC	1,762 (5.0%)	NC
• 66–75	2,157 (23.6%)	12,258 (21.8%)	NC	6,294 (17.8%)	NC
• 76–85	4,160 (45.4%)	27,985 (49.9%)	NC	18,612 (52.6%)	NC
• ≥86	1,901 (20.8%)	13,348 (23.8%)	NC	7,914 (22.4%)	NC
Sex, N (%)					
• Male	3,033 (33.1%)	22,860 (40.7%)	NC	14,477 (40.9%)	NC
• Female	6,121 (66.9%)	33,259 (59.3%)	NC	20,862 (59.0%)	NC
MCI prior to diagnosis of AD, N (%)	395 (4.3%)	2,944 (5.2%)	NC	2,919 (8.3%)	NC

MCI=mild cognitive impairment; NC=not captured; NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; InGef RDB=InGef Research Database; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); IPCI=The Integrated Primary Care Information.

Attrition tables

Table S3. Attrition of the study population for objectives 1 and 5b.

	NAJS	DK-DHR	InGef RDB	IQVIA DA Germany	IPCI
First treatment with acetylcholinesterase inhibitor or memantine, N	30,149	122,516	76,418	112,532	8,977
First treatment with acetylcholinesterase inhibitor or memantine after AD cohort entry date	10,085	49,355	26,209	11,102	1,266
First treatment with acetylcholinesterase inhibitor or memantine before 31 December 2023	9,909	49,200	25,546	10,648	1,185

NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); InGef RDB=InGef Research Database; IPCI=The Integrated Primary Care Information; N=number of people meeting criterion.

Table S4. Attrition of the study population for objectives 2, 3b, 4a–b, 4d, and 5a.

	NAJS	DK-DHR	InGef RDB	IQVIA DA Germany	IPCI
Record of AD diagnosis, N (%)	33,360	130,430	109,541	153,321	13,923
First AD diagnosis after 1 January 2014	24,195	63,768	109,541	123,313	10,341
First AD diagnosis before 31 December 2023	21,237	57,742	103,650	103,238	9,292
≥365 days prior observation	20,756	57,483	72,790	37,236	7,379
Age ≥18 years at date of first AD diagnosis	20,721	57,479	72,782	37,197	7,379
No prior death date	20,218	57,462	72,767	37,182	7,379

NAJS=National Public Health Information System; DK-DHR=Danish Data Health Registries; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); InGef RDB=InGef Research Database; IPCI=The Integrated Primary Care Information; N=number of people meeting criterion.

Results of the analyses stratified by sex, by age, and in the subgroup of individuals with MCI prior to AD

Prevalence of pharmacological treatments post-diagnosis of AD (objective 2)

Prevalence of pharmacological treatments post-diagnosis of AD by sex

The prevalence of acetylcholinesterase inhibitor, antipsychotic, and memantine prescriptions was generally similar between males and females in the three time windows after diagnosis of AD. However, the prevalence of pharmacological treatment prescriptions was higher among males than females in IPCI. The difference was largest in the time window five years after diagnosis, in which the prevalence of pharmacological treatment prescriptions was 44.2% among males versus 37.6% of females (see ShinyApp at EUPAS1000000827).

The prevalence of acetylcholinesterase inhibitor prescriptions one, three, and five years after diagnosis was similar between males and females with incident AD in DK-DHR and IQVIA DA Germany. The prevalence of acetylcholinesterase inhibitor prescriptions was approximately 3% to 4% lower among females than males during one, three, and five years after diagnosis in NAJS, InGef RDB, and IPCI. For example, during the first year after diagnosis, 22.3% of females with incident AD were prescribed acetylcholinesterase inhibitors versus 25.2% of males with incident AD in NAJS, 32.5% of females versus 35.9% of males in InGef RDB, and 13.5% of females versus 17.3% of males in IPCI.

The prevalence of memantine prescriptions was similar between males and females with incident AD in the three time windows after diagnosis of AD.

The prevalence of antipsychotic prescriptions during the first year after diagnosis of AD was 47.3% among females versus 41.6% among males in NAJS, 40.8% among females versus 37.6% among males in InGef RDB, and 26.0% among females versus 23.7% among males in IQVIA DA Germany, while the prevalence was similar between females and males in DK-DHR and IPCI. The prevalence of antipsychotic prescriptions during the first five years after diagnosis of AD was 58.7% among females versus 53.2% among males in NAJS, 27.1% among females versus 29.6% among males in DK-DHR, 58.1% among females versus 55.5% among males in InGef RDB, 36.6% among females versus 35.0% among males in IQVIA DA Germany, and 23.3% among females versus 28.0% among males in IPCI.

Prevalence of pharmacological treatments post-diagnosis of AD by age

The prevalence of pharmacological treatment prescriptions for AD (i.e. of acetylcholinesterase inhibitors, memantine, or antipsychotics) during the first year after diagnosis of AD was the lowest in the age group 18–55 years in NAJS, DK-DHR, InGef RDB, and IQVIA DA Germany. In these four data sources, the prevalence of pharmacological treatment prescriptions for AD ranged from 32.9% in IQVIA DA Germany to 83.3% DK-DHR in the age group 18–55 years, from 41.4% in IQVIA DA Germany to 93.6% in DK-DHR in the age group 56–65 years, from 49.4% in IQVIA DA Germany to 95.3% in DK-DHR in the age group 66–75 years, from 52.7% in IQVIA DA Germany to 94.8% in DK-DHR in the age group 76–85 years, and from 51.6% in IQVIA DA Germany to 89.7% in DK-DHR in the age group ≥86 years. However, the prevalence of pharmacological treatment prescriptions for AD was the highest in the age group 18–55 years in IPCI: 38.0% versus 35.6% in the age group 56–65 years, 33.2% in the age group 66–75 years, 27.4% in the age group 76–85 years, and 21.2% in the age group ≥86 years.

The prevalence of acetylcholinesterase inhibitor prescriptions during the first year after diagnosis of AD was the highest in the age group 18–55 years IPCI: 30.0%, versus 26.3% in the age group 56–65 years, 24.6% in the age group 66–75 years, 15.1% in the age group 76–85 years, and 5.5% in the age group ≥86 years. In the other data sources, the prevalence of acetylcholinesterase inhibitor prescriptions during the first year after diagnosis of AD ranged from 7.5% in IQVIA DA Germany to 70.8% in DK-DHR in the age group 18–55 years, from 21.3% in IQVIA DA Germany to 85.3% in DK-DHR in the age group 55–65 years, from 28.5% in

IQVIA DA Germany to 84.4% in DK-DHR in the age group 66–75 years, from 28.9% in IQVIA DA Germany to 77.2% in DK-DHR in the age group 76–85 years, and from 12.8% in NAJS to 60.9% in DK-DHR in the age group ≥86 years.

The prevalence of memantine prescriptions during the first year after diagnosis of AD was the lowest in the age group 18–55 years in NAJS, DK-DHR, InGef RDB, and IQVIA DA Germany. The prevalence of memantine prescriptions during the first year after diagnosis of AD was higher in each subsequent age group in DK-DHR: 15.1% in the age group 18–55 years, 16.4% in the age group 56–65 years, 22.2% in the age group 66–75 years, 28.0% in the age group 76–85 years, and 36.5% in the age group ≥86 years. However, the highest prevalence of memantine prescriptions during the first year after diagnosis of AD was observed in the age group 66–75 years in NAJS and in the age group 76–85 years in both InGef RDB and IQVIA DA Germany. The prevalence of memantine prescriptions during the first year after diagnosis of AD in NAJS was 13.0% in the age group 18–55 years, 36.6% in the age group 56–65 years, 49.3% in the age group 66–75 years, 47.0% in the age group 76–85 years, and 31.9% in the age group ≥86 years. The prevalence of memantine prescriptions during the first year after diagnosis of AD in InGef RDB was 9.9% in the age group 18–55 years, 13.7% in the age group 56–65 years, 16.7% in the age group 66–75 years, 16.9% in the age group 76–85 years, and 11.4% in the age group ≥86 years. The prevalence of memantine prescriptions during the first year after diagnosis of AD in IQVIA DA Germany was 4.0% in the age group 18–55 years, 8.6% in the age group 56–65 years, 12.3% in the age group 66–75 years, 13.4% in the age group 76–85 years, and 11.0% in the age group ≥86 years. In IPCI, <5 prescriptions of memantine were recorded among individuals with incident AD during the first year after diagnosis of AD in the age groups 18–55 years and the prevalence of memantine prescriptions during the first year after diagnosis of AD was <1% in each of the other age groups.

The prevalence of antipsychotic prescriptions during the first year after diagnosis of AD during the first year after diagnosis ranged from 16.5% in DK-DHR to 35.8% in NAJS in the age group 18–55 years (although the event count was <5 in IPCI), from 12.5% in IPCI to 38.4% in NAJS in the age group 56–65 years, from 10.9% in IPCI to 39.5% in NAJS in the age group 66–75 years, from 12.5% in DK-DHR to 46.1% in NAJS in the age group 76–85 years, and from 16.5% in IPCI to 54.7% in NAJS in the age group ≥86 years.

The treatment patterns by age during the first three years after diagnosis of AD and during the first five years after were similar to those during the first year after, although the prevalence of prescriptions of each treatment was higher in the longer time windows.

Prevalence of pharmacological treatments post-diagnosis of AD among the subgroup with MCI prior to AD

The prevalence of pharmacological treatment prescriptions for AD (i.e. acetylcholinesterase inhibitors, memantine, or antipsychotics) was slightly higher in the subgroup with MCI prior to AD diagnosis than in the overall cohort. The prevalence of pharmacological treatment prescriptions for AD during the first year after diagnosis in the subgroup with MCI prior to AD ranged from 68.3% in IQVIA DA Germany to 95.2% in DK-DHR. The prevalence of acetylcholinesterase inhibitor prescriptions for AD in the subgroup with MCI prior to AD ranged from 38.0% in InGef RDB to 82.8% in DK-DHR, which was higher than the prevalence among the overall cohort with incident AD. The prevalence of memantine prescriptions for AD during the first year after diagnosis in the subgroup with MCI prior to AD ranged from 11.9% in DK-DHR to 41.9% InGef RDB, which was similar to the prevalence in the overall cohort with incident AD. The prevalence of antipsychotic for AD during the first year after diagnosis in the subgroup with MCI prior to AD ranged from 11.9% in DK-DHR to 41.9% in InGef RDB, which was higher than among the overall cohort with incident AD in InGef RDB, but lower in NAJS, DK-DHR, and IQVIA DA Germany.

The treatment patterns among the subgroup with MCI prior to AD diagnosis during the first three years after diagnosis of AD and during the first five years after were similar to those during the first year after, although the prevalence of prescription of each treatment was higher in the longer time windows.

Timing of pharmacological treatments following AD diagnosis (objective 3a)

Timing of pharmacological treatments following AD diagnosis by sex

Figures S1a–e present the proportion of the females and males with incident AD who initiated a pharmacological treatment for AD (i.e. acetylcholinesterase inhibitors, memantine, or antipsychotics) within five years after the date of AD diagnosis.

The time from diagnosis until pharmacological treatment initiation for AD (i.e. acetylcholinesterase inhibitors, memantine, or antipsychotics) was similar between females and males in all data sources, except for IPCI. In IPCI, twenty-five percent of the females initiated a pharmacological treatment within 510 days [95% CI: 475–565] after diagnosis, while twenty-five percent of the males initiated a pharmacological treatment within 385 days [95% CI: 342–450].

The time from AD diagnosis until twenty-five percent of the individuals initiated acetylcholinesterase inhibitors was longer among females than males in NAJS and InGef RDB. In NAJS, twenty-five percent of the females initiated acetylcholinesterase inhibitors within 697 days [95% CI: 535–878] after AD diagnosis, while twenty-five percent of the males initiated acetylcholinesterase inhibitors within 322 days [95% CI: 214–435]. In InGef RDB, twenty-five percent of the females initiated acetylcholinesterase inhibitors within 90 days [95% CI: 87–94] after AD diagnosis, while twenty-five percent of the males initiated acetylcholinesterase inhibitors within 76 days [95% CI: 74–79]. The time from AD diagnosis until treatment initiation with acetylcholinesterase inhibitors was similar among females and males in DK-DHR, IQVIA DA Germany, and IPCI.

The time from AD diagnosis until half of the individuals initiated memantine in NAJS was 1,184 days [95% CI: 987–1,388] among females, which was longer than the 787 days [95% CI: 665–940] days among males. The time from diagnosis until memantine initiation was similar among females and males in DK-DHR, InGef DB, and IQVIA DA Germany. Less than five percent of the individuals initiated acetylcholinesterase inhibitors up to five years after AD diagnosis among both females and males in IPCI.

The time from AD diagnosis until antipsychotic initiation was shorter among females than males in NAJS and InGef RDB, longer among females than males in DK-DHR, and similar between females and males in IQVIA DA Germany and IPCI. The time from diagnosis until half of the individuals initiated antipsychotics was 1,134 days [95% CI: 1,074–1,231] among females versus 1,467 days [95% CI: 1,344–1,620] among males in NAJS and 1,155 days [95% CI: 1,128–1,189] among females versus 1,237 days [95% CI: 1,196–1,275] among males in InGef RDB. In DK-DHR, the time from diagnosis until twenty-five percent of the individuals initiated antipsychotics was 1,436 days [95% CI: 1,403–1,471] among females versus 1,235 days [95% CI: 1,209–1,277] among males.

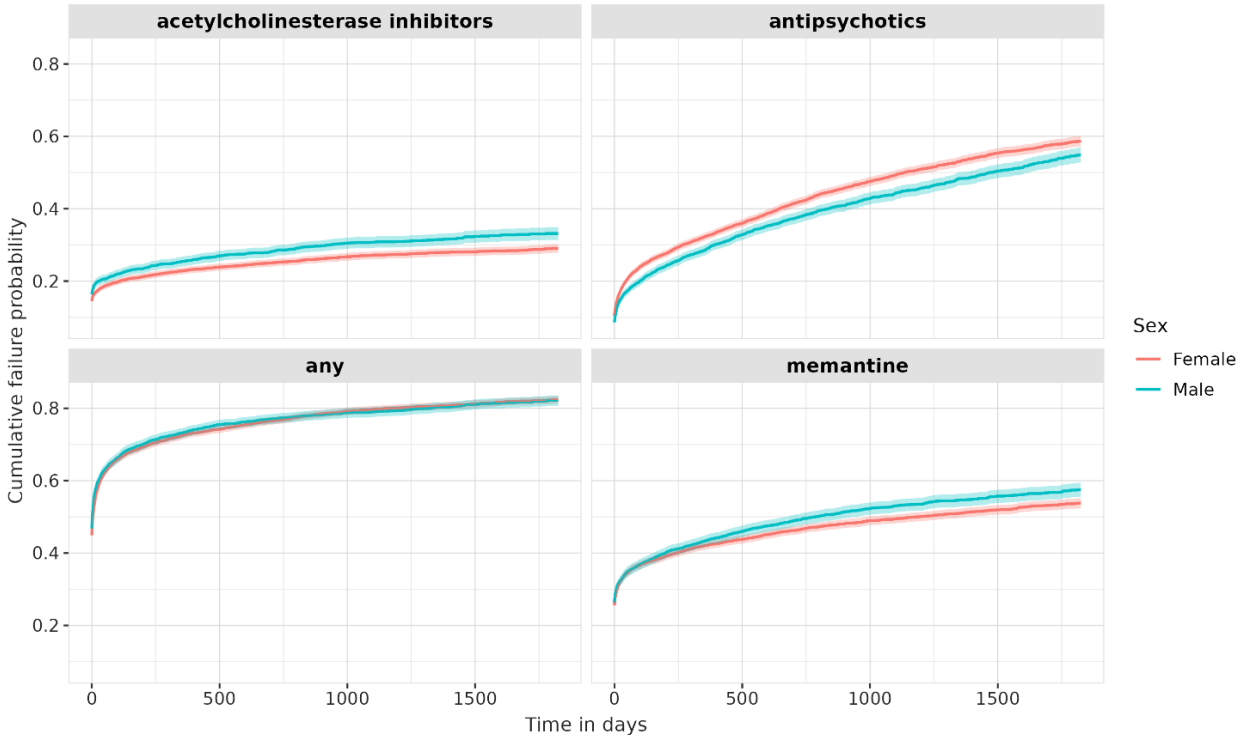


Figure S1a. Probability of treatment initiation for AD after AD diagnosis among females and males in NAJS.

AD=Alzheimer's disease; NAJS=National Public Health Information System.

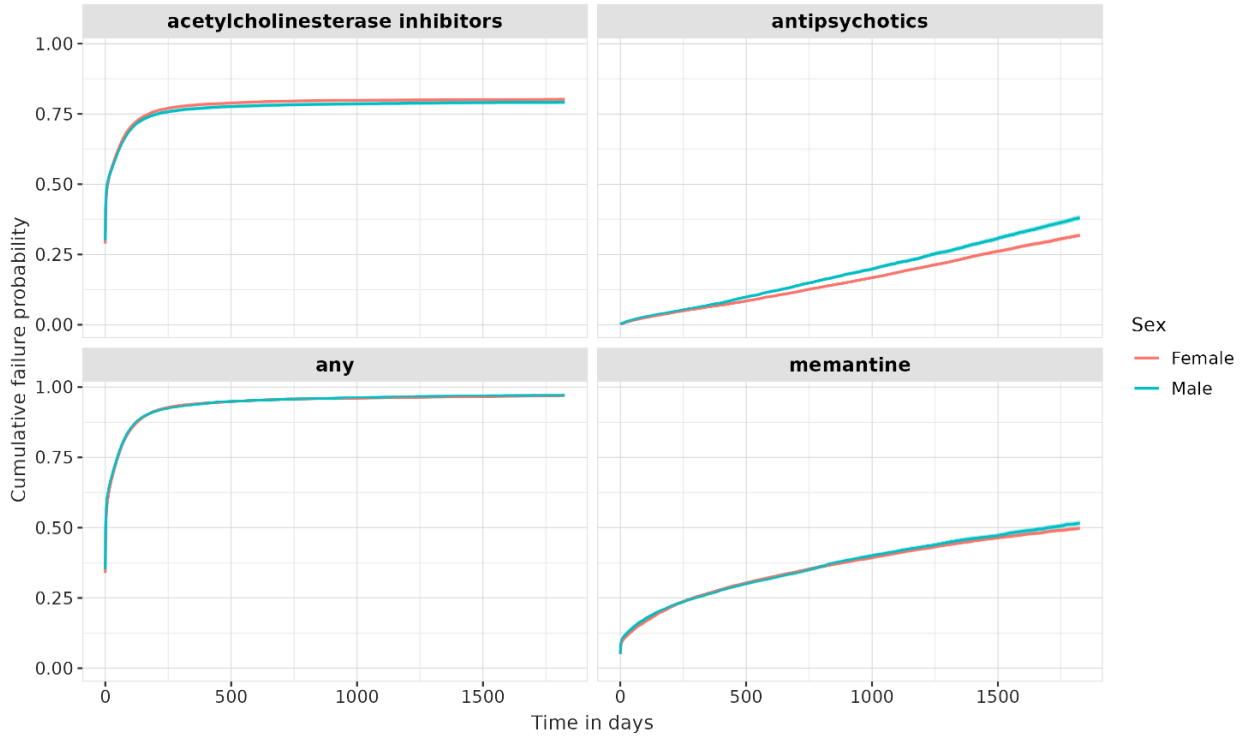


Figure S1b. Probability of treatment initiation for AD after AD diagnosis among females and males in DK-DHR.

AD=Alzheimer's disease; DK-DHR=Danish Data Health Registries.

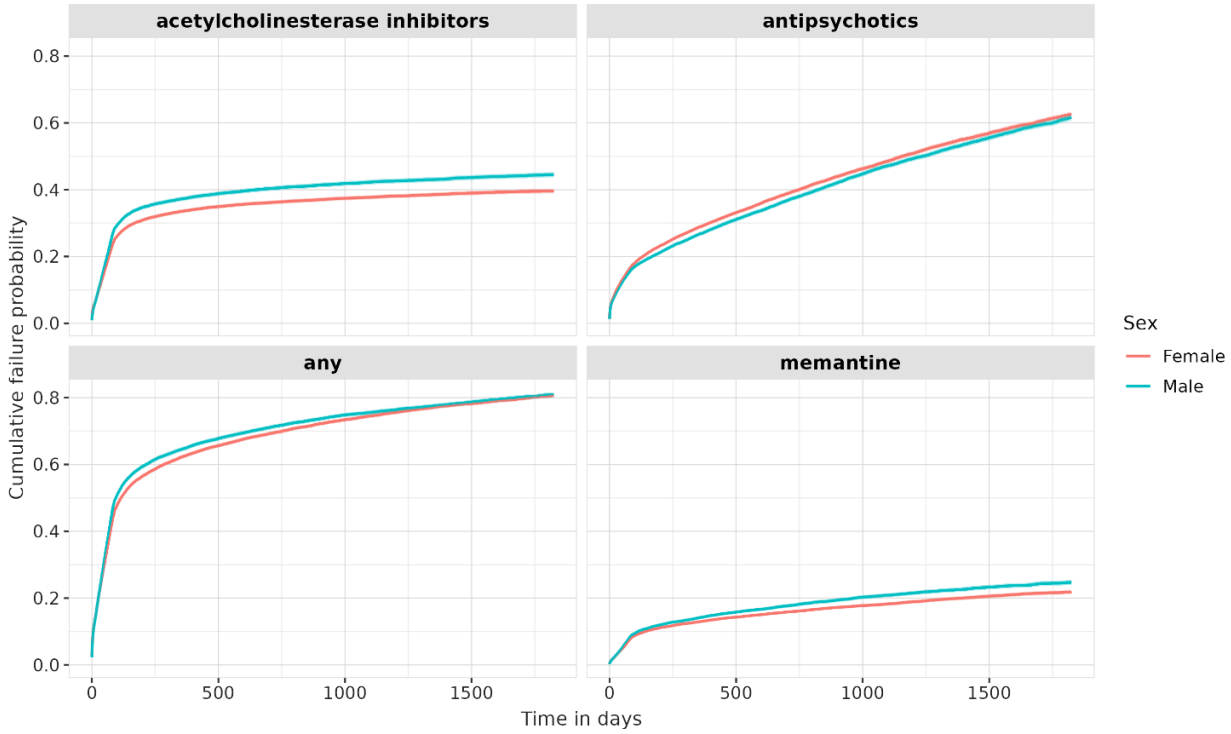


Figure S1c. Probability of treatment initiation for AD after AD diagnosis among females and males in InGef RDB.

AD=Alzheimer's disease; InGef RDB=InGef Research Database; IPCI=The Integrated Primary Care Information.

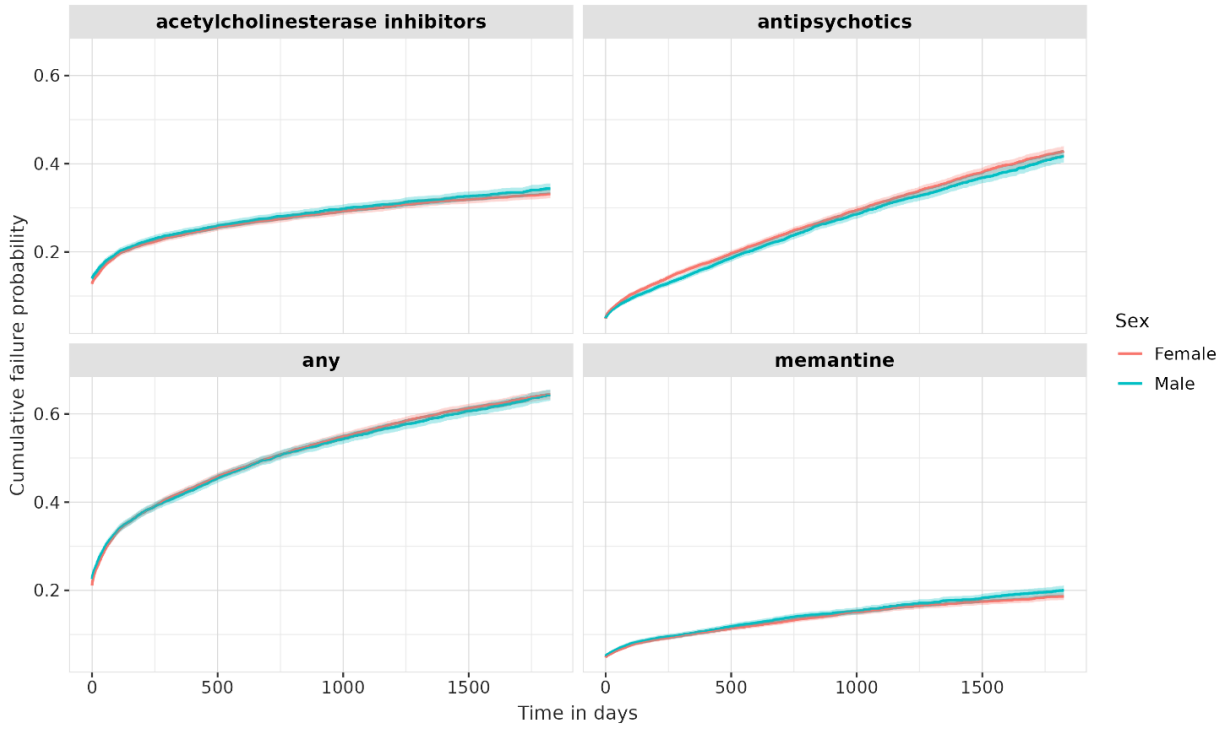


Figure S1d. Probability of treatment initiation for AD after AD diagnosis among females and males in IQVIA DA Germany.

AD=Alzheimer's disease; IQVIA DA=IQVIA Disease Analyzer Germany (IQVIA DA Germany); InGef RDB=InGef Research Database.

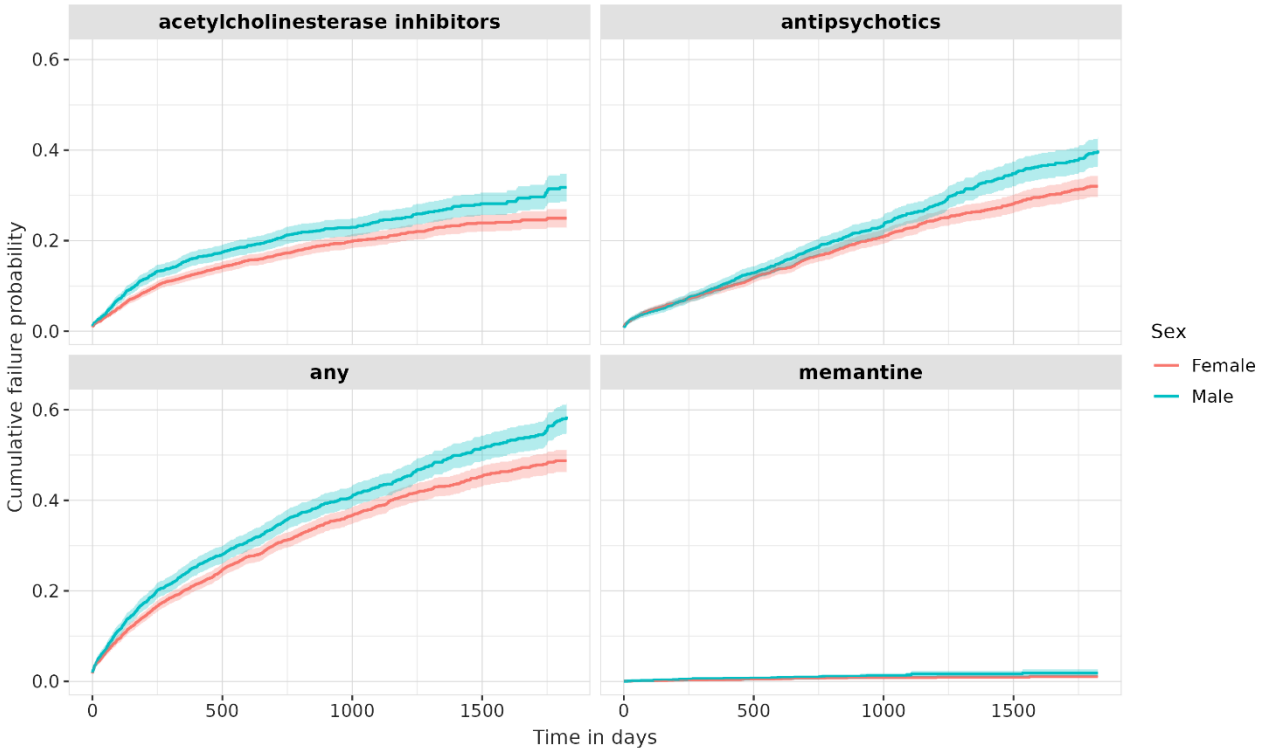


Figure S1e. Probability of treatment initiation for AD after AD diagnosis among females and males in IPCI.

AD=Alzheimer's disease; IPCI=The Integrated Primary Care Information.

Timing of pharmacological treatments following AD diagnosis by age

Twenty-five percent of the individuals initiated a pharmacological treatment for AD (i.e. acetylcholinesterase inhibitors, memantine, or antipsychotics) on the day of diagnosis in each of the age groups in DK-DHR and NAJS, except for the age group 18–55 years, in which less than twenty-five percent of the individuals initiated a treatment up to five years after diagnosis. In InGef RDB, the time from diagnosis until twenty-five percent of the individuals initiated a treatment was 71 days in the age group 18–55 years, which was longer than the approximately 40 days in each of the other age groups. In IQVIA DA Germany, less than twenty-five percent of the individuals in the age group 18–55 years initiated a treatment within five years after diagnosis, while the time from diagnosis until twenty-five percent of the individuals initiated a treatment was 159 days [95% CI: 86–292] in the age group 56–65 years, 24 days [95% CI: 14–35] in the age group 66–75 years, 5 days [95% CI: 1–8] in the age group 76–85 years, and 20 days [95% CI: 13–28] in the age group ≥86 years. In IPCI, the time from diagnosis until twenty-five percent of the individuals initiated a treatment was 252 days [95% CI: 212–833] in the age group 18–55 years, 255 days [95% CI: 180–461] in the age group 56–65 years, 286 days [95% CI: 241–367] in the age group 66–75 years, 483 days [95% CI: 430–544] in the age group 76–85 years, and 707 days [95% CI: 659–844] in the age group ≥86 years.

Five percent of the individuals initiated acetylcholinesterase inhibitors on the day of diagnosis across all age groups in NAJS, DK-DHR, and IQVIA DA Germany (except for the age group 18–55 years in IQVIA DA Germany, in which five percent initiated acetylcholinesterase inhibitors within 56 days [95% CI: 29–461] after AD diagnosis). Five percent of the individuals in InGef RDB initiated acetylcholinesterase inhibitors within twenty days after AD diagnosis across age groups. Five percent of the individuals in IPCI initiated acetylcholinesterase inhibitors within 165 days [95% CI: 27–232] after AD diagnosis in the age group 18–55 years, 52 days [95% CI: 7–87] in the age group 56–65 years, 45 days [95% CI: 34–59] in the age group 66–75

years, 85 days [95% CI: 64–101] in the age group 76–85 years, and 405 days [95% CI: 255–845] in the age group ≥86 years.

Five percent of the individuals with incident AD initiated memantine on the day of AD diagnosis across all age groups in NAJS. Five percent of the individuals in DK-DHR initiated memantine within 84 days [95% CI: 26–140] after AD diagnosis in the age group 18–55 years, 91 days [95% CI: 58–136] in the age group 56–65 years, 6 days [95% CI: 3–11] in the age group 66–75 years, 1 day [95% CI: 0–1] in the age group 76–85 years, and 0 days [95% CI: 0–0] in the age group ≥86 years. Five percent of the individuals in InGef RDB initiated memantine within 115 days [95% CI: 62–252] after AD diagnosis in the age group 18–55 years, 59 days [95% CI: 48–73] in the age group 56–65 years, 52 days [95% CI: 48–57] in the age group 66–75 years, 45 days [95% CI: 42–48] in the age group 76–85 years, and 61 days [95% CI: 57–67] in the age group ≥86 years. Less than five percent of the individuals in the age group 18–55 years initiated memantine within five years after AD diagnosis in IQVIA DA Germany. In the other age groups in IQVIA DA Germany, the time between AD diagnosis until five percent initiated memantine was 87 days [95% CI: 18–317] in the age group 56–65 years, 9 days [95% CI: 0–34] in the age group 66–75 years, 0 days [95% CI: 0–0] in the age group 76–85 years, and 16 days [95% CI: 3–36] in the age group ≥86 years. Less than five percent of the individuals across all age groups in IPCI initiated memantine within five years after AD diagnosis.

The time from AD diagnosis until five percent of the individuals initiated antipsychotics was generally shorter in the higher age groups. Five percent of the individuals in NAJS initiated antipsychotics within 87 days [95% CI: 26–282] after AD diagnosis in the age group 18–55 years, 14 days [95% CI: 0–56] in the age group 56–65 year, 0 days [95% CI: 0–1] in the age group 66–75 years, 0 days [95% CI: 0–0] in the age group 76–85 years, and 0 days [95% CI: 0–0] in the age group ≥86 years. Five percent of the individuals in DK-DHR initiated antipsychotics within 341 days [95% CI: 132–538] after AD diagnosis in the age group 18–55 years, 384 days [95% CI: 306–502] in the age group 56–65 years, 322 days [95% CI: 293–360] in the age group 66–75 years, 260 days [95% CI: 244–280] in the age group 76–85 years, and 161 days [95% CI: 138–184] in the age group ≥86 years. Five percent of the individuals in InGef RDB initiated antipsychotics within 74 days [95% CI: 51–143] after AD diagnosis in the age group 18–55 years, 38 days [95% CI: 25–56] in the age group 56–65 years, 15 days [95% CI: 12–20] in the age group 66–75 years, 5 days [95% CI: 4–6] in the age group 76–85 years, and 2 days [95% CI: 2–3] in the age group ≥86 years. Five percent of the individuals in IQVIA DA Germany initiated antipsychotics within 15 days [95% CI: 0–195] after AD diagnosis in the age group 18–55 years, 35 days [95% CI: 13–132] in the age group 56–65 years, 29 days [95% CI: 13–48] in the age group 66–75 years, 2 days [95% CI: 0–6] in the age group 76–85 years, and 0 days [95% CI: 0–0] in the age group ≥86 years. Less than five percent of the individuals in the age group 18–55 years initiated antipsychotics within five years after AD diagnosis in IPCI. In the other age groups in IPCI, the time between AD diagnosis until five percent initiated memantine was 227 days [95% CI: 69–554] in the age group 56–65 years, 232 days [95% CI: 179–324] in the age group 66–75 years, 130 days [95% CI: 83–174] in the age group 76–85 years, and 77 days [95% CI: 44–119] in the age group ≥86 years.

Timing of pharmacological treatments following AD diagnosis among the subgroup with MCI prior to AD

The time from AD diagnosis until half of the individuals initiated a pharmacological treatment for AD (i.e. acetylcholinesterase inhibitors, memantine, or antipsychotics) was shorter among the subgroup with MCI prior to AD diagnosis than among the overall cohort in NAJS, DK-DHR, and IQVIA DA Germany, while it was similar between the subgroup with MCI prior to AD diagnosis and the overall cohort in InGef RDB. The time from diagnosis until half of the individuals in the subgroup with MCI prior to AD initiated a pharmacological treatment for AD was 0 days [95% CI: 0–0] in NAJS, 1 days [95% CI: 1–1] in DK-DHR, 70 days [95% CI: 49–96] in IQVIA DA Germany, and 113 days [95% CI: 98–139] in InGef RDB.

The time from AD diagnosis until twenty-five percent of the individuals initiated acetylcholinesterase inhibitors was shorter among the subgroup with MCI prior to AD diagnosis than among the overall cohort in NAJS, InGef RDB, and IQVIA DA Germany, while twenty-five percent of the individuals initiated

acetylcholinesterase inhibitors on the day of AD diagnosis both among the subgroup with MCI prior to AD diagnosis and among the overall cohort in DK-DHR. Twenty-five percent of the individuals with MCI prior to AD diagnosis initiated acetylcholinesterase inhibitors on the day of AD diagnosis in NAJS and IQVIA DA Germany, while twenty-five percent of the individuals with MCI prior to AD initiated acetylcholinesterase inhibitors within 63 days [95% CI: 56–73] days after AD diagnosis in InGef RDB. Seventy-five percent of the subgroup with MCI prior to AD diagnosis initiated acetylcholinesterase inhibitors within 64 days [95% CI: 54–80] after AD diagnosis In DK-DHR, which was shorter than in the overall cohort.

The time from AD diagnosis until memantine initiation was shorter among the subgroup with MCI prior to AD diagnosis than among the overall cohort in NAJS, but longer in DK-DHR and InGef RDB, while five percent of the individuals initiated memantine on the day of AD diagnosis or the day after in IQVIA DA Germany both among the subgroup with MCI prior to AD diagnosis and among the overall cohort. In NAJS, half of the individuals with MCI prior to AD diagnosis initiated memantine within 110 days [95% CI: 34–273] after AD diagnosis. In DK-DHR, twenty-five percent of the individuals with MCI prior to AD diagnosis initiated memantine within 518 days [95% CI: 443–616] after AD diagnosis. In InGef RDB, five percent of the individuals with MCI prior to AD diagnosis initiated memantine within 66 days [95% CI: 57–87] after AD diagnosis.

The time from diagnosis until twenty-five percent of the individuals initiated antipsychotics was longer among the subgroup with MCI prior to AD diagnosis than among the overall cohort in NAJS, DK-DHR, and InGef RDB, while it was similar between the subgroup with MCI prior to AD diagnosis and the overall cohort in IQVIA DA Germany. The time from diagnosis until twenty-five percent of the individuals with incident AD initiated antipsychotics was 508 days [95% CI: 414–646] in NAJS, 1,674 days [95% CI: 1,539–1,812] in DK-DHR, 369 days [95% CI: 310–442] in InGef RDB, and 806 days [95% CI: 737–922] in IQVIA DA Germany.

Sequences of pharmacological treatments following AD diagnosis (objective 3b)

Sequences of pharmacological treatments following AD diagnosis by sex

The proportion of individuals with incident AD who were not prescribed a pharmacological treatment for AD (i.e. acetylcholinesterase inhibitors, memantine, or antipsychotics) within five years after diagnosis was slightly lower among females than males in DK-DHR (6.5% versus 7.1%), InGef RDB (23.0% versus 23.4%), IQVIA DA Germany (43.5% versus 43.8%), and NAJS (21.5% versus 23.7%). In IPCI, however, the percentage was higher among females than males (67.9% versus 62.4%).

Antipsychotics were the most prescribed as the first treatment after AD diagnosis among females in InGef RDB and IPCI, while acetylcholinesterase inhibitors were the most prescribed as the first treatment after AD diagnosis among males in InGef RDB and IPCI. Antipsychotics were prescribed as the first treatment after AD diagnosis to 35.8% of the females in InGef RDB and to 16.4% in IPCI. Acetylcholinesterase inhibitors were prescribed as the first treatment after AD diagnosis to 31.1% of the males in InGef RDB and to 19.1% in IPCI. In the other data sources, the most prescribed first treatments after diagnosis of AD were similar between females and males.

The most common treatments were generally similar between females and males with incident AD across data sources. However, in NAJS, one treatment sequence was more common among females, and another sequence was more common among males. The sequence of treatment prescriptions that was more common among females was antipsychotics combined with memantine as the first treatment after AD diagnosis followed by memantine (prescribed to 3.5% of females with incident AD). The sequence that was more common among males with incident AD was acetylcholinesterase inhibitors as the first treatment after AD diagnosis followed by acetylcholinesterase inhibitors combined with antipsychotics (prescribed to 3.0% of males with incident AD).

Sequences of pharmacological treatments following AD diagnosis by age

The proportion of individuals with incident AD who were not prescribed a pharmacological treatment for AD (i.e. acetylcholinesterase inhibitors, memantine, or antipsychotics) within five years after diagnosis ranged from 19.6% in DK-DHR to 71.3% in IQVIA DA Germany in the age group 18 to 55 years, from 6.4% in DK-DHR to 60.4% in IQVIA DA Germany in the age group 56 to 65 years, from 4.4% in DK-DHR to 57.7% in IPCI in the age group 66 to 75 years, from 5.1% in DK-DHR to 65.9% in IPCI in the age group 76 to 85 years, and from 11.2% in DK-DHR to 73.0% in IPC in the age group ≥86 years.

The most prescribed first treatments after AD diagnosis were similar between each age group and the overall cohort in DK-DHR. The most prescribed first treatments after AD diagnosis were similar between the overall cohort and the age groups 56–65 years, 66–75 years, and 76–85 years in NAJS, InGef RDB, and IQVIA DA Germany. In these three data sources, the most prescribed first treatment after AD diagnosis was antipsychotics in the age groups 18–55 years and ≥86 years. In IPCI, 34.4% of the individuals in the age group 18–55 years were prescribed acetylcholinesterase inhibitors as the first treatment after diagnosis, while neither memantine nor antipsychotics were prescribed to this age group as the first treatment after diagnosis. The treatments that were prescribed as the first treatment after diagnosis to individuals with incident AD in the age groups 56–65 years and 66–75 years in IPCI were acetylcholinesterase inhibitors (prescribed to approximately 30% of individuals in each age group) and antipsychotics (prescribed to approximately 13% of individuals in each age group), while memantine was not prescribed as the first treatment after diagnosis in either age group. In the age group 76–85 years in IPCI, 17.0% of individuals with incident AD were prescribed acetylcholinesterase inhibitors as the first treatment after AD diagnosis, 16.7% were prescribed antipsychotics, and 0.4% were prescribed memantine. In the age group ≥86 years in IPCI, 5.7% of individuals with incident AD were prescribed acetylcholinesterase inhibitors as the first treatment after AD diagnosis, 21.0% were prescribed antipsychotics, and 0.3% were prescribed memantine.

The sequences of prescriptions for different treatments that were the most common were generally similar between each age group and the overall cohort in DK-DHR. Among individuals with incident AD in the age group 18–55 years, treatment sequences were not observed in NAJS, and they were observed in only 2.8% of individuals in InGef RDB and 0.8% in IQVIA DA Germany. The treatment sequences that were the most common were generally similar between the overall cohort and the age groups 56–65 years, 66–75 years, 76–85 years, and ≥86 years in NAJS, InGef RDB, and IQVIA DA Germany. In IPCI, only two treatment sequences were observed in each of the age groups 66–75 years, 76–85 years, and ≥86 years, while no sequences were observed in the other age groups.

Sequences of pharmacological treatments following AD diagnosis among the subgroup with MCI prior to AD

The proportion of individuals with incident AD who were not prescribed a pharmacological treatment for AD (i.e. acetylcholinesterase inhibitors, memantine, or antipsychotics) within five years of diagnosis was slightly smaller among the subgroup with AD than among the overall cohort. Among the subgroup with AD, the proportion who were not prescribed a pharmacological treatment for AD within five years of diagnosis was 5.0% in DK-DHR, 21.7% in InGef RDB, 27.6% in IQVIA DA Germany, and 13.3% in NAJS.

The proportion of individuals with incident AD who were prescribed acetylcholinesterase inhibitors as the first treatment after diagnosis was larger among the subgroup with MCI prior to AD diagnosis than among the overall cohort across data sources. The proportion of individuals with MCI prior to AD diagnosis who were prescribed acetylcholinesterase inhibitors as the first treatment after diagnosis was 82.7% in DK-DHR, 33.1% in InGef RDB, 42.9% in IQVIA DA Germany, and 26.0% in NAJS. The proportion of individuals with incident AD who were prescribed memantine as the first treatment after diagnosis was smaller among the subgroup with MCI prior to AD diagnosis than among the overall cohort in DK-DHR and InGef, but larger in IQVIA DA Germany and NAJS. The proportion of individuals with MCI prior to AD diagnosis who were prescribed memantine as the first treatment after diagnosis was 11.3% in DK-DHR, 6.8% in InGef RDB, 14.6% in IQVIA DA Germany, and 43.5% in NAJS. The proportion of individuals with incident AD who were

prescribed antipsychotics as the first treatment after diagnosis was smaller among the subgroup with MCI prior to AD diagnosis than among the overall cohort in DK-DHR, IQVIA DA Germany, and NAJS, but slightly larger in InGef RDB. The proportion of individuals with MCI prior to AD diagnosis who were prescribed antipsychotics as the first treatment after diagnosis was 0.9% in DK-DHR, 13.9% in IQVIA DA Germany, 11.9% in NAJS, and 36.3% in InGef RDB.

The treatment sequences that were the most common were generally similar between the subgroup with MCI and the overall cohort. However, in NAJS, the sequence starting with acetylcholinesterase inhibitor monotherapy and followed by a combination of acetylcholinesterase inhibitor with antipsychotics was more common among the subgroup with MCI prior to AD diagnosis than among the overall cohort.

No sequences of four or more treatments were prescribed to >5% of individuals with MCI prior to AD in InGef RDB and IQVIA DA Germany. In DK-DHR, 7.4% of individuals with MCI prior to AD were prescribed acetylcholinesterase inhibitors followed by acetylcholinesterase inhibitors + memantine, acetylcholinesterase inhibitor monotherapy, and acetylcholinesterase inhibitors + memantine. In NAJS, 5.6% of individuals with MCI prior to AD diagnosis were prescribed memantine followed by antipsychotics + memantine, memantine, and antipsychotics + memantine.

Frequency of hospitalisations, outpatient visits, and caregiver support by sex and age and among the subgroup with MCI prior to AD (objectives 4a–c)

The frequency of hospitalisations, outpatient visits, and caregiver support was similar between females and males with incident AD during each of the follow-up windows and in all data sources.

The frequency of hospitalisations was similar between age groups in each of the follow-up windows across data sources.

Outpatient visits within five years after AD diagnosis were less frequent in the higher age groups in NAJS, DK-DHR, and IQVIA DA Germany. For example, in DK-DHR, the median [IQR] number of outpatient visits within five years after AD diagnosis was 16 [9–27] in the age group 18–55 years, 14 [8–25] in the age group 56–65 years, 12 [6–22] in the age group 66–75 years, 9 [5–17] in the age group 76–85 years, and 7 [3–11] in the age group ≥86 years. In IPCI, the median number of outpatient visits within five years after AD diagnosis was approximately 15 in the age groups from 18 to 85 years, compared to 8 in the age group ≥86 years.

The frequency of caregiver support was higher in the higher age groups in each of the three time windows in IQVIA DA Germany. The frequency of caregiver support within five years after AD diagnosis in IQVIA DA Germany was 7.4% in the age group 18–55 years, 6.6% in the age groups 56–65 years, 7.7% in the age group 66–75 years, 9.2% in the age group 76–85 years, and 12.7% in the age group ≥86 years. The frequency of caregiver support varied between age groups in each of the time windows in NAJS and DK-DHR.

The frequency of hospitalisation was similar between individuals with MCI prior to AD diagnosis and the overall cohort in each of the follow-up windows across data sources.

The frequency of outpatient visits in each of the time windows was slightly higher among the subgroup with MCI prior to AD diagnosis than among the overall cohort in NAJS and DK-DHR, while it was slightly lower in IQVIA DA Germany. The median [IQR] number of outpatient visits up to five years after AD diagnosis in the subgroup with MCI prior to AD diagnosis was 81 [41–137] in NAJS, 11 [6–21] in DK-DHR, and 14 [5–32] in IQVIA DA Germany.

The frequency of caregiver support in each of the time windows was higher among the subgroup with MCI prior to AD diagnosis than among the overall cohort in NAJS and DK-DHR, while it was lower in IQVIA DA Germany. The frequency of caregiver support within five years after AD diagnosis was 68.5% in NAJS, 3.4% in DK-DHR, and 6.0% in IQVIA DA Germany.

Time from AD diagnosis to caregiver support by sex and age and among the subgroup with MCI prior to AD (objective 4d)

Less than five percent of individuals with incident AD in DK-DHR received caregiver support within five years after diagnosis among females, males, each of the age groups, and the subgroup with MCI prior to AD diagnosis.

The time from diagnosis of AD to caregiver support was shorter among females than males in both NAJS and IQVIA DA Germany. The time between diagnosis of AD until five percent received caregiver support was 791 days [95% CI: 733–868] among females versus 954 days [95% CI: 876–1,051] among males in NAJS and 39 days [95% CI: 25–56] among females versus 53 days [95% CI: 30–77] among males in IQVIA DA Germany.

The time between diagnosis of AD until five percent of the individuals received caregiver support was similar between age groups in NAJS (within 100 days in the age groups 18–55 years and higher). In IQVIA DA Germany, less than five percent of the individuals with incident AD in the age groups 18–55 years and 56–65 years received caregiver support within five years after diagnosis. The time between diagnosis of AD until five percent of the individuals had a record of caregiver support was shorter in the higher age groups in IQVIA DA Germany: 1,105 days [95% CI: 957–1,334] in the age group 66–75 years, 863 days [95% CI: 772–956] in the age group 76–85 years, and 516 days [95% CI: 451–617] in the age group ≥86 years.

The time from diagnosis of AD to caregiver support was similar between the subgroup with MCI prior to AD and the overall population with a first record of AD diagnosis both in NAJS and in IQVIA DA Germany.

<u>Overall survival from AD diagnosis (objective 5a)</u>

Overall survival from AD diagnosis by sex

Twenty-five percent of the individuals died within 346 days [95% CI: 326–366] after AD diagnosis among females versus 288 days [95% CI: 266–311] among males in NAJS, 883 days [95% CI: 869–897] among females versus 741 days [95% CI: 723–756] among males in DK-DHR, 1,643 days [95% CI: 1,634–1,694] among females versus 1,481 days [95% CI: 1,460–1,551] among males in InGef RDB, and 1,365 days [95% CI: 1,274–1,492] among females versus 1,056 days [95% CI: 959–1,166] among males in IPCI.

The 5-year survival probability after AD diagnosis was higher among females than males: 39.0% [95%CI: 38.1%–40.1%] among females versus 34.2% [95%CI: 32.9%–35.6%] among males in NAJS, 42.6% [95%CI: 41.9%–43.2%] among females versus 36.1% [95%CI: 35.3%–36.8%] among males in DK-DHR, 72.2% [95%CI: 71.6%–72.8%] among females versus 69.5% [95%CI: 68.7%–70.2%] among males in InGef RDB, and 68.1% [95%CI: 65.9%–70.3%] among females versus 59.6% [95%CI: 56.8%–62.5%] among males in IPCI.

Overall survival from AD diagnosis by age

Less than twenty-five percent of the individuals died within five years after AD diagnosis in the age group 18–55 years in all data sources. The time between AD diagnosis until twenty-five percent of the individuals died in NAJS was 1,437 days [95% CI: 1,249–1,700] in the age group 56–65 years, 761 days [95% CI: 717–832] in the age group 66–75 years, 301 days [95% CI: 283–323] in the age group 76–85 years, and 89 days [95% CI: 82–97] in the age group ≥86 years. The time between AD diagnosis until twenty-five percent of the individuals died in DK-DHR was 1,689 days [95% CI: 1,605–1,776] in the age group 56–65 years, 1,279 days [95% CI: 1,243–1,308] in the age group 66–75 years, 857 days [95% CI: 842–872] in the age group 76–85 years, and 493 days [95% CI: 478–507] in the age group ≥86 years. Less than twenty-five percent of the individuals died within five years after AD diagnosis in the age groups 56–65 years and 66–75 years in InGef RDB and IPCI. The time between AD diagnosis until twenty-five percent of the individuals died in InGef RDB was 1,644 days [95% CI: 1,642–1,729] in the age group 76–85 years and 912 days [95% CI: 887–914] in the age group ≥86 years. The time between AD diagnosis until twenty-five percent of the individuals died in

IPCI was 1,300 days [95% CI: 1,218–1,412] in the age group 76–85 years and 599 days [95% CI: 538–652] in the age group ≥86 years.

The 5-year survival probability after AD diagnosis was lower in the higher age groups. The 5-year survival probability after AD diagnosis ranged from 76.6% [95% CI: 72.8%–80.6%] in NAJS to 97.7% [95% CI: 93.4%–100.0%] in IPCI in the age group 18–55 years, from 71.1% [95% CI: 68.2%–74.1%] in NAJS to 90.6% [95% CI: 89.3%–92.0%] in InGef RDB in the age group 56–65 years, from 52.3% [95% CI: 50.7%–54.1%] in NAJS to 82.8% [95% CI: 81.9%–83.7%] in InGef RDB in the age group 66–75 years, from 32.0% [95% CI: 30.9%–33.1%] in NAJS to 72.0% [95% CI: 71.3%–72.7%] in InGef RDB in the age group 76–85 years, and from 13.1% [95% CI: 11.7%–14.6%] in NAJS to 52.3% [95% CI: 51.1%–53.5%] in InGef RDB in the age group ≥86 years.

Overall survival from AD diagnosis among the subgroup with MCI prior to AD

Twenty-five percent of the individuals with MCI prior to AD diagnosis died within 689 days [95% CI: 598–792] after AD diagnosis in NAJS and within 1,024 days [95% CI: 979–1,087] in DK-DHR. Less than twenty-five percent of the individuals with MCI prior to AD died within five years after diagnosis in InGef RDB. The 5-year survival probability after AD diagnosis among the subgroup with MCI prior to AD diagnosis was 49.1% [95% CI: 45.4%–53.1%] in NAJS, 49.7% [95% CI: 47.4%–52.1%] in DK-DHR, and 74.7% [95% CI: 72.6%–76.9%] in InGef RDB.

Overall survival from the first treatment prescription for AD (objective 5b)

Overall survival from the first treatment prescription for AD by sex

The time between the first treatment prescription for AD (i.e. acetylcholinesterase inhibitors or memantine) until twenty-five percent of the individuals died was 346 days [95% CI: 326–366] among females versus 288 days [95% CI: 266–311] among males in NAJS, 883 days [95% CI: 869–897] among females versus 741 days [95% CI: 723–756] among males in DK-DHR, 1,643 days [95% CI: 1,634–1,694] among females versus 1,481 days [95% CI: 1,460–1,551] among males in InGef RDB, and 1,365 days [95% CI: 1,274–1,492] among females versus 1,056 days [95% CI: 959–1,166] among males in IPCI. The 5-year survival probability after the first treatment prescription for AD ranged from 43.3% [95% CI: 41.8%–44.8%] in NAJS to 77.4% [95% CI: 76.4%–78.4%] in InGef RDB among females, while it ranged from 35.0% [95% CI: 33.1%–37.1%] in NAJS to 73.7% [95% CI: 72.5%–74.9%] in InGef RDB among males.

Overall survival from the first treatment prescription for AD by age

Less than twenty-five percent of the individuals with a first treatment prescription for AD in the age group 18–55 years died within five years after the first prescription in all data sources. In NAJS, the time between the first prescription until twenty-five percent of the individuals died was 1,339 days [95% CI: 1,082–1,544] in the age group 56–65 years, 910 days [95% CI: 846–977] in the age group 66–75 years, 521 days [95% CI: 493–548] in the age group 76–85 years, and 231 days [95% CI: 204–263] in the age group ≥86 years. Less than twenty-five percent of the individuals in DK-DHR, InGef RDB, and IPCI with a first treatment prescription for AD in the age group 56–65 years died within five years after the first prescription. In DK-DHR, the time between the first prescription until twenty-five percent of the individuals died was 1,323 days [95% CI: 1,292–1,357] in the age group 66–75 years, 904 days [95% CI: 887–920] in the age group 76–85 years, and 551 days [95% CI: 536–565] in the age group ≥86 years. Less than twenty-five percent of the individuals in InGef RDB and IPCI with a first treatment prescription for AD in the age groups 56–65 years and 66–75 years died within five years after the first prescription. The time between the first prescription until twenty-five percent of the individuals died in the age group ≥86 years was 1,123 days [95% CI: 1,051–1,203] in InGef RDB and 913 days [95% CI: 707–1,145] in IPCI.

The 5-year survival probability after the first treatment prescription for AD was lower in the higher age groups. The 5-year survival probability after the first prescription in the age group 18–55 years ranged from 74.0% [95% CI: 69.3%–79.1%] in DK-DHR to 90.8% [95% CI: 86.3%–95.7%] in InGef RDB. The survival probability in IPCI could not be calculated in this age group because <5 individuals died within five years

after diagnosis. The 5-year survival probability after the first prescription ranged from 67.3% [95% CI: 62.6%–72.4%] in NAJS to 92.9% [95% CI: 87.1%–99.1%] in IPCI in the age group 56–65 years, from 54.1% [95% CI: 51.9%–56.5%] in NAJS to 83.2% [95% CI: 81.8%–84.6%] in InGef RDB in the age group 66–75 years, from 36.0% [95% CI: 34.3%–37.7%] in NAJS to 75.4% [95% CI: 74.4%–76.4%] in InGef RDB in the age group 76–85 years, and from 15.1% [95% CI: 12.7%–17.9%] in NAJS to 58.3% [95% CI: 55.9%–60.8%] in InGef RDB in the age group ≥86 years.

Overall survival from the first treatment prescription for AD in the subgroup with MCI prior to AD

Twenty-five percent of the individuals with MCI prior to AD diagnosis died within 918 days [95% CI: 791–1,033] after the first prescription in NAJS and within 1,084 days [95% CI: 1,022–1,130] after the first prescription in DK-DHR. Less than twenty-five percent of the individuals with MCI prior to AD diagnosis died within five years after the first treatment prescription for AD in InGef RDB. The 5-year survival probability after the first prescription was 53.3% [95% CI: 48.8%–58.3%] in NAJS, 50.3% [95% CI: 47.9%–52.9%] in DK-DHR, and 81.0% [95% CI: 78.2%–83.8%] in InGef RDB.

ANNEX VI. Glossary

Additional definitions are available in the EMA Glossary of terms https://www.ema.europa.eu/en/about-us/glossaries.

Aggregated Data

Data collected and combined from multiple sources to generate summary information, typically anonymised.

Benefit-Risk Assessment

Evaluation of the positive therapeutic effects of a medicine compared to its risks (e.g. side effects).

Common Data Model (CDM)

A standardised data structure that enables data from multiple sources to be harmonised, making analysis consistent and reproducible. DARWIN EU® utilises the OMOP CDM maintained by the OHDSI community.

Complex Studies (C3)

Studies requiring the development or customisation of specific study designs, protocols, and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data. Examples include etiological studies measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome in a defined population considering sources of bias, potential confounding factors, and effect modifiers.

Coordination Centre (CC)

The central hub responsible for managing and overseeing the activities within DARWIN EU®. It is based at Erasmus University Medical Center in Rotterdam, the Netherlands.

Data Access

The process of obtaining permission to use specific datasets for regulatory or scientific studies.

Data Quality Framework

A set of standards and procedures to ensure accuracy, completeness, timeliness, and consistency of data used in DARWIN EU®.

Data Source

A database or repository of structured health-related data, such as electronic health records (EHRs), insurance claims, or registries.

DARWIN EU®

The European Medicines Agency's (EMA) federated network of real-world data sources designed to generate evidence to support regulatory decision-making.

EMA (European Medicines Agency)

The regulatory body responsible for the evaluation and supervision of medicinal products in the EU, overseeing DARWIN EU®.

Evidence Generation

The process of analysing real-world data to produce scientific information that can inform healthcare or regulatory decisions.

Federated Network

A data infrastructure where data remain at their original location but can be analysed in a harmonised way across multiple partners using a common model and tools.

GDPR (General Data Protection Regulation)

The EU regulation governing the protection of personal data and privacy, crucial to how DARWIN EU® handles health data.

Health Technology Assessment (HTA)

A systematic evaluation of properties and impacts of health technology, often using DARWIN EU® data to support assessments.

Metadata

Descriptive information about a data source (e.g. its content, quality, and structure), essential for identifying relevant databases in DARWIN EU® studies.

Off-the-Shelf Studies (OTS)

Studies for which a standard protocol per study/analysis type and standardised analytics may be developed and applied or adapted, typically relating to a descriptive research question. This includes studies on disease epidemiology, for example, the estimation of the prevalence or incidence of health outcomes in defined time periods and population groups, or drug utilisation studies at the population or patient level.

OHDSI (Observational Health Data Sciences and Informatics)

An open-science collaborative community that develops tools and standards (including the OMOP CDM) to enable large-scale analytics of observational health data. OHDSI provides the technical and scientific foundation for DARWIN EU®'s analytical ecosystem.

Patient-Level Data

Data related to individuals, de-identified, used for longitudinal or detailed analyses.

OMOP (Observational Medical Outcomes Partnership)

A common data model (CDM) that standardises the structure and content of observational healthcare data, enabling systematic analysis across disparate datasets. DARWIN EU® uses the OMOP CDM to ensure interoperability and consistency in real-world evidence generation.

Real-World Data (RWD)

Data relating to individual health status or healthcare delivery that is collected from routine clinical practice rather than from randomised controlled trials.

Real-World Evidence (RWE)

Clinical evidence derived from the analysis of RWD, used to inform decisions by regulators, payers, or clinicians.

Regulatory Decision-Making

The process by which authorities like EMA assess data to authorise, monitor, or modify the use of medicines in the EU.

Routine Repeated Studies (RR)

Studies that are either Off-the-Shelf or Complex studies repeated on a regular basis, following the same protocol and study code, but with updated data and/or different data partners.

Study Protocol

A detailed plan describing how a specific real-world study will be conducted, including objectives, design, data sources, and analyses.

Very Complex Studies (C4)

Studies which cannot rely only on electronic health care databases, or which would require complex methodological work, for example, due to the occurrence of events that cannot be defined by existing diagnosis codes, including events that do not yet have a diagnosis code, where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations. These studies might require the collection of data prospectively, or the inclusion of new (not previously onboarded) data sources.