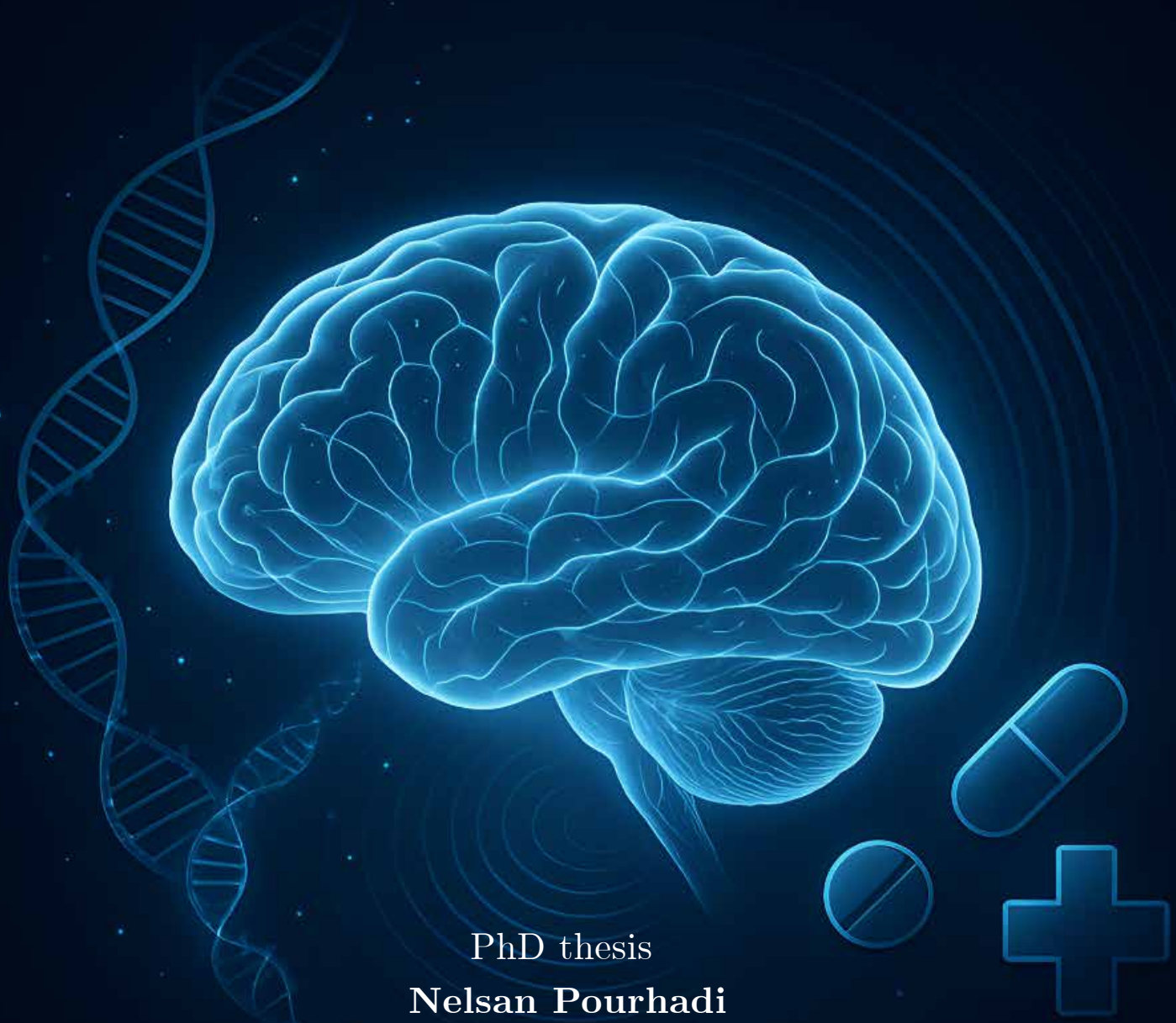
UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCES

Commonly used Medications and Dementia



PhD thesis

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This thesis has been submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen on 31 January 2025

To my family

List of Manuscripts

STUDY I: PROTON PUMP INHIBITORS AND DEMENTIA

Pourhadi N, Janbek J, Jensen-Dahm C, Gasse C, Laursen TM, Waldemar G. Proton pump inhibitors and dementia: A nationwide population-based study. Alzheimer's & Dementia. 2024;20(2):837-845. https://doi.org/10.1002/alz.13477

STUDY II: OPIOIDS AND DEMENTIA

Pourhadi N, Janbek J, Gasse C, Laursen TM, Waldemar G, Jensen-Dahm C. Opioids and Dementia in the Danish Population. JAMA Network Open. 2024;7(11):e2445904. https://doi.org/10.1001/jamanetworkopen.2024.45904

STUDY III: BLADDER DRUGS AND DEMENTIA

Pourhadi N, Janbek J, Gasse C, Munk Laursen T, Meaidi A, Jensen-Dahm C, Waldemar G. Bladder drugs and the risk of dementia: Danish nationwide active-comparator study. BMJ Medicine 2025;4:e001125. https://bmjmedicine.bmj.com/content/4/1/e001125

STUDY IV: POLYPHARMACY AND DEMENTIA

Pourhadi N, Jensen-Dahm C, Munk Laursen T, Gasse C, Waldemar G, Janbek J. Polypharmacy in people with dementia: a nationwide Danish study. 2025 (Submitted)

Preface

This PhD project was conducted at the Danish Dementia Research Centre (DDRC), Department of Neurology at Copenhagen University Hospital – Rigshospitalet. I am grateful for the financial support from the Research Fund of Rigshospitalet and from the Danish Dementia Research Centre supported by the Danish Ministry of Health, whose contributions made this work possible.

From the earliest stages of this PhD, I have been privileged to work within a research environment that fosters collaboration, curiosity, and a deep commitment to expanding the understanding of dementia and improving the lives of people with dementia and their caregivers. My sincere gratitude goes to my principal supervisor, Gunhild Waldemar, who welcomed me into her research team. Your ability to combine a rigorous scientific approach with genuine compassion for patients has contributed to shaping my research trajectory and my perspective on clinical practice. Thank you for the unique level of responsibility entrusted to me. Your openness to my ideas and genuine trust in my capabilities aided me in developing both competence and confidence in leading this work.

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Finally, I extend my sincerest thanks to all those who contributed to this thesis, directly or indirectly. Your guidance, encouragement, and support have left a lasting impact on this project and on my journey as a researcher. It is my hope that this thesis adds to our collective understanding of pharmacological products and dementia and inspires further research and initiatives to create positive change in people's lives and in society.

Thank you,
Nelsan Pourhadi, January 2025

List of Abbreviations

AD	Alzheimer's Disease
AMI	Acute Myocardial Infarction
ATC	Anatomical Therapeutic Chemical Classification System
CNS	Central Nervous System
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CVD	Cardiovascular Disease
DDD	Defined Daily Dose
ICD	International Classification of Diseases
IRR	Incidence Rate Ratio
OMEQ	Oral Morphine Equivalent Dose
OR	Odds Ratio
PPI	Proton Pump Inhibitor
TSD	Total Standardised Dose

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English Summary

Dementia presents a growing global health challenge, affecting millions of individuals worldwide as well as their relatives, healthcare systems, and society. As the disease is incurable, establishing factors that may influence dementia risk is essential to facilitate prevention. Extensively used medications including proton pump inhibitors, opioids, and anticholinergic bladder drugs have been suggested to affect brain health and cognition, but their long-term influences remain uncertain. With the existing literature being limited and reporting conflicting findings, this PhD project examines the use of these commonly prescribed medications and their possible associations with dementia risk focusing on addressing limitations in previous studies and unanswered aspects of the research questions.

Meanwhile, older adults, particularly those with dementia, frequently experience polypharmacy, which may elevate the risk of adverse effects. Further, the concurrent use of multiple central nervous system-active medications such as antipsychotics and opioids, can be particularly concerning due to the potential of worsening cognitive function. Understanding polypharmacy trends and prescribing patterns is essential to evaluating initiatives and promoting safer medication use in this vulnerable population. As such, this project additionally investigates the extent and trends of polypharmacy and the use of central nervous system-active medications among individuals with and without dementia.

The overarching aim of this project was to investigate whether the use of proton pump inhibitors, opioids, and bladder anticholinergics respectively is associated with an increased risk of dementia and additionally to update occurrences and trends of polypharmacy. Using national Danish healthcare registries, the studies examined a nationwide population to investigate long-term medication use and associated dementia risks as well as polypharmacy patterns in Denmark with focus on people with dementia.

The findings showed higher associated rates of dementia before 90 years of age among users of proton pump inhibitors, irrespective of treatment timing. High levels of opioid use (more than 90 treatment days with a standard dosage) were similarly associated with higher rates of dementia before 90. Use of bladder anticholinergic drugs was associated with an increased dementia rate compared to those who did not use these medications, but not when compared with users of another bladder drug with a different mechanism of action. Further, the findings showed that individuals with dementia were markedly more likely to use multiple medications, including central nervous system-active drugs, than those without dementia. Nonetheless, polypharmacy levels among people with dementia have declined over the past decade.

Owing to the observational nature of the project, these results do not verify a causal relationship between the studied medications and dementia risk, as other health conditions or unmeasured factors may contribute to the observed associations. Nonetheless, while these medications play a crucial role in treating various conditions, the findings note the importance of rational medication use as these might potentially pose risks related to cognition and dementia. While polypharmacy levels have declined, a considerable proportion of individuals with dementia continue to experience polypharmacy including high usage of central nervous system-active drugs. These findings highlight both the potential usefulness of and ongoing need to support safe prescribing to balance treatment benefits and potential risks in people with and without dementia. Future research should focus on determining whether these associations reflect causal relationships and further explore the long-term safety of these medications regarding dementia and cognitive function while also considering the importance of careful comparison groups as additionally highlighted in the findings of this project. Finally, monitoring and identifying strategies to optimise drug safety and prescribing practices is essential.

Dansk Resumé | Danish Summary

Demens udgør en voksende global sundhedsudfordring, der påvirker millioner af mennesker samt deres pårørende, sundhedsvæsnet og samfundet. Da sygdommen er uhelbredelig, er det afgørende at identificere faktorer, der kan påvirke demensrisikoen for at styrke forebyggende indsatser. Visse udbredte lægemidler, herunder protonpumpehæmmere, opioider og antikolinerge blæremidler, er blevet mistænkt for at have en indflydelse på hjernens helbred og kognitive funktioner, men de langsigtede konsekvenser er fortsat uklare. Eksisterende forskning er begrænset og viser modstridende resultater. Dette PhD projekt undersøger derfor brugen af disse lægemidler og deres potentielle sammenhæng med risikoen for demens, med særligt fokus på begrænsninger i tidligere studier og ubesvarede aspekter af forskningsspørgsmålene.

Polyfarmaci er udbredt blandt ældre, særligt hos personer med demens, hvilket kan øge risikoen for alvorlige bivirkninger. Samtidig brug af flere lægemidler som virker på centralnervesystemet såsom antipsykotika og opioider, er særligt problematisk, da det potentielt yderligere kan forværre kognitive funktioner. For at fremme en mere sikker medicinanvendelse er det vigtigt at forstå tendenser og omfanget af polyfarmaci. Derfor undersøger dette projekt også forekomsten og udviklingen af polyfarmaci samt brugen af lægemidler med virkning på centralnervesystemet hos personer med og uden demens.

Det primære formål med projektet var at undersøge om brugen af protonpumpehæmmere, opioider og antikolinerge blæremidler hver især er associeret med en øget risiko for demens, samt at kortlægge omfanget og udviklingen af polyfarmaci. Ved hjælp af nationale danske sundhedsregistre undersøgte projektet den voksne befolkning i Danmark for at belyse langtidsbrug af disse lægemidler og deres potentielle sammenhæng med demensrisiko samt mønstre i polyfarmaci forekomst med særligt fokus på personer med demens.

Resultaterne viste en øget forekomst af demens før 90-årsalderen blandt brugere af protonpumpehæmmere, uanset hvornår behandlingen var påbegyndt. Tilsvarende var højt forbrug af opioider (over 90 dages behandling med en standarddosering) associeret med en højere demensrisiko før 90 år. Brug af antikolinerge blæremidler var forbundet med en øget demensrisiko sammenlignet med personer, der ikke brugte disse lægemidler, men ikke når de blev sammenlignet med brugere af et andet blæremiddel med en anden virkningsmekanisme. Resultaterne vedrørende polyfarmaci viste, at personer med demens havde markant højere niveauer af polyfarmaci, herunder forbrug af lægemidler med virkning på centralnervesystemet, sammenlignet med personer uden demens. Dog er omfanget af polyfarmaci blandt personer med demens faldet over det seneste årti.

Grundet projektets observationelle karakter kan resultaterne ikke fastslå en direkte årsagssammenhæng mellem de undersøgte lægemidler og demens, da andre faktorer kan have påvirket sammenhængene. Mens disse lægemidler er vigtige i behandlingen af mange sygdomme, understreger fundene vigtigheden af en rationel tilgang til medicinbrug, da lægemidlerne potentielt kan udgøre en risiko for hjernen og kognitionen. Selvom polyfarmaci er blevet mindre udbredt blandt personer med demens, oplever en betydelig andel fortsat polyfarmaci, herunder særlig høj eksponering for lægemidler med virkning på centralnervesystemet. Fundene i dette projekt peger på et vedvarende behov for at fremme en sikker og velovervejet medicinordination, der balancerer behandlingens fordele med mulige risici for personer med og uden demens. Fremtidig forskning bør fokusere på, hvorvidt de observerede sammenhænge afspejler egentlige kausale mekanismer, og yderligere undersøge disse lægemidlers langsigtede effekter i forhold til demens og kognitiv funktion. Det er afgørende at fortsætte med at udvikle og evaluere initiativer og forskning, der bidrager til at øge lægemiddelsikkerhed.

Background

This section provides an overview of dementia's impact and modifiable risk factors focusing on potential pharmacological contributors. It highlights existing evidence on the associations between medications and dementia risk, alongside the implications of polypharmacy in dementia care. Finally, this section features critical knowledge gaps and methodological challenges in this research.

DEMENTIA

Dementia is a progressive neurological disorder characterised by the gradual deterioration of cognitive and functional abilities[1]. Individuals with dementia often experience difficulties with memory, decision-making, language, and performing everyday tasks, leading to an increasing reliance on caregivers. This decline significantly impacts their independence and quality of life. Beyond the individual, dementia imposes complex challenges on families, caregivers, healthcare systems, and society as a whole[1].

Globally, dementia affects an estimated 55 million individuals, a figure expected to triple by 2050 due to global ageing trends[2]. In Denmark, an estimated 97,000 individuals live with dementia, and the annual incidence exceeds 8,000 new cases[3,4]. These trends highlight the need to address dementia at multiple levels, including prevention, early diagnosis, and comprehensive care.

Of dementia cases, 45% are considered potentially preventable or delayable by addressing modifiable risk factors as recently reported in the 2024 update of the Lancet Commission on dementia[5]. This report underscored the importance of targeting 14 key modifiable risk factors, including cardiovascular health, lifestyle-related factors, and newly recognised contributors such as vision impairment[5]. Effective interventions targeting these risk factors could alter the trajectory of the disease. With dementia remaining incurable and considering the rising number of older adults worldwide, identifying further modifiable risk factors is essential to strengthen preventive efforts[5].

DRUGS AND THE RISK OF DEMENTIA

The role of pharmacological products in relation to dementia risk has gained increasing attention[5]. In this project, the three drug classes proton pump inhibitors (PPIs), opioids, and bladder anticholinergics were selected for investigation due to their extensive usage combined with emerging evidence on potential risks to brain health[6–8]. These widely used medications have been associated with neurological side effects, such as impaired cognition, sedation, and hallucinations, suggesting abilities to interact with the central nervous system (CNS)[9–11]. Although the side effects are mainly thought to be reversible, the long-term effects of these drugs on cognition and dementia risk remain poorly understood.

The widespread use of PPIs, opioids, and bladder anticholinergics raises concerns about potential overprescription. PPIs, for instance, are extensively used in Denmark to manage acid-related disorders, but their use has risen significantly without a corresponding increase in indications for usage[12,13]. Similar reports of PPI prescription patterns have been demonstrated across several Western and Eastern countries, indicating a global trend of overuse[14–19].

In parallel, opioids remain widely prescribed for chronic non-cancer pain, despite limited evidence supporting their long-term efficacy in pain management or quality of life improvements[20–24]. Chronic non-cancer pain is increasingly common, leading to a growing number of individuals requiring effective pain management strategies[25].

Finally, while clinical recommendations emphasise reducing anticholinergic burden to minimise cognitive risks, anticholinergic drugs including bladder anticholinergics are frequently used among older adults[26–28]. While these three medication classes serve several important purposes for many individuals, their overuse may result in potential risks outweighing benefits, particularly given the limited understanding of their long-term impact on cognition and dementia risk[29].

Evidence from experimental studies highlights the potential of these drugs to exhibit neurodamaging effects through a range of mechanisms. In mouse models, the PPI lansoprazole has been shown to elevate brain β-amyloid levels, a protein fundamental to Alzheimer's disease pathology[30]. Additionally, PPIs have demonstrated a strong inhibitory effect on choline acetyltransferase, the enzyme necessary for acetylcholine synthesis, potentially impairing cholinergic signalling[31]. Furthermore, these drugs have been associated with impaired endothelial function and increased risk of thrombotic events, including stroke[32–34].

Opioids cross the blood-brain barrier and interact with the CNS and preclinical studies have demonstrated oxidative stress and opioid-induced neuroinflammation [35,36]. Evidence from autopsy studies[37] have highlighted increased accumulation of β-amyloid and tau proteins in the brains of individuals with high opioid exposure, hypothesising a potential role of opioids in promoting neurodegeneration[38–40].

Lastly, bladder anticholinergics can potentially disrupt brain cholinergic pathways by blocking the neurotransmitter acetylcholine, which is important for cognitive function[41]. Subtypes of these drugs exhibit varying blood-brain barrier permeability potentially leading to differential levels of neurological side effects[42]. While these studies offer valuable hypotheses, it remains uncertain whether the findings are applicable to human populations, necessitating further studies to assess their relevance in clinical settings.

Previous population-based studies

Previous studies on the association between PPI use and dementia risk have reported mixed findings, with some observing positive associations[6,43–46] while others show no significant association[47–49]. Methodological variability across designs and follow-up may explain these inconsistencies[50]. Many studies did not implement lag-time windows to address potential bias nor account for the timing of PPI use relative to dementia[51]. Although, two studies reported differential associations according to age-intervals at dementia diagnosis, most did not consider this aspect[43,44].

The evidence is scarce regarding the association between long-term opioid use and dementia risk. Some studies have reported an associated increased dementia risk particularly with opioid use, although they were challenged by potential protopathic bias and confounding by indication[52–54]. Another study found no such association with Alzheimer's disease but called for further investigations in populations with higher exposure levels[55]. Additionally, timing of exposure to opioids and specific use of weak opioids remains largely unexplored.

Many studies have reported anticholinergic bladder drugs to be associated with an elevated dementia risk, but with conflicting findings

regarding specific anticholinergic subtypes[8]. Importantly, most studies did not employ an active comparator such as the beta-3 agonist bladder drug, mirabegron[56]. Further, long-term use of bladder drugs and the timing of their use relative to dementia onset remains understudied.

As such, these findings highlight the potential associations between the exposure drugs of interest and dementia risk, but further research is needed to address previous limitations, biases, and conflicting results.

POLYPHARMACY AND DEMENTIA

Polypharmacy, typically defined as the concurrent use of five or more medications, is a concern among older adults, particularly those with dementia[57]. While multimorbidity in dementia often necessitates pharmacological treatment, cognitive impairment complicates the evaluation of drug efficacy and the reporting of adverse effects, increasing the risk of inappropriate medication use[58]. This heightens the vulnerability of individuals with dementia to the potential harms of polypharmacy, including hospitalisations, and increased mortality[59].

CNS-active polypharmacy, defined as the concurrent use of three or more CNS-active drugs such as psychotropics, sedatives, or opioids, is of particular concern[60]. These medications are often prescribed to manage behavioral and psychological symptoms of dementia, despite limited evidence of long-term efficacy and the potential for serious adverse effects, including cognitive decline, sedation, and falls [61].

In 2014, around 63% of people with dementia in Denmark were exposed to polypharmacy compared to 35% of those without dementia[62]. While the specific occurrence of CNS-active polypharmacy has not been reported in Denmark, a study from the United States reported a prevalence of around 14% in older adults with dementia, with similar patterns observed in Australia[63,64]. These findings highlight interplays between dementia care, multimorbidity, and medication use.

Monitoring trends in polypharmacy provides important insights into prescribing practices as well as potential targeted interventions. For example, a previous study documented a decrease in the use of potentially inappropriate medications among older adults in Denmark between 2000 and 2015[65]. Whether the prevalence of polypharmacy and CNS-active polypharmacy has changed since then, possibly influenced by recent safe prescribing initiatives such as a national clinical guideline on dementia and medicine published by the Danish Health Authority, remains uncertain[66–72].

GAPS IN THE KNOWLEDGE

The long-term effects of PPIs, opioids, and bladder anticholinergics on cognition and dementia risk remain incompletely understood, even after several decades on the market[73]. While previous studies have provided valuable insights, significant knowledge gaps persist, particularly regarding nuanced aspects of the exposures. The association between cumulative long-term drug use and dementia risk remains underexplored, as does the timing of exposure, which may influence the observed outcome that is characterised by underlying neuropathological processes that span over decades[74]. Certain subtypes of exposure drugs also pose unanswered questions. For example, differences in blood-brain barrier penetration of different bladder anticholinergics and variation in analgesic strengths of opioids may yield differential association with cognition and dementia, yet evidence on these factors is scarce. Similarly, evidence on specific clinical

target populations of the exposure drugs, such as opioids used in chronic non-cancer pain is sparse.

An additional area of interest is the employing of active comparators, especially for bladder drugs, where the beta-3 agonist mirabegron can potentially be utilised. Active-comparator designs can be used to address indication biases, but evidence is incomplete likely due to limited access to validated active comparators[75,76]. Moreover, while some studies have suggested differentiations between drug exposure and dementia based on the age at diagnosis and dementia subtypes, this remains largely uncertain and calls for further investigation stratifying the study outcome[43,44]. Addressing these gaps is essential to advancing a nuanced understanding of the relationships between use of these drugs and dementia.

KEY CHALLENGES IN STUDYING DRUG USE AND DEMENTIA RISK

Investigating the relationship between drug use and dementia risk is methodologically complex due to the multifaceted nature of dementia and the limitations inherent to pharmaco-epidemiological studies[5,77]. Thus, the findings should be interpreted in the context of the limitations. Several key challenges must be considered and addressed to increase robustness and validity of findings.

Reverse causation poses an important challenge, as dementia has a long preclinical phase often spanning decades during which subtle symptoms such as mood changes, cognitive difficulties, or bladder dysfunction may influence prescribing patterns long before a clinical diagnosis[78]. For example, early dementia-related bladder symptoms could prompt the use of anticholinergic bladder drugs, introducing protopathic bias, where the drug appears to contribute to dementia risk but is actually prescribed in response to its early symptoms[79].

Confounding by indication is another notable issue, as the underlying conditions that necessitate medication use may themselves be risk factors for dementia[80]. For instance, diabetes is a well-documented dementia risk factor and simultaneously leads to the use of antidiabetic drugs. Such relationships challenge the disentangling of the effects of the medication from those of the condition it treats.

Misclassification of exposures and outcomes can further impact study validity. Accurate identification of drug exposure requires comprehensive and reliable medication data, including dosage and timing of use. Similarly, dementia diagnosis is prone to misclassification, as it encompasses a range of etiologies and to a degree remains underdiagnosed[81]. High-quality validated data on dementia diagnoses and exposure data are essential to address these matters.

The decades-long neuropathological progression of dementia necessitates large sample sizes and extended follow-up periods to capture potential temporal relationships between drug exposure and disease outcomes[74]. Additionally, comprehensive evaluation of confounding factors such as age, sex, socioeconomic status, comorbidities, and other medication use, is crucial to investigate associations of used drugs on dementia risk[5].

Observational studies assessing drug exposure and dementia risk are susceptible to residual confounding. Particularly when relying on large-scale registry data such as nationwide registries that often lack lifestyle and genetic factors known to affect dementia risk[82–84]. While socioeconomic status and comorbid conditions like cardiovascular disease and diabetes can serve as proxies and provide partial adjustments, they

fail to fully account for unmeasured factors such as obesity, physical activity, and genetic predisposition[82–84]. Although controlling for potential downstream consequences of unhealthy lifestyle, such as hypertension, can reduce bias, residual confounding remains inevitable, warranting careful interpretation and refining methodologies and integrating broader datasets to enhance validity.

Methodological strategies to mitigate bias include the use of active-comparator designs, which compare the drug of interest to an alternative treatment for the same indication rather than to no treatment, thereby addressing potential biases related to the indications of drug use[80]. Lag-time windows, which exclude exposures close to dementia diagnosis, are similarly important, namely, to address reverse causation[85]. Studying subpopulations with less heterogeneity, such as those with certain indications, characteristics, or specific age groups, can further enhance the assessment of the validity of findings.

The national Danish registries

The national Danish registries provide a reliable foundation for studying the complex relationships between drug use and dementia risk. These nationwide, population-based registries cover the entire Danish population and offer extensive longitudinal data. While not without limitations, their scope and comprehensiveness facilitate the addressing of many of the challenges in this research.

The Danish National Prescription Registry, provides detailed information on redeemed prescriptions in Denmark since 1995, allowing precise measurement of drug exposure[86]. The Danish National Patient Registry and the Danish Psychiatric Central Research Registry complement this by offering validated diagnostic data, including dementia diagnoses with high positive predictive values[81,87]. This supports accurate classification of both exposures and outcomes, and the registries' long follow-up periods are particularly beneficial for studying dementia, given its decades-long progression. Further, the ability to link data across these registries using unique personal identification numbers also enables evaluation of potential confounders, such as comorbidities and socioeconomic factors.

However, the registries are not without limitations[87]. Misclassification of diagnoses or drug exposures can occur, and residual confounding remains a possibility for example since the national registers do not hold data on life-style factors[88]. Careful study design and interpretation remain essential to account for inherent limitations and enhance the internal and external validity of findings.

Aims

The overarching aim of this PhD project was to investigate the use of commonly prescribed pharmacological products and associations with dementia risk. The study drugs of interest were proton pump inhibitors, opioids, and bladder anticholinergics. The project focused on investigating understudied aspects of the research questions as well as addressing previous limitations and biases. An additional aim was to study polypharmacy among people with dementia compared to people without dementia.

Study objectives:

Study I: Proton pump inhibitors and dementia

- To investigate cumulative exposure to proton pump inhibitors and the associated age-related risk of all-cause dementia.
- To investigate the aspect of timing of the exposure.

Study II: Opioids and dementia

- To investigate cumulative non-cancer exposure to opioids and the associated age-related risk of all-cause dementia.
- To investigate the association among individuals with chronic non-cancer pain and with the exclusive use of weak opioids.

Study III: Bladder drugs and dementia

- To investigate cumulative exposure to bladder anticholinergics and the associated risk of all-cause dementia compared to non-use and compared to an active comparator of mirabegron users.
- To investigate the association according to timing of the exposure and anticholinergic subtype.

Study IV: Polypharmacy and dementia

- To investigate the prevalence, time trends and adjusted odds ratio of polypharmacy and CNS-active polypharmacy in people with dementia compared to people without dementia.
- To identify the most frequently used pharmacological subgroups.

Methods

This section describes the data sources, study populations and analytical approaches used to investigate the research questions of interest. It details the specific study designs, variable assessment, statistical modelling, and study-specific analyses applied in this project.

DATA SOURCE AND SOURCE POPULATION

This project was based on data from the national Danish registries. All four studies were population-based and utilised the same nationwide source population of adult Danish residents. The study populations of interest were identified by combining individual-level data across several national Danish registries. The Civil Registration System in Denmark provides all residents with a unique personal identification number[89], with encrypted versions used across registries for consistent and accurate data linkage. The Civil Registration System established in 1968 included demographic data on sex and date of birth, immigration, emigration, and death. Diagnoses were identified from the Danish National Patient Registry[89] and the Danish Psychiatric Central Research Registry [90] holding data on diagnoses from Danish hospitals since 1977 and 1969, respectively (outpatient data was added in 1995). Data on medication use was obtained from the Danish National Prescription Registry[86], which has recorded all prescriptions filled at Danish community pharmacies since 1995. Information on socioeconomic status and living situation were drawn from the Danish Education Register[91] and Care Home Data, respectively [92].

STUDY DESIGNS AND STUDY POPULATIONS

This project employed different observational study designs and study populations according to the specific objectives and research questions of each individual study as displayed in Table 1. While study I-III used nested case-control designs within nationwide cohorts, study III additionally used an active-comparator, new-user study design. Follow-up for the latter study population initiated in 2013, the year from which the active comparator drug, mirabegron, entered the market. Finally, study IV was a series of cross-sectional studies of the Danish population.

Matching of cases and controls

The nested case-control design is a sampling strategy involving cases and a representative pool of non-cases selected from a well-defined cohort with a defined follow-up period[77]. This project employed incidence density matching to generate nested case-control populations within the respective nationwide source cohorts[93]. On the date of case occurrence (index date) during cohort follow-up, each case was sex- and age-matched to five eligible non-cases drawn from the source cohort. At the time of matching, all non-cases were still at risk of developing the outcome, thereby contributing with risk-time. This sampling process results in a nested case-control population composed of unique risk sets, each containing one case and five matched controls. All incident cases detected during the follow-up were included in the matched population, along with a representative control sample selected from the source cohort. Consequently, estimates derived from conditional logistic regression in this design can be interpreted as rate ratios, reflecting the association between the exposure and outcome in the entire source cohort[94].

Table 1. Characteristics of study designs and populations

	Study I PPIs & dementia	Study II Opioids & dementia	Study III Bladder drugs & dementia		Study IV Polypharmacy & dementia
			General population	Active-comparator population	
Design	Nested case-control study	Nested case-control study	Nested case-control study	Nested case-control study	Cross-sectional study
Study population	Nationwide open cohort (eligible n=1.98 million)	Nationwide open cohort (eligible n=1.87 million)	Nationwide open cohort (eligible n=2.26 million)	Nationwide open cohort (eligible n=58,242)	Nationwide closed cohort (eligible n=1.18 million)
Inclusion	Individuals 60-75 years in 2000-2018	Individuals 60-75 years in 2000-2020	Individuals 60-75 years in 2000-2022	New users of bladder drugs 60-75 years in 2013-2022	Individuals 65+ years in 2022
Exclusion	History of dementia	History of dementia, opioid addiction, opioid use in terminal illness, or cancer	History of dementia or mirabegron use	History of dementia	History of dementia diagnosed before age 65 years
Follow-up*	Up to 19 years (2000-2018)	Up to 21 years (2000-2020)	Up to 23 years (2000-2022)	Up to 9.5 years (2013-2022)	-

Note. *Follow-up ended with dementia, emigration, death, an exclusion criterion, or end of study.

IDENTIFICATION OF DEMENTIA

This project defined late-onset all-cause dementia as the earliest occurrence of either a recorded dementia diagnosis or a filled prescription with dementia-specific medication at age 60 years or older (65 years or older in Study IV). Table 2 displays exact International Classification of Diseases, 8th and 10th Revision (ICD-8 and ICD-10) codes and Anatomical Therapeutic Chemical (ATC) classification codes. In Denmark, dementia is predominantly diagnosed and managed in specialised hospital-based memory clinics, making it possible to identify cases through the Danish National Patient Registry, which provides diagnoses with a high positive predictive value of 86%[81]. Prescription data further enabled identification of individuals with dementia diagnosed and managed in primary healthcare settings.

Table 2. Dementia diagnosis and drug codes

Diagnoses	
Dementia type	**ICD-8/10 Code**
Alzheimer's disease	290.10, F00, G30
Vascular dementia	293.09-19, F01
Frontotemporal dementia	290.11, F02.0, G31.0A/B
Unspecified dementia	290.09/19, F03, G31.9
Other dementias	290.18, G31.8, F02.1-8
Medication	
Drug name	**ATC Code**
Donepezil	N06DA02
Rivastigmine	N06DA03
Galantamine	N06DA04
Memantine	N06DX01

IDENTIFICATION OF DRUG USE

Comprehensive details about the use of drugs were retrieved from the Danish National Prescription Registry, holding a complete record of prescriptions dispensed in Denmark starting from 1995. An individual was defined as exposed upon the redemption of a prescription with the exposure drug of interest between 1995 and during the exposure observation period. Prescription records include details on ATC code, date of purchase, package size, unit strength, dosage, and mode of administration. Table 3 displays the exposure drugs and ATC codes of interest used in this project.

PPIs, opioids, and bladder drugs

Cumulative exposure to specific drugs was calculated using standardised metrics, based on the total quantity of drugs redeemed during the observation period. For study I (PPIs) and study III (bladder drugs), the exposure drugs were calculated and cumulated in Daily Defined Doses (DDDs) due to relatively little individual variation in the daily dosages of these drugs[95]. Study II (opioids) applied standardised opioid conversion ratios to calculate equivalent doses (oral morphine equivalent doses (OMEQs) and total standardised doses (TSDs)), ensuring consistency with established methodologies and comparability across previous studies[54,55,96].

Table 3. Study drugs of interest and ATC-codes

Study I PPIs	**Study II** Opioids	**Study III** Bladder drugs	**Study IV** Polypharmacy
Proton pump inhibitors	Analgesic strong opioids	Anticholinergics	Polypharmacy
Omeprazole (A02BC01)	Morphine (N02AA01, N02AA04, N02AG01)	Emepron (G04BD01)	All ATC-codes except N06D (anti-dementia drugs)
Pantoprazole (A02BC02)	Oxycodone (N02AA05/55)	Flavoxate (G04BD02)	
Lansoprazole (A02BC03)	Buprenorphine (N02AE01)	Oxybutynin (G04BD04)	CNS-active drugs
Rabeprazole (A02BC04)	Fentanyl (N02AB03)	Tolterodine (G04BD07)	Antidepressants (N06A)
Esomeprazole (A02BC05)	Hydromorphone (N02AA03)	Solifenacin (G04BD08)	Antipsychotics (N05A)
	Ketobemidone (N02AB01, N02AG02)	Trospium (G04BD09)	Antiepileptics (N03A)
	Dextromoramide (N02AC01)	Darifenacin (G04BD10)	Anxiolytics (N05B)
		Fesoterodin (G04BD11)	Hypnotics (N05C)
	Analgesic weak opioids	Beta-3 agonist	Opioids (N02A, N07BC)
	Pethidine (N02AB02)	Mirabegron (G04BD12)	
	Codeine (N02AJ06, N02AJ07)		
	Tramadol (N02AX02)		
	Tapantadol (N02AX06)		
	Dextropropoxyphene (N02AC04)		
	Pentazocine (N02AD0)		
	Antitussive agents		
	Codeine (R05DA04, R05FA02)		
	Opium (R05FA02)		
	Dextromethorphan (R05DA09)		
	Ethylmorphine (R05DA01)		
	Noscapine (R05DA07)		

One TSD corresponds to a standard daily dosage of 30 mg oral morphine (or equivalent). These calculations accommodated the variations in potencies and dosages across different drug formulations, ensuring a consistent measure of exposure. After cumulating and transforming/ standardising the prescriptions of the respective exposure drugs of interest within the study populations, drug use was further categorised into a priori defined intervals based on clinical relevance as well as previous studies to facilitate comparability.

Polypharmacy

In study IV, polypharmacy was defined as filling prescriptions for five or more distinct medications, classified at the ATC drug substance level 5, within the first quarter of 2022 (January 1 to March 31). This approach, which evaluates drug use over three consecutive months, has been previously validated for estimating the number of concurrently used medications[57,97]. Anti-dementia drugs were excluded since polypharmacy was studied among people with dementia vs. people without dementia. In line with prior research[63], CNS-active polypharmacy was defined during the same period as filling prescriptions for three or more distinct CNS-active medications (Table 3), also classified at the ATC level 5.

CONFOUNDING VARIABLES

Potential confounding variables included as covariates in the statistical models comprised factors with known or suspected associations with both the outcome and the exposure, i.e., dementia risk and use of the respective exposure drugs[21,98,99]. Age and sex constituted demographic confounders which were accounted for in the matching process. Highest educational attainment was included as a socioeconomic confounder and categorised into either primary/secondary school, vocational education, or university education.

Potential confounders associated with health were identified through the presence of diagnoses or the use of condition-specific medication. These included diabetes, hypertension, dyslipidaemia, cardiovascular disease (CVD). The latter encompassed the presence of ischemic heart disease, stroke, or the use of oral antithrombotic medications. These variables were included as they are established risk factors for dementia and may influence medication use[21,98,99]. Additionally, overall somatic comorbidity burden was considered by using a standardised comorbidity index, the Charlson Comorbidity Index (CCI)[100]. Diagnose codes included in the definitions of the abovementioned confounding variables were omitted from the CCI. Study IV (polypharmacy and dementia) additionally considered psychotic disorders, anxiety disorders, and mood disorders as psychiatric comorbidities.

STUDY I-III DATA ANALYSIS

Statistical model

Conditional logistic regression was used in study I-III to calculate adjusted incidence rate ratios (IRRs) with corresponding 95% confidence intervals (CIs) to examine associations between the use of the exposure drug of interest and the risk of dementia. The analyses assessed both ever-use and cumulative use of the exposure drugs. The default reference group was non-users of the respective exposure drug, except for the analysis on new users of bladder drugs in study III, where the reference group comprised users of the active comparator, mirabegron. Data management and analyses were conducted using

R and SAS statistical software (SAS Institute Version 9.4; R Core Team, 2020)[101].

Timing of the exposure and outcome

Timing of the exposure was defined according to the index date which allowed for calculation of the time between the date of the first or last filled prescription and the date of dementia incidence/matching. This calculation enabled investigating the timing aspect of drug use by categorising exposed individuals' user status of the drug according to both treatment initiation and recency of use. Considering the slow development of many dementias, drug exposure temporally close to the diagnosis is less likely to be causally associated with the outcome[74].

Previous studies have observed an indication of PPI use and opioid use to be differentially associated with dementia occurring in different ages[44,52]. Therefore, study I-II investigated associations between the drug exposure and the risk of dementia stratified in ten-year age intervals (60-69 years, 70-79 years, 80-89 years, and 90+ years at diagnosis).

Lag time

In studies I-III, a default five-year lag time window was applied between the exposure and outcome. Thus, the default exposure observation period was from 1995 (initiation of the prescription register) until five years before the index date (date of dementia/matching). Hence, prescriptions of the exposure drug of interest five years prior to the index date were ignored.

The rationale for including lag time windows was to address the potential of reverse causation or protopathic bias where early symptoms of the outcome determine use of the exposure drug of interest[85]. Protopathic bias is particularly relevant to consider when investigating dementia as an outcome due to the tendency of slow, gradual development often over the course of several years. Thus, this approach aimed to mitigate the influence of symptoms related to undiagnosed dementia on prescription patterns of the exposure drug. As the potential mechanisms related to the associations of interest are unknown, the chosen length of the lag time window was arbitrary and based on previous studies in the topic.

Adjustment and sensitivity analyses

As covariates, all models included the potential confounding variables assessed at the beginning of the lag time window, if applied. Around 2% of the study population had unavailable information on highest obtained educational level, thus, were categorised separately as missing.

To address the potential indication of reverse causation, sensitivity analyses were conducted using different lengths of lag time windows as well as no lag for comparison with the main results. To evaluate possible time-varying influences of confounders, additional analyses were performed with confounders assessed at baseline. Lastly, mortality rates were estimated for exposed individuals compared to non-exposed to explore the potential indication of competing risks of death.

STUDY I-III SPECIFIC ANALYSES

In addition to the abovementioned main and sensitivity analyses, each individual study within this project incorporated specific analytical approaches and analyses in subpopulation tailored to the research question at hand. These additional methods were designed to address study-specific objectives and mitigate potential related biases.

Study I

Sensitivity analyses in distinct subpopulations addressed potential biases.

(1) A subpopulation of individuals with a CCI score of zero was analysed to examine the associations in a population with a relatively low burden of chronic somatic conditions.

(2) A subpopulation of individuals without a history of stroke was analysed since stroke could act as a potential intermediary on the pathway between PPI use and dementia as previously reported[32–34].

(3) A subpopulation of individuals 60-65 years in 2000 was analysed ensuring similar exposure circumstances regarding age, calendar time, and the availability of prescription data used to assess PPI use. This sensitivity analysis particularly accounted for time trends in the use of PPIs in Denmark which has increased rapidly over the course of the study[12].

Study II

Sensitivity analyses conducted in three distinct subpopulations targeted potential indication bias.

(1) A subpopulation of individuals registered with a chronic non-cancer pain diagnosis within a decade prior to study entry, focusing on opioid exposure subsequent to chronic pain diagnosis. This analysis aimed to tackle the potential of confounding by pain and the related conditions. As specified in previous research, pain-intensive conditions comprised neuropathic pain, arthritic pain, intervertebral disc pain, specific back disorders, and posttraumatic fracture pain[21]. Individuals with opioid prescriptions predating their pain diagnosis by more than one year were excluded.

(2) Analyses restricted to individuals using weak opioids (Table 3), excluding those prescribed strong opioids to mitigate potential confounding effects associated with stronger opioid use. Among weak opioids, tramadol is the most commonly prescribed in Denmark, with increasing usage trends observed between 1999 and 2017, particularly in individuals below 80 years[102].

(3) Analyses restricted to individuals prescribed opioids specifically for cough suppression (opioid antitussives, Table 3). Those prescribed any opioid classified as analgesic were excluded to reduce potential confounding by indication from analgesic opioid use.

Finally, to examine the possibility of false-positive diagnosis of dementia resulting from reversible opioid-induced cognitive dysfunction, a post hoc analysis was conducted. This was achieved by defining opioid user status based on the latest redeemed prescription with a 30-day extension period.

Study III

Besides employing an active comparator, this study examined the aspect of timing of exposure to anticholinergic bladder drugs. Anticholinergics are mainly hypothesised to potentially affect the cognition via anticholinergic effects in the brain[8]. Thus, active users of such drugs may be at higher risk of cognitive impairment (reversible or irreversible) and a diagnosis of dementia compared to past users. Therefore, to investigate potential short-term influences of drug exposure close the dementia diagnosis, this study defined user status of bladder anticholinergics according to the last filled prescription before index date.

Additionally, this study focused on stratification of subtypes of bladder anticholinergics. This was based on previous studies which have suggested varying dementia risks among different

anticholinergic subtypes, potentially due to differences in their ability to cross the blood-brain barrier[103,104].

STUDY IV ANALYSIS

The period prevalence proportions of overall polypharmacy and CNS-active polypharmacy were calculated for individuals with and without dementia. Age- and sex-standardised period prevalence proportions were derived using direct standardisation.

Logistic regression was employed to estimate odds ratios (ORs) and 95% CIs, comparing the odds of polypharmacy and CNS-active polypharmacy in individuals with dementia vs. individuals without dementia. Applied models included an unadjusted model, a model adjusted for age, sex, and education, and a fully adjusted model including additional adjustments for CCI scores and psychiatric comorbidities.

This study further examined time trends in the prevalences of polypharmacy and CNS-active polypharmacy according to dementia status by conducting multiple cross-sectional studies of the adult Danish population from 2012 to 2022. Additionally, polypharmacy prevalences according to dementia status were examined according to living situation to observe potential differences among community dwelling individuals and nursing home residents.

Finally, this study aimed to identify specific pharmacological subgroups most frequently used among individuals with dementia who experience polypharmacy and CNS-active polypharmacy.

ETHICS AND APPROVALS

This study utilised pseudonymised data from national Danish registries, accessed with the necessary approvals from the Danish Data Protection Agency and the Danish Health Data Authority. In accordance with Danish law, ethics committee approval and patient consent are not required for registry-based research.

Results

Overall, compared with non-use, this project observed positive associations between the use of PPIs and opioids respectively and the risk of all-cause dementia occurring before age 90. Bladder anticholinergics were found to be positively associated with dementia risk when comparing with non-use, but not when comparing with mirabegron use. Additionally, this project observed increased prevalence and adjusted odds ratios of polypharmacy and CNS-active polypharmacy in people with dementia compared to those without dementia. A general outline of the study results is provided in Table 4, followed by sections detailing each study's individual findings.

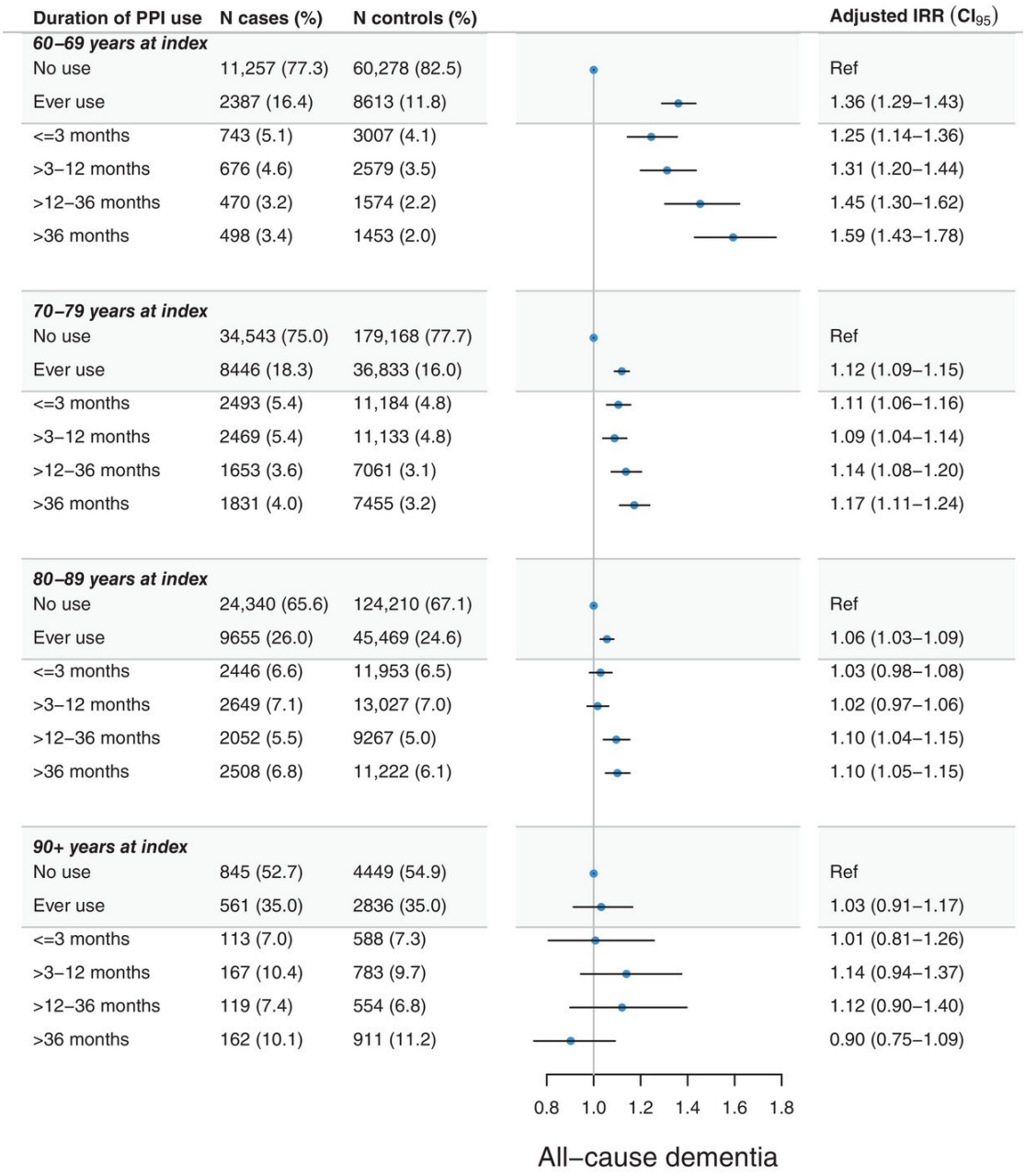
Table 4. Overview of studies and overall findings

	Study I **PPIs & dementia**	**Study II** **Opioids & dementia**	**Study III** **Bladder drugs & dementia**		**Study IV** **Polypharmacy & dementia**
			General population	*Active-comparator population*	
Study population	N=1,983,785	N=1,872,854	N=2,261,615	N=58,242	N=1,184,366
Cases with dementia	N=99,384	N=93,638	N=129,254	N=2,198	N=38,252
Median follow-up time	10.3 years	11.8 years	11.3 years	3.7 years	-
Overall finding	Increased rate of dementia in users vs. non-users	Increased rate of dementia in users vs. non-users	Increased rate of dementia in users vs. non-users	No increased rate of dementia in users vs. active comparator	Increased prevalence/ odds ratio in dementia vs. no dementia

STUDY I: PROTON PUMP INHIBITORS AND DEMENTIA

A nationwide cohort of 1,983,785 eligible Danish adults was followed from 2000-2018 with a median duration of follow-up (first to third quartile) of 10.3 years (5.1–15.6 years). During follow-up, 99,384 (5.0%) cases of all-cause dementia were matched to 496,920 controls. Median diagnosis age was 78 years (73-83 years) and 55.4% had female sex. Generally, comorbidities were more frequent in cases vs. controls. 21.2% of cases and 18.9% of controls were classified as exposed to PPIs. Figure 1 presents adjusted IRRs for age-stratified all-cause dementia by PPI use. Exposure to PPIs was positively associated with dementia before age 90, with IRRs ranging from 1.36 (95% CI, 1.29–1.43) in cases aged 60–69 years to 1.06 (1.03–1.09) in those aged 80–89 years. Overall, higher cumulative PPI use exhibited higher IRRs of dementia.

Figure 1. IRRs of association between cumulative PPI use and dementia reprinted from Pourhadi et al[105].



Note. Applying five years lag time. Covariates: Education, diabetes, CVD, hypertension, and dyslipidaemia.

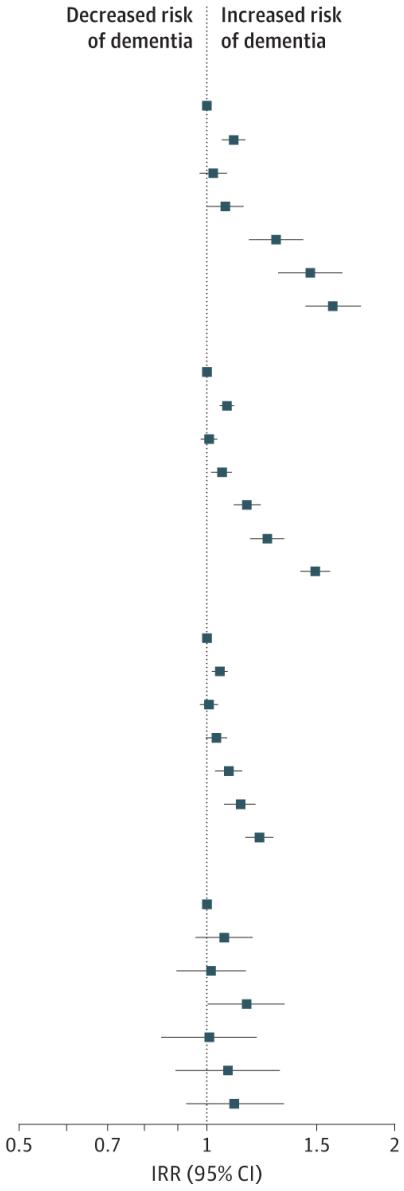
Associations decreased with advancing age at diagnosis. No association was observed for individuals aged 90+ years. PPI use was positively associated with dementia before 90 years of age irrespective of the timing of treatment initiation up to above 15 years before index. Associations decreased in a subpopulation with a CCI score of zero but remained statistically significant for dementia before age 80. Estimates among individuals without stroke and among individuals aged 60–65 years in 2000 were comparable with those in the main study population. Sensitivity analyses with no lag time and two-year lag exhibited comparable results. Compared with non-use, PPI use was associated with an increased mortality rate.

STUDY II: OPIOIDS AND DEMENTIA

The nationwide cohort comprised 1,872,854 individuals, with 93,638 (5.0%) developing all-cause dementia during follow-up from 2000-2020. Among dementia cases, 55.0% were female, and the median age at diagnosis was 78 years (73–83 years). These cases were matched to 468,190 controls. The median follow-up time was 11.8 years (7.3–15.8 years). Comorbidities were more frequent in dementia cases compared to controls. Among dementia cases, 55.8% had used opioids, compared to 52.9% of controls. For cases, the median cumulative opioid exposure was 35 TSDs (13–122 TSDs), compared to 33 TSDs (12–94 TSDs) among controls, with the median age at the time of the first prescription being 66 years (60–70 years). Oral tramadol was the most frequently used weak opioid, while oral morphine and oxycodone were the most common strong opioids.

Figure 2. IRRs of association between cumulative opioid use and dementia reprinted from Pourhadi et al[106].

Cumulative opioid use (TSDs)	Cases, No. (%)	Controls, No. (%)	IRR (95% CI)
60-69 Years at index			
No use	7343 (53.5)	39974 (58.2)	1 [Reference]
Ever use	6395 (46.5)	28716 (41.8)	1.10 (1.06-1.15)
0-30	3312 (24.1)	16907 (24.6)	1.02 (0.98-1.07)
31-90	1413 (10.3)	6592 (9.6)	1.07 (1.00-1.14)
91-200	611 (4.4)	2233 (3.3)	1.29 (1.17-1.42)
201-500	428 (3.1)	1306 (1.9)	1.46 (1.30-1.64)
>500	631 (4.6)	1678 (2.4)	1.59 (1.44-1.76)
70-79 Years at index			
No use	20597 (48.2)	109909 (51.4)	1 [Reference]
Ever use	22160 (51.8)	103876 (48.6)	1.08 (1.05-1.10)
0-30	10529 (24.6)	54327 (25.4)	1.01 (0.98-1.04)
31-90	5396 (12.6)	26004 (12.2)	1.06 (1.02-1.09)
91-200	2404 (5.6)	10294 (4.8)	1.16 (1.11-1.22)
201-500	1603 (3.7)	6197 (2.9)	1.25 (1.18-1.32)
>500	2228 (5.2)	7054 (3.3)	1.49 (1.42-1.57)
80-89 Years at index			
No use	12866 (36.8)	67292 (38.5)	1 [Reference]
Ever use	22063 (63.2)	107353 (61.5)	1.05 (1.02-1.08)
0-30	9392 (26.9)	48148 (27.6)	1.01 (0.98-1.04)
31-90	5580 (16.0)	27628 (15.8)	1.04 (1.00-1.07)
91-200	2748 (7.9)	12883 (7.4)	1.08 (1.03-1.14)
201-500	1890 (5.4)	8486 (4.9)	1.13 (1.07-1.19)
>500	2453 (7.0)	10208 (5.8)	1.21 (1.16-1.27)
≥90 Years at index			
No use	600 (27.1)	3123 (28.2)	1 [Reference]
Ever use	1614 (72.9)	7947 (71.8)	1.07 (0.96-1.18)
0-30	585 (26.4)	3017 (27.3)	1.01 (0.90-1.15)
31-90	440 (19.9)	1997 (18.0)	1.16 (1.01-1.33)
91-200	216 (9.8)	1129 (10.2)	1.01 (0.85-1.20)
201-500	170 (7.7)	832 (7.5)	1.08 (0.89-1.31)
>500	203 (9.2)	972 (8.8)	1.11 (0.93-1.33)



Note. Applying five years lag time. Covariates: Education, diabetes, CVD, hypertension, dyslipidaemia, CCI.

Exposure to opioids was associated with slightly higher rates of dementia before age 90 years (Figure 2). Cumulative use of ≤90 TSDs did not exhibit consistent association with dementia; however, exposure above 90 TSDs showed increasing IRRs of dementia. For individuals aged 60–69 years at index, IRRs ranged from 1.29 (1.17–1.42) for 91–200 TSDs to 1.59 (1.44–1.76) for >500 TSDs. Similar trends were observed in older age groups, though with smaller effect sizes, and no associations were identified for dementia diagnosed at 90+ years.

In a subpopulation with chronic non-cancer pain diagnoses, dementia rates were lower compared to the main study population, but exposure above 90 TSDs remained positively associated with risk of dementia. Exposure restricted to weak opioids only yielded results comparable to the main analyses. Exclusive use of opioid antitussives was not associated with dementia, except for exposure above 200 TSDs before age 80 years. In a post hoc analysis, cumulative opioid use exceeding 90 TSDs was positively associated with dementia before age 90 years regardless of user status (timing of exposure according to the index date). Separate sensitivity analyses with one-year lag time windows and baseline covariates yielded results similar to main findings. Opioid use exceeding 90 TSDs was positively associated with rates of mortality.

STUDY III: BLADDER DRUGS AND DEMENTIA

A total of 2,261,615 individuals from the general Danish population were followed from 2000 to 2022, during which 129,254 cases of dementia were identified and matched to 646,270 controls. Dementia cases had a median age at diagnosis of 78.5 years (73.5–83.2) and 55.8% were female. Compared to controls, dementia cases used bladder anticholinergics more frequently (6.2% vs. 4.2%) and exhibited higher prevalences of comorbidities.

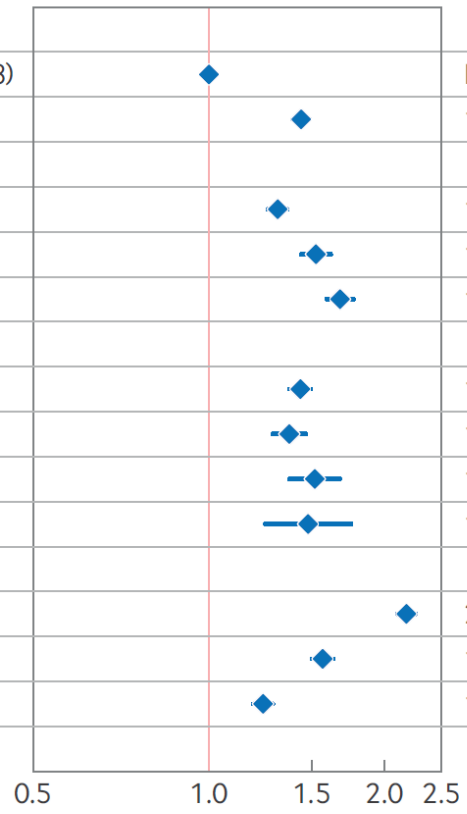
A separate population of 58,242 new users of bladder drugs followed from 2013 to 2022, included 2,198 dementia cases matched to 10,990 controls. In this population, 43.6% exclusively used beta-3 agonist (mirabegron), 38.1% used anticholinergics only, and 18.3% were categorised as mixed users, having been exposed to both. The age at treatment initiation was comparable for mirabegron users and anticholinergic users (median: 73.7 vs. 73.4 years), as was cumulative drug exposure (median: 90 DDDs (30–360 DDDs) vs. 100 DDDs (30–360 DDDs)). The prevalence of comorbidities was similar between the two groups.

In the general population, exposure to anticholinergic bladder drugs was associated with an increased IRR of all-cause dementia compared with non-use of bladder drugs, IRR: 1.44 (1.40–1.48) (Figure 3). Increasing cumulative use exhibited increasingly higher rates. All anticholinergic subtypes were positively associated with dementia. Current use within one year of index showed an IRR of 2.18 (2.11–2.25) while the IRR of past use >5 years was 1.24 (1.20–1.28). Sensitivity analyses without a lag time showed slightly higher dementia rates compared to analyses with a five-year lag.

In a population of new users of bladder drugs, when applying an active comparator of mirabegron users, bladder anticholinergic use was slightly negatively associated with dementia risk, IRR 0.82 (0.74–0.92) (Figure 4). No anticholinergic subtype was associated with increased risk of dementia. Findings from sensitivity analyses with a two-year lag were consistent with the main analyses without lag. Compared to mirabegron, exposure to bladder anticholinergics was associated with a mortality rate ratio of 1.04 (0.98–1.11).

Figure 3. IRRs of the association between cumulative bladder anticholinergics use and dementia compared to non-use reprinted from Pourhadi et al[107].

Anticholinergic bladder drug	No of cases (%)	No of controls (%)	Incidence rate ratio (95% CI)	Incidence rate ratio (95% CI)
Ever use				
No use	121 203 (93.8)	618 834 (95.8)		Reference
Ever use	8051 (6.2)	27 436 (4.2)		1.44 (1.40 to 1.48)
Cumulative use				
1-90 DDDs	4117 (3.2)	15 425 (2.4)		1.31 (1.27 to 1.36)
91-365 DDDs	1764 (1.4)	5685 (0.9)		1.53 (1.44 to 1.61)
>365 DDDs	2170 (1.7)	6326 (1.0)		1.68 (1.59 to 1.76)
Subtype				
Tolterodine	3283 (2.5)	11 234 (1.7)		1.43 (1.38 to 1.49)
Solifenacin	1326 (1.0)	4771 (0.7)		1.37 (1.29 to 1.46)
Trospium	526 (0.4)	1704 (0.3)		1.52 (1.37 to 1.37)
Fesoterodine	188 (0.1)	628 (0.1)		1.48 (1.26 to 1.74)
User status				
Current user	5711 (4.4)	12 837 (2.0)		2.18 (2.11 to 2.25)
Recent user	3778 (2.9)	11 865 (1.8)		1.57 (1.51 to 1.63)
Past user	4647 (6.3)	18 304 (2.8)		1.24 (1.20 to 1.28)



Note. Adjustment for education, diabetes, CVD, hypertension, dyslipidaemia, and CCI. Five years lag time applied except for in user status analysis (final treatment day according to index date - Current: Within 1 year; Recent: 1-5 years; Past: >5 years).

STUDY IV: POLYPHARMACY AND DEMENTIA

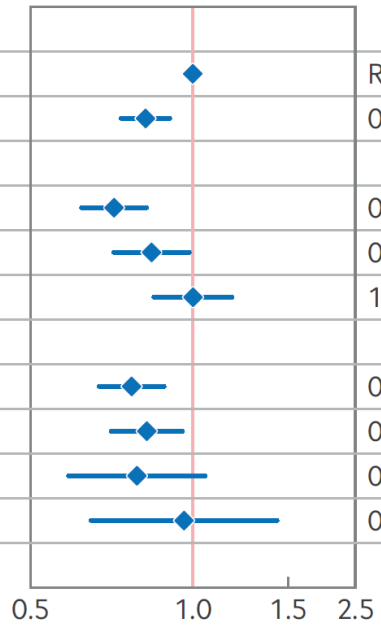
The study population consisted of 1,184,366 individuals aged 65 years or older, among whom 38,252 (3.2%) had dementia, with 59.4% of these being female a baseline age of 82 years (77–87 years). People with dementia exhibited higher rates of somatic and psychiatric comorbidities compared to those without dementia whose median age at baseline was 74 years (70–80 years).

In the first quarter of 2022, polypharmacy was prevalent in 56.2% (age- and sex-standardised 51.6%) of individuals with dementia compared to 35.6% of those without dementia (Table 5). The prevalence of CNS-active polypharmacy in the first quarter of 2022 was 10.1% (standardised 10%) in individuals with dementia and 2.3% in those without dementia.

Among individuals with dementia, the fully adjusted OR for polypharmacy was 1.47 (1.44–1.51) compared to those without dementia (Table 5). For CNS-active polypharmacy, the OR was 2.70 (2.59–2.81).

Figure 4. IRRs of the association between cumulative bladder anticholinergics use and dementia compared to an active comparator (beta-3 agonist, mirabegron) reprinted from Pourhadi et al[107].

Bladder drug user status	No of cases (%)	No of controls (%)	Incidence rate ratio (95% CI)	Incidence rate ratio (95% CI)
Ever use				
Mirabegron	1011 (46.0)	4735 (43.1)		Reference
Anticholinergic bladder drug	752 (34.2)	4274 (38.9)		0.82 (0.74 to 0.91)
Cumulative use				
1-90 DDDs	297 (13.5)	1944 (17.7)		0.72 (0.62 to 0.82)
91-365 DDDs	239 (10.9)	1334 (12.1)		0.84 (0.72 to 0.78)
>365 DDDs	216 (9.8)	996 (9.1)		1.00 (0.85 to 1.18)
Subtype				
Tolterodine	329 (15.0)	1978 (18.0)		0.77 (0.67 to 0.89)
Solifenacin	259 (11.8)	1486 (13.5)		0.82 (0.71 to 0.96)
Trospium	58 (2.6)	342 (3.1)		0.79 (0.59 to 1.05)
Fesoterodine	32 (1.5)	155 (1.4)		0.96 (0.65 to 1.43)



Note. Adjustment for education, diabetes, CVD, hypertension, dyslipidaemia, and CCI.

Figure 5 illustrates trends in polypharmacy prevalence from 2012 to 2022 by dementia status. For individuals with dementia, the prevalence of polypharmacy decreased from 65.1% (standardised 59.3%) in 2012 to 56.2% (standardised 51.6%) in 2022. In contrast, polypharmacy prevalence remained largely unchanged during the same period among individuals without dementia, at around 35%.

A similar time trend pattern was observed for CNS-active polypharmacy among individuals with dementia which declined from 15.0% (standardised 15.7%) in 2012 to 10.0% (standardised 10.1%) in 2022. The prevalence decreased from 3.5% in 2012 to 2.3% in 2022 among individuals without dementia.

Among individuals with dementia who experienced polypharmacy, the most frequently used pharmacological drug classes included medications for the treatment and prevention of cardiovascular diseases. For people with dementia experiencing CNS-active polypharmacy, antidepressants, opioids, and antipsychotics were the most commonly used CNS-active drug groups.

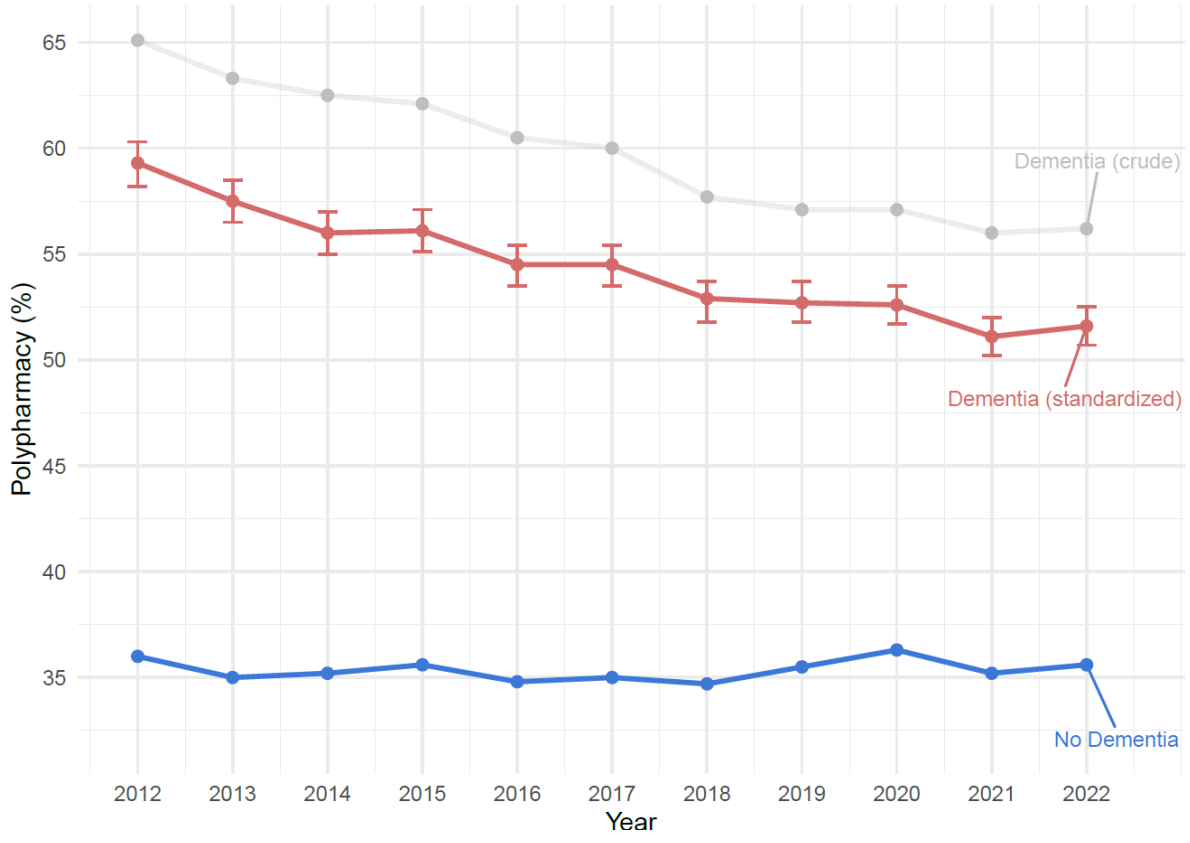
Among community-dwelling individuals, polypharmacy was more common in those with dementia (50.0%) compared to those without dementia (34.8%). In nursing homes, however, polypharmacy was less frequent in residents with dementia (64.8%) compared to those without dementia (73.8%). For CNS-active polypharmacy, the prevalences among people with and without dementia were 6.1% vs. 2.0% in community settings and 15.5% vs. 14.8% in nursing homes.

Table 5. Period prevalence proportion and odds ratios (OR) of polypharmacy in individuals with dementia compared to individuals without dementia reprinted from Pourhadi et al[108].

Dementia status	Prevalence %	Age/sex-standardised prevalence % (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Polypharmacy					
Dementia	56.2	51.6 (50.7-52.5)	2.32 (2.27-2.37)	1.62 (1.59-1.66)	1.47 (1.44-1.51)
No dementia	35.6	35.9 (35.8-36.0)	1	1	1
CNS-active polypharmacy					
Dementia	10.1	10.1 (9.5-10.7)	4.75 (4.58-4.92)	3.80 (3.66-3.94)	2.70 (2.59-2.81)
No dementia	2.3	2.3 (2.3-2.3)	1	1	1

Note. Model 1: Unadjusted. Model 2: Adjustment for age, sex, and education. Model 3: Additional adjustment for CCI score and psychiatric disorders.

Figure 5. Time trends of the crude and age-/sex-standardised prevalence of polypharmacy according to dementia status reprinted from Pourhadi et al[108].



Discussion

This research project identified associations between PPI use and opioid use respectively and an elevated risk of dementia before age 90 years. For bladder anticholinergics, an associated elevated dementia risk was found when compared with non-use, however, not when comparing to an active comparator, mirabegron. Additionally, the project highlighted a higher prevalence and increased adjusted odds ratio of polypharmacy and CNS-active polypharmacy among individuals with dementia compared to those without. The following section will discuss important study findings in detail and interpreting them within the context of existing literature.

KEY FINDINGS, INTERPRETATION, AND EXISTING RESEARCH

Proton pump inhibitors and dementia

This nationwide study observed PPI use to be associated with a higher rate of dementia before 90 years of age. The highest risk estimates were observed for the highest levels of cumulative exposure and among individuals diagnosed with dementia before age 70 years. Associations declined with older ages at dementia diagnosis. Increased dementia rates were observed regardless of timing of PPI initiation up to over 15 years before dementia diagnosis.

These findings align with previous and subsequent observational studies reporting positive associations between PPI use and dementia risk[6,43–46]. Specifically, two prior studies reporting age-specific associations similarly identified higher risk estimates at younger age at dementia diagnosis [43,44].

A recently published post hoc analysis of an American-Australian cohort of 18,934 individuals aged 65+ years reported no association between PPI use and incident dementia or markers of cognitive decline[109]. In that study, the maximum follow-up time after enrolment was seven years (compared to 19 years in the corresponding study of this project). Thus, that study was limited in studying long-term PPI use and the long-term association with dementia risk. Since dementia is mainly a slowly developing neurodegenerative disease, long follow-up time is fundamental to explore potential drug-related risk associations.

A study of Finnish registry data reported no clinically significant risk of Alzheimer's disease associated with PPI use[47]. Differences may lie in the narrower exposure period assessed in the Finnish study and not considering contributions from vascular cognitive decline due to its exclusive focus on Alzheimer's disease. Additionally, as with most previous studies on the topic, no stratification by age at dementia diagnosis was considered in the Finnish study. The observed variability in PPI-associated risk of dementia in this project indicates the relevance of accounting for age at diagnosis which may interact significantly with the association.

Dementia at different ages might represent distinct conditions with varying characteristics and risk profiles[110]. The stronger association observed among younger dementia cases could reflect a potential critical window of exposure or an age-dependent diminishing role of individual potential risk factors on prolonged neurodegeneration. However, potential causality remains uncertain as residual confounding cannot be ruled out. For instance, if unmeasured adverse lifestyle factors were differentially distributed based on exposure status and age[83]. Furthermore, while evidence of dose-response

relationships may support a potential causal link, it could also represent confounding effects, such as increased underlying indication bias with higher levels of exposure. Overall, the findings warrant further investigation, particularly to identify critical periods of PPI exposure and to discern whether the observed associations represent causality or pre-existing dementia risk among users of the medication.

Opioids and dementia

This nationwide study found no consistent association between cumulative opioid exposure limited to 90 TSDs and dementia risk. Cumulative exposure beyond 90 TSDs was associated with a modest increase in dementia rate before age 90. In sensitivity analyses, the association remained evident for exclusive use of weak opioids, in people with chronic non-cancer pain diagnoses, and in people finalising treatment five or more years before dementia diagnosis.

The findings align with previous and subsequent studies in the topic reporting opioid-associated increased risk of dementia in (1) a British population with chronic pain[111], (2) the Israeli general population[52], (3) a Taiwanese population with chronic pain[53], (4) a Korean population with chronic non-cancer pain[7], and (5) a Korean population with musculoskeletal pain using tramadol[112]. Study II in this project furthermore observed the association mainly to be confined to opioid exposure above 90 TSDs and dementia before 90 years, both for mixed opioid use and weak opioids only.

No significant association was found between opioids and Alzheimer's disease in a study based on the national Finnish registries[55]. This difference may be attributed to variations in opioid consumption, with Finland reporting significantly lower usage compared to its Scandinavian counterparts, where Denmark had the highest levels[113,114]. Additionally, that study had maximum 16 years of prescription records compared to 26 years in the corresponding study of this project. The extended follow-up period combined with Denmark's higher levels of opioid exposure makes it as a suitable setting for studying associations with dementia.

Considering the risk of impaired cognition related to opioid use, it may either unmask symptoms of underlying dementia pathology or mimic symptoms of dementia, which could be reversible when opioid treatment ceased[115]. Sensitivity analyses addressed the possibility of such false positive dementia diagnoses, and showed consistency in associations, also in individuals who had discontinued opioids more than five years before diagnosis.

It is possible that chronic pain or its related conditions contribute to the observed association between opioids and dementia as reflected in the analyses of individuals with chronic non-cancer pain. On the other hand, prior studies have reported an association between chronic pain and dementia but failed to account for the use of pain medications[116]. As such, it remains to be fully elucidated whether opioids play a mediating role in this relationship, warranting further investigation.

Bladder drugs and dementia

This nationwide study found anticholinergic bladder drugs to be associated with an elevated risk of dementia compared to non-use, but not compared to an active comparator of mirabegron. Subgroup analyses did not indicate significant differences among specific anticholinergic drug types. In comparison to non-use of bladder drugs, dementia rates were highest for use of bladder anticholinergics closest to the diagnosis.

These findings align with earlier research identifying an association between anticholinergic bladder drug use and dementia risk[117]. However, findings related to the active comparator differ from previous studies reporting a persisting association when comparing with mirabegron use[104,118,119]. Importantly, due to mirabegron being a relatively new bladder drug on the market, previous investigations were affected by limited data availability on its use.

A newly published UK-based study found increased rates of dementia for various bladder drug classes, including mirabegron[75]. However, the majority of mirabegron users in that study had prior exposure to bladder anticholinergics, complicating direct comparisons. In contrast, in Denmark, where both anticholinergic drugs and beta-3 agonists are prescribed as first-line therapies for overactive bladder, the study population allowed for a more balanced comparison utilising mirabegron as an active comparator[120]. Thus, differences in treatment practices, follow-up, and study designs likely contribute to differences in findings across the present and previous studies.

While earlier research suggested that anticholinergic drug subtypes might vary in their potential neurological side effects based on their ability to cross the blood-brain barrier, this study did not indicate significant differences in associated dementia risk[42,75,103,104]. This observation may point to other factors, such as the underlying bladder conditions necessitating treatment, rather than intrinsic drug-specific effects on cognition. The timing of drug exposure also appeared to play a role, with associated dementia risk being most pronounced when drug use occurred closer to diagnosis. This pattern may be affected by protopathic bias, where dementia-associated bladder symptoms led to treatment with anticholinergic bladder drugs. Alternatively, it could reflect short-term effects of these medications on cognitive function.

The lack of an association between anticholinergic bladder drugs and an increased risk of dementia when compared to mirabegron may suggest confounding by indication (lower urinary tract symptoms) when not applying an active comparator[56]. Meanwhile, increasing clinical caution around anticholinergics and physician prescribing patterns could also have affected the observed associations, with mirabegron being favoured for patients perceived to have higher dementia risk, such as frail patients or those with mild cognitive impairment[26,29,121–123]. Still, comparable characteristics between users of the two drug classes reduce the likelihood of this potential bias. Finally, while the long-term cognitive effects of beta-3 agonists remain unclear, both drug classes might contribute to dementia risk[124]. Studies with long follow-up are needed to investigate the cognitive safety profile of both bladder drugs classes.

Polypharmacy and dementia

This study demonstrated that in 2022, 56% of individuals with dementia had polypharmacy, and 10% had CNS-active polypharmacy, compared to 36% and 2% among those without dementia. After adjustment for covariates including comorbidities, the odds ratio of polypharmacy and CNS-active polypharmacy remained markedly higher in people with dementia. There was a declining time trend in prevalences of polypharmacy and CNS-active polypharmacy, which decreased from 65% and 15% in 2012, respectively.

The results align with earlier research reporting widespread but declining use of polypharmacy in older adults with dementia in Denmark between 2000-2015[65]. Comparable findings have been

observed in the US, where polypharmacy was driven by diverse medication classes, including sedatives and anticholinergics[125]. The present study expands on prior work by demonstrating a recent decade-long decline in polypharmacy among individuals with dementia in Denmark but continued disparity in medication burden compared to those without dementia.

The finding of highly prevalent CNS-active polypharmacy in individuals with dementia is consistent with a study based on 2018 data from the United States, where around 14% of older adults with dementia had CNS-polypharmacy, particularly with antipsychotics, antidepressants, and opioids[63]. Similarly, psychotropic polypharmacy was recently observed to be significantly widespread among Australians with dementia where opioids and antipsychotics were among most used medication types[64].

Several factors likely contributed to the observed decline in polypharmacy among individuals with dementia. Initiatives aimed at improving prescribing practices, including a national clinical guideline on dementia and medicine published in 2018 by the Danish Health Authority[72] may have raised awareness of medication risks particularly among vulnerable patient groups such as those with dementia thus, facilitating medication reviews.

Consistent with prior findings, individuals with dementia residing in nursing homes had a lower prevalence of polypharmacy in comparison to those without dementia[62]. This may be attributed to an increasing focus on non-pharmacological practices in dementia care[69] coupled with proactive deprescribing efforts[66,67]. Additionally, advanced dementia may result in the discontinuation of preventive therapies, lowering overall drug use, whereas nursing home residents without dementia often face health conditions unrelated to cognitive decline, contributing to higher polypharmacy rates. Despite these improvements, the persistently high prevalence of polypharmacy in dementia highlights the need for targeted research and interventions.

POTENTIAL MECHANISMS

All three drug classes, PPIs, opioids, and bladder anticholinergics, have abilities to cross the blood-brain barrier[103,126], allowing them to interact with the central nervous system. Many potential mechanisms have been hypothesised between these drugs and dementia, but the extent to which long-term exposure might influence cognition or neurodegenerative processes in humans remains unclear[30,38].

Listed neurological side effects of these drug classes reflect the potential of affecting the brain. For instance, PPIs have been associated with hearing, vision, and memory impairments[9]. In a randomised trial, short-term use of PPIs was linked to impairments of cognition[127]. Neurological side effects of opioid use include sedation, delirium, and impaired cognition[128]. Likewise, bladder anticholinergics can induce confusion, hallucinations, and memory dysfunction[129]. While these adverse reactions are generally believed to be reversible, the scarcity of evidence on sustained, chronic exposure raises concerns about possible cumulative or long-term influences on the brain.

Several potential mechanisms have been hypothesised through animal studies, experimental models, and autopsy findings. In mice, PPIs may increase β-amyloid accumulation[30], implicating pathways related to Alzheimer's disease. PPIs have been further hypothesised to decrease central acetylcholine levels by inhibiting the acetylcholine biosynthesising enzyme[31]. Moreover, prolonged

PPI use has been associated with vascular endothelial dysfunction, which could exacerbate cerebrovascular damage[32,34]. Autopsy studies in individuals with long-term opioid use or abuse have reported heightened β-amyloid and tau deposits[37,40], suggesting that opioids might contribute to neurodegeneration and neuroinflammation[41]. Meanwhile, anticholinergic bladder drugs may disrupt cholinergic signalling, a key process in cognition, and some subtypes appear to penetrate the blood-brain barrier more readily than others [41].

Crucially, specific mechanisms related to cognition and dementia remain poorly characterized, but these findings collectively point to potential pathways related to neurodegeneration, ranging from cholinergic dysregulation to inflammatory and vascular effects. Elucidating how these processes potentially interrelate in humans and whether some drugs pose higher neurological risks than others will require additional research e.g., by integrating long-term observational data and mechanistic studies.

Findings from the studies of this project underscore that timing of exposure including critical windows of exposure according to age could be of particular importance. Positive associations were observed even with large time gaps between exposure to PPIs and opioids respectively and dementia diagnosis. Thus, the possibility of long-term influences cannot be ruled out. In contrast, higher risk estimates observed among current users of bladder anticholinergics could reflect short-term effects on cognition, potentially through cholinergic dysfunction, but may also be influenced by protopathic bias.

It is essential to recognise that observational studies such as those included in this project cannot infer causation or directly identify biological pathways. Nevertheless, the findings contribute to our understanding of plausible pathways and factors that warrant further investigation.

STRENGTHS

A key strength of these studies lies in the utilisation of comprehensive, high-quality Danish national registries, which minimise both information and selection biases. Denmark offers an ideal setting for this research owing to its universal healthcare model ensuring equitable access to healthcare and prescription medications. Many validation studies have examined the accuracy of Danish registry data, significantly contributing to assessing the reliability and scientific validity of studies employing these registries[81,87,130].

The prescription registry ensures complete and reliable data on drug dispensations, enabling accurate exposure assessment. The inclusion of the entire nationwide population mitigates selection bias, ensuring a representative sample across diverse demographic and socioeconomic strata. Moreover, the large sample size allowed for the identification and analysis of homogeneous subpopulations in close alignment with the clinical target population of the drugs studied. For example, for non-cancer use of opioid, the target population specifically included individuals without cancer or opioid use disorder.

The relatively long follow-up periods in these studies provided an opportunity to investigate long-term associations between drug exposures and disease outcomes. Long-term associations are particularly important when investigating dementia as an outcome due to its long pre-clinical phase that potentially include symptoms which could alter prescription patterns and introduce bias[74]. Furthermore, the availability of

a broad range of variables, including demographic, socioeconomic, and health-related factors enabled adjustment for several relevant confounders.

Finally, the studies employed specifically tailored strategies to reduce bias and address understudied research questions and previous limitations. Application of lag-time windows, subpopulation analyses, active comparators, and stratified analyses of the exposure and outcome facilitated the conduct of these studies. Further details on these applied strategies are outlined in the following section.

LIMITATIONS AND ADDRESSING METHODOLOGICAL CONSIDERATIONS

This section discusses key limitations of the studies in this project, alongside important methodological considerations. Each limitation is critically evaluated in terms of its potential impact on the findings and interpretation, as well as strategies implemented to address these challenges. These include performing analyses to assess the impact of potential biases on the results. By providing a clear appraisal, this section aims to enhance understanding of the study findings while identifying areas for potential improvements in future research.

Detection of drug use

Medication exposure in these studies was derived from the Danish National Prescription Registry, which reliably captured all prescriptions dispensed in Denmark since 1995. However, prescriptions filled prior to 1995 were not recorded, leading to potential underestimation of cumulative drug exposure for long-term users who initiated therapy before the registry's inception. Moreover, prescription records do not confirm actual drug consumption, as individuals may not adhere to prescribed regimens. Similarly, although assumed to be minor, over-the-counter drug use was not captured, further contributing to potential exposure misclassification[131]. The inability to detect prescriptions prior to 1995 or over-the-counter drugs could lead to misclassification of true users as having shorter or no exposure, which might underestimate observed associations between drug use and dementia risk. Meanwhile, discrepancies between prescription filling and actual drug consumption could overestimate exposure by classifying actual non-users and users.

Despite the lack of pre-1995 prescription data, overall positive associations between medication use and dementia risk were observed. These findings suggest that the potential underestimation of exposure did not materially affect the overall interpretation. Furthermore, incorporating cumulative exposure metrics that tracked prescription refills throughout the study duration improved the likelihood of capturing actual drug use, particularly for consistent users with multiple refills, i.e., those with higher exposure levels. The individually selected study timeframes and specific age inclusion criteria were designed to additionally maximise the ability to accurately identify drug exposure within the study population.

Finally, in relation to polypharmacy, indications or appropriateness of drug use were not evaluated. Although adjustments were made for diagnoses of somatic and psychiatric comorbidities, the increased occurrence of polypharmacy among people with dementia might represent a greater burden of multimorbidity rather than inappropriate medication.

Reverse causation/confounding by indication

Reverse causation and confounding by indication are critical challenges in pharmacoepidemiologic studies exploring the relationship between drug use and dementia risk[78,80]. Reverse causation arises when early, undiagnosed dementia symptoms such as cognitive decline, behavioural changes, or secondary somatic symptoms lead to the initiation of specific medications. This temporal misalignment could suggest that drug use caused dementia when early dementia symptoms actually led to drug prescribing. Confounding by indication, in contrast, occurs when the underlying condition for which a drug is prescribed (e.g., chronic pain) independently affects the risk of dementia, thereby distorting the observed association. While these biases are distinct, they can coexist and complicate the interpretation of findings.

Potential reverse causation could have interfered with the associations investigated in study I-III. For example, individuals in the early stages of dementia might be prescribed bladder anticholinergics to manage urinary symptoms related to undiagnosed dementia, leading to the false impression that this medication increases dementia risk. Similarly, confounding by indication may have affected the association if the condition prompting drug use (e.g., chronic pain related conditions) is itself a risk factor for dementia. Thus, these biases can potentially obscure the true relationship between the exposure and outcome of interest.

The studies employed several strategies aiming at addressing such potential biases. First, an active-comparator design was utilised in study III where a non-anticholinergic bladder drug with the same indication, the beta-3 agonist mirabegron, served as the reference group. This mitigated bias by comparing drugs prescribed for the same clinical indication but with different mechanisms of action. Thus, reduces the likelihood of attributing dementia risk to the drug if it is actually driven by the underlying indication of drug use. A potential limitation of using such an active comparator is the lack of knowledge regarding its true association with dementia, which may affect the reliability of the comparator.

Studies I and II did not include active comparators due to the absence of valid pre-established comparators for the respective exposures. For instance, histamine type-2 receptor antagonists used to treat gastric acid related conditions have previously been associated with cognitive decline[76] and dementia[132]. Additionally, other non-opioid analgesics such as nonsteroidal anti-inflammatory drugs or antiepileptics used in pain management could serve as a comparison group in study II. However, these drugs are not prescribed for the same indications as opioids and their associations with dementia are uncertain.

Second, sensitivity analyses focused on specific subpopulations with an assumed lower probability of reverse causation/confounding by indication and evaluated the associations across different prescribing contexts. For instance, in study II, analyses restricted to those diagnosed with chronic pain conditions or individuals using weak opioids could reduce the likelihood of confounding by pain or by strong opioid use, respectively.

Lastly, analyses of the timing of drug exposure relative to dementia diagnosis were important in tackling reverse causation. Lag-time windows were applied to exclude drug use close to the dementia diagnosis, minimising the risk of capturing medication prescribed in response to early, undiagnosed dementia symptoms[85]. For instance, study III found that applying a five-year lag period compared with no lag attenuated the observed associations between bladder

anticholinergics and dementia, suggesting that recent exposure may have been reflective of prodromal dementia or actual short-term drug-related cognitive effects. On the other hand, in study II, opioid use discontinued more than five years before a dementia diagnosis remained positively associated with dementia risk, implying that short-term cognitive dysfunction of opioids was not the sole contributor to this relationship.

Nevertheless, while these strategies improve robustness of analyses, they cannot entirely eliminate the biases at hand, underscoring the need for continued refinement of methods and additional longitudinal research to better understand these associations.

Competing risk of death

Competing risks represent an inherent challenge in pharmacoepidemiologic studies using real-world data[133]. Specifically, competing risk of death prevents the occurrence of the primary outcome of interest i.e., dementia. This could affect the association if mortality is differentially distributed among exposed and unexposed.

Study I-III addressed this issue in sensitivity analyses exploring the potential of differential mortality according to exposure status. Users of PPIs, opioids, and bladder anticholinergics generally exhibited higher mortality rates compared to non-users, thereby reducing the probability of surviving long enough to receive a dementia diagnosis. While this could lead to an underestimation of the true associations with dementia, the observed positive associations across the studies suggest that the findings are not materially biased toward overestimation based on competing death risk. Therefore, the overall interpretation and conclusions were unlikely to be significantly impacted by this issue.

In the studies of this project, the primary objective was to explore the overall tendencies and directions of associations between drug exposures and dementia risk within relevant populations rather than estimating absolute risks of dementia while accounting for competing risk[133]. Nevertheless, future research could incorporate competing risk models to quantify the impact of this issue more precisely.

Dementia etiology and underdiagnosis

The validity of dementia syndrome diagnoses in national Danish registries is high, but the diagnostic accuracy for dementia subtypes (e.g., vascular dementia, Lewy body dementia, frontotemporal dementia) remained low during the study period[81]. The inability to differentiate reliably between dementia subtypes restricted stratified analyses, potentially obscuring subtype-specific associations that could provide greater biological insight. Such nuances cannot be systematically explored with all-cause dementia as the primary outcome. Accordingly, the study findings should be interpreted with this limitation in mind. The studies highlighted the need for future research incorporating valid data on dementia etiology, allowing for more detailed stratifications and enhanced understanding of drug-specific associations according to dementia subtypes.

Additionally, underdiagnosis of dementia in the population may result in some true cases being classified as non-cases, particularly in older populations and in early disease stages[134]. This could affect observed associations by misclassification. For example, it is conceivable that individuals with limited interaction with the healthcare system may both go undiagnosed and be less likely to receive the studied drugs. However, underdiagnosis was not assumed to substantially differ according to exposure,

thereby minimising its impact on the overall findings.

Residual bias

Although, the studies in this project applied strategies to mitigate bias, residual confounding is an inherent limitation arising from unmeasured factors in observational data. For instance, individuals prescribed the drugs of interest might systematically differ from non-users in ways that are not fully captured by registry data. Unmeasured variables included specific lifestyle factors (e.g., dietary habits, smoking, physical activity) and genetic predispositions, which were unaccounted for due to unavailability within the national Danish registries[82–84]. Additionally, healthcare-seeking patterns or physician-level prescribing practices such as a tendency to avoid certain drugs in older or frail patients could introduce bias by influencing both drug use and dementia risk. The latter is a particular important consideration for bladder anticholinergics and mirabegron. Heightened clinical caution regarding anticholinergics may have led to mirabegron being preferred for patients perceived with greater dementia risk, which could influence its validity as an active comparator[26].

Strategies to reduce residual confounding included restricting analyses to relevant homogenised subpopulations, active comparator design, and comprehensive adjustment for available confounders. Statistical models included key covariates such as comorbidities and sociodemographic factors. Some of these (e.g., hypertension or diabetes) could reflect downstream consequences of unmeasured adverse lifestyle factors, partially mitigating their influence. While it is not possible to fully eliminate residual confounding, these approaches can strengthen the robustness and support the interpretation of the findings. Continued refinement of methodologies and incorporation of additional data sources, such as subpopulation with available genetic or lifestyle information, could further reduce this limitation in future studies[82,83,134].

Generalisability

The generalisability of the study findings primarily applies to populations and healthcare systems similar to Denmark's. While the external validity may be limited for populations with vastly different healthcare systems or prescribing practices, the observed drug use patterns align with those reported in several other countries, providing a broader context for interpretation. For instance, over-prescribing of PPIs has not only been reported in Denmark, but also across Europe, North America, and Asia[13,15,135,136]. Additionally, while opioid use in Denmark during the study period was higher than in neighbouring Nordic nations[113,114], it was comparable to levels seen in other European countries such as the United Kingdom and Germany and approached those seen in North America[102,137].

The demographic profile of Denmark, characterised by an ageing population, is comparable to that of many Western countries and increasingly aligns with ageing Eastern nations[138]. With drug use patterns consistent with global trends, Denmark provides a relevant context for addressing these research questions. While this enhances the external validity of the findings, further studies across diverse populations and settings are essential.

IMPLICATIONS AND INTERVENTIONS

The findings from this thesis, while limited by the observational design and inability to establish causality, note the potential risks associated with widely prescribed medications,

including PPIs, opioids, and bladder anticholinergics[105,108]. While the evidence informing clinical implications must be solid, robust data on the long-term safety of these medications, particularly regarding dementia, remains scarce. Although the observed associations with dementia risk could be influenced by bias, thus cannot be interpreted as causal, they address the importance of caution in prescribing practices, as pharmacological products inherently carry risks of side effects. A potential adverse outcome as serious as dementia warrants careful consideration of the risk-benefit balance when initiating or continuing these medications.

Overprescription of certain medications, e.g., PPIs and opioids, have been reported globally, often extending beyond their recommended clinical indications[19,24]. This highlights opportunities for interventions to support prescribing practices. Initiatives and tools such as medication reviews, evidence-based guidelines, and increased awareness and education on the potential risks could support safer prescribing practices[139–142]. For instance, a newly published drug utilisation study reported a 35% decline in tramadol use in Denmark between 2019-2023 likely influenced by regulations and increased attention in media[143]. The relevance extends further into the context of polypharmacy, which is widespread among older adults with dementia. CNS-active polypharmacy is of particular concern, given the increased vulnerability to CNS-related side effects[60]. Addressing unnecessary polypharmacy in this population is essential, with evidence suggesting that regular medication reviews, nursing home initiatives, and the integration of non-pharmacological alternatives can help mitigate potential risks associated with these medications[66,67,69,139–142].

Pharmacological products should be reserved for situations with a clear indication, where the expected benefits exceed the potential risks. This process involves shared decision-making between the patient and the physician, tailored to the patient's unique circumstances and health profile.

Finally, these findings also highlight the need for further research to better understand the long-term safety profiles of these medications, particularly regarding cognition and dementia. A synergistic approach involving observational research, randomised trials, and mechanistic studies is essential for building a scientifically rigorous understanding of associations and causal pathways.

Conclusions and Perspectives

This research examined associations between commonly prescribed drugs, including PPIs, opioids, and anticholinergic bladder drugs, and dementia risk, along with polypharmacy patterns in dementia. The findings provide insight into previously hypothesised pharmacological risk factors for dementia and emphasise key areas for future investigation.

CONCLUSIONS

An association was observed between PPI use and elevated rates of dementia prior to age 90, with higher risk estimates for younger cases and higher cumulative exposures. Similarly, opioid exposure exceeding 90 TSDs was associated with modestly elevated dementia rates in individuals under 90. Associations persisted across subpopulations, including weak opioid users and individuals with chronic non-cancer pain diagnoses. These findings underline the potential importance of timing of the exposure and age at dementia diagnosis, necessitating further investigation.

Anticholinergic bladder drugs were associated with an increased dementia risk compared to non-use, with the highest rates for current users. However, no such association was observed when compared to mirabegron. The findings highlight the usefulness of employing an active comparator to address potential bias and call for further research into dementia-related safety profiles of both drug classes.

Finally, this project demonstrated higher prevalence and odds of polypharmacy and CNS-active polypharmacy among individuals with dementia compared to those without dementia. While these rates have declined over time, the findings underscore the continued importance of ensuring safer prescribing practices.

Collectively, the studies emphasise the need to further explore potential causality, investigate dementia subtype-specific risks, and assess critical exposure windows. Such insights can contribute to shaping clinical guidelines and safer medication use for individuals with and without dementia.

FUTURE RESEARCH

The findings of this project emphasise the need for further research to address critical gaps in understanding the relationships between exposure to the study drugs of interest and dementia risk. Ongoing monitoring of the long-term safety and efficacy of widely prescribed drugs, such as PPIs, opioids, and bladder anticholinergics, remains essential while also acknowledging the essential roles of the drugs in treating diseases and symptoms. It is crucial to investigate whether the observed associations signify causal relationships or arise from a predisposition to dementia in those prescribed the treatments. Observational studies using real-world data are instrumental in this regard, though their limitations must be recognised. Thus, further combination with mechanistic studies and randomised trials is important to provide a more complete understanding of potential drug effects on cognition and dementia.

Future studies should examine associations between the study drugs of interest and different dementia subtypes. Given the distinct neuropathological features of conditions like Alzheimer's disease and vascular dementia, these subtypes may have different associations with drug exposures. Often understudied, the timing

of drug use and potential critical exposure windows in relation to age at dementia diagnosis may interact significantly with the associations of interest thus, warrants further exploration. Such findings could help informing more precise clinical recommendations.

Studies in diverse populations and across different healthcare systems where prescribing practices vary can enhance generalisability. Moreover, combining registry data from multiple countries, for example within Scandinavian collaborations, presents an opportunity to enable more detailed analyses.

The combination of national registry data with cohort data on lifestyle-related factors could help tackle potential residual confounding from unmeasured variables in the Danish registries. Furthermore, prioritising the use of active comparators when feasible, and rigorously evaluate their validity is important to mitigate and evaluate the impact of bias on study findings.

Given the high prevalence of polypharmacy, particularly CNS-active polypharmacy, among individuals with dementia, it is important to refine and investigate strategies to optimise prescribing practices. Finally, since the study drugs of interest potentially pose risks on brain health, future studies should additionally evaluate exposure to these drugs among individuals with dementia particularly in relation to disease progression, mortality, or hospitalisation.

As such, future research should build upon the findings of this project by integrating diverse approaches to advance the understanding of drug-related dementia risks and supporting safer prescribing practices.

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Appendix | Journal Articles

Study I Pourhadi N, Janbek J, Jensen-Dahm C, Gasse C, Laursen TM, Waldemar G. Proton pump inhibitors and dementia: A nationwide population-based study. Alzheimer's & Dementia. 2024;20(2):837-845. https://doi.org/10.1002/alz.13477

Study II Pourhadi N, Janbek J, Gasse C, Laursen TM, Waldemar G, Jensen-Dahm C. Opioids and Dementia in the Danish Population. JAMA Network Open. 2024;7(11):e2445904. https://doi.org/10.1001/jamanetworkopen.2024.45904

Study III Pourhadi N, Janbek J, Gasse C, Munk Laursen T, Meaidi A, Jensen-Dahm C, Waldemar G. Bladder drugs and the risk of dementia: Danish nationwide active-comparator study. BMJ Medicine 2025;4:e001125. https://bmjmedicine.bmj.com/content/4/1/e001125

Study IV Pourhadi N, Jensen-Dahm C, Munk Laursen T, Gasse C, Waldemar G, Janbek J. Polypharmacy in people with dementia: a nationwide Danish study. 2025 (Submitted)

STUDY I

Proton Pump Inhibitors and Dementia: A Nationwide Population-Based Study

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RESEARCH ARTICLE

Proton pump inhibitors and dementia: A nationwide population-based study

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Abstract

INTRODUCTION: Proton pump inhibitors (PPIs) may increase dementia risk. However, it is currently unknown whether timing of exposure or age at dementia diagnosis influence the risk.

METHODS: We assessed associations between cumulative PPI use and dementia at different ages in a nationwide Danish cohort of 1,983,785 individuals aged 60 to 75 years between 2000 and 2018.

RESULTS: During follow-up, there were 99,384 all-cause dementia incidences. Incidence rate ratio (IRR) of dementia with PPI ever-use compared with never-use was 1.36 (95% CI, 1.29 to 1.43) for age 60 to 69 years at diagnosis, 1.12 (1.09 to 1.15) for 70 to 79 years, 1.06 (1.03 to 1.09) for 80 to 89 years, and 1.03 (0.91 to 1.17) for 90+ years. Longer treatment duration yielded increasing IRRs. For cases below 90 years, increased dementia rate was observed regardless of treatment initiation up to >15 years before diagnosis.

DISCUSSION: Regardless of timing of treatment initiation, PPI use was associated with increased dementia rate before age 90 years. Dementia rates increased with younger age at diagnosis.

KEYWORDS
Alzheimer's disease, dementia, pharmacoepidemiology, proton pump inhibitor, risk factor

Highlights

- After following 1,983,785 individuals for a median of 10 years, 99,384 developed dementia
- PPIs were used by 21.2% of cases and 18.9% of controls
- PPI use was associated with increased dementia rate regardless of time of treatment onset
- Magnitude of associations increased with younger age at diagnosis
- PPI use was not associated with dementia occurring after age 90 years

1 | BACKGROUND

Worldwide, around 55 million people live with dementia, and with 10 million new cases annually, this number is expected to increase considerably due to an aging world population, making the disease and its consequences a major global public health challenge.[1] Recognizing potential modifiable risk factors for dementia is of high priority.[1]

Proton pump inhibitors (PPIs) suppress acid production in the stomach and are used to treat gastric acid-related conditions such as peptic ulcers and gastroesophageal reflux disease. Worldwide, the use of PPIs has increased rapidly over the last two decades, particularly among adults aged 40 years and above.[2–6] In Denmark, the total PPI use increased sixfold between 2000 and 2021.[7] Studies reported overprescription of PPIs in both primary and secondary care with around 50% of prescriptions not being accompanied with valid indications for treatment.[8–10]

PPIs pass through the blood-brain barrier[11] and their use has been associated with neurological adverse reactions such as migraine, peripheral neuropathies, and impairment of hearing, vision, and memory.[12–14] A recent study showed that PPIs potently and selectively inhibit the enzyme responsible for biosynthesis of the neurotransmitter acetylcholine (choline-acetyltransferase), and thereby may inhibit neuronal signaling in the brain.[15]

In mice, PPIs increased brain beta-amyloid levels,[16] and thus may be involved in the pathological process of development of Alzheimer's disease (AD).[17] However, whether this applies to humans and leads to dementia is currently unknown.

Previous studies investigating the association between PPIs and risk of dementia reported conflicting findings with some studies reporting a positive association,[18–21] while other studies showed a negative or neutral association.[22–24] This could possibly be owing to the heterogeneity between data availability and study design.[25]

Although not specifically designed to investigate risk differences according to age at dementia diagnosis, two previous studies observed greater risk estimates among the youngest cases of dementia compared to older cases.[18,20] However, most previous studies did not take this into account,[19,21–24] and thus, the association between PPI use and dementia risk in relation to age at dementia diagnosis remains largely unexplored.

Furthermore, the majority of studies did not consider the timing of PPI use according to dementia diagnosis, and many did not apply latency windows between the exposure and outcome. Both factors are important when assessing a slowly progressing disease such as dementia in order to reduce reverse causation/protopathic bias.[26]

In this nationwide population-based study addressing previously understudied aspects of the association between PPI use and dementia risk, we aimed to assess the influence of age at dementia diagnosis, and timing of PPI use according to the diagnosis.

RESEARCH IN CONTEXT

1. **Systematic review**: The existing literature on PPI use and risk of dementia is inconsistent with previous observational studies reporting conflicting findings. Most studies did not differentiate by age at diagnosis or consider the timing of exposure to PPI according to the diagnosis.
2. **Interpretation**: Our study based on highly valid real-world data from Denmark found that PPI use, regardless of timing of treatment initiation, was associated with increased risk of all-cause dementia before age 90 years. We consistently observed higher dementia rates with younger age at dementia diagnosis.
3. **Future directions**: Results from our data contribute with evidence highlighting age at dementia diagnosis to interact substantially with the association between PPI use and dementia risk. The increasing body of evidence related to potential serious adverse effects of PPIs call for scientific attention. Mechanistic studies are warranted to investigate the link between PPIs and cognition, and the interaction with age.

2 | METHODS

2.1 | Study population and design

We identified a nationwide cohort of Danish residents aged 60 to 75 years in year 2000 or turning 60 years between 2000 and 2018. Exclusion criteria were registration of a dementia diagnosis (since 1977) or treatment with a dementia-specific drug (since 1995) before study entry. To ensure sufficient information on previous medication use, we did not include individuals who immigrated to Denmark after 1995 (the initial year of prescription data availability). Included individuals were followed from January 1, 2000, or their 60th birthday, whichever came later, for up to 19 years until first onset of dementia, emigration, death, or December 31, 2018, whichever came first. The study population was established by linking the following nationwide Danish registers: (1) the National Patient Registry,[27] (2) the Danish Psychiatric Central Research Registry,[28] (3) the Danish National Prescription Registry,[29] and (4) the Danish Education Registry[30] (Table S1). All the registers included a pseudonymized unique personal identification number assigned to all residents in Denmark, permitting unambiguous linkage of data on the individual level.[27]

Within the nationwide cohort, we nested a case-control population comprising all cases of dementia that occurred during follow-up, each matched with a set of control individuals sampled from the cohort. On the date of dementia incidence (index date), each dementia case was matched to five dementia-free controls of the same sex and birth year (ie, age) through incidence density sampling.[31]

2.2 | Outcome

The primary outcome of interest was late-onset all-cause dementia (defined as dementia of any etiology from age 60 years). An individual was considered to have dementia either from the date of first dementia diagnosis or first redemption of a dementia-specific drug (Table S1). In Denmark, dementia is typically diagnosed in hospital memory clinics, enabling identification of cases through diagnoses from the National Patient Registry, providing data on all diagnoses given in Danish

hospitals since 1977.[27] The validity of dementia syndrome diagnoses in Danish hospital registers is high.[32] Prescriptions with dementia-specific medication (for Alzheimer's disease, Lewy body dementia, and Parkinson's disease dementia) from the National Prescription Registry allow for identification of cases diagnosed and managed in primary care.[29] The age at dementia diagnosis/index date was grouped in 10-year age groups (60 to 69 years; 70 to 79 years; 80 to 89 years; 90+ years).

2.3 | Exposure

Information on PPI use (Anatomical Therapeutic Chemical Classification System [ATC] code A02BC) in the nested case-control population was obtained from the Danish National Prescription Registry, holding complete data on all prescriptions redeemed from pharmacies in Denmark since January 1995. Prescriptions included the ATC-code, date of purchase, package size, unit size, and number of purchased packages.

In Denmark, PPIs are primarily used through prescriptions (only around 2% of the total PPI use in the study period was bought over-the-counter[7]).

Five-year exposure lag time windows before index date (ie, omitting any prescriptions of PPI between the date of dementia diagnosis/matching and 5 years prior) was consistently applied to diminish reverse causation bias[26] (ie, reducing the confounding impact of potential changes in prescription patterns of PPI in the prodromal stages before dementia diagnosis).

A PPI user was defined as an individual who redeemed at least two prescriptions of PPI between 1995 and the beginning of the lag time window. Individuals only redeeming one prescription were categorized separately. PPI subtypes have different potencies and thus, different recommended daily dosages. Therefore, cumulative exposure to PPIs (whether continuous or discontinuous) was calculated as the total number of defined daily doses (DDDs) redeemed from prescriptions between January 1, 1995, until 5 years before the dementia incidence or matching. DDDs were calculated from prescription information on the quantity of purchased PPI (Table S2). Timing of treatment according to dementia diagnosis was computed as the time between the date of first PPI prescription and the index date.

2.4 | Confounding variables

Age, sex, and highest attained educational level (low; medium; high) were considered demographic and socioeconomic confounders. Health-related confounders included (1) the presence of cardiovascular disease (CVD) defined as a diagnosis of stroke, the presence of ischemic heart disease including acute myocardial infarction, or use of oral antithrombotic medication including anticoagulants; (2) diabetes mellitus type 1 or 2 defined from diagnoses or use of antidiabetics; (3) hypertension defined from diagnoses or use of antihypertensive drugs; and (4) dyslipidemia defined from diagnoses or use of statins. The health-related confounders were included since they are acknowledged risk factors for dementia[33,34] as well as associated to use of PPI.[35] Variables were assessed at the beginning of the lag time window. Exact definitions of covariates are shown in Table S1.

2.5 | Statistical analysis

We applied conditional logistic regression with categorical variables on the matched case-control population and calculated adjusted incidence rate ratios (IRRs) with 95% confidence intervals (CIs) for the associations between PPI use and dementia according to age on index date. PPI never-users constituted the reference group in all analyses. Associations between ever-use of PPI (at least two prescriptions) as well as cumulative treatment duration (categorized as ≤3 months; >3 to 12 months; >12 to 36 months; >36 months) and all-cause dementia were assessed. Additionally, association between timing of treatment initiation (ever-use) according to index date and all-cause dementia was assessed. The timing of PPI initiation was categorized as follows: (1) within 5 years of index; (2) >5 to 10 years before index; (3) >10 to 15 years before index; and (4) >15 years before index. For the PPI initiation subcategory of within 5 years of index, the 5-year lag time window was not applied.

All models included the above-mentioned confounding variables as covariates. For educational level, <2% of the population had missing information, and thus were categorized separately as "unknown". Information on all the remaining confounders was available for all included individuals. Data were analyzed and categorized using SAS software version 9.4 (SAS Institute) and R statistical software (R Core Team, 2020).[36]

2.6 | Sensitivity analyses

To test for the robustness of results, sensitivity analyses in three separate subpopulations were performed as follows: (1) association between PPI use and dementia in a subpopulation restricted to individuals with a Charlson Comorbidity Index[37] (CCI) score of zero (dementia and peptic ulcer disease were excluded from CCI definition) in order to test for associations among individuals expected to have a relatively low burden of chronic somatic comorbidity; (2) association between PPI use and dementia in a subpopulation restricted to individuals without stroke, since stroke could potentially be an intermediary on the causal pathway between PPI use and dementia[38]; and (3) association between PPI use and dementia in a subpopulation restricted to individuals aged 60 to 65 years in 2000, where all included individuals had similar circumstances of exposure to PPI (in terms of age and calendar time) as well as prescription data availability used to measure the exposure.

An additional sensitivity analysis tested the association between each PPI subtype and dementia.

All main analyses were repeated with 2-year lag time and without lag time instead of the standard 5-year lag time window.

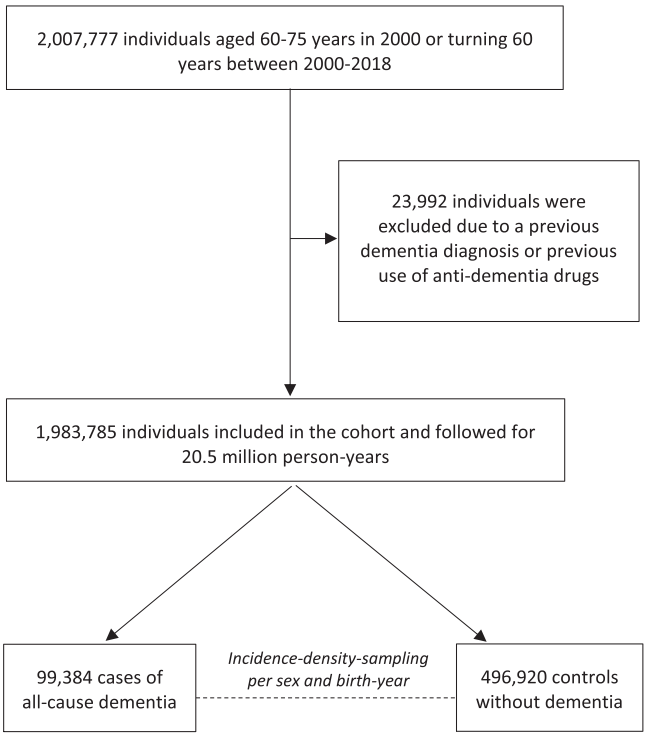

FIGURE 1 Flowchart of the establishment of the cohort and nested case-control population. During follow-up, 486,312 individuals were censored due to emigration ($n = 11{,}970$) or death ($n = 474{,}342$).

To test for potential competing risk of death among users of PPI, an analysis estimating the association between PPI use and mortality rate was performed (ever-use vs never-use).

3 | RESULTS

The nationwide cohort included 1,983,785 eligible individuals followed for a total of 20.5 million person-years with a median (first-third quartile) follow-up time of 10.3 years (5.1 to 15.6 years). During follow-up, there were 99,384 (5.0%) incidences of all-cause dementia. The establishment of the cohort and nested case-control population is shown in Figure 1. Among all dementia cases, 55.4% were women, and the median age at time of diagnosis was 79 years (74 to 83 years) for women and 77 years (72 to 82 years) for men. Characteristics of cases and their matched controls are specified in Table 1.

Users of PPIs (at least two prescriptions) comprised 21.2% of dementia cases and 18.9% of controls, while 7.4% of cases and 7.1% of controls redeemed one prescription only. The median age at first PPI prescription was 68 years for both cases and controls.

Figure 2 reports adjusted IRRs of all-cause dementia according to ever-use and cumulative use of PPI stratified by age groups at index. Ever-use of PPI was associated with an increased IRR of all-cause dementia occurring before age 90 years ranging from IRR 1.36 (95% CI, 1.29 to 1.43) among cases 60 to 69 years old on index to IRR 1.06 (1.03 to 1.09) among cases 80 to 89 years old on index. Increasing treatment duration of PPI yielded increasing IRRs in a duration-response manner. Overall, associations reduced consistently with older age at dementia diagnosis, and were neutral among those aged 90+ years at diagnosis.

Regardless of timing of treatment initiation up to >15 years before index, ever-use of PPI was associated with an increased rate of dementia occurring before age 90 years (Figure 3). No category of timing of treatment initiation was associated with dementia after age 89 years.

TABLE 1 Characteristics of nested case-control population.

	All-cause dementia (n=99,384)	Controls (n=469,920)
Sex: Female	55,105 (55.4)	275,525 (55.4)
Age at index (years, median)	78 (73.0 to 82.6)	78 (73.0 to 82.6)
Follow-up (years, median)	11.1 (7.0 to 14.8)	18.2 (14.1 to 19.0)
Year of diagnosis (median)	2012 (2008 to 2015)	–
Cardiovascular disease (CVD)	43,006 (43.3)	185,950 (37.4)
Stroke	7333 (7.4)	22,046 (4.4)
IHD/AMI	17,819 (17.9)	79,482 (16.0)
OAT/OAC	39,082 (39.3)	168,999 (34.0)
Diabetes	10,482 (10.5)	38,418 (7.7)
Hypertension	61,763 (62.1)	288,986 (58.2)
Dyslipidemia	28,065 (28.2)	126,799 (25.5)
Educational level		
Low	51,218 (51.5)	246,521 (49.6)
Medium	34,009 (34.2)	172,612 (34.7)
High	12,493 (12.6)	69,039 (13.9)
Unknown	1664 (1.7)	8748 (1.8)
PPI user (2+ prescriptions)	21,049 (21.2)	93,751 (18.9)
Age at treatment initiation (years, median)	68 (62 to 73)	68 (63 to 73)
Duration of treatment (months, median)	3.7 (0.9 to 21.2)	3.6 (0.9 to 18.6)
One prescription only	7350 (7.4)	35,064 (7.1)

Note. Values are shown either in 'number of individuals (%)' or 'median (first-third quartile)'. Shown numbers of PPI use include 5 years lag time window. Abbreviations: AMI, acute myocardial infarction; CVD, cardiovascular disease; IHD, ischemic heart disease; OAT, oral antithrombotic medication; OAC, oral anticoagulants; PPI, proton pump inhibitor.

3.1 | Sensitivity analyses

In a subpopulation of individuals with a CCI score of zero, estimates of PPI use and dementia generally reduced compared to those of the main population, but overall associations with dementia occurring before age 80 years remained stable (Figure S1). Results remained robust in sensitivity analyses assessing the association between PPI use and all-cause dementia in (1) a subpopulation of individuals without stroke

Duration of PPI use	N cases (%)	N controls (%)	Adjusted IRR (CI_{95})
60–69 years at index			
No use	11,257 (77.3)	60,278 (82.5)	Ref
Ever use	2387 (16.4)	8613 (11.8)	1.36 (1.29–1.43)
<=3 months	743 (5.1)	3007 (4.1)	1.25 (1.14–1.36)
>3–12 months	676 (4.6)	2579 (3.5)	1.31 (1.20–1.44)
>12–36 months	470 (3.2)	1574 (2.2)	1.45 (1.30–1.62)
>36 months	498 (3.4)	1453 (2.0)	1.59 (1.43–1.78)
70–79 years at index			
No use	34,543 (75.0)	179,168 (77.7)	Ref
Ever use	8446 (18.3)	36,833 (16.0)	1.12 (1.09–1.15)
<=3 months	2493 (5.4)	11,184 (4.8)	1.11 (1.06–1.16)
>3–12 months	2469 (5.4)	11,133 (4.8)	1.09 (1.04–1.14)
>12–36 months	1653 (3.6)	7061 (3.1)	1.14 (1.08–1.20)
>36 months	1831 (4.0)	7455 (3.2)	1.17 (1.11–1.24)
80–89 years at index			
No use	24,340 (65.6)	124,210 (67.1)	Ref
Ever use	9655 (26.0)	45,469 (24.6)	1.06 (1.03–1.09)
<=3 months	2446 (6.6)	11,953 (6.5)	1.03 (0.98–1.08)
>3–12 months	2649 (7.1)	13,027 (7.0)	1.02 (0.97–1.06)
>12–36 months	2052 (5.5)	9267 (5.0)	1.10 (1.04–1.15)
>36 months	2508 (6.8)	11,222 (6.1)	1.10 (1.05–1.15)
90+ years at index			
No use	845 (52.7)	4449 (54.9)	Ref
Ever use	561 (35.0)	2836 (35.0)	1.03 (0.91–1.17)
<=3 months	113 (7.0)	588 (7.3)	1.01 (0.81–1.26)
>3–12 months	167 (10.4)	783 (9.7)	1.14 (0.94–1.37)
>12–36 months	119 (7.4)	554 (6.8)	1.12 (0.90–1.40)
>36 months	162 (10.1)	911 (11.2)	0.90 (0.75–1.09)

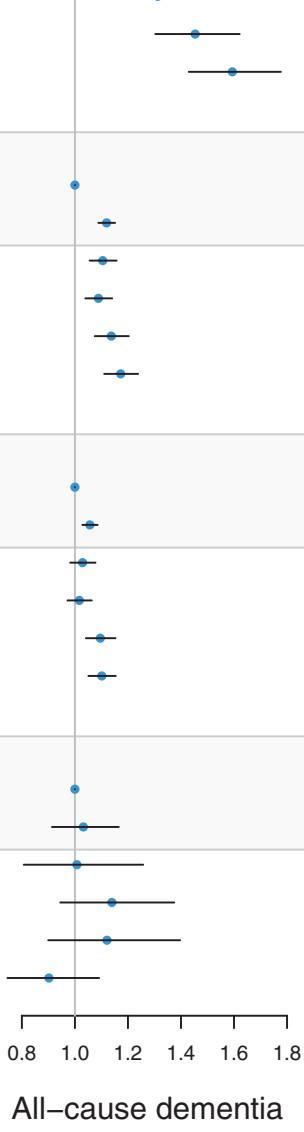

FIGURE 2 Adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CIs) of the association between cumulative duration of proton pump inhibitor (PPI) use and all-cause dementia. Adjustments were made for educational level, cardiovascular disease, diabetes, hypertension, and dyslipidemia, with a 5-year lag time window applied. Estimates for "one prescription only" are not shown.

(Figure S2), as well as in (2) a subpopulation of individuals aged 60 to 65 years in year 2000 (Figure S3).

Ever-use of each PPI subtype yielded comparable results with elevated rates of dementia before age 80 years (Figure S4).

In an analysis estimating competing risk of death, ever-use of PPI was associated with an increased rate of death, adjusted IRR 2.24 (2.22 to 2.25).

Associations remained largely unchanged in sensitivity analyses with no lag time and with a 2-year lag time instead of a 5-year lag time.

4 | DISCUSSION

In this real-world population-based case-control study nested in a nationwide cohort of individuals aged 60 to 75 years in 2000 to 2018, PPI use was associated with an increased rate of all-cause dementia before age 90 years. Associations displayed a duration-response pattern and were largest among the youngest cases of dementia (age 60 to 69 years at diagnosis) and decreased with advancing age at diagnosis. Initiation of treatment with PPI up to >15 years prior to diagnosis

PPI initiation according to index	N cases (%)	N controls (%)	Adjusted IRR (CI_{95})
60–69 years at index			
No use	9199 (63.1)	53,367 (73.1)	Ref
<=5 years before index*	1656 (11.4)	4992 (6.8)	1.79 (1.69–1.91)
>5–10 years before index	1105 (7.6)	3753 (5.1)	1.56 (1.46–1.68)
>10–15 years before index	778 (5.3)	2972 (4.1)	1.39 (1.28–1.52)
>15 years before index	504 (3.5)	1888 (2.6)	1.44 (1.30–1.60)
70–79 years at index			
No use	28,492 (61.8)	153,834 (66.7)	Ref
<=5 years before index*	4924 (10.7)	19,561 (8.5)	1.31 (1.27–1.36)
>5–10 years before index	3564 (7.7)	15,562 (6.7)	1.16 (1.11–1.21)
>10–15 years before index	2927 (6.4)	12,365 (5.4)	1.21 (1.16–1.26)
>15 years before index	1955 (4.2)	8906 (3.9)	1.11 (1.06–1.17)
80–89 years at index			
No use	19,721 (53.1)	102,068 (55.1)	Ref
<=5 years before index*	4097 (11.0)	18,447 (10.0)	1.13 (1.09–1.17)
>5–10 years before index	3399 (9.2)	16,042 (8.7)	1.07 (1.03–1.11)
>10–15 years before index	3328 (9.0)	15,677 (8.5)	1.07 (1.02–1.11)
>15 years before index	2928 (7.9)	13,750 (7.4)	1.08 (1.03–1.12)
90+ years at index			
No use	697 (43.5)	3692 (45.5)	Ref
<=5 years before index*	139 (8.7)	672 (8.3)	1.08 (0.88–1.33)
>5–10 years before index	154 (9.6)	788 (9.7)	1.03 (0.85–1.25)
>10–15 years before index	170 (10.6)	844 (10.4)	1.08 (0.90–1.31)
>15 years before index	237 (14.8)	1204 (14.9)	1.01 (0.85–1.19)

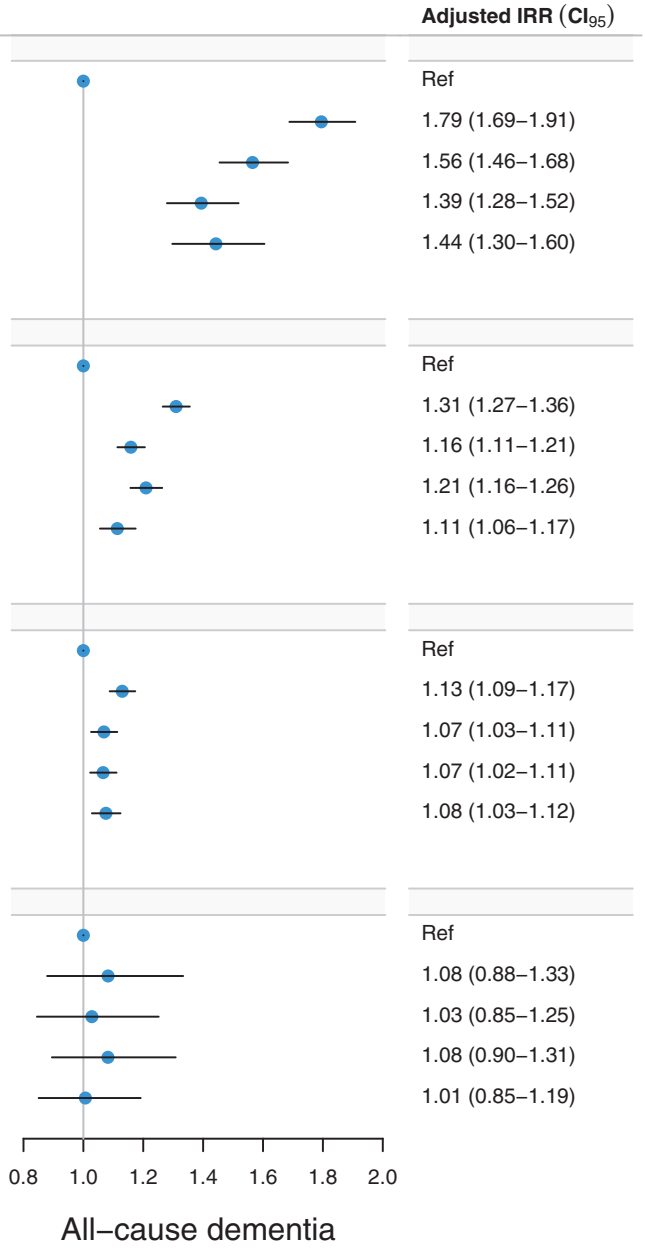

FIGURE 3 Adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CIs) of the association between timing of initiation of proton pump inhibitor (PPI) use and all-cause dementia. Adjustments were made for educational level, cardiovascular disease, diabetes, hypertension, and dyslipidemia. Asterisks (*) denote that for the category of "<= 5 years before index" there was no 5-year lag time window applied, whereas a 5-year lag time window was applied for all other categories. Estimates for "one prescription only" are not shown.

was associated with an increased dementia rate. PPI use showed risk estimates close to unity for dementia occurring in age 80 to 89 years, and no association was observed for dementia occurring from age 90 years. Sensitivity analyses supported the overall findings.

In line with recent observational studies, we found an increased rate of dementia with PPI use.[18–21] Our findings of larger associations with dementia occurring in earlier ages are consistent with two previous studies that stratified by age at dementia diagnosis.[18,20] In contrast, a study based on national Finnish registers by Taipale et al. reported no clinically meaningful association between PPIs and AD.[23] In that study, individuals had a maximum of 17 years of available exposure history compared to 24 years in our study. Since only AD cases were included, potential increased risk of vascular cognitive decline cannot be ruled out.

We observed that the age at dementia diagnosis interacted significantly with the association of interest, that is, the magnitude of the effect of PPI use on dementia rate differed depending on this variable. Previous studies that reported no association between PPIs and dementia, including Taipale et al., did not stratify by age at dementia diagnosis.[22,23] Thus, potential risk differences according to age at diagnosis were not accounted for and may therefore explain the differences between study findings.

Our finding of higher risk estimates for PPI initiation closest to dementia diagnosis could represent an acceleration of dementia neuropathology related to PPI use, but these results are more likely influenced by reverse causation. Nevertheless, PPI initiation up to >15 years before dementia diagnosis consistently yielded increased dementia rates before age 90 years, potentially indicative of a long-acting influence of PPIs on the brain in congruence with underlying neurobiological processes leading to dementia which expectedly progress gradually over decades.[39]

A study by Friesen et al. based on registers from one Canadian province followed three cohorts with different age groups at study start and found highest risk estimates for dementia with PPI use in the youngest cohort (start age 46 to 55 years).[24] Although the authors did not stratify by age at dementia diagnosis, this aligns with our study results displaying higher dementia rates occurring at a younger age. Overall, Friesen et al. reported no consistently increased dementia risk with PPI use. However, while the highest cumulative dose category of PPI use in Friesen et al. was >180 DDDs, corresponding to about >6 months' duration, we assessed longer duration intervals up to >36 months (>1095 DDDs). Considering our observation of the largest associations with long-term PPI use, further stratification of cumulative PPI use in Friesen et al. may have yielded different results.

The observed association between cumulative PPI exposure and increased dementia rate may be explained by PPI-related impacts on cognition, for example, through neurodegeneration and/or cerebrovascular damage.[15,16,40] One clinical trial found impairment in different cognitive domains among individuals randomized to short-term PPI use.[13] PPIs can affect brain cells through various mechanisms, for example, by increasing beta-amyloid levels, involved in the development of AD.[16] Long-term exposure may additionally increase vascular dysfunction by impairing endothelial function,[40] thereby accelerating the progression of cerebrovascular damage potentially leading to vascular dementia. Listed side-effects of PPI use include neurological, psychological, and psychiatric symptoms/conditions.[12,14] Although the mechanisms of these side effects have not been fully described, they suggest non-negligible effects on the nervous system related to PPI use. Mechanistic studies are needed to investigate the potential link between PPI use and cognition. Furthermore, future studies should explore if the potential PPI-associated risk of dementia varies across dementia subtypes.

The association between PPI use and dementia was unambiguously largest among the youngest cases of dementia, potentially suggestive of a critical window of exposure where midlife PPI use affects dementia risk to a larger degree compared to late-life use. Further, the finding could signify a declining impact of individual risk factors with advancing age owing to lengthy ongoing neuropathological processes. Arguably, dementia occurring at different ages can be considered different diseases in terms of characteristics and risk factors.[41] Whether the finding is causal has yet to be determined.

Residual confounding factors could still have impacted the results, especially if unmeasured risk factors for dementia (eg, lifestyle-related) were more prevalent in PPI users compared to non-users, and if such potential differences between exposed and unexposed participants were more pronounced in the younger age groups compared to the older age groups.

The sensitivity analysis restricted to individuals with a CCI score of zero aimed at reducing confounding from somatic comorbidity. Though the associations to some extent decreased in magnitude, the overall findings remained stable, indicating that the observed association was not entirely explained by somatic comorbidity as defined in the CCI.

Nevertheless, based on our real-world data consistently showing the highest PPI-associated dementia risk among the youngest cases of dementia, we have identified age at diagnosis as an important effect-modifier. This influence should be investigated in future studies, especially as to whether it translates to a critical window of exposure which could shape the basis for future guidelines and interventions. In the context of PPIs being among the most prescribed drugs worldwide and with high prevalence of inappropriate use, further elucidation of long-term safety in relation to dementia as well as interventions promoting appropriate use is an important public health matter.[2–6,8–10]

Strengths of the study include the large nationwide study population, long follow-up period, highly valid dementia diagnoses,[32] extensive details on cumulative exposure to PPI based on redeemed prescriptions, and information on confounding factors. These strengths were important to reliably investigate the research question of interest.

This study had limitations. First, data on prescriptions before 1995, over-the-counter use, and in-hospital intravenous use of PPI throughout the study period were not available, leading to underestimating PPI use in the cohort and possible misclassification of PPI users as non-users, resulting in possible bias toward the null. However, PPI use before 1995 as well as over-the-counter use and intravenous use was relatively limited; thus, we do not consider this limitation to have impacted the interpretation or generalizability of our findings.[7] Our study period and age-restrictions were chosen to enhance detectability of exposure among cohort members. Additionally, PPI users had a higher mortality rate compared to non-users. This competing risk of death further diluted the association between PPI use and dementia. However, since our main finding was increased risk, we do not expect the competing death risk to have impacted the overall interpretation.

Second, we could not differentiate between vascular dementia and neurodegenerative etiologies of dementia due to low validity of non-AD subtype diagnoses.[32] Considering the previously reported positive association between PPI use and risk of stroke,[38] the observed association with all-cause dementia could be reflecting the association with stroke. However, the sensitivity analysis restricted to individuals without stroke supported the main results, making it improbable that our findings are entirely explained by stroke as an intermediary on the causal pathway.

Third, dementia is underdiagnosed in the general population, but we do not expect potential under-registered dementia diagnoses to be differentially distributed among exposed and non-exposed, and thus should not impact the external validity of our findings. This study was based on national Danish registers and is therefore generalizable to populations with similar demographics and healthcare. Nonetheless, increasing and inappropriate PPI use has been reported in both West-

ern and Eastern countries with rates comparable to those of the Danish population, making Denmark a relevant research setting for the aim of our study.[2–6,8–10]

Finally, we cannot exclude residual confounding by indication particularly among long-term PPI users. Although labelled indications for PPIs are not known to be associated with dementia, these individuals may have a higher prevalence of unmeasured factors related to dementia risk such as obesity and smoking.[42] Danish healthcare registers do not hold information on lifestyle factors and therefore these could not be taken directly into account.[43] Nonetheless, we adjusted for important consequences related to unhealthy lifestyle, for example, hypertension, dyslipidemia, diabetes, and CVD. Although we included several potential confounders and greatly limited reverse causation with 5-year lag windows, biases from residual confounding cannot be ruled out. Still, the results remained robust in sensitivity analyses aiming at reducing potential confounding.

In conclusion, exposure to PPIs was found to be associated with an increased rate of all-cause dementia occurring before 90 years of age regardless of time of treatment initiation according to the diagnosis. Longer cumulative duration of PPI use yielded higher risk estimates. Further studies are warranted to determine if these findings represent a causal effect of PPIs on dementia risk, and to explore risk differences according to age at dementia diagnosis and dementia subtypes.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

Studies based on national Danish registers do not require patient consent or ethical approval under Danish legislation. The Danish Health Data Board and the Danish Data Protection Agency approved this study (ID No. P-2021-250).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Supplementary Material

Proton pump inhibitors and dementia: a nationwide population-based study

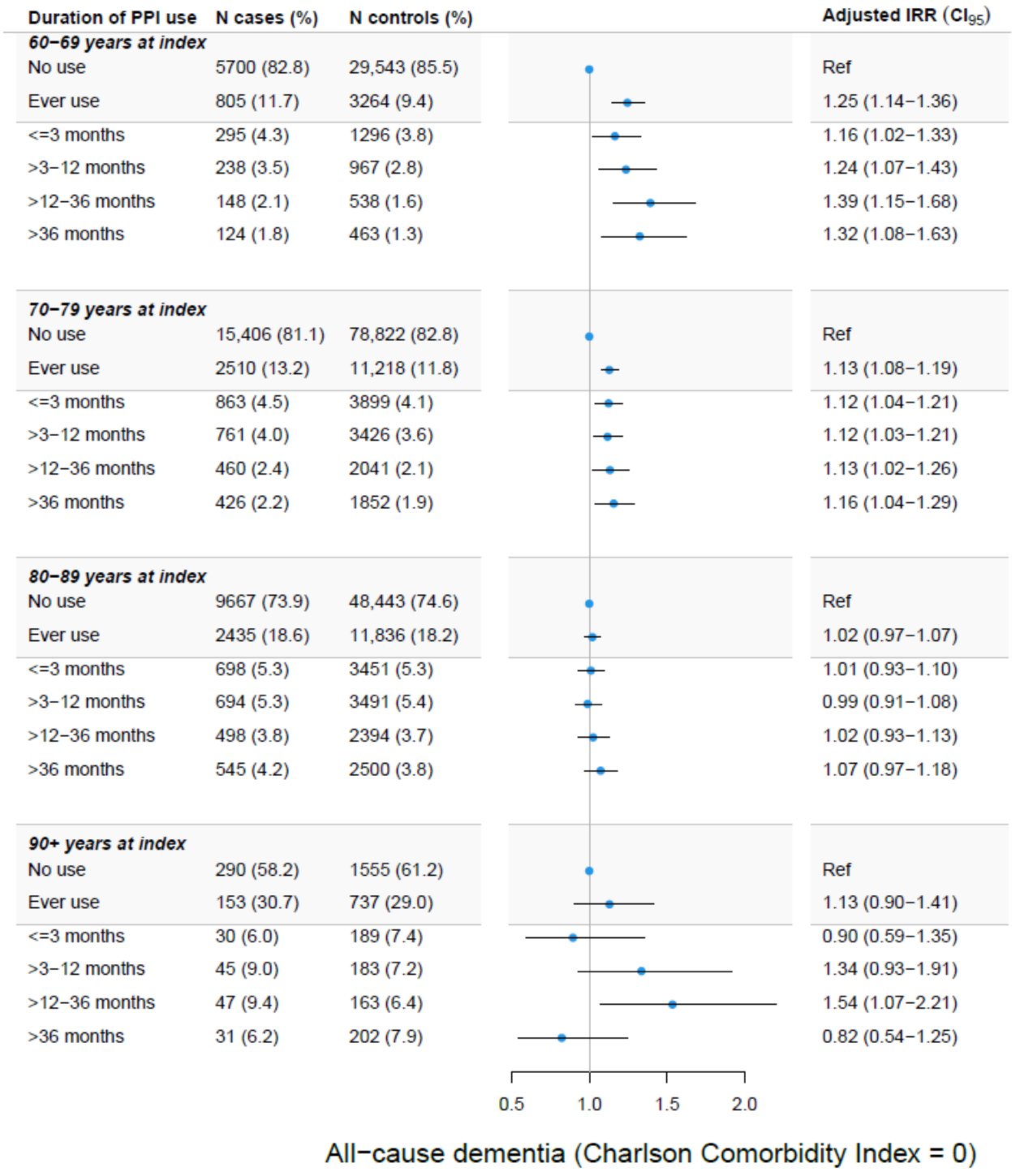
Table S1. Diagnosis- and drug codes

Variable	Data source	Data availability	Classification system	Definition	
				ICD 8 & 10	ATC
Dementia	The National Patient Register, The Danish Psychiatric Central Research Registry & The National Prescription Registry	1977-2018 & 1995-2018	International Classification of Diseases and Related Health Problems, 8th and 10th revision (ICD-8 and ICD-10) and Anatomical Therapeutic Chemical Classification System (ATC)	290, F00, F01, F02, F03, G30, G31.8-9	N06D
PPI-use	The National Prescription Registry	1995-2018	ATC	-	A02B
Stroke	The National Patient Registry	1977-2018	ICD-8 and ICD-10	430, 431, 432, 433, 434, 436, I60-I64, I69	-
Ischemic heart disease & acute myocardial infarction	The National Patient Registry & The National Prescription Registry	1977-2018 & 1995-2018	ICD-8, ICD-10, and ATC	410.99, I20-I25	C01DA
Oral antithrombotic medication & anticoagulants	The National Prescription Registry	1995-2018	ATC	-	B01A
Diabetes Mellitus	The National Patient Registry & The National Prescription Registry	1977-2018 & 1995-2018	ICD-8, ICD-10, and ATC	249, 250, E10-E14	A10
Hypertension	The National Patient Registry & The National Prescription Registry	1977-2018 & 1995-2018	ICD-8, ICD-10, and ATC	400, 401, 402, 403, 404, 410.09, 411.09, 412.09, 413.09, 414.09, 435.09, 437.00, 437.01, 437.08, 437.09, 438.09, I10-I13, I15	C02-C04, C07-C09
Dyslipidemia	The National Patient Registry & The National Prescription Registry	1977-2018 & 1995-2018	ICD-8, ICD-10, and ATC	279.00, E78.0	C10
Education	The Danish Education Registry	1980-2018	Highest obtained education - International Standard Classification of Education	**Definition**	
				Low; Medium; High	

Table S2. Definition of dose levels (mg) and Defined Daily Doses (DDDs) for orally administered PPIs.

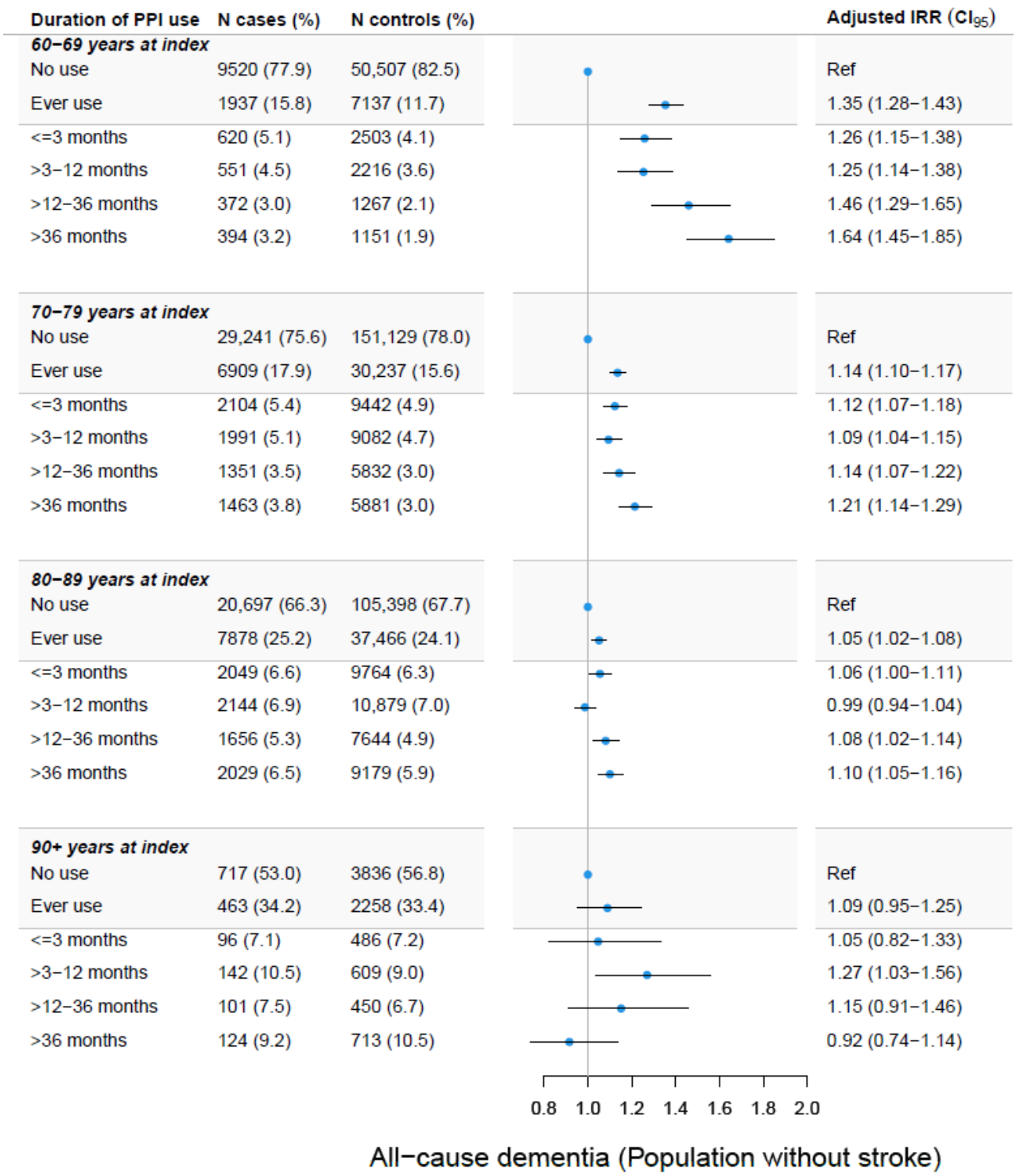
Dose (mg)	**PPI drug (ATC-code)**				
	Omeprazole (A02BC01)	**Pantoprazole** (A02BC02)	**Lansoprazole** (A02BC03)	**Rabeprazole** (A02BC04)	**Esomeprazole** (A02BC05)
Low	≤10	≤20	≤15	≤10	-
Standard	20	40	30	20	20
High	>20	>40	>30	>20	>20
DDD	20	40	30	20	30

Figure S1. Adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) of the association between cumulative duration of PPI use and all-cause dementia in individuals with CCI score zero



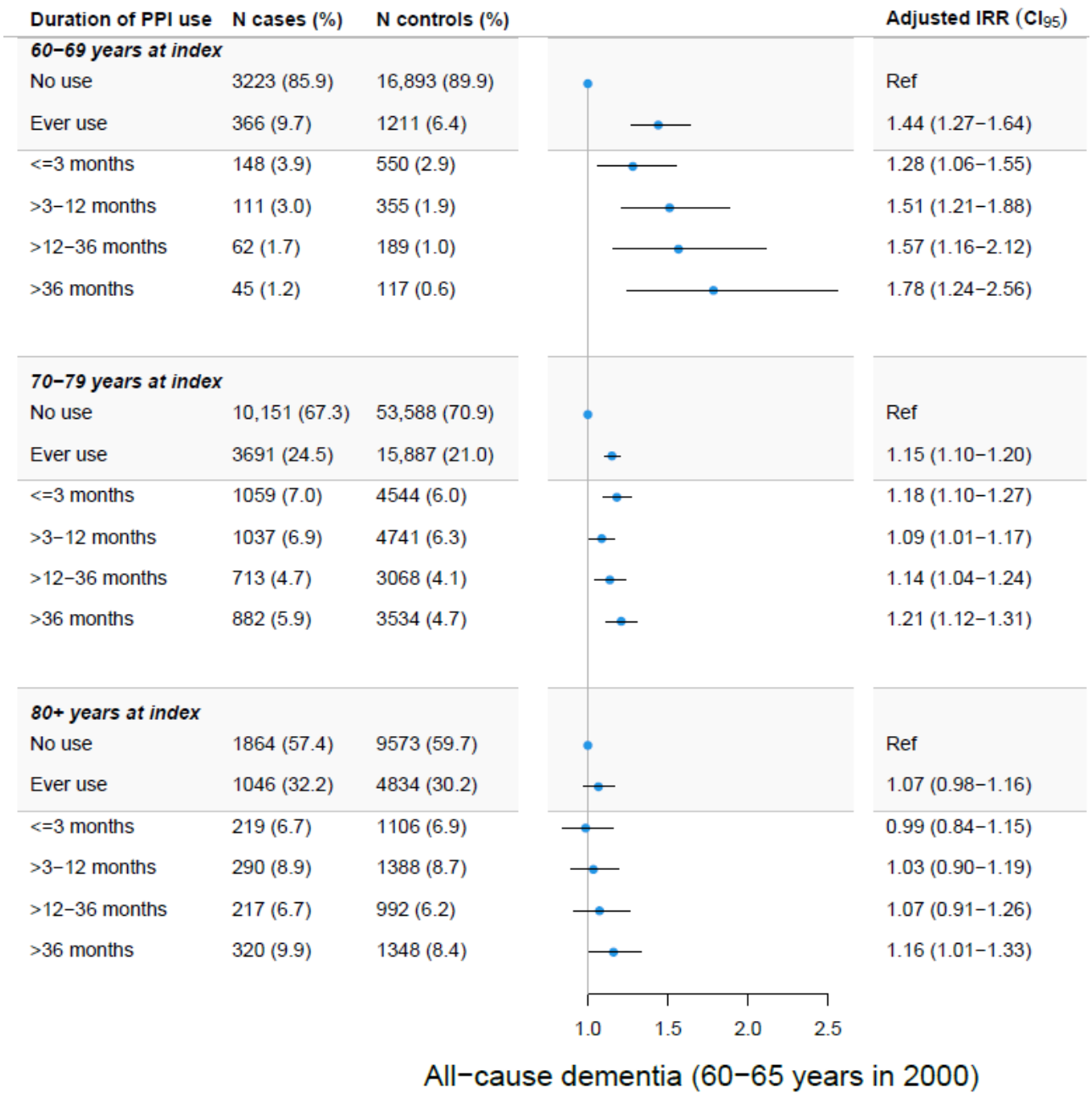
Note. Adjusted for educational level, CVD, diabetes, hypertension, and dyslipidemia. Five-year lag-time window applied. Estimates for "one prescription only" are not shown.

Figure S2. Adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) of the association between cumulative duration of PPI use and all-cause dementia in individuals without stroke



Note. Adjusted for educational level, CVD, diabetes, hypertension, and dyslipidemia. Five-year lag-time window applied. Estimates for "one prescription only" are not shown.

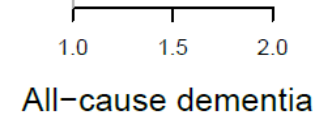
Figure S3. Adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) of the association between cumulative duration of PPI use and all-cause dementia in individuals aged 60-65 years in 2000



Note. Adjusted for educational level, CVD, diabetes, hypertension, and dyslipidemia. Five-year lag-time window applied. Estimates for "one prescription only" are not shown.

Figure S4. Adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) of the association between ever use of PPI subtypes use and all-cause dementia

PPI subtype	N cases (%)	N controls (%)	Adjusted IRR (CI_{95})
60–69 years at index			
No use	11,257 (77.3)	60,278 (82.5)	Ref
Omeprazole only	482 (3.3)	1,770 (2.4)	1.37 (1.23–1.52)
Pantoprazole only	184 (1.3)	631 (0.9)	1.44 (1.21–1.71)
Lansoprazole only	297 (2.0)	1,236 (1.7)	1.18 (1.04–1.35)
Esomeprazole only	149 (1.0)	555 (0.8)	1.32 (1.10–1.59)
70–79 years at index			
No use	34,543 (75.0)	179,168 (77.7)	Ref
Omeprazole only	1,705 (3.7)	7,313 (3.2)	1.14 (1.08–1.21)
Pantoprazole only	679 (1.5)	2,748 (1.2)	1.20 (1.10–1.31)
Lansoprazole only	1,090 (2.4)	4,917 (2.1)	1.09 (1.02–1.17)
Esomeprazole only	476 (1.0)	2,202 (1.0)	1.07 (0.97–1.19)
80–89 years at index			
No use	24,340 (65.6)	124,210 (67.1)	Ref
Omeprazole only	1,229 (3.3)	5,816 (3.1)	1.06 (0.99–1.13)
Pantoprazole only	916 (2.5)	4,146 (2.2)	1.10 (1.02–1.18)
Lansoprazole only	1,179 (3.2)	6,006 (3.2)	0.98 (0.92–1.04)
Esomeprazole only	625 (1.7)	3,122 (1.7)	0.99 (0.91–1.09)
90+ years at index			
No use	845 (52.7)	4,449 (54.9)	Ref
Omeprazole only	53 (3.3)	301 (3.7)	0.94 (0.69–1.28)
Pantoprazole only	65 (4.1)	299 (3.7)	1.08 (0.81–1.44)
Lansoprazole only	87 (5.4)	394 (4.9)	1.11 (0.86–1.44)
Esomeprazole only	26 (1.6)	100 (1.2)	1.41 (0.90–2.23)



Note. Adjusted for educational level, CVD, diabetes, hypertension, and dyslipidemia. Five-year lag-time window applied. Estimates for categories "one prescription only", "mixed use" (use of two or more PPI subtypes), and "Rabeprazole only" are not shown, the latter due to low number of cases.

STUDY II

Opioids and Dementia in the Danish Population

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Opioids and Dementia in the Danish Population.
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Original Investigation | Neurology

Opioids and Dementia in the Danish Population

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Abstract

IMPORTANCE Opioids have been studied as a potential risk factor for dementia, but evidence concerning long-term noncancer opioid use and exclusive use of weak opioids and associated dementia risk is sparse.

OBJECTIVE To assess the association between cumulative noncancer use of opioids and risk of age-related all-cause dementia.

DESIGN, SETTING, AND PARTICIPANTS This nested case-control study within a population-based cohort included 1 872 854 individuals without previous dementia, cancer, opioid addiction, or opioid use in terminal illness. Data were obtained from national Danish registers. Each individual who developed dementia during follow-up was incidence-density matched to 5 dementia-free controls. Statistical analysis was performed from August 2023 to March 2024.

EXPOSURE Cumulative opioid exposure was based on filled prescriptions available from 1995 through 2020.

MAIN OUTCOMES AND MEASURES Conditional logistic regression provided adjusted incidence rate ratios (IRRs) for associations between opioids and dementia.

RESULTS Among 1 872 854 individuals without previous dementia, cancer, opioid addiction, or opioid use in terminal illness included in the study, 93 638 (5.0%) developed all-cause dementia during follow-up (51 469 [55.0%] female; median [IQR] age, 78.1 [73.0-82.8] years) and were matched to 468 190 control individuals (257 345 [55.0%] female; median [IQR] age, 78.0 [73.0-82.8] years). Opioid use up to 90 total standardized doses (TSDs) was not consistently associated with dementia risk. Opioid exposure above 90 TSDs yielded increased IRRs of dementia occurring before age 90 years ranging from 1.29 (95% CI, 1.17-1.42) for 91 to 200 TSDs to 1.59 (95% CI, 1.44-1.76) for greater than 500 TSDs for age-band 60 to 69 years at dementia diagnosis. Corresponding IRRs were 1.16 (95% CI, 1.11-1.22) to 1.49 (95% CI, 1.42-1.57) for age-band 70 to 79 years and 1.08 (95% CI, 1.03-1.14) to 1.21 (95% CI, 1.16-1.27) for 80 to 89 years. Sensitivity analyses corroborated associations in individuals with chronic noncancer pain and with use of weak opioids.

CONCLUSIONS AND RELEVANCE This study found that opioid use of less than 90 TSDs was not significantly associated with increased dementia risk. Above 90 TSDs of opioid use was associated with an elevated dementia risk before age 90 years, which persisted in individuals with chronic noncancer pain and in individuals solely exposed to weak opioids. Further research should ascertain whether the findings denote causality between opioids and dementia risk.

JAMA Network Open. 2024;7(11):e2445904. doi:10.1001/jamanetworkopen.2024.45904

Key Points

Question Is cumulative use of opioids for noncancer pain associated with increased risk of dementia?

Findings In this nested case-control study within a population-based cohort including 93 638 individuals with dementia in Denmark, there was no significant association between noncancer opioid use below 90 total standardized doses (TSDs) and dementia risk, whereas opioid use above 90 TSDs was associated with increased dementia risk. This association persisted among individuals with chronic pain diagnoses and with use of weak opioids only.

Meaning These results suggest that further research is warranted to ascertain the potential link between opioids and dementia.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Worldwide, dementia is a growing public health challenge with over 10 million new cases annually and a rapidly increasing global prevalence.[1] Identification of modifiable risk factors is crucial, as the disease remains incurable.[1] Opioids have been studied as a potential risk factor, but it is currently unknown whether its use increases dementia risk.

Global opioid use has more than doubled from 2000 to 2019.[2] Studies report of increasing use with advancing age in Europe and the US.[3,4] Chronic noncancer pain is a highly prevalent condition affecting around 20% of adults.[5] In Denmark, the prevalence increased from 20% to 28% between 2000 and 2017, with an annual incidence of 2.7%.[6] Opioids are frequently used to treat chronic noncancer pain, but evidence of the effect on pain management and quality of life is lacking.[7]

Serious adverse effects of opioids include respiratory depression, addiction, and increased mortality.[8] Although opioid-related neurological adverse effects (eg, altered cognition, sedation, and delirium) are thought to be reversible,[9] less is known about the long-term safety.[10] Opioids can affect the brain through neuroinflammation,[11] and Alzheimer-related brain changes of β-amyloid and tau deposition have been demonstrated postmortem in individuals with opiate use disorder.[12]

Evidence concerning effects of long-term opioid use on cognition and dementia is limited. Only a few previous studies have investigated this research question with inconsistent findings.[13-16]

A community-based cohort study reported a positive association between the highest cumulative opioid doses and dementia.[13] A Finnish register-based study found opioid use not to be associated with Alzheimer disease but called for further studies in populations with higher opioid exposure levels.[14] An Israeli cohort study reported increased dementia risk for opioid use between ages 75 and 80 years,[15] suggesting a potential critical window of exposure. Additionally, a study reported increased dementia risk in an Asian population with chronic pain.[16] However, in the latter 2 studies, biases including protopathic bias may have influenced the findings because no lag-time windows were applied between the exposure and outcome. Furthermore, most previous studies were limited by not considering chronic pain related to opioid use, thus they were susceptible to confounding by indication.

Focusing on addressing previous limitations and understudied aspects of the research question, this nationwide population-based study investigated the association between cumulative noncancer opioid use and age-related risk of all-cause dementia. Associations were further assessed in subpopulations with chronic noncancer pain and with use of weak opioids only.

Methods

Ethics Approval

According to Danish law, register-based studies are not required to obtain ethical approval or patient consent. This study was approved by the Danish Health Data Authority and the Danish Data Protection Agency. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.[17]

Study Population and Design

This population-based study used a nested case-control design within a nationwide cohort to assess the associated risk of late-onset all-cause dementia with cumulative noncancer opioid use. We identified an open cohort of individuals aged 60 to 75 years between 2000 and 2020 by linking national Danish registers[18-22] through an encrypted unique personal identification number assigned to all Danish residents (eTable 1 in Supplement 1). Exclusion criteria were previous history of dementia, opioid addiction, opioid use in terminal illness, or cancer except nonmelanoma skin cancer, the latter due to focusing on noncancer opioid use (eTable 1 in Supplement 1). Included individuals were followed for up to 21 years until dementia, death, emigration, an exclusion criterion, or end of study (December 31, 2020).

Within the cohort, we applied a nested case-control design yielding a matched population of all incident dementia cases during follow-up (2000-2020) and a representative group of noncases/controls sampled from the source cohort. By incidence-density matching (risk set sampling)[23] on the date of dementia incidence (index date), we matched each case by birth year and sex to 5 eligible, uncensored dementia-free controls. The matched population included unique risk-sets each including 1 dementia case and 5 noncases who were still at risk at index date.[24]

Dementia

All-cause dementia was defined as dementia of any etiology from age 60 years identified from the first date of dementia diagnosis or filled prescription with antidementia medication (eTable 1 in Supplement 1). In Denmark, dementia is typically diagnosed in hospital memory clinics. Dementia syndrome hospital diagnoses have high validity,[25] and were provided by The National Patient Register holding data on Danish hospital diagnoses since 1977.[19] Filled prescriptions with antidementia medication (used for Alzheimer disease, Lewy body dementia, and Parkinson disease dementia) permitted identification of dementia cases diagnosed and treated in primary care.[22] Age at index date was grouped in 10-year age groups (60-69; 70-79; 80-89; ≥90), as previous studies have found interaction between age at diagnosis and exposure to other pharmacological products.[26]

Opioid Use

Information on opioid use was drawn from The National Prescription Register providing complete data on all prescriptions redeemed from Danish pharmacies since 1995 (eTable 2 in Supplement 1). Besides the Anatomical Therapeutic Chemical code, prescription data included the date of purchase, number of purchased packages, package size, strength, dosage, and form or mode of administration.

To accommodate differences in potencies and dosages across various opioid formulations and modes of administration, the specific equianalgesic ratio of each opioid subtype was used to calculate the oral morphine equivalent dose (OMEQ) consistent with previous studies (eTable 2 in Supplement 1).[27] The amount of OMEQ was converted into total standardized doses (TSDs) where 1 TSD corresponds to 30 mg oral morphine equivalents[13,14] (eTable 2 in Supplement 1).

Dementia neuropathology typically develop gradually over decades, thus, a 5-year lag-time window was consistently applied to address reverse causation/protopathic bias (ie, when early symptoms of dementia lead to opioid use). Consequently, we omitted opioid prescriptions redeemed within 5 years of index.

An individual was considered exposed from first prescription redemption of any opioid between 1995 and the beginning of the lag-time window. The cumulative number of TSDs was categorized similarly as in previous studies: 0 to 30; 31 to 90; 91 to 200; 201 to 500; and more than 500.[28,29]

Confounders

As potential confounders, we included all available variables known or suspected to be associated with dementia risk and opioid use.[28] These included sociodemographic confounders; age, sex, and educational level (elementary/secondary school; vocational education; university education). Health-related confounders defined from diagnoses and prescriptions with disease-specific medication included diabetes, hypertension, dyslipidemia, and cardiovascular disease defined by diagnosis of ischemic heart disease or stroke, or prescription with oral antithrombotic medication. The Charlson Comorbidity Index (CCI) was included as a comorbidity burden measure.[29] Covariates were measured at the beginning of the lag-time window. Exact definitions of variables are displayed in eTable 1 in Supplement 1.

Statistical Analysis

Conditional logistic regression yielded adjusted incidence rate ratios (IRRs) and 95% CIs for associations between cumulative opioid use and dementia according to age at index.[23] The reference group was individuals who had not received opioids, and analyses included 5-year lag-time windows.

All models included the potential confounders as covariates; 1.8% had missing information on educational level, hence, subcategorized separately as missing in analyses. Information on the remaining covariates was accessible for all individuals. χ^2 test provided *P* values for descriptive variables. Two-sided $P < .05$ was considered statistically significant. Data management and analysis was performed from August 2023 to March 2024 using R statistical software version 4.3.2 (R Project for Statistical Computing) and SAS software version 9.4 (SAS Institute).[30] Incidence-density matching was performed using the R program incidenceMatch from the package tagteam/heaven accessible on Github.

Sensitivity analyses in separate subpopulations addressed potential confounding by indication. First, subpopulation restricted to individuals with chronic noncancer pain[28] diagnosed within 10 years of study entry to increase the probability of pain-related symptoms and related subsequent opioid use. All individuals had pain-intensive diagnoses, thus aiming to reduce confounding by chronic pain and related conditions. Diagnoses constituted specific pain-intensive back diagnoses, intervertebral disc pain, arthritic pain, posttraumatic fracture pain, and neuropathic pain as seen in previous research (eTable 1 in Supplement 1).[28] Opioid prescription more than 1 year before the pain diagnosis led to exclusion.

Second, subpopulation restricted to weak opioid use (eTable 2 in Supplement 1) as the exposure of interest. Prescription with strong opioids led to exclusion, thus eliminating potential confounding attributed to strong opioid use. Tramadol is the most frequently used opioid in Denmark and was prescribed at increasing doses over the study period, particularly among age groups younger than 80 years.[31]

Third, subpopulation with indication for opioid use restricted to cough suppressants (ie, opioid antitussives) (eTable 2 in Supplement 1). Prescription with any analgesic opioid led to exclusion, thereby addressing potential confounding by indication from opioids with analgesic indication.

A post hoc sensitivity analysis addressed potential false-positive dementia diagnoses due to reversible opioid-related cognitive impairment by analyzing opioid user status defined according to the date of last filled prescription plus 30 additional days.

To analyze the potential of reverse causation, main analyses were additionally conducted with a shorter 1-year lag-time window for comparison. To analyze indication of potential time-varying effects of confounders, main analyses were additionally conducted with confounders defined at baseline. Finally, we estimated mortality rates among individuals receiving opioids vs those not receiving opioids for indication of potential competing risk of death.

Results

In the nationwide cohort of 1 872 854 individuals, 93 638 (5.0%) developed all-cause dementia during follow-up (51 469 [55.0%] female; median [IQR] age, 78.1 [73.0-82.8] years) and were matched to 468 190 control individuals (257 345 [55.0%] female; median [IQR] age, 78.0 [73.0-82.8] years). Median (IQR) follow-up time was 11.8 (7.3-15.8) years. **Figure 1** shows the cohort and nested case-control formation. The median (IQR) age at diagnosis was 78 (73-83) years and 51 469 (55.0%) were female. Overall, comorbidities were more prevalent in dementia cases compared with controls (**Table**).

Individuals who had ever received opioids constituted 52 232 dementia cases (55.8%) and 247 892 controls (52.9%). The median (IQR) cumulative opioid use was 35 (13-122) TSDs for cases and 33 (12-94) TSDs for controls. Median (IQR) age at first opioid prescription was 66 (60-70) years. The most-used strong opioids were oral morphine and oxycodone, whereas the most-used weak opioid was oral tramadol. eTable 3 in Supplement 1 displays comprehensive details on opioid formulations and usage.

Opioid ever use compared with nonuse was associated with a slightly elevated IRR of dementia for 10-year age bands occurring before age 90 (**Figure 2**). Overall, cumulative opioid exposure of less than or equal to 90 TSDs was not consistently associated with dementia, although, IRRs for 31 to

90 TSDs reached statistical significance for ages 70 to 79 years and at least 90 years at index. Increasing exposure to more than 90 TSDs exhibited increasing IRRs of dementia ranging from 1.29 (95% CI, 1.17-1.42) for 91 to 200 TSDs to 1.59 (95% CI, 1.44-1.76) for greater than 500 TSDs in individuals aged 60 to 69 years at index. Corresponding IRRs for ages 70 to 79 years and 80 to 89 years at index were 1.16 (95% CI, 1.11-1.22) to 1.49 (95% CI, 1.42-1.57) and 1.08 (95% CI, 1.03-1.14) to 1.21 (1.16-1.27), respectively. Opioid use did not show a statistically significant association with dementia occurring at age 90 years or older.

Sensitivity Analyses

Among individuals with specified chronic noncancer pain, dementia rates decreased compared with the entire study population. Overall, associations persisted for exposure greater than 90 TSDs, although based on fewer cases and with limited statistical precision (**Figure 3**). Notably, for ages 60 to 69 years at index, opioid ever use did not exhibit a statistically significant association with dementia. This was similarly the case for 91 to 200 TSDs for age bands of 60 to 79 years.

Exclusive use of weak opioids was associated with slightly increased IRRs of dementia before 90 years of age ranging from 1.15 (95% CI, 1.08-1.22) for 60 to 69 years to 1.07 (95% CI, 1.03-1.11) for 80 to 89 years age band (**Figure 4**). Use of greater than 30 TSDs exhibited elevated dementia rates, except for the category 91 to 200 TSDs for cases aged 80 to 89 years.

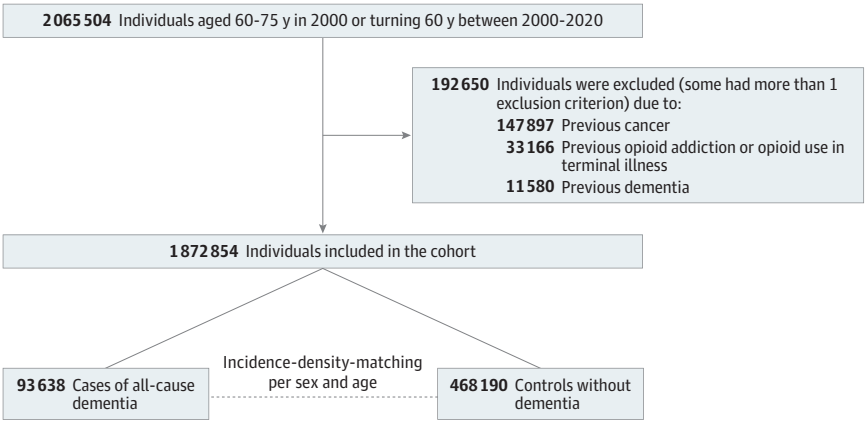
Regardless of user status (timing of last treatment day according to index), at least 90 TSDs of opioids was positively associated with dementia before age 90 years (eFigure 1 in Supplement 1). Exclusive use of opioid antitussives was not associated with dementia apart from greater than 200 TSDs for dementia up to age 80 years (eFigure 2 in Supplement 1). Main findings remained largely unchanged in sensitivity analyses with 1-year lag-time and with covariates assessed at baseline (eFigure 3 and eFigure 4 in Supplement 1). Compared with nonuse, opioid use greater than 90 TSDs was associated with increased mortality rate (eFigure 5 in Supplement 1).

Discussion

In this nationwide study, cumulative opioid use up to 90 TSDs was found not to be uniformly associated with dementia risk. Exposure to more than 90 TSDs of opioids was associated with slightly increased dementia rates primarily before age 90 years at diagnosis. For exposure above 90 TSDs, the overall associations persisted among individuals receiving weak opioids only and among individuals with chronic noncancer pain, although with limited statistical precision.

Our findings align with a recent study reporting elevated dementia risk among individuals receiving opioids in an Asian population with chronic pain.[16] Additionally, we observed that the

Figure 1. Cohort and Nested Case-Control Population Flowchart



During follow-up, 670 200 individuals were censored due to incident cancer (n = 370 407), opioid addiction or opioid use in terminal illness (n = 37 882), emigration (n = 12 011), or death (n = 249 900).

increased risk was consistent with opioid use above 90 TSDs and dementia occurring before age 90 years, both in the general cancer-free population and in individuals with pain-intensive diagnoses. Furthermore, we found that associations persisted among individuals solely exposed to weak opioids.

Table. Characteristics of Nested Case-Control Population

Variable	All-cause dementia (n = 93 638)	Controls (n = 468 190)	*P* value
Sex, No. (%)			
Female	51 469 (55.0)	257 345 (55.0)	>.99
Male	42 169 (45.0)	210 845 (45.0)	
Age at index, median (IQR), y	78.1 (73.0-82.8)	78.0 (73.0-82.8)	.70
Age at index, No. (%), y			
60-69	13 738 (14.7)	68 690 (14.7)	>.99
70-79	42 757 (45.7)	213 785 (45.7)	
80-89	34 929 (37.3)	174 645 (37.3)	
≥90	2214 (2.4)	11 070 (2.4)	
Follow-up time, median (IQR), y	11.8 (7.3-15.8)	11.8 (7.3-15.8)	>.99
Year of index, median (IQR)	2013 (2008-2017)	2013 (2008-2017)	>.99
Opioid ever use, No. (%)	52 232 (55.8)	247 892 (52.9)	<.001
Cumulative opioid use, median (IQR), TSDs[a]	34.8 (13.3-121.8)	32.5 (11.7-94.0)	<.001
Cumulative opioid use, No. (%), TSDs[a]			
0-30	23 818 (25.4)	122 399 (26.1)	<.001
31-90	12 829 (13.7)	62 221 (13.3)	
91-200	5979 (6.4)	26 539 (5.7)	
201-500	4091 (4.4)	16 821 (3.6)	
>500	5515 (5.9)	19 912 (4.3)	
Age at opioid initiation, median (IQR), y[a]	65.5 (59.6-70.2)	65.8 (59.8-70.4)	<.001
Education, No. (%)			
Elementary/secondary school	47 198 (50.4)	228 256 (48.8)	<.001
Vocational education	32 693 (34.9)	164 333 (35.1)	
University education	12 098 (12.9)	67 059 (14.3)	
Missing	1649 (1.8)	8542 (1.8)	
Cardiovascular disease, No. (%)	41 868 (44.7)	182 032 (38.9)	<.001
Stroke, No. (%)	8852 (9.5)	27 384 (5.8)	<.001
Ischemic heart disease, No. (%)	19 063 (20.4)	85 015 (18.2)	<.001
Antithrombotic medication, No. (%)	36 952 (39.5)	161 266 (34.4)	<.001
Diabetes, No. (%)	10 830 (11.6)	40 020 (8.5)	<.001
Hypertension, No. (%)	58 479 (62.5)	274 758 (58.7)	<.001
Dyslipidemia, No. (%)	28 803 (30.8)	130 250 (27.8)	<.001
Charlson Comorbidity Index, No. (%)			
0	81 716 (87.3)	418 681 (89.4)	<.001
1	9696 (10.4)	40 996 (8.8)	
2	1701 (1.8)	6672 (1.4)	
≥3	525 (0.6)	1841 (0.4)	
AIDS/HIV	18 (0.0)	70 (0.0)	.42
Chronic pulmonary disease	4147 (4.4)	17 658 (3.8)	<.001
Heart failure	2289 (2.4)	9456 (2.0)	<.001
Hemiplegia/paraplegia	83 (0.1)	305 (0.1)	.02
Mild liver disease	323 (0.3)	866 (0.2)	<.001
Peptic ulcer disease	1644 (1.8)	5609 (1.2)	<.001
Peripheral vascular disease	2727 (2.9)	11 029 (2.4)	<.001
Kidney disease	638 (0.7)	2617 (0.6)	<.001
Rheumatic disease	1873 (2.0)	8935 (1.9)	.06
Severe liver disease	111 (0.1)	240 (0.1)	<.001

[a] Numbers relating to opioid use include 5-year lag-time window.

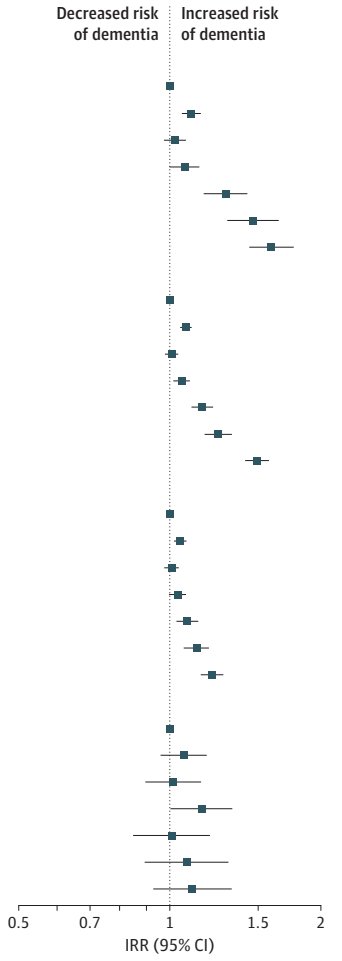
A Finnish registry-based study reported no association between opioid use and Alzheimer disease.[14] Differences in our findings may be explained by the relatively lower opioid consumption in Finland compared with other Scandinavian countries during the study period.[32,33] In 2006, the annual average opioid use was 1979 mg OMEQ per Norwegian receiving opioids vs 6025 mg OMEQ per Dane receiving opioids,[32] making Denmark a relevant setting to investigate high opioid exposure and dementia risk.[32,33]

Furthermore, in our study, exposure history was available for a longer period (maximum 26 years vs maximum 16 years in the Finnish study), and we additionally stratified by age at dementia diagnosis, which interacted with the association exhibiting decreasing rates with advancing age at diagnosis. Dementia in different ages potentially vary in underlying pathology and risk factors. Thus, this observation could represent a critical window of exposure or the diminishing influence of specific risk factors on neuropathology advancing over decades. Finally, low number of cases and unexposed aged greater than 90 years may also have influenced the findings for this age group.

Unexpectedly, among those receiving weak opioids, 31 to 90 TSDs showed positive associations with dementia. Potentially, the exposure intervals of weak opioid use may correspond to longer treatment duration with lower potent doses compared with strong opioids. Whether longer duration of opioid exposure with lower analgesic potency may influence cognition to a larger extent than shorter-term exposure with higher analgesic potency should be investigated in future research.

Figure 2. Adjusted Incidence Rate Ratios (IRRs) of Cumulative Opioid Use and All-Cause Dementia According to Age at Index

Cumulative opioid use (TSDs)	Cases, No. (%)	Controls, No. (%)	IRR (95% CI)
60-69 Years at index			
No use	7343 (53.5)	39 974 (58.2)	1 [Reference]
Ever use	6395 (46.5)	28 716 (41.8)	1.10 (1.06-1.15)
0-30	3312 (24.1)	16 907 (24.6)	1.02 (0.98-1.07)
31-90	1413 (10.3)	6592 (9.6)	1.07 (1.00-1.14)
91-200	611 (4.4)	2233 (3.3)	1.29 (1.17-1.42)
201-500	428 (3.1)	1306 (1.9)	1.46 (1.30-1.64)
>500	631 (4.6)	1678 (2.4)	1.59 (1.44-1.76)
70-79 Years at index			
No use	20 597 (48.2)	109 909 (51.4)	1 [Reference]
Ever use	22 160 (51.8)	103 876 (48.6)	1.08 (1.05-1.10)
0-30	10 529 (24.6)	54 327 (25.4)	1.01 (0.98-1.04)
31-90	5396 (12.6)	26 004 (12.2)	1.06 (1.02-1.09)
91-200	2404 (5.6)	10 294 (4.8)	1.16 (1.11-1.22)
201-500	1603 (3.7)	6197 (2.9)	1.25 (1.18-1.32)
>500	2228 (5.2)	7054 (3.3)	1.49 (1.42-1.57)
80-89 Years at index			
No use	12 866 (36.8)	67 292 (38.5)	1 [Reference]
Ever use	22 063 (63.2)	107 353 (61.5)	1.05 (1.02-1.08)
0-30	9392 (26.9)	48 148 (27.6)	1.01 (0.98-1.04)
31-90	5580 (16.0)	27 628 (15.8)	1.04 (1.00-1.07)
91-200	2748 (7.9)	12 883 (7.4)	1.08 (1.03-1.14)
201-500	1890 (5.4)	8486 (4.9)	1.13 (1.07-1.19)
>500	2453 (7.0)	10 208 (5.8)	1.21 (1.16-1.27)
≥90 Years at index			
No use	600 (27.1)	3123 (28.2)	1 [Reference]
Ever use	1614 (72.9)	7947 (71.8)	1.07 (0.96-1.18)
0-30	585 (26.4)	3017 (27.3)	1.01 (0.90-1.15)
31-90	440 (19.9)	1997 (18.0)	1.16 (1.01-1.33)
91-200	216 (9.8)	1129 (10.2)	1.01 (0.85-1.20)
201-500	170 (7.7)	832 (7.5)	1.08 (0.89-1.31)
>500	203 (9.2)	972 (8.8)	1.11 (0.93-1.33)



Adjusted for educational level, cardiovascular disease, diabetes, hypertension, dyslipidemia, and Charlson Comorbidity Index score. Five-year lag-time window applied. TSD indicates total standardized daily dose.

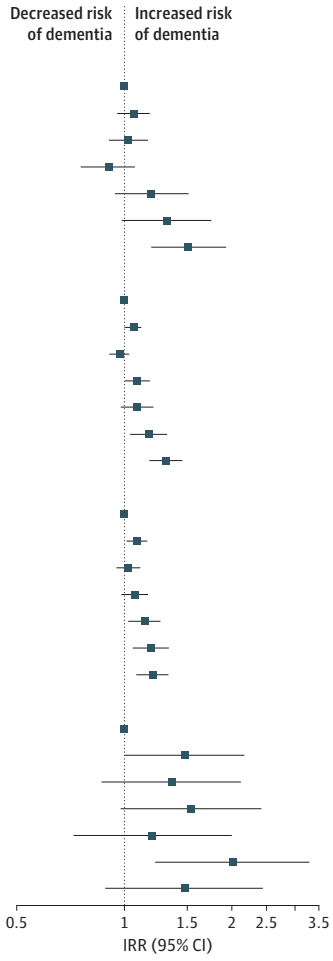
Previous studies have reported associations between opioid use and cognitive impairment in neuropsychological tests.[34] Thus, its usage could increase the probability of getting diagnosed with dementia by either demasking clinical dementia symptoms related to underlying neuropathology or by mimicking potentially reversible dementia symptoms. The latter possibility was tackled by applying a 5-year lag-time window and by the sensitivity analysis assessing user status demonstrating increased dementia rates even among individuals finalizing treatment more than 5 years before index.

Opioids cross the blood-brain barrier and target receptors in the central nervous system relating to pain transmission pathways.[35] Autopsy studies have reported increased deposition of Alzheimer disease related proteins β-amyloid and tau in individuals with high opioid usage and opioid use disorder.[12,36] Thus, high opioid exposure may influence neurodegeneration and subsequent cognitive impairment.[36] Still, the potential link between opioids and dementia is not completely understood, emphasizing the need for future studies to investigate opioids' role in dementia development, particularly according to dementia etiology. This study highlights a potential long-acting influence of high opioid exposure unrelated to the strength of the opioid.

A population-based study found persistent pain to be associated with accelerated cognitive decline and dementia.[37] However, the study did not account for use of analgesics; therefore, the authors hypothesized that the observed association could be mediated by opioid use.

Figure 3. Adjusted Incidence Rate Ratios (IRRs) of Cumulative Opioid Use and All-Cause Dementia According to Age at Index in a Population of Individuals With Chronic Noncancer Pain Diagnosis

Cumulative opioid use (TSDs)	Cases, No. (%)	Controls, No. (%)	IRR (95% CI)
60-69 Years at index			
No use	1292 (58.9)	6841 (62.4)	1 [Reference]
Ever use	902 (41.1)	4129 (37.6)	1.06 (0.96-1.17)
0-30	440 (20.1)	2178 (19.9)	1.03 (0.91-1.16)
31-90	191 (8.7)	1022 (9.3)	0.90 (0.76-1.07)
91-200	101 (4.6)	392 (3.6)	1.19 (0.94-1.50)
201-500	65 (3.0)	235 (2.1)	1.31 (0.99-1.75)
>500	105 (4.8)	302 (2.8)	1.51 (1.19-1.92)
70-79 Years at index			
No use	4044 (48.1)	21 429 (51.0)	1 [Reference]
Ever use	4360 (51.9)	20 591 (49.0)	1.06 (1.01-1.11)
0-30	1734 (20.6)	9260 (22.0)	0.97 (0.91-1.03)
31-90	1108 (13.2)	5174 (12.3)	1.09 (1.01-1.17)
91-200	540 (6.4)	2431 (5.8)	1.09 (0.98-1.20)
201-500	408 (4.9)	1678 (4.0)	1.17 (1.04-1.31)
>500	570 (6.8)	2048 (4.9)	1.31 (1.18-1.45)
80-89 Years at index			
No use	1740 (27.4)	9351 (29.4)	1 [Reference]
Ever use	4618 (72.6)	22 439 (70.6)	1.09 (1.02-1.15)
0-30	1655 (26.0)	8615 (27.1)	1.03 (0.95-1.10)
31-90	1177 (18.5)	5826 (18.3)	1.07 (0.99-1.16)
91-200	652 (10.3)	3021 (9.5)	1.14 (1.03-1.26)
201-500	479 (7.5)	2111 (6.6)	1.19 (1.06-1.33)
>500	655 (10.3)	2866 (9.0)	1.20 (1.08-1.33)
≥90 Years at index			
No use	36 (13.1)	241 (17.5)	1 [Reference]
Ever use	239 (86.9)	1134 (82.5)	1.48 (1.01-2.16)
0-30	61 (22.2)	305 (22.2)	1.36 (0.87-2.12)
31-90	62 (22.5)	286 (20.8)	1.54 (0.98-2.41)
91-200	36 (13.1)	208 (15.1)	1.20 (0.72-1.99)
201-500	42 (15.3)	147 (10.7)	2.01 (1.22-3.29)
>500	38 (13.8)	188 (13.7)	1.47 (0.89-2.45)



Adjusted for educational level, cardiovascular disease, diabetes, hypertension, dyslipidemia, and Charlson Comorbidity Index score. Five-year lag-time window applied. TSD indicates total standardized daily dose.

We cannot rule out that our findings were influenced by confounding by indication. Still, the results among individuals with pain-intensive diagnoses indicate that the observed association between opioids and dementia is likely partly but not entirely explained by the hypothesized influence of chronic pain or the underlying conditions leading to pain.

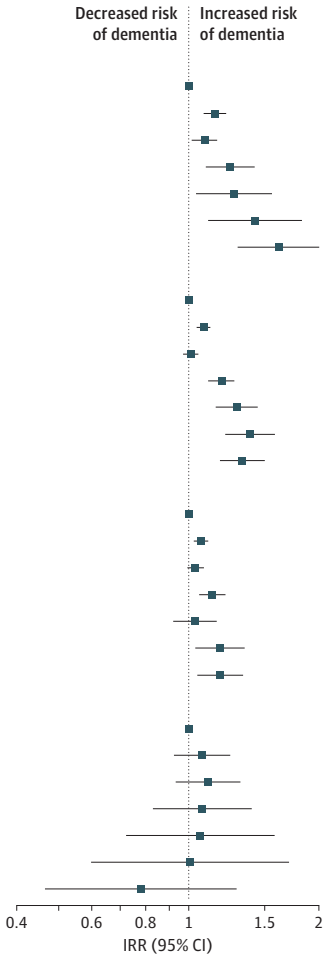
Chronic noncancer pain presents a global public health challenge with both a high and increasing prevalence.[5,6] Opioids are frequently used for such indications, and inappropriate prescribing has been reported in both Eastern and Western countries.[38] Particularly, use of the weak opioid tramadol is widespread and increasing and may lead to long-term use of strong opioids.[28] In our study, dementia rates remained elevated when restricting to weak opioids only. Therefore, we call for scientific attention and further research exploring the long-term brain safety of opioids and interventions aimed at reducing inappropriate opioid use.

Our study findings are generalizable to populations with comparable health care and demographics. The comprehensive Danish registers are a relevant data foundation for addressing the present research question, especially considering the relatively high and increasing use of prescription opioids in Denmark during the study period proximal to that of North America, as also seen in several other European countries such as Germany and Austria.[31,39]

Study strengths include a large nationwide sample with long follow-up, diminishing selection bias, and exposure assessment via redeemed prescriptions, hindering information bias. Highly valid dementia diagnoses were used and inclusion of several relevant confounding variables.[25]

Figure 4. Adjusted Incidence Rate Ratios (IRRs) of Cumulative Use of Weak Opioids and All-Cause Dementia According to Age at Index

Cumulative opioid use (TSDs)	Cases, No. (%)	Controls, No. (%)	IRR (95% CI)
60-69 Years at index			
No use	6500 (75.0)	34 197 (78.9)	1 [Reference]
Ever use	2169 (25.0)	9148 (21.1)	1.15 (1.08-1.22)
0-30	1500 (17.3)	6856 (15.8)	1.09 (1.02-1.16)
31-90	334 (3.9)	1241 (2.9)	1.25 (1.10-1.42)
91-200	130 (1.5)	457 (1.1)	1.27 (1.04-1.55)
201-500	86 (1.0)	270 (0.6)	1.42 (1.11-1.83)
>500	119 (1.4)	324 (0.7)	1.61 (1.30-2.00)
70-79 Years at index			
No use	18 127 (73.4)	93 847 (76.0)	1 [Reference]
Ever use	6560 (26.6)	29 588 (24.0)	1.08 (1.05-1.12)
0-30	4259 (17.3)	20 899 (16.9)	1.01 (0.97-1.05)
31-90	1167 (4.7)	4717 (3.8)	1.19 (1.11-1.27)
91-200	438 (1.8)	1584 (1.3)	1.29 (1.16-1.44)
201-500	312 (1.3)	1050 (0.9)	1.39 (1.22-1.58)
>500	384 (1.6)	1338 (1.1)	1.33 (1.19-1.50)
80-89 Years at index			
No use	11 061 (64.2)	57 003 (66.1)	1 [Reference]
Ever use	6174 (35.8)	29 172 (33.9)	1.07 (1.03-1.11)
0-30	3919 (22.7)	19 151 (22.2)	1.04 (1.00-1.08)
31-90	1207 (7.0)	5343 (6.2)	1.13 (1.06-1.21)
91-200	385 (2.2)	1860 (2.2)	1.03 (0.92-1.16)
201-500	306 (1.8)	1296 (1.5)	1.18 (1.04-1.34)
>500	357 (2.1)	1522 (1.8)	1.18 (1.05-1.33)
≥90 Years at index			
No use	492 (55.6)	2553 (57.7)	1 [Reference]
Ever use	393 (44.4)	1872 (42.3)	1.07 (0.92-1.24)
0-30	245 (27.7)	1131 (25.6)	1.11 (0.93-1.31)
31-90	80 (9.0)	378 (8.5)	1.07 (0.83-1.40)
91-200	32 (3.6)	152 (3.4)	1.06 (0.72-1.58)
201-500	18 (2.0)	91 (2.1)	1.01 (0.60-1.70)
>500	18 (2.0)	120 (2.7)	0.77 (0.47-1.28)



Adjusted for educational level, cardiovascular disease, diabetes, hypertension, dyslipidemia, and Charlson Comorbidity Index score. Five-year lag-time window applied. TSD indicates total standardized daily dose.

Limitations

This study had limitations. One limitation included unavailable information on opioid exposure before 1995, resulting in underestimating the amount of opioid use, thereby, potentially diluting the observed association. Considering reporting an overall positive association with dementia, we do not expect this limitation to have materially impacted the interpretation.

Another limitation was residual confounding, including potential confounding by indication cannot be ruled out in observational studies. We could not differentiate between opioid use and the underlying disorder leading to treatment. Nonetheless, tackling such potential confounding, associations remained stable for highest levels of opioid exposure among individuals with chronic noncancer pain and with exposure restricted to weak opioids. Severity and duration of chronic pain was unavailable, but sensitivity analyses suggested that pain was partially but not entirely responsible for the increased dementia risk. Potential residual confounding from unmeasured variables, including lifestyle-related factors such as alcohol use and/or alcohol use disorder or underregistered opioid addiction, cannot be ruled out because national Danish registers do not hold these data. Still, we reduced potential reverse causation bias with a 5-year lag-time window, and we were able to adjust for several known conditions associated with unhealthy lifestyle that may affect dementia risk. Additionally, influence from competing risk of death cannot be excluded (particularly in the oldest individuals aged above 90 years), although this was reduced by excluding individuals with cancer, opioid use disorder, and usage in terminal illness. Based on our findings of increased mortality rate among those with opioid use greater than 90 TSDs, we assume at worst an underestimation of the observed association with dementia. Thus, we do not expect this competing risk to have materially impacted the conclusions.

Conclusions

This study found cumulative opioid exposure below 90 TSDs not to be uniformly associated with increased dementia risk, although some models found a statistically significant positive association with 31 to 90 TSDs. Exposure to more than 90 TSDs was associated with a slightly increased dementia risk. Chronic pain could partly explain associations but not entirely. For greater than 90 TSDs, associations overall persisted in individuals with chronic noncancer pain and individuals receiving weak opioids. While the clinical importance mainly relates to opioid use greater than 90 TSDs, the increased global opioid use over the past 2 decades and prevalence of chronic noncancer pain highlight the importance of exploring our findings further. Future studies are warranted to study opioid use and risk of dementia subtypes.

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SUPPLEMENT 1.

eTable 1. Diagnosis and Drug Codes
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eTable 3. Opioid Formulations and Usage Among Opioid Users in the Matched Population
eFigure 1. Adjusted Incidence Rate Ratios (IRR) and 95% Confidence Intervals (CI) of the Association Between User Status by Cumulative Use of Opioids and All-Cause Dementia According to Age at Index
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eFigure 5. Adjusted Mortality Rate Ratios (RR) and 95% Confidence Intervals (CI) of the Association Between Cumulative Opioid Use and Mortality According to Age at Index

SUPPLEMENT 2.

Data Sharing Statement

Supplemental Online Content

Pourhadi N, Janbek J, Gasse C, Laursen TM, Waldemar G, Jensen-Dahm C. Opioids and dementia in the Danish population. *JAMA Netw Open.* 2024;7(11):e2445904. doi:10.1001/jamanetworkopen.2024.45904

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Diagnosis and drug codes

Variable		Data source	Period of data availability	Classification system	Definition	
					ICD 8 & 10	ATC code
Dementia		The National Patient Register, The Danish Psychiatric Central Research Register & The National Prescription Register	1977-2020 & 1995-2020	ICD-8, ICD-10, & ATC	290, F00, F01, F02, F03, G30, G31.8-9	N06D
Opioid use		The National Prescription Register	1995-2020	ATC	-	N02A, R05DA, R05FA02
Opioid addiction or opioid use in terminal illness		The National Patient Register, The Danish Psychiatric Central Research Register & The National Prescription Register	1977-2020 & 1995-2020	ICD-8, ICD-10, & ATC	30409, 30419, F112-114	N02A+injection administration, N02AE01+ sublingual administration, N07BC
Cancer (except non-melanoma skin cancer)		The National Patient Register	1977-2020	ICD-8 & ICD-10	14-20 (except 173), C (except C44)	-
Cardio-vascular disease	Stroke	The National Patient Register	1977-2020	ICD-8 & ICD-10	430-434, 436, I60-I64, I69	-
	Ischemic heart disease & acute myocardial infarction	The National Patient Register & The National Prescription Register	1977-2020 & 1995-2020	ICD-8, ICD-10, & ATC	410.99, I20-I25	C01DA
	Oral antithrombotic medication & anticoagulants	The National Prescription Register	1995-2020	ATC	-	B01A
Diabetes Mellitus		The National Patient Register & The National Prescription Register	1977-2020 & 1995-2020	ICD-8, ICD-10, & ATC	249-250, E10-E14	A10
Hypertension		The National Patient Register & The National Prescription Register	1977-2020 & 1995-2020	ICD-8, ICD-10, & ATC	400-404, 410.09, 411.09, 412.09, 413.09, 414.09, 435.09, 437.00, 437.01, 437.08, 437.09, 438.09, I10-I13, I15	C02-C04, C07-C09
Dyslipidemia		The National Patient Register & The National Prescription Register	1977-2020 & 1995-2020	ICD-8, ICD-10, & ATC	279.00, E78.0	C10
Education			1980-2020		**Definition**	

	Danish Education Registers		Highest obtained education - International Standard Classification of Education	Elementary/secondary school; Vocational education; University education	
Variable	**Data source**	**Period of data availability**	**Classification system**	**Definition**	
				ICD 8 & 10	**ATC code**
Charlson Comorbidity Index (modified)					
Congestive heart failure	The National Patient Register	1977-2020	ICD-8 & ICD-10	42709, 42710, 42711, 42719, 42899, 78249, I50, I110, I130, I132	
Peripheral vascular disease				440, 441, 442, 443, 444, 445, I70, I71, I72, I73, I74, I77	
Chronic pulmonary disease				490-493, 515-518, J40-J47, J60-J67, J684, J701, J703, J841, J920, J961, J982, J983	
Connective tissue disease				712, 716, 734, 446, 13599, M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86	
Ulcer disease				53091, 53098, 531-534, K221, K25-K28	
Mild liver disease				571, 57301, 57304, B18, K700-K703, K709, K71, K73, K74, K760	
Hemiplegia				344, G81, G82	
Moderate to severe renal disease				403, 404, 580-585, 59009, 59319, 75310-75319, 792, I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61	
Moderate to severe liver disease				07000, 07002, 07004, 07006, 07008, 57300, 45600-45609, B150, B160, B162, B190, K704, K72, K766, I85	
AIDS				07983, B21-B24	
Chronic non-cancer pain					
Pain-intensive back diagnoses/intervertebral disc pain	The National Patient Register	1977-2020	ICD-8 & ICD-10	M43, M45, M46, M48-51, M81, M82, 713, 72309, 725, 839	
Arthritic pain				M05-08, M10-19, M23-25, M36, M77, R26, 27400, 27401, 7120-7123, 714, 715	
Posttraumatic fracture pain				S12, S22, S32, S42, S43, S53, T02, T08, T91, 805-807, 811, 812, 831, 832, 8490, 8491	
Neuropathic pain				M792, M890, G50, G52-64, G82, G97, R29, 24903, 25003, 30391, 34302, 34303, 35401, 35408, 35409, 35100, 35101, 35109	

eTable 2. Equianalgesic ratio for various opioids and formulations

Drug	ATC-codes	Administration	Equianalgesic ratio*
Analgesic strong opioids			
Morphine	N02AA01, N02AA04, N02AG01	Oral/rectal	1
Morphine	N02AA01, N02AA04	Parenteral	3
Oxycodone	N02AA05, N02AA55	Oral	1.5
Buprenorphine	N02AE01	Sublingual	50
Buprenorphine	N02AE01	Transdermal	110
Fentanyl	N02AB03	Sublingual	50
Fentanyl	N02AB03	Transdermal/nasal/oral	100
Hydromorphone	N02AA03	Oral	6
Ketobemidone	N02AB01, N02AG02	Oral/rectal	1
Ketobemidone	N02AG02	Parenteral	3
Dextromoramide	N02AC01	Oral	3
Analgesic weak opioids			
Pethidine	N02AB02	Oral/rectal	0.1
Codeine	N02AJ06, N02AJ07	Oral	0.1
Tramadol	N02AX02	Oral/rectal	0.2
Tapantadol	N02AX06	Oral	0.4
Dextropropoxyphene	N02AC04	Oral	0.15
Pentazocine	N02AD01	Oral/rectal	0.5
Antitussives			
Codeine	R05DA04, R05FA02	Oral	0.1
Opium	R05FA02	Oral	1
Dextromethorphan	R05DA09	Oral	1
Ethylmorphine	R05DA01	Oral	0.1
Noscapine	R05DA07	Oral	0.1

* Svendsen K, Borchgrevink P, Fredheim O, Hamunen K, Mellbye A, Dale O. Choosing the unit of measurement counts: The use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. *Palliat Med* 2011; 25: 725–32.

Calculation of Total Standardized Dose (TSD)

The oral morphine equivalent dose (OMEQ) is a measurement unit that considers the analgesic potency of each opioid according to its type and mode of administration by using the equianalgesic ratio (EAR). The specific OMEQ is calculated by multiplying the opioid dose with its respective EAR:

$$OMEQ = [Opioid\ dose] * EAR$$

One TSD is defined as 30 mg oral morphine per day.

TSD is calculated by dividing the total amount of OMEQ (in milligrams) by 30 mg:

$$TSD = \frac{OMEQ(mg)}{30\ mg}$$

eTable 3. Opioid formulations and usage among opioid users in the matched population

Drug	ATC-codes	Mode of administration	Most frequently used dosage per unit	EAR[a]	Users, No. (%)[b]	Used TSDs, No. (%)[c]
Analgesic strong opioids						
Morphine	N02AA01 N02AA04 N02AG01	Oral	10 mg	1	20,093 (6.7)	10,419,479 (12.6)
		Rectal	10 mg	1	677 (0.2)	28,661 (<0.1)
Oxycodone	N02AA05 N02AA55	Oral	5 mg	1.5	22,395 (7.5)	6,424,820 (7.8)
Ketobemidone	N02AB01	Oral	5 mg	1	24,129 (8.0)	3,286,200 (4.0)
	N02AG02	Rectal	10 mg	1	3944 (1.3)	223,030 (0.3)
Fentanyl	N02AB03	Oral	0.6 mg	100	<20 (<0.1)	<100 (<0.1)
		Transdermal	25 µg/hour	100	2474 (0.8)	3,497,676 (4.2)
Buprenorphine	N02AE01	Transdermal	5 µg/hour	110	4644 (1.5)	1,488,005 (1.8)
Hydromorphone	N02AA03	Oral	8 mg	6	65 (<0.1)	48,400 (0.1)
Dextromoramide	N02AC01	Oral	5 mg	3	45 (<0.1)	3,500 (<0.1)
Analgesic weak opioids						
Tramadol	N02AX02	Oral	50 mg	0.2	147,611 (49.2)	38,382,494 (46.4)
		Rectal	100 mg	0.2	1061 (0.4)	65,413 (0.1)
Codeine	N02AJ06 N02AJ07	Oral	30.6 mg	0.1	57,584 (19.2)	2,000,137 (2.4)
Dextropropoxyphene	N02AC04	Oral	65 mg	0.15	7863 (2.6)	4,810,093 (5.8)
Pethidine	N02AB02	Oral	25 mg	0.1	1959 (0.7)	110,412 (0.1)
		Rectal	100 mg	0.1	2361 (0.8)	424,508 (0.5)
Tapantadol	N02AX06	Oral	50 mg	0.4	138 (<0.1)	45,600 (0.1)
Pentazocine	N02AD01	Oral	50 mg	0.5	417 (0.1)	302,533 (0.4)
		Rectal	50 mg	0.5	28 (<0.1)	17,508 (<0.1)
Antitussives						
Opium	R05FA02	Oral	1.7 mg	1	146,843 (48.9)	7,012,634 (8.5)
Codeine	R05DA04 R05FA02	Oral	25 mg	0.1	99,626 (33.2)	3,908,259 (4.7)
Dextromethorphan	R05DA09	Oral	3 mg	1	8335 (2.8)	239,530 (0.3)
Ethylmorphine	R05DA01	Oral	1.7 mg	0.1	4317 (1.4)	7938 (<0.1)
Noscapine	R05DA07	Oral	25 mg	0.1	2244 (0.7)	6735 (<0.1)

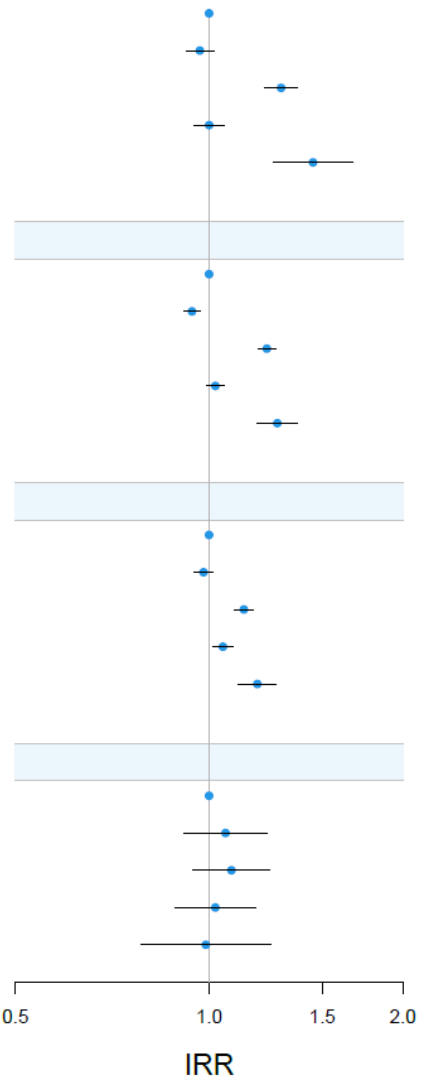
[a] Equianalgesic ratio

[b] The total number of unique opioid users was n=300,124

[c] The total number of used TSDs was n=82,753,573

eFigure 1. Adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) of the association between user status by cumulative use of opioids and all-cause dementia according to age at index.

User status, cumulative opioid use (TSDs)	Cases (n, %)	Controls (n, %)	IRR(CI_{95})
60–69 years at index			
No use	5,352 (39.0)	31,118 (45.3)	Reference
Last treatment day within 5 yr of index, <90 TSDs	3,110 (22.6)	15,782 (23.0)	0.97 (0.92–1.02)
Last treatment day within 5 yr of index, 90+ TSDs	2,617 (19.0)	8,013 (11.7)	1.29 (1.22–1.37)
Last treatment day 5+ yr before index, <90 TSDs	2,380 (17.3)	12,864 (18.7)	1.00 (0.95–1.06)
Last treatment day 5+ yr before index, 90+ TSDs	279 (2.0)	913 (1.3)	1.45 (1.26–1.67)
70–79 years at index			
No use	14,549 (34.0)	81,468 (38.1)	Reference
Last treatment day within 5 yr of index, <90 TSDs	9,673 (22.6)	51,728 (24.2)	0.94 (0.91–0.97)
Last treatment day within 5 yr of index, 90+ TSDs	9,794 (22.9)	36,304 (17.0)	1.23 (1.19–1.27)
Last treatment day 5+ yr before index, <90 TSDs	7,711 (18.0)	40,287 (18.8)	1.02 (0.99–1.06)
Last treatment day 5+ yr before index, 90+ TSDs	1,030 (2.4)	3,998 (1.9)	1.28 (1.19–1.37)
80–89 years at index			
No use	8,741 (25.0)	48,179 (27.6)	Reference
Last treatment day within 5 yr of index, <90 TSDs	7,649 (21.9)	40,411 (23.1)	0.98 (0.95–1.01)
Last treatment day within 5 yr of index, 90+ TSDs	10,181 (29.1)	44,568 (25.5)	1.13 (1.10–1.17)
Last treatment day 5+ yr before index, <90 TSDs	7,158 (20.5)	36,254 (20.8)	1.05 (1.02–1.09)
Last treatment day 5+ yr before index, 90+ TSDs	1,200 (3.4)	5,233 (3.0)	1.19 (1.11–1.27)
90+ years at index			
No use	407 (18.4)	2,181 (19.7)	Reference
Last treatment day within 5 yr of index, <90 TSDs	450 (20.3)	2,205 (19.9)	1.06 (0.91–1.23)
Last treatment day within 5 yr of index, 90+ TSDs	753 (34.0)	3,554 (32.1)	1.08 (0.94–1.24)
Last treatment day 5+ yr before index, <90 TSDs	494 (22.3)	2,547 (23.0)	1.02 (0.89–1.18)
Last treatment day 5+ yr before index, 90+ TSDs	110 (5.0)	583 (5.3)	0.99 (0.78–1.25)

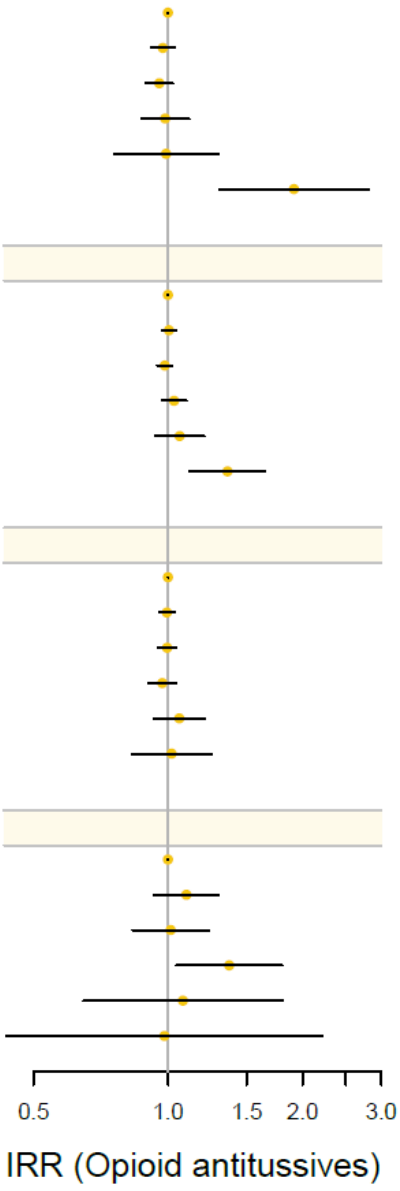


Footnote: Adjusted for educational level, cardiovascular disease, diabetes, hypertension, dyslipidemia, and CCI score. No lag-time window applied.

TSD = Total standardized daily dose.

eFigure 2. Adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) of the association between cumulative use of opioid antitussives and all-cause dementia according to age at index.

Cumulative opioid use (TSDs)	Cases (n, %)	Controls (n, %)	IRR(CI_{95})
60–69 years at index			
No use	5,887 (77.9)	29,497 (78.1)	Reference
Ever use	1,667 (22.1)	8,273 (21.9)	0.97 (0.92–1.04)
0–30	1,226 (16.2)	6,222 (16.5)	0.96 (0.89–1.03)
31–90	336 (4.4)	1,652 (4.4)	0.99 (0.87–1.11)
91–200	67 (0.9)	308 (0.8)	0.99 (0.76–1.30)
>200	38 (0.5)	91 (0.2)	1.91 (1.30–2.81)
70–79 years at index			
No use	16,055 (74.3)	81,005 (75.0)	Reference
Ever use	5,553 (25.7)	27,035 (25.0)	1.00 (0.97–1.04)
0–30	3,849 (17.8)	19,249 (17.8)	0.98 (0.95–1.02)
31–90	1,268 (5.9)	5,958 (5.5)	1.03 (0.97–1.10)
91–200	300 (1.4)	1,356 (1.3)	1.06 (0.94–1.21)
>200	136 (0.6)	472 (0.4)	1.36 (1.12–1.65)
80–89 years at index			
No use	9,470 (68.9)	47,522 (69.2)	Reference
Ever use	4,271 (31.1)	21,183 (30.8)	0.99 (0.96–1.04)
0–30	2,901 (21.1)	14,399 (21.0)	1.00 (0.95–1.04)
31–90	984 (7.2)	4,980 (7.2)	0.97 (0.90–1.04)
91–200	276 (2.0)	1,273 (1.9)	1.06 (0.93–1.21)
>200	110 (0.8)	531 (0.8)	1.02 (0.83–1.25)
90+ years at index			
No use	448 (62.1)	2,330 (64.6)	Reference
Ever use	273 (37.9)	1,275 (35.4)	1.10 (0.93–1.30)
0–30	168 (23.3)	852 (23.6)	1.01 (0.83–1.23)
31–90	79 (11.0)	297 (8.2)	1.37 (1.05–1.80)
91–200	19 (2.6)	90 (2.5)	1.08 (0.65–1.80)
>200	7 (1.0)	36 (1.0)	0.98 (0.44–2.21)

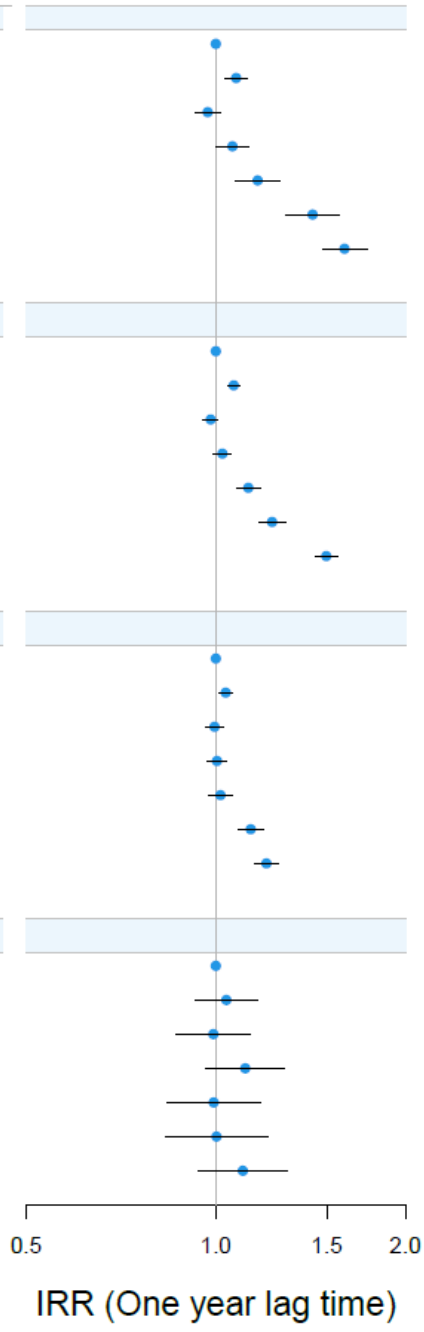


Footnote: Adjusted for educational level, cardiovascular disease, diabetes, hypertension, dyslipidemia, and CCI score. Five-year lag-time window applied.

TSD = Total standardized daily dose. Further stratification to >500 TSDs was not possible due to low number of cases.

eFigure 3. Adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) of the association between cumulative opioid use and all-cause dementia according to age at index with one-year lag-time.

Cumulative opioid use (TSDs)	Cases (n, %)	Controls (n, %)	IRR(CI_{95})
60–69 years at index			
No use	5,765 (42.0)	32,603 (47.5)	Reference
Ever use	7,973 (58.0)	36,087 (52.5)	1.08 (1.04–1.12)
0–30	3,522 (25.6)	19,128 (27.8)	0.97 (0.93–1.02)
31–90	1,901 (13.8)	8,906 (13.0)	1.06 (1.00–1.13)
91–200	854 (6.2)	3,410 (5.0)	1.17 (1.07–1.27)
201–500	647 (4.7)	1,970 (2.9)	1.42 (1.29–1.57)
>500	1,049 (7.6)	2,673 (3.9)	1.60 (1.47–1.74)
70–79 years at index			
No use	15,853 (37.1)	86,544 (40.5)	Reference
Ever use	26,904 (62.9)	127,241 (59.5)	1.07 (1.04–1.09)
0–30	10,807 (25.3)	58,019 (27.1)	0.98 (0.96–1.01)
31–90	6,561 (15.3)	32,900 (15.4)	1.02 (0.99–1.06)
91–200	3,361 (7.9)	14,874 (7.0)	1.13 (1.08–1.17)
201–500	2,397 (5.6)	9,480 (4.4)	1.23 (1.17–1.29)
>500	3,778 (8.8)	11,968 (5.6)	1.50 (1.44–1.56)
80–89 years at index			
No use	9,847 (28.2)	51,634 (29.6)	Reference
Ever use	25,082 (71.8)	123,011 (70.4)	1.04 (1.01–1.06)
0–30	8,817 (25.2)	45,784 (26.2)	1.00 (0.96–1.03)
31–90	6,161 (17.6)	31,416 (18.0)	1.00 (0.97–1.04)
91–200	3,403 (9.7)	16,999 (9.7)	1.02 (0.97–1.06)
201–500	2,712 (7.8)	12,077 (6.9)	1.14 (1.08–1.19)
>500	3,989 (11.4)	16,735 (9.6)	1.20 (1.15–1.26)
90+ years at index			
No use	457 (20.6)	2,345 (21.2)	Reference
Ever use	1,757 (79.4)	8,725 (78.8)	1.04 (0.93–1.17)
0–30	531 (24.0)	2,752 (24.9)	0.99 (0.86–1.14)
31–90	453 (20.5)	2,097 (18.9)	1.11 (0.96–1.29)
91–200	256 (11.6)	1,336 (12.1)	0.99 (0.84–1.18)
201–500	196 (8.9)	1,017 (9.2)	1.00 (0.83–1.21)
>500	321 (14.5)	1,523 (13.8)	1.10 (0.94–1.30)

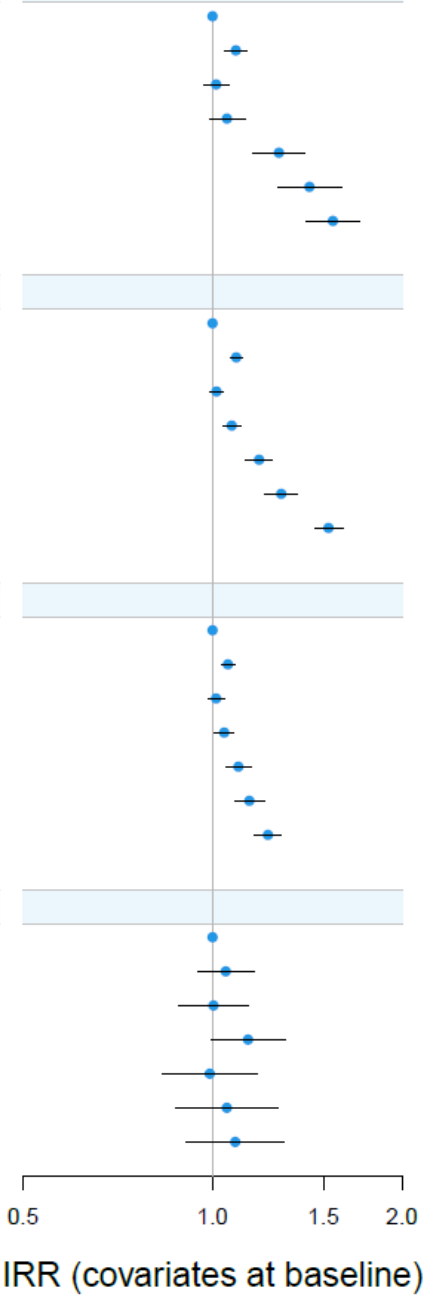


Footnote: Adjusted for educational level, cardiovascular disease, diabetes, hypertension, dyslipidemia, and CCI score. One-year lag-time window applied.

TSD = Total standardized daily dose

eFigure 4. Adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) of the association between cumulative opioid use and all-cause dementia according to age at index with covariates defined at baseline.

Cumulative opioid use (TSDs)	Cases (n, %)	Controls (n, %)	IRR(CI_{95})
60–69 years at index			
No use	7,343 (53.5)	39,974 (58.2)	Reference
Ever use	6,395 (46.5)	28,716 (41.8)	1.09 (1.05–1.13)
0–30	3,312 (24.1)	16,907 (24.6)	1.01 (0.97–1.06)
31–90	1,413 (10.3)	6,592 (9.6)	1.05 (0.99–1.13)
91–200	611 (4.4)	2,233 (3.3)	1.27 (1.16–1.40)
201–500	428 (3.1)	1,306 (1.9)	1.43 (1.27–1.60)
>500	631 (4.6)	1,678 (2.4)	1.55 (1.41–1.72)
70–79 years at index			
No use	20,597 (48.2)	109,909 (51.4)	Reference
Ever use	22,160 (51.8)	103,876 (48.6)	1.09 (1.07–1.12)
0–30	10,529 (24.6)	54,327 (25.4)	1.01 (0.99–1.04)
31–90	5,396 (12.6)	26,004 (12.2)	1.07 (1.04–1.11)
91–200	2,404 (5.6)	10,294 (4.8)	1.19 (1.13–1.24)
201–500	1,603 (3.7)	6,197 (2.9)	1.29 (1.21–1.36)
>500	2,228 (5.2)	7,054 (3.3)	1.53 (1.45–1.61)
80–89 years at index			
No use	12,866 (36.8)	67,292 (38.5)	Reference
Ever use	22,063 (63.2)	107,353 (61.5)	1.06 (1.03–1.08)
0–30	9,392 (26.9)	48,148 (27.6)	1.01 (0.98–1.04)
31–90	5,580 (16.0)	27,628 (15.8)	1.04 (1.01–1.08)
91–200	2,748 (7.9)	12,883 (7.4)	1.10 (1.05–1.15)
201–500	1,890 (5.4)	8,486 (4.9)	1.14 (1.08–1.21)
>500	2,453 (7.0)	10,208 (5.8)	1.22 (1.17–1.29)
90+ years at index			
No use	600 (27.1)	3,123 (28.2)	Reference
Ever use	1,614 (72.9)	7,947 (71.8)	1.05 (0.95–1.17)
0–30	585 (26.4)	3,017 (27.3)	1.00 (0.89–1.14)
31–90	440 (19.9)	1,997 (18.0)	1.14 (0.99–1.31)
91–200	216 (9.8)	1,129 (10.2)	0.99 (0.83–1.18)
201–500	170 (7.7)	832 (7.5)	1.05 (0.87–1.27)
>500	203 (9.2)	972 (8.8)	1.09 (0.91–1.30)

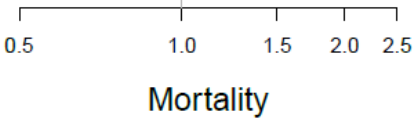


Footnote: Adjusted for educational level, cardiovascular disease, diabetes, hypertension, dyslipidemia, and CCI score at baseline. Five-year lag-time window applied.

TSD = Total standardized daily dose

eFigure 5. Adjusted mortality rate ratios (RR) and 95% confidence intervals (CI) of the association between cumulative opioid use and mortality according to age at index.

Cumulative opioid use (TSDs)	Died (n, %)	Controls (n, %)	Mortality RR(CI_{95})
60–69 years at index			
No use	37,360 (54.4)	211,851 (61.6)	Reference
Ever use	31,372 (45.6)	131,809 (38.4)	1.04 (1.02–1.06)
0–30	14,136 (20.6)	79,386 (23.1)	0.89 (0.87–0.91)
31–90	6,729 (9.8)	29,672 (8.6)	0.99 (0.96–1.03)
91–200	3,297 (4.8)	9,999 (2.9)	1.26 (1.20–1.32)
201–500	2,529 (3.7)	5,763 (1.7)	1.51 (1.43–1.59)
>500	4,681 (6.8)	6,989 (2.0)	2.10 (2.01–2.20)
70–79 years at index			
No use	50,112 (48.6)	285,736 (55.4)	Reference
Ever use	52,973 (51.4)	229,689 (44.6)	1.04 (1.02–1.06)
0–30	22,077 (21.4)	124,593 (24.2)	0.90 (0.88–0.92)
31–90	11,824 (11.5)	55,738 (10.8)	0.98 (0.96–1.00)
91–200	6,114 (5.9)	21,804 (4.2)	1.17 (1.13–1.21)
201–500	4,868 (4.7)	12,910 (2.5)	1.42 (1.37–1.47)
>500	8,090 (7.8)	14,644 (2.8)	1.95 (1.89–2.01)
80–89 years at index			
No use	23,482 (34.2)	135,396 (39.5)	Reference
Ever use	45,117 (65.8)	207,599 (60.5)	1.04 (1.02–1.06)
0–30	16,701 (24.3)	94,331 (27.5)	0.92 (0.90–0.94)
31–90	10,581 (15.4)	53,815 (15.7)	0.97 (0.94–0.99)
91–200	5,807 (8.5)	24,934 (7.3)	1.08 (1.04–1.11)
201–500	4,726 (6.9)	15,896 (4.6)	1.29 (1.24–1.34)
>500	7,302 (10.6)	18,623 (5.4)	1.65 (1.60–1.70)
90+ years at index			
No use	2,473 (26.2)	13,617 (28.9)	Reference
Ever use	6,965 (73.8)	33,573 (71.1)	1.03 (0.98–1.09)
0–30	2,335 (24.7)	12,789 (27.1)	0.96 (0.90–1.02)
31–90	1,746 (18.5)	8,985 (19.0)	0.98 (0.92–1.05)
91–200	1,008 (10.7)	4,751 (10.1)	1.04 (0.95–1.13)
201–500	728 (7.7)	3,092 (6.6)	1.13 (1.03–1.24)
>500	1,148 (12.2)	3,956 (8.4)	1.38 (1.27–1.49)



Footnote: Adjusted for educational level, cardiovascular disease, diabetes, hypertension, dyslipidemia, and CCI score. Five-year lag-time window applied.

TSD = Total standardized daily dose

STUDY III

Bladder Drugs and the Risk of Dementia: Danish Nationwide Active-Comparator Study

Pourhadi N, Janbek J, Gasse C, Munk Laursen T, Meaidi A, Jensen-Dahm C, Waldemar G.
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Bladder drugs and risk of dementia: Danish nationwide active comparator study

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ABSTRACT

OBJECTIVE To assess the association between cumulative use of anticholinergic bladder drugs and risk of all cause dementia compared with non-use and use of the β3 agonist bladder drug, mirabegron.

DESIGN Danish nationwide active comparator study.

SETTING National Danish registries, 1 January 2000 to 31 December 2022.

PARTICIPANTS 129 254 individuals with dementia were matched by age and sex to 646 270 controls without dementia, identified from a cohort of 2.26 million individuals aged 60-75 years between 2000 and 2022 with no previous dementia. Two separate nested case-control populations were studied: the general population and an active comparator population of 58 242 new users of bladder drugs (2198 developed dementia and were matched to 10 990 controls). Information on medication use was based on filled prescriptions and defined daily doses.

MAIN OUTCOME MEASURES Conditional logistic regression provided incidence rate ratios for associations between anticholinergic bladder drugs and dementia compared with non-use and mirabegron use adjusted for educational level, cardiovascular disease, diabetes, hypertension, dyslipidaemia, and Charlson Comorbidity Index.

RESULTS Compared with non-use, ever use of anticholinergic bladder drugs was associated with an increased risk of dementia, with an incidence rate ratio of 1.44 (95% confidence interval (CI) 1.40 to 1.48). The incidence rate ratio increased with increasing cumulative drug use, from 1.31 (95% CI 1.27 to 1.36) for 1-90 defined daily doses to 1.68 (1.59 to 1.76) for >365 defined daily doses. Compared with non-use, all types of anticholinergic bladder drugs were associated with increased incidence rate ratios for dementia: tolterodine 1.43 (95% CI 1.38 to 1.49), solifenacin 1.37 (1.29 to 1.46), trospium 1.52 (1.37 to 1.67), and fesoterodine 1.48 (1.26 to 1.74). The increased risk of dementia with use of anticholinergic bladder drugs was not seen when compared directly with the use of the β3 agonist mirabegron (incidence rate ratio 0.82, 95% CI 0.74 to 0.92), irrespective of the type of anticholinergic drug.

CONCLUSIONS In this study, all types of anticholinergic bladder drugs were associated with an increased risk of dementia compared with non-use, but not when applying the active comparator of the β3 agonist bladder drug mirabegron. These findings highlight the relevance of using an active comparator. Future research should evaluate the risk of cognitive impairment and dementia for both types of bladder drugs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Observational studies have reported an increased risk of dementia with the use of anticholinergic bladder drugs, but most did not consider an active comparator and thus were limited by potential bias

⇒ Head-to-head comparisons are lacking between anticholinergic bladder drugs and the β3 agonist, mirabegron, on the risk of dementia

⇒ Little is known about the different types of anticholinergic bladder drugs as well as the timing of use and the associated risk of dementia

WHAT THIS STUDY ADDS

⇒ Compared with non-use of bladder drugs, use of anticholinergic bladder drugs was associated with an increased risk of all cause dementia, with current and recent use showing the strongest association

⇒ Compared with the use of mirabegron, no increased risk of dementia was found with the use of anticholinergic bladder drugs, regardless of the type of anticholinergic drug

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Validating and using active comparators can be useful to deal with potential biases when studying bladder drugs and the associated risk of dementia

⇒ Studies are needed to investigate the influence of both types of bladder drugs on cognition and the risk of dementia

Introduction

Globally, more than 55 million people live with dementia, presenting an expanding public health concern.[1] Dementia is incurable and is a major cause of death and disability worldwide,[1] and therefore establishing modifiable risk factors is important. Known neurological side effects of anticholinergic drugs include impaired memory and confusion.[2 3] Consequently, several studies have reported that the use of anticholinergic bladder drugs might increase the risk of dementia, potentially because of disruption of cholinergic signalling in the brain, contributing to cognitive decline.[4 5] Most previous studies on this topic, however, did not assess the long term use of bladder drugs or the timing of use in relation to the risk of dementia. These studies were also limited by protopathic bias because bladder symptoms could be an early sign of undiagnosed dementia.[6–10] As such, most studies did not use an active comparator, such as the β3 agonist bladder drug, mirabegron, to deal with this potential bias of reverse causation.

Both anticholinergic and β3 agonist bladder drugs have the same clinical target population. Although little is known about the long term effects of β3 agonists, these drugs are not thought to be associated with dementia, in contrast with anticholinergic agents. Thus the use of mirabegron could be a potential active comparator when examining the associated risk of dementia with the use of anticholinergic bladder drugs.[11 12]

Various subtypes of anticholinergic bladder drugs have shown different neurological side effects in randomised clinical trials, such as cognitive impairment, sedation, and hallucinations, potentially because of differences in their ability to penetrate the blood-brain barrier.[13] However, evidence is sparse on the association between specific anticholinergic subtypes and the risk of dementia when compared with β3 agonist bladder drugs.[14–16] In this nationwide active comparator study, we assessed the associated risk of dementia with cumulative use of anticholinergic bladder drugs compared with both non-use and use of the β3 agonist mirabegron. We further studied the influence of different anticholinergic bladder drugs and timing of use.

Methods

Study design and populations

We conducted a nested case-control study within a Danish nationwide cohort. Based on the Danish national registries, we identified two separate open cohorts of Danish residents (online supplemental table S1). The primary cohort was the general population where we examined the use of anticholinergic bladder drugs compared with non-use, and the associated risk of dementia. The secondary cohort was a population of new users of bladder drugs where we compared anticholinergic bladder drugs with the β3 agonist bladder drug mirabegron and the associated risk of dementia. Thus we used an active comparator, new user study design.

The primary cohort of the general population was individuals aged 60-75 years between 1 January 2000 and 31 December 2022 with no previous history of dementia. One of the aims of the study was to investigate anticholinergic bladder drugs and the associated risk of dementia compared with non-use of bladder drugs, without the potential influence of the use of mirabegron. Therefore, we excluded individuals from the date of filling a prescription for mirabegron (Anatomical Therapeutic Chemical (ATC) code G04BD12), which was introduced in Denmark in mid-2013. Thus this primary population included users of anticholinergic bladder drugs and non-users of bladder drugs and was followed for up to 23 years, from 1 January 2000 until the occurrence of dementia, emigration, death, a filled prescription for mirabegron, or the end of follow-up (31 December 2022).

The secondary cohort of new users of bladder drugs were individuals aged 60-75 years between 2013 and 2022, from the first prescription of any bladder drug after 1 July 2013. We excluded individuals with a previous history of dementia or use of bladder drugs before mirabegron entered the market (1 July 2013). This population was followed for up to 9.5 years, from 1 July 2013 until the occurrence of dementia, emigration, death, or the end of follow-up (31 December 2022).

We identified the study populations from four nationwide Danish registries: Danish National Patient Registry,[17] Danish National Prescription Registry,[18] Danish Psychiatric Central Research Registry,[19] and Danish Education Registries[20] (online supplemental table S1). Data from the registries can be linked by a pseudonymised personal identification number given to all Danish residents.

We nested a case-control population within each of the two nationwide cohorts, generating two matched populations of incident cases of dementia coupled with a set of controls for each incident case. On the date of incident dementia during follow-up (index date), each case was matched by age and sex to five controls with no dementia from the respective source cohort.[21]

Diagnosis of dementia

Individuals with late onset, all cause dementia from age 60 years were identified from registered diagnoses of dementia syndrome of any aetiology or from prescriptions for antidementia drug treatment (ATC code N06D), whichever came first (online supplemental table S1). Hospital diagnoses of dementia were obtained from the National Patient Registry and have high validity.[22] Prescriptions of antidementia drug treatment (provided by the National Prescription Registry) used for Alzheimer's disease, Lewy body dementia, and Parkinson's disease dementia were included to identify individuals with dementia who received a diagnosis and were treated in primary care. In Denmark, dementia is mainly diagnosed in hospital memory clinics.

Use of bladder drugs

We obtained information on the use of anticholinergic bladder drugs (ATC code G04BD except G04BD12) and mirabegron (G04BD12), from the National Prescription Registry. The National Prescription Registry has complete data on all drugs prescribed from Danish pharmacies since 1995.

For each user of anticholinergic bladder drugs in the primary cohort of the general population, the number of defined daily doses and cumulative use was calculated from 1995 up to five years before the index date and categorised as 1-90, 91-365, and >365 defined daily doses. Thus we applied a five year lag time between the use of bladder drugs

and the date of dementia for cases or the equivalent matching date for controls. As such, any prescriptions for anticholinergic bladder drugs within five years of the index date were ignored in the main analyses when comparing users of bladder drugs with non-users. As done in previous studies,[23 24] this lag time was applied to reduce reverse causation or protopathic bias (ie, when early signs or symptoms of undiagnosed dementia (such as bladder symptoms) determines the use of the drug of interest (bladder drugs)).

Anticholinergic bladder drugs were further categorised by type: tolterodine (G04BD07), solifenacin (G04BD08), trospium (G04BD09), and fesoterodine (G04BD11). Because of the low number of users, darifenacin, flavoxate, and oxybutynin could not be studied. To investigate the timing of use of anticholinergic bladder drugs compared with non-use, user status was defined, from the date of the last treatment day according to the index date, as current user (within one year of the index date), recent user (1-5 years before the index date), or past user (>5 years before the index date). Thus no lag time period was applied in the definition and subanalysis of user status.

In the secondary study population of new users of bladder drugs, the number of defined daily doses was cumulated from study entry until the index date. As such, no lag time period was applied by default because reverse causation or protopathic bias was presumably diminished by the reference group being users of mirabegron.

Confounders

The choice of covariates was based on the literature and data availability to include sociodemographic and health related potential confounders with known or suspected associations with the risk of dementia and use of bladder drugs (exact definitions in online supplemental table S1). The highest obtained educational level was included as a socioeconomic confounder and categorised as elementary or secondary school, vocational education, and university education.

Dyslipidaemia, hypertension, and diabetes were defined from diagnoses or from prescriptions for specific drug treatments. Cardiovascular disease was defined as the presence of stroke, ischaemic heart disease, or acute myocardial infarction, or the use of antithrombotic drug treatment. As a measure of the burden of somatic comorbidity, the Charlson Comorbidity Index was identified from diagnoses (0, 1, 2, or ≥3).[25] Variables were assessed at the index date or at the beginning of the lag time period, if applied.

Statistical analysis

Conditional logistic regression gave adjusted incidence rate ratios and 95% confidence intervals (CIs) for associations between cumulative use and user status of anticholinergic bladder drugs and dementia. The reference group in the general population was never users of bladder drugs and the reference group in the population of new users of bladder drugs was users of a mirabegron. In the population of new users of bladder drugs, individuals who had prescriptions for both anticholinergic bladder drugs and mirabegron were categorised separately as mixed users.

Examining potential differences according to the ability of different anticholinergic bladder drugs to penetrate the blood-brain-barrier, we conducted analyses grouped by anticholinergic subtypes.[13–15] Among all of the included individuals, 1.8% had missing information for education and were categorised as missing. All statistical models included the confounding variables as covariates. Data were analysed with SAS software version 9.4 (SAS Institute) and R statistical software.[26]

Sensitivity analyses

For the population of new users of bladder drugs, analyses were further conducted with a two year lag time period to reduce potential confounding from the clinical, physician level selection of individuals with impaired cognition or a higher risk of dementia to receive mirabegron instead of anticholinergic bladder drugs because of increased awareness of the side effects of anticholinergic drugs.[27] For the general population, analyses were also conducted without a lag time. Mortality rate was estimated among users of anticholinergic bladder drugs versus users of mirabegron for an indication of the potential competing risk of death.[28]

Patient and public involvement

The design of the study, analysis, and manuscript writing did not involve patients or members of the public because the study was carried out without funding or staff for their inclusion. The study findings, however, will be communicated to the public and healthcare professionals through press releases, conference presentations, and social media posts.

Results

We followed 2.26 million eligible individuals in the general Danish population from 2000 to 2022, and observed 129 254 incidences of dementia which were matched to 646 270 controls. The secondary study population, followed from 2013 to 2022, comprised 58 242 new users of bladder drugs of whom 2198 developed dementia and were matched to 10 990 controls. Figure 1 shows how the main and secondary study populations were established.

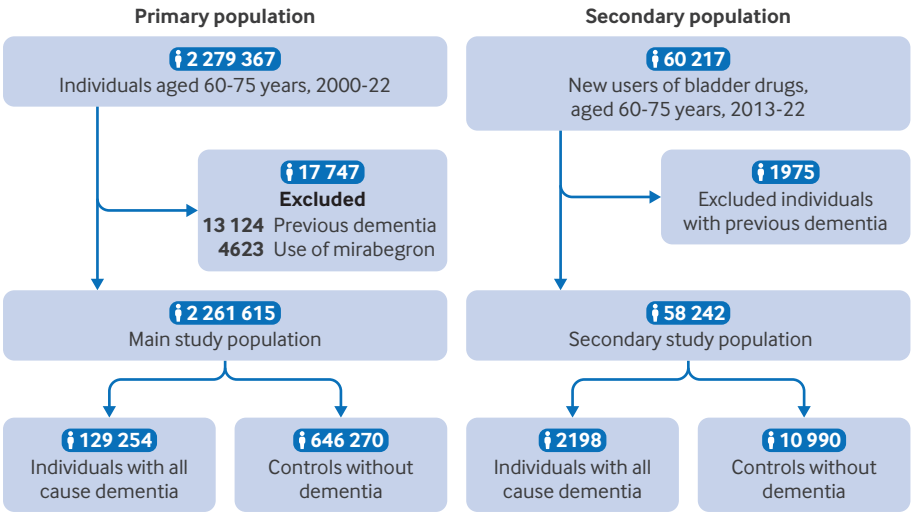

Figure 1 | Flowchart of selection of the study populations and nested case-control populations. During follow-up in the general population, 693 888 individuals were censored because of emigration (n=14 080), death (n=620 707), or use of mirabegron (n=59 097)

Table 1 shows the characteristics of the main nested case-control population. Among individuals with dementia, 55.8% were women and median age at diagnosis was 78.5 years (interquartile range (IQR) 73.5-83.2). Individuals with dementia had more comorbidities than controls, and were more likely to have used anticholinergic bladder drugs (6.2% *v* 4.2%) with a higher cumulative use (median 90 (IQR 30-435) *v* 60 (28-320) defined daily doses).

Table 2 shows characteristics of the secondary population according to the use of bladder drugs. Among new users of bladder drugs, 5746 (43.6%) used mirabegron only, 5026 (38.1%) used anticholinergic drugs only, and 2416 (18.3%) used both types and were categorised separately as mixed users. Users of both mirabegron and anticholinergic bladder drugs had a similar age at the start of treatment (median 73.7 *v* 73.4 years) and median cumulative drug use (90 (IQR 30-360) *v* 100 (30-360) defined daily doses). Comorbidities, other than dementia, were comparable among users of mirabegron and anticholinergic drugs.

Compared with non-use in the general population, ever use of anticholinergic bladder drugs was associated with an increased incidence rate ratio for all cause dementia of 1.44 (95% CI 1.40 to 1.48) that increased with increasing cumulative use (figure 2). All of the anticholinergic bladder drugs were associated with increased incidence rate ratios for dementia. The rate of dementia was highest for current users (incidence rate ratio 2.18, 95% CI 2.11 to 2.25) and lowest for past users (1.24, 1.20 to 1.28). The sensitivity analysis without a lag time gave overall higher rates of dementia with use of anticholinergic bladder drugs than the main analysis with a lag time of five years (online supplemental figure S1).

Compared with the use of mirabegron in the population of new users of bladder drugs, anticholinergic bladder drugs were not associated with an increased risk of dementia, but rather a slightly reduced incidence rate ratio (0.82, 95% CI 0.74 to 0.92) (figure 3). Incidence rate ratios according to the different anticholinergic drugs were 0.77 (0.67 to 0.89) for tolterodine, 0.82 (0.71 to 0.96) for solifenacin, 0.79 (0.59 to 1.05) for trospium, and 0.96 (0.65 to 1.43) for fesoterodine. The sensitivity analysis with a two year lag time among new users of bladder drugs gave similar findings to the main analysis without a lag time (online supplemental figure S2). Compared with the use of mirabegron, use of anticholinergic bladder drugs was associated with a mortality rate ratio of 1.04 (95% CI 0.98 to 1.11) (online supplemental figure S3).

Discussion

Principal findings

Although this nationwide study showed an increased risk of dementia associated with anticholinergic bladder drugs compared with non-use, we found no increased risk of dementia compared with the use of the β3 agonist, mirabegron. We found no consistent risk difference among the different anticholinergic bladder drugs. Current and recent use of anticholinergic bladder drugs showed the highest dementia rates compared with non-use of bladder drugs.

Comparison with other studies

Consistent with several previous studies, we found that the use of anticholinergic bladder drugs was positively associated with the risk of dementia compared with non-use in the general population.[29] Compared with the use of a β3 agonist bladder drug, however, anticholinergic bladder drugs were not associated with an increased risk of dementia, in contrast with findings of previous studies reporting positive associations between anticholinergic drugs

Table 1 | Characteristics of cases of all cause dementia and controls with no dementia in the general population

Variable	Cases (n=129 254)	Controls (n=646 270)
Sex (women)	72 126 (55.8)	360 630 (55.8)
Median (IQR) age at index date (years)	78.5 (73.5-83.2)	78.5 (73.5-83.2)
Median (IQR) follow-up time (years)	12.7 (8.1-16.8)	19.6 (15.4-23.0)
Median (IQR) year of index date	2014 (2009-18)	2014 (2009-18)
Use of anticholinergic bladder drugs	8051 (6.2)	27 436 (4.2)
Median (IQR) cumulative use (defined daily doses)	90 (30-435)	60 (28-320)
Median (IQR) age at start of treatment (years)	72.5 (67.1-77.2)	73.0 (67.6-77.7)
User status:*		
Current user	5711 (4.4)	12 837 (2.0)
Recent user	3778 (2.9)	11 865 (1.8)
Past user	4647 (3.6)	18 304 (2.8)
Education:		
Elementary or secondary school	63 161 (48.9)	304 924 (47.2)
Vocational education	45 977 (35.6)	232 657 (36.0)
University education	17 768 (13.7)	96 791 (15.0)
Missing	2348 (1.8)	11 898 (1.8)
Cardiovascular disease:	57 759 (44.7)	252 767 (39.1)
Stroke	12 359 (9.6)	39 849 (6.2)
Ischaemic heart disease	27 549 (21.3)	122 971 (19.0)
Antithrombotic drug treatment	49 118 (38.0)	215 294 (33.3)
Diabetes	15 565 (12.0)	59 798 (9.3)
Hypertension	83 683 (64.7)	395 435 (61.2)
Dyslipidaemia	43 412 (33.6)	196 929 (30.5)
Charlson Comorbidity Index:		
0	83 935 (64.9)	441 556 (68.3)
1	20 326 (15.7)	89 173 (13.8)
2	16 797 (13.0)	80 092 (12.4)
≥3	8196 (6.3)	35 449 (5.5)
AIDS or HIV	33 (0.0)	159 (0.0)
Chronic pulmonary disease	10 834 (8.4)	47 011 (7.3)
Heart failure	6419 (5.0)	26 153 (4.0)
Hemiplegia or paraplegia	372 (0.3)	1501 (0.2)
Mild liver disease	1652 (1.3)	5238 (0.8)
Peptic ulcer disease	7821 (6.1)	30 917 (4.8)
Peripheral vascular disease	7506 (5.8)	31 178 (4.8)
Renal disease	1758 (1.4)	7506 (1.2)
Rheumatic disease	5742 (4.4)	26 535 (4.1)
Severe liver disease	309 (0.2)	912 (0.1)
Any malignancy	15 984 (12.4)	79 396 (12.3)
Metastatic solid tumour	904 (0.7)	4391 (0.7)
Leukaemia	316 (0.2)	1807 (0.3)
Lymphoma	783 (0.6)	3703 (0.6)

Data are number (%) unless indicated otherwise.

Values for use of anticholinergic bladder drugs (except user status) include a five year lag time period.

*User status was defined from the latest treatment day according to the index date: current user=within one year of the index date; recent user=1-5 years before the index date; and past user=>5 years before the index date.

IQR, interquartile range.

and dementia compared with mirabegron.[14 30 31] These studies, however, were particularly affected by limited data on the use of the relatively newly marketed mirabegron. The most recent study, based on Korean national health data, had a maximum of six years of mirabegron use (2015-20) compared with 9.5 years in our study (2013-22).[31] Another study based on data from a Canadian province had <3 years of prescription data on the use of mirabegron.[30] A study based on the same Canadian data considered the use of bladder drugs only within the previous 6-12 months before a diagnosis of dementia and therefore did not examine long term use.[14]

The most recent study, based on UK registry data, reported increased odds ratios for dementia with the use of different bladder drugs, including mirabegron.[16] In that study, however, mirabegron was mainly a second line treatment for overactive

Table 2 | Characteristics of new users of bladder drugs, according to type of bladder drug

Variable	Mirabegron drug users (n=5746)	Anticholinergic drug users (n=5026)	Mixed users (n=2416)
Dementia	1011 (17.6)	752 (15.0)	435 (18.0)
Sex (women)	1813 (31.6)	1763 (35.1)	1038 (43.0)
Median (IQR) age at index date (years)	76.4 (72.6-79.4)	76.2 (72.4-79.2)	77 (73.4-79.7)
Median (IQR) follow-up time (years)	4.9 (2.9-6.8)	4.8 (2.7-7.1)	5.5 (3.7-7.3)
Median (IQR) year of index date	2020 (2018-21)	2020 (2018-21)	2020 (2019-22)
Median (IQR) cumulative use (defined daily doses)	90 (30-360)	100 (30-360)	450 (175-1096)
Median (IQR) age at start of treatment (years)	73.7 (70.1-76.5)	73.4 (69.9-76.4)	73.1 (69.6-76.0)
One prescription only	1949 (33.9)	2148 (42.7)	—
Education:			
Elementary or secondary school	1810 (31.5)	1628 (32.4)	764 (31.6)
Vocational education	2589 (45.1)	2315 (46.1)	1105 (45.7)
University education	1246 (21.7)	994 (19.8)	512 (21.2)
Missing	101 (1.8)	89 (1.8)	35 (1.4)
Cardiovascular disease:	2961 (51.5)	2544 (50.6)	1229 (50.9)
Stroke	540 (9.4)	491 (9.8)	252 (10.4)
Ischaemic heart disease	1421 (24.7)	1230 (24.5)	565 (23.4)
Antithrombotic drug treatment	2664 (46.4)	2262 (45.0)	1114 (46.1)
Diabetes	989 (17.2)	826 (16.4)	435 (18.0)
Hypertension	4149 (72.2)	3670 (73.0)	1840 (76.2)
Dyslipidaemia	2960 (51.5)	2484 (49.4)	1276 (52.8)
Charlson Comorbidity Index:			
0	2717 (47.3)	2535 (50.4)	1026 (42.5)
1	955 (16.6)	831 (16.5)	406 (16.8)
2	1200 (20.9)	961 (19.1)	570 (23.6)
3+	874 (15.2)	699 (13.9)	414 (17.1)
AIDs/HIV	<10 (<0.2)	<10 (<0.2)	<10 (<0.4)
Chronic pulmonary disease	844 (14.7)	653 (13.0)	366 (15.1)
Heart failure	448 (7.8)	352 (7.0)	154 (6.4)
Hemiplegia/paraplegia	49 (0.9)	59 (1.2)	36 (1.5)
Mild liver disease	139 (2.4)	92 (1.8)	46 (1.9)
Peptic ulcer disease	353 (6.1)	313 (6.2)	170 (7.0)
Peripheral vascular disease	559 (9.7)	456 (9.1)	249 (10.3)
Renal disease	166 (2.9)	159 (3.2)	80 (3.3)
Rheumatic disease	339 (5.9)	304 (6.0)	188 (7.8)
Severe liver disease	18 (0.3)	24 (0.5)	11 (0.5)
Any malignancy	1354 (23.6)	1112 (22.1)	651 (26.9)
Metastatic solid tumour	118 (2.1)	78 (1.6)	47 (1.9)
Leukaemia	36 (0.6)	31 (0.6)	10 (0.4)
Lymphoma	89 (1.5)	69 (1.4)	57 (2.4)

Data are number (%) unless indicated otherwise.
IQR, interquartile range.

bladder syndrome, and so most users of mirabegron had previously used anticholinergic bladder drugs. Therefore, the authors called for future research to study mirabegron users who had not previously used anticholinergic bladder drugs. In Denmark, both mirabegron and anticholinergic bladder drugs are recommended pharmacological treatments for patients with an overactive bladder,[32] also reflected by the comparable distribution of users of mirabegron versus users of anticholinergic bladder drugs in the population of new users of bladder drugs. Hence differences in research setting, follow-up time, and data availability or inclusion might explain our different findings. Our study was designed to examine the long term use of both anticholinergic bladder drugs and mirabegron and the associated subsequent long term risk of dementia.

Although with conflicting results, previous studies have reported differential risks of dementia with different anticholinergic bladder drugs, potentially explained by differences in penetrating the blood-brain barrier.[13–16] Overall, solifenacin, tolterodine, and fesoterodine have previously been found to be associated with an increased risk of dementia whereas trospium has not.[14 31] Trospium has a low ability to cross the blood-brain barrier and an

Anticholinergic bladder drug	No of cases (%)	No of controls (%)	Incidence rate ratio (95% CI)
Ever use			
No use	121 203 (93.8)	618 834 (95.8)	Reference
Ever use	8051 (6.2)	27 436 (4.2)	1.44 (1.40 to 1.48)
Cumulative use			
1-90 DDDs	4117 (3.2)	15 425 (2.4)	1.31 (1.27 to 1.36)
91-365 DDDs	1764 (1.4)	5685 (0.9)	1.53 (1.44 to 1.61)
>365 DDDs	2170 (1.7)	6326 (1.0)	1.68 (1.59 to 1.76)
Subtype			
Tolterodine	3283 (2.5)	11 234 (1.7)	1.43 (1.38 to 1.49)
Solifenacin	1326 (1.0)	4771 (0.7)	1.37 (1.29 to 1.46)
Trospium	526 (0.4)	1704 (0.3)	1.52 (1.37 to 1.37)
Fesoterodine	188 (0.1)	628 (0.1)	1.48 (1.26 to 1.74)
User status			
Current user	5711 (4.4)	12 837 (2.0)	2.18 (2.11 to 2.25)
Recent user	3778 (2.9)	11 865 (1.8)	1.57 (1.51 to 1.63)
Past user	4647 (6.3)	18 304 (2.8)	1.24 (1.20 to 1.28)

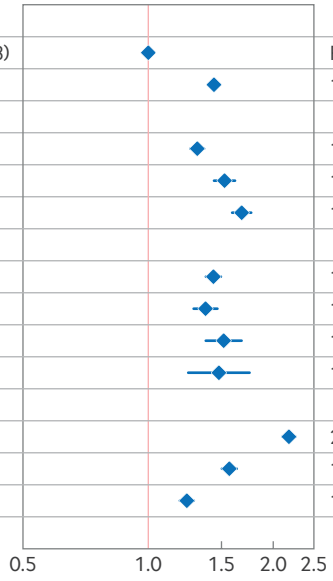

Figure 2 | Adjusted incidence rate ratios and 95% confidence intervals (CIs) of the association between cumulative use of anticholinergic bladder drugs and all cause dementia compared with no use in the general population. User status was defined from the latest treatment day according to the index date: current user=within one year of the index date; recent user=1-5 years before the index date; and past user=>5 years before the index date. Adjusted for educational level, cardiovascular disease, diabetes, hypertension, dyslipidaemia, and Charlson Comorbidity Index. Five year lag time period was applied except in the user status subanalysis. DDD=defined daily dose

anticholinergic effect on cognition score of zero. In contrast, the anticholinergic effect on cognition score for tolterodine is two out of three, with markedly increased penetration of the blood-brain barrier.[33] We did not find significant differences in the risk of dementia across different anticholinergic drugs, however, which could indicate a potential influence of the indication of the drugs or patient characteristics rather than the actual drugs. Nonetheless, we did not evaluate other measures of cognition, other than dementia and use of antidementia drug treatment.

Although previous studies did not investigate the effect of timing of use of anticholinergic drugs, we found that the associated risk of dementia compared with non-use seemed to be highest for drug use close to the time of the diagnosis of dementia. Also, in the sensitivity analysis without a lag time, we found higher risk estimates than the main analysis with a

Bladder drug user status	No of cases (%)	No of controls (%)	Incidence rate ratio (95% CI)
Ever use			
Mirabegron	1011 (46.0)	4735 (43.1)	Reference
Anticholinergic bladder drug	752 (34.2)	4274 (38.9)	0.82 (0.74 to 0.91)
Cumulative use			
1-90 DDDs	297 (13.5)	1944 (17.7)	0.72 (0.62 to 0.82)
91-365 DDDs	239 (10.9)	1334 (12.1)	0.84 (0.72 to 0.78)
>365 DDDs	216 (9.8)	996 (9.1)	1.00 (0.85 to 1.18)
Subtype			
Tolterodine	329 (15.0)	1978 (18.0)	0.77 (0.67 to 0.89)
Solifenacin	259 (11.8)	1486 (13.5)	0.82 (0.71 to 0.96)
Trospium	58 (2.6)	342 (3.1)	0.79 (0.59 to 1.05)
Fesoterodine	32 (1.5)	155 (1.4)	0.96 (0.65 to 1.43)

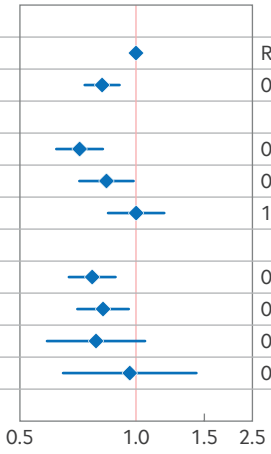

Figure 3 | Adjusted incidence rate ratios and 95% confidence intervals (CIs) of the association between cumulative use of anticholinergic bladder drugs and all cause dementia compared with users of mirabegron in a population of new users of bladder drugs. Adjusted for educational level, cardiovascular disease, diabetes, hypertension, dyslipidaemia, and Charlson Comorbidity Index. No lag time period was applied. DDD=defined daily dose

lag time. This finding could reflect the influence of protopathic bias or short term cognitive side effects of anticholinergic bladder drugs.

The absence of a positive association between anticholinergic bladder drugs and dementia when compared with mirabegron, could mean that the association, compared with non-use, is influenced by reverse causation or indication bias. Thus the observed association in our study and previous studies might in part reflect an underlying association between lower urinary tract symptoms and dementia rather than an effect of the drug used to treat the condition.[10]

Nevertheless, other explanations cannot be ruled out. Firstly, both types of bladder drugs might increase the risk of dementia, but knowledge is limited about the long term neurological effects of β3 agonists.[34] Further studies are needed to examine the influence of bladder drugs on cognition and the risk of dementia. Secondly, individuals with higher risk profiles for dementia could be selected by prescribing doctors to receive mirabegron over anticholinergic drugs for their bladder symptoms,[35] which might explain the observed negative association. Findings from the sensitivity analyses with a two year lag time as well as the similarity of health related characteristics between new users of anticholinergic bladder drugs and mirabegron, however, indicate that this explanation is less likely. Patients could be selected at the physician level, however, based on other factors, such as frailty or mild cognitive impairment, which cannot be directly determined from the national Danish registries. If present, this potential bias is likely to be more pronounced in the more recent years owing to increased awareness of limiting the use of centrally acting anticholinergic drugs especially in older adults with cognitive impairment or dementia.[27 36–38]

Strengths and weaknesses of this study

The strengths of the study include reduced selection bias by studying a nationwide population with a long follow-up period. Information bias was reduced by using filled prescriptions to measure drug use. Dementia diagnoses, defining the outcome of interest, had high validity.[22] We tackled protopathic bias and confounding by indication by applying an active comparator, new user study design with adjustment for several potential confounders and application of a lag time period. Since the introduction of mirabegron into the Danish market in 2013, it has been used increasingly and represented 43% of prescribed urological bladder drugs in 2022, making Denmark a relevant research setting for our study question of comparing anticholinergic bladder drugs with mirabegron.[39]

Our study limitations included our inability to differentiate between the different causes of dementia because of under-registration and also the low validity of diagnoses of dementia subtypes in Danish hospital registries during the study period.[22] The anticholinergic bladder drugs darifenacin, flavoxate, and oxybutynin could not be evaluated individually because of the low number of users in Denmark.[39]

Although we adjusted for several relevant potential confounders, residual confounding cannot be ruled out considering the known association between bladder symptoms and dementia.[40] We specifically dealt with this confounding by implementing the use of mirabegron as an active comparator. Although both anticholinergic bladder drugs and β3 agonists could potentially affect the risk of dementia, this finding suggests the possibility of residual bias when comparing bladder drug use with non-use. By contrast, residual confounding from physician level selection of individuals with a higher risk of dementia to receive mirabegron could occur, although the similarities between the characteristics of users of anticholinergic bladder drugs versus users of mirabegron argues against this potential bias substantially affecting the study findings.

Finally, competing risk of death among users of anticholinergic bladder drugs was not directly accounted for. Nevertheless, considering that the mortality rate was only marginally, and insignificantly, increased compared with users of mirabegron, the study findings and interpretation are unlikely to have been affected.

Conclusions

In this study, we found that the use of anticholinergic bladder drugs was associated with an increased risk of dementia compared with non-use in the general population, but not compared with use of mirabegron in a population of users of bladder drugs. Current use gave the highest risk estimates. We found no differences in risk for the different types of anticholinergic bladder drugs. More studies are needed to further investigate the risk of cognitive impairment and dementia for both anticholinergic bladder drugs and mirabegron.

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Contributors The study was initiated by NP, GW, CJ-D, and JJ. All authors contributed to the study design and methods. NP, JJ, CJ-D, GW, and TML had access to the data. Data was verified by NP and JJ, and analyses were conducted by NP. All authors contributed to interpretation. NP drafted the manuscript, and all authors contributed

to review and editing. All authors had access to the analysed data, approved the final version of the manuscript, and agreed with submission for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. NP is the guarantor. Transparency: The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the Copenhagen University Hospital-Rigshospitalet and the Danish Ministry of Health for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval According to Danish law, studies based on the national Danish registries are not required to obtain ethical approval or patient consent. This study was approved by the Danish Health Data Authority and the Danish Data Protection Agency (ID No P-2021-250).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. This study was based on raw data derived from the national Danish registries only available with approval from the Danish Health Data Board and the Danish Data Protection Agency. Because the data were accessible on an individual level, data sharing is restricted by the General Data Protection Regulation (GDPR) of European Union law. The protocol and programme code for the study can be accessed on request from the corresponding author.

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Supplementary Material

Bladder drugs and the risk of dementia:

Danish nationwide active-comparator study

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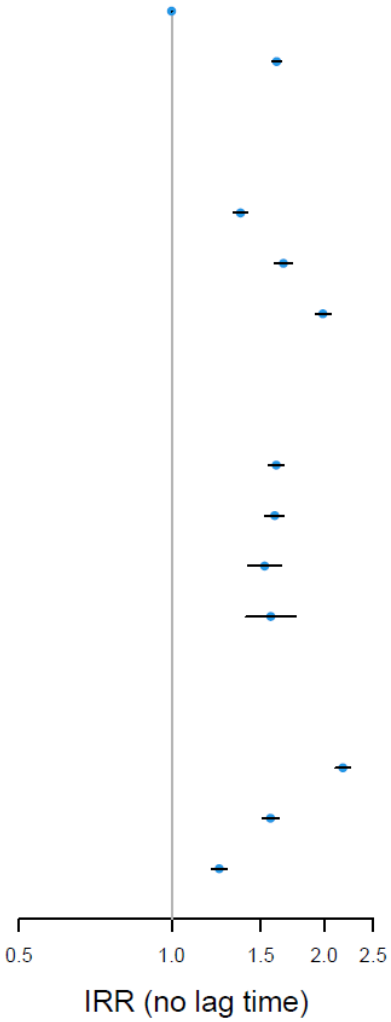
Supplementary Table S1. Diagnosis- and drug codes

Variable		Data source	Period of data availability	Classification system	Definition	
					ICD 8 & 10	ATC code
Dementia		The National Patient Registry, The Danish Psychiatric Central Research Registry & The National Prescription Registry	1977-2022 & 1995-2022	ICD-8, ICD-10, & ATC	290, F00, F01, F02, F03, G30, G31.8-9	N06D
Anticholinergic bladder drugs		The National Prescription Registry	1995-2022	ATC	-	G04BD except G04BD12
Beta-3 agonist bladder drugs						G04BD12
Cardio-vascular disease	Stroke	The National Patient Registry	1977-2022	ICD-8 & ICD-10	430-434, 436, I60-I64, I69	-
	Ischemic heart disease & acute myocardial infarction	The National Patient Registry & The National Prescription Registry	1977-2022 & 1995-2022	ICD-8, ICD-10, & ATC	410.99, I20-I25	C01DA
	Oral antithrombotic medication & anticoagulants	The National Prescription Registry	1995-2022	ATC	-	B01A
Diabetes Mellitus		The National Patient Registry & The National Prescription Registry	1977-2022 & 1995-2022	ICD-8, ICD-10, & ATC	249-250, E10-E14	A10
Hypertension		The National Patient Registry & The National Prescription Registry	1977-2022 & 1995-2022	ICD-8, ICD-10, & ATC	400-404, 410.09, 411.09, 412.09, 413.09, 414.09, 435.09, 437.00, 437.01, 437.08, 437.09, 438.09, I10-I13, I15	C02-C04, C07-C09
Dyslipidaemia		The National Patient Registry & The National Prescription Registry	1977-2022 & 1995-2022	ICD-8, ICD-10, & ATC	279.00, E78.0	C10
Charlson Comorbidity Index (modified)						
Congestive heart failure		The National Patient Registry	1977-2022	ICD-8 & ICD-10	42709, 42710, 42711, 42719, 42899, 78249, I50, I110, I130, I132	
Peripheral vascular disease					440, 441, 442, 443, 444, 445, I70, I71, I72, I73, I74, I77	

Chronic pulmonary disease				490-493, 515-518, J40-J47, J60-J67, J684, J701, J703, J841, J920, J961, J982, J983
Connective tissue disease				712, 716, 734, 446, 13599, M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
Ulcer disease				53091, 53098, 531-534, K221, K25-K28
Mild liver disease				571, 57301, 57304, B18, K700-K703, K709, K71, K73, K74, K760
Hemiplegia				344, G81, G82
Moderate to severe renal disease				403, 404, 580-585, 59009, 59319, 75310-75319, 792, I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Moderate to severe liver disease				07000, 07002, 07004, 07006, 07008, 57300, 45600-45609, B150, B160, B162, B190, K704, K72, K766, I85
AIDS				07983, B21-B24
Any tumor				140-194, C00-C75
Leukaemia				204-207, C91-C95
Lymphoma				200-203, 27559, C81-C86, C88, C90, C96
Metastatic solid tumor				195-198, 199, C76-C80
Socioeconomic variable				
Education	Danish Education Registries	1980-2022	Highest obtained education - International Standard Classification of Education	Definition: Elementary/secondary school; Vocational education; University education

Supplementary Figure S1. Adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) of the association between cumulative anticholinergic bladder drug use and dementia compared with no use in the general population without lag time.

Anticholinergic bladder drug	Cases (n, %)	Controls (n, %)	IRR(CI_{95})
Ever use			
No use	115,115 (89.1)	603,248 (93.3)	Ref
Ever use	14,139 (10.9)	43,022 (6.7)	1.61 (1.58 to 1.65)
Cumulative use			
1–90 DDDs	5,862 (4.5)	21,132 (3.3)	1.37 (1.33 to 1.41)
91–365 DDDs	3,204 (2.5)	9,475 (1.5)	1.66 (1.60 to 1.73)
>365 DDDs	5,070 (3.9)	12,399 (1.9)	1.99 (1.92 to 2.06)
Subtype			
Tolterodine	5,230 (4.0)	15,967 (2.5)	1.61 (1.56 to 1.66)
Solifenacin	2,998 (2.3)	9,292 (1.4)	1.60 (1.53 to 1.67)
Trospium	904 (0.7)	2,897 (0.4)	1.53 (1.42 to 1.65)
Fesoterodine	421 (0.3)	1,315 (0.2)	1.57 (1.41 to 1.75)
User status			
Current user	5,711 (4.4)	12,837 (2.0)	2.18 (2.11 to 2.25)
Recent user	3,778 (2.9)	11,865 (1.8)	1.57 (1.51 to 1.63)
Past user	4,647 (3.6)	18,304 (2.8)	1.24 (1.20 to 1.28)



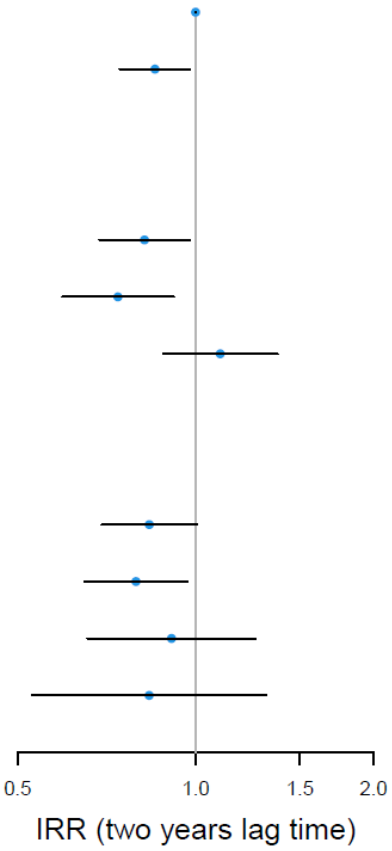
Footnote: User status defined from the latest treatment day according to index: Current: Within 1 year of index; Recent: 1-5 years before index; Past: >5 years before index.

Adjusted for educational level, cardiovascular disease, diabetes, hypertension, dyslipidaemia, and CCI score. No lag-time window applied.

DDD = Defined Daily Dose

Supplementary Figure S2. Adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) of the association between cumulative use of anticholinergics and dementia compared with users of beta-3 agonists in a population of new bladder drug users with two years lag time.

Bladder drug user status	Cases (n, %)	Controls (n, %)	IRR(CI_{95})
Ever use			
Beta−3 agonist bladder drug	573 (26.1)	2,716 (24.7)	Ref
Anticholinergic bladder drug	438 (19.9)	2,415 (22.0)	0.85 (0.74 to 0.98)
Cumulative use			
Anticholinergic, 1−90 DDDs	205 (9.3)	1,183 (10.8)	0.82 (0.69 to 0.98)
Anticholinergic, 91−365 DDDs	116 (5.3)	737 (6.7)	0.74 (0.59 to 0.92)
Anticholinergic, >365 DDDs	117 (5.3)	495 (4.5)	1.10 (0.88 to 1.38)
Subtype			
Tolterodine	179 (8.1)	1,004 (9.1)	0.84 (0.69 to 1.00)
Solifenacin	147 (6.7)	873 (7.9)	0.79 (0.65 to 0.97)
Trospium	47 (2.1)	245 (2.2)	0.91 (0.66 to 1.26)
Fesoterodine	23 (1.0)	130 (1.2)	0.83 (0.53 to 1.32)



Footnote: Adjusted for educational level, cardiovascular disease, diabetes, hypertension, dyslipidaemia, and CCI score. Two-years lag-time window applied.

DDD = Defined Daily Dose

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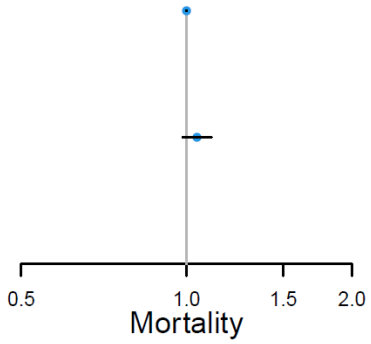
Supplementary Figure S3. Adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) of the association between use of anticholinergics and mortality compared with users of beta-3 agonists in a population of new bladder drug users.

Bladder drug ever use	Died (n, %)	Controls (n, %)	IRR(CI_{95})
Beta−3 agonist bladder drug	3,281 (42.0)	16,568 (42.5)	1.00 (1.00 to 1.00)
Anticholinergic bladder drug	3,161 (40.5)	15,784 (40.4)	1.04 (0.98 to 1.11)



Footnote: Adjusted for educational level, cardiovascular disease, diabetes, hypertension, dyslipidaemia, and CCI score. No lag-time window applied.

DDD = Defined Daily Dose

STUDY IV

Polypharmacy in People with Dementia: A Nationwide Danish Study

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Polypharmacy in people with dementia:

A nationwide Danish study

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Abstract

Importance: Polypharmacy, particularly central nervous system (CNS)-active polypharmacy, is widespread in individuals with dementia and may accelerate cognitive decline and increase hospitalization and mortality risks. Identifying the extent and trends of polypharmacy is essential for optimizing medication use in this vulnerable population.

Objective: To examine the prevalence, time trends, and adjusted odds of polypharmacy and CNS-active polypharmacy in older adults with dementia compared to those without dementia.

Design: A series of nationwide cross-sectional population-based studies.

Setting: National Danish registers.

Participants: The study included all Danish residents aged ≥65 years (N=1,184,366) as of January 1, 2022, including 38,252 individuals with dementia. Dementia, along with somatic and psychiatric comorbidities, was identified through hospital diagnoses, while medication use was assessed based on filled prescriptions. Historical trends were examined from 2012 to 2022.

Exposure: Dementia diagnosis or dementia-specific medication use.

Main Outcomes and Measures: Polypharmacy was defined as concurrent use of ≥5 medications, and CNS-active polypharmacy as ≥3 CNS-active drugs (antidepressants, antipsychotics, antiepileptics, anxiolytics, hypnotics, or opioids). Age- and sex-standardized prevalences were calculated by direct standardization. Adjusted odds ratios (ORs) for polypharmacy and CNS-active polypharmacy were estimated using logistic regression.

Results: Among 1,184,366 individuals in 2022, 38,252 (3.2%) had dementia (59.4% female) with median age of 82 years (IQR, 77–87 years). Polypharmacy was identified in 56.2% of those with dementia, compared to 35.6% without dementia, fully adjusted OR, 1.47 (95% CI, 1.44–1.51). CNS-active polypharmacy was observed in 10.1% of individuals with dementia and 2.3% of those without, fully adjusted OR, 2.70 (95% CI, 2.59–2.81). Cardiovascular medications were the most frequently used among individuals with dementia experiencing polypharmacy. For CNS-active polypharmacy, antidepressants, opioids, and antipsychotics were most common. Between 2012 and 2022, polypharmacy prevalence in dementia declined from 65.1% to 56.2%, and CNS-active polypharmacy from 15.0% to 10.1%.

Conclusions and Relevance: While polypharmacy and CNS-active polypharmacy in dementia have declined over the past decade, likely influenced by targeted safer prescribing initiatives, they remain disproportionately high in individuals with dementia. The findings reinforce the need for continued interventions to support safe medication use in dementia care.

Introduction

Polypharmacy among older adults, commonly defined as simultaneous use of five or more drugs, is associated with several adverse outcomes including hospitalization, increased mortality, and drug-drug interactions[1,2]. Although prescribed in accordance with labelled indications, the harms of some pharmacological products may outweigh the benefits, particularly in older adults with dementia[2,3]. Additionally, dementia complicates the assessment and reporting of both the effectiveness and side effects of medications[4].

The high prevalence of multimorbidity and polypharmacy in people with dementia coupled with increased vulnerability to the risks of polypharmacy give rise to clinical and public health challenges[2,5]. People with dementia often have somatic and psychiatric comorbidities leading to complex medical and psychosocial needs. Despite limited evidence of efficacy, behavioral and psychological symptoms are often treated pharmacologically with central nervous system (CNS)-active drugs i.e., psychotropic medications and opioids. CNS-active polypharmacy among people with dementia may further worsen cognition and accelerate the progression of symptoms[6]. Additionally, anticholinergics and sedatives have been associated with increased mortality and hospitalization among people with dementia[7]. As such, interventions to optimize prescribing practices are crucial, especially for this vulnerable population[8].

Nationwide data on the presence of polypharmacy and CNS-active polypharmacy in adults with dementia is limited. In Denmark, from 2000 to 2015, the use of potentially inappropriate medication declined among older adults[9]. Nonetheless, in 2014, 62.6% of individuals with dementia were exposed to polypharmacy versus 35.1% in individuals without dementia[10]. However, it is unknown whether this is entirely explained by differential burden of somatic and psychiatric comorbidity or whether subsequent recommendations on safe prescribing including non-pharmacological practises[11,12] have altered the presence of polypharmacy and CNS-active polypharmacy[8,13–16].

To update previous findings, the aim of this nationwide cross-sectional study of the Danish population aged 65+ years was to investigate the prevalence and odds of polypharmacy and CNS-active polypharmacy considering burden of disease in individuals with dementia compared to individuals without dementia. Additionally, we investigated time trends of polypharmacy levels, the influence of living situation (community-dwelling or nursing home), and the most frequently used drugs in the older adult Danish population.

Methods

Study design and population

Using the national Danish registers, we conducted a nationwide cross-sectional study of the Danish population. The study population comprised a cohort of all Danish residents aged 65 years and above at baseline on 1 January 2022. A history of young onset dementia before age 65 years was an exclusion criterion due to the focus on late-onset all-cause dementia. Individuals immigrating to Denmark after 1 January 2022 were not included. Individuals who died or emigrated during the study period from 1 January 2022 to 31 March 2022 were included in the study population.

This study was based on national register data from the (1) Danish National Patient Register[17], (2) Danish Psychiatric Central Research Register[18], (3) Danish National Prescription Register[19], (4) Danish Education Register[20], and (5) Care Home Data [21]. In Denmark, all residents are assigned a unique personal identification number registered in the Civil Registration System[22] allowing for reliable linkage of data across the registers.

Dementia

Dementia status was assessed for the study population on 1 April 2022 (end of study period). People with dementia included individuals with prevalent late-onset all-cause dementia (from age 65+ years) registered before 1 April 2022. Dementia was defined as the first date of a registered dementia syndrome diagnosis or treatment with dementia-specific medication (Appendix Table 1). Dementia syndrome diagnoses in Danish hospital registers have high validity with a positive predictive value of 85.8%[23].

Polypharmacy

Information on use of pharmacological products in the study population was drawn from the National Danish Prescription Register providing complete data on all prescriptions redeemed from Danish community pharmacies since 1995. Drug use was identified through the specific Anatomical Therapeutic Chemical (ATC) codes. Other than the ATC-code, prescription data further included the date of purchase, package/unit size, and generic drug name.

Polypharmacy was defined as prescription redemption of five or more different drugs (ATC drug substance level 5) within the first quarter of 2022 (1 January to 31 March). This definition of evaluating drug use within three consecutive months has previously been validated and used to estimate the number of concurrently used drugs[1,24]. Polypharmacy included all filled prescriptions provided by the prescription register except for anti-dementia medication which were excluded.

CNS-active polypharmacy was defined as prescription redemption of three or more different CNS-active drugs (ATC level 5) within the first quarter of 2022. This definition corresponds to a previous study on CNS-active polypharmacy among individuals with dementia[25]. CNS-active drugs included antidepressants (N06A), antipsychotics (N05A), antiepileptics (N03A), anxiolytics (N05B), hypnotics (N05C), and opioids (N02A, N07BC).

Comorbidity and other variables

Sociodemographic variables comprised age, sex, educational level (elementary/secondary school; vocational education; university education) and living situation (community dwelling; nursing home). The presence of chronic somatic comorbidity as defined in diagnoses of the Charlson Comorbidity Index[26] and psychiatric comorbidity was assessed from International Classification of Diseases 8th and 10th revision (ICD-8 and ICD-10) diagnoses provided by the Danish National Patient Register and the Danish Psychiatric Central Research Register (Appendix Table 1). Psychiatric comorbidities included psychotic disorders, mood disorders, and anxiety disorders. Variables were assessed at baseline on 1 January 2022.

Data analysis

Descriptive statistics were applied to evaluate polypharmacy, CNS-active polypharmacy, and categorical and continuous characteristics. The polypharmacy period prevalence proportion was calculated from the number of individuals with

polypharmacy during the first quarter of 2022 as the numerator, and the total number of individuals as the denominator. Calculations were performed separately for polypharmacy and CNS-active polypharmacy in people with and without dementia. The age- and sex-standardized period prevalence proportions in people with dementia, and confidence intervals (CI) were calculated by direct standardization according to the age- and sex- distribution in people without dementia.

Logistic regression analyses providing odds ratios (ORs) and 95% CIs were used to compare the odds of polypharmacy in people with dementia compared with those without. Three models were applied: (1) crude model, (2) adjustment for age, sex, and education, (3) further adjustment for CCI score and psychiatric disorders.

Among individuals with dementia, the most frequently used pharmacological subgroups (ATC level 3) and the single most frequently used specific generic drug within each pharmacological subgroup were identified and ranked for all drugs in people with polypharmacy and for CNS-active drugs in people with CNS-active polypharmacy.

We additionally studied time trends in the period prevalence proportion of polypharmacy and CNS-active polypharmacy by performing individual cross-sectional analyses for the years 2012-2021 in separate populations with the same inclusion/exclusion criteria as the main study population. Furthermore, the presence of polypharmacy in 2022 was calculated stratified by living situation (community dwelling; nursing home).

Data were processed and analyzed using SAS software version 9.4 (SAS Institute) and R statistical software (R Core Team, 2020)[27].

Results

Among the entire study population of 1,184,366 individuals aged 65+ years, 38,252 (3.2%) had dementia of which 59.4% were female. The median age at baseline (IQR) was 82 years (77-87 years) for people with dementia and 74 years (70-80 years) for people without dementia. Overall, people with dementia had a higher prevalence of somatic and psychiatric comorbidity. Detailed characteristics across the study population are shown in Table 1.

The prevalence proportion of polypharmacy in the first quarter of 2022 was 56.2% among people with dementia and 35.6% among people without dementia (Table 2). After age- and sex-standardization, the prevalence of polypharmacy in individuals with dementia was 51.6%. For CNS-polypharmacy, the prevalences were 10.1% (standardized 10%) and 2.3% respectively for individuals with and without dementia. The fully adjusted OR (95% CI) of polypharmacy among people with dementia was 1.47 (1.44-1.51) compared to people without dementia while the OR was 2.70 (2.59-2.81) for CNS-polypharmacy (Table 2). Detailed characteristics of the study population according to polypharmacy status are displayed in Supplementary Table S2.

Table 3 ranks the most frequently used pharmacological subgroups and the most frequently used generic drug within each respective subgroup among individuals with dementia and polypharmacy/CNS-active polypharmacy. The most used drug groups particularly included drugs used in the treatment and prevention of cardiovascular disease. The most used CNS-active drug groups included antidepressants, opioids, and antipsychotics.

Figure 1 demonstrates polypharmacy time trends according to dementia status. The prevalence of

polypharmacy among people with dementia declined between 2012-2022 from 65.1% (standardized 59.3%) to 56.2% (standardized 51.6%) while it remained stable for people without dementia at around 35-36%. For CNS-active polypharmacy among people with dementia, the prevalence declined from 15.0% (standardized 15.7%) in 2012 to 10.0% (standardized 10.1%) in 2022 (Figure 2). For people without dementia, the prevalence declined from 3.5% to 2.3%. Exact values for time trends are shown in Supplementary Tables S3-S4.

For community-dwelling individuals, the prevalence of polypharmacy was higher among people with dementia compared to people without dementia (50.0% versus 34.8%) (Supplementary Table S5). In contrast, for individuals living in nursing home, polypharmacy was less frequent among people with dementia compared to people without dementia (64.8% versus 73.8%). The corresponding prevalences for CNS-active polypharmacy were 6.1% versus 2.0% for community-dwelling individuals and 15.5% versus 14.8% for nursing home residents.

Discussion

In this nationwide Danish study, 56% of people with dementia had polypharmacy and 10% had CNS-active polypharmacy in 2022 (36% and 2% for people without dementia). The prevalence declined from 65% in 2012 for polypharmacy, and from 15% for CNS-active polypharmacy. Despite this trend, the odds of experiencing polypharmacy were 1.47-fold higher for people with dementia than those without, and 2.7-fold higher in CNS-active polypharmacy even after adjustment for sociodemographic and health-related covariates.

Our findings align with a previous Danish study documenting declining use of potentially inappropriate medication in people with dementia from 2000 to 2015[9]. Comparable to our observations, the authors still reported a widespread use of polypharmacy in the older population with a markedly higher prevalence in people with dementia[10]. Our findings further align with studies reporting extensive use of polypharmacy in individuals with dementia in the US driven by diverse medication classes[28]. This study confirms a nationwide decades-long decline in polypharmacy while documenting persistent disparities in medication load among individuals with and without dementia.

Our finding of markedly higher prevalence and odds ratio of CNS-active polypharmacy among people with dementia compared to people without dementia is in line with a recent study based on US data. In that study, 14% of older adults with dementia experienced CNS-active polypharmacy in 2018, particularly with high exposure to antidepressants, antipsychotics, and opioids similar to our Danish findings[25]. In addition, recent findings demonstrate that psychotropic polypharmacy is highly prevalent among Australians with dementia, particularly involving the use of antipsychotics and opioids[29]. This reliance on psychotropic medications across healthcare systems underscores the urgent need for safer prescribing practices to mitigate potential risks, including cognitive impairment and adverse health outcomes[2,30].

While the prevalence of polypharmacy remained relatively low and stable for people without dementia throughout the last decade, there was a declining trend among people with dementia. Several factors may have influenced this seemingly positive development. Both national[15,16] and international guidelines and initiatives with particular focus on dementia have heightened awareness of medication risks,

prompting clinicians to conduct more frequent and systematic medication reviews[14]. For instance, in 2018, the Danish Health Authority published a national clinical guideline on dementia and medicine[16]. Additionally, non-pharmacological interventions for behavioral and psychological symptoms of dementia have been recommended and emphasized during the study period[11,12]. Updated prescribing tools (e.g., the updated Beers Criteria) may also have influenced deprescribing efforts, while published evidence and dissemination of such[25,31] continues to draw attention to potential issues and posed interventions.

The indication or appropriateness of drug use was not considered, thus, the presence of polypharmacy itself did not distinguish between potentially appropriate or inappropriate medications. Thus, higher polypharmacy prevalence in dementia may partly reflect multimorbidity rather than inappropriate prescribing. For instance, as reflected by the list of most used drug classes, individuals with dementia frequently use antihypertensives, antithrombotic agents, lipid modifying agents, and antidepressants likely due to higher prevalence of the conditions treated. On the other hand, although people with dementia may perceive pain differently, chronic pain is not expected to be more frequent in dementia, thus, the high ranking of opioids cannot be adequately explained by dementia itself[32].

In contrast to community-dwelling individuals, we observed a lower prevalence of polypharmacy among dementia residents in nursing homes than residents without dementia corroborating similar findings from a previous Danish study on the topic[10]. This relatively lower occurrence of polypharmacy in nursing home residents with dementia is likely influenced by that fact that residents in nursing homes without dementia are likely there for health-related reasons (requiring medication) different than those with dementia, whose presence is largely driven by cognitive and functional decline. Second, the difference might also be due to specific nursing home initiatives such as nursing home physicians and prioritization of nonpharmacological interventions for behavioral disturbances[11–13,33–36]. Regular medication audits and staff education may have further reduced medication load in this setting. Another possibility is that patients with advanced dementia may discontinue certain preventive therapies, contributing to a lower total count of prescribed medications. Overall, nursing homes might serve as relevant settings for investigating and improving safe prescribing strategies.

Despite improvements, the high prevalence of polypharmacy in dementia necessitates targeted interventions and further research. Future studies should investigate specific drugs/drug classes contributing to medication burden and the impact of deprescribing efforts in real-world settings. Furthermore, the development of dementia-specific treatment guidelines incorporating both pharmacological and nonpharmacological management is critical[11,12,16].

Strengths and limitations

The national Danish registers enable highly valid assessment of prescription patterns and diagnoses at the individual level of a nationwide population minimizing both selection and information bias.

This study has limitations. First, while polypharmacy was based on filled prescriptions in accordance with previous literature[1,24,25], we could not ensure that the medication was consumed. Information on drugs bought over the counter was not available, thus, leading to an underestimation of drug use. Second, while

dementia syndrome diagnoses in Danish hospital registers have a high positive predictive value, dementia is expectedly underdiagnosed in the population as a whole potentially leading to misclassification. Third, residual bias cannot be ruled out in the adjusted analyses of odds of polypharmacy in dementia vs no dementia. Naturally, drug use itself is intrinsically related to the conditions treated with the drugs. On the other hand, comorbidities may be on the pathway between dementia and polypharmacy. Therefore, our model adjusting for somatic/psychiatric comorbidities should be interpreted with this in mind.

In conclusion, both polypharmacy and CNS-active polypharmacy declined among individuals with dementia between 2012-2022 suggesting growing awareness of the associated risks. Nonetheless, the prevalence of polypharmacy remains substantially higher in dementia, reflecting the clinical challenges posed by multimorbidity and neuropsychiatric symptoms. The findings highlight the continued need for safer prescribing practices taking morbidities and associated medication risks into account.

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Tables and Figures

Table 1. Baseline characteristics of the study population according to dementia status

Variable	All-cause dementia (n=38,252)	No dementia (n=1,146,114)
Sex, No. (%)		
Female	22,718 (59.4)	616,278 (53.8)
Male	15,534 (40.6)	529,836 (46.2)
Age, median (IQR), y	82 (77-87)	74 (70-80)
Age, No. (%), y		
65-70	937 (2.4)	286,412 (25.0)
70-75	3,879 (10.1)	296,787 (25.9)
75-80	8,560 (22.4)	275,514 (24.0)
80-85	9,972 (26.1)	158,786 (13.9)
85+	14,904 (39.0)	128,615 (11.2)
Education, No. (%)		
Elementary/secondary school	15,882 (41.5)	361,218 (31.5)
Vocational education	14,926 (39.0)	509,571 (44.5)
University education	6,634 (17.3)	257,727 (22.5)
Missing	810 (2.1)	17,598 (1.5)
Charlson Comorbidity Index, No. (%)		
0	12,523 (32.7)	529,312 (46.2)
1-2	16,019 (41.9)	416,326 (36.3)
3-5	8,195 (21.4)	163,716 (14.3)
6+	1,515 (4.0)	36,760 (3.2)
Cerebrovascular.disease	9,977 (26.1)	146,723 (12.8)
Diabetes with complications	2,265 (5.9)	44,659 (3.9)
Diabetes without complications	3,059 (8.0)	61,043 (5.3)
Myocardial.infarction	2,914 (7.6)	70,506 (6.2)
AIDS/HIV	<20 (<0.1)	828 (0.1)
Chronic pulmonary disease	5,239 (13.7)	131,610 (11.5)
Heart failure	3,299 (8.6)	67,569 (5.9)
Hemiplegia/paraplegia	187 (0.5)	4,968 (0.4)
Mild liver disease	637 (1.7)	17,463 (1.5)
Peptic ulcer disease	2,744 (7.2)	49,391 (4.3)
Peripheral vascular disease	3,276 (8.6)	77,029 (6.7)
Renal disease	1,612 (4.2)	30,825 (2.7)
Rheumatic disease	2,437 (6.4)	61,786 (5.4)
Severe liver disease	164 (0.4)	4,639 (0.4)
Any malignancy	8,620 (22.5)	221,791 (19.4)
Metastatic solid tumor	436 (1.1)	17,445 (1.5)
Leukemia	183 (0.5)	6,511 (0.6)
Lymphoma	458 (1.2)	14,718 (1.3)
Psychiatric comorbidity, No. (%)	7,958 (20.8)	107,515 (9.4)
Psychotic disorders	1,131 (3.0)	14,638 (1.3)
Mood disorders	5,696 (14.9)	58,054 (5.1)
Anxiety disorders	3,572 (9.3)	65,548 (5.7)

Table 2. Period prevalence proportion and odds ratios (OR) of polypharmacy in individuals with dementia compared to individuals without dementia.

Dementia status	Prevalence %	Age/sex-standardized prevalence % (95% CI)	Crude OR (95% CI)	Adjusted OR[c] (95% CI)	Adjusted OR[d] (95% CI)
Polypharmacy[a]					
Dementia	56.2	51.6 (50.7-52.5)	2.32 (2.27-2.37)	1.62 (1.59-1.66)	1.47 (1.44-1.51)
No dementia	35.6	35.9 (35.8-36.0)	1	1	1
CNS-active polypharmacy[b]					
Dementia	10.1	10.1 (9.5-10.7)	4.75 (4.58-4.92)	3.80 (3.66-3.94)	2.70 (2.59-2.81)
No dementia	2.3	2.3 (2.3-2.3)	1	1	1

[a]Concurrent use of ≥5 drugs

[b]Concurrent use of ≥3 CNS-active drugs

[c]Adjusted for age, sex, and educational level.

[d]Additionally adjusted for CCI score and psychiatric disorders.

Table 3. Most frequently used pharmacological subgroups and products among individuals with dementia and polypharmacy

Rank	ATC 3rd level	Pharmacological subgroup	Most frequent generic drug
Most used drug groups/drugs in people with dementia and polypharmacy			
1	N02B	Other analgesics and antipyterics	Paracetamol
2	B01A	Antithrombotic agents	Acetylsalicylic acid
3	N06A	Antidepressants	Sertraline
4	A06A	Drugs for constipation	Macrogol
5	C10A	Lipid modifying agents	Atorvastatin
6	J01C	Penicillins	Pivmecillinam
7	N02A	Opioids	Tramadol
8	A02B	Drugs for acid related disorders	Pantoprazole
9	C07A	Beta blocking agents	Metoprolol
10	A12B	Potassium	Potassium chloride
11	C08C	Selective calcium channel blockers	Amlodipine
12	C03C	High-ceiling diuretics	Furosemide
13	A10B	Glucose lowering drugs, excl. insulins	Metformin
14	N05A	Antipsychotics	Quetiapine
15	N05C	Hypnotics and sedatives	Zopiclone
16	C09C	Angiotensin II receptor blockers	Losartan
17	R03A	Adrenergics, inhalants	Terbutaline
18	N04B	Dopaminergic agents	Pramipexole
19	C09A	ACE inhibitors	Enalapril
20	B03B	Vitamin B12 and folic acid	Vitamin B12
Most used CNS-active drug groups/drugs in people with dementia and CNS-active polypharmacy			
1	N06A	Antidepressants	Sertraline
2	N02A	Opioids	Tramadol
3	N05A	Antipsychotics	Quetiapine
4	N05C	Hypnotics and sedatives	Zopiclone
5	N03A	Antiepileptics	Lamotrigine
6	N05B	Anxiolytics	Oxazepam
7	N07B	Drugs used in addictive disorders	Buprenorphine

Figure 1. Time trends of the crude and age-/sex-standardized prevalence of polypharmacy according to dementia status

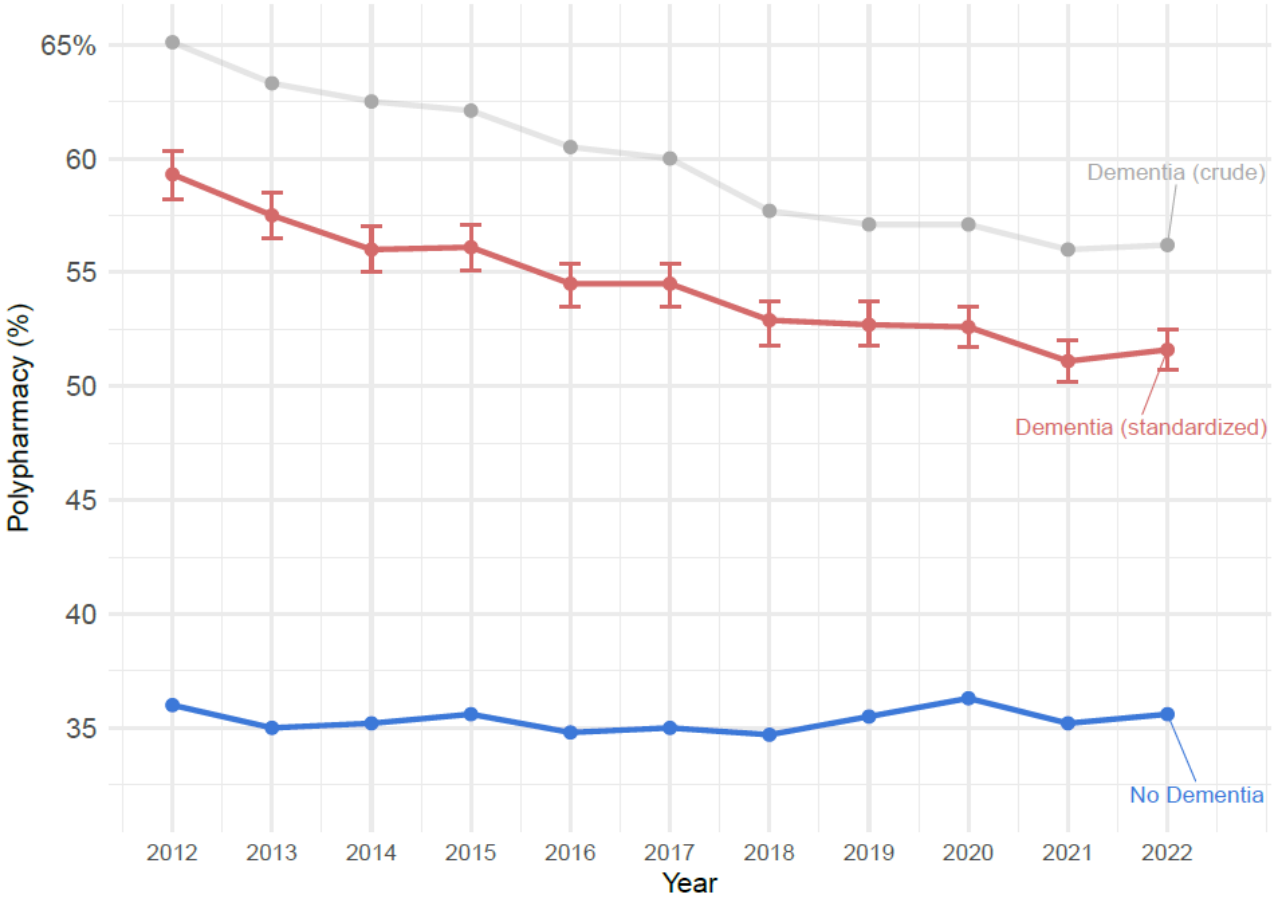
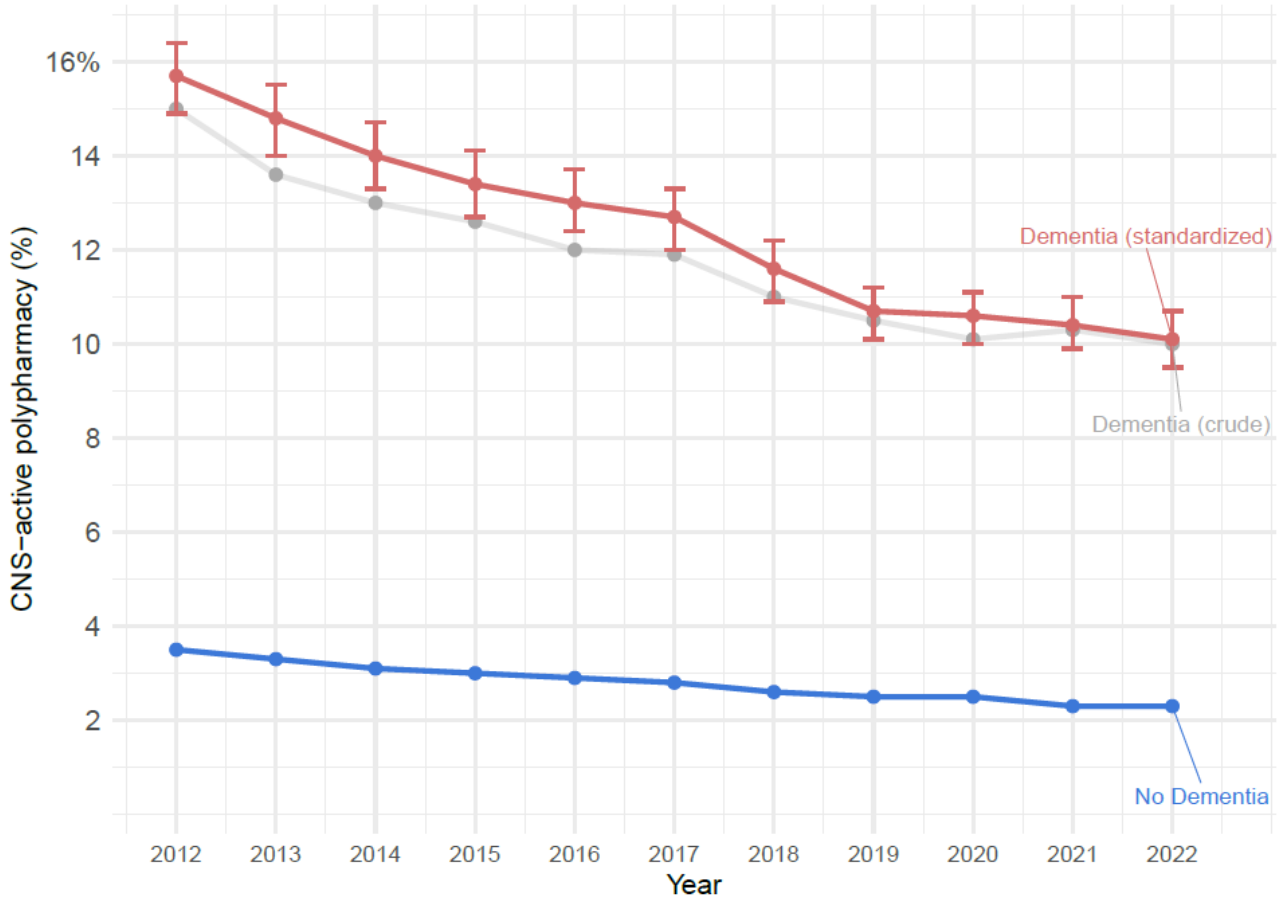


Figure 2. Time trends of the crude and age-/sex-standardized prevalence of CNS-active polypharmacy according to dementia status



Supplement

Polypharmacy in people with dementia:

a nationwide Danish study

Supplementary table S1. Diagnosis- and drug codes

Variable	Data source	Data availability	Classification system	Definition	
				ICD 8 & 10	ATC
Dementia	The National Patient Registry, The Danish Psychiatric Central Research Registry & The National Prescription Registry	1970-2022 & 1995-2022	ICD-8 ICD-10 ATC	290.10, 293.09-19, 290.11, 290.09, 290.19, 290.18, F00, G30, F01, F02.0, G31.0A, G31.0B, F03, G31.9, G31.8, F02.1-F02.8	N06D
Polypharmacy	The National Prescription Registry	1995-2022	ATC	-	All ATC-codes except N06D 5+ different drugs on the substance level (ATC level 5) within 3 months
CNS-active polypharmacy	The National Prescription Registry	1995-2022	ATC	-	Antidepressants N06A Antipsychotics N05A Antiepileptics N03A Anxiolytics N05B Hypnotics N05C Opioids N02A, N07BC 3+ different drugs on the substance level (ATC level 5) within 3 months
Charlson Comorbidity Index					
Myocardial infarction	The National Patient Registry	1977-2022	ICD-8 ICD-10	410, I21, I22, I23	
Congestive heart failure				42709, 42710, 42711, 42719, 42899, 78249, I50, I110, I130, I132	
Peripheral vascular disease				440, 441, 442, 443, 444, 445, I70, I71, I72, I73, I74, I77	
Cerebrovascular disease				430- 4398, I60- I69, G45, G46	
Chronic pulmonary disease				490-493, 515-518, J40-J47, J60-J67, J684, J701, J703, J841, J920, J961, J982, J983	
Connective tissue disease				712, 716, 734, 446, 13599, M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86	
Ulcer disease				53091, 53098, 531-534, K221, K25-K28	

Mild liver disease				571, 57301, 57304, B18, K700-K703, K709, K71, K73, K74, K760
Diabetes I and II without complications				24900, 24906, 24907, 24909, 25000, 25006, 25007, 25009, E100, E101, E109, E110, E111, E119
Hemiplegia				344, G81, G82
Moderate to severe renal disease				403, 404, 580-585, 59009, 59319, 75310-75319, 792, I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Moderate to severe liver disease				07000, 07002, 07004, 07006, 07008, 57300, 45600-45609, B150, B160, B162, B190, K704, K72, K766, I85
Diabetes with complications				24901-24905, 24908, 25001-25005, 25008, E102-E108, E112-E118
Any tumor				140-194, C00-C75
Leukaemia				204-207, C91-C95
Lymphoma				200-203, 27559, C81-C86, C88, C90, C96
Metastatic solid tumor				195-198, 199, C76-C80
AIDS				07983, B21-B24
Psychiatric comorbidity				
Psychotic disorders	The Danish Psychiatric Central Research Registry	1977-2022	ICD-8 ICD-10	295.x9, 269.89, 297.x9, 298.29-99, 299.04-05, 299.09, 301.83, F20-29
Mood disorders				296.x9 (except 296.89), 298.09, 298.19, 300.49, 301.19, F30-39
Anxiety disorders				300.x9 (except 300.49), 305.x9, 305.68, 307.99, F40-48
Autism spectrum disorders				299.00-03, F84 except F84.2-84.4
Hyperkinetic disorders				306.x9, 308-0x, F90.0, 98.8C
Socioeconomic variable				
Education	Danish Education Registries	1980-2022	Highest obtained education - International Standard Classification of Education	Definition: elementary/secondary school; vocational education; university education

Supplementary table S2. Baseline characteristics of the study population according to polypharmacy status

Variable	No polypharmacy (n=753,418)	Both regular and CNS polypharmacy (n= 28,555)	Regular polypharmacy only (n=400,822)	CNS polypharmacy only (n=1,571)
Sex, No. (%)				
Female	403,008 (53.5)	19,208 (67.3)	215,748 (53.8)	1,032 (65.7)
Male	350,410 (46.5)	9,347 (32.7)	185,074 (46.2)	539 (34.3)
Age at entry, median (IQR), y	73 [69, 78]	77 [71, 84]	77 [72, 82]	74 [69.0, 79.5]
Age at entry, No. (%), y				
65-70	214,479 (28.5)	5,098 (17.9)	67,331 (16.8)	441 (28.1)
70-75	206,307 (27.4)	5,829 (20.4)	88,138 (22.0)	392 (25.0)
75-80	174,464 (23.2)	6,390 (22.4)	102,875 (25.7)	345 (22.0)
80-85	91,749 (12.2)	4,948 (17.3)	71,872 (17.9)	189 (12.0)
85+	66,419 (8.8)	6,290 (22.0)	70,606 (17.6)	204 (13.0)
Education, No. (%)				
Elementary/secondary school	211,845 (28.1)	12,285 (43.0)	152,411 (38.0)	559 (35.6)
Vocational education	339,979 (45.1)	10,955 (38.4)	172,987 (43.2)	576 (36.7)
University education	190,266 (25.3)	4,844 (17.0)	68,838 (17.2)	413 (26.3)
Missing	11,328 (1.5)	471 (1.6)	6,586 (1.6)	23 (1.5)
Charlson Comorbidity Index, No. (%)				
0	433,311 (57.5)	6,539 (22.9)	101,170 (25.2)	815 (51.9)
1-2	245,144 (32.5)	11,550 (40.4)	175,107 (43.7)	544 (34.6)
3-5	61,471 (8.2)	7,935 (27.8)	102,348 (25.5)	157 (10.0)
6+	13,492 (1.8)	2,531 (8.9)	22,197 (5.5)	55 (3.5)
Dementia	16,588 (2.2)	3,663 (12.8)	17,828 (4.4)	173 (11.0)
Cerebrovascular.disease	65,838 (8.7)	7,245 (25.4)	83,461 (20.8)	156 (9.9)
Diabetes with complications	8,664 (1.1)	2,150 (7.5)	36,096 (9.0)	14 (0.9)
Diabetes without complications	18,768 (2.5)	2,565 (9.0)	42,725 (10.7)	44 (2.8)
Myocardial.infarction	24,737 (3.3)	2,319 (8.1)	46,329 (11.6)	35 (2.2)
AIDS/HIV	552 (0.1)	20 (0.1)	266 (0.1)	<10 (<0.7)
Chronic pulmonary disease	51,770 (6.9)	6,940 (24.3)	78,009 (19.5)	130 (8.3)
Heart failure	16,907 (2.2)	3,179 (11.1)	50,738 (12.7)	44 (2.8)
Hemiplegia/paraplegia	1,890 (0.3)	488 (1.7)	2,767 (0.7)	10 (0.6)
Mild liver disease	8,328 (1.1)	991 (3.5)	8,745 (2.2)	36 (2.3)
Peptic ulcer disease	21,612 (2.9)	3,188 (11.2)	27,254 (6.8)	81 (5.2)
Peripheral vascular disease	29,259 (3.9)	3,349 (11.7)	47,643 (11.9)	54 (3.4)
Renal disease	10,070 (1.3)	1,680 (5.9)	20,655 (5.2)	32 (2.0)
Rheumatic disease	30,481 (4.0)	2,471 (8.7)	31,212 (7.8)	59 (3.8)
Severe liver disease	2,228 (0.3)	322 (1.1)	2,238 (0.6)	15 (1.0)
Any malignancy	133,444 (17.7)	7,447 (26.1)	89,188 (22.3)	332 (21.1)
Metastatic solid tumor	9,691 (1.3)	972 (3.4)	7,178 (1.8)	40 (2.5)
Leukemia	3,729 (0.5)	221 (0.8)	2,736 (0.7)	<10 (<0.7)
Lymphoma	8,383 (1.1)	596 (2.1)	6,181 (1.5)	16 (1.0)
Psychiatric comorbidity, No. (%)	52,768 (7.0)	13,582 (47.6)	48,247 (12.0)	876 (55.8)
Psychotic disorders	7,561 (1.0)	2,702 (9.5)	5,285 (1.3)	221 (14.1)
Mood disorders	25,600 (3.4)	10,126 (35.5)	27,354 (6.8)	670 (42.6)
Anxiety disorders	32,359 (4.3)	8,006 (28.0)	28,307 (7.1)	448 (28.5)

Supplementary table S3. Values for time trends of the prevalence of polypharmacy according to dementia status between 2012-2022

	Dementia		No dementia	
Year	**Prevalence %**	**Age/sex-standardized prevalence % (95% CI)**	**Prevalence %**	**Age/sex-standardized prevalence % (95% CI)**
2012	65.1	59.3 (58.2-60.3)	36.0	36.5 (36.4-36.6)
2013	63.3	57.5 (56.5-58.5)	35.0	35.4 (35.4-35.5)
2014	62.5	56.0 (55.0-57.0)	35.2	35.6 (35.5-35.7)
2015	62.1	56.1 (55.1-57.1)	35.6	36.0 (35.9-36.1)
2016	60.5	54.5 (53.5-55.4)	34.8	35.2 (35.1-35.3)
2017	60.0	54.5 (53.5-55.4)	35.0	35.4 (35.3-35.5)
2018	57.7	52.9 (51.8-53.7)	34.7	35.1 (35.0-35.1)
2019	57.1	52.7 (51.8-53.7)	35.5	35.8 (35.7-35.9)
2020	57.1	52.6 (51.7-52.5)	36.3	36.6 (36.6-36.7)
2021	56.0	51.1 (50.2-52.0)	35.2	35.5 (35.4-35.6)
2022	56.2	51.6 (50.7-52.5)	35.6	35.9 (35.8-36.0)

Supplementary table S4. Values for time trends of the prevalence of CNS-active polypharmacy according to dementia status between 2012-2022

	Dementia		No dementia	
Year	**Prevalence %**	**Age/sex-standardized prevalence % (95% CI)**	**Prevalence %**	**Age/sex-standardized prevalence % (95% CI)**
2012	15.0	15.7 (14.9-16.4)	3.5	3.6 (3.6-3.6)
2013	13.6	14.8 (14.0-15.5)	3.3	3.3 (3.3-3.3)
2014	13.0	14.0 (13.3-14.7)	3.1	3.1 (3.1-3.2)
2015	12.6	13.4 (12.7-14.1)	3.0	3.0 (3.0-3.1)
2016	12.0	13.0 (12.4-13.7)	2.9	2.9 (2.9-3.0)
2017	11.9	12.7 (12.0-13.3)	2.8	2.9 (2.8-2.9)
2018	11.0	11.6 (10.9-12.2)	2.6	2.6 (2.6-2.7)
2019	10.5	10.7 (10.1-11.2)	2.5	2.5 (2.5-2.6)
2020	10.1	10.6 (10.0-11.1)	2.5	2.5 (2.4-2.5)
2021	10.3	10.4 (9.9-11.0)	2.3	2.4 (2.3-2.4)
2022	10.0	10.1 (9.5-10.7)	2.3	2.3 (2.3-2.3)

Supplementary table S5. Prevalence of polypharmacy and CNS-active polypharmacy according to dementia status stratified by living situation

Living situation	Dementia status	Prevalence %	Age/sex-standardized prevalence % (95% CI)
Polypharmacy			
Community-dwelling	Dementia	50.0	46.3 (45.2-47.4)
	No dementia	34.8	35.0 (34.9-35.1)
Nursing home	Dementia	64.8	64.7 (64.0-65.5)
	No dementia	73.8	74.0 (73.4-74.6)
CNS-active polypharmacy			
Community-dwelling	Dementia	6.1	6.7 (6.1-7.2)
	No dementia	2.0	2.1 (2.0-2.1)
Nursing home	Dementia	15.5	15.6 (15.0-16.2)
	No dementia	14.8	14.8 (14.3-15.2)

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