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Fingerprints of young onset Alzheimer's disease

Nationwide nested case-control studies exploring early signs and symptoms

PhD Thesis

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DANISH DEMENTIA RESEARCH CENTRE

This thesis has been submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen 20 November 2024

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Preface and acknowledgments

This PhD project took place at the Danish Dementia Research Centre (*Nationalt Videnscenter for Demens*), Department of Neurology, Copenhagen University Hospital - Rigshospitalet from 2021-2024. The project is part of a larger epidemiological project revolving around medication use, health, and mortality in patients with dementia and their caregivers. The Danish Dementia Research Centre receives financial support from the Danish Ministry of Health. This specific project was supported by *Rigshospitalets Jubilæumsfond* and *Knud Højgaards fond* in the form of grants for conference participation.

The first seeds for this project were planted during my time working as a medical doctor at the Memory Clinic at the Danish Dementia Research Centre. Working here, I saw a wide range of patients with various dementia subtypes along different stages of the disease course. One of the things that particularly resonated with me was the experiences of younger patients. These patients often had a long diagnostic journey before reaching the memory clinic. Witnessing firsthand the profound impact that a dementia diagnosis had on these individuals, their daily lives, and their families left a lasting impression. These experiences highlighted how critical accurate and timely diagnosis is for this patient group. I became increasingly aware of the emotional, social, and practical burdens they faced, burdens that seemed compounded by their age. When I began to consider writing a PhD, I was struck by the relatively limited research focused on young onset dementia. In close collaboration with my supervisors, I was able to shape a project that addressed this gap, and which I find very meaningful.

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List of manuscripts

This thesis is based on the following four original studies:

Study 1 Damsgaard L., Janbek J., Laursen T.M, Gunhild W., Jensen-Dahm C. Healthcare utilization prior to a diagnosis of young-onset Alzheimer's disease: a nationwide nested case-control study. *J Neurol.* 2023;270:6093–6102.
doi.org/10.1007/s00415-023-11974-x [1]

Study 2 Damsgaard L., Janbek J., Laursen T.M., Høgh P., Vestergaard K., Gottrup H., Jensen-Dahm C., Waldemar G. Mapping morbidity 10 years prior to a diagnosis of young onset Alzheimer's disease. *Alzheimer's Dement.* 2024;20:2373–2383.
doi.org/10.1002/ alz.13681 [2]

Study 3 Damsgaard L., Janbek J., Laursen T.M., Vestergaard K., Gottrup H., Jensen-Dahm C., Waldemar G. Prescription medication use in the 10 years prior to diagnosis of young onset Alzheimer's disease: a nationwide nested case-control study. *Alzheimers Res Ther*. 2024;16(1):150.
doi:10.1186/s13195-024-01523-7 [3]

Study 4 Damsgaard L., Pedersen J., Laursen T.M., Nabe-Nielsen K., Hendriks S., Jensen-Dahm C., Waldemar G., Janbek J. Patterns of sick leave and unemployment prior to a diagnosis of young onset Alzheimer's disease.
Submitted

Abbreviations

ATC	Anatomical therapeutic chemical
CI	Confidence interval
CRR	Contact rate ratio
DanDem	The Danish Quality Database for Dementia
GP	General Practitioner
ICD	International Classification of Diseases
IRR	Incidence rate ratio
LOAD	Late onset Alzheimer's disease
MCI	Mild cognitive impairment
YOAD	Young onset Alzheimer's disease

Abstract

Dementia is a syndrome characterized by persistent cognitive decline to an extent where it affects activities of daily living. The most common causes are gradually progressive neurodegenerative diseases. Dementia is classified into young onset and late onset dementia according to age at symptom onset (before or after age 65 years). While Alzheimer's disease is the most prevalent cause of dementia in both categories, the majority of dementia research has focused on late onset Alzheimer's disease, with considerably less attention given to young onset Alzheimer's disease (YOAD). Timely diagnosis poses a major challenge in the diagnostic trajectory of YOAD with long diagnostic delays described. This delays appropriate care, contributes to financial strain, and impacts families, often including children still living at home.

This thesis investigated potential early warning signs of YOAD, with the aim to increase the knowledge needed to reduce diagnostic delays and facilitate timely diagnosis. It is based on four nationwide, retrospective, nested case-control studies comparing all YOAD patients diagnosed in Danish memory clinics within the respective study periods, compared to a matched control sample drawn from the entire Danish population. The studies examined healthcare utilization, morbidity, medication use, and occupational markers (unemployment and long-term sick leave) during the decade prior to dementia diagnosis.

The studies demonstrated higher rates of contacts with the general practitioner up to a decade prior to diagnosis for YOAD cases compared to controls, with a steep increase in psychiatric healthcare use in the year immediately prior to diagnosis. Increased psychiatric morbidity and corresponding medication use, particularly depression and stress-related disorders, were also observed up to 10 years before YOAD diagnosis. Furthermore, YOAD cases had higher rates of unemployment and long-term sick leave well before diagnosis.

These findings point to a prolonged period of vulnerability for YOAD patients, extending up to a decade prior to formal diagnosis, especially characterized by psychiatric disorders as early signs – or early consequences – of dementia. This project underscores the importance of improving timely diagnosis. This can lessen burdens on patients, caregivers, and families, and reduce societal impacts from heightened healthcare use and occupational instabilities. Our findings imply that physicians should consider memory clinic referrals for patients presenting with first onset of depression or stress in midlife, particularly when atypical, treatment-resistant, or accompanied by occupational challenges.

Resume

Demens er et syndrom karakteriseret ved vedvarende svækkelse af kognitive funktioner i en sådan grad at det påvirker dagligdags funktioner. De hyppigste årsager er fremadskridende neurodegenerative sygdomme. Demens opdeles i tidligt- og sent indsættende demens afhængig af symptomdebut (før eller efter 65 år). Selvom Alzheimers sygdom er den hyppigste årsag til demens i begge grupper, har forskningen primært fokuseret på sent indsættende Alzheimers sygdom, mens tidligt indsættende Alzheimers sygdom (*young onset Alzheimer's disease*, YOAD) har fået mindre opmærksomhed. Rettidig diagnostik udgør en stor udfordring hos denne gruppe, hvor der ofte er lange forsinkelser på korrekt diagnose. Dette forsinker adgangen til passende pleje, medfører ofte økonomiske problemer, og er en stor belastning for familien, som ofte inkluderer hjemmeboende børn.

Denne afhandling undersøgte potentielle tidlige tegn på YOAD med det formål at bidrage til at nedbringe forsinkelser på korrekt diagnose. Afhandlingen er baseret på fire landsdækkende, retrospektive, nestede case-kontrol studier, der sammenlignede alle YOAD-patienter diagnosticeret på en dansk hukommelsesklinik i de respektive studieperioder med en matchet kontrolgruppe udvalgt fra hele den danske befolkning. Studierne undersøgte forbrug af sundhedsydelser, sygdomme og medicinforbrug, samt arbejdsløshed og langtidssygemeldinger i årtiet forud for demensdiagnosen.

Studierne viste, at YOAD-patienter havde et øget antal kontakter med deres praktiserende læger op til et årti før diagnosen, med en markant stigning i kontakter til psykiatrien i året umiddelbart før diagnose. Vi observerede også øget psykiatrisk sygdom og tilsvarende medicinforbrug, særligt depression og stress-relaterede lidelser, op til 10 år før diagnosen. Derudover havde YOAD-patienter højere rater af arbejdsløshed og langtidssygemeldinger længe før diagnosen.

Disse fund tyder på en længere periode med øget sårbarhed for YOAD-patienter, som kan strække sig op til et årti forud for den formelle diagnose og som særligt er kendetegnet ved psykiatriske lidelser som tidlige tegn på – eller konsekvenser af – demens. Projektet understreger vigtigheden af at forbedre rettidig diagnostik for at mindske byrden for patienter, omsorgspersoner og familier, samt reducere de samfundsmæssige konsekvenser af potentielt unødvendige lægekontakter og ustabilitet i tilknytning til arbejdsmarkedet. Vores fund antyder, at man bør overveje henvisning til en hukommelsesklinik for patienter med debut af depression eller stress i 40-60-årsalderen, særligt ved atypiske symptomer, hvis behandlingsresistent, eller hvis ledsaget af arbejdsmæssige udfordringer.

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1. Background

1.1 Dementia

Dementia is a syndrome characterized by persistent cognitive decline to an extent where it affects activities of daily living[4]. Dementia can be caused by a multitude of different etiologies[5], most often progressive, neurodegenerative diseases[6]. While different causes of dementia may present with distinct symptom patterns[5], many symptoms are shared across dementia subtypes. These include memory impairment, behavioral changes, communication difficulties[7], and neuropsychiatric symptoms[8]. Dementia is classified according to the age of onset into late onset dementia (symptom onset at 65 years or older) and young onset dementia (symptom onset before the age of 65 years)[9].

1.2 Young onset dementia

Although late onset dementia has been the focus of extensive research, considerably less attention has been given to young onset dementia. In 2019, the global prevalence of dementia was estimated at 57.4 million people living with dementia[10], while a 2021 study estimated that 3.9 million people aged 30-64 years are living with young onset dementia[11]. Despite the relative rarity, young onset dementia requires significant attention and resources from dementia professionals, as well as patients, families, and caregivers alike.

While young and late onset dementia share many commonalities in the challenges faced, some challenges are distinctive to young onset dementia patients. Unlike late onset dementia, which typically occurs after retirement, young onset dementia often strikes individuals in the midst of their careers and family life. This abrupt shift can profoundly disrupt life plans, as most patients are forced to leave the workforce far earlier than anticipated[12], causing severe financial strain[13] often greater than seen in individuals with late onset dementia[14]. Additionally, many of these individuals still have children living at home, and a young onset dementia diagnosis significantly alters family dynamics and places unexpected emotional and practical burdens on the entire household[15].

For healthcare professionals, young onset dementia also poses a challenge. For younger individuals with onset of cognitive symptoms, the list of differential diagnoses is very long[16], and the suspicion of dementia is not always straightforward. This is likely, in part, due to differences in clinical presentation between young and late onset dementia[17], as well as misattribution of cognitive symptoms to conditions such as stress, depression, and burn-out[16,18]. Insights gained from research on late onset dementia may not always be applicable to individuals with young onset dementia, further complicating clinical assessment and diagnosis.

1.3 Young onset Alzheimer's disease

Alzheimer's disease is the most prevalent etiology in those diagnosed with both late and young onset dementia, estimated to account for at least 60% of late onset dementia cases[19] (late onset Alzheimer's disease, LOAD) and 34% of young onset dementia cases[9]. Alzheimer's disease debuting before age 65 years is in the literature commonly referred to as either early onset Alzheimer's disease, young onset Alzheimer's disease, or younger onset Alzheimer's disease[20]. In this thesis and the accompanying papers, the term young onset Alzheimer's disease (YOAD) is used, but I note here for the readers' understanding that these terms are synonymous.

Alzheimer's disease is a neurodegenerative disease characterized by the accumulation of amyloid-beta plaques and tau neurofibrillary tangles, with brain pathology assumed to develop years, likely even decades, before the onset of cognitive symptoms[21,22]. This gradual neurodegeneration suggests the likelihood of a prolonged prodromal phase. A study investigating neuropsychological performance prior to a formal Alzheimer's disease diagnosis found cognitive impairment in individuals up to eight years before and poorer performance found closer to diagnosis, concluding that "the progression of the pre-clinical cognitive changes appears to mirror the progression of the pathophysiology of preclinical Alzheimer's disease"[23].

Like Alzheimer's disease, α-synucleinopathies such as Parkinson's disease and dementia with Lewy bodies are neurodegenerative diseases with abnormal protein deposition causing cell damage and thus functional decline, especially characterized by progressive motor dysfunction[24,25]. Like in Alzheimer's disease, there is a long preclinical phase, with studies suggesting a preclinical period extending at least 20 years before motor manifestations[24]. Epidemiological studies on non-motor manifestations, including constipation, anxiety and depression, REM sleep behavior disorder, and olfactory impairment, have provided strong evidence that these non-motor symptoms can precede the onset of Parkinson's disease by several years. This has shifted the perception of Parkinson's disease from a primarily motor-symptom disorder to one with a prolonged latency period, marked by the gradual appearance of various non-motor symptoms before the characteristic motor symptoms emerge[26]. A similar potential for a better understanding of Alzheimer's disease exists by exploring the very earliest symptoms, including whether non-cognitive symptoms predate cognitive symptoms. This might further help in ensuring timely diagnosis, improvements in which are needed especially for those with YOAD.

1.4 Clinical features of young onset Alzheimer's disease

While the underlying pathological definitions and the diagnostic criteria of YOAD and LOAD are the same, apart from age at symptom onset, researchers remain divided over whether there are marked differences between the two. The age cut-off of 65 years was not chosen due to biological mechanisms,

but rather a somewhat arbitrary cut-off based on typical retirement age, separating young onset and late onset into two groups primarily based on the differing consequences for the individual[20]. Nevertheless, several studies have found symptoms to differ between YOAD and LOAD[28–32]. Studies comparing presenting symptoms in memory clinic settings between YOAD and LOAD have found memory symptoms most common among LOAD, and non-memory symptoms more common in YOAD, with other symptoms such as language and concentration[29] or apraxia and visuospatial dysfunction[30] instead more prominent. Differences in the rate of neuropsychiatric symptoms have also been described, with a higher number of YOAD patients experiencing depression prior to[31] and at the time of diagnosis[32] compared to LOAD. Similarly, a study examining pre-diagnostic symptoms of (all-cause) young onset dementia found that only 5% of young onset dementia cases reported cognitive symptoms 5 years before diagnosis[27]. However, a large proportion of the cases had affective symptoms as an early feature, most commonly anxiety symptoms and depression. A recent study suggests that such differences may, in part, be due to differential effects of risk factors on the cognitive trajectory in YOAD and LOAD[33].

Additionally, several studies describe a faster rate of progression for YOAD compared to LOAD[29,34,35], though this may also reflect differences in the ability to compensate for cognitive deficits, or that patients with YOAD are further along on the diagnostic trajectory at the time of diagnosis than those with LOAD due to a longer diagnostic delay[36]. The atypical non-memory presentation, the relative rarity, and the longer list of differential diagnoses for cognitive symptoms in younger individuals may all contribute to this diagnostic delay. This highlights the crucial need for timely diagnosis and early intervention in patients with YOAD.

1.5 Genetics in young onset Alzheimer's disease

In light of the potentially differing clinical features of YOAD compared to LOAD described in **section 1.4**, research has increasingly focused on the underlying biological mechanisms that may contribute to such differences. Studies have identified greater temporoparietal atrophy[37] and greater synaptic loss[38] in YOAD, suggesting that genetic and environmental factors could differentially influence disease development in younger and older individuals, with genetic factors shown to contribute to a larger number of cases in YOAD than LOAD[39]. Though the vast majority of YOAD cases are sporadic, around 10-15% are estimated to be due to autosomal dominant mutations, most commonly in the amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*) genes[39], all involved in cleavage or aggregation of the amyloid precursor protein[40]. In addition to these known mutations, several genetic risk factors have been described, with apolipoprotein E ε4 allele being the most significant.

Individuals carrying one or two copies of the ε4 allele have an increased risk of developing Alzheimer's disease and tend to have an earlier onset[40].

Although genetic predispositions, including known mutations and risk alleles, contribute to the onset of YOAD, knowledge of early signs and symptoms remains crucial for timely and accurate diagnosis. Understanding and identifying prodromal symptoms, irrespective of genetic background, plays a significant role in improving the diagnostic process for young onset dementia cases.

1.6 Time to diagnosis in young onset Alzheimer's disease

Increased knowledge of early, prodromal symptoms may aid in establishing a timely diagnosis. While definition of the term timely diagnosis varies, one study proposes the following definition:

> *"…we defined "timely diagnosis" of Alzheimer's disease as the diagnosis made at a time when individuals first become worried enough to seek help and come to the attention of clinicians because of concerns about changes in cognition, behavior, or functioning …"*[41]

Timely diagnosis poses a major challenge in the diagnostic trajectory of young onset dementia[36,42–44]. A 4.7-year time lag between symptom onset and final diagnosis of dementia has been found in a study of all-cause young onset dementia, with longer time to diagnosis among the younger study participants and when depression was present[44]. Younger patients face longer diagnostic delays than those with late onset dementia, on average around 11 months longer, mainly due to longer time to referral to specialist centers[43].

In a study on time to diagnosis specifically for YOAD patients the authors found a substantial diagnostic delay, even in those with a typical presentation[45]. Results from the cohort of 223 patients showed an average time lag of 3.4 years from onset of symptoms to the first visit to the general practitioner (GP) and an average time lag of 5.5 years from symptom onset to diagnosis. Nearly 70% of the study participants were employed when symptoms appeared, and over two-thirds of them reported experiencing work-related difficulties before symptoms became apparent elsewhere, highlighting the societal impact of YOAD. A timely diagnosis gives patients and caregivers the chance to start treatment to alleviate symptoms and to avoid medications that may worsen symptoms, as well as plan for the future and seek appropriate care[41].

The substantial time-lag from first GP visit to final diagnosis also highlights the key role of GPs in the diagnostic trajectory of YOAD. A qualitative study among Dutch GPs and occupational therapists

uncovered several barriers that impede timely diagnosis[18]. Firstly, the low prevalence of young onset dementia was highlighted. Many study participants noted that dementia is often not considered when evaluating patients under 65 years of age, leading to a lack of prioritization in training to improve knowledge about young onset dementia. Secondly, difficulties in recognizing symptoms were mentioned. The GPs and occupational therapists noted that symptoms are frequently misattributed to burnout, depression, or other conditions, hindering accurate diagnosis. Lastly, some GPs expressed reluctance about discussing a potentially serious condition with younger patients and even suggested that it might be better to delay a diagnosis due to the absence of effective treatments. Thus, it seems increased knowledge is needed to assess meaningful tools to aid diagnosis in primary care, including disseminating knowledge on the immense benefits of a diagnosis, including the possibility of initiating symptomatic treatment, avoiding potentially harmful treatments, and establishing psychosocial efforts to help with daily functioning.

Novel anti-amyloid monoclonal antibody treatments have been in use for a few years in the United States, among other countries, following approvals of aducanumab in 2021 and lecanemab in 2023 by the United States Food and Drug Administration[46]. While no antibody treatments have been in use in Europe so far, the European Medicines Agency just recently recommended granting marketing authorization to lecanemab[47]. These advancements in disease-modifying treatments might bring a push to move from timely diagnosis to even earlier detection, as these treatments will be more effective if initiated at an early point in the disease trajectory. This further calls for increased knowledge about the earliest signs and symptoms of YOAD.

1.7 Gaps in current knowledge

Despite advancements in understanding Alzheimer's disease, there remains a critical gap in knowledge regarding the early symptoms of YOAD. There is limited research on prodromal symptoms and the vast majority of research centers on LOAD. Due to the many both functional and clinical differences, this is often not directly transferable to those with YOAD. The long diagnostic delay in YOAD highlights the need for a better understanding of the prodromal phase of YOAD to provide timely intervention and appropriate management. This may be even more critical in a near future where advancements in disease-modifying treatments may shift the focus to earlier identification than what is desirable today. Identifying subtle cognitive, behavioral, or functional changes preceding the classic symptoms of dementia is vital for improving diagnostic timeliness and precision. Bridging these knowledge gaps is essential to reduce diagnostic delays and to mitigate the adverse impacts of delayed diagnosis on patients' and caregivers' lives.

2. Aims

2.1 Overall aim

The overall aim of this PhD thesis was to explore potential early warning signs of YOAD that may be leveraged for timely diagnosis.

2.2 Study-specific aims

Study 1: To describe patterns in healthcare utilization characteristic of the prodromal phase of YOAD, and to identify any specific types of healthcare contacts with a more pronounced association than others.

Study 2: To explore whether individuals diagnosed with YOAD differ from cognitively healthy, matched adults in terms of reasons for hospital contacts in the 10 years preceding diagnosis, in order to describe potential patterns in morbidity that characterize the prodromal phase of YOAD.

Study 3: To explore whether individuals diagnosed with YOAD have an altered prescription medication use pattern in the 10 years preceding diagnosis, compared to cognitively healthy, matched adults.

Study 4: To explore patterns of labor market participation and occupational instability prior to diagnosis in patients with YOAD by investigating patterns of long-term sick leave absence and unemployment compared to cognitively healthy, matched adults.

3. Methods

The overarching methodology is presented in detail here. The study-specific methods are described in greater detail in each of the study manuscripts and corresponding supplementary materials. An overview of the study-specific methods is presented study-by-study in **section 3.6**.

3.1 Data sources

Denmark maintains well over 200 government-owned registries, managed and overseen by Statistics Denmark, and from an epidemiological perspective, the Danish population represents an open dynamic cohort with complete long-term follow-up, censored only at emigration or death[48]. In the following, I provide an overview of the main registers used throughout the four studies on which this thesis is based. Table 1 shows how the data sources were used in each of the studies.

3.1.1 The Danish Civil Registration System

The Danish Civil Registration System, established in 1968, assigns a unique 10-digit personal identification number to all Danish residents[49]. This number is consistent across all registers, enabling easy and unambiguous individual-level record linkage across all Danish registers[49]. The civil registration system includes individual information on sex, date and place of birth, citizenship, place of residence, civil status, and continuously updated information on vital status[50].

3.1.2 The Danish Quality Database for Dementia

The Danish Quality Database for Dementia (DanDem) has nationwide coverage from 2016 onwards[51]. The database is part of the Danish Clinical Quality Program – National Clinical Registries (RKKP)[52]. All healthcare facilities that accept referrals for diagnostic evaluation of suspected dementia and cognitive impairment are required to enter information into the database for every patient following the completion of the diagnostic evaluation. Recorded variables include the level of cognitive decline (if any), etiology, the severity of the dementia syndrome at the time of diagnosis (if applicable), and diagnostic investigations performed, including results of selected cognitive tests.

3.1.3 The Danish National Patient Register

The Danish National Patient Register has collected data from all Danish hospitals with nationwide coverage since 1978[53]. Initially, the register covered inpatients in somatic wards with psychiatric inpatient contacts registered elsewhere. In 1995 and onwards, the registry was expanded to further include all outpatient and emergency room contacts and to cover both somatic and psychiatric healthcare contacts[54]. Key variables in the register include the patient identifier, hospital and department, date of

admission and discharge, as well as clinical data such as diagnoses, radiological procedures, and surgical and other invasive procedures performed[53]. Information on diagnoses is coded according to the International Classification of Diseases (ICD) system; initially according to ICD-8, and from 1994 to ICD-10. ICD-9 was never implemented in Denmark[54].

3.1.4 The Danish Psychiatric Central Research Register

The Danish Psychiatric Central Research Register has full data coverage on all psychiatric hospital admissions from 1970 onwards. In 1995, outpatient and emergency room contacts were included, and the register became an integrated part of the Danish National Patient Register. Thus, the content and data structure for these two registers are the same[55].

3.1.5 The Danish National Prescription Registry

The Danish National Prescription Registry has recorded detailed information on redeemed drug prescriptions since 1995[56]. The register contains information on all redeemed prescriptions at community pharmacies, including prescriptions dispensed to nursing home residents[57]. The register contains information about the individual using the drug, the prescriber (medical specialty), the pharmacy, and the prescribed drug (date of dispensing, product name, anatomical therapeutic chemical (ATC) code, etc.)[57]. The ATC code is a global system composed of a five-level classification system run by the World Health Organization's Collaborating Centre for Drug Statistics Methodology[58]. The register does not contain information about drugs sold without a prescription or prescriptions issued by a physician but not filled by the patient[57].

3.1.6 The National Health Service Register

Information on contacts with the primary healthcare sector has been recorded in the National Health Service Register with national coverage since 1990[59]. The register includes information about healthcare services provided by healthcare professionals contracted with the tax-funded public healthcare system, including GPs, private practicing medical specialists, physiotherapists, psychologists, dentists, and chiropractors. Variables include type of healthcare provider, type of service (ordinary consultation, telephone consultation, home visit, preventive consultation, email consultation, or out-of-hours services), and additional services performed (e.g., blood samples, procedures, and other laboratory tests)[59]. The register contains minimal clinical information, as reasons for contacts are not collected routinely.

3.1.7 The Labor Market Accounts Register

Several different registers detailing the labor market status of the population exist, each containing slightly different information. For the purpose of this project, we chose to utilize data from the Labor Market Accounts Register[60], which was established in 2008. Variables include information on socio-economic status, including employment, retirement, disability pension, long-term sick leave, unemployment, etc., and exact timing of all such events. The register further includes details of those outside of the workforce due to education, parental or other types of leave, etc.

3.1.8. The Population Education Register

The Population Education Register defines the highest completed level of education for each individual using an eight-digit code[61], translatable to the International Standard Classification of Education codes[62].

Table 1. Data sources used for each study

	CRS	DanDem	DNPR	DPCRR	DNPrR	NHSR	LMAR	PER
Study 1								
Case and control sampling		X	X	X	X			
Exposure(s)			X	X		X		
Outcome		X						
Linkage and covariates	X							X
Study 2								
Case and control sampling		X	X	X	X			
Exposure(s)			X	X				
Outcome		X						
Linkage and covariates	X							X
Study 3								
Case and control sampling		X	X	X	X			
Exposure(s)					X			
Outcome		X						
Linkage and covariates	X							X
Study 4								
Case and control sampling		X	X	X	X			
Exposure(s)							X	
Outcome		X						
Linkage and covariates	X							X

Data sources for the selection of cases and controls, exposure(s), outcome, and covariates in each of the four studies. **CRS**: The Danish Civil Registration System, **DanDem**: The Danish Quality Database for Dementia, **DNPR**: The Danish National Patient Registry, **DPCRR**: The Danish Psychiatric Central Research Register, **NHSR**: The National Health Service Register, **LMAR**: The Labor Market Accounts Register, **PER**: The Population Education Register

3.2 Study design and population

We conducted four nationwide, retrospective, incidence density-matched nested case-control studies, all of which were exploratory. The definition of the study population was shared across all four studies and is detailed below:

3.2.1 Overall exclusion criteria

Alzheimer's disease in young age is prevalent among those with Down syndrome[63] and other developmental disorders. Describing the prodromal phase for this patient group would require other measures than those addressed here and falls outside of the scope of these studies. Therefore, we excluded individuals with Down syndrome and mental retardation from both the case and the control group. Furthermore, to ensure completeness of data, both cases and controls were required to have been alive and living in Denmark throughout the entire study period. Further exclusion criteria for controls are described with the control definition below. Codes for the identification of exclusion criteria are presented in Table 2.

Table 2. Exclusion criteria for selection of cases and controls

	CASES	CONTROLS
Developmental disorders and mental retardation: ICD-8: 311-315, 759.3, ICD-10: DF70-DF79, DQ90	X	X
Not living in Denmark in entire retrospective period	X	X
Dementia or mild cognitive impairment diagnosis: ICD-8: 290.09-11, 290.18-19, 293.09-19, ICD 10: F00.0-00.9, F01.0-01.9, F02.0-F02.8, F03.9, F04.0-F04.9, F06.7 G30.0-G30.9, G31.0A, G31.0B, G31.8, G31.8E, G31.9		X
Dementia medication: ATC code N06DA02-4, N06DX01		X
Entry in DanDem		X

ICD: International classification of diseases, **ATC**: Anatomical therapeutic chemical code, **DanDem**: The Danish Quality Database for Dementia. *Adapted from the supplementary information of Study 1, 2 and 3 - Damsgaard et al.*[1–3].

3.2.2 Case definition

For all studies, we wanted to include all patients diagnosed with YOAD, defined as having symptom onset before age 65 years[9]. As none of the Danish registers contain information about the timing of symptoms, we had to approximate time of symptom onset using the available data. Prior research has shown a mean time from symptom onset to final diagnosis of around 5 years for YOAD patients[44,45]. Therefore, we included those diagnosed before age 70 years, assuming a 5-year time lag between symptom onset and diagnosis. As we were interested in the prodromal phase, we included both patients diagnosed with mild cognitive impairment (MCI) and dementia, with etiology registered as Alzheimer's disease. While etiology is not routinely established in all MCI patients, thorough diagnostic investigations may be performed based on patient preference, provided there are good clinical reasons

for doing so. Cases were identified from DanDem from start of the register (2016) and up to and including 2018 (**Study 1**), 2020 (**Study 2** and **3**), or 2022 (**Study 4**), thus encompassing all patients diagnosed with YOAD at a Danish memory clinic in the given time frame (except those fulfilling exclusion criteria). The diagnosis of Alzheimer's disease was made according to the National Institute on Aging – Alzheimer's Association workgroups (NIA-AA) criteria[64], and disease severity was determined based on ICD-10 criteria[65]. Index time was set to date of diagnosis in DanDem.

3.2.3 Control definition

Each case was matched with either three (**Study 1**, **2**, and **3**) or five (**Study 4**) controls on exact birthdate and sex. Each control was randomly drawn from the full risk set (the entire Danish population). Exclusion criteria for controls were 1) dementia prior to index date, determined as having a record of a dementia diagnosis in the Danish National Patient Register or the Danish Psychiatric Central Research Register or a redeemed prescription of antidementia medication in the Danish National Prescription Registry, and 2) no entry in DanDem (i.e., no visits or referrals to a memory clinic).

3.2.4 Matching

Incidence density matching was used, meaning each control was at risk of YOAD at matching date (index date). In **Study 1, 2,** and **3** we used a 1:3 matching ratio, and in **Study 4** we used a 1:5 matching ratio. In incidence density sampling, the odds of exposure among the cases compared to the controls directly reflect the ratio of the incidence rates because the control selection process mirrors the person-time at risk. Mathematically, the study design ensures that each control is chosen based on the time they are at risk and matched to cases accordingly, so the odds ratio from the case-control analysis estimates the incidence rate ratio (IRR) from a cohort analysis[66]. As noted in a paper from the American Journal of Epidemiology[67], though many case-control studies refer to estimates as odds ratios regardless of the chosen matching procedures, it is misleading to label the results from an incidence-density sampling setup as odds ratios because they are more correctly interpreted as relative risk measures. Therefore, the estimates of the negative binomial and conditional logistic regression analyses are denominated as IRRs throughout this thesis and the accompanying papers.

3.3 Covariates

Covariates included age, sex, civil status at index date (information on which stemmed from the Civil Registration System), and educational level at age 40 years or at index date, whichever came first (information on which was drawn from the Population Education Register). All estimates from the analyses in each of the studies were presented unadjusted and adjusted for all covariates.

3.4 Statistical software

All data management was performed using SAS 9.4 software. All statistical analyses were performed in SAS 9.4, except for the negative binomial regression analysis in **Study 1**, where STATA/MP 17.0 software was used.

3.5 Significance level

Results of statistical analyses are presented with 95% confidence intervals (CI), corresponding to a 5% significance level. Given that all four studies are exploratory we decided not to adjust for multiple comparisons. However, it is important to note that due to the numerous analyses conducted, the CIs should be regarded merely as approximate indicators of overall trends.

3.6 Study-specific methods

3.6.1 Study 1

Exposure: healthcare utilization

In **Study 1**, the exposure of interest was number and type of healthcare contacts, divided by:

Primary care contacts: this was defined as a record in the National Health Service Register, and further divided into the following categories: 1) GP contacts, 2) Contacts with a private practicing medical specialist, 3) Contacts with a physiotherapist, or 4) Contacts with a psychologist. For the latter two it was only possible to include visits by referral from the public sector, and thus visits paid fully out-of-pocket by the patient are not included.

Secondary care contacts: secondary care contacts were divided into either somatic or psychiatric contacts and were defined as a record in the Danish National Patient Register or the Danish Psychiatric Central Research Register. This was further subdivided into inpatient admissions, outpatient contacts, and emergency room contacts.

Statistical analysis: negative binomial regression analysis

Associations between the listed types of healthcare contacts and subsequent YOAD were analyzed using negative binomial regression analysis (except psychiatric outpatient contacts), producing IRRs – denominated in this study as contact rate ratios (CRRs). We calculated CRRs in three time-intervals: 10->5 years prior to index date, 5->1 year prior to index date, and ≤1 year prior to index date. To account for matching clusters and correlation between observations for the same person in different time periods, robust variance estimation was applied. These analyses were performed in STATA, using the vce(cluster) function to allow for intragroup correlation.

Cumulative incidence function

For psychiatric outpatient contacts, individual visits within an overall follow-up course could not be traced due to data limitations. Therefore, we counted psychiatric outpatient follow-ups rather than individual visits and instead measured the proportion of cases and controls, respectively, with a psychiatric outpatient contact during the 10-year study period using a cumulative incidence function.

Sensitivity analyses

We repeated the negative binomial regression analyses while stratifying the study population by 1) disease severity (MCI/mild dementia, moderate/severe dementia), 2) age at index date (age <60 years, age ≥60 years), and 3) sex (male, female).

3.6.2 Study 2

Exposure: morbidity

In **Study 2**, the exposure of interest was morbidity prior to index date, assessed using discharge diagnoses in the Danish National Patient Register and the Danish Psychiatric Central Research Register. Diagnoses were grouped according to chapters in the ICD-10 classification[68], omitting all contacts related to pregnancy, childbirth, or the perinatal period, and congenital malformations and chromosomal abnormalities. Furthermore, as prior MCI or dementia diagnosis was a censoring criterion for controls, we omitted these ICD-10 codes from the analyses for cases.

Statistical analysis: conditional logistic regression analysis

For each ICD-10 chapter, we used conditional logistic regression analysis to examine the association between having at least one diagnosis within the chapter and subsequent YOAD diagnosis. For the main analysis, we calculated IRRs for the whole study period, as well as in three time-intervals: 10->5 years prior to index date, 5->1 year prior to index date, and ≤1 year prior to index date.

Analyses of the most frequent morbidities

In addition to the analysis described above of morbidity categorized by overall ICD-10 chapters, we wanted to examine morbidity in greater detail. However, as examining all specific diagnoses would produce an excessive number of estimates, we opted to identify the three most prevalent diagnoses within each disease category in the study population. This was done on a two-digit level, that is by combining the ICD-10 chapter identifier (e.g., A) plus two digits (e.g., 01), that is, A01. Associations between these specific diagnostic codes and subsequent YOAD were examined by conditional logistic regression analysis in the entire 10-year study period.

Sensitivity analyses

We repeated the main analyses while stratifying the study population by 1) disease severity (MCI/mild dementia, moderate/severe dementia), 2) age at index date (age <55 years, age ≥55 years), and 3) sex (male, female). Furthermore, we repeated the main analysis while censoring all contacts in the 6 months preceding index date to avoid counting diagnoses given as part of the diagnostic evaluation of dementia. We also repeated the analysis while omitting MCI patients and their controls.

Post-hoc analysis

After conducting the planned analyses, we decided to investigate the association between all sub-chapters of the ICD-10 chapter F (mental and behavioral disorders) and a subsequent YOAD diagnosis overall and in the three time intervals, following the same methodology as the main analysis.

3.6.3 Study 3

Exposure: prescription medication

In **Study 3**, the exposure of interest was prescription medication, assessed as redeemed prescriptions in the Danish National Prescription Registry. Prescription medication was divided into categories based on ATC main groups (i.e., 1st digit of the ATC code). Medication use was further subdivided into subcategories largely based on therapeutic subgroups in the ATC system, though as these were in some cases deemed too broad, more detailed subcategories were chosen for some medications. Only subcategories with a use-prevalence of >5% were included in the analyses. Furthermore, as prior antidementia medication was a censoring criterion for controls, these medications were also omitted from the analyses for cases.

Statistical analysis: conditional logistic regression analysis

The statistical analysis in **Study 3** was conducted using the same methodology as in **Study 2** described in **section 3.6.2**, using ATC main groups instead of ICD-10 chapters. Analyses of medication subcategories were only done for the entire 10-year study period, except for nervous system medication; based on the findings from **Study 1** and **Study 2**, we decided a priori to examine the subcategory "nervous system medication" both overall and in the three time intervals.

Sensitivity analyses

We repeated the main analyses while stratifying the study population by 1) disease severity (MCI/mild dementia, moderate/severe dementia), 2) age at index date (age <55 years, age ≥55 years), and 3) sex (male, female). Furthermore, we repeated the main analysis while censoring all prescriptions in the 6

months preceding index date to avoid counting prescriptions made as part of the diagnostic evaluation of dementia. We also repeated the analysis while omitting MCI patients and their controls.

Post-hoc analyses

After conducting the planned analyses, we decided to repeat the "nervous system medication" subcategory analysis, limiting the analysis to first-ever prescriptions in each time interval compared to never-users. Furthermore, we conducted post-hoc analyses examining which subcategories drove the decreased IRRs found in the time interval ≤1 year prior to index date.

3.6.4 Study 4

Exposures: unemployment, long-term sick leave

In **Study 4**, the exposures of interest were unemployment and long-term sick leave. Exposure data was extracted from the labor market accounts register. Unemployment was defined as having a registration of social benefits relating to unemployment (unemployment benefits (in Danish: *dagpenge*) or social benefits (in Danish: *kontanthjælp*)). Long-term sick leave was defined as a registration of sick leave lasting more than 30 consecutive days (this time limit was chosen due to data availability, as short-term sick leave (≤30 days) is generally paid by the employer and not registered in public databases).

Censoring

Individuals were censored if they were no longer at risk for the exposures, either temporarily or permanently. Those outside the workforce due to education or (parental) leave were temporarily censored but could re-enter the study upon the end of their absence. Participants with both exposures in a given period were included in both analyses, while those with only one exposure were included as exposed in the relevant analysis and temporarily censored in the other. Individuals employed in a "flex job," on disability pension, or retired were permanently censored starting from the interval when these statuses were first recorded.

Statistical analysis: conditional logistic regression analysis

We used conditional logistic regression analysis to examine the association between each of the two exposures and subsequent YOAD, compared to the reference group. The reference group included all study participants who were part of the active workforce in a given interval – that is, those with a registration of paid employment, no registration of either exposure, and no censoring events. The two exposures were examined in yearly time intervals corresponding to years before index date (12-<13 years, 11-<12 years, …, <1 year).

Quantifying long-term sick leave

In addition to examining the association between having at least one period of long-term sick leave and subsequent YOAD in a given time interval, we wanted to also quantify the amount of time spent on long-term sick leave. We presented these as percentages of the cases and controls, respectively, with annual durations of 0, 1, 2-3, 4-6, or more than 6 months of long-term sick leave, until censoring or index date.

Sensitivity analyses

We repeated the main analyses while stratifying the study population by 1) disease severity (MCI/mild dementia, moderate/severe dementia), and 2) sex (male, female). Furthermore, we repeated the main analysis while limiting the study population to only include those with index date before March 1st, 2020, to ensure the COVID-19 pandemic[69,70] did not impact the results.

3.7 Ethics and approvals

The studies included in this thesis are part of a larger project at the Danish Dementia Research Centre revolving around medication use, health, and mortality in patients with dementia. Approvals for this project have been granted by the Danish Data Protection Agency, the Danish Health Data Authority, and Statistics Denmark. All data management and analyses were conducted on the remote servers of Statistics Denmark using pseudonymized data with strict adherence to their data protection requirements. Danish law does not require ethics committee approval or informed patient consent for these types of studies.

4. Summary of results

Though the study population was expanded study-by-study as we were able to include more years for case-finding, baseline characteristics were nearly identical across the studies. The study population had a near 60/40 women/men ratio in all studies, and educational attainment and civil status were evenly distributed among cases and controls. Across the studies, 60-64% of cases had MCI or mild dementia at the time of diagnosis, with 36-40% of cases diagnosed at the moderate/severe stage of the dementia syndrome. Figure 1 shows the number of cases and controls included in each study and select key findings, presented in-depth in the following sections.

For the four studies, a similar set of sensitivity analyses were run. Common across all the studies was that sensitivity analyses generally did not alter the overall trends observed. Stratifying on age and sex did not meaningfully impact results, whereas stratifying on disease severity at index date generally amplified findings somewhat for those with moderate/severe dementia at time of diagnosis, with changes becoming apparent slightly earlier for those more affected, but without altering the directionality of the overall trends. **Study 4** had a follow-up time in part congruent with COVID-19 years; however, sensitivity analysis limiting the study period to pre-COVID-19 years did not change the results.

Figure 1. Summary of study population and key findings from each study

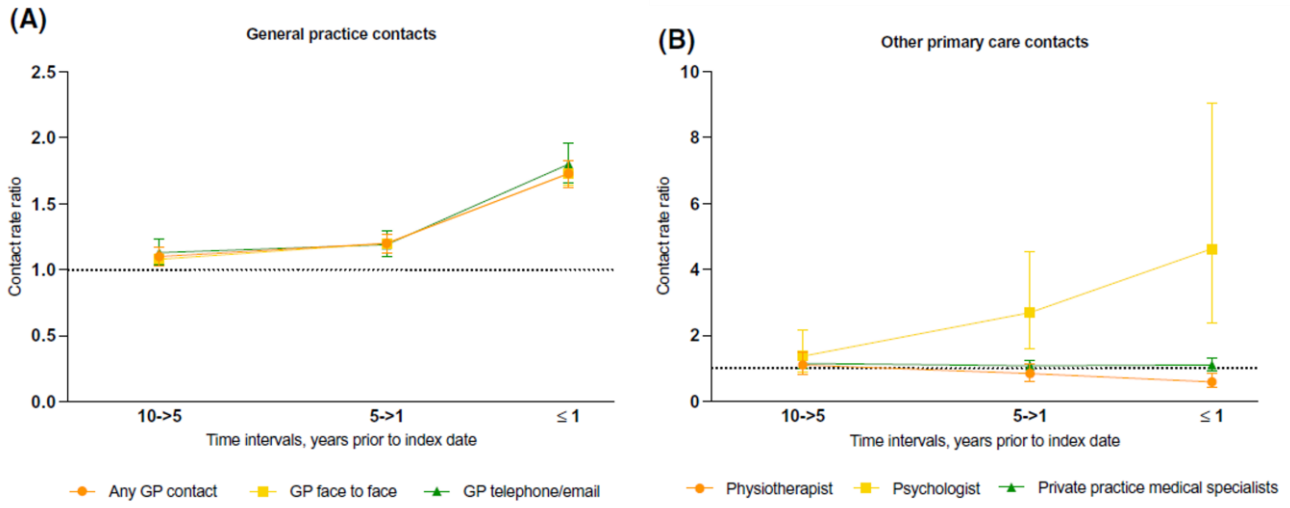
	Study population	Exposure	Outcome measure / key findings
Study 1 →	1082 cases 3246 controls	Healthcare utilization	**Outcome measure: Contact rate ratio (CRR)** • CRRs were significantly increased for GP contacts in the entire 10-year study period • CRR for psychiatric inpatient admissions in the ≤1 year prior to ID: 8.31 (3.35-20.60) • CRR for psychiatric emergency contacts in the ≤1 year prior to ID: 8.69 (4.29 – 17.62)
Study 2 →	1745 cases 5235 controls	Hospital-diagnosed morbidity	**Outcome measure: Incidence rate ratio (IRR) of morbidity vs no morbidity** • IRRs for Mental and behavioral disorders: • 10->5 years prior to ID: 1.43 (1.-14-1.79), 5->1 years prior: 2.48 (2.02-3.04), ≤1 year prior: 8.19 (6.27-10.70) • Subcategory-analysis of psychiatric disorders: stress and depression have high IRRs from 5 years prior to ID
Study 3 →	1745 cases 5235 controls	Prescription medication use	**Outcome measure: IRR of prescription medication use vs no use** • YOAD cases had around 20% increased use of nervous system medication 10->5 and 5->1 year prior to ID, increasing to IRR 1.57 (1.39-1.78) in the ≤1 year prior • Of 46 subcategories, 7 had significantly increased IRRs. Highest IRRs: antidepressants and antipsychotics
Study 4 →	2434 cases 12.170 controls	Unemployment, Long-term sick leave	**Outcome measure: IRR of unemployment/long-term sick leave vs active workforce** • Unemployment increased from 4-<5 years prior to ID – IRR 7.52 (4.72-11.98) in the ≤1 year prior • Long-term sick leave increased from 7-<8 years prior - IRR 29.59 (18.97-46.14) in the ≤1 year prior • In the ≤1 year prior to ID, 46% of cases and 2% of controls had >4 months of long-term sick leave

ID: index date. 95% confidence intervals are presented in parentheses after estimates.

4.1 Study 1

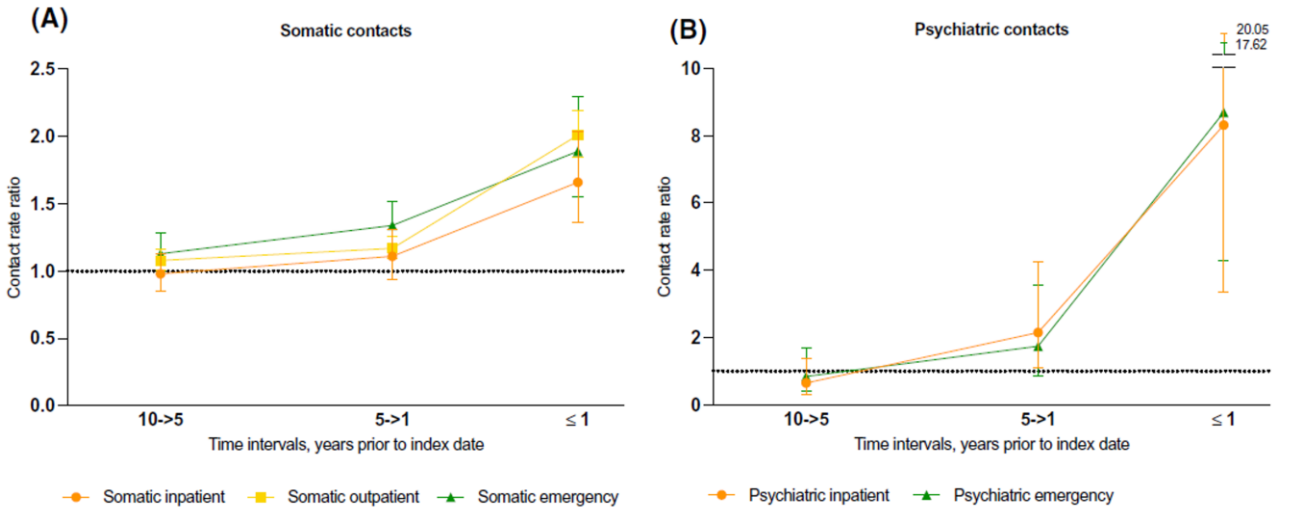
CRRs were increased for all types of healthcare contacts in the year prior to index date with two exceptions (Figures 2 and 3); private practicing medical specialists (non-significant increase, CRR 1.10 (95% CI 0.93 – 1.31)) and physiotherapists (significantly decreased, CRR 0.59 (95% CI 0.41 – 0.85)).

Figure 2. Contact rate ratios for primary care contacts



Contact rate ratios are plotted for contacts with a general practitioner (**GP**) **(A)** and other primary healthcare contacts **(B)**. Error bars represent 95% confidence intervals. The contact rate ratios presented are adjusted for age, sex, highest attained educational level at age 40 (or at time of diagnosis, whichever came first), and civil status at index date. Note that the Y-axis has differing values for **(A)** and **(B)**. Reprinted from Damsgaard et al.[1]

Figure 3. Contact rate ratios for secondary care contacts



Contact rate ratios are plotted for somatic contacts **(A)** and psychiatric contacts **(B)**. Error bars represent 95% confidence intervals. The contact rate ratios presented are adjusted for age, sex, highest attained educational level at age 40 (or at time of diagnosis, whichever came first), and civil status at index date. Note that the Y-axis has differing values for **(A)** and **(B)**. Reprinted from Damsgaard et al.[1]

The largest increase in the year leading up to diagnosis was found for psychologist and psychiatric inpatient and outpatient visits, the latter two with over eight-fold increases in CRR for YOAD cases compared to controls. The same trend was found for psychiatric outpatient contacts, where the cumulative incidence function showed a higher cumulative incidence of outpatient contacts starting from

around 3.5 years prior to diagnosis, rapidly increasing nearing index date. Other than GP contacts, CRRs more than one year before diagnosis were either non-significant or only slightly increased; the main exception was psychologist contacts in the 5->1 year interval (CRR 2.69, 95% CI 1.58 – 4.56). CRRs for GP contacts were significantly increased throughout the entire 10-year study period.

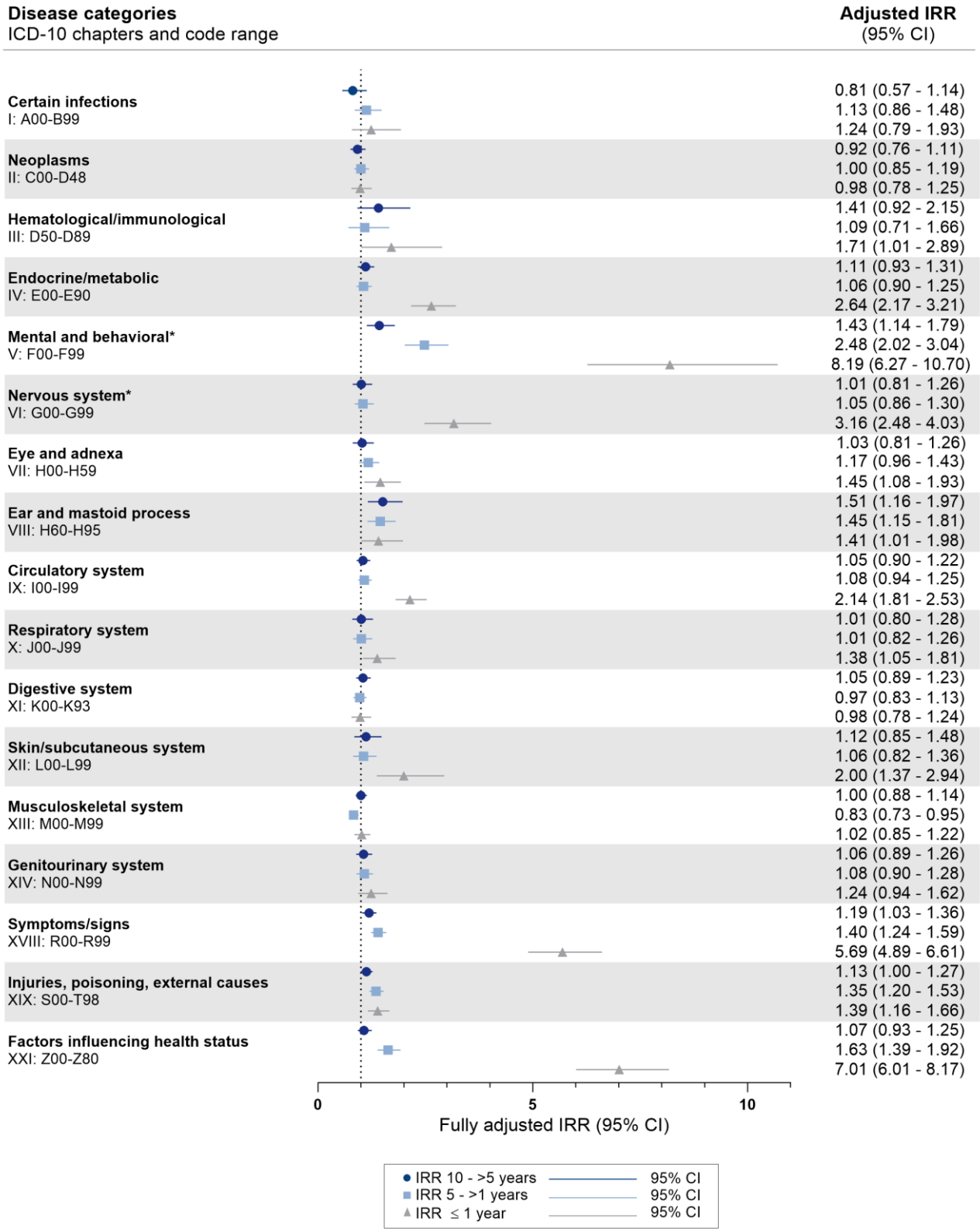
4.2 Study 2

Figure 4 shows IRRs for a diagnosis within the examined disease categories for YOAD cases compared to controls in three time intervals. Looking first at the period 10->5 years prior to index date, IRRs were only significantly increased for a few disease categories; Diseases of the ear and mastoid process (IRR 1.51, 95% CI 1.16 – 1.97), Mental and behavioral disorders (IRR 1.43, 95% CI 1.14 – 1.79), and Symptoms/signs not classified elsewhere (IRR 1.19, 95% CI 1.03 – 1.36). In the 5->1 years prior to index date, these three categories remained significantly increased, with the addition of Injuries, poisonings and other external causes and Factors influencing health status. The highest increase in this time interval was found for Mental and behavioral disorders, with an IRR of 2.48 (95% CI 2.02 – 3.04). In the ≤1 year prior to index date, significantly increased IRRs were found for 12 of the 17 disease categories examined. The highest increase in this time interval was again Mental and behavioral disorders, with an IRR of 8.19 (95% CI 6.27 – 10.70).

In the analysis of the most frequent diagnoses among the study population, the largest increases were found for two diagnostic codes often given as part of a diagnostic evaluation; the ICD-10 codes R41 (symptoms involving cognitive functions) and Z01 (other special examinations and investigations of persons without complaint or reported diagnosis). If looking at diagnostic codes for specific disorders/diseases, the highest IRRs were found for the three most frequent diagnostic codes in the Mental and behavioral disorders category: F10 (mental and behavioral disorders due to use of alcohol), F43 (reaction to severe stress), and F32 (depressive episode). A significant decrease was found only for one diagnosis; E66 (Obesity) had an IRR of 0.59 (95% CI 0.43 – 0.81).

Based on these results we did a post-hoc analysis examining all sub-categories of the Mental and behavioral disorders category in the three time intervals. As this was a post-hoc analysis significance should be interpreted carefully; looking, therefore, at the bigger trends, we found convincing increases in the 5->1 year interval for the three subcategories Organic, including symptomatic, mental disorders (excluding MCI and dementia diagnoses), Mood/affective disorders, and Neurotic, including stress-related and somatoform disorders. In the ≤1 year prior to index date, IRRs for these subcategories remained increased, while increases were also observed for Mental and behavioral disorders due to psychoactive substance use, and Schizophrenia, schizotypal, and delusional disorders.

Figure 4. Incidence rate ratios for YOAD by disease categories



Incidence rate ratios (**IRR**s) for YOAD are plotted by disease categories in three time-intervals prior to index date. For the reference group (controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals. The IRRs presented are adjusted for age, sex, highest attained educational level at age 40 (or at time of diagnosis, whichever came first), and civil status at index date. *Excluding MCI and dementia diagnoses.
Reprinted from Damsgaard et al.[2]

4.3 Study 3

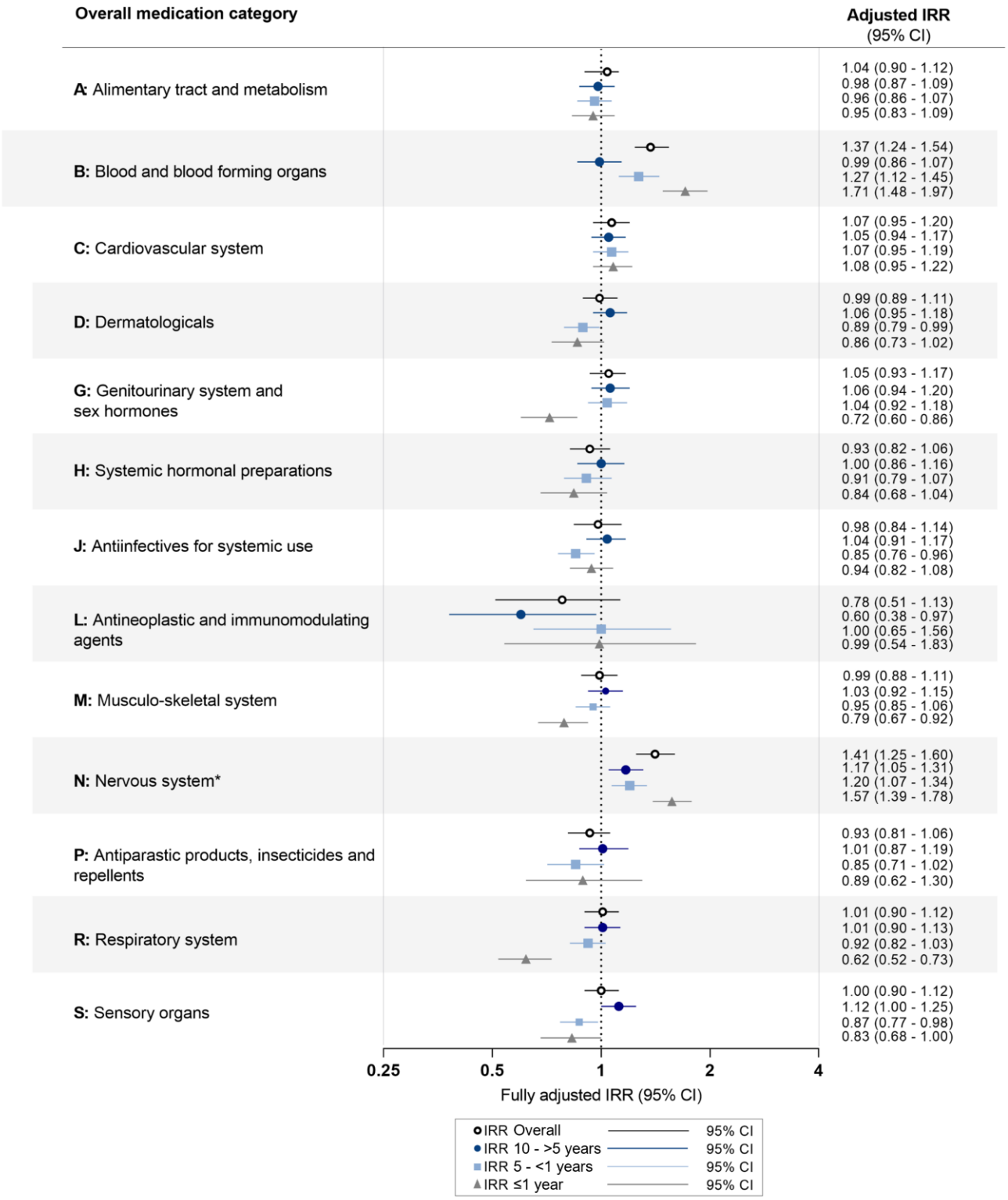
Looking at the proportion of cases and controls, respectively, with at least one redeemed prescription within each of the overall categories, the percentages were nearly the same. Notable exceptions were Blood and blood-forming organs medications, where 36% of cases and 29% of controls had redeemed prescriptions, and Nervous system medication, where 75% of cases and 68% of controls had redeemed prescriptions. These two medication categories were also the only two for which we found significant increases in IRR; for medication in the Blood and blood-forming organs category, IRR was increased from 5->1 years prior to index date (1.27, 95% CI 1.12 – 1.45), increasing to 1.71 (95% CI 1.48 – 1.97) in the ≤1 year prior to index date (Figure 5).

For medications in the Nervous system category, IRRs were increased throughout all time intervals, increasing from 1.17 (95% CI 1.05 – 1.31) in the 10->5 years prior, to an IRR of 1.57 (95% CI 1.39 – 1.78) in the ≤1 year prior to index date. Examining Nervous system drugs by subcategories in the three time intervals, we found significantly increased IRRs for antidepressants throughout all intervals, increasing from 1.43 (95% CI 1.25 – 1.64) 10->5 years prior to index date to 3.62 (95% CI 3.09 – 4.24) in the ≤1 year prior to index date. Antipsychotics had increased IRRs from 5->1 years prior, with an IRR of 3.62 (95% CI 3.09 – 4.24) in the ≤1 year prior to index date. Anxiolytics had a slightly increased IRR only in the ≤1 year prior to index date. In a post-hoc analysis, first-ever prescriptions of nervous system drugs showed IRRs over 10 for antipsychotic and antidepressant use in the year before diagnosis when compared to never-users.

Three of the overall categories had decreased IRRs in the ≤1 year prior to index date. In a post-hoc analysis, we examined which medication subcategory mainly drove the association – the overall categories and their drivers (*in parentheses*) were: Genitourinary system and sex hormones (*sex hormones*), Musculoskeletal system (*anti-inflammatory and antirheumatic drugs*), and Respiratory system products (*all subcategories*).

Associations between all medication subcategories (with a use-prevalence of at least 5%) and YOAD diagnosis were examined in the entire 10-year study period. Of the 46 subcategories examined, seven had significantly increased IRRs. Aside from the Nervous system subcategories, which are described above, IRRs were increased for drugs for constipation (IRR 1.48, 95% CI 1.22 – 1.78), antianemic preparations (IRR 1.63, 95% CI 1.38 – 1.93), and antithrombotic preparations (IRR 1.27, 95% CI 1.12 – 1.45). Slight decreases were found for use of diuretics (IRR 0.83, 95% CI 0.73 – 0.95) and Corticosteroids for systemic use (IRR 0.85, 95% CI 0.74 – 0.97).

Figure 5. Incidence rate ratios for YOAD by medication categories



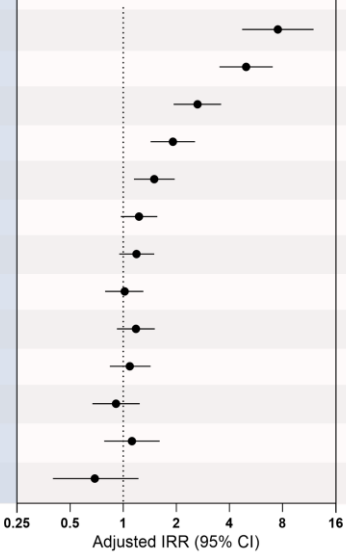
Incidence rate ratios (**IRR**s) for YOAD are plotted by medication categories overall and in three time-intervals prior to index date. For the reference group (controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals. The IRRs presented are adjusted for age, sex, highest attained educational level at age 40 (or at time of diagnosis, whichever came first), and civil status at index date. *Excluding dementia medication. Reprinted from Damsgaard et al.[3]

4.4 Study 4

Figure 6 shows the association between having a period of unemployment in a given time interval (compared to those working throughout that interval) and subsequent YOAD, for cases compared to controls. A significant difference was seen from 4-<5 years prior to index date (IRR 1.50 (95% CI 1.15 – 1.96), with IRRs gradually increasing to an IRR of 7.52 (95% CI 4.72 – 11.98) in the <1 year prior to diagnosis. In the five years prior to index date, 11% of (non-censored) cases and 8% of (non-censored) controls had at least one period of unemployment. The proportion of controls with periods of unemployment was more or less unchanged across time intervals, whereas for cases, 40% had been unemployed within the <1 year before diagnosis.

Figure 6. Incidence rate ratios for unemployment and YOAD

Unemployment	Cases			Controls			
Time interval	Unemployed n (%)	Active workforce n (%)	Censored n	Unemployed n (%)	Active workforce n (%)	Censored n	Adjusted IRR (95% CI)
< 1 year prior to index date	84 (40%)	125 (60%)	2225	251 (8%)	3039 (92%)	8880	7.52 (4.72 - 11.98)
1 - <2 years prior to index date	102 (23%)	349 (77%)	1983	261 (7%)	3489 (93%)	8420	4.97 (3.51 - 7.04)
2 - <3 years prior to index date	94 (15%)	514 (85%)	1826	292 (7%)	3948 (93%)	7930	2.64 (1.93 - 3.59)
3 - <4 years prior to index date	94 (13%)	651 (87%)	1689	339 (7%)	4436 (93%)	7395	1.91 (1.43 - 2.55)
4 - <5 years prior to index date	99 (11%)	813 (89%)	1522	425 (8%)	5062 (92%)	6683	1.50 (1.15 - 1.96)
5 - <6 years prior to index date	118 (11%)	992 (89%)	1324	504 (8%)	5720 (92%)	5946	1.23 (0.97 - 1.56)
6 - <7 years prior to index date	120 (10%)	1105 (90%)	1209	515 (8%)	6157 (92%)	5498	1.19 (0.95 - 1.50)
7 - <8 years prior to index date	98 (8%)	1066 (92%)	1270	484 (8%)	5722 (92%)	5964	1.02 (0.79 - 1.30)
8 - <9 years prior to index date	102 (10%)	946 (90%)	1386	453 (8%)	5052 (92%)	6665	1.18 (0.92 - 1.51)
9 - <10 years prior to index date	86 (10%)	784 (90%)	1564	403 (8%)	4203 (91%)	7564	1.09 (0.84 - 1.43)
10 - <11 years prior to index date	59 (9%)	630 (91%)	1745	337 (9%)	3304 (91%)	8529	0.91 (0.67 - 1.24)
11 - <12 years prior to index date	44 (9%)	427 (91%)	1963	227 (9%)	2258 (91%)	9685	1.12 (0.78 - 1.61)
12 - <13 years prior to index date	17 (7%)	239 (93%)	2178	114 (9%)	1124 (91%)	10932	0.69 (0.40 - 1.22)

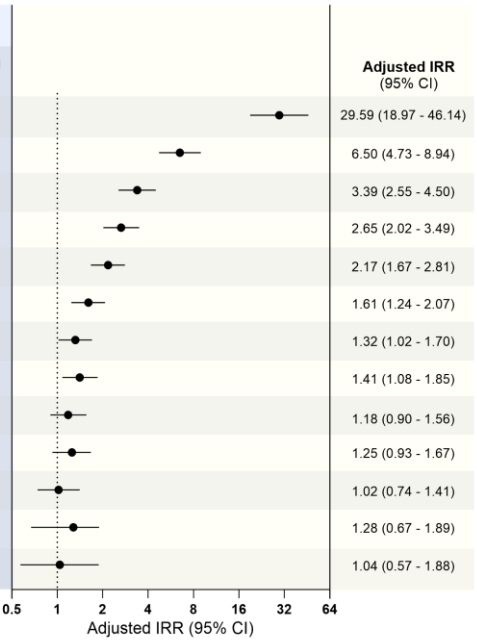


Incidence rate ratios (**IRR**s) for unemployment and YOAD are plotted in time-intervals prior to index date. For the reference group (controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals. The IRRs presented are adjusted for age, sex, highest attained educational level at age 40 (or at time of diagnosis, whichever came first), and civil status at index date.

Figure 7 shows the association between having a period of long-term sick leave in a given time interval (compared to those working throughout that interval) and subsequent YOAD, for cases compared to controls. A significant difference was seen from 7-<8 years prior to index date (IRR 1.41 (95% CI 1.08 – 1.85), with IRRs gradually increasing to an IRR of 29.59 (95% CI 18.97 – 46.14) in the <1 year prior to diagnosis. In this time interval, 67% of (non-censored) cases and 7% of controls had at least one period of long-term sick leave, with 26% of cases having had more than 6 months of long-term sick leave vs. 1% of controls.

Figure 7. Incidence rate ratios for long-term sick leave and YOAD

Long-term sick leave	Cases			Controls			
Time interval	Sick leave n (%)	Active workforce n (%)	Censored n	Sick leave n (%)	Active workforce n (%)	Censored n	Adjusted IRR (95% CI)
< 1 year prior to index date	253 (67%)	125 (33%)	2054	224 (7%)	3039 (93%)	8907	29.59 (18.97 - 46.14)
1 - <2 years prior to index date	139 (28%)	346 (72%)	1944	238 (6%)	3489 (94%)	8443	6.50 (4.73 - 8.94)
2 - <3 years prior to index date	118 (19%)	514 (81%)	1800	263 (6%)	3948 (94%)	7959	3.39 (2.55 - 4.50)
3 - <4 years prior to index date	119 (15%)	651 (85%)	1662	310 (7%)	4436 (93%)	7424	2.65 (2.02 - 3.49)
4 - <5 years prior to index date	115 (12%)	813 (88%)	1504	326 (6%)	5062 (94%)	6782	2.17 (1.67 - 2.81)
5 - <6 years prior to index date	103 (9%)	992 (91%)	1337	375 (6%)	5720 (94%)	6075	1.61 (1.24 - 2.07)
6 - <7 years prior to index date	101 (8%)	1105 (92%)	1226	416 (6%)	6157 (94%)	5597	1.32 (1.02 - 1.70)
7 - <8 years prior to index date	84 (7%)	1066 (93%)	1282	356 (6%)	5722 (94%)	6092	1.41 (1.08 - 1.85)
8 - <9 years prior to index date	77 (8%)	946 (92%)	1409	337 (6%)	5052 (94%)	6781	1.18 (0.90 - 1.56)
9 - <10 years prior to index date	70 (8%)	784 (92%)	1578	289 (6%)	4203 (94%)	7678	1.25 (0.93 - 1.67)
10 - <11 years prior to index date	53 (8%)	630 (92%)	1749	264 (7%)	3304 (93%)	8602	1.02 (0.74 - 1.41)
11 - <12 years prior to index date	40 (9%)	427 (91%)	1965	177 (7%)	2258 (93%)	9735	1.28 (0.67 - 1.89)
12 - <13 years prior to index date	17 (7%)	239 (93%)	2176	80 (7%)	1124 (93%)	10966	1.04 (0.57 - 1.88)



Incidence rate ratios (**IRR**s) for long-term sick leave and YOAD are plotted in time-intervals prior to index date. For the reference group (controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals. The IRRs presented are adjusted for age, sex, highest attained educational level at age 40 (or at time of diagnosis, whichever came first), and civil status at index date.

5. Discussion

In the following, I discuss a number of key findings divided into four sections: healthcare utilization, depression and stress-related disorders, other morbidity and medication, and labor market participation. Each section includes a discussion about how the finding relates to other research and possible interpretations. Following this, I discuss strengths and limitations as well as some of the methodological considerations that have emerged through this project. Finally, I will present my conclusions, including clinical implications, societal implications, and future research directions.

5.1 Healthcare utilization

We found that individuals with YOAD have increased healthcare utilization in the year leading up to diagnosis across any type of primary or secondary care contact, with the highest increase seen for psychiatric contacts. Notably, from five to one year prior to diagnosis, individuals with YOAD had nearly three times the number of psychologist contacts compared to controls. GP contacts were significantly increased throughout the entire 10-year study period, indicating a sustained higher utilization of healthcare services long before diagnosis.

While there is a gap in the literature when it comes to studies on healthcare utilization prior to a diagnosis of YOAD, a number of studies have examined healthcare utilization and/or healthcare utilization costs prior to a diagnosis of late onset dementia (or not stratifying on age). Some studies used Alzheimer's disease as the outcome, and others looked at all-cause dementia or cognitive decline. These studies often examined a shorter time period prior to diagnosis with the majority looking at the period 1-3 years prior[71,72,81–84,73–80], while two studies examined healthcare utilization in the 5 years prior to diagnosis[85,86]. One study examining healthcare costs in a 10-year period prior to diagnosis was found[87].

Of the studies examining the 1-3 years prior, the majority found increased healthcare use throughout the investigated period[71,72,74–81], while some studies only found an increase immediately prior[83,84]. Some studies did not find major differences in healthcare use between cases and controls; Leibson et al. examined acute care use for persons with and without Alzheimer's disease and found no significant differences in the use of acute care services in the year before disease onset[73], and Zhu et al. found rates of inpatient and outpatient visits similar between dementia patients and controls in the 2 years before incident dementia; though use of home health and skilled nursing care was already higher among dementia patients[82]. While the study populations, study periods, and examined measures all differ slightly from what we have investigated, the majority of these studies (with few exceptions) seem to

point to a shared conclusion with ours; that healthcare utilization increases already in the years leading up to a dementia diagnosis.

Of the two studies examining a 5-year period before dementia diagnosis, a German study examined GP contacts[85] and a Finnish register-based study examined hospital care costs[86]. In the German study, cases with dementia had a significantly higher contact frequency than controls, with a sharp increase in the year immediately prior to diagnosis. Interestingly, the Finnish study found hospital care costs to increase only starting from 0.5-1 year prior to diagnosis; though not YOAD specific, and healthcare cost is not exactly the same as healthcare utilization, it seems to show an underlying increase in secondary contacts increasing only later in the prodromal phase. Overall, these findings are comparable to what we found; increased healthcare utilization in primary care long before diagnosis, with secondary care contacts primarily increasing closer to the date of dementia diagnosis.

In a Swedish study from 2021, healthcare costs were examined for inpatient, outpatient, and primary care contacts for all-cause dementia patients over a 10-year period[87]. While healthcare costs and healthcare utilization are two somewhat different measures, healthcare costs do reflect the underlying healthcare utilization – especially comparable in a Scandinavian context where access to healthcare is generally associated with a very low degree of personal payment or is free. In this study, the authors found increased healthcare costs during the period 10 years prior to dementia diagnosis, with primary care contacts the most commonly used form of healthcare. While the specific estimates derived from their analyses are not directly comparable to ours due to the difference in measures examined, it does point towards a common conclusion of increased healthcare use, especially in primary care, up to a decade before dementia diagnosis. This thus seems to not only apply to YOAD, as found in our study, but may also be applicable to late onset dementia cases and other causes of dementia than Alzheimer's disease.

To conclude; while no studies have reported specifically on healthcare utilization in young onset dementia, our findings for the YOAD population are overall consistent with findings from prior research on healthcare utilization in late onset (all-cause) dementia.

The significant increase in GP contacts over the decade leading up to diagnosis suggests that individuals with YOAD may experience subtle early changes that prompt repeated interactions with healthcare providers. This could reflect a long period of nonspecific symptoms which may not immediately raise a suspicion of cognitive impairment or dementia, especially among the younger patients in whom dementia is a relatively rare disease. The sustained higher healthcare utilization points to a pattern of increased vulnerability or health concerns well before YOAD is recognized clinically. It raises the

possibility that earlier markers or warning signs of YOAD may be present but not yet recognized as part of the disease trajectory. This is emphasized by the fact that around 40% of YOAD cases in our studies were diagnosed at an advanced stage in their dementia disease, implying that the challenge around timely diagnosis observed in international studies[36,42–45] is also a problem in a Danish context.

The increased use of psychologists and the steep rise in psychiatric contacts in the year prior to diagnosis may indicate that many individuals with YOAD present with symptoms often initially attributed to psychiatric disorders, such as depression, anxiety, or stress. This underscores the diagnostic complexity of YOAD, as early symptoms may overlap with psychiatric conditions or occur comorbidly, potentially leading to misdiagnosis or delayed recognition of the underlying neurodegenerative disease.

5.2 Depression and stress-related disorders

In the post-hoc analysis of Mental and behavioral disorders in **Study 2**, the highest increases were found for Mood/affective disorders and Neurotic, stress-related and somatoform disorders, both with around a 3-fold increase 5->1 years prior, and an 8-9 fold increase in the year immediately prior to diagnosis. A 5-fold increase was found for Schizophrenia, schizotypal and delusional disorders in the one year prior to diagnosis. While significance in post-hoc analyses should be interpreted cautiously, the magnitude of these associations is noteworthy. These trends are supported by the findings of **Study 3**, in which we found antidepressant use increased throughout the entire 10-year study period, with YOAD cases around 3.5 times more likely to have used antidepressants in the year prior to diagnosis. Antipsychotics were increased from 5->1 year prior, and YOAD cases were also around 3.5 times more likely to have used antipsychotics in the year prior to diagnosis. In a post-hoc analysis, we examined those with a first-ever prescription within the time intervals compared to never users; this reinforced the effects with IRRs over 10 for both antidepressants and antipsychotics in the year prior to diagnosis.

The majority of research about depression prior to a dementia diagnosis revolves around depression as a risk factor. The 2024 Lancet Commission on Dementia prevention, intervention, and care concludes that the link between depression and dementia is likely bidirectional and that depression can be both a risk factor for dementia, a symptom of evolving dementia, a reaction to, or a cause of cognitive impairment[88]. The dearth of research examines the link between depression and late onset dementia[89–97], while a study by Hendriks et al. examined risk factors for young onset all-cause dementia in the UK Biobank[98]. Here, they found a hazard ratio of 3.25 (95% CI 2.08 – 5.09) of young onset dementia following depression. As there are a number of differences between this study and ours (examining risk vs exploratory research, all-cause dementia vs Alzheimer's disease, no time periods, etc.) a direct

comparison of estimates is not meaningful; however, the study by Hendriks et al. does show an association, whether causal or not, between depression and young onset dementia similar to what we found.

The following section discusses studies that explore associations between depression and YOAD/dementia without focusing on risk assessment. A case-control study investigating pre-diagnostic symptoms of young onset dementia in primary care during the five years preceding diagnosis identified affective symptoms, with depression and anxiety being the most prevalent affective disorders in the four years prior to diagnosis[27]. While our study on morbidity before YOAD diagnosis is limited to diagnoses made in secondary care, antidepressant medication use can serve as a proxy for depression. Therefore, these findings are most comparable to results from **Study 3**, which examines prescription medication use and includes (some of) those individuals only followed in primary care. The study on pre-diagnostic symptoms in primary care thus aligns with our results, suggesting that depression and corresponding medication use are common pre-diagnostic signs of young onset dementia. Similarly, a study examining administrative claims before dementia diagnosis found an increased odds ratio of depression in the two years prior to dementia diagnosis of around 1.80 for both young and late onset[99].

A Norwegian study examined the use of a range of medications, including antidepressants and antipsychotics, prior to initiation of acetylcholinesterase inhibitors – that is, drugs approved for the treatment of either Alzheimer's disease or Lewy body dementia, though the study assumes the initiation of treatment as a surrogate marker for an Alzheimer's disease diagnosis[100]. Age-adjusted prevalence ratios were calculated, comparing use prevalence between those with dementia and the general population. The prevalence ratios were consistently higher for those with subsequent dementia during the 4-year pre-diagnostic study period, and this was especially true for those aged 37-64 years at the time of acetylcholinesterase inhibitor initiation. A study by Couret et al. found a greater likelihood of psychiatric disease and behavioral symptoms among 65-74 and 75-84-year-olds subsequently diagnosed with dementia, compared to those aged 85+, though only examining the year immediately prior to diagnosis[101]. Similarly, a scoping review of signs and symptoms preceding the diagnosis of Alzheimer's disease found depressive symptoms common prior to a diagnosis of YOAD[31]. This is in line with findings of a higher prevalence of post-diagnostic depression in YOAD than LOAD[14,32], suggesting this may also be true in the prodromal phase. Studies have shown an increased disease awareness in young onset dementia patients compared to late onset[102,103]; interestingly, increased disease awareness has been shown to be associated with depressive symptoms[104], perhaps responsible in part for the larger prevalence of depression in YOAD than LOAD found in most studies.

Thus, our findings support the large body of literature showing an association between depression and subsequent dementia. This seems to be true for all-cause dementia as well as specifically for Alzheimer's disease, with some studies pointing towards a potentially stronger association among those with young onset dementia than for late onset dementia. It seems likely that depression may serve as an early sign of YOAD – and perhaps, that depression is an early consequence of YOAD.

Several studies have examined stress as a risk factor for dementia, with two Danish register-based studies finding associations between stress and subsequent dementia[105,106], and a Swedish register-based study finding a positive association between chronic stress and Alzheimer's disease[107], aligning well with our findings of increased IRRs for Reaction to severe stress and other stress-related disorders.

The findings described above emphasize the need for greater awareness of how psychiatric symptoms might mask the onset of YOAD and highlight the importance of considering neurodegenerative causes when evaluating new-onset psychiatric symptoms, particularly in younger adults. Depression and stress could potentially be major contributors to the delay YOAD patients face in receiving a timely diagnosis; in an Italian study investigating whether time from symptom onset to diagnosis differed between young onset dementia and late onset dementia, the authors found significantly longer time to diagnosis in young onset dementia[43]. The time from the first assessment at a specialist clinic to diagnosis was nearly identical in the two groups, with the time to first assessment the main cause of the difference; once patients visited a dementia specialist clinic, the time required for the diagnostic work-up was similar for both young onset and late onset patients. This indicates that the delays in diagnosis were primarily influenced by how long it took patients to reach the specialist clinics after the onset of symptoms. Longer time to first assessment was positively correlated with the presence of coexisting depression. This is supported by another study examining time to diagnosis in young onset dementia, which found that depression more than doubled the time to dementia diagnosis[44]. Given the associations found between a diagnosis of depression and the use of antidepressants and subsequent YOAD in **Study 2** and **Study 3**, and the large impact depression has on time to diagnosis, it seems that tools for diagnosing patients with comorbid depression and/or stress (or patients whose symptoms have been misattributed to depression or stress) present an important opportunity to shorten the diagnostic delay faced by YOAD patients.

The increased use of antipsychotic medication up to 5 years prior to YOAD diagnosis found in **Study 3** deserves mentioning as well. This is supported by a large Swedish register-based study examining psychiatric disorders before a dementia diagnosis, which found psychotic disorders, among others, to

be increased up to 7 years prior to an Alzheimer's disease diagnosis, with stronger associations with younger age[95]. The authors argue that this may be a reflection of the neuropsychiatric symptoms prevalent in Alzheimer's disease, shown to often start in the early disease stages and increase in severity along the dementia disease course[8]. Thus, the increased use of antipsychotics – and the highly increased CRRs of psychiatric inpatient and outpatient visits observed in **Study 1** – may well reflect the onset of neuropsychiatric symptoms of YOAD. As the use of antipsychotics among patients with dementia has been shown to significantly increase mortality[108], this adds to the urgent call for a timely diagnosis to help make informed decisions on the use of antipsychotic medication in this patient group, to avoid initiating potentially harmful treatments unknowingly.

5.3 Other morbidity and medication

In **Study 2**, we found increased IRRs for injuries up to 5 years prior to YOAD diagnosis, with diagnoses of injuries to the head and forearms the most prevalent in the study population, occurring 25-45% more frequently among YOAD cases than controls. This is similar to what is seen in patients who go on to be diagnosed with Parkinson's disease, with findings from a large, Swedish, register-based study showing an odds ratio of 1.19 (95% CI 1.08 – 1.31) for injurious falls 7-10 years prior to a diagnosis of Parkinson's disease[109]. In **Study 3**, we found that YOAD patients were 43% more likely to have redeemed a prescription for Drugs for constipation during the 10-year study period. Associations between laxative use and Alzheimer's disease[110,111] and all-cause dementia have previously been reported[110,112]. Furthermore, constipation is a well-described early symptom of α-synucleinopathies such as Parkinson's disease and dementia with Lewy bodies[113]. Our findings pointing towards increased susceptibility to injuries and constipation could thus suggest that these could be broad symptoms of neurodegeneration or could hint at dual pathology of Alzheimer's disease and dementia with Lewy bodies, which is common in both YOAD and LOAD[114].

We found significantly increased IRRs for a number of conditions (and/or medications used to treat them) which are well-established risk factors for dementia[88,115]. These include hypertension, hearing loss, conditions associated with excessive alcohol consumption, thrombotic disease, etc. While our studies are not suitably designed to determine risk, the associations found may reflect associations between risk factors and YOAD rather than prodromal symptoms. As this was outside the scope of this thesis, these associations are not discussed in greater detail here.

In **Study 2** and **Study 3**, a few diagnoses and medications came out with high IRRs interpreted as part of the diagnostic process and therefore not discussed in greater detail. These were the overall disease categories Symptoms/signs not classified elsewhere and Factors influencing health status in the <1

year prior, containing unspecific diagnostic codes often routinely registered during a diagnostic evaluation. Similarly, the Mental and behavioral disorders subcategory Organic, including symptomatic, mental disorders includes diagnostic codes such as F04 Organic amnesic syndrome, a diagnosis that may be given during the diagnostic evaluation of dementia, and might thus also be related to the diagnostic process itself (though the subcategory also contains the ICD-10 code F05 Delirium – while this would have been interesting to examine further, interpretation of the increase in IRR for this subcategory is unfortunately hindered by us not subdividing further into specific diagnoses). Use of Anxiolytics was increased in the year immediately prior to diagnosis. It was not possible to discern whether this was prescribed due to symptoms of anxiety or to reduce anxiety-related reactions to an MRI brain scan, often performed as part of the diagnostic work-up in the memory clinic.

5.4 Labor market participation

In **Study 4**, we found YOAD patients significantly more likely to be unemployed or on long-term sick leave in the years leading up to diagnosis compared to controls, starting from 5 or 8 years prior, respectively. Notably, unemployment rates were over 7 times higher for YOAD patients in the year before diagnosis, and long-term sick leave peaked at a near 30-fold increase in the same timeframe. Almost half of the YOAD patients had four or more months of sick leave that year, compared to only 2% of controls. This indicates that YOAD patients not only experience higher rates of long-term sick leave but also spend more time on sick leave annually.

As research into labor market participation prior to dementia diagnosis primarily revolves around the role of retirement age in cognitive decline and dementia risk[116–119], we were not able to find studies quantitively examining the roles of sick leave or unemployment in the YOAD prodrome. However, several qualitative studies have explored themes revolving around the working life in those with young onset dementia: in a study about the financial consequences of young onset dementia, one caregiver mentioned that as symptoms were misinterpreted, the individual with young onset dementia lost their job and, consequently, their source of income long before receiving a formal diagnosis[13]. Another study showed that for dementia patients in paid employment, reduced capacity to carry out habituated routines would alert the patients themselves to the advancing cognitive problems[120], in some cases leading to initiation of medical investigation, but in other cases leading to termination of employment[121].

Our study suggests a prolonged prodromal phase where workplace cognitive demands exceed available resources. This is supported by previous research showing that individuals with YOAD often experience their first symptoms at work[120,122]. Additionally, our findings indicate that long-term sick leave

occurs before unemployment, which may lead to individuals with prodromal YOAD being fired or quitting. Sick leave could thus contribute to some unemployment cases, and there may be a shared cause for both.

The studies included in this thesis collectively point towards a prolonged period of time characterized by increased healthcare utilization, seeking especially psychologists and psychiatric care, and increased psychiatric morbidity and medication use. These findings likely point towards YOAD patients having symptoms often misattributed to stress or depression, or that these occur comorbidly. In light of the findings from **Study 4**, it appears that stress and depression may significantly contribute to the high rates of unemployment and long-term sick leave. This aligns with results from a Danish study on labor market trajectories following long-term sick leave, where 35% of the study population identified mental health issues as the reason for their sick leave. Among those, 71% reported experiencing stress and burnout, while 56% identified depression as a factor[123].

5.5 Strengths and limitations

5.5.1 Nationwide, high-quality registers

A major strength of the studies included in this thesis is the use of the high-quality nationwide Danish registers. The Danish registers generally contain detailed, reliable, and complete data on the entire population from cradle to grave, with a prevalence of "disappeared persons" in the Civil Registration System of only around 0.3%, allowing for nationwide studies with virtually complete long-term follow-up on emigration and death[49]. The Danish registers are considered one of the most comprehensive collections of data, encompassing nearly every aspect of life, including healthcare, education, employment, civil status, and much more[124]. Three qualities are key in ensuring the quality of these registries: one, Denmark has tax-funded health care with residency-based entitlement. Two, routinely collected administrative and health data provides longitudinal data, and three, individual-level linkage of all records ensures lifelong follow-up[48]. The Danish National Patient Register, a cornerstone in Danish health-related register-based research, is internationally considered to be one of the most comprehensive of its kind[54].

With the extensive Danish welfare system comes (theoretically) equal access to free healthcare services, paid sick leave, retirement schemes, etc., limiting problems with selection bias. On the other hand, a limitation of using these registers for research is that they are primarily built for administrative purposes, not for research, and the registers do not always contain the variables desired for a particular

research project or the validity of some variables are not always sufficient, as discussed in **section 5.5.2**.

While the perhaps most widely used study design for epidemiological research is the cohort study, this was not feasible for studying YOAD due to low validity of a diagnosis of young onset dementia in the registers (see detailed description in **section 5.5.2**). Being able to link the nationwide register data with the quality database DanDem for YOAD case finding provided a novel approach to studying this relatively rare disease in a large study population while ensuring that all cases are diagnosed by specialists in memory clinics. It further allowed for detailed variables beyond the administrative Danish health registers such as scores from cognitive examinations and detailed information on etiology also in (some) cases with MCI.

The availability of long-term data with no loss to follow-up allowed us to explore trajectories over time. This allowed us to monitor changes over a decade or more, providing valuable insights into long-term patterns and trends.

5.5.2 Quality assessment of exposures

Validity of healthcare contacts

A primary strength of **Study 1** lies in the comprehensive nature of the healthcare contact data which offers a high degree of validity compared to studies relying on claims data. The use of the Danish registers, which systematically record all healthcare interactions, ensures virtually complete data coverage. Denmark has universal health coverage with very few exceptions, minimizing selection bias caused by the inability to afford medical care. This is in stark contrast with the majority of healthcare utilization studies which, due to lack of other opportunities, often resort to using claims data from insurance schemes, criticized for favoring a healthier study population[125]. Thus, GP and secondary care data are deemed to have a high validity.

An exception to the universal health coverage model, though, is psychologists and physiotherapists (as discussed in detail in **section 5.5.3**). Use of these providers can happen by paying out-of-pocket without a referral, through a private health insurance, or at a discounted price with a referral. For psychologists, GPs can refer a patient only if they fulfill certain criteria, including individuals affected by severe mental or disabling illness, and individuals with mild to moderate depression or anxiety. This could lead to bias in the estimates of psychologist and physiotherapist visits. Given the higher rates of depression among YOAD cases found in **Study 2** and **Study 3**, the increase in psychologist use may well

reflect the underlying increase in depression within this group, by which YOAD cases would be more likely to be referred to a psychologist.

Validity of diagnostic codes

While the Danish national registers are comprehensive and provide near-universal coverage, it is well-documented that the validity of specific diagnostic codes within the Danish National Patient Register and the Danish Psychiatric Central Research Register varies. For example, dementia diagnoses in these registers are generally reliable for late onset dementia[126], supporting their use in register-based studies for defining dementia cases. However, for younger individuals, the validity is lower due to over-registration, with only 59% of registered diagnoses in this group being accurate[127]. This was the primary reason behind the choice to use the quality database DanDem for case finding, thus allowing us a novel approach to study YOAD which had not previously been feasible due to this low validity.

Similarly, it is important to consider how validity of other diagnostic codes may impact the results of the analyses, especially in **Study 2** where the exposure of interest is morbidity as assessed by diagnostic codes. A prior diagnosis of depression was one of the main findings of this study. A high positive predictive value of a diagnosis of depression in the relevant registers has previously been reported[128]; however, many individuals suffering from depression will not be captured, leading us to likely only capture the more severe cases[129]. Thus, those with a registered diagnosis of depression are likely to be correctly identified, which is a strength – but we do not capture all those with depression, which is a limitation. Similarly, a study examining the validity of diagnoses of stress-related disorders found a high validity of the diagnostic codes in the ICD-10 chapter F43 (the second most prevalent diagnostic code in the Mental and behavioral disease category in **Study 2**)[130].

The high validity of the diagnostic codes used to identify some of the main findings is a major strength of the studies; however, the fact that not all diagnostic codes are equally valid constitutes a major limitation. We could have possibly overlooked associations between morbidity and YOAD if other diagnostic codes are severely under-registered. For example, in our prior research on sleep disorders prior to a dementia diagnosis, we found a remarkably low number of registered insomnia diagnoses compared to the estimated national prevalence[131], hinting at problems with validity. Similarly, diagnostic codes like obesity, found to have a decreased IRR for YOAD in **Study 2**, are not routinely registered unless of relevance to the given hospital admission, meaning this association likely has another underlying cause that is hard to discern from the available data. These issues might cause us to miss associations between diagnoses and YOAD, even if they are more prevalent in the prodromal phase.

Validity of codes for identification of prescription medication

The Danish National Prescription Registry provides data of high quality, ensuring information on all redeemed prescriptions. Registration is done by an automated process from the electronic dispensing systems of community pharmacies, with the use of bar codes throughout the dispensing process minimizing the risk of data entry errors[56]. A smaller limitation regarding the validity of medication is not having access to information on over-the-counter medication purchases. A major limitation is medications with double indications or medications used off-label. For example, tricyclic antidepressants are often used to treat neuropathic pain, while some antiepileptic medications, such as lamotrigine, may be used to prevent depressive episodes in bipolar disorders. Thus, as the register does not contain medication indications, this could cause us to either over or underestimate some associations.

Validity of occupational data

The Labor Market Accounts Register is considered to be of relatively high quality[132]. The information on workdays and benefits are linked with tax payments, which are usually subtracted by the employer before salary payments or are automatically paid for social benefits. Thus, limited misclassification in the labor market participation measure is expected. While the validity of the available variables was deemed high, we did encounter a minor limitation in the data available. While the main objective was to look at unemployment and long-term sick leave, we were curious to see whether there was an equally strong association between short-term sick leave and YOAD. However, as information on short-term sick leave is only available for a select few (sick leave paid by the employer is not tracked in the registers; usually sick leave <30 days is paid by the employer but may be refunded by the public sector in case of chronic illness), this was not feasible to examine. Furthermore, we had initially hoped to compare retirement age between cases and controls, but as we found discrepancies in the data suggesting poor discrimination between different types of retirement, such comparisons were rendered meaningless.

5.5.3 Potential bias and confounding

Detection bias

All four studies were, to a greater or lesser extent, vulnerable to detection bias. Those with high healthcare utilization naturally encounter a healthcare professional more often than those with lower healthcare utilization, thereby increasing the chances of cognitive symptoms being detected and a diagnostic evaluation of dementia being initiated. Similarly, the study examining hospital-diagnosed morbidity relies on individuals having had contact with the secondary healthcare system, and likewise, those initiating a new medical treatment are likely to have seen a physician. The analysis of

unemployment rates is probably less affected by detection bias; however, individuals on long-term sick leave are usually required by their employer to provide a medical certificate, which again entails having had contact with a healthcare professional, which raises the likelihood of cognitive symptoms being noticed. However, around 40% of cases had moderate/severe dementia at the time of diagnosis, suggesting frequent contact with a healthcare professional does not in itself facilitate a timely diagnosis.

Healthy worker bias

The results of **Study 4** are likely influenced by a degree of the selection bias commonly referred to as "healthy worker bias". Specifically, if individuals with cognitive issues are more likely to be on disability pension or to choose early retirement when eligible, this could mean that some of those most likely to receive a YOAD diagnosis are censored from the analysis. This may lead to a focus on individuals who are affected to a lesser extent. Although it is challenging to determine the exact direction of this bias, we speculate that the selection of healthier individuals primarily impacts the case population, potentially resulting in an underestimation of the association's magnitude. Therefore, it is important to remember that the results of these analyses are mainly generalizable to individuals who remain part of the active workforce.

Social inequalities in access to healthcare services and social benefits

While in theory, the entire Danish population has equal access to free universal healthcare, various barriers exist that create social inequalities in healthcare access. For instance, those with higher education and income are more likely to reside in densely populated areas with shorter travel distances to healthcare services; in contrast, those with lower education and income face longer travel distances and tend to utilize health services less frequently[133]. Furthermore, certain healthcare services, such as physiotherapists and psychologists, require some out-of-pocket payments even upon referral. Additionally, despite having medication subsidies, individuals still need to pay out-of-pocket for prescription medications. To qualify for unemployment benefits, one must also pay annual membership fees to an unemployment insurance fund (though the lower-paying social benefit is accessible without membership requirements). Therefore, the assumption of equal access to healthcare services and social benefits is inherently biased, potentially favoring a more affluent segment of the population among those registered with the exposures.

Proxy measures

Throughout the studies, we often use proxy measures; that is, an indirect variable used to estimate or reflect a variable that is difficult to measure directly. An example of this is the use of prescription

medication to assess underlying symptoms and disorders. The use of proxy measures in this research is determined by the variables available, which are often dictated by administrative considerations rather than research needs. Data in registers is typically not specifically collected for research purposes, limiting the scope of feasible examination. For instance, in **Study 2**, which focuses on prior morbidity, we are restricted to hospital-diagnosed morbidity. While it would have been beneficial to investigate morbidity diagnosed in primary care, the quality of such data is inadequate. This likely lead to a significant underestimation of the depression prevalence within the study population. Although we attempted to mitigate this limitation in **Study 3** by incorporating medication data, it is important to note that not all patients with depression are treated with antidepressants. Furthermore, approximately 10% of medications prescribed by GPs go unfulfilled[134], a further limitation in using medication as a proxy for symptoms. If this issue affects cases and controls equally, it may not greatly impact our estimates; however, if it disproportionately affects cases or specific indications for medication, the results could be skewed, undermining the utility of medications as proxies for certain conditions.

Stress-related disorders present an even greater challenge in terms of underestimation. Most patients suffering from such disorders are likely managed solely in primary care, where medical treatment is not frequently initiated. Consequently, we may capture only a fraction of individuals with stress-related disorders in our study population. Theoretically, if the prevalence of stress-related disorders is equivalent between cases and controls, this would not affect the relative measures. However, if we assume that stress-related disorders are more prevalent among cases, this could lead to an underestimation of the association between stress-related disorders and YOAD.

The assumption that unemployment or social benefits can serve as a proxy for unemployment is another limitation, as not all unemployed individuals receive such benefits. Some may choose not to apply for unemployment or social benefits, resulting in a loss of income. We speculate that difficulties in navigating the application process or meeting the criteria for benefit eligibility may disproportionately affect cases, leading to an underestimation of unemployment rates. Nonetheless, we regard it as a relatively robust proxy.

5.5.4 Other limitations

A lot of the research on YOAD considers genetic causes. This is especially important in risk factor studies, where genetic mutations or genetic risk factors may contribute greatly to found associations, especially for those with young onset, where genetic mutations contribute to a larger number of Alzheimer's disease cases[39]. We did not have genetic information for the patients included in the studies

included in this thesis; however, we also feel this is of lesser added value given the scope of the studies being to describe the prodromal phase. However, there could be some genetic variations that may cause a more rapid decline and therefore difference in the observed trajectories over time, and thus under optimal conditions it might have been interesting to see if results would differ based on genetic sub-analyses; however, for this to produce meaningful estimates (i.e., narrow confidence intervals), this would require much larger groups than what would be feasible given the number of cases.

Another limitation of the study was the inability to precisely remove contacts related to the diagnostic process from the analyses, as reasons for primary care contacts are not available and not all hospital contacts related to the diagnostic evaluation of dementia will be coded with a dementia diagnosis but may instead have more unspecific diagnostic codes. However, sensitivity analyses censoring events in the 6 months prior to index date in **Study 2** and **Study 3** did not alter the results.

Generally, stratification (in sensitivity analyses) is limited in use due to small numbers. Especially in **Study 4**, where the at-risk study population grows small closer to index date due to censoring on retirement, statistical uncertainty increases with the smaller groups. This especially affects sensitivity analyses where the study population is further stratified, hindering meaningful interpretation of sensitivity analyses in the intervals closest to index date.

In summary, major strengths of the studies included the use of the high-quality Danish public registers, the use of the quality database DanDem for case finding, and the long study period, while detection bias, healthy worker bias, and having to use proxy measures of exposures were major limitations.

5.6 Methodological considerations and reflections

5.6.1 Exploratory research

In research, exploratory studies differ from hypothesis-driven studies in that the former aim to investigate relationships or identify patterns without a predefined hypothesis, whereas the latter test specific, predetermined hypotheses. A key consideration in all research is the handling of multiple comparisons[135]. Unlike hypothesis-driven research, where adjusting for multiple comparisons is standard practice to control for false positives, exploratory studies often forgo such adjustments. This is considered acceptable in exploratory contexts, as the primary goal is to generate new hypotheses or identify potential associations rather than draw definitive conclusions[135]. Findings from our exploratory studies should be interpreted in this light, with an emphasis on identifying trends or areas warranting further investigation rather than confirming specific effects. Given this exploratory nature, future research is needed to refine these findings into testable hypotheses and to conduct hypothesis-driven studies to validate and substantiate the initial observations.

Furthermore, it is crucial to clarify that our studies focus merely on associations, not causality, and therefore should not be interpreted as risk studies. For an epidemiologic study to approximate causality, it would require different methodological considerations, for example utilizing longitudinal cohorts with measures to account for reverse causation and potential confounding factors. Therefore, readers should not interpret the results as evidence of direct causal relationships, but rather as a basis for generating hypotheses and guiding future research.

The exploratory nature of the studies also guided our choice of only selecting a minimal list of covariates to adjust for in the studies. Extensive adjustment is typically aimed at reducing bias in causal analyses[136]; however, since our research was not primarily focused on establishing causality, comprehensive adjustments could have obscured the very associations we wanted to examine.

5.6.2 Case definition and choice of index date

As we did not have information on date of symptom onset, we had to approximate this in order to apply the age-cut-off criteria for YOAD (<65 years at time of symptom onset). Based on prior research, assuming a 5-year time lag from symptom onset to diagnosis seemed reasonable[36,44,45]. Consequently, we included all individuals diagnosed before age 70. However, this assumes homogeneity in the time from symptom onset to diagnosis, which in reality is likely more heterogeneous, thus grouping patients at different points in the disease trajectory together in the examined time intervals. This is a limitation in examining the very earliest symptoms.

Furthermore, we decided to include patients with MCI due to Alzheimer's disease. While etiology is not established for all MCI patients, given a suspicion of Alzheimer's disease pathology and after thorough counseling, some patients choose to undergo biomarker examination to determine etiology. There are good arguments for and against including these; in wanting to examine the earliest symptoms of YOAD, including those at the earliest point in the dementia disease trajectory may add valuable information. On the other hand, estimates have shown that only a third of patients with MCI due to AD will progress to dementia over a 5-year period[137]. Due to the low number of individuals with MCI included in the studies (4-6% of YOAD cases), this is mostly a principal discussion as there were too few cases with MCI to substantially change the estimates (as demonstrated in **Study 2** and **Study 3**, where sensitivity analyses omitting those with MCI and their controls did not change the estimates).

5.6.3 Matching

In the first three studies, we used a 1:3 matching ratio. The main rationale behind this choice was the consideration of a potentially significant number of undiagnosed or primary sector-diagnosed cases with cognitive problems. By selecting a 1:3 ratio, the intention was to mitigate the risk of inadvertently

matching a case with a control with undiagnosed dementia. This approach aimed to potentially "dilute" the impact of such tendencies when matching cases with multiple controls; having a single control with undiagnosed dementia would compromise the match, but the likelihood of three controls under the age of 70 having undiagnosed dementia is exceedingly low, thereby ensuring more robust comparisons. On the other hand, the magnitude of bias has been shown to increase with increasing numbers of controls in nested case-control studies[138], and therefore we found a 1:3 ratio to strike a suitable balance between the above considerations. However, in **Study 4**, we opted for a 1:5 matching ratio. The choice to increase the number of controls was made due to the use of a more dynamic study population, as the study design for **Study 4** included censoring study participants during follow-up. Therefore, we increased the number of controls to maintain an appropriate ratio of cases to controls even after censoring.

6. Conclusions and perspectives

6.1 Conclusions

This PhD project demonstrates an increased vulnerability for YOAD patients up to a decade prior to diagnosis. This vulnerability appears as several potential early warning signs characterized by increased healthcare utilization, increased psychiatric morbidity – particularly depression and stress-related disorders – and periods of unemployment or long-term sick leave. Increased knowledge on early signs of YOAD among primary healthcare professionals may help in determining when to refer a patient to a memory clinic for evaluation of potential cognitive deficits and help pave the way towards improving timely diagnosis. Additionally, the project highlights the need for improvements in timely diagnosis to alleviate the burden on patients, caregivers, and families, with the potential also to mitigate societal impacts from increased healthcare use and occupational instabilities.

6.2 Clinical implications

The findings of this PhD project highlight key clinical implications, as it shows the need for tools that distinguish YOAD from other causes, such as stress and depression, particularly in primary care settings. Delayed diagnosis seems to increase the proportion of YOAD patients experiencing mental health crises and financial consequences of unemployment and sick leave periods, which might be mitigated through earlier intervention. The high concentration of psychiatric contacts just before diagnosis points to a critical window where early detection could help prevent symptom progression and alleviate the burden on the patients experiencing psychiatric symptoms and on psychiatric and emergency services.

The large proportion of patients diagnosed at advanced stages of the disease, along with signs of increased vulnerability up to a decade prior to dementia diagnosis, suggests that the long diagnostic delays observed in international studies may well also be a problem in a Danish context, highlighting the need for interventions to ensure timely diagnosis. Though further research is needed to translate findings from these exploratory studies to practice, our findings imply that physicians may consider referring patients to examination in a memory clinic if they show increased healthcare utilization, and stress or depression with first onset in midlife, atypical presentation or not responding to treatment, especially if accompanied by occupational instabilities.

6.3 Societal implications

Our findings underscore several critical societal impacts associated with the early identification and timely diagnosis of YOAD. First, raising public awareness about dementia as a disorder not only

affecting the elderly can encourage younger individuals experiencing cognitive symptoms to seek help earlier, which is crucial for reducing diagnostic delays and giving the patients the support needed to manage life with a dementia diagnosis. Secondly, this research highlights substantial, often hidden, economic and social costs that precede formal diagnosis. For healthcare systems, earlier recognition of YOAD-related vulnerabilities could reduce repeated, often non-specific healthcare visits and thus associated costs. At a personal level, a timely diagnosis could mitigate the financial strain caused by prolonged unemployment and extended sick leave due to yet undiagnosed dementia, as a timely diagnosis may aid patients in restructuring the remaining working life to meet available resources or in applying for disability pension, thus ensuring that these individuals can maintain a steady income.

A shift towards timelier diagnosis could also alleviate caregiving demands on families, who otherwise bear significant emotional and financial burdens when caregiving support is delayed. Thus, implementing improved diagnostic pathways for YOAD offers the potential to enhance patient and caregiver well-being, while also promoting more sustainable healthcare and labor market systems.

6.4 Future research implications

Future research should aim at validating the found associations in hypothesis-driven studies. Of particular interest is the associations between psychiatric symptoms and disorders and YOAD, and future research could aim to refine early detection methods by developing tools to distinguish cognitive symptoms in YOAD from those caused by depression or stress-related disorders alone. A Danish study on the validity of a diagnosis of young onset dementia in the Danish registers showed frequent misdiagnosis of dementia in patients with depression[127], showing the immense difficulty in distinguishing between the basis of cognitive deficits among younger patients. Thus, a deeper understanding of distinguishing symptoms and whether depression and stress-related disorders manifest differently in YOAD could lead to improved diagnostic protocols and reduce misdiagnosis, especially in primary care and psychiatric settings.

While we demonstrated occupational instabilities as periods of unemployment and long-term sick leave, future studies could examine YOAD patients' specific trajectories in the workplace, to assess whether those remaining in paid employment until time of diagnosis had frequent job changes or were transferred to less demanding jobs within the same workplace, for example by tracking changes in income. This could add additional information on how labor market participation is impacted in the prodromal phase of YOAD.

Furthermore, future research could examine prodromal signs and symptoms for other dementia types while accounting for differences in etiology. For vascular dementia it might be relevant, for instance, to take into account the heterogeneity in the prodromal phase due to the differences in the mechanism of vascular damage (small vessel damage causing progressive onset of dementia symptoms, post-stroke dementia often causing a more acute onset of symptoms). Studies on dementia with Lewy bodies could leverage insights from Parkinson's disease research, while research on frontotemporal dementia should consider the significant genetic components in young onset cases.

7. References

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8. Appendix (Study 1 – 4)

8.1 Study 1

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ORIGINAL COMMUNICATION

Healthcare utilization prior to a diagnosis of young-onset Alzheimer's disease: a nationwide nested case–control study

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Abstract

Objective Our aim was to identify changes in healthcare utilization prior to a young-onset Alzheimer's disease diagnosis.
Methods In a retrospective incidence density matched nested case–control study using national health registers, we examined healthcare utilization for those diagnosed with young-onset Alzheimer's disease in Danish memory clinics during 2016–2018 compared with age- and sex-matched controls. Negative binomial regression analysis produced contact rate ratios.
Results The study included 1082 young-onset Alzheimer's disease patients and 3246 controls. In the year preceding diagnosis, we found increased contact rate ratios for all types of contacts except physiotherapy. Contact rate ratios for contacts with a general practitioner were significantly increased also > 1–5 and > 5–10 years before diagnosis. The highest contact rate ratios were for psychiatric emergency contacts (8.69, 95% CI 4.29–17.62) ≤ 1 year before diagnosis.
Interpretation Results demonstrate that young-onset Alzheimer's disease patients have increased healthcare utilization from 5 to 10 years prior to diagnosis. Awareness of specific alterations in health-seeking behaviour may help healthcare professionals provide timely diagnoses.

Keyword Young-onset dementia · Alzheimer's disease · Healthcare utilization · Early warning signs · Registry-based · Epidemiology

Background

While Alzheimer's disease (AD) is most often thought of as an affliction in the older population, AD is the most prevalent cause of dementia among both those with young-onset dementia [1] and those with late-onset dementia [2]. Young-onset AD (YOAD) thus affects individuals in the prime of their career with potentially devastating effects for both patients and their families, who may be financially dependent on the patient and may include children still living at home.

Increasing evidence suggests that AD pathology develops years and even decades before the onset of cognitive symptoms [3] and that cognitive changes can be detected well before onset of clinical AD [4]. A recent Norwegian retrospective study of 223 patients based on review of medical records found a substantial diagnostic delay in patients with YOAD with an average time lag of 3.4 years from onset of symptoms to first visit to their general practitioner (GP) and 5.5 years from symptom onset to diagnosis [5]. This highlights the need for improvement in making a timely diagnosis in this patient group. A timely diagnosis offers

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patients and caregivers the opportunity to obtain treatment to control symptoms and avoid medications that may worsen symptoms, as well as plan for the future and seek appropriate care [6]. This is especially true for those with YOAD due to changes in work ability and family roles. In YOAD, symptoms at time of diagnosis have been described to often differ from those seen in individuals with late-onset AD (LOAD) [7]. As the majority of research in the field of AD is focused on LOAD, there is a need for increased knowledge on the specific diagnostic challenges in young-onset dementia.

Understanding healthcare utilization patterns in the years preceding AD diagnosis may be a new piece in the puzzle of timely detection and may help to demonstrate whether these patients show vulnerability prior to diagnosis and, if so, for how long. The aim of this study was to describe patterns in healthcare utilization characteristic of the prodromal phase of YOAD and to identify any specific types of healthcare contacts with a more pronounced association than others.

Methods

Data source

Since 1968, all people living in Denmark have been registered in the Civil Registration System (CRS) with a unique 10-digit personal identification number. This number is used in all national registers, enabling accurate linkage between the registers [8]. Cases were identified from the Danish Quality Database for Dementia (DanDem), which was established in 2016. It is mandatory for every secondary healthcare facility which accepts referrals for dementia to enter information in DanDem upon completion of the diagnostic evaluation, including level of cognitive decline (normal cognition, mild cognitive impairment, or mild, moderate or severe dementia), aetiology, diagnostic investigations performed and results of cognitive tests. It thus follows that DanDem contains detailed data on every patient seen at a Danish memory clinic from 2016 onwards. Information on contacts with the primary healthcare sector was drawn from the National Health Service Registry (NHSR), which includes information on patients, providers and health services with national coverage since 1990 [8]. Information on contacts with the secondary healthcare sector was drawn from the Danish National Patient Registry (DNPR) and the Danish Psychiatric Central Research Register (DPCRR). DNPR and DPCRR contain information on all somatic and psychiatric hospital contacts since 1977 and 1969, respectively, with outpatient data added in 1995 [9, 10]. The Danish National Prescription Registry (DNPrR) was used to draw information on filled prescription medication used in the exclusion of potential controls [11].

Study design and population

We conducted a retrospective incidence density matched nested case–control study. Cases were defined as all individuals diagnosed with YOAD in a Danish memory clinic during the years 2016–2018 and their matched controls were drawn randomly from the same nationwide cohort of all Danish residents.

Overall exclusion criteria

We excluded individuals with Down syndrome (International classification of diseases (ICD)-8: 759.3, ICD-10: Q90) and mental retardation (ICD-8: 311–315, ICD-10: F70–F79) as morbidity prior to AD diagnosis for this patient group would require other surrogate measures of morbidity than those addressed in the present study.

To ensure completeness of data, cases and controls must have lived in Denmark throughout the 10-year retrospective period. Controls were not eligible if they had a diagnosis of dementia prior to index date. All exclusion criteria can be seen in Online Resource Table S1.

Case definition

By convention, YOAD is defined as dementia due to AD with symptom onset before age 65 years. Due to the often long time lag between symptom onset and diagnosis [5], all patients diagnosed with mild cognitive impairment (MCI) or dementia due to AD before age 70 years were included. Thus, cases were identified from DanDem as individuals with a first diagnosis of MCI or dementia due to AD from start of register (2016) through 2018 aged < 70 years at time of diagnosis. Index date was the date when the person was diagnosed with AD.

Controls

Cases were matched 1:3 with controls on birthdate and sex using incidence density matching. Controls were randomly selected from the entire population with the following criteria: (1) no entry in DanDem before index date (i.e. not referred to or seen at a memory clinic), (2) no MCI or dementia diagnosis in DNPR or DPCRR before index date and (3) no redeemed prescription for antidementia medication in DNPrR before index date (ICD codes for identification of dementia diagnosis and anatomical therapeutic chemical (ATC) codes for dementia medication can be found in Online Resource Table S1).

Definition of healthcare contacts

The exposures of interest were the number and type of contacts within the primary or secondary healthcare sector. In the secondary healthcare data (somatic and psychiatric contacts), any contact with an ICD code indicating MCI or dementia (Online Resource Table S1) was censored for cases in the 6 months prior to index date to avoid counting those contacts that were part of the diagnostic process.

Primary care

Primary care contacts were defined as a record in NHSR in one of the following categories: face-to-face contact with a GP, a telephone or email contact with a GP, any type of contact with a private practice medical specialist, or any contact with a physiotherapist or clinical psychologist by referral. There is no public record of visits to a physiotherapist or psychologist if a patient chooses to visit one without referral from the public sector, and thus, such visits are not included in the contact counts. For GP contacts, we also combined face-to-face and telephone/email contacts into 'any GP contact'.

Secondary care—somatic contacts

In this study, the term 'somatic' is used to refer to non-psychiatric disorders, encompassing physical health issues distinct from psychological or psychiatric conditions. Somatic contacts were defined as a record in DNPR in one of the following categories: inpatient admission, outpatient contact or emergency contact. For inpatient admissions, if a patient was discharged and re-admitted in < 24 h, this was considered a continuation of the same admission and was counted as one admission. Outpatient contacts were defined as every time a patient was present at a hospital for an outpatient consultation.

Secondary care—psychiatric contacts

Psychiatric contacts were defined as a record in DPCRR in one of the following categories: inpatient admission, outpatient contact or emergency contact. Inpatient admissions were defined the same as described above. As individual visits within a longer follow-up are not available for psychiatric outpatient contacts, these contacts were counted as numbers of follow-up processes rather than individual visits.

Covariates

Analyses were adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis, whichever came first) and civil status at index date.

Statistical analysis

Main analysis

We analysed associations between all the above listed types of healthcare contacts except psychiatric outpatient contacts and dementia using a negative binomial regression analysis, which produces an odds ratio. Given the use of incidence density matching, this can be interpreted as an incidence rate ratio [12], or in this case, a contact rate ratio (CRR). CRRs were calculated for three time intervals: 10-> 5 years prior to index date, 5-> 1 years prior to index date and ≤ 1 year prior to index date. Robust variance estimation was applied to account for matching clusters and correlation between observations for the same person in different periods using the vce(cluster) function in STATA to allow for intragroup correlation.

As number of individual visits were not available for psychiatric outpatient data, we instead measured the proportion of persons in our study with a psychiatric outpatient contact during the 10 years prior to dementia diagnosis by a cumulative incidence function.

Analyses were adjusted for the listed covariates.

Sensitivity analysis

In a sensitivity analysis, cases were stratified on disease severity. Here, patients were grouped as either MCI/mild dementia or moderate/severe dementia at time of diagnosis. Analyses were then performed as described above, comparing the disease severity groups with their respective matched controls. Furthermore, sensitivity analyses were performed stratifying cases by age at diagnosis and sex.

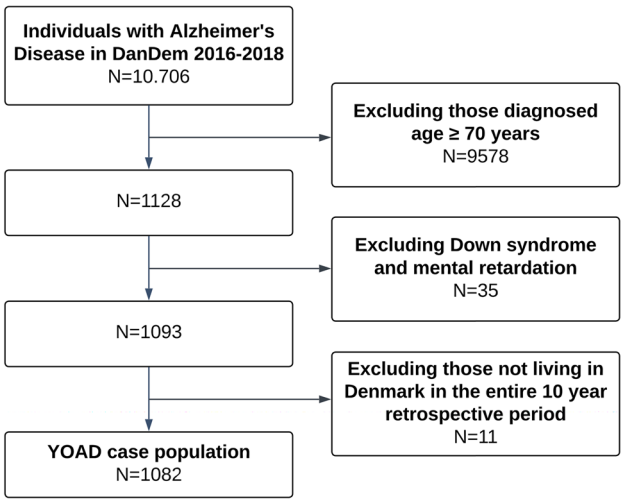

Fig. 1 Flowchart of case selection. *DanDem* Danish Quality Database for Dementia, *YOAD* young-onset Alzheimer's disease

Table 1 Baseline characteristics of study population

	Cases $n=1082$	Controls $n=3246$
Age at index date, mean years (sd) [range]	64.5 (5.1) [29.2–69.9]	64.5 (5.1) [29.2–69.9]
Sex, male/female, *n* (%)	456 (42%)/626 (58%)	1368 (42%)/1878 (58%)
Level of cognitive decline at diagnosis, *n* (%)		
Mild cognitive impairment	39 (4%)	–
Mild dementia	611 (56%)	–
Moderate dementia	346 (32%)	–
Severe dementia	86 (8%)	–
Cognitive examination scores at first visit[a], mean (sd)		
MMSE	20.8 (5.6)	–
ACE	65.4 (15.2)	–
Educational attainment at age 40, *n* (%)		
Low	734 (68%)	2218 (69%)
Medium	239 (22%)	679 (21%)
High	62 (6%)	189 (6%)
Unknown	47 (4%)	147 (5%)
Civil status at index date, *n* (%)		
Married	685 (63%)	2030 (63%)
Divorced	197 (18%)	568 (18%)
Widowed	86 (8%)	247 (8%)
Never married	100 (9%)	357 (11%)
Unknown	14 (1%)	31 (1%)
Individuals with ≥ 1 contact in primary care, *n* (%)[b]		
General practice	1082 (100%)	3227 (99%)
Psychology	61 (6%)	75 (2%)
Physiotherapy	502 (46%)	1.510 (47%)
Private practice medical specialist	930 (86%)	2.674 (82%)
Individuals with ≥ 1 contact in secondary care, *n* (%)[b]		
Somatic inpatient	658 (61%)	1720 (53%)
Somatic outpatient	1026 (95%)	2829 (87%)
Somatic emergency	687 (37%)	1716 (53%)
Psychiatric inpatient	61 (6%)	75 (2%)
Psychiatric outpatient	155 (14%)	127 (4%)
Psychiatric emergency	73 (7%)	82 (3%)

Where percentages do not add up to 100%, this is due to rounding up/down

[a]MMSE: mini-mental state examination (reliable information for 988 YOAD patients). ACE: Addenbrooke's Cognitive Examination (reliable information for 660 YOAD patients)

[b]Percentages in this section of the table represent the number of people with at least 1 contact during the 10-year period out of the total case/control population

Data management was performed using SAS 9.4 software. Negative binomial regression analyses were performed using STATA/MP 17.0 software.

Results

There were 10,706 individuals with a diagnosis of AD in DanDem between 2016 and 2018. Of these, 1128 were diagnosed before age 70 years. After exclusions, there were 1082 cases (Fig. 1). The mean age at time of diagnosis was 64.5 years (range 29.2–69.9 years, Table 1), and 58% of the patients were female. At the initial assessment in a memory clinic, mean Mini-Mental State Examination (MMSE) score was 20.8 points and mean Addenbrooke's cognitive examination (ACE) score was 65.4 points. Among the cases, 60% were diagnosed with either MCI or mild dementia at time of diagnosis, and the remaining 40% were diagnosed with moderate/severe dementia. Cases and controls were similar in terms of education and civil status.

Figures 2, 3 and Table 2 show the adjusted CRR for YOAD cases compared to controls (contact rates and

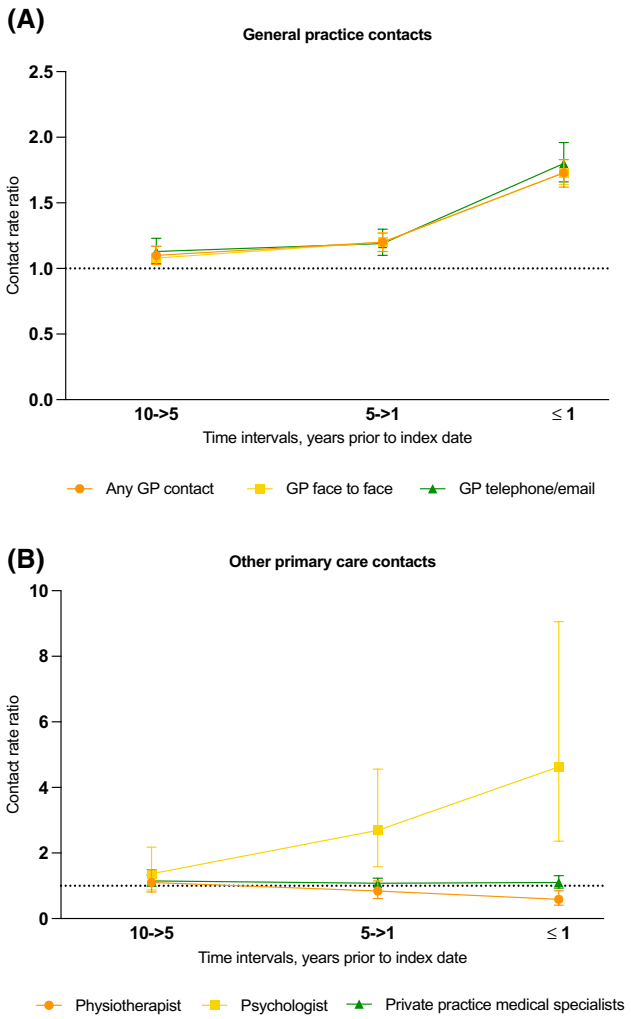

Fig. 2 Contact rate ratios, primary care contacts. Contact rate ratios (CRRs) are plotted for young-onset Alzheimer's disease patients for contacts with a general practitioner (**A**) and other secondary healthcare contacts (**B**). Error bars represent 95% confidence intervals. The CRRs presented are adjusted for age, sex, highest attained educational level at age 40 (or at time of diagnosis, whichever came first) and civil status at index date. Note that the Y-axis have differing values for A and B. Unadjusted estimates are presented in Online Resource Table S3 and adjusted estimates are presented in Table 2. *GP* general practitioner

unadjusted CRRs in Online Resource Tables S2 and S3). In the year prior to index date, CRRs for all investigated types of contacts were significantly increased except for private practice medical specialist contacts (insignificant CRRs) and contacts to a physiotherapist by referral (significantly decreased, CRR 0.59, 95% CI 0.41–0.85). Across all types of GP contacts, CRRs were significantly increased throughout the 10-year retrospective period and increased steadily to the highest level in the time interval immediately preceding dementia diagnosis where YOAD patients had a 73% higher contact rate (any type) than their matched controls (CRR 1.73, 95% CI 1.64–1.83).

The largest increase in CRR was for psychologist and psychiatric contacts in the year immediately preceding diagnosis, though confidence intervals are wide as these estimates are based on relatively few contacts, partly owing to the fact that the interval immediately prior to diagnosis is much shorter than the other intervals. The CRR for psychology contacts was 4.63 (95% CI 2.36–9.06). For psychiatric inpatient and emergency contacts, CRR in the year prior to diagnosis was increased eightfold compared to controls (psychiatric inpatient admissions: CRR 8.31, 95% CI 3.35–20.60, psychiatric emergency contacts: CRR 8.69, 95% CI 4.29–17.62). A similar tendency can be seen in the cumulative incidence function for psychiatric outpatient contacts (Fig. 4), where the cumulative incidence is significantly higher for cases compared to controls from 3.5 years prior to diagnosis.

Apart from the GP contacts, CRRs in the > 1–5 and > 5–10 years prior to diagnosis were generally either insignificant or only minorly increased. The only other clear change in the 5-> 1 year interval was for psychologist contacts (CRR 2.69, 95% CI 1.58–4.56).

For those with moderate/severe dementia, the increase in contact rates generally occurred earlier than for those with MCI/mild dementia at time of diagnosis. For GP contacts, those with moderate/severe dementia had an increase in contact rates already 5–10 years prior, whereas the increase only occurred from 1 to 5 years prior for those with MCI/mild dementia (Online Resource Table S4). For psychologist contacts, those with moderate/severe dementia had the highest CRR in the 5-> 1 year interval (3.59, 95% CI 1.77–7.31), whereas for those with MCI/mild dementia the highest CRR was found in the year immediately preceding diagnosis (CRR 5.17, 95% CI 2.32–11.50). The increased CRR for psychiatric contacts found in the main analysis was largely driven by those with moderate/severe dementia, for whom CRRs were highly increased in the year preceding diagnosis with a CRR for psychiatric emergency contacts of 23.76 (95% CI 7.59–74.38, Online Resource Table S5). A sensitivity analysis stratifying YOAD patients by age and sex yielded similar results as in the main analysis (Online Resource Table S6).

Discussion

This nested case–control study found that patients with YOAD generally have a higher healthcare utilization than their age- and sex-matched controls in the year preceding diagnosis. The increase in healthcare utilization could be traced back potentially as long as 10 years for GP contacts. Only 60% of the patients in our study were classified as

having MCI or mild dementia at the time of diagnosis in a memory clinic, while the remaining 40% were already at the moderate/severe stage of the disease at diagnosis. In the sensitivity analysis examining healthcare utilization in YOAD patients according to disease severity at time of diagnosis, CRRs were generally higher and increased earlier for those with moderate/severe dementia than for those with MCI/mild dementia, indicating a window of opportunity for a more timely diagnosis.

To our knowledge, this is the first study to examine healthcare utilization patterns prior to dementia diagnosis in YOAD patients, while there have been some studies examining healthcare utilization prior to a diagnosis of late-onset dementia or not stratifying by age [13–27]. The majority of studies on healthcare utilization prior to a dementia diagnosis examined only the time period 1–2 years prior to diagnosis and found increased healthcare utilization/cost throughout the study periods [18, 21–23]. A few studies examined 2–3 years prior to diagnosis and found increased healthcare utilization only immediately preceding diagnosis [24, 25]. The longest examined time prior to dementia diagnosis was in the study by Ramakers et al. [17], who examined GP contacts in the five years prior to dementia diagnosis and found an increase throughout the entire study period. A study from the UK utilized data from both general practitioners and hospital contacts, wherein they found healthcare utilization significantly increased in patients with LOAD throughout the 3-year study period before diagnosis, especially in the 6 months immediately preceding diagnosis [13]. The authors suggest this may reflect the diagnostic process or may reflect that those with AD are less able to maintain healthy habits and compliance with pharmacotherapy.

In a population of patients with AD and related disorders, Desai et al. examined whether healthcare resource use was related to disease severity at the time of initial cognitive assessment and found an increase in healthcare utilization years before dementia diagnosis, which increased with disease severity at the time of assessment [20]. Although they measured disease severity by MMSE or Montreal Cognitive Assessment (MoCA) score, whereas we determined disease severity according to ICD-10 research criteria for dementia staging, our results are in line.

Although these previous studies focused on LOAD, the longest examined period was 5 years retrospectively, and the methodology differs, the results are in line with ours. Thus, these findings on YOAD are consistent with the findings from studies on LOAD; healthcare utilization is increased several years before dementia diagnosis, especially immediately preceding diagnosis, and is influenced by disease severity. This study was designed to explore the overall contact rates, and further exploration of the reasons behind these contacts should be done in a suitably designed future study.

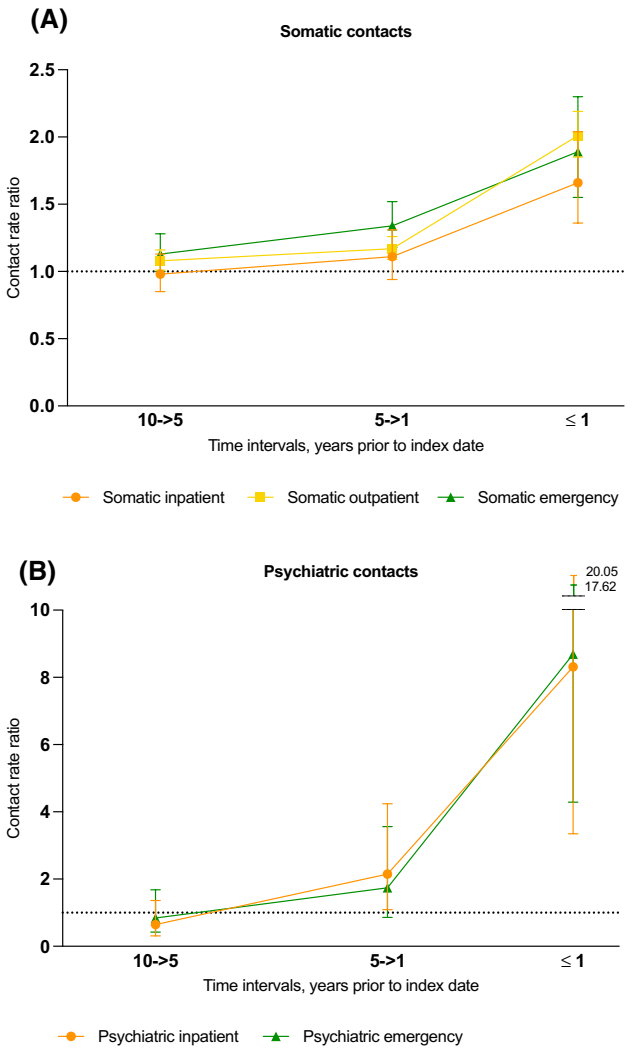

Fig. 3 Contact rate ratios, secondary care contacts. Contact rate ratios (CRRs) are plotted for young-onset Alzheimer's disease patients for somatic healthcare contacts (**A**) and psychiatric healthcare contacts (**B**). Error bars represent 95% confidence intervals. The CRRs presented are adjusted for age, sex, highest attained educational level at age 40 (or at time of diagnosis, whichever came first) and civil status at index date. Note that the Y-axis have differing values for A and B. Unadjusted estimates are presented in Online Resource Table S3 and adjusted estimates are presented in Table 2

Our results add to these previous studies by providing additional insight into the younger AD patients whose healthcare utilization patterns have not previously been described. Those with moderate/severe dementia seem to exhibit signs of vulnerability throughout the entire study period, likely suggesting that these patients have had dementia symptoms and deteriorating health for a long period, rather than a rapid disease course. Furthermore, these patients have a drastically increased CRR for both

Table 2 Consultation rate ratios by type of healthcare contact, fully adjusted

Consultation rate ratios (CRR)	Adjusted*		
	CRR	95% CI	*P* value
Primary care			
Any GP contact			
10-> 5 years prior to index date	1.10	1.03–1.17	0.003
5-> 1 years prior to index date	1.20	1.13–1.27	≤.00001
≤ 1 year prior to index date	1.73	1.64–1.83	≤.00001
GP Face-to-face contacts			
10-> 5 years prior to index date	1.08	1.01–1.14	0.021
5-> 1 years prior to index date	1.20	1.13–1.28	≤.00001
≤ 1 year prior to index date	1.67	1.58–1.76	≤.00001
GP telephone/email contacts			
10-> 5 years prior to index date	1.13	1.04–1.23	0.004
5-> 1 years prior to index date	1.19	1.10–1.30	≤.00001
≤ 1 year prior to index date	1.80	1.66–1.96	≤.00001
Physiotherapist			
10-> 5 years prior to index date	1.10	0.81–1.49	0.560
5-> 1 years prior to index date	0.84	0.61–1.15	0.279
≤ 1 year prior to index date	0.59	0.41–0.85	0.005
Psychologist			
10-> 5 years prior to index date	1.37	0.87–2.18	0.178
5-> 1 years prior to index date	2.69	1.58–4.56	≤.00001
≤ 1 year prior to index date	4.63	2.36–9.06	≤.00001
Private practice medical specialist			
10-> 5 years prior to index date	1.15	0.99–1.33	0.069
5-> 1 years prior to index date	1.08	0.95–1.23	0.240
≤ 1 year prior to index date	1.10	0.93–1.31	0.277
Secondary care			
Somatic inpatient admissions			
10-> 5 years prior to index date	0.98	0.85–1.13	0.797
5-> 1 years prior to index date	1.11	0.94–1.31	0.217
≤ 1 year prior to index date	1.66	1.36–2.04	≤.00001
Somatic outpatient contacts			
10-> 5 years prior to index date	1.08	1.01–1.16	0.028
5-> 1 years prior to index date	1.17	1.09–1.26	≤.00001
≤ 1 year prior to index date	2.01	1.85–2.19	≤.00001
Somatic emergency admissions			
10-> 5 years prior to index date	1.13	1.00–1.28	0.045
5-> 1 years prior to index date	1.34	1.18–1.52	≤.00001
≤ 1 year prior to index date	1.89	1.55–2.30	≤.00001
Psychiatric inpatient admissions			
10-> 5 years prior to index date	0.65	0.31–1.36	0.255
5-> 1 years prior to index date	2.15	1.09–4.24	0.028
≤ 1 year prior to index date	8.31	3.35–20.60	≤.00001
Psychiatric emergency admissions			
10-> 5 years prior to index date	0.84	0.42–1.68	0.618
5-> 1 years prior to index date	1.74	0.86–3.56	0.125
≤ 1 year prior to index date	8.69	4.29–17.62	≤.00001

GP general practitioner, *CRR* contact rate ratio, *CI* confidence interval

*Adjusted for age, sex, highest attained educational level at age 40 (or at time of diagnosis, whichever came first) and civil status at index date. CRRs are presented in time intervals prior to the date of dementia diagnosis for cases and compared to the control group of individuals free of dementia at index date. Unadjusted estimates are presented in Supplementary Table S2

psychiatric inpatient and emergency admissions, likely portraying how immensely difficult it can be to recognize dementia symptoms in young patients, which may lead to misinterpretation of symptoms. Though confidence intervals for these associations are very wide, even if the true value of the CRRs is near the lower bounds of the confidence intervals, this is still a large increase compared to the controls. Dementia symptoms could be misinterpreted as psychiatric diseases such as stress, anxiety or depression, or these diseases may occur comorbidly [28], blurring the picture of the dementia symptoms and hindering timely diagnosis. It also seems likely that dementia symptoms are overlooked entirely until patients are admitted with delirium or behavioural and psychological symptoms of dementia, all of which occur more frequently and more severely further along the disease course [29, 30]. Similarly, the timing of the peak in psychologist contacts differs according to disease severity with those with MCI/mild dementia having the highest CRR for psychologist contacts in the year prior to diagnosis. For those with moderate/severe dementia, this seems to happen earlier, perhaps reflecting a timing of when symptoms begin to markedly impact functioning of the patients at work or at home. The explanation for these findings is likely found in a long time lag between symptom onset and diagnosis. There may also be an unwillingness among young patients with cognitive complaints in being referred to a memory clinic or a lack of disease insight which may also add to the diagnostic delay.

Another possible explanation for the overall increased healthcare utilization long before diagnosis could be that comorbidities such as diabetes, hypertension, cardiovascular disease and a multitude of other chronic diseases may lead to frequent GP visits. These are also risk factors for developing dementia or for a more rapid cognitive decline [31], and the increased contact rate and dementia diagnosis may thus share a common cause. Failure to comply with planned treatment regimens due to cognitive decline could lead to a general health deterioration, which could also lead to increased healthcare utilization. If healthy habits are increasingly compromised, this could also explain why we see a decreased use of physiotherapy visits by referral prior to diagnosis in the present study.

Our study had several limitations. The study design is vulnerable to detection bias; those who see a medical doctor frequently are more likely to be referred to a memory clinic and receive a diagnosis upon experiencing symptoms than those who do not regularly see a doctor, whereas symptoms of dementia in those who do not frequently see

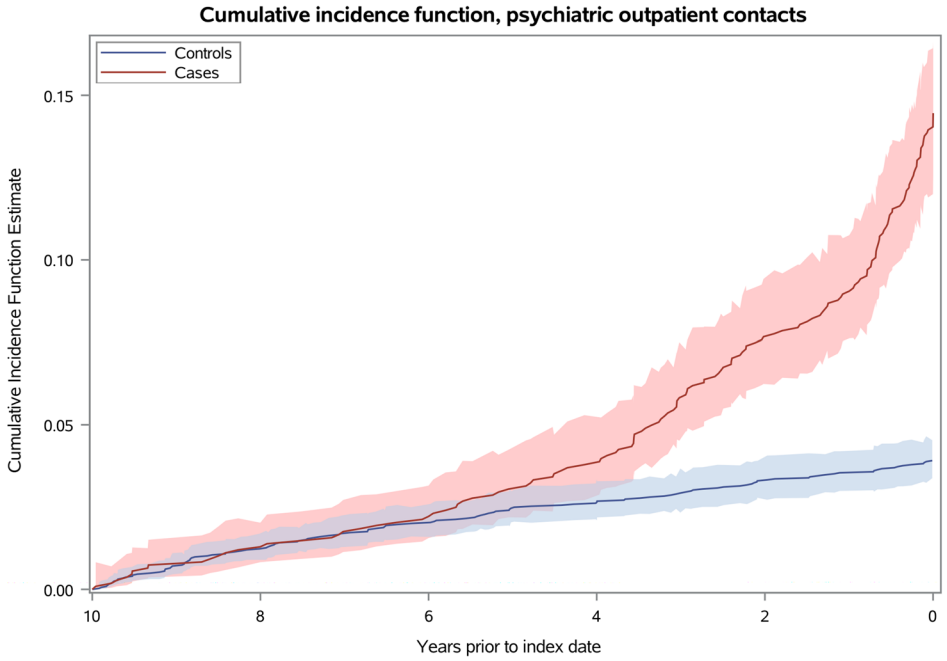

Fig. 4 Cumulative incidence function, psychiatric outpatient contacts. The figure shows the cumulative incidence of psychiatric outpatient contacts for dementia cases and controls, respectively, over a 10-year period prior to the index date, which is the date of diagnosis for the dementia cases. The x-axis represents time in years, and the y-axis represents the cumulative incidence of psychiatric outpatient contacts

a doctor may go unnoticed. It is noteworthy, though, that only 60% of cases were diagnosed in the early stages of the disease, suggesting that seeing a doctor frequently is not necessarily sufficient to receive a timely diagnosis.

While censoring of contacts related to the diagnostic process in the memory clinic was attempted, it is not possible to completely remove all such contacts if not specifically marked with a dementia diagnosis. Furthermore, the primary care registers used does not contain reasons for contacts and censoring could not be done. For these reasons, GP and outpatient contacts in the time interval immediately before diagnosis should be interpreted taking this into account. This should not, however, majorly influence results further back in time.

Another limitation is the unavailability of genetic information in the registers. This is especially relevant for those with YOAD, where genetic mutations contribute to a larger number of AD cases than what is seen in LOAD [32].

A major strength of the present study is the use of nationwide healthcare registers. The majority of previous studies relied on claims/insurance data [18–27], which may result in a tendency to favour a healthier population [33]. In Denmark, the health services examined were, with few exceptions, free of charge, and data on healthcare contacts were drawn from the Danish healthcare registers which contain detailed, reliable and complete data on all contacts with a GP or hospital, limiting problems with selection bias. Thus, there is equal access to healthcare services for all and virtually full data coverage. However, for physiotherapy and psychologist contacts we only had data for those referred within the Danish public sector. Physiotherapists and clinical psychologists can also be seen using out-of-pocket payment or a private health insurance, and thus, these results should be interpreted with caution.

In conclusion, this study demonstrated an altered healthcare utilization pattern across all 12 investigated types of contacts in the year immediately preceding diagnosis. GP contacts were significantly increased throughout the entire 10-year study period, particularly for those with moderate/severe dementia at time of diagnosis. There was a substantial increase especially for psychiatric contacts, showcasing the need for a more timely diagnosis, which could perhaps decrease avoidable hospitalizations due to psychiatric symptoms of yet undiagnosed dementia. Increased healthcare utilization in young patients with cognitive complaints could potentially be an early warning sign of AD, though further research into such early warning signs is needed to paint a full picture of the earliest phases of YOAD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-023-11974-x.

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Author contributions All authors contributed to the conception and design of the study; LD, JJ and TML: contributed to the acquisition and analysis of data. The first draft of the manuscript was written by LD, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability All of the data used in this study are derived from the Danish National and Public Health registries. These data are collected and stored by the relevant authorities and cannot be made public or accessed by unauthorized parties. Access to such data is given via standard rules and regulations of data access outlined by the Danish Data Protection Agency and Danish Health Data Authority.

Declarations

Conflicts of interest The authors have no competing interests to declare that are relevant to the content of this article.

Ethics approval This research project was approved by the Danish Data Protection Agency, Statistics Denmark and the Danish Health Data Authority. Danish law does not require ethics committee approval or informed patient consent.

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Supplementary

Healthcare utilization prior to a diagnosis of young onset Alzheimer's disease: A nationwide nested case-control study
Damsgaard L, Janbek J, Laursen TM, Waldemar G, Jensen-Dahm C. Journal of Neurology

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Contents:

Table S1. Exclusion criteria

	Cases	Controls
Developmental disorders and mental retardation ICD-8: 311-315, 759.3, ICD-10: F70-F79, Q90	X	X
Not living in Denmark in 10-year retrospective period	X	X
Dementia or mild cognitive impairment diagnosis ICD-8: 290.09-11, 290.18-19, 293.09-19, ICD 10: F00.0-00.9, F01.0-01.9, F02.0-F02.8, F03.9, F04.0-F04.9, F06.7 G30.0-G30.9, G31.0A, G31.0B, G31.8, G31.8E, G31.9	*	X
Dementia medication ATC code N06DA02-4, N06DX01		X
Entry in DanDem		X

* ICD-codes used for censoring contacts 6 months before dementia diagnosis for cases

Abbreviations: ICD: International classification of diseases, ATC: Anatomical Therapeutic Chemical, DanDem: Danish Dementia Quality Database.

Table S2. Contact rates for primary and secondary care contacts

Primary care	Contact rates per person-year		Secondary care	Contact rates per person-year	
Any GP contact	**Cases**	**Controls**	**Somatic inpatient admissions**	**Cases**	**Controls**
10->5 years prior to index date	41.33	37.60	10->5 years prior to index date	0.68	0.71
5->1 years prior to index date	38.24	31.83	5->1 years prior to index date	0.77	0.70
≤1 year prior to index date	14.42	8.37	≤1 year prior to index date	0.36	0.22
GP Face to face contacts			**Somatic outpatient contacts**		
10->5 years prior to index date	22.89	21.33	10->5 years prior to index date	2.92	2.67
5->1 years prior to index date	21.35	17.85	5->1 years prior to index date	2.87	2.50
≤1 year prior to index date	7.64	4.65	≤1 year prior to index date	1.38	0.71
GP telephone/email contacts			**Somatic emergency admissions**		
10->5 years prior to index date	18.44	16.28	10->5 years prior to index date	0.64	0.57
5->1 years prior to index date	16.90	13.98	5->1 years prior to index date	0.68	0.51
≤1 year prior to index date	6.79	3.72	≤1 year prior to index date	0.27	0.14
Physiotherapist			**Psychiatric inpatient admissions**		
10->5 years prior to index date	9.50	8.10	10->5 years prior to index date	0.03	0.03
5->1 years prior to index date	7.05	7.89	5->1 years prior to index date	0.05	0.04
≤1 year prior to index date	1.40	2.11	≤1 year prior to index date	0.04	0.01
Psychologist			**Psychiatric emergency admissions**		
10->5 years prior to index date	0.36	0.36	10->5 years prior to index date	0.04	0.04
5->1 years prior to index date	0.57	0.24	5->1 years prior to index date	0.05	0.04
≤1 year prior to index date	0.24	0.06	≤1 year prior to index date	0.06	0.01
Private practice medical specialist					
10->5 years prior to index date	5.57	4.99			
5->1 years prior to index date	4.72	4.43			
≤1 year prior to index date	1.26	1.18			

Contact rates are presented in time intervals prior to index date (date of diagnosis for cases) for cases and controls separately by type of contact.
Abbreviations: GP: general practitioner

Table S3. Contact rate ratios for primary and secondary care contacts, unadjusted

Primary care	Unadjusted			Secondary care	Unadjusted		
Any GP contact	**CRR**	**95 % CI**	**P-value**	**Somatic inpatient admissions**	**CRR**	**95 % CI**	**P-value**
10->5 years prior to index date	1.10	1.03-1.17	0.003	10->5 years prior to index date	0.96	0.83-1.10	0.540
5->1 years prior to index date	1.20	1.13-1.28	≤.00001	5->1 years prior to index date	1.10	0.93-1.29	0.268
≤1 year prior to index date	1.72	1.62-1.83	≤.00001	≤1 year prior to index date	1.63	1.33-2.01	≤.00001
GP Face to face contacts				**Somatic outpatient contacts**			
10->5 years prior to index date	1.07	1.01-1.14	0.023	10->5 years prior to index date	1.09	1.02-1.17	0,011
5->1 years prior to index date	1.20	1.13-1.27	≤.00001	5->1 years prior to index date	1.15	1.07-1.23	≤.00001
≤1 year prior to index date	1.64	1.55-1.74	≤.00001	≤1 year prior to index date	1.92	1.78-2.08	≤.00001
GP telephone/email contacts				**Somatic emergency admissions**			
10->5 years prior to index date	1.13	1.04-1.24	0.005	10->5 years prior to index date	1.12	0.99-1.27	0.071
5->1 years prior to index date	1.21	1.11-1.32	≤.00001	5->1 years prior to index date	1.33	1.17-1.52	≤.00001
≤1 year prior to index date	1.82	1.67-1.99	≤.00001	≤1 year prior to index date	1.90	1.56-2.33	≤.00001
Physiotherapist				**Psychiatric inpatient admissions**			
10->5 years prior to index date	1.17	0.45-0.97	0.310	10->5 years prior to index date	0.76	0.38-1.50	0.424
5->1 years prior to index date	0.89	0.66-1.21	0.465	5->1 years prior to index date	1.45	0.57-3.65	0.433
≤1 year prior to index date	0.67	0.86-1.60	0.035	≤1 year prior to index date	6.50	2.16-19.60	0.001
Psychologist				**Psychiatric emergency admissions**			
10->5 years prior to index date	0.98	0.65-1.46	0.917	10->5 years prior to index date	1.01	0.52-1.96	0.980
5->1 years prior to index date	2.33	1.56-3.49	≤.00001	5->1 years prior to index date	1.23	0.53-2.81	0.631
≤1 year prior to index date	4.32	2.47-7.57	≤.00001	≤1 year prior to index date	6.77	3.05-15.04	≤.00001
Private practice medical specialist							
10->5 years prior to index date	1.12	0.97-1.28	0.119				
5->1 years prior to index date	1.07	0.94-1.21	0.312				
≤1 year prior to index date	1.07	0.91-1.25	0.424				

CRRs are presented in time intervals prior to the date of dementia diagnosis for cases and compared to the control group of individuals free of dementia at index date.

Abbreviations: GP: general practitioner, CRR: contact rate ratio, CI: confidence interval.

Table S4. Sensitivity analysis – Contact rate ratios by level of cognitive decline at diagnosis in primary care

Primary care	MCI / Mild dementia						Moderate / severe dementia					
	Unadjusted			Adjusted			Unadjusted			Adjusted		
Any GP contact	**CRR**	**95 % CI**	**P-value**	**CRR**	**95 % CI**	**P-value**	**CRR**	**95 % CI**	**P-value**	**CRR**	**95 % CI**	**P-value**
10->5 years prior to index date	1.01	0.94-1.09	0.801	1.03	0.95-1.11	0.484	1.23	1.11-1.36	≤.00001	1.20	1.09-1.32	≤.00001
5->1 years prior to index date	1.14	1.06-1.23	0.001	1.16	1.08-1.25	≤.00001	1.29	1.17-1.43	≤.00001	1.26	1.14-1.39	≤.00001
≤1 year prior to index date	1.60	1.49-1.72	≤.00001	1.65	1.54-1.76	≤.00001	1.91	1.73-2.12	≤.00001	1.87	1.70-2.07	≤.00001
GP Face to face contacts												
10->5 years prior to index date	1.01	0.94-1.10	0.728	1.03	0.95-1.12	0.417	1.16	1.06-1.28	0.002	1.14	1.04-1.26	0.007
5->1 years prior to index date	1.18	1.09-1.27	≤.00001	1.21	1.12-1.30	≤.00001	1.22	1.11-1.35	≤.00001	1.21	1.10-1.33	≤.00001
≤1 year prior to index date	1.65	1.54-1.77	≤.00001	1.70	1.59-1.82	≤.00001	1.63	1.48-1.80	≤.00001	1.62	1.47-1.79	≤.00001
GP telephone/email contacts												
10->5 years prior to index date	1.00	0.91-1.11	0.928	1.02	0.93-1.13	0.670	1.32	1.14-1.52	≤.00001	1.29	1.12-1.48	≤.00001
5->1 years prior to index date	1.09	0.98-1.22	0.106	1.11	1.00-1.23	0.046	1.38	1.20-1.59	≤.00001	1.32	1.15-1.52	≤.00001
≤1 year prior to index date	1.54	1.38-1.71	≤.00001	1.57	1.42-1.75	≤.00001	2.26	1.97-2.60	≤.00001	2.19	1.91-2.50	≤.00001
Physiotherapist												
10->5 years prior to index date	1.11	0.77-1.61	0.563	1.03	0.72-1.47	0.871	1.24	0.75-2.05	0.398	1.20	0.76-1.89	0.428
5->1 years prior to index date	0.92	0.64-1.33	0.669	0.85	0.60-1.19	0.345	0.85	0.51-1.44	0.552	0.81	0.50-1.32	0.394
≤1 year prior to index date	0.66	0.40-1.07	0.093	0.59	0.38-0.92	0.021	0.68	0.37-1.24	0.205	0.60	0.34-1.05	0.074
Psychologist												
10->5 years prior to index date	1.15	0.68-1-95	0.608	1.43	0.78-2.61	0.250	0.77	0.41-1.44	0.411	1.75	0.75-4.09	0.198
5->1 years prior to index date	2.55	1.51-4.29	≤.00001	2.65	1.31-5.33	0.007	1.99	1.08-3.69	0.028	3.59	1.77-7.31	≤.00001
≤1 year prior to index date	4.49	2.31-8.73	≤.00001	5.17	2.32-11.50	≤.00001	3.82	1.37-10.65	≤.00001	3.31	1.16-9-47	0.025
Private practice medical specialist												
10->5 years prior to index date	1.23	1.02-1.49	0.024	1.25	1.02-1.54	0.036	0.97	0.81-1.17	0.746	0.99	0.82-1.19	0.909
5->1 years prior to index date	1.25	1.07-1.47	0.005	1.25	1.06-1.48	0.007	0.84	0.69-1.02	0.073	0.84	0.69-1.02	0.084
≤1 year prior to index date	1.28	1.03-1.59	0.024	1.31	1.04-1.64	0.020	0.79	0.63-0.99	0.048	0.80	0.63-1.01	0.058

CRRs are presented in time intervals prior to the date of dementia diagnosis for cases and compared to the control group of individuals free of dementia at index date.
Abbreviations: MCI: Mild cognitive impairment, CRR: contact rate ratio, CI: confidence interval, GP: general practitioner

Table S5. Sensitivity analysis – Contact rate ratios by level of cognitive decline at diagnosis in secondary care

Secondary care	MCI / Mild dementia						Moderate / severe dementia					
	Unadjusted			Adjusted			Unadjusted			Adjusted		
Somatic inpatient admissions	**CRR**	**95 % CI**	**P-value**	**CRR**	**95 % CI**	**P-value**	**CRR**	**95 % CI**	**P-value**	**CRR**	**95 % CI**	**P-value**
10->5 years prior to index date	0.93	0.77-1.13	0.477	0.97	0.81-1.18	0.791	0.99	0.80-1.23	0-911	0.98	0.78-1.22	0.842
5->1 years prior to index date	0.95	0.78-1.15	0.577	0.99	0.82-1.20	0.900	1.33	1.01-1.75	0-043	1.28	0.97-1.70	0.079
≤1 year prior to index date	1.25	0.96-1.63	0.101	1.34	1.03-1.75	0.028	2.26	1.64-3.10	≤.00001	2.17	1.58-2.97	≤.00001
Somatic outpatient contacts												
10->5 years prior to index date	1.13	1.03-1.23	0.010	1.11	1.01-1.22	0.037	1.05	0.94-1.16	0.396	1.05	0.94-1.17	0.374
5->1 years prior to index date	1.19	1.09-1.30	≤.00001	1.20	1.09-1.31	≤.00001	1.10	0.98-1.23	0.118	1.13	0.99-1.28	0.061
≤1 year prior to index date	2.14	1.94-2.36	≤.00001	2.25	2.02-2.50	≤.00001	1.65	1.45-1.89	≤.00001	1.71	1.49-1.96	≤.00001
Somatic emergency admissions												
10->5 years prior to index date	0.98	0.84-1.14	0.775	1.03	0.88-1.21	0.703	1.35	1.11-1.64	0.002	1.31	1.09-1.59	0.005
5->1 years prior to index date	1.21	1.03-1.42	0.019	1.26	1.08-1.48	0.004	1.54	1.25-1.90	≤.00001	1.49	1.21-1.84	≤.00001
≤1 year prior to index date	1.36	1.03-1.80	0.031	1.41	1.07-1.86	0.014	2.82	2.13-3.75	≤.00001	2.69	2.03-3.55	≤.00001
Psychiatric inpatient admissions												
10->5 years prior to index date	0.34	0.12-0.96	0.042	0.30	0.09-0.99	0.048	2.55	1.10-5.89	0.029	2.01	0.93-4.36	0.076
5->1 years prior to index date	0.64	0.21-1.94	0.429	1.96	0.86-4.50	0.111	5.25	1.63-16.91	≤.00001	3.60	1.26-10.28	0.016
≤1 year prior to index date	2.79	0.75-10.30	0.125	6.36	2.60-15.59	≤.00001	19.5	4.72-80.59	≤.00001	14.70	3.70-58.46	≤.00001
Psychiatric emergency admissions												
10->5 years prior to index date	0.44	0.15-1.28	0.134	0.31	0.11-0.85	0.024	3.25	1.49-7.08	0.003	2.45	1.20-5.01	0.014
5->1 years prior to index date	0.52	0.15-1.80	0.302	1.70	0.66-4.34	0.270	3.66	1.35-9.89	0.011	3.02	1.20-7.58	0.019
≤1 year prior to index date	2.86	0.91-9.04	0.073	4.55	1.68-12.27	0 003	24.00	7.06-73.30	≤.00001	23.76	7.59-74.38	≤.00001

CRRs are presented in time intervals prior to the date of dementia diagnosis for cases and compared to the control group of individuals free of dementia at index date.
Abbreviations: MCI: Mild cognitive impairment, CRR: contact rate ratio, CI: confidence interval.

Table S6. Sensitivity analysis - Contact rate ratios by type of healthcare contact, stratified by age and sex

Consultation rate ratios (CRR)	Age at index <60 years*			Age at index ≥60*			Male**			Female**		
Any GP contact	**CRR**	**95 % CI**	**P-value**	**CRR**	**95 % CI**	**P-value**	**CRR**	**95 % CI**	**P-value**	**CRR**	**95 % CI**	**P-value**
10->5 years prior to index date	1.12	0.97-1.28	0.119	1.09	1.02-1.17	0.011	1.07	0.97-1.19	0.176	1.11	1.03-1.20	0.005
5->1 years prior to index date	1.26	1.11-1.42	≤.00001	1.19	1.11-1.27	≤.00001	1.16	1.05-1.27	0.003	1.23	1.14-1.33	≤.00001
≤1 year prior to index date	1.98	1.74-2.24	≤.00001	1.68	1.57-1.79	≤.00001	1.82	1.67-2.00	≤.00001	1.67	1.56-1.80	≤.00001
Somatic inpatient admissions												
10->5 years prior to index date	0.92	0.68-1.25	0.604	0.99	0.84-1.16	0.865	0.82	0.66-1.03	0.083	1.10	0.91-1.33	0.305
5->1 years prior to index date	1.21	0.87-1.67	0.254	1.08	0.90-1.30	0.411	1.01	0.80-1.27	0.918	1.18	0.94-1.48	0.164
≤1 year prior to index date	2.20	1.50-3.25	≤.00001	1.55	1.23-1.95	≤.00001	1.66	1.24-2.24	0.001	1.66	1.27-2.18	≤.00001
Somatic outpatient contacts												
10->5 years prior to index date	1.10	0.90-1.34	0.336	1.08	1.81-2.16	0.045	1.06	0.90-1.24	0.487	1.10	1.02-1.19	0.013
5->1 years prior to index date	1.19	1.02-1.39	0.030	1.17	1.07-1.27	≤.00001	1.33	1.14-1.54	≤.00001	1.10	1.02-1.19	0.013
≤1 year prior to index date	2.17	1.72-2.74	≤.00001	1.98	1.00-1.67	≤.00001	2.94	2.51-3.44	≤.00001	1.62	1.48-1.78	≤.00001
Somatic emergency admissions												
10->5 years prior to index date	1.00	0.78-1.28	0.996	1.16	1.01-1.33	0.030	1.13	0.94-1.35	0.201	1.13	0.96-1.33	0.136
5->1 years prior to index date	1.34	1.02-1.76	0.038	1.34	1.16-1.54	≤.00001	1.23	1.02-1.49	0.032	1.42	2.30-1.68	≤.00001
≤1 year prior to index date	1.82	1.17-2.82	0.008	1.90	1.53-2.36	≤.00001	2.10	1.56-2.83	≤.00001	1.74	1.34-2.26	≤.00001
Psychiatric inpatient admissions												
10->5 years prior to index date	0.37	0.90-1.49	0.161	0.75	0.35-1.61	0.463	0.89	0.40-1.99	0.781	0.71	0.25-2.01	0.514
5->1 years prior to index date	2.08	0.34-12.70	0.426	2.08	1.36-5.74	0.005	1.53	0.53-4.42	0.428	3.64	1.76-7.52	≤.00001
≤1 year prior to index date	12.36	3.46-44.17	≤.00001	8.93	3.47-22.97	≤.00001	12.14	4.64-31.70	≤.00001	8.67	2.99-25.10	≤.00001
Psychiatric emergency admissions												
10->5 years prior to index date	0.55	0.08-3.57	0.526	1.02	0.50-2.07	0.959	1.24	0.52-2.96	0.633	0.77	0.30-1.98	0.585
5->1 years prior to index date	1.56	0.37-6.51	0.541	2.23	1.02-4.89	0.044	0.67	0.24-1.87	0.447	3.54	1.62-7.78	0.002
≤1 year prior to index date	9.91	1.58-62.11	0.014	12.12	5.96-24.67	≤.00001	12.64	4.97-32.13	≤.00001	10.03	4.53-22.17	≤.00001

* Adjusted for age, sex (except **), highest attained educational level at age 40 (or at time of diagnosis, whichever came first) and civil status at index date. CRRs are presented in time intervals prior to the date of dementia diagnosis for cases and compared to the control group of individuals free of dementia at index date.

Sensitivity analysis presented for a selection of types of contacts. Remaining types of contacts are equally similar to the results found in the main analysis.

Abbreviations: CRR: contact rate ratio, CI: confidence interval. GP: general practitioner

8.2 Study 2

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RESEARCH ARTICLE

Mapping morbidity 10 years prior to a diagnosis of young onset Alzheimer's disease

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Abstract

INTRODUCTION: Early symptoms in young onset Alzheimer's disease (YOAD) may be misinterpreted, causing delayed diagnosis. This population-based study aimed to map morbidity prior to YOAD diagnosis.

METHODS: In a register-based incidence density matched nested case-control study, we examined hospital-diagnosed morbidity for people diagnosed with YOAD in Danish memory clinics during 2016-2020 compared to controls in a 10-year period. Conditional logistic regression produced incidence rate ratios (IRRs).

RESULTS: The study included 1745 cases and 5235 controls. YOAD patients had a higher morbidity burden in the year immediately before dementia diagnosis, for certain disorders up to 10 years before. This was especially evident for psychiatric morbidity with the highest increased IRRs throughout the entire period and IRR 1.43 (95% confidence interval 1.14–1.79) in the 5–10-years before dementia diagnosis.

DISCUSSION: YOAD patients display a different pattern of morbidity up to 10 years prior to diagnosis. Awareness of specific alterations in morbidity may improve efforts toward a timely diagnosis.

KEYWORDS
Alzheimer's disease, early warning signs, epidemiology, morbidity, registry-based, young onset dementia

Highlights

- Retrospective, nested case-control study of young onset Alzheimer's disease (YOAD).
- YOAD cases had a higher morbidity burden than controls.
- YOAD cases had a higher psychiatric morbidity burden up to 10 years before diagnosis.
- Altered morbidity patterns could serve as an early warning sign of YOAD.

1 | BACKGROUND

While several studies have sought to describe the earliest symptoms of Alzheimer's disease (AD),[1] to our knowledge, no previous studies have broadly explored morbidity prior to a diagnosis of young onset AD (YOAD). Studies examining morbidity prior to an AD or all-cause dementia diagnosis usually target one prespecified disease or symptom, often as risk studies, as outlined in the 2020 Lancet Commission's report on dementia prevention, intervention, and care.[2] Here, evidence was gathered on, among others, hearing impairment, traumatic brain injury, hypertension, diabetes, cardiovascular disease, depression, and sleep disorders and subsequent dementia. Other studies have found associations between many diverse diseases and symptoms and a future diagnosis of all-cause dementia, such as infectious diseases,[3] inflammatory bowel disease,[4] stress diagnoses,[5] anxiety,[6] and so forth. Further studies that stratify on etiology are needed, as (co)morbidity burden is likely heterogeneous between different causes of dementia. Furthermore, the vast majority of studies on risk factors and early symptoms in AD have focused on late onset AD (LOAD). As morbidity generally tends to increase with increasing age, there is likely a difference in the pattern of morbidity for those diagnosed with YOAD compared to those diagnosed with LOAD even based on age alone. Therefore, the knowledge on morbidity preceding LOAD is unlikely to be directly transferable to YOAD patients.

Due to the risk of reverse causation, it is often challenging to establish whether a disease or symptom is a risk factor for dementia or an early manifestation of the dementia disorder. Regardless, increased knowledge on such diseases and symptoms may serve as early warning signs. In a study of pre-diagnostic symptoms of 89 young-onset dementia patients, only 5% of patients reported cognitive symptoms five years before diagnosis.[7] Establishing key features of the pre-diagnostic phase of YOAD, including both cognitive and non-cognitive symptoms, may help patients, caregivers, and especially general practitioners (GPs) recognize the need for memory clinic referral during the early phase of clinical deterioration. Studies have shown a large diagnostic delay in young onset dementia, which may have detrimental effects on work life, financial stability, and family roles.[8,9] Thus, minimizing diagnostic delay is key in ensuring timely diagnosis and support. Furthermore, an early diagnosis allows for timely initiation of treatment, which may be especially important with advances in early biomarkers and the emergence of disease-modifying treatments.

In a previous study, we demonstrated that YOAD patients have increased healthcare utilization from 10 years before diagnosis,[10] and the present study elaborates on those findings.

The aim of this study was to explore whether individuals diagnosed with YOAD differ from cognitively healthy matched adults in terms of reasons for hospital contacts 10 years preceding diagnosis, in order to describe potential patterns that characterize the prodromal phase of YOAD.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors searched PubMed for literature on dementia and prior morbidity. Only few studies were found, focusing on either late onset Alzheimer's disease or young onset all-cause dementia.
2. **Interpretation**: This study demonstrated a higher morbidity burden among patients with young onset Alzheimer's disease (YOAD) than controls, detectable up to as long as 10 years before dementia diagnosis. There was a substantial increase in psychiatric diagnoses, supporting prior reports on the significance of stress and depression in the years leading up to diagnosis.
3. **Future directions**: Altered hospital-diagnosed morbidity patterns in young patients with cognitive complaints may be an early warning sign of YOAD. Future studies should further explore early symptoms and morbidity prior to a diagnosis of YOAD by exploring consultations in the general practice setting and the use of prescription medication. This approach may help to identify patients at high risk of YOAD earlier than today.

2 | METHODS

2.1 | Data sources

Cases were identified from the Danish Quality Database for Dementia (DanDem). The database was established in 2016, and it is mandatory for all secondary healthcare facilities that accept referrals for diagnostic evaluation of cognitive impairment and dementia to enter information in DanDem upon completion of diagnostic evaluation. Thus, DanDem contains information on all patients seen at Danish memory clinics from 2016 onward. Variables included are, among others, etiology, severity of the dementia syndrome at time of diagnosis (if applicable), and diagnostic investigations performed, including results of selected cognitive tests. Furthermore, we used the Danish National Patient Registry (DNPR) and the Danish Psychiatric Central Research Register (DPCRR), which contain information on all somatic and psychiatric diagnoses given in the secondary healthcare sector since 1977 and 1969, respectively, with outpatient data added in 1995.[11,12] The Danish National Prescription Registry (DNPrR)[13] was used to draw information on filled prescription medication used in the censoring of potential controls. Covariates were identified from the Population Education Register[14] and the Civil Registration System, with the latter also used for accurate linkage between the registers through each Danish citizen's unique 10-digit personal identification number.[15]

2.2 | Study design and population

We conducted a retrospective incidence density matched nested case-control study following the approach of our previous study on YOAD.[10] Cases included all individuals diagnosed with mild cognitive impairment (MCI) or dementia due to AD (YOAD) in a Danish memory clinic between 2016 and 2020. Matched controls were drawn from a nationwide cohort of all Danish citizens.

2.2.1 | Case definition

By convention, YOAD is defined as dementia due to AD with symptom onset before age 65 years. As information on the time of symptom onset for patients was not available, we approximated symptom onset by including all patients diagnosed with mild cognitive impairment (MCI) or dementia due to AD before age 70 years, assuming a 5-year time lag between symptom onset and final diagnosis, as prior research has shown mean time to diagnosis around 5 years for YOAD patients.[8,9] The AD diagnosis was made according to the National Institute on Aging-Alzheimer's Association workgroups (NIA-AA) criteria,[16] and disease severity was determined based on International Classification of Diseases (ICD) 10 criteria.[17] Thus, cases were individuals with a first diagnosis of MCI or dementia with AD etiology in DanDem from the start of the register (2016) through 2020. Index date was the date of diagnosis (and the date of matching for controls).

2.2.2 | Control definition

Each case was matched with three controls drawn from the full risk set, the entire Danish population, on age and sex. Each control was at risk for YOAD at matching date. Thus, incidence density matching was used, allowing odds ratios from conditional logistic regression analyses to be interpreted as incidence rate ratios (IRR).[18] Controls were randomly selected with the following criteria: (1) no entry in DanDem before index date (never referred to or seen at a memory clinic), (2) no MCI or dementia diagnosis in DNPR or DPCRR before index date, (3) no redeemed prescription for antidementia medication in DNPrR before index date. ICD codes for identification of MCI and dementia diagnosis in DNPR/DPCRR and anatomical therapeutic chemical (ATC) codes for identification of dementia medication in DNPrR can be found in Table S1.

2.2.3 | Overall censoring criteria

Individuals with Down syndrome (ICD-8: 759.3, ICD-10: DQ90) and Mental Retardation (ICD-8: 311-315, ICD-10: DF70-DF79) were censored. To ensure completeness of data, cases and controls who did not live in Denmark throughout the study period were also censored. As incidence density matching was used, controls were censored if they had a dementia diagnosis or a redeemed prescription of antidementia medication prior to diagnosis. Censoring criteria and specific diagnostic codes used to determine these can be seen in Table S1.

2.3 | Definition of morbidity

Primary and secondary discharge diagnoses from in- and outpatient hospital contacts were drawn from DNPR and DPCRR. Diagnoses were grouped according to overall categories of diseases and health problems, based on chapters in the ICD-10 classification (chapters I-XIV, XVIII-XIX, and XXI). The study population was considered exposed if they had at least one diagnosis within each of these categories during the 10 years prior to the index date. All contacts related to pregnancy, childbirth or the perinatal period, and congenital malformations and chromosomal abnormalities (ICD-10 chapters XV, XVI, XVII) and procedural codes (ICD-10 chapter XX) were excluded. As any prior MCI or dementia diagnosis was a censoring criterion for controls, these ICD-10 codes (Table S1) were censored.

2.4 | Covariates

Analyses were adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis, whichever came first), and civil status at index date.

2.5 | Data analysis

2.5.1 | Main analysis

For each disease category we used a conditional logistic regression model to investigate the association between having at least one diagnosis within the corresponding ICD-10 chapter and subsequent diagnosis of YOAD. Each matched set served as a stratum in the regression model. IRRs were calculated (a) for the entire 10-year period, (b) for diagnosis in the 10 - >5-year interval prior to index date, (c) for the 5 - >1-year interval prior to index date, and (d) for the ≤1-year interval prior to index date, to investigate latency between symptoms/diagnoses and dementia diagnosis. In addition, the three most prevalent diagnoses (on a two-digit level, e.g., A01) within each disease category in the study population were identified, and the association between each specific diagnosis and YOAD was investigated.

2.5.2 | Sensitivity analysis

In a sensitivity analysis, patients were grouped by YOAD disease severity, examining those with MCI/mild dementia or moderate/severe dementia, compared with their respective matched controls. In another sensitivity analysis, all contacts in the 6 months preceding the index date were censored. Furthermore, sensitivity analyses were performed stratifying cases by sex and by age at diagnosis (age < 55 years, age ≥ 55 years).

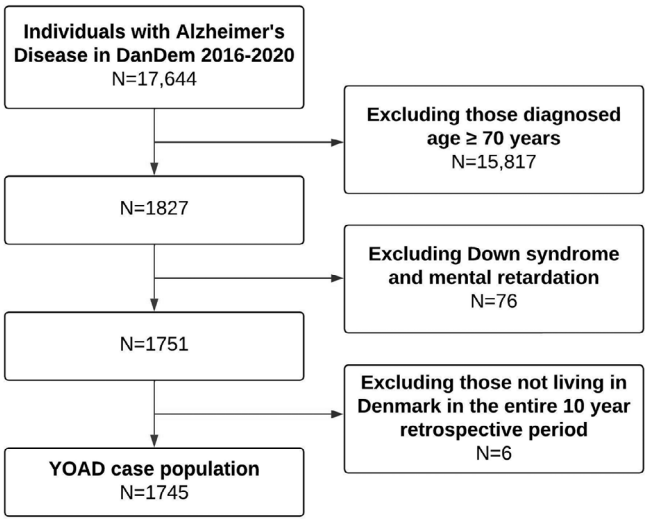

FIGURE 1 Flowchart of case selection. DanDem: Danish Quality Database for Dementia, YOAD, young onset Alzheimer's disease.

2.5.3 | Post hoc analysis

Based on the main results, post-hoc analyses were done investigating the association between ICD-10 codes F00-F09 (Organic, including symptomatic, mental disorders) (excluding MCI or dementia diagnoses, see Table S1), F10-19 (Mental and behavioral disorders due to psychoactive substance use), F20-29 (Schizophrenia, schizotypal and delusional disorders), F30-39 (Mood [affective] disorders), F40-F48 (Neurotic, stress-related and somatoform disorders), F50-59 (Behavioral syndromes associated with physiological disturbances and physical factors), F60-69 (Disorders of adult personality and behavior), and F99 (Unspecified mental disorder) and subsequent diagnosis of YOAD.

Analyses were presented in two adjustment models; one unadjusted, and one adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis, whichever came first), and civil status at index date. A 5% significance level was applied for all analyses.

Data management was performed using SAS 9.4 software. This research project was approved by the Danish Data Protection Agency, Statistics Denmark, and the Danish Health Data Authority. Danish law does not require ethics committee approval or informed patient consent.

3 | RESULTS

There were 17,644 individuals with a diagnosis of AD in DanDem between 2016 and 2020. Of these, 1827 were diagnosed before age 70 years. After censoring, there were 1745 cases (Figure 1). The mean age at diagnosis was 64.5 years, and 58% of the patients were female (Table 1). There were 63% of the cases diagnosed with either MCI or mild dementia at time of diagnosis, and 37% diagnosed with moderate/severe dementia. The covariates were evenly distributed among cases and controls.

Figure 2 shows the overall adjusted IRRs for a diagnosis within the disease categories in YOAD cases compared to controls (unadjusted IRRs in Table S2). The highest overall increase was found for the categories Factors influencing health status with an IRR of 8.80 (95% confidence interval [CI] 5.74–13.48), Mental and behavioral disorders (IRR 3.18, 95% CI 2.73–3.71), and Symptoms/signs not classified elsewhere (IRR 2.45, 95% CI 2.19–2.74).

When looking at the retrospective period 10 - >5 years prior to index date (Figure 3), significantly increased IRRs were only found for a few disease categories, with the most notable increases found in Diseases of the ear and mastoid process (IRR 1.51, 95% CI 1.16–1.97) and Mental and behavioral disorders (IRR 1.43, 95% CI 1.14–1.79). In the 5 - >1 year prior to index date, significantly increased IRRs were found for Mental and behavioral disorders, Diseases of the ear and mastoid process, Symptoms/signs not classified elsewhere, Injuries, poisonings, and other external causes, and Factors influencing health status, with Mental and behavioral disorders the disease category with the highest IRR (2.48, 95% CI 2.02–3.04).

In the period immediately preceding index date, 12 out of the 17 disease categories investigated showed significantly increased IRRs. In a sensitivity analysis (Table S3), all contacts registered during the 6 months before index date were censored, thus investigating the time period ≤1 year–6 months prior to index date; IRRs for all but Hematological/immunological diseases, Diseases of the eye and adnexa, Diseases of the ear and mastoid process, and Diseases of the respiratory system remained significantly increased.

Figure 4 shows the three most frequent diagnoses within each disease category in the entire study population and corresponding IRRs (unadjusted IRRs in Table S4). The largest increase was found for the ICD-10 code R41 (symptoms involving cognitive functions) in the category Symptoms/signs not classified elsewhere with an IRR of 90.84 (95% CI 52.29–157.87) (of cases, 23% had been given this diagnosis at least once during the study period, and for controls this was 0.3%) and for the code Z01 (other special examinations and investigations of persons without complaint or reported diagnosis) in the category Factors influencing health status with an IRR of 4.65 (95% CI 3.63–5.96). The three most prominently increased IRRs for specific diseases/disorders were found for the three psychiatric codes: F10 (mental and behavioral disorders due to use of alcohol), F43 (reaction to severe stress and adjustment disorders), and F32 (depressive episode).

In the post-hoc analysis exploring the association between relevant Mental and behavioral disorders' subcategories and YOAD, IRRs were significantly increased across nearly all subcategories, most prominently F00 (Organic, including symptomatic, mental disorders) (Figure 5). In all performed analyses, adjustment generally did not impact the estimates (Tables S2-S6).

We conducted a sensitivity analysis dividing the study population by dementia syndrome severity, grouping cases with MCI/mild dementia and moderate/severe dementia, and comparing them to their respective control groups. While the magnitude of the associations differed somewhat, the overall patterns observed were generally similar to those found in the main analysis (Table S5). A sensitivity analysis stratifying YOAD patients by age and sex yielded similar results as

TABLE 1 Baseline characteristics of study population.

	Cases $n = 1745$	Controls $n = 5235$
Age at index date, mean years (SD) [range]	64.5 (5.1) [35.8–69.9]	64.5 (5.1) [35.5–69.9]
Sex, male/female, *n* (%)	726 (42%)/1019 (58%)	2178 (42%)/3057 (58%)
Dementia syndrome severity at time of diagnosis, *n* (%)		
Mild cognitive impairment	84 (5%)	–
Mild dementia	1010 (58%)	–
Moderate dementia	530 (30%)	–
Severe dementia	121 (7%)	–
Cognitive examination scores at first visit,[a] mean (SD)		
MMSE	21.0 (5.5)	–
ACE	65.2 (15.4)	–
Educational attainment at age 40, *n* (%)		
Low	1184 (68%)	3629 (69%)
Medium	374 (21%)	1118 (21%)
High	104 (6%)	268 (5%)
Unknown	83 (5%)	220 (5%)
Civil status at index date, *n* (%)		
Married	1094 (63%)	3377 (65%)
Divorced	321 (18%)	869 (17%)
Widowed	133 (8%)	349 (7%)
Never married	177 (10%)	611 (12%)
Unknown	20 (1%)	29 (1%)
Individuals with ≥1 diagnosis within each category, *n* (%)		
Certain infections	123 (7%)	365 (7%)
Neoplasms	363 (21%)	1065 (20%)
Hematological/immunological	67 (4%)	161 (3%)
Endocrine/metabolic	446 (26%)	1042 (20%)
Mental and behavioral[b]	389 (22%)	428 (8%)
Nervous system[b]	307 (18%)	647 (12%)
Eye and adnexa	258 (15%)	660 (13%)
Ear and mastoid process	188 (11%)	409 (8%)
Circulatory system	589 (34%)	1516 (29%)
Respiratory system	245 (14%)	658 (13%)
Digestive system	456 (26%)	1355 (26%)
Skin/subcutaneous system	168 (10%)	436 (8%)
Musculoskeletal system	689 (39%)	2465 (41%)
Genitourinary system	375 (21%)	1037 (20%)
Symptoms/signs not classified elsewhere	999 (57%)	1842 (35%)
Injuries, poisonings, external causes	896 (51%)	2331 (45%)
Factors influencing health status	1721 (99%)	4723 (90%)

Note: Where percentages do not add up to 100%, this is due to rounding up/down.
Abbreviation: Sd, standard deviation.
[a]MMSE, Mini-Mental State Examination (reliable information for 1590 YOAD patients); ACE, Addenbrooke's Cognitive Examination (reliable information for 1173 YOAD patients).
[b]Excluding dementia diagnosis.

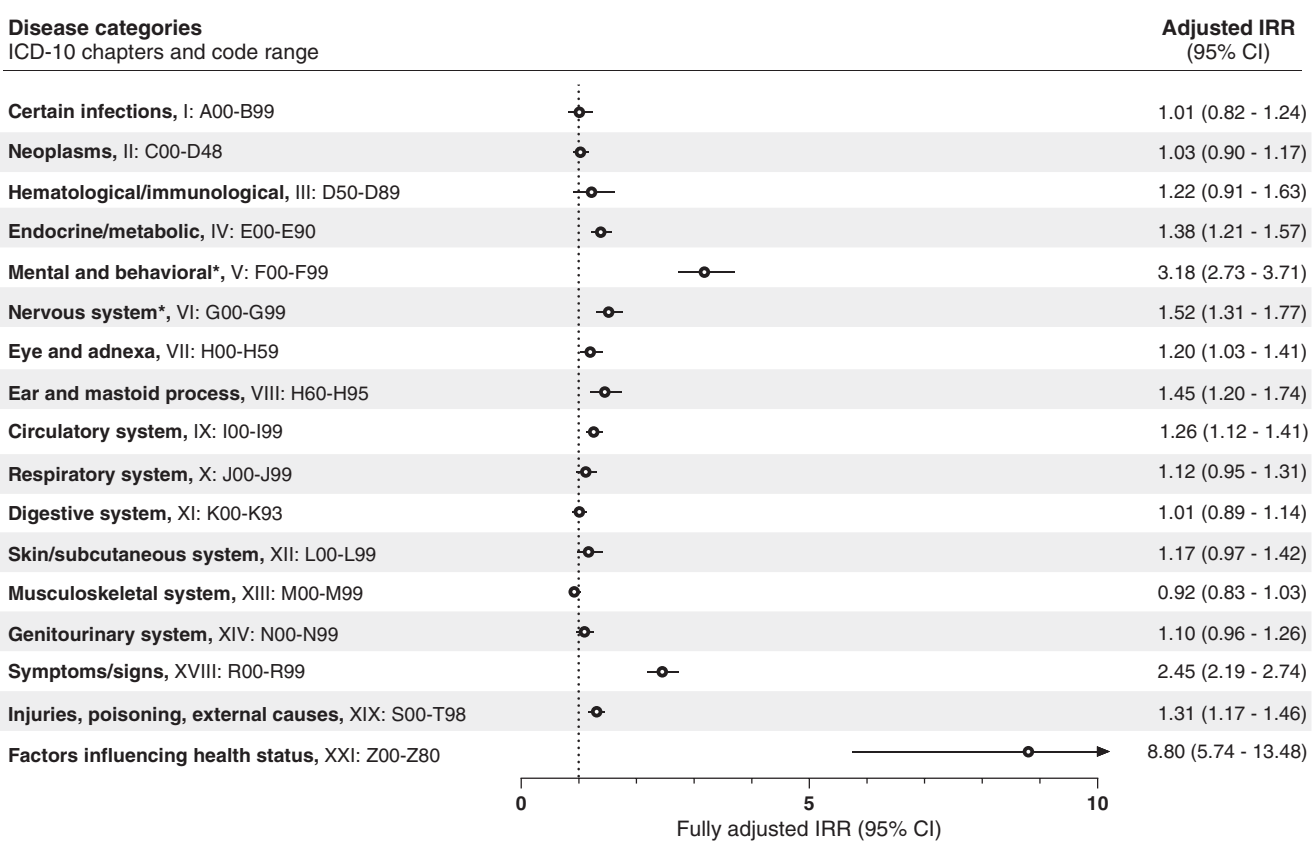

FIGURE 2 Incidence rate ratios (IRRs) for young onset Alzheimer's disease are plotted by disease categories in the 10-year retrospective study period. For the refence group (dementia-free controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals (CI). The IRRs presented are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis, whichever came first), and civil status at index date. Unadjusted estimates are presented in Table S2. * Excluding mild cognitive impairment and dementia diagnoses. ICD: International Classification of Diseases.

in the main analysis, as did removing those with MCI (results not shown).

4 | DISCUSSION

In this nested case-control study, we found that YOAD patients had a higher morbidity burden than age- and sex-matched controls, particularly in the year immediately preceding AD diagnosis, and for certain disorders up to 10 years prior. This was especially evident for psychiatric morbidity, following which the likelihood of AD diagnosis was increased by 43% if diagnosed in the 5- to 10-year interval prior to YOAD. Among the most frequent psychiatric diagnoses in the study population were stress and depression, both of which increased the likelihood of YOAD diagnosis. In an analysis of psychiatric subcategories, all of these had significantly increased IRRs, though as this was a post-hoc analysis, these results should be interpreted with caution.

In the year immediately preceding diagnosis, YOAD patients had a larger morbidity burden than the cognitively healthy controls across multiple disease categories. This aligns with findings from our previous study,[10] where we found increased healthcare utilization across all types of healthcare contacts in the year preceding YOAD diagnosis.

In examining the most frequent diagnoses among the study population, Symptoms involving cognitive functions and Other special examinations and investigations of persons without complaint had the highest IRRs for YOAD compared to controls. It is likely that these diagnostic codes were registered as part of the diagnostic evaluation leading up to referral or given at the initial memory clinic visit. In the sensitivity analysis censoring all diagnoses given 6 months before YOAD diagnosis, the disease categories containing these specific diagnostic codes were still significantly increased, perhaps signaling that diagnostic evaluation is often intricate and protracted due to the necessity for supplementary examinations. These diagnostic codes are rather unspecific though, perhaps implying that these patients have had symptoms for a long time without suspicion of dementia, supporting the need for aids in timely diagnosis.[19,20] Increased IRRs for diagnoses of injuries to the head and forearm suggests that YOAD patients may be more prone to injuries. In a large, register-based study from Sweden, Nyström et al. assessed the association between injurious falls and Parkinson's disease up to 10 years prior to diagnosis and found an odds ratio of 1.19 (95% CI 1.08–1.31) in the time interval 7 to <10 years before diagnosis,[21] which is comparable to IRRs found in the present study. Thus, injuries related to falls could potentially be an early symptom of neurodegeneration, even in younger patients.

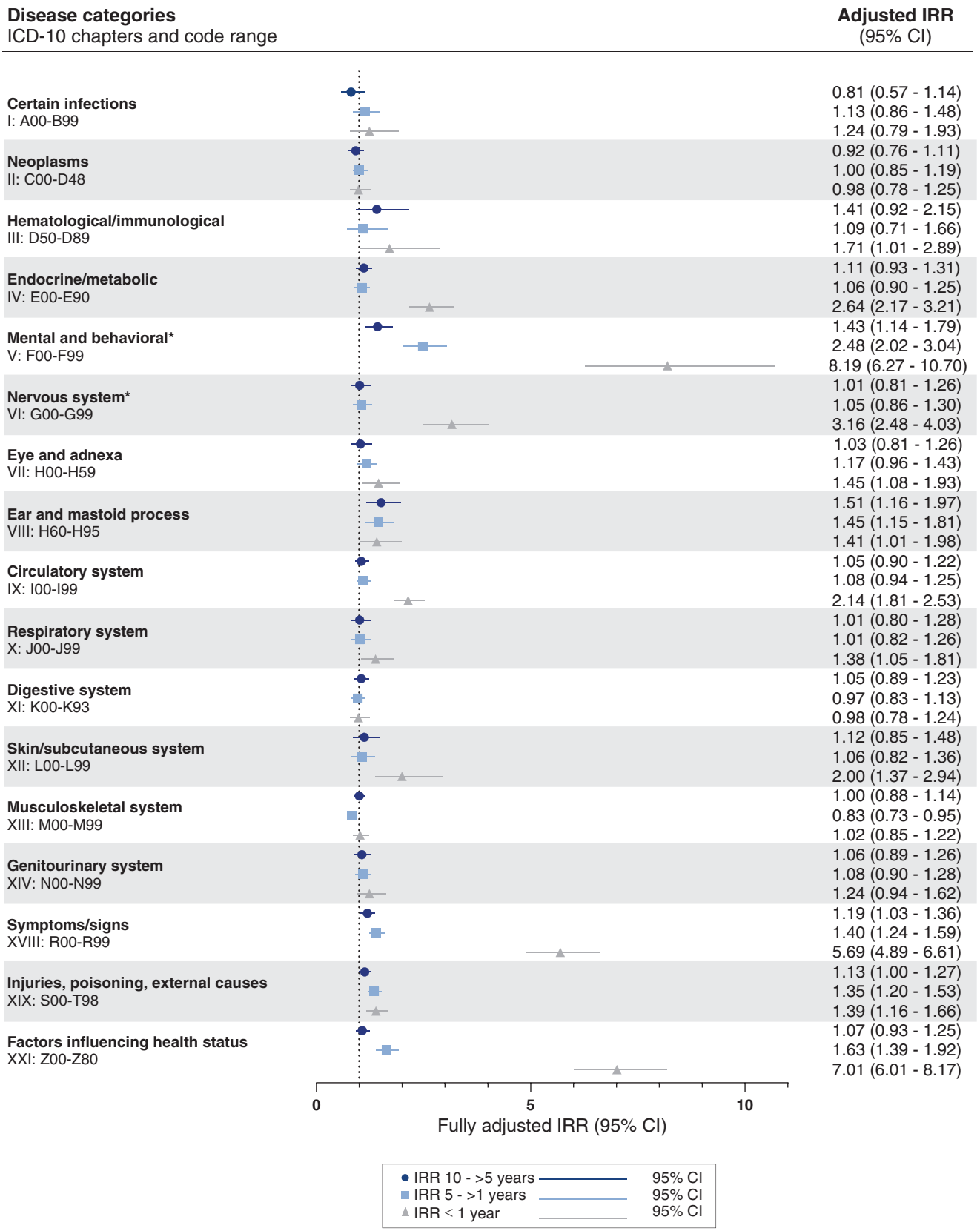

FIGURE 3 Incidence rate ratios (IRRs) for young onset Alzheimer's disease are plotted by disease categories in three time-intervals prior to diagnosis. For the refence group (dementia-free controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals (CI). The IRRs presented are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis, whichever came first), and civil status at index date. Unadjusted estimates are presented in Table S2. * Excluding mild cognitive impairment and dementia diagnoses. ICD: International Classification of Diseases.

Disease category	Most frequent diagnoses	n	Adjusted IRR (95% CI)
Certain infections	A46: Erysipelas	111	1.06 (0.69 - 1-63)
	A41: Other sepsis	95	1.00 (0.63 - 1.59)
	A49: Bacterial infection of unspecified site	58	1.45 (0.84 - 2.51)
Neoplasms	D12: Benign neoplasm of colon etc.	391	1.23 (0.98 - 1.54)
	C44: Other malignant neoplasms of skin	172	1.06 (0.74 - 1.49)
	D17: Benign lipomatous neoplasm	110	0.83 (0.53 - 1.31)
Hematological/ immunological	D64: Other anaemias	82	1.26 (0.78 - 2.03)
	D50: Iron deficiency anaemia	47	1.36 (0.73 - 2.52)
	D68: Other coagulation defects.	22	0.30 (0.07 - 1.29)
Endocrine/ metabolic	E78: Disorders of lipoprotein metabolism etc.	498	1.64 (1.35 - 1.99)
	E11: Type 2 diabetes mellitus	401	1.20 (0.96 - 1.51)
	E66: Obesity	280	0.59 (0.43 - 0.81)
Mental and behavioral	F10: Alcohol-related mental disorders	225	2.12 (1.62 - 2.79)
	F43: Reaction to severe stress	191	2.77 (2.06 - 3.70)
	F32: Depressive episode	159	3.48 (2.54 - 4.77)
Nervous system	G56: Mononeuropathies of arm	192	0.73 (0.51 - 1.05)
	G47: Sleep disorders	163	1.02 (0.71 - 1.45)
	G45: Transient cerebral ischaemic attacks	114	1.56 (1.05 - 2.31)
Eye and adnexa	H25: Senile cataract	301	1.66 (1.31 - 2.12)
	H26: Other cataract	94	1.03 (0.77 - 1.65)
	H35: Other retinal disorders	94	0.56 (0.32 - 0.97)
Ear and mastoid process	H91: Other hearing loss	362	1.51 (1.20 - 1.90)
	H93: Other disorders of ear	161	1.30 (0.92 - 1.83)
	H90: Conductive and sensorineural hearing loss	126	1.33 (0.91 - 1.95)
Circulatory system	I10: Essential hypertension	1024	1.38 (1.19 - 1.60)
	I20: Angina pectoris	309	1.26 (0.95 - 1.58)
	I25: Chronic ischaemic heart disease	298	1.11 (0.85 - 1.44)
Respiratory system	J44: Chronic obstructive pulmonary disease	249	1.06 (0.79 - 1.41)
	J18: Pneumonia, organism unspecified	243	1.07 (0.80 - 1.43)
	J45: Asthma	169	1.09 (0.77 - 1.54)
Digestive system	K57: Diverticular disease of intestine	284	1.09 (0.84 - 1.43)
	K59: Other intestinal disorders	229	1.33 (1.00 - 1.77)
	K40: Inguinal hernia	216	0.99 (0.72 - 1.37)
Skin/subcutaneous system	L02: Cutaneous abscess etc.	100	1.19 (0.77 - 1.85)
	L08: Other local infections of skin	71	1.43 (0.87 - 2.37)
	L40: Psoriasis	58	1.24 (0.70 - 2.19)
Musculoskeletal system	M17: Gonarthrosis	495	1.08 (0.88 - 1.33)
	M75: Shoulder lesions	481	0.92 (0.74 - 1.14)
	M23: Internal derangement of knee	349	0.96 (0.75 - 1.24)
Genitourinary system	N39: Other disorders of urinary system	235	1.34 (1.01 - 1.78)
	N30: Cystitis	190	1.39 (1.02 - 1.91)
	N81: Female genital prolapse	163	0.99 (0.69 - 1.42)
Symptoms/signs	R10: Abdominal and pelvic pain	576	1.03 (0.85 - 1.25)
	R41: Symptoms involving cognitive functions*	415	90.8 (52.3 - 157.9)
	R07: Pain in throat and chest	302	1.27 (0.98 - 1.64)
Injuries, poisining, external causes	S61: Open wound of wrist and hand	486	1.25 (1.02 - 1.53)
	S52: Fracture of forearm	338	1.45 (1.15 - 1.84)
	S01: Open wound of head	280	1.55 (1.20 - 1.99)
Factors influencing health status	Z01: Investigations without complaints	6039	4.65 (3.63 - 5.96)
	Z03: Observation	3338	2.59 (2.31 - 2.91)
	Z12: Screening for neoplasms	1643	0.92 (0.78 - 1.06)

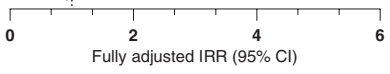

FIGURE 4 Incidence rate ratios (IRRs) for young onset Alzheimer's disease are plotted for the three most frequent diagnoses in the study population in each disease category. For the refence group (dementia-free controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals (CI). The IRRs presented are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis, whichever came first), and civil status at index date. Unadjusted estimates are presented in Table S4. * Note that for the diagnostic code R41, estimate and CI is outside the graph limits.

The current study aimed at describing pre-diagnostic symptoms of YOAD. While there is overlap between associations found in the present study and conditions previously described as risk factors for late-onset dementia (such as hearing loss, hypertension, depression, etc.),[2] our study did not aim to determine whether these conditions may also constitute a risk factor for YOAD (methods to tackle reverse causation and confounding would be needed). A large epidemiological study has suggested that patients with young onset all-cause dementia have a larger vascular comorbidity burden than those without dementia.[22] AD-specific research shows that the prevalence of vascular risk factors is not elevated in YOAD patients, were apolipoprotein E (APOE) ε4 allele, that is, genetic risk factors, were

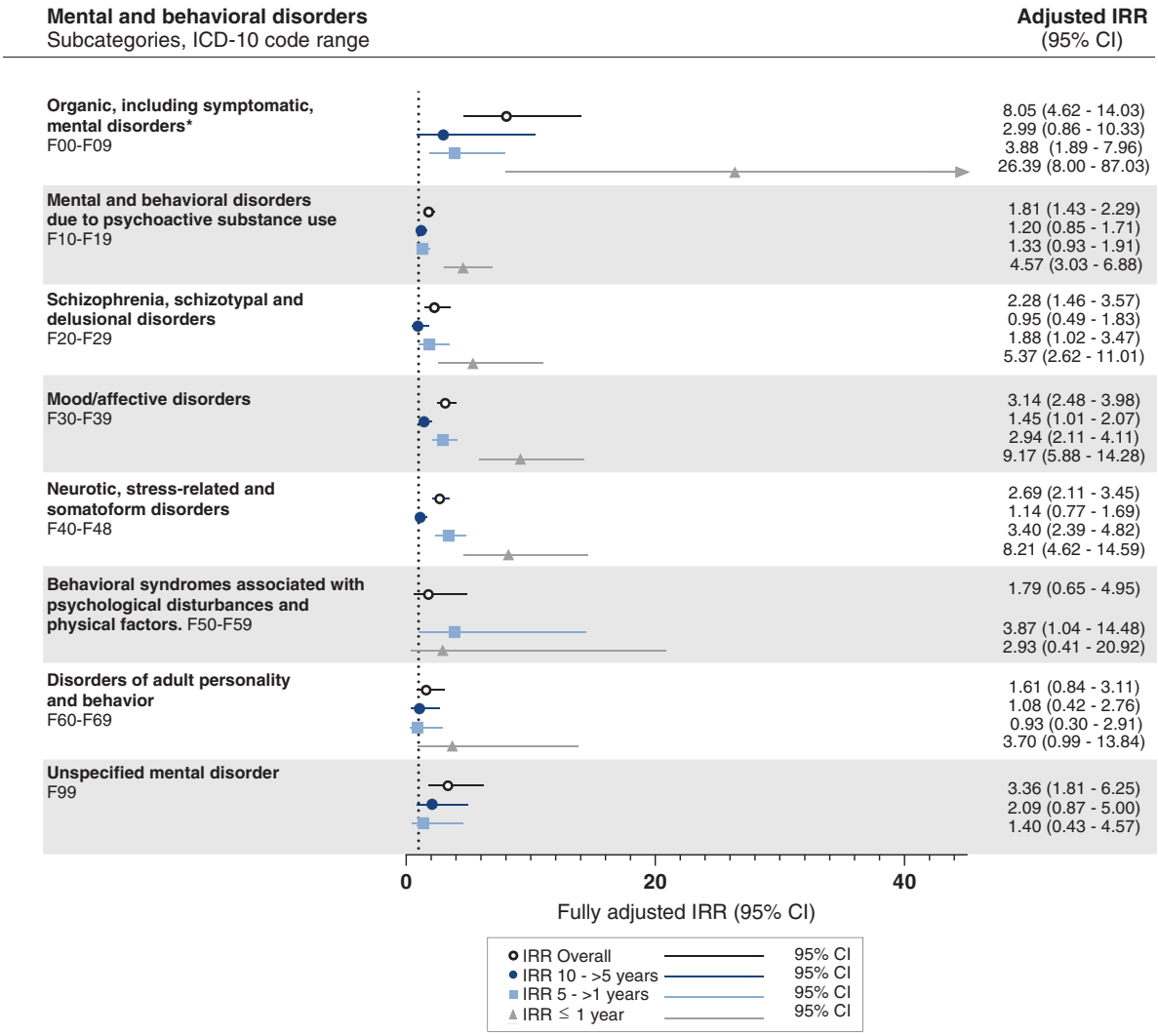

FIGURE 5 Incidence rate ratios (IRRs) for young onset Alzheimer's disease are plotted by subcategories of mental and behavioral disorders prior to diagnosis. For the refence group (dementia-free controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals (CI). The IRRs presented are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis, whichever came first), and civil status at index date. Where no estimates are presented, there were too few events to analyze. Unadjusted estimates are presented in Table S6. ICD: International Classification of Diseases. * Excluding mild cognitive impairment and dementia diagnoses.

instead more prominent.[23] Future studies may examine the specific risk profile of YOAD, where APOE status would be relevant to include.

To our knowledge, no previous studies have examined the relationship between prior morbidity and YOAD. However, one study investigating morbidity prior to young onset all-cause dementia found an increased odds ratio of dementia following anxiety, depression, diabetes, and stroke in the 2 years before dementia diagnosis.[24] Similarly, a case-control study of pre-diagnostic symptoms in young onset all-cause dementia found depression and anxiety among the most prevalent early symptoms.[7] This is consistent with our results, where associations were also found for all corresponding disease categories.

Two other studies investigated morbidity preceding LOAD; a Taiwanese study of 4600 LOAD cases and 4600 controls found that anxiety, functional digestive disorder, psychopathology-specific symptoms, disorders of the vestibular system, concussion, disorders of the urinary system, disorders of refraction and accommodation, and hearing loss were positively associated with LOAD.[25] Likewise, a study based on the Baltimore Longitudinal Study of Aging found depression, erectile dysfunction, gait abnormalities, hearing loss, and nervous and musculoskeletal symptoms positively associated with LOAD.[26] While some of these overlap with associations found in the present study (hearing loss, depression, disorders of the urinary system), others were not commonly found in our cohort (disorders of the vestibular system, disorders of refraction etc.).

Morbidity generally tends to increase with increasing age, and there is likely a difference in the morbidity pattern for those diagnosed with YOAD compared to LOAD based on age alone. Thus, morbidity in LOAD may differ considerably from morbidity in YOAD.

The association between psychiatric morbidity and dementia deserves particular attention. Prior studies have shown an association between mid- or late-life depression and subsequent dementia in LOAD, suggesting that depression that begins in late-life may be part of the AD prodrome.[1,27–30] Results from the present study suggest this to be true for YOAD as well. Prior research has demonstrated a higher prevalence of depression in YOAD compared to LOAD,[31] and it remains an area of great importance for clinicians to assess, both pre- and post-diagnosis. Several studies have also shown an association between a diagnosis of stress in midlife and risk of dementia assuming stress as a risk factor for,[5,32] or early symptom in, dementia. In the present study, the association between psychiatric diagnoses and dementia was especially convincing immediately before the diagnosis of YOAD, suggesting that stress and depression may also be important early signs of YOAD.

Our study had several limitations. Inherent in the study design is the risk of detection bias; patients with comorbidities are more likely to see a medical doctor frequently, making them more likely to be referred to a memory clinic and receive a diagnosis upon experiencing cognitive symptoms than those who do not regularly see a doctor. However, 37% of cases were diagnosed in the moderate/severe stages of dementia, suggesting that frequent doctor visits do not guarantee a timely diagnosis. While censoring of contacts related to the diagnostic process in the memory clinic was attempted, it is not possible to completely remove all such contacts if not specifically marked with a dementia diagnosis. However, a sensitivity analysis removing all contacts 6 months prior to the index date yielded comparable results to the main analysis. Furthermore, as we did not have the date of symptom onset, we had to approximate this by using age at diagnosis. Another limitation of the present study is that the registers do not contain diagnostic information on morbidity from GPs. Patients with stress and depression are often seen by a GP or referred to a psychologist; therefore, we are likely to only register the more severe cases in the present study.

A major strength of the present study is the use of nationwide healthcare registers to assess morbidity registered at hospital contacts. In Denmark, hospital services are free of charge and the Danish healthcare registers contain detailed, reliable, and complete data on all hospital contacts. Thus, there is equal access to healthcare services for all and virtually full data coverage, limiting problems with selection bias. The use of DanDem for AD case finding ensures that all cases are diagnosed by specialists in memory clinics and allows access to detailed variables beyond the Danish registers. This allowed a novel approach to establish a large case cohort with a relatively rare disease.

Epidemiological studies on signs and symptoms in the prodromal phase of Parkinson's disease have helped to understand the course of the development of symptoms, and have changed the understanding of Parkinson's disease from a motor-symptom disease to a disease of long latency, characterized by the progressive emergence of multiple non-motor-symptoms before onset of the typical motor-symptoms.[33] There is a similar potential for better understanding the disease course in YOAD, where epidemiological studies such as ours may help move toward a better understanding of the earliest disease stages. Especially the identification of psychiatric morbidity as a possible early sign of YOAD could potentially have an impact on screening instruments for early dementia, with more focus on behavioral and affective signs and symptoms along with cognitive assessment.

In conclusion, this study demonstrated a higher morbidity burden among YOAD patients than their matched controls, detectable up to as long as 10 years before dementia diagnosis. There was a substantial increase in psychiatric diagnoses, supporting prior research on stress and depression in the years leading up to diagnosis. Onset of psychiatric diseases or unspecific cognitive symptoms in midlife could potentially be an early warning sign of YOAD and may help guide GPs in which patients with cognitive complaints should be referred to a memory clinic. In our study, more than a third of all patients diagnosed with YOAD were diagnosed at an advanced stage in their disease, highlighting the need for tools to support a timely diagnosis. Future studies should further explore early symptoms and morbidity prior to a diagnosis of YOAD by exploring associations between reasons for GP contacts or use of prescription medication.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

This research project was approved by the Danish Data Protection Agency, Statistics Denmark, and the Danish Health Data Authority. Danish law does not require ethics committee approval or informed patient consent.

DATA AVAILABILITY STATEMENT

All of the data used in this study are derived from the Danish National and Public Health registries. These data are collected and stored by the relevant authorities and cannot be made public or accessed by unauthorized parties. Access to such data is given via standard rules and regulations of data access outlined by the Danish Data Protection Agency and Danish Health Data Authority.

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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 tables and figures

Mapping morbidity 10 years prior to a diagnosis of young onset Alzheimer's disease

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Contents:

Table S1. Censoring criteria

	Cases	Controls
Developmental disorders and mental retardation ICD-8: 311-315, 759.3, ICD-10: DF70-DF79, DQ90	X	X
Not living in Denmark in 10-year retrospective period	X	X
Dementia or mild cognitive impairment diagnosis ICD-8: 290.09-11, 290.18-19, 293.09-19, ICD 10: F00.0-00.9, F01.0-01.9, F02.0-F02.8, F03.9, F04.0-F04.9, F06.7 G30.0-G30.9, G31.0A, G31.0B, G31.8, G31.8E, G31.9	*	X
Dementia medication ATC code N06DA02-4, N06DX01		X
Entry in DanDem		X

* ICD-codes registered in the Danish National Patient Register are censored in the conditional logistic regression and frequency analyses. This does not impact case selection.
ICD: International classification of diseases, ATC: Anatomical therapeutic chemical code, DanDem: Danish Quality Database for Dementia

Table S2. Incidence rate ratios by disease category overall and in three time-intervals

ICD-10 code range and chapters	Time-period	Unadjusted		Adjusted	
		IRR	95% CI	IRR	95% CI
A00-B99 I	**Overall**	**1.01**	**0.82-1.25**	**1.01**	**0.82-1.24**
Certain infections	10->5 years prior to index date	0.80	0.56-1.27	0.81	0.57-1.14
	5->1 years prior to index date	1.13	0.86-1.49	1.13	0.86-1.48
	≤1 year prior to index date	1.29	0.83-2.01	1.24	0.79-1.93
C00-D48 II	**Overall**	**1.03**	**0.90-1.18**	**1.03**	**0.90-1.17**
Neoplasms	10->5 years prior to index date	0.92	0.76-1.11	0.92	0.76-1.11
	5->1 years prior to index date	1.01	0.85-1.19	1.00	0.85-1.19
	≤1 year prior to index date	1.00	0.79-1.26	0.98	0.78-1.25
D50-D89 III	**Overall**	**1.26**	**0.94-1.68**	**1.22**	**0.91-1.63**
Hematological/immunological diseases	10->5 years prior to index date	1.42	0.93-2.17	1.41	0.92-2.15
	5->1 years prior to index date	1.14	0.75-1.74	1.09	0.71-1.66
	≤1 year prior to index date	1.74	1.03-2.94	1.71	1.01-2.89
E00-E90 IV	**Overall**	**1.38**	**3.22-1.57**	**1.38**	**1.21-1.57**
Endocrine/metabolic diseases	10->5 years prior to index date	1.11	0.94-1.31	1.11	0.93-1.31
	5->1 years prior to index date	1.07	0.91-1.26	1.06	0.90-1.25
	≤1 year prior to index date	2.66	2.19-3.24	2.64	2.17-3.21
F00-F99 V	**Overall**	**3.14**	**2.70-3.65**	**3.18**	**2.73-3.71**
Mental and behavioral disorders*	10->5 years prior to index date	1.45	1.16-1.81	1.43	1.14-1.79
	5->1 years prior to index date	2.52	2.06-3.08	2.48	2.02-3.04
	≤1 year prior to index date	8.07	6.19-10.52	8.19	6.27-10.70
G00-G99 VI	**Overall**	**1.52**	**1.31-1.76**	**1.52**	**1.31-1.77**
Diseases of the nervous system*	10->5 years prior to index date	1.00	0.80-1.24	1.01	0.81-1.26
	5->1 years prior to index date	1.06	0.86-1.30	1.05	0.86-1.30
	≤1 year prior to index date	3.16	2.48-4.02	3.16	2.48-4.03
H00-H59 VII	**Overall**	**1.20**	**1.03-1.41**	**1.20**	**1.03-1.41**
Diseases of the eye and adnexa	10->5 years prior to index date	1.02	0.81-1.29	1.03	0.81-1.30
	5->1 years prior to index date	1.17	0.96-1.43	1.17	0.96-1.43
	≤1 year prior to index date	1.47	1.10-1.96	1.45	1.08-1.93
H60-H95 VIII	**Overall**	**1.44**	**1.20-1.73**	**1.45**	**1.20-1.74**
Diseases of the ear and mastoid process	10->5 years prior to index date	1.51	1.16-1.97	1.51	1.16-1.97
	5->1 years prior to index date	1.43	1.14-1.80	1.45	1.15-1.81
	≤1 year prior to index date	1.40	1.00-1.96	1.41	1.01-1.98
I00-I99 IX	**Overall**	**1.25**	**1.12-1.41**	**1.26**	**1.12-1.41**
Diseases of the circulatory system	10->5 years prior to index date	1.05	0.90-1.22	1.05	0.90-1.22
	5->1 years prior to index date	1.08	0.94-1.25	1.08	0.94-1.25
	≤1 year prior to index date	2.14	1.81-2.53	2.14	1.81-2.53

ICD-10 code range and chapters	Time-period	Unadjusted		Adjusted	
		IRR	95% CI	IRR	95% CI
J00-J99 X	**Overall**	**1.14**	**0.97-1.34**	**1.12**	**0.95-1.31**
Diseases of the respiratory system	10->5 years prior to index date	1.02	0.81-1.29	1.01	0.80-1.28
	5->1 years prior to index date	1.05	0.85-1.30	1.01	0.82-1.26
	≤1 year prior to index date	1.42	1.09-1.87	1.38	1.05-1.81
K00-K93 XI	**Overall**	**1.01**	**0.90-1.15**	**1.01**	**0.89-1.14**
Diseases of the digestive system	10->5 years prior to index date	1.05	0.89-1.21	1.05	0.89-1.23
	5->1 years prior to index date	0.97	0.83-1.13	0.97	0.83-1.13
	≤1 year prior to index date	0.99	0.79-1.26	0.98	0.78-1.24
L00-L99 XII	**Overall**	**1.17**	**0.97-1.42**	**1.17**	**0.97-1.42**
Diseases of the skin/subcutaneous system	10->5 years prior to index date	1.12	0.85-1.47	1.12	0.85-1.48
	5->1 years prior to index date	1.06	0.82-1.37	1.06	0.82-1.36
	≤1 year prior to index date	2.00	1.37-2.93	2.00	1.37-2.94
M00-M99 XIII	**Overall**	**0.92**	**0.83-1.03**	**0.92**	**0.83-1.03**
Diseases of the musculoskeletal system	10->5 years prior to index date	1.00	0.88-1.34	1.00	0.88-1.14
	5->1 years prior to index date	0.83	0.73-0.95	0.83	0.73-0.95
	≤1 year prior to index date	1.02	0.85-1.22	1.02	0.85-1.22
N00-N99 XIV	**Overall**	**1.11**	**0.97-1.27**	**1.10**	**0.96-1.26**
Diseases of the genitourinary system	10->5 years prior to index date	1.06	0.89-1.27	1.06	0.89-1.26
	5->1 years prior to index date	1.08	0.91-1.29	1.08	0.90-1.28
	≤1 year prior to index date	1.26	0.96-1.65	1.24	0.94-1.62
R00-R99 XVIII	**Overall**	**2.46**	**2.20-2.76**	**2.45**	**2.19-2.74**
Symptoms/signs not classified elsewhere	10->5 years prior to index date	1.19	1.04-1.37	1.19	1.03-1.36
	5->1 years prior to index date	1.41	1.25-1-59	1.40	1.24-1.59
	≤1 year prior to index date	5.73	4.93-6.66	5.69	4.89-6.61
S00-T98 XIX	**Overall**	**1.32**	**1.81-1.47**	**1.31**	**1.17-1.46**
Injuries, poisoning, and other external causes	10->5 years prior to index date	1.14	1.01-1.28	1.13	1.00-1.27
	5->1 years prior to index date	1.36	1.21-1.54	1.35	1.20-1.53
	≤1 year prior to index date	1.40	1.17-1.67	1.39	1.16-1.66
Z00-Z80 XXI	**Overall**	**8.50**	**5.56-12.99**	**8.80**	**5.74-13.48**
Factors influencing health status etc.	10->5 years prior to index date	1.07	0.93-1.24	1.07	0.93-1.25
	5->1 years prior to index date	1.61	3.37-1.90	1.63	1.39-1.92
	≤1 year prior to index date	6.90	5.92-8.04	7.01	6.01-8.17

Incidence rate ratios (IRRs) for young onset Alzheimer's disease are presented overall and in 3 time-intervals prior to diagnosis with 95% confidence intervals (CI). The adjusted IRRs are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis if age at diagnosis <40 years), and civil status at index date. ICD: International classification of diseases

* Excluding mild cognitive impairment and dementia diagnoses

Table S3. Sensitivity analysis censoring contacts 6 months before index date - Incidence rate ratios by disease category overall and in three time-intervals

ICD-10 code range and chapters	Time-period	Unadjusted		Adjusted	
		IRR	95% CI	IRR	95% CI
A00-B99 I	**Overall**	0.99	0.79-1.23	0.98	0.79-1.22
Certain infections	10->5 years prior to index date	0.80	0.56-1.13	0.81	0.57-1.14
	5->1 years prior to index date	1.13	0.86-1.49	1.13	0.86-1.48
	≤1 year-6 months prior to index date	1.09	0.53-2.11	1.04	0.54-2.02
C00-D48 II	**Overall**	1.03	0.90-1.18	1.03	0.90-1.18
Neoplasms	10->5 years prior to index date	0.92	0.76-1.11	0.92	0.76-1.11
	5->1 years prior to index date	1.00	0.85-1.19	1.00	0.85-1.19
	≤1 year-6 months prior to index date	1.04	0.77-1.41	1.03	0.76-1.40
D50-D89 III	**Overall**	1.21	0.89-1.65	1.17	0.86-1.60
Hematological/immunological	10->5 years prior to index date	1.42	0.93-2.17	1.41	0.92-2.15
diseases	5->1 years prior to index date	1.14	0.75-1.74	1.09	0.71-1.66
	≤1 year-6 months prior to index date	1.83	0.87-3.88	1.84	0.87-3.90
E00-E90 IV	**Overall**	1.18	1.04-1.35	1.18	1.03-1.35
Endocrine/metabolic diseases	10->5 years prior to index date	1.11	0.94-1.31	1.11	0.93-1.31
	5->1 years prior to index date	1.07	0.91-1.26	1.06	0.90-1.25
	≤1 year-6 months prior to index date	1.81	1.38-2.38	1.79	1.36-2.35
F00-F99 V	**Overall**	2.47	2.11-2.90	2.48	2.11-2.91
Mental and behavioral disorders*	10->5 years prior to index date	1.45	1.16-1.81	1.43	1.14-1.79
	5->1 years prior to index date	2.52	2.06-3.08	2.48	2.02-3.04
	≤1 year-6 months prior to index date	5.10	3.59-7.26	5.14	3.60-7.32
G00-G99 VI	**Overall**	1.19	1.01-1.40	1.19	1.02-1.40
Diseases of the nervous system*	10->5 years prior to index date	1.00	0.80-1.24	1.01	0.81-1.26
	5->1 years prior to index date	1.06	0.86-1.30	1.05	0.86-1.30
	≤1 year-6 months prior to index date	2.12	1.49-3.01	2.13	1.50-3.03
H00-H59 VII	**Overall**	1.13	0.96-1.33	1.13	0.96-1.33
Diseases of the eye and adnexa	10->5 years prior to index date	1.02	0.81-1.29	1.03	0.81-1.30
	5->1 years prior to index date	1.17	0.96-1.43	1.17	0.96-1.43
	≤1 year-6 months prior to index date	0.79	0.51-1.24	0.79	0.50-1.24
H60-H95 VIII	**Overall**	1.39	1.15-1-68	1.40	1.16-1.69
Diseases of the ear and mastoid	10->5 years prior to index date	1.51	1.16-1.97	1.51	1.16-1.97
process	5->1 years prior to index date	1.43	1.14-1.80	1.45	1.15-1.81
	≤1 year-6 months prior to index date	0.86	0.52-1.44	0.89	0.54-1.49
I00-I99 IX	**Overall**	1.10	0.97-1.24	1.10	0.97-1.24
Diseases of the circulatory system	10->5 years prior to index date	1.05	0.90-1.22	1.05	0.90-1.22
	5->1 years prior to index date	1.08	0.94-1.25	1.08	0.94-1.25
	≤1 year-6 months prior to index date	1.63	1.29-2.06	1.63	1.29-2.06

ICD-10 code range and chapters	Time-period	Unadjusted		Adjusted	
		IRR	95% CI	IRR	95% CI
J00-J99 X	**Overall**	1.13	0.96-1.33	1.11	0.94-1.31
Diseases of the respiratory system	10->5 years prior to index date	1.02	0.81-1.29	1.01	0.80-1.28
	5->1 years prior to index date	1.05	0.85-1.30	1.01	0.82-1.26
	≤1 year-6 months prior to index date	1.37	0.95-1.97	1.33	0.92-1.91
K00-K93 XI	**Overall**	1.03	0.91-1-17	1.03	0.90-1.16
Diseases of the digestive system	10->5 years prior to index date	1.05	0.90-1.23	1.05	0.89-1.23
	5->1 years prior to index date	0.97	0.83-1.13	0.97	0.83-1.13
	≤1 year-6 months prior to index date	1.03	0.76-1.40	1.01	0.74-1.38
L00-L99 XII	**Overall**	1.11	0.92-1.35	1.12	0.92-1.36
Diseases of the skin/subcutaneous system	10->5 years prior to index date	1.12	0.85-1.47	1.12	0.85-1.48
	5->1 years prior to index date	1.06	0.82-1.37	1.06	0.82-1.36
	≤1 year-6 months prior to index date	2.46	1.48-4.08	2.49	1.50-4.15
M00-M99 XIII	**Overall**	0.90	0.80-1.00	0.90	0.80-1.00
Diseases of the musculoskeletal system	10->5 years prior to index date	1.00	0.88-1.14	1.00	0.88-1.14
	5->1 years prior to index date	0.83	0.73-0.95	0.83	0.73-0.95
	≤1 year-6 months prior to index date	0.94	0.73-1.20	0.94	0.73-1.20
N00-N99 XIV	**Overall**	1.10	0.96-1.26	1.09	0.95-1.25
Diseases of the genitourinary system	10->5 years prior to index date	1.06	0.89-1.27	1.06	0.89-1.26
	5->1 years prior to index date	1.08	0.91-1.29	1.08	0.90-1.28
	≤1 year-6 months prior to index date	1.37	0.96-1.96	1.32	0.92-1.89
R00-R99 XVIII	**Overall**	1.50	1.35-1.68	1.49	1.34-1.67
Symptoms/signs not classified elsewhere	10->5 years prior to index date	1.19	1.04-1.37	1.19	1.03-1.36
	5->1 years prior to index date	1.41	1.25-1.59	1.40	1.24-1.59
	≤1 year-6 months prior to index date	2.15	1.75-2.64	2.13	1.73-2.62
S00-T98 XIX	**Overall**	1.31	1.17-1.46	1.30	1.16-1.45
Injuries, poisoning, and other external causes	10->5 years prior to index date	1.14	1.01-1.28	1.13	1.00-1.27
	5->1 years prior to index date	1.36	1.21-1.54	1.35	1.20-1.53
	≤1 year-6 months prior to index date	1.29	1.01-1.65	1.29	1.01-1.66
Z00-Z80 XXI	**Overall**	1.95	1.56-2.44	1.99	1.59-2.49
Factors influencing health status etc	10->5 years prior to index date	1.07	0.93-1.24	1.07	0.93-1.25
	5->1 years prior to index date	1.61	1.37-1.90	1.63	1.39-1.92
	≤1 year-6 months prior to index date	2.16	1.92-2.42	2.17	1.93-2.43

Incidence rate ratios (IRRs) for young onset Alzheimer's disease cases are presented overall and in 3 time-intervals prior to diagnosis with 95% confidence intervals (CI) after censoring all contacts in the 6 months prior to index date. The adjusted IRRs are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis if age at diagnosis <40 years), and civil status at index date. ICD: International classification of diseases

* Excluding mild cognitive impairment and dementia diagnoses

Table S4. Most frequent diagnoses within each disease category and corresponding incidence rate ratios

ICD-10 code range and chapters	Most frequent diagnoses	n	Unadjusted		Adjusted	
			IRR	95% CI	IRR	95% CI
A00-B99 I						
Certain infections	A46: Erysipelas	111	1.06	0.69-1.63	1.06	0.69-1.63
	A41: Other sepsis	95	1.01	0.64-1.61	1.00	0.63-1.59
	A49: Bacterial infection of unspecified site	58	1.46	0.85-2.53	1.45	0.84-2.51
C00-D48 II						
Neoplasms	D12: Benign neoplasm of colon etc.	391	1.22	0.98-1.53	1.23	0.98-1.54
	C50: Malignant neoplasm of breast	172	1.07	0.75-1.51	1.06	0.74-1.49
	D17: Benign lipomatous neoplasm	110	0.83	0.52-1.30	0.83	0.53-1.31
D50-D89 III						
Hematological/immunological diseases	D64: Other anaemias	82	1.32	0.82-2.12	1.26	0.78-2.03
	D50: Iron deficiency anaemia	47	1.41	0.76-2.60	1.36	0.73-2.52
	D68: Other coagulation defects	22	0.30	0.07-1.28	0.30	0.07-1.29
E00-E90 IV						
Endocrine/metabolic diseases	E78: Disorders of lipoprotein metabolism etc.	498	1.63	1.34-1.97	1.64	1.35-1.99
	E11: Type 2 diabetes mellitus	401	1.20	0.96-1.50	1.20	0.96-1.51
	E66: Obesity	280	0.59	0.43-0.81	0.59	0.43-0.81
F00-F99 V						
Mental and behavioral disorders*	F10: Alcohol-related mental disorders	225	2.12	1.62-2.79	2.12	1.62-2.79
	F43: Reaction to severe stress	191	2.82	2.11-3.78	2.77	2.06-3.70
	F32: Depressive episode	159	3.57	2.60-4.89	3.48	2.54-4.77
G00-G99 VI						
Diseases of the nervous system*	G56: Mononeuropathies of arm	192	0.73	0.51-1.04	0.73	0.51-1.05
	G47: Sleep disorders	163	1.01	0.71-1.44	1.02	0.71-1.45
	G45: Transient cerebral ischaemic attacks	114	1.51	1.02-2.23	1.56	1.05-2.31
H00-H59 VII						
Diseases of the eye and adnexa	H25: Senile cataract	301	1.67	1.31-2.12	1.66	1.31-2.12
	H26: Other cataract	94	1.03	0.64-1.65	1.03	0.77-1.65
	H35: Other retinal disorders	94	0.56	0.32-0.98	0.56	0.32-0.97
H60-H95 VIII						
Diseases of the ear and mastoid process	H91: Other hearing loss	362	1.50	1.19-1.88	1.51	1.20-1.90
	H93: Other disorders of ear	161	1.28	0.91-1.80	1.30	0.92-1.83
	H90: Conductive and sensorineural hearing loss	126	1.34	0.91-1.96	1.33	0.91-1.95
I00-I99 IX						
Diseases of the circulatory system	I10: Essential hypertension	1024	1.39	1.20-1.60	1.38	1.19-1.60
	I20: Angina pectoris	309	1.22	0.95-1.57	1.23	0.95-1.58
	I25: Chronic ischaemic heart disease	298	1.11	0.85-1.44	1.11	0.85-1.44

ICD-10 code range and chapters	Most frequent diagnoses	n	Unadjusted		Adjusted	
			IRR	95% CI	IRR	95% CI
J00-J99 X						
Diseases of the respiratory system	J44: Chronic obstructive pulmonary disease	249	1.09	0.82-1.45	1.06	0.79-1.41
	J18: Pneumonia, organism unspecified	243	1.01	0.82-1.48	1.07	0.80-1.43
	J45: Asthma	169	1.09	0.77-1.54	1.09	0.77-1.54
K00-K93 XI						
Diseases of the digestive system	K57: Diverticular disease of intestine	284	1.09	0.83-1.42	1.09	0.84-1.43
	K59: Other intestinal disorders	229	1.34	1.00-1.78	1.33	1.00-1.77
	K40: Inguinal hernia	216	0.99	0.72-1.37	0.99	0.72-1.37
L00-L99 XII						
Diseases of the skin/subcutaneous system	L02: Cutaneous abscess etc.	100	1.17	0.75-1.82	1.19	0.77-1.85
	L08: Other local infections of skin	71	1.45	0.88-2.40	1.43	0.87-2.37
	L40: Psoriasis	58	1.24	0.71-2.19	1.24	0.70-2.19
M00-M99 XIII						
Diseases of the musculoskeletal system	M17: Gonarthrosis	495	1.08	0.88-1.33	1.08	0.88-1.33
	M75: Shoulder lesions	481	0.91	0.74-1.14	0.92	0.74-1.14
	M23: Internal derangement of knee	349	0.96	0.75-1.23	0.96	0.75-1.24
N00-N99 XIV						
Diseases of the genitourinary system	N39: Other disorders of urinary system	235	1.36	1.03-1.80	1.34	1.01-1.78
	N30: Cystitis	190	1.41	1.03-1.92	1.39	1.02-1.91
	N81: Female genital prolapse	163	1.00	0.70-1.43	0.99	0.69-1.42
R00-R99 XVIII						
Symptoms/signs not classified elsewhere	R10: Abdominal and pelvic pain	576	1.04	0.85-1.26	1.03	0.85-1.25
	R41: Symptoms involving cognitive functions	415	90.86	52.29-157.86	90.84	52.27-157.87
	R07: Pain in throat and chest	302	1.27	0.99-1.64	1.27	0.98-1.64
S00-T98 XIX						
Injuries, poisoning, and other external causes	S61: Open wound of wrist and hand	486	1.25	1.02-1.54	1.25	1.02-1.53
	S52: Fracture of forearm	338	1.47	1.16-1.86	1.45	1.15-1.84
	S01: Open wound of head	280	1.56	1.21-2.01	1.55	1.20-1.99
Z00-Z80 XXI						
Factors influencing health status etc	Z01: Investigations without complaints	6039	4.53	3.54-5.79	4.65	3.63-5.96
	Z03: Observation	3338	2.60	2.32-2.91	2.59	2.31-2.91
	Z12: Screening for neoplasms	1643	0.91	0.78-1-06	0.92	0.78-1.06

Incidence rate ratios (IRRs) for young onset Alzheimer's disease for the three most frequent diagnoses in the study population in each disease category with 95% confidence intervals (CI). The adjusted IRRs are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis if age at diagnosis <40 years), and civil status at index date. ICD: International classification of diseases

* Excluding mild cognitive impairment and dementia diagnoses

Table S5. Sensitivity analysis by dementia syndrome severity at time of diagnosis - Incidence rate ratios by disease category overall and in three time-intervals

ICD-10 code range and chapters		Time-period	MCI/MILD DEMENTIA				MODERATE/SEVERE DEMENTIA			
			Unadjusted		Adjusted		Unadjusted		Adjusted	
			IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
A00-B99	**I**	**Overall**	**0.95**	**0.72-1.24**	**0.97**	**0.74-1.27**	**1.13**	**0.91-1.56**	**1.07**	**0.76-1.51**
		10->5 years prior to index date	0.93	0.61-1.40	0.96	0.64-1.45	0.58	0.30-1.10	0.59	0.31-1.13
		5->1 years prior to index date	0.97	0.68-1.38	0.98	0.68-1.41	1.43	0.94-2.19	1.37	0.89-2.10
		≤1 year prior to index date	0.79	0.41-1.53	0.84	0.43-1.63	2.22	1.19-4.15	1.89	1.00-3.60
C00-D48	**II**	**Overall**	**1.01**	**0.85-1.19**	**1.00**	**0.84-1.19**	**1.07**	**0.86-1.32**	**1.09**	**0.88-1.35**
Neoplasms		10->5 years prior to index date	0.93	0.74-1.18	0.94	0.74-1.19	0.89	0.66-1.20	0.92	0.68-1.25
		5->1 years prior to index date	0.94	0.75-1.67	0.94	0.75-1.67	1.12	0.86-1.47	1.14	0.87-1.49
		≤1 year prior to index date	0.87	0.63-1.19	0.88	0.64-1.20	1.21	0.85-1.72	1.20	0.84-1.72
D50-D89	**III**	**Overall**	**0.97**	**0.65-1.44**	**1.00**	**0.67-1.50**	**1.78**	**1.15-2.75**	**1.63**	**1.05-2.53**
Hematological/immunological diseases		10->5 years prior to index date	1.10	0.60-2.00	1.10	0.61-2.01	1.89	1.03-3.47	1.82	0.98-3.37
		5->1 years prior to index date	0.94	0.54-1.65	0.98	0.55-1.72	1.51	0.79-2.89	1.36	0.70-2.64
		≤1 year prior to index date	1.13	0.52-2.42	1.18	0.55-2.54	2.79	1.31-5.93	2.65	1.24-5.69
E00-E90	**IV**	**Overall**	**1.27**	**1.08-1.50**	**1.31**	**1.11-1.54**	**1.58**	**1.29-1.94**	**1.51**	**1.22-1.86**
Endocrine/metabolic diseases		10->5 years prior to index date	1.04	0.84-1.29	1.07	0.86-1.32	1.23	0.93-1.61	1.19	0.90-1.57
		5->1 years prior to index date	0.97	0.79-1.20	1.00	0.81-1.23	1.24	0.96-1.60	1.18	0.91-1.53
		≤1 year prior to index date	2.61	2.03-3.35	2.68	2.08-3.45	2.74	2.00-3.75	2.55	1.85-3.51
F00-F99	**V**	**Overall**	**2.39**	**1.97-2.91**	**2.56**	**2.10-3.12**	**4.78**	**3.73-6.11**	**4.47**	**3.48-5.75**
Mental and behavioral disorders*		10->5 years prior to index date	1.16	0.86-1.56	1.20	0.89-1.63	1.98	1.42-2.77	1.81	1.28-2.55
		5->1 years prior to index date	1.87	1.44-2.45	2.01	1.53-2.63	3.82	2.78-5.24	3.41	2.47-4.71
		≤1 year prior to index date	6.08	4.39-8.42	6.43	4.63-8.94	13.20	8.23-21.19	15.56	7.77-20.33
G00-G99	**VI**	**Overall**	**1.35**	**1.12-1.63**	**1.38**	**1.14-1.67**	**1.85**	**1.45-2.35**	**1.85**	**1.45-2.36**
		10->5 years prior to index date	0.83	0.62-1.10	0.84	0.63-1.12	1.39	0.97-1.98	1.42	0.99-2.04
		5->1 years prior to index date	0.91	0.69-1.19	0.93	0.71-1.22	1.33	0.97-1.83	1.33	0.96-1.84
		≤1 year prior to index date	3.06	2.26-4.16	3.10	2.28-4.21	3.32	2.24-4.91	3.33	2.23-4.96
H00-H59	**VII**	**Overall**	**1.18**	**0.97-1.43**	**1.18**	**0.97-1.44**	**1.25**	**0.97-1.62**	**1.25**	**0.97-1.56**
Diseases of the eye and adnexa		10->5 years prior to index date	1.01	0.76-1.35	1.02	0.76-1.36	1.04	0.70-1.54	1.02	0.69-1.52
		5->1 years prior to index date	1.15	0.90-1.48	1.16	0.90-1.49	1.20	0.85-1.70	1.24	0.87-1.76
		≤1 year prior to index date	1.25	0.86-1.82	1.25	0.86-1.83	1.88	1.20-2.96	1.82	1.15-2.89
H60-H95	**VIII**	**Overall**	**1.47**	**1.67-1.85**	**1.47**	**1.17-1-86**	**1.38**	**1.02-1.88**	**1.42**	**1.04-1.94**
Diseases of the ear and mastoid process		10->5 years prior to index date	1.50	1.08-2.10	1.48	1.06-2.08	1.53	1.00-2.33	1.49	0.97-2.29
		5->1 years prior to index date	1.47	1.12-1.95	1.48	1.12-1.96	1.35	0.92-2.00	1.40	0.94-2.08
		≤1 year prior to index date	1.58	1.04-2.40	1.55	1.02-2.36	1.12	0.63-2.00	1.17	0.65-2.12
I00-I99	**IX**	**Overall**	**1.24**	**1.07-1.43**	**1.26**	**1.09-1.46**	**1.28**	**1.06-1.56**	**1.28**	**1.05-1.55**
Diseases of the circulatory system		10->5 years prior to index date	1.00	0.82-1.21	1.00	0.83-1.22	1.14	0.90-1.45	1.13	0.88-1.44
		5->1 years prior to index date	1.07	0.90-1.28	1.09	0.91-1.30	1.10	0.87-1.38	1.10	0.87-1.39
		≤1 year prior to index date	2.05	1.66-2.54	2.06	1.67-2.55	2.30	1.75-3.02	2.28	1.73-3.01

ICD-10 code range and chapters	Time-period	MCI/MILD DEMENTIA				MODERATE/SEVERE DEMENTIA			
		Unadjusted		Adjusted		Unadjusted		Adjusted	
		IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
J00-J99 X	**Overall**	**1.12**	**0.91-1.36**	**1.14**	**0.93-1.39**	**1.18**	**0.91-1.53**	**1.12**	**0.86-1.46**
Diseases of the respiratory system	10->5 years prior to index date	0.92	0.68-1.23	0.93	0.69-1.25	1.23	0.85-1.77	1.20	0.83-1.74
	5->1 years prior to index date	1.02	0.78-1.34	1.04	0.80-1.37	1.09	0.77-1.53	1.01	0.71-1.42
	≤1 year prior to index date	1.53	1.10-2.13	1.56	1.12-2.17	1.25	0.78-1.98	1.13	0.70-1.82
K00-K93 XI	**Overall**	**0.91**	**0.78-1.07**	**0.92**	**0.78-1.08**	**1.19**	**0.98-1.46**	**1.18**	**0.96-1.44**
Diseases of the digestive system	10->5 years prior to index date	1.04	0.84-1.27	1.05	0.85-1.29	1.06	0.81-1.39	1.03	0.78-1.35
	5->1 years prior to index date	0.86	0.71-1.05	0.87	0.71-1.05	1.17	0.92-1.50	1.16	0.91-1.49
	≤1 year prior to index date	0.67	0.47-0.94	0.67	0.48-0.95	1.55	1.11-2.16	1.51	1.08-2.11
L00-L99 XII	**Overall**	**1.07**	**0.84-1.36**	**1.08**	**0.85-1.37**	**1.37**	**1.01-1.85**	**1.32**	**0.97-1.79**
Diseases of the skin/subcutaneous system	10->5 years prior to index date	1.10	0.78-1.56	1.10	0.78-1.56	1.15	0.73-1.80	1.10	0.70-1.74
	5->1 years prior to index date	0.96	0.70-1.33	0.96	0.70-1.33	1.26	0.83-1.92	1.24	0.81-1.90
	≤1 year prior to index date	1.26	0.72-2.18	1.27	0.73-2.20	3.39	1.94-5.94	3.21	1.82-5.67
M00-M99 XIII	**Overall**	**1.02**	**0.88-1.17**	**1.02**	**0.88-1.17**	**0.79**	**0.65-0.95**	**0.79**	**0.66-0.96**
Diseases of the musculoskeletal system	10->5 years prior to index date	1.08	0.92-1.26	1.09	0.93-1.28	0.89	0.72-1.10	0.88	0.71-1.09
	5->1 years prior to index date	0.90	0.77-1.06	0.91	0.77-1.07	0.73	0.59-0.90	0.73	0.59-0.91
	≤1 year prior to index date	1.10	0.88-1.38	1..11	0.88-1.40	0.90	0.67-1.22	0.92	0.68-1.24
N00-N99 XIV	**Overall**	**1.18**	**1.00-1.39**	**1.19**	**1.01-1.41**	**1.00**	**0.80-1.25**	**1.00**	**0.80-1.25**
Diseases of the genitourinary system	10->5 years prior to index date	1.09	0.88-1.36	1.09	0.87-1.36	1.01	0.76-1.36	1.02	0.76-1.37
	5->1 years prior to index date	1.19	0.96-1.48	1.22	0.98-1.51	0.91	0.67-1.22	0.88	0.65-1.19
	≤1 year prior to index date	1.11	0.77-1.61	1.16	0.80-1.68	1.47	0.99-2.18	1.44	0.97-2.15
R00-R99 XVIII	**Overall**	**2.31**	**2.01-2.66**	**2.32**	**2.01-2.67**	**2.76**	**2.29-3.23**	**2.73**	**2.26-3.30**
Symptoms/signs not classified elsewhere	10->5 years prior to index date	1.14	0.96-1.36	1.15	0.96-1.37	1.28	1.02-1.61	1.26	1.00-1.58
	5->1 years prior to index date	1.41	1.20-1.65	1.42	1.21-1.66	1.41	1.16-1.72	1.39	1.14-1.70
	≤1 year prior to index date	5.54	4.58-6.69	5.55	4.59-6.72	6.08	4.74-7.78	6.00	4.67-7.71
S00-T98 XIX	**Overall**	**1.34**	**1.17-1.54**	**1.34**	**1.17-1.54**	**1.28**	**1.07-1.53**	**1.25**	**1.04-1.49**
Injuries, poisoning, and other external causes	10->5 years prior to index date	1.17	1.01-1.36	1.18	1.01-1.37	1.08	0.90-1.32	1.05	0.86-1.28
	5->1 years prior to index date	1.35	1.16-1.58	1.36	1.16-1.59	1.37	1.12-1.68	1.34	1.10-1.64
	≤1 year prior to index date	1.26	1.00-1.58	1.28	1.01-1.61	1.66	1.24-2.22	1.62	1.20-2.18
Z00-Z80 XXI	**Overall**	**7.29**	**4.50-11.82**	**7.53**	**4.63-12.22**	**12.82**	**5.22-31.52**	**13.82**	**5.59-34.13**
Factors influencing health status etc.	10->5 years prior to index date	0.99	0.82-1.18	0.99	0.83-1.18	1.27	0.98-1.64	1.27	0.98-1.65
	5->1 years prior to index date	1.68	1.38-2.06	1.70	1.39-2.08	1.49	1.14-1.96	1.55	1.17-2.05
	≤1 year prior to index date	8.76	7.11-10.79	9.03	7.31-11.15	4.95	3.95-6.21	5.21	4.13-6.57

Incidence rate ratios (IRRs) for young onset Alzheimer's disease cases are presented overall and in 3 time-intervals prior to diagnosis with 95% confidence intervals (CI) according to dementia syndrome severity at time of diagnosis (patients with mild cognitive impairment (MCI) or mild dementia compared to their controls, and patients with moderate/severe dementia compared to their controls). The adjusted IRRs are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis if age at diagnosis <40 years), and civil status at index date. ICD: International classification of diseases

* Excluding mild cognitive impairment and dementia diagnoses

Table S6. Post-hoc analysis - Incidence rate ratios for psychiatric subcategories

ICD-10 code range and chapters	Time-period	Unadjusted		Adjusted	
		IRR	95% CI	IRR	95% CI
DF00-09	**Overall**	8.37	4.81-14.55	8.05	4.62-14.03
Organic, including symptomatic,	10->5 years prior to index date	3.00	0.87-10.36	2.99	0.86-10.33
mental disorders*	5->1 years prior to index date	4.15	2.04-8.48	3.88	1.89-7.96
	≤1 year prior to index date	27.00	8.19-89.00	26.39	8.00-87.03
DF10-19	**Overall**	1.84	1.46-2.33	1.81	1.43-2.29
Mental and behavioral disorders due to	10->5 years prior to index date	1.23	0.87-1.74	1.20	0.85-1.71
psychoactive substance use	5->1 years prior to index date	1.40	0.98-1.99	1.33	0.93-1.91
	≤1 year prior to index date	4.62	3.07-6.94	4.57	3.03-6.88
DF20-29	**Overall**	2.25	1.45-3.50	2.28	1.46-3.57
Schizophrenia, schizotypal and	10->5 years prior to index date	0.95	0.49-1.82	0.95	0.49-1.83
delusional disorders	5->1 years prior to index date	1.84	1.00-3.38	1.88	1.02-3.47
	≤1 year prior to index date	5.25	2.58-10.67	5.37	2.62-11.01
DF30-39	**Overall**	3.20	2.53-4.04	3.14	2.48-3.98
Mood/affective disorders	10->5 years prior to index date	1.50	1.05-2.14	1.45	1.01-2.07
	5->1 years prior to index date	3.02	2.17-4.21	2.94	2.11-4.11
	≤1 year prior to index date	9.23	5.93-14.37	9.17	5.88-14.28
DF40-48	**Overall**	2.74	2.15-3.50	2.69	2.11-3.45
Neurotic, stress-related and	10->5 years prior to index date	1.19	0.81-1.76	1.14	0.77-1.69
somatoform disorders	5->1 years prior to index date	3.48	2.46-4.93	3.40	2.39-4.82
	≤1 year prior to index date	8.14	4.59-14.43	8.21	4.62-14.59
DF50-59	**Overall**	1.80	0.65-4.95	1.79	0.65-4.95
Behavioral syndromes associated with	10->5 years prior to index date				
physiological disturbances and physical	5->1 years prior to index date	3.75	1.01-13.97	3.87	1.04-14.48
factors	≤1 year prior to index date	3.00	0.42-21.30	2.93	0.41-20.92
DF60-69	**Overall**	1.68	0.87-3.23	1.61	0.84-3.11
Disorders of adult personality and	10->5 years prior to index date	1.13	0.44-2.88	1.08	0.42-2.76
behavior	5->1 years prior to index date	1.00	0.32-3.10	0.93	0.30-2.91
	≤1 year prior to index date	3.75	1.01-13.97	3.70	0.99-13.84
DF99	**Overall**	3.39	1.83-6.28	3.36	1.81-6.25
Unspecified mental disorder	10->5 years prior to index date	2.25	0.95-5.34	2.09	0.87-5.00
	5->1 years prior to index date	1.33	0.41-4.33	1.40	0.43-4.57
	≤1 year prior to index date				

Incidence rate ratios (IRRs) for young onset Alzheimer's disease are presented by subcategories of mental and behavioral disorders in 3 time-intervals prior to diagnosis with 95% confidence intervals (CI). The adjusted IRRs are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis if age at diagnosis <40 years), and civil status at index date. Where no estimates are presented, there were too few events to analyze.
ICD: International classification of diseases
* Excluding mild cognitive impairment and dementia diagnoses

8.3 Study 3

Alzheimer's Research & Therapy

RESEARCH

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Prescription medication use in the 10 years prior to diagnosis of young onset Alzheimer's disease: a nationwide nested case-control study

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Abstract

Background Patients with young onset Alzheimer's disease (YOAD) face long diagnostic delays. Prescription medication use may provide insights into early signs and symptoms, which may help facilitate timely diagnosis.

Methods In a register-based nested case-control study, we examined medication use for everyone diagnosed with YOAD in a Danish memory clinic during 2016–2020 compared to cognitively healthy controls. Prescription medication use were grouped into 13 overall categories (*alimentary tract and metabolism, blood and blood forming organs, cardiovascular system, dermatologicals, genitourinary system and sex hormones, systemic hormonal preparations, antiinfectives for systemic use, antineoplastic and immunomodulating agents, musculo-skeletal system, nervous system, antiparasitic products, respiratory system*, and *sensory organs*). Further stratifications were done for predetermined subcategories with a use-prevalence of at least 5% in the study population. Conditional logistic regression produced odds ratios, which given the use of incidence-density matching is interpretable as incidence rate ratios (IRRs). The association between prescription medication use and subsequent YOAD diagnosis was examined in the entire 10-year study period and in three time-intervals.

Results The study included 1745 YOAD cases and 5235 controls. In the main analysis, several overall categories showed significant associations with YOAD in one or more time-intervals, namely *blood and blood forming organs* and *nervous system*. Prescription medication use in the *nervous system* category was increased for YOAD cases compared to controls already 10->5 years prior to diagnosis (IRR 1.17, 95% CI 1.05–1.31), increasing to 1.57 (95% CI 1.39–1.78) in the year preceding diagnosis. This was largely driven by antidepressant and antipsychotic use, and especially prominent for first-time users.

Conclusions In this study, medication use in several categories was associated with YOAD. Onset of treatment-requiring psychiatric symptoms such as depression or psychosis in mid-life may serve as potential early indicators of YOAD.

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Keywords Young onset dementia, Alzheimer's disease, Medication, Early warning signs, Registry-based, Epidemiology

Background

Long diagnostic delays have been described in patients with young onset Alzheimer's disease (YOAD) [1, 2], and a more comprehensive picture of the early warning signs of YOAD could be key in facilitating a timely diagnosis in this often overlooked patient group. In prior studies, we have shown that patients diagnosed with YOAD have increased healthcare utilization across all primary and secondary healthcare providers up to 10 years prior to dementia diagnosis, with a major surge in psychiatric healthcare use leading up to diagnosis [3]. Additionally, YOAD patients had increased hospital-diagnosed morbidity prior to diagnosis, especially psychiatric morbidity such as stress and depression [4]. Examining prescription medication use prior to YOAD may help us gather further insights into these early signs and may also serve as a proxy for symptoms and diseases not requiring hospital contact.

To our knowledge, no prior studies have examined medication use prior to a diagnosis of YOAD, though several studies have examined the association between specific types of medication and late onset Alzheimer's disease (LOAD) or late onset all-cause dementia. These are often either risk factor studies or studies of agents that may be repurposed for treatment of dementia. For instance, such studies have concluded that exposure to strong anticholinergic drugs [5], benzodiazepines [6, 7], lithium [8], and antiepileptic drugs [9] is associated with an increased risk of (all-cause) dementia. However, given the age-related changes in morbidity burden and medication use, findings from studies involving older populations may not be directly applicable to individuals with YOAD.

The aim of this study was to explore whether individuals diagnosed with YOAD have an altered prescription medication use pattern in the 10-year lead-in to diagnosis, compared to cognitively healthy, matched adults.

Methods

Data sources

Cases were identified from the Danish Quality Database for Dementia (DanDem). All Danish healthcare facilities that accept referrals for diagnostic evaluation of dementia and cognitive impairment must enter information such as etiology, severity of the dementia syndrome at time of diagnosis (if applicable), and diagnostic investigations performed including results of selected cognitive tests, upon completion of diagnostic evaluation. DanDem contains information on all patients seen at Danish Memory clinics from establishment of the database in 2016 onwards. Information on medication use was drawn from the Danish National Prescription Registry (DNPrR), containing detailed information on all redeemed prescriptions since 1995 [10] using the World Health Organization's Anatomical Therapeutic Chemical (ATC) code system [11]. The Danish National Patient Register (DNPR) and the Danish Psychiatric Central Research Register (DPCRR) were used for information on diagnoses given in hospitals, used in the selection/exclusion of cases and controls [12, 13]. Covariates were identified from the Population Education Register [14] and the Civil Registration System, with the latter also used for linkage between registers through each Danish citizen's unique 10-digit personal identification number [15, 16].

Study design and population

We conducted a retrospective nested case-control study following the approach of our previous studies on this population [3, 4]. Associations between prescription medication and YOAD were examined over a 10-year period. This period was chosen to account for the gradual onset and progression of pathology in Alzheimer's disease [17], allowing for a comprehensive exploration of potential associations between medication use and disease onset.

Case definition

By convention, YOAD is defined as dementia due to Alzheimer's disease (AD) with symptom onset before age 65 years. As the registries used do not contain information about time of symptom onset, we approximated this using date of diagnosis. As previous studies have shown an average of around 5 years from symptom onset to final diagnosis [1, 2], we included all patients diagnosed with mild cognitive impairment (MCI) or dementia due to AD before age 70 years, assuming symptom onset before age 65. Cases were identified from DanDem as individuals with a first diagnosis of MCI due to AD or dementia due to AD from start of register (2016) through 2020. Some cases also had a previous record related to dementia in other registers. For all cases, index time was set to time of diagnosis in DanDem (further details on choice of index date in supplementary methods 2.2.1.S).

Control definition

For each case, three age- and sex-matched controls were drawn from the full risk set (the entire Danish population). Incidence-density-sampling was used, as each control was at risk for YOAD at matching date. This allowed the odds ratios from the conditional logistic

regression to be interpreted as incidence rate ratios (IRR) [18]. Exclusion criteria for controls were prior dementia (determined by dementia diagnosis in DNPR or DPCRR or redeemed prescription of antidementia medication in DNPrR) or memory clinic visits prior to index date (codes for identification of exclusion criteria: table S1).

Exclusion

Individuals with a primary/secondary diagnostic code indicating Down syndrome (ICD-8: 759.3, ICD-10: DQ90) and Mental Retardation (ICD-8: 311–315, ICD-10: DF70-DF79) were excluded from the study population. To ensure completeness of data, cases and controls must have lived in Denmark in the 10-year retrospective period. All exclusion criteria can be seen in table S1.

Exposure and covariates

Exposure

Medication use was defined based on all redeemed prescriptions in the DNPrR in the 10-year study period. Medications were grouped according to (1) overall category (corresponding to ATC main groups, i.e., 1st digit of the ATC-code) and (2) subcategories grouping medications by indication (largely based on ATC therapeutic subgroups, but where relevant more detailed subcategories were chosen using three- or four-digit ATC-codes). Table S2 shows the definition of overall categories, subcategories, and corresponding ATC-codes. For chosen subcategories where <5% of the study population had at least one redeemed prescription, these were included in the overall category's "other" group for the regression analysis, as comparisons of medication use among fewer individuals would not yield meaningful results.

Covariates

Analyses were done in two models; one unadjusted, one adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis, whichever came first), and civil status at index date.

Data analysis

Main analysis

For each overall category we used a conditional logistic regression model to investigate the association between having at least one redeemed prescription within the category and subsequent diagnosis of YOAD, yielding IRRs. Each matched set served as a stratum in the regression model. IRRs were calculated for each overall category for (a) the entire 10-year period, (b) the 10->5-year interval prior to diagnosis, (c) the 5->1 year interval prior to diagnosis, and (d) the ≤1-year interval prior to diagnosis to investigate latency between medication use and dementia diagnosis. As we have previously found psychiatric healthcare use and psychiatric morbidity to be significantly increased prior to YOAD [3, 4], we decided a-priori to examine medication in the *nervous system* subcategories in time-intervals. Associations between the medication use in the remaining subcategories and YOAD were assessed only in the entire 10-year period.

As any prior dementia medication resulted in exclusion for controls, ATC codes for antidementia medication (table S1) were omitted for cases in the conditional logistic regression analyses.

Sensitivity analysis

In a sensitivity analysis, we repeated the analysis of overall categories in the 10-year study period while grouping by disease severity to examine those with MCI/mild dementia or moderate/severe dementia, compared with their respective matched controls. Furthermore, this analysis was repeated stratifying on age (age<55 years, age≥55 years) and on sex, as well as omitting cases with MCI and their respective controls from the analyses. To ensure potential delays between actual and registered time of diagnosis did not impact results, we additionally conducted a sensitivity analysis repeating the analysis of overall categories in the <1 year interval while omitting the 6 months immediately prior to index date.

In a post hoc analysis exploring associations between *nervous system* medication and YOAD, we limited the analyses to first-ever prescriptions in each time interval compared to never-users. Furthermore, we conducted a post-hoc analysis examining which subcategories where the main causes of the decreased IRRs in the <1 year interval in relevant overall categories.

Results are presented with 95% confidence intervals (CI), corresponding to a 5% significance level. As the study is exploratory in nature we did not correct for multiple comparisons, though it is important to keep in mind that with numerous analyses, CIs cannot be interpreted as usual and should serve merely as a loose indicator. Results are presented unadjusted and adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis, whichever came first), and civil status at index date. All statistical analyses were performed with SAS 9.4 software using the PROC logistic procedure. This research project was approved by the Danish Data Protection Agency, Statistics Denmark, and the Danish Health Data Authority. Danish law does not require ethics committee approval or informed patient consent.

Results

Out of 17,644 patients diagnosed with AD in DanDem between 2016 and 2020, 1827 were diagnosed before age 70 years. After exclusion criteria were applied, there were 1745 YOAD cases, who were matched with 5235 controls. The mean age at time of diagnosis was 64.5 years,

and 42% were male (Table 1). At time of diagnosis, 5% of cases were categorized as having MCI, 58% as having mild dementia, and 37% with moderate/severe dementia due to AD. Cases and controls were similar in terms of educational attainment and civil status.

The proportion of cases and controls with a redeemed prescription within each overall category were nearly identical across all categories, except for medications in *blood and blood forming organs* (36% of cases, 29% of controls) and in *nervous system* (75% of cases, 68% of controls). For *blood and blood forming organs* medication, we found an IRR of 1.27 (95% CI 1.12–1.45) in the 5->1 years prior to diagnosis, increasing to 1.71 (95% CI 1.48–1.97) in the year immediately preceding YOAD diagnosis, compared to controls. *Nervous system* medications were increased with around 20% in both the 10->5- and 5->1-year periods, increasing to an IRR of 1.57 (95% CI 1.39–1.78) in the year before diagnosis (Fig. 1). The remaining overall categories had IRRs around 1, except *genitourinary system and sex hormones*, *musculo-skeletal system*, and *respiratory system* products, where IRRs were slightly decreased in the year prior to diagnosis. In a post-hoc analysis we examined the main drivers of the decreased IRRs; these were sex hormones,

Table 1 Baseline characteristics of study population

	Cases *n* = 1745	**Controls *n* = 5235**
Age at index date, mean years (sd) [range]	64.5 (5.1) [35.8–69.9]	64.5 (5.1) [35.5–69.9]
Sex, male/female, *n* (%)	726 (42%) / 1019 (58%)	2178 (42%) / 3057 (58%)
Dementia syndrome severity at time of diagnosis, *n* (%)		
Mild cognitive impairment	84 (5%)	-
Mild dementia	1010 (58%)	-
Moderate dementia	530 (30%)	-
Severe dementia	121 (7%)	-
Cognitive examination scores at first visit*, mean (sd)		
MMSE	21.0 (5.5)	-
ACE	65.2 (15.4)	-
Educational attainment at age 40, *n* (%)		
Low	1184 (68%)	3629 (69%)
Medium	374 (21%)	1118 (21%)
High	104 (6%)	268 (5%)
Unknown	83 (5%)	220 (5%)
Civil status at index date, *n* (%)		
Married	1094 (63%)	3377 (65%)
Divorced	321 (18%)	869 (17%)
Widowed	133 (8%)	349 (7%)
Never married	177 (10%)	611 (12%)
Unknown	20 (1%)	29 (1%)
Individuals with ≥ 1 prescription within each overall category, *n* (%)		
A: Alimentary tract and metabolism	944 (54%)	2821 (54%)
B: Blood and blood forming organs	625 (36%)	1534 (29%)
C: Cardiovascular system	1145 (66%)	3360 (64%)
D: Dermatologicals	1044 (60%)	3142 (60%)
G: Genitourinary system and sex hormones	660 (39%)	1981 (38%)
H: Systemic hormonal preparations	413 (24%)	1303 (25%)
J: Antiinfectives for systemic use	1498 (86%)	4502 (86%)
I: Antineoplastic and immunomodulating agents	37 (2%)	140 (3%)
M: Musculo-skeletal system	1192 (68%)	3588 (69%)
N: Nervous system†	1310 (75%)	3564 (68%)
P: Antiparasitic products, insecticides, and repellents	371 (21%)	1171 (22%)
R: Respiratory system	951 (55%)	2842 (54%)
S: Sensory organs	892 (51%)	2668 (51%)

Abbreviations and additional information

*MMSE: Mini-Mental State Examination (reliable information for 1590 YOAD patients). ACE: Addenbrooke's Cognitive Examination (reliable information for 1173 YOAD patients). † Not including antidementia medication

Sd: standard deviation

Note: Where percentages do not add up to 100%, this is due to rounding up/down

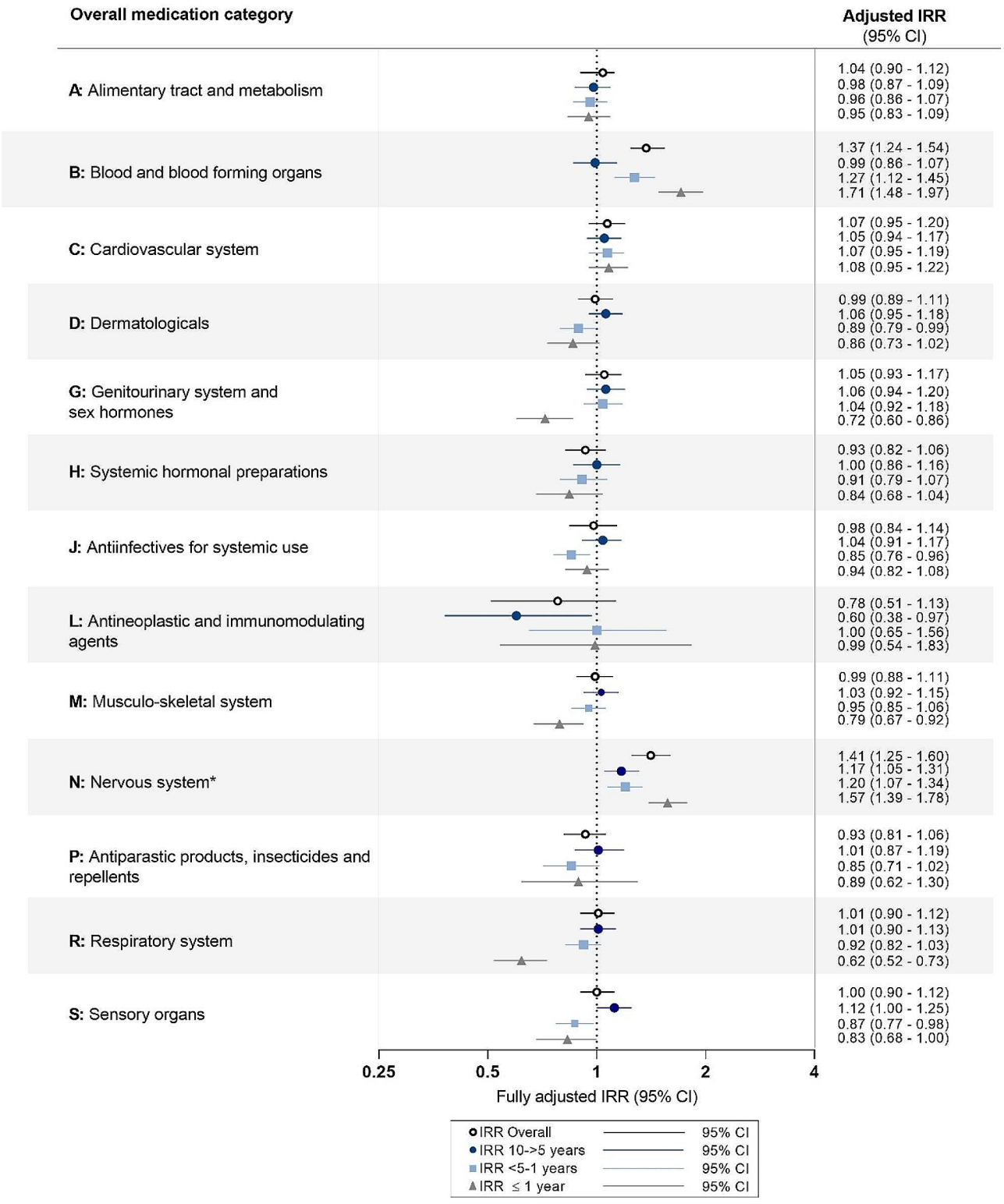

Fig. 1 Incidence rate ratios by overall medication category in the 10-year study period and in time intervals. Incidence rate ratios (IRRs) for young onset Alzheimer's disease are plotted by overall medication categories in the 10-year retrospective study period and in three time-intervals prior to diagnosis. Conditional logistic regression analyses produced odds ratios, which given the use of incidence-density-sampling is interpretable as IRRs. For the refence group (dementia-free controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals (CI). The IRRs presented are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis, whichever came first), and civil status at index date. Unadjusted estimates are presented in table S3. * Not including dementia medication (see ATC-codes used in table S3)

antiinflammatory and antirheumatic drugs, and all respiratory subcategories, respectively (data not shown).

Figure 2 shows associations between medication subcategories (with a use-prevalence of at least 5%) and YOAD diagnosis. Of the 46 subcategories examined, seven had significantly increased IRRs. The most notable increases were found for use of antidepressants, antipsychotics, antianemic preparations, antithrombotic preparations, and drugs for constipation, with smaller increases for anxiolytics and other nervous system

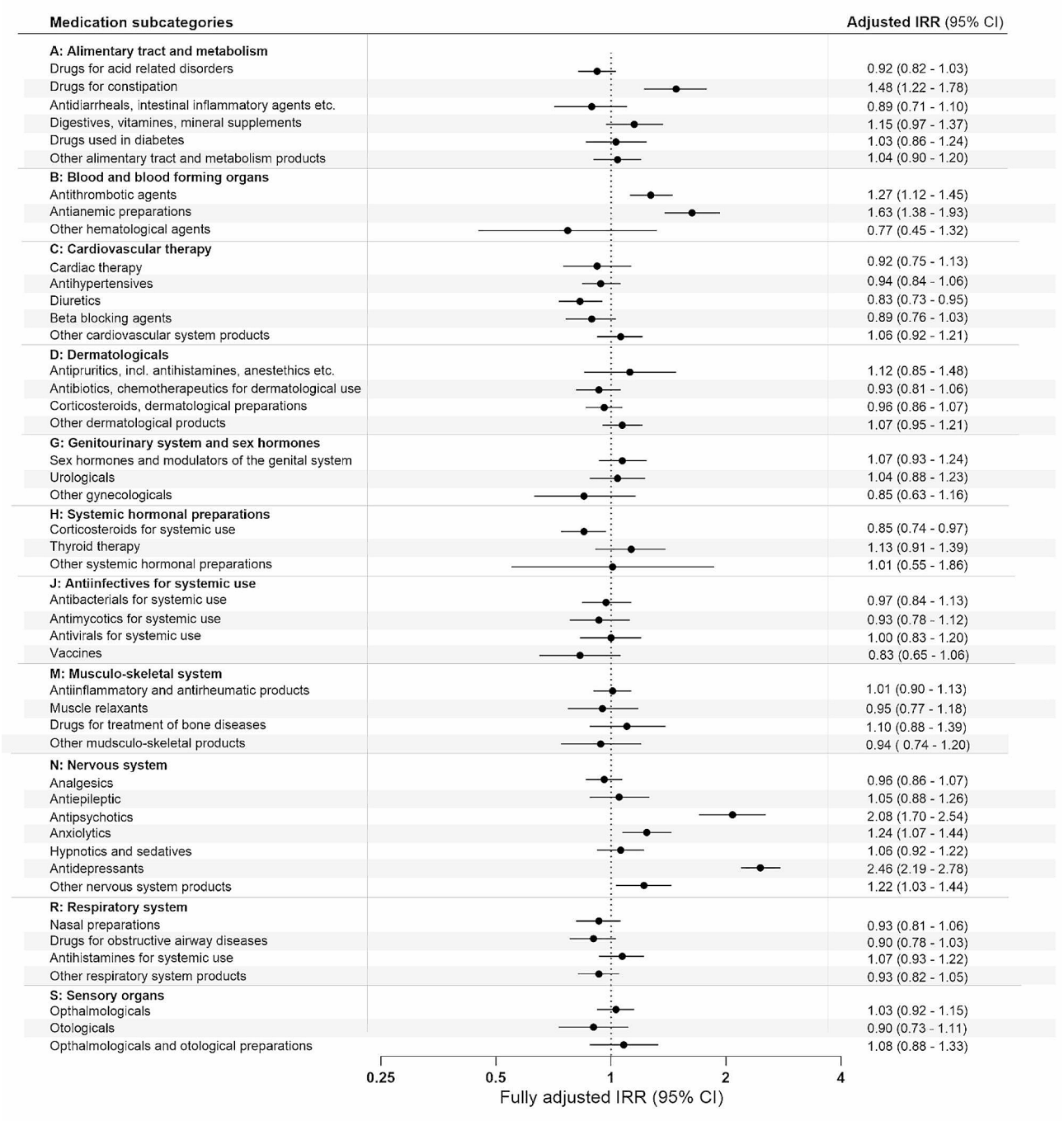

Fig. 2 Incidence rate ratios by medication subcategories in the 10-year retrospective study period. Incidence rate ratios (IRRs) for young onset Alzheimer's disease are plotted by medication subcategories in the 10-year retrospective study period. Conditional logistic regression analyses produced odds ratios, which given the use of incidence-density-sampling is interpretable as IRRs. For the refence group (dementia-free controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals (CI). The IRRs presented are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis, whichever came first), and civil status at index date. Unadjusted estimates are presented in table S4

products. Looking at *nervous system* drugs in time-intervals (Fig. 3), the increased use of antidepressants became apparent already 10->5-years prior to diagnosis (IRR 1.43, 95% CI 1.25–1.64) and increased steadily as index date approached. Antipsychotic use was increased from 5->1-year prior to diagnosis, while the use of anxiolytics only showed an increased IRR in the year prior to diagnosis. In a post-hoc analysis examining only first-ever prescriptions of *nervous system* drugs compared to never-users, these effects were reinforced with IRRs over 10 found for both antipsychotic- and antidepressant use in the year preceding diagnosis (figure S1).

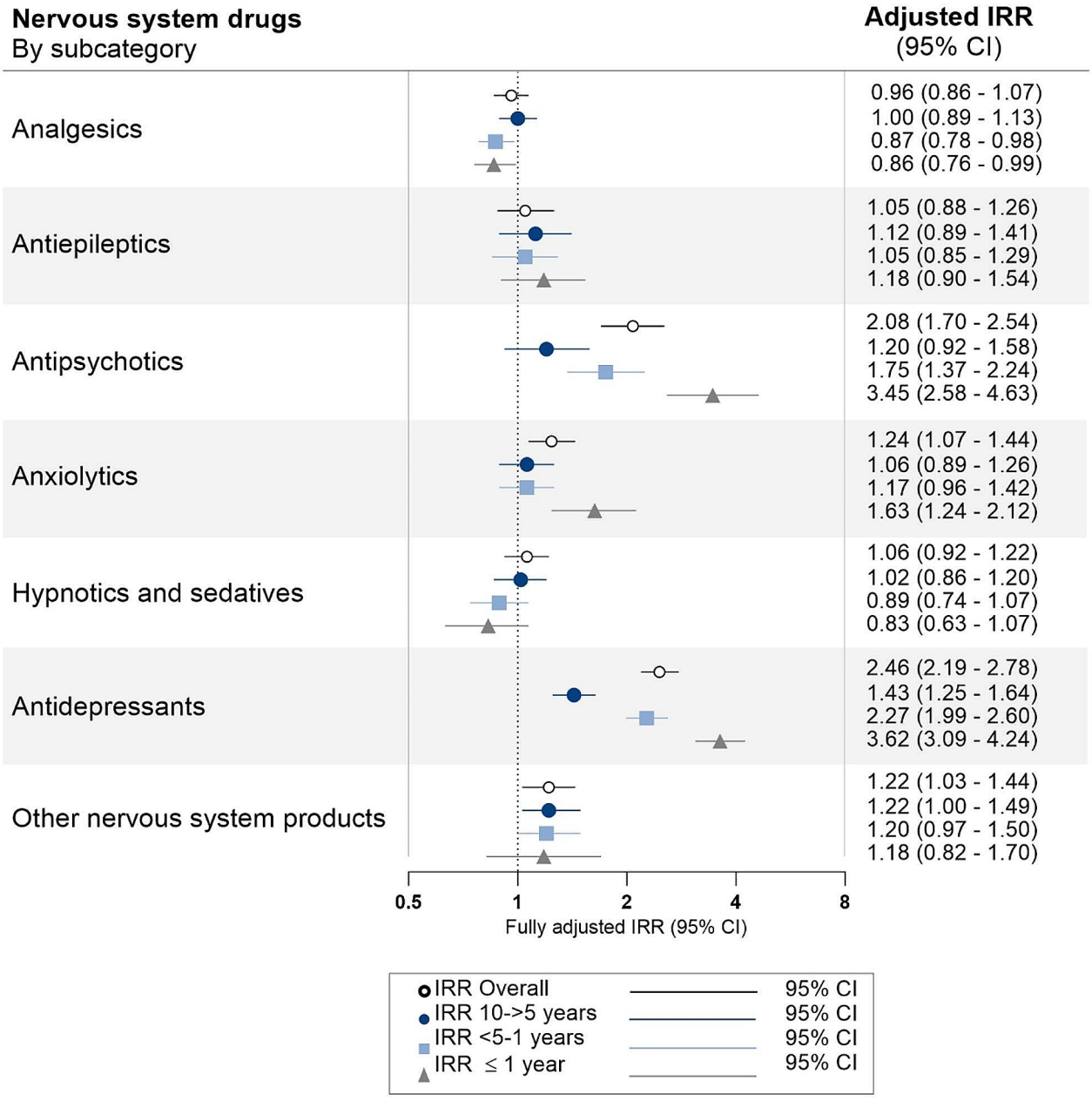

Fig. 3 Incidence rate ratios by nervous system subcategories in the 10-year study period and in time intervals. Incidence rate ratios (IRRs) for young onset Alzheimer's disease are plotted by *nervous system* subcategories in the 10-year retrospective study period and in three time-intervals prior to diagnosis. Conditional logistic regression analyses produced odds ratios, which given the use of incidence-density-sampling is interpretable as IRRs. For the refence group (dementia-free controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals (CI). The IRRs presented are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis, whichever came first), and civil status at index date. Unadjusted estimates are presented in table S5

In a sensitivity analysis stratifying by dementia syndrome severity at index date, we divided the study population in two groups: cases with MCI/mild dementia and their controls, and cases with moderate/severe dementia and their controls. Results were similar to those found in the main analysis, though the magnitude of the association between the use of *nervous system* medication and YOAD differed slightly (figure S2). Furthermore, we stratified the study population by sex (figure S3) and age (figure S4), which yielded results similar to those found in the main analysis, as did omitting cases with MCI (table S10) and prescription medication use in the six months prior to index date (table S11). Unadjusted estimates are presented for all analyses in tables S3-S11. Adjustment generally did not impact the estimates.

Discussion

In this nationwide nested case-control study, we found notable variations in medication use between individuals with a YOAD diagnosis and those without. Particularly noteworthy were differences in utilization of *nervous system* medications. Those with YOAD had a 17% increased use of medications within the *nervous system* category already in the 10->5 years leading up to index date, increasing to 57% in the year immediately prior. This was largely driven by the use of antidepressants and antipsychotics, and the difference between cases and controls was more pronounced when comparing those with a first-ever prescription to never-users. Hence, initiation of these medications in mid-life could potentially serve as an indicator of YOAD. We note, though, that all confidence intervals (and hence, significance) should be interpreted with caution given the number of associations examined.

To our knowledge, this is the first study exploring medication use prior to YOAD, though a few studies have broadly examined medication use prior to all-cause dementia or LOAD. One such study showed associations between Sertraline, Escitalopram, and Mirtazapine (all medications used to treat depression) and AD with hazard ratios around 2-3 [19], while a study specifically investigating antidepressants found a slight increase in the rate of antidepressant use among AD patients already 9 years before diagnosis [20]. This aligns with our findings, implying an association between depression and AD, perhaps showing that depression is part of the AD prodrome both in YOAD and LOAD, or that early dementia symptoms such as apathy, withdrawal, and changes in mood and behaviour, are misinterpreted as symptoms of depression. This corresponds with our previous findings of increased psychiatric healthcare utilization [3] and depression diagnoses [4] in the 10 years prior to YOAD diagnosis, rising as time of diagnosis approaches. This could reflect either a prodromal increased susceptibility to depression among those with AD pathology but as yet without dementia symptoms, or dementia symptoms misinterpreted as depression. It may also reflect depression occurring comorbidly with YOAD or depression unrelated to dementia symptoms and pathology. Another study found that those who experienced onset of psychotic symptoms after the age of 50 years had a greater risk for cognitive impairment. This was particularly pronounced in carriers of the *APOE* ε4 allele [21], an important genetic risk factor in YOAD. In line with these findings, the present study found a significant association between first-time use of antipsychotic medication and YOAD as much as five years prior to dementia diagnosis. Our findings thus support their conclusion; that onset of psychotic symptoms in later life could warrant cognitive evaluation in a memory clinic.

In addition to our findings for medication in the *nervous system* category, another key finding was an increased IRR for the overall category *blood and blood forming organs* medications from <5 years prior to YOAD diagnosis. Subcategories with increased IRR within this chapter were antithrombotic agents and antianemic preparations. Vascular disease is known to increase the risk of LOAD [22], and oral anticoagulant use have been shown to be higher among those who are later diagnosed with AD [23]. Our findings also imply an association between vascular diseases and YOAD, perhaps indicating that vascular risk factors may play a role also in YOAD. However, the present study did not aim to assess risk, for which measures to mitigate reverse causation etc. would be needed.

Aside from drugs in the two discussed categories (*nervous system* and *blood and blood forming organs*), we also noted significant associations in our study of either increased or decreased IRRs for other medications. We discuss these findings in the following but note that given the number of associations examined, marginally significant results should be interpreted cautiously.

A significantly increased IRR was found for the subcategory drugs for constipation. This mirrors findings from two large studies where hazard ratios of around 1.3–2.3 were found for AD following prior laxative use [24, 25]. Similar associations have been found between laxative use and all-cause dementia [26]. Constipation is a well-known early symptom in dementia with Lewy bodies and Parkinson's disease [27], and further research could investigate whether it may be an early marker of YOAD as well or perhaps an expression of dual pathology of AD and dementia with Lewy bodies.

In the following we address findings related to decreased IRRs. Within the <1 year period leading up to index date, medication in the category *genitourinary system and sex hormones* had an IRR of 0.72, with the decrease largely driven by the subcategory sex hormones.

The most commonly used form of medication within this subcategory was estradiol vaginal tablets. A nationwide Danish cohort study examining use of vaginal estrogen found no association with AD, with the authors suggesting impaired ability to act on urogenital symptoms and diminished compliance with already initiated therapy just prior to diagnosis [28], which could also be the explanation for our findings. Another decreased IRR in the <1 year interval was found for *musculo-skeletal system drugs*, driven by antiinflammatory and antirheumatic drugs. The role of inflammation in AD pathology has been a topic of scientific interest in recent years [29], with some studies suggesting antiinflammatory drugs may lower the risk of dementia [30]. However, our study is not suitably designed to determine risk factors, and given the proximity to YOAD diagnosis, this decreased IRR in the year prior to diagnosis is likely explained by other factors and potential bias such as reverse causality. Lastly, in the analysis of subcategories we found a decreased IRR for corticosteroids for systemic use, albeit borderline significant. While Prednisone was found to be associated with lower rates of dementia in another study [19], mechanisms behind this possible association is unclear, and further research is warranted.

Limitations

Our study had several limitations. First, although healthcare is free of charge in Denmark, there is (some) out-of-pocket payment for prescription medication, perhaps favouring more resourceful individuals among medication users. Second, in viewing medications as a proxy measure of symptoms and diseases, dual uses of some drugs may cause us to miss valuable information – for example, some drugs registered in the ATC-system as antiepileptic drugs are also commonly used for psychiatric disorders, leading to a potential under-estimation of the use of drugs with psychiatric indication. Likewise, some drugs registered for psychiatric disorders are sometimes used for other indications (the use of tricyclic antidepressants for neuropathic pain, for example), leading to a potential over-estimation. Third, some of the analyses – especially those of first-ever prescriptions – are prone to detection bias; those starting a new medication will likely have been seen by a doctor, increasing the likelihood of detection of cognitive symptoms. However, looking for example at antidepressant use, we find a near four-fold use among YOAD cases in the main analysis, and a near 13-fold first-ever use. While detection bias may be a contributing factor, we find it unlikely that this alone can entirely explain the large difference between ever-users and first-ever users. Fourth, as the present study is exploratory in nature, causal inferences cannot be made. Consequently, we encourage future research to investigate the potential causal roles of the associations found while employing the appropriate methodologies to assess causality.

A major strength of our study is the use of the high-quality Danish registers. Using the quality registry DanDem for case finding allowed us to establish a large case cohort while ensuring that diagnosis of YOAD was made by specialists in memory clinic settings, and to include detailed variables about disease severity, test scores, etc. The use of nationwide healthcare registers to assess covariates and exposure information allowed for virtually full data coverage, limiting selection bias. We have previously examined morbidity prior to a diagnosis of YOAD, however due to data availability it was only possible to examine hospital-diagnosed morbidity. Looking at prescription medication allows us to supplement the knowledge gained previously by adding a proxy for symptoms not necessarily necessitating a hospital contact. Future research should aim at exploring the intricate interplay between different medication categories, morbidity, and concurrent morbidities or medication use.

Conclusions

The key takeaway from our study is that the onset of depression or psychotic symptoms in mid-life may serve as potential early indicators of YOAD. This is consistent with our previous findings of increased psychiatric healthcare utilization and morbidity in this patient group [3, 4]. These findings underscore the importance of considering mental health symptoms as a potential part of the prodromal phase of YOAD, providing valuable insights for early detection as awareness of early symptoms may help facilitate a timely diagnosis. Future studies could examine the predictive value of these psychiatric symptoms in identifying individuals with undiagnosed YOAD.

Abbreviations

YOAD	Young onset Alzheimer's disease
LOAD	Late-onset Alzheimer's disease
DanDem	The Danish Quality Database for Dementia
DNPrR	The Danish National Prescription Registry
ATC	Anatomical Therapeutic Chemical
DNPR	The Danish National Patient Register
DPCRR	The Danish Psychiatric Central Research Register
MCI	Mild cognitive impairment
AD	Alzheimer's disease
IRR	Incidence rate ratio
CI	Confidence intervals

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-024-01523-7.

Supplementary Material 1

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Author contributions
Study conception and/or design of the work: LD, JJ, TML, KV, HG, CJD, GW; Data acquisition, analysis and/or interpretation of data: LD, JJ, TML, GW; Drafting the manuscript: LD; Revising the manuscript: JJ, TML, KV, HG, CJD, GW; All authors have reviewed and approved the final manuscript.

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Data availability
All data used in this study are derived from the Danish National and Public Health registries. These data are collected and stored by the relevant authorities and cannot be made public or accessed by unauthorized parties. Access to such data is given via standard rules and regulations of data access outlined by the Danish Data Protection Agency and Danish Health Data Authority.

Declarations

Ethics approval and consent to participate
This research was conducted in accordance with Danish law, which does not require ethics committee approval or informed patient consent for register-based research. The project was approved by the Danish Data Protection Agency, Statistics Denmark, and the Danish Health Data Authority.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Publisher's Note

Supplementary - Medication use in the 10 years prior to diagnosis of young onset Alzheimer's disease

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Content:

Supplementary methods:

2.2.1.S Case definition: index date

For the present study, we chose date of diagnosis in DanDem as index date. Of cases, 64% had a diagnostic code of dementia or mild cognitive impairment (ICD-8 or ICD-10 codes listed in table S1) in DNPR/DPCRR prior to date of diagnosis in DanDem, with a median time of 93 days between the two. In some of the Danish memory clinics, patients are routinely coded by administrative personnel with an unspecified dementia-code upon being referred to the memory clinic prior to diagnostic assessment, and some are given a dementia-code in the registers by the referring department without cognitive evaluation; therefore, the diagnostic code is often given before the actual time of diagnosis. The median time of 93 days corresponds well with usual time frame from first referral to diagnosis in the memory clinics. Furthermore, prior research has shown a high validity of dementia-codes for individuals with late onset dementia in the Danish registers, though validity of dementia subtypes is generally low[1]. For patients with young onset dementia, though, there is a low validity of dementia diagnosis in DNPR/DPCRR[2,3]. For these reasons, index date from DanDem was chosen for all cases, as this represents the most reliable source of information on the date of AD diagnosis.

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Supplementary tables

Table S1. Exclusion criteria

	Cases	Controls
Developmental disorders and mental retardation ICD-8: 311-315, 759.3, ICD-10: DF70-DF79, DQ90	X	X
Not living in Denmark in 10-year retrospective period	X	X
Dementia or mild cognitive impairment diagnosis ICD-8: 290.09-11, 290.18-19, 293.09-19, ICD 10: F00.0-00.9, F01.0-01.9, F02.0-F02.8, F03.9, F04.0-F04.9, F06.7 G30.0-G30.9, G31.0A, G31.0B, G31.8, G31.8E, G31.9		X
Dementia medication ATC code N06DA02-4, N06DX01	*	X
Entry in DanDem		X

* These ATC codes registered in the Danish National Prescription Registry are omitted in the analyses.
ICD: International classification of diseases, ATC: Anatomical therapeutic chemical code, DanDem: Danish Quality Database for Dementia

Table S2. Overall categories, subcategories, and corresponding ATC codes

Overall category	ATC code	Subcategory	ATC codes
Alimentary tract and metabolism	A	Drugs for acid related disorders	A02
		*Antiemetics and antinauseants**	*A04**
		Drugs for constipation	A06
		Antidiarrheals, intestinal antiinflammatory/antiinfective agents	A07
		*Antiobesity preparations, excl. diet products**	*A08**
		Digestives, vitamins and mineral supplements, tonics	A09, A11, A12, A13
		Drugs used in diabetes	A10
		Other alimentary tract and metabolism products	A01, A03, A04, A05, A08, A14, A15, A16
Blood and blood forming organs	B	Antithrombotic agents	B01
		*Antihemorrhagics**	*B02**
		Antianemic preparations	B03
		Other hematological agents	B02, B05, B06
Cardiovascular system	C	Cardiac therapy	C01
		Antihypertensives	C02, C08, C09
		Diuretics	C03
		Beta blocking agents	C07
		Other cardiovascular system products	C04, C05
Dermatologicals	D	Antipruritics, incl. antihistamines, anesthetics, etc., antipsoriasis	D04, D05
		Antibiotics and chemotherapeutics for dermatological use	D06
		Corticosteroids, dermatological preparations	D07
		*Anti-acne preparations**	*D10**
		Other dermatological products	D01, D02, D03, D08, D09, D10, D11
Genito urinary system and sex hormones	G	*Gynecological antiinfectives and antiseptics**	*G01**
		Sex hormones and modulators of the genital system	G03
		Urologicals	G04
		Other gynecologicals	G01, G02
Systemic hormonal preparations, excluding sex hormones and insulin	H	*Pituitary and hypothalamic hormones and analogues**	*H01**
		Corticosteroids for systemic use	H02
		Thyroid therapy	H03
		*Pancreatic hormones**	*H04**
		*Calcium homeostasis**	*H05**
		Other systemic hormonal preparations	H01, H04, H05
Antiinfectives for systemic use	J	Antibacterials for systemic use	J01
		Antimycotics for systemic use	J02
		Antivirals for systemic use	J05
		Vaccines	J07
		Other antiinfective products†	*J04, J06†*
Antineoplastic and immunomodulating agents	L	*Antieneoplastic agents‡*	*L01‡*
		Endocrine therapy‡	*L02‡*

		Immunostimulants‡	*L03‡*
		Immunosuppressants‡	*L04‡*
Musculo-skeletal system	M	Antiinflammatory and antirheumatic products	M01
		*Muscle relaxants**	*M03**
		*Antigout preparations**	*M04**
		Drugs for treatment of bone diseases	M05
		Other musculo-skeletal products	M02, M03, M04, M09
Nervous system	N	Analgesics	N02
		Antiepileptics	N03
		*Anti-parkinson drugs**	*N04**
		Antipsychotics	N05A
		Anxiolytics	N05B
		Hypnotics and sedatives	N05C
		Antidepressants	N06A, N06B
		Other nervous system products	N01, N04, N07, N06C
Antiparasitic products, insecticides, and repellents	P	*None chosen ‡*	*‡*
Respiratory system	R	Nasal preparations	R01
		*Throat preparations**	*R02*
		Drugs for obstructive airway diseases	R03
		Antihistamines for systemic use	R06
		Other respiratory system products	R02, R05, R07
Sensory organs	S	Ophthalmologicals	S01
		Otologicals	S02
		Ophthalmologicals and otological preparations	S03

Subcategories in cursive were not individually analyzed:
* These categories were proposed as individual categories, but due to <5% of the study population having at least one redeemed prescription during the study period, these subcategories were combined with the "other" category within that overall category.
† As there were <5% of the study population with a redeemed prescription in the proposed "other" category, this was omitted from the analysis.
‡ Within the overall category Antineoplastic and immunomodulating agents, there were no proposed subcategories where >5% of the study population had a redeemed prescription. Within the Antiparasitic products, insecticides and repellents no relevant subcategories were proposed. Therefore, there were no relevant subcategories to examine for these two overall categories.
The ATC main group "Various" were omitted from all analyses due to low number of observations.

Table S3. Incidence rate ratios for medication use in overall categories, overall and in time-intervals

Overall category	Time-interval	Unadjusted		Adjusted	
		IRR	95% CI	IRR	95% CI
Alimentary tract and metabolism	**Overall**	1.01	0.90-1.13	1.04	0.90-1.12
A	10->5 years prior to index date	0.98	0.88-1.10	0.98	0.87-1.09
	5->1 years prior to index date	0.96	0.86-1.07	0.96	0.86-1.07
	≤1 year prior to index date	0.95	0.83-1.09	0.95	0.83-1.09
Blood and blood forming organs	**Overall**	1.36	1.21-1.53	1.37	1.24-1.54
B	10->5 years prior to index date	0.99	0.86-1.14	0.99	0.86-1.14
	5->1 years prior to index date	1.28	1.12-1.45	1.27	1.12-1.45
	≤1 year prior to index date	1.70	1.48-1.96	1.71	1.48-1.97
Cardiovascular system	**Overall**	1.07	0.95-1.20	1.07	0.95-1.20
C	10->5 years prior to index date	1.04	0.93-1.16	1.05	0.94-1.17
	5->1 years prior to index date	1.06	0.95-1.18	1.07	0.95-1.19
	≤1 year prior to index date	1.07	0.94-1.21	1.08	0.95-1.22
Dermatologicals	**Overall**	0.99	0.89-1.11	0.99	0.89-1.11
D	10->5 years prior to index date	1.06	0.95-1.18	1.06	0.95-1.18
	5->1 years prior to index date	0.89	0.80-0.99	0.89	0.79-0.99
	≤1 year prior to index date	0.87	0.74-1.03	0.86	0.73-1.02
Genito urinary system and sex hormones	**Overall**	1.05	0.94-1.18	1.05	0.93-1.17
G	10->5 years prior to index date	1.06	0.94-1.20	1.06	0.94-1.20
	5->1 years prior to index date	1.05	0.93-1.18	1.04	0.92-1.18
	≤1 year prior to index date	0.72	0.61-0.86	0.72	0.60-0.86
Systemic hormonal preparations, excluding sex hormones and insulin	**Overall**	0.93	0.82-1.06	0.93	0.82-1.06
	10->5 years prior to index date	1.00	0.87-1.17	1.00	0.86-1.16
H	5->1 years prior to index date	0.93	0.78-1.08	0.91	0.79-1.07
	≤1 year prior to index date	0.84	0.68-1.05	0.84	0.68-1.04
Antiinfectives for systemic use	**Overall**	0.99	0.84-1.16	0.98	0.84-1.14
J	10->5 years prior to index date	1.04	0.92-1.18	1.04	0.91-1.17
	5->1 years prior to index date	0.86	0.77-0.96	0.85	0.76-0.96
	≤1 year prior to index date	0.95	0.82-1.09	0.94	0.82-1.08
Antineoplastic and immunomodulating agents	**Overall**	0.79	0.55-1.14	0.78	0.51-1.13
L	10->5 years prior to index date	0.60	0.38-0.96	0.60	0.38-0.97
	5->1 years prior to index date	1.01	0.65-1.57	1.00	0.65-1.56
	≤1 year prior to index date	1.00	0.54-1.84	0.99	0.54.1.83
Musculo-skeletal system	**Overall**	0.99	0.88-1.11	0.99	0.88-1.11
M	10->5 years prior to index date	1.03	0.92-1.14	1.03	0.92-1.15
	5->1 years prior to index date	0.95	0.85-1.06	0.95	0.85-1.06
	≤1 year prior to index date	0.79	0.68-0.93	0.79	0.67-0.92

Nervous system*	**Overall**	1.42	1.25-1.60	1.41	1.25-1.60
N	10->5 years prior to index date	1.18	1.06-1.31	1.17	1.05-1.31
	5->1 years prior to index date	1.21	1.08-1.35	1.20	1.07-1.34
	≤1 year prior to index date	1.58	1.40-1.79	1.57	1.39-1.78
Antiparasitic products, insecticides, and repellents	**Overall**	0.94	0.82-1.07	0.93	0.81-1.06
P	10->5 years prior to index date	1.02	0.87-1.19	1.01	0.87-1.19
	5->1 years prior to index date	0.86	0.72-1.03	0.85	0.71-1.02
	≤1 year prior to index date	0.90	0.62-1.31	0.89	0.62-1.30
Respiratory system	**Overall**	1.01	0.90-1.13	1.01	0.90-1.12
R	10->5 years prior to index date	1.01	0.90-1.13	1.01	0.90-1.13
	5->1 years prior to index date	0.92	0.82-1.03	0.92	0.82-1.03
	≤1 year prior to index date	0.62	0.53-0.73	0.62	0.52-0.73
Sensory organs	**Overall**	1.01	0.90-1.12	1.00	0.90-1-12
S	10->5 years prior to index date	1.12	1.00-1.25	1.12	1.00-1.25
	5->1 years prior to index date	0.87	0.77-0.98	0.87	0.77-0.98
	≤1 year prior to index date	0.84	0.69-1.01	0.83	0.68-1.00

*Dementia medication (table S1) is omitted in the conditional logistic regression

Table S4. Incidence rate ratios for medication use in subcategories (nervous system products presented in table S5)

Overall category	n	Subcategory	Unadjusted		Adjusted	
			IRR	95% CI	IRR	95% CI
Alimentary tract and metabolism	2670	Drugs for acid related disorders	0.93	0.83-1.04	0.92	0.82-1.03
A	575	Drugs for constipation	1.50	1.24-1.80	1.48	1.22-1.78
	496	Antidiarrheals, intestinal antiinflammatory/antiinfective agents	0.89	0.72-1.10	0.89	0.71-1.10
	749	Digestives, vitamins and mineral supplements, tonics	1.16	0.98-1.38	1.15	0.97-1.37
	678	Drugs used in diabetes	1.03	0.86-1.34	1.03	0.86-1.24
	1172	Other alimentary tract and metabolism products	1.04	0.90-1.20	1.04	0.90-1.20
Blood and blood forming organs	1668	Antithrombotic agents	1.27	1.12-1.44	1.27	1.12-1.45
B	701	Antianemic preparations	1.64	1.39-1.94	1.63	1.38-1.93
	82	Other hematological agents	0.78	0.46-1.34	0.77	0.45-1.32
Cardiovascular system	564	Cardiac therapy	0.92	0.75-1.13	0.92	0.75-1.13
C	2687	Antihypertensives	0.94	0.84-1.05	0.94	0.84-1.06
	1642	Diuretics	0.84	0.73-0.95	0.83	0.73-0.95
	1345	Beta blocking agents	0.89	0.77-1.02	0.89	0.76-1.03
	1290	Other cardiovascular system products	1.05	0.92-1.21	1.06	0.92-1.21
Dermatologicals	266	Antipruritics, incl. antihistamines, anesthetics, etc., antipsoriasis	1.12	0.85-1.48	1.12	0.85-1.48
D	1427	Antibiotics and chemotherapeutics for dermatological use	0.94	0.82-1.08	0.93	0.81-1.06
	3004	Corticosteroids, dermatological preparations	0.96	0.86-1.07	0.96	0.86-1.07
	2140	Other dermatological products	1.08	0.96-1.21	1.07	0.95-1.21
Genito urinary system and sex hormones	1652	Sex hormones and modulators of the genital system	1.07	0.92-1.23	1.07	0.93-1.24
G	1011	Urologicals	1.06	0.90-1.25	1.04	0.88-1.23
	252	Other gynecologicals	0.85	0.62-1.15	0.85	0.63-1.16
Systemic hormonal preparations, excluding sex	1300	Corticosteroids for systemic use	0.86	0.74-0.99	0.85	0.74-0.97
hormones and insulin	501	Thyroid therapy	1.13	0.92-1.40	1.13	0.91-1.39
H	56	Other systemic hormonal preparations	1.00	0.54-1.84	1.01	0.55-1.86
Antiinfectives for systemic use	5889	Antibacterials for systemic use	0.98	0.84-1.14	0.97	0.84-1.13
J	769	Antimycotics for systemic use	0.94	0.79-1.13	0.93	0.78-1.12
	678	Antivirals for systemic use	1.00	0.83-1.20	1.00	0.83-1.20
	385	Vaccines	0.84	0.66-1.08	0.83	0.65-1.06
Musculo-skeletal system	4578	Antiinflammatory and antirheumatic products	1.01	0.90-1.13	1.01	0.90-1.13
M	493	Muscle relaxants	0.96	0.78-1.19	0.95	0.77-1.18
	414	Drugs for treatment of bone diseases	1.11	0.88-1.39	1.10	0.88-1.39
	375	Other musculo-skeletal products	0.94	0.74-1.21	0.94	0.74-1.20
Respiratory system	1541	Nasal preparations	0.93	0.82-1.06	0.93	0.81-1.06
R	1424	Drugs for obstructive airway diseases	0.90	0.79-1.04	0.90	0.78-1.03
	1406	Antihistamines for systemic use	1.07	0.94-1.22	1.07	0.93-1.22
	1884	Other respiratory system products	0.93	0.82-1.05	0.93	0.82-1.05
Sensory organs	3210	Ophthalmologicals	1.04	0.93-1.16	1.03	0.92-1.15
S	533	Otologicals	0.90	0.73-1.11	0.90	0.73-1.11
	518	Ophthalmologicals and otological preparations	1.08	0.88-1.32	1.08	0.88-1.33

Table S5. Incidence rate ratios for medication use in *nervous system* subcategory in time-intervals

Nervous system subcategory	n	Time-interval	Unadjusted		Adjusted	
			IRR	95% CI	IRR	95% CI
Analgesics	4080	**Overall**	0.96	0.86-1.08	0.96	0.86-1.07
		10->5 years prior to index date	1.01	0.90-1.13	1.00	0.89-1.13
		5->1 years prior to index date	0.88	0.79-0.98	0.87	0.78-0.98
		≤1 year prior to index date	0.88	0.77-1.00	0.86	0.76-0.99
Antiepileptics	728	**Overall**	1.06	0.89-1.26	1.05	0.88-1.26
		10->5 years prior to index date	1.12	0.89-1.41	1.12	0.89-1.41
		5->1 years prior to index date	1.06	0.86-1.31	1.05	0.85-1.29
		≤1 year prior to index date	1.20	0.92-1.57	1.18	0.90-1.54
Antipsychotics	448	**Overall**	2.10	1.72-2.55	2.08	1.70-2.54
		10->5 years prior to index date	1.21	0.92-1.58	1.20	0.92-1.58
		5->1 years prior to index date	1.78	1.40-2.28	1.75	1.37-2.24
		≤1 year prior to index date	3.51	2.63-4.69	3.45	2.58-4.63
Anxiolytics	1003	**Overall**	1.26	1.08-1.46	1.24	1.07-1.44
		10->5 years prior to index date	1.08	0.91-1.28	1.06	0.89-1.26
		5->1 years prior to index date	1.19	0.98-1.44	1.17	0.96-1.42
		≤1 year prior to index date	1.63	1.25-2.13	1.63	1.24-2.12
Hypnotics and sedatives	1219	**Overall**	1.07	0.93-1.23	1.06	0.92-1.22
		10->5 years prior to index date	1.03	0.87-1.22	1.02	0.86-1.20
		5->1 years prior to index date	0.90	0.75-1.08	0.89	0.74-1.07
		≤1 year prior to index date	0.84	0.65-1.09	0.83	0.63-1.07
Antidepressants	1759	**Overall**	2.45	2.19-2.77	2.46	2.19-2.78
		10->5 years prior to index date	1.44	1.26-1.64	1.43	1.25-1.64
		5->1 years prior to index date	2.29	2.00-2.61	2.27	1.99-2.60
		≤1 year prior to index date	3.63	3.10-4.25	3.62	3.09-4.24
Other nervous system products	754	**Overall**	1.22	1.03-1.44	1.22	1.03-1.44
		10->5 years prior to index date	1.23	1.00-1.50	1.22	1.00-1.49
		5->1 years prior to index date	1.20	0.97-1.49	1.20	0.97-1.50
		≤1 year prior to index date	1.17	0.82-1.68	1.18	0.82-1.70

Table S6. Post-hoc analysis - Incidence rate ratios for first-ever medication use in *nervous system* subcategory (compared to never-users)

Nervous system subcategory	Time-interval	Unadjusted		Adjusted	
		IRR	95% CI	IRR	95% CI
Analgesics	10->5 years prior to index date	0.95	0.82-1.26	0.95	0.82-1.09
	5->1 years prior to index date	0.91	0.78-1.06	0.91	0.78-1.06
	≤1 year prior to index date	1.29	0.95-1.77	1.25	0.92-1.72
Antiepileptics	10->5 years prior to index date	1.20	0.91-1.59	1.21	0.92-1.61
	5->1 years prior to index date	1.01	0.76-1.33	0.99	0.75-1.31
	≤1 year prior to index date	0.88	0.46-1.68	0.87	0.46-1.66
Antipsychotics	10->5 years prior to index date	1.33	0.93-1.91	1.33	0.92-1.91
	5->1 years prior to index date	2.95	2.04-4.27	2.84	1.96-4.13
	≤1 year prior to index date	13.66	6.64-28.12	13.37	6.49-27.57
Anxiolytics	10->5 years prior to index date	1.23	0.89-1.43	1.10	0.87-1.40
	5->1 years prior to index date	1.28	0.92-1.77	1.25	0.90-1.73
	≤1 year prior to index date	6.13	3.42-10.98	6.12	3.41-10.97
Hypnotics and sedatives	10->5 years prior to index date	1.15	0.93-1.42	1.15	0.93-1.41
	5->1 years prior to index date	1.05	0.79-1.39	1.04	0.78-1.37
	≤1 year prior to index date	1.92	1.11-3.32	1.92	1.11-3.33
Antidepressants	10->5 years prior to index date	1.46	1.21-1.76	1.45	1.20-1.75
	5->1 years prior to index date	4.17	3.31-5.25	4.09	3.25-5.16
	≤1 year prior to index date	12.81	8.46-19.40	12.73	8.39-19.29
Other nervous system products	10->5 years prior to index date	1.12	0.88-1.41	1.11	0.88-1.40
	5->1 years prior to index date	1.15	0.85-1.57	1.15	0.85-1.56
	≤1 year prior to index date	1.32	0.60-2.92	1.35	0.61-2.99

Table S7. Sensitivity analysis by dementia syndrome severity at time of diagnosis – incidence rate ratios by overall categories

Overall category	MCI/MILD DEMENTIA				MODERATE/SEVERE DEMENTIA			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Alimentary tract and metabolism A	0.86	0.75-0.99	0.87	0.76-1.00	1.33	1.10-1.60	1.29	1.07-1.55
Blood and blood forming organs B	1.26	1.08-1.46	1.28	1.01-1.49	1.54	1.28-1.86	1.51	1.25-1.83
Cardiovascular system C	1.05	0.91-1.22	1.07	0.92-1.24	1.09	0.90-1.33	1.07	0.88-1.30
Dermatologicals D	0.96	0.84-1.11	0.96	0.83-1.10	1.05	0.87-1.26	1.04	0.86-1.26
Genito urinary system and sex hormones G	1.14	0.99-1.31	1.13	0.98-1.31	0.91	0.75-1.10	0.92	0.76-1.12
Systemic hormonal preparations, excluding sex hormones and insulin H	0.95	0.80-1.12	0.96	0.81-1.13	0.92	0.74-1.13	0.89	0.72-1.10
Antiinfectives for systemic use J	1.02	0.84-1.25	1.01	0.83-1.24	0.93	0.72-1.20	0.92	0.71-1.20
Antineoplastic and immunomodulating agents L	0.80	0.50-1.29	0.82	0.52-1.31	0.77	0.43-1.37	0.75	0.42-1.35
Musculo-skeletal system M	0.97	0.83-1.12	0.98	0.84-1.13	1.03	0.85-1.25	1.01	0.84-1.23
Nervous system* N	1.21	1.04-1.41	1.24	1.06-1.44	1.93	1.55-2.41	1.88	1.50-2.35
Antiparasitic products, insecticides, and repellents P	0.91	0.77-1.08	0.91	0.77-1.08	0.98	0.79-1.21	0.95	0.76-1.18
Respiratory system R	1.08	0.84-1.24	1.08	0.94-1.24	0.90	0.75-1.07	0.89	0.74-1.07
Sensory organs S	1.05	0.91-1.20	1.04	0.91-1.19	0.94	0.78-1.12	0.94	0.79-1.17

*Dementia medication (table S1) is omitted in the conditional logistic regression

Table S8. Sensitivity analysis by age at time of diagnosis – incidence rate ratios by overall categories

Overall category	AGE <55 years				AGE ≥55 YEARS			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Alimentary tract and metabolism A	0.82	0.52-1.29	0.77	0.49-1.23	1.02	0.91-1.15	1.02	0.91-1.14
Blood and blood forming organs B	0.98	0.57-1.69	0.90	0.52-1.56	1.39	1.23-1.56	1.39	1.23-1.57
Cardiovascular system C	0.89	0.59-1.38	0.85	0.55-1.33	1.08	0.96-1.22	1.09	0.96-1.23
Dermatologicals D	0.92	0.59-1.42	0.92	0.59-1.45	0.98	0.89-1.12	0.99	0.89-1.11
Genito urinary system and sex hormones G	1.29	0.78-2.11	1.26	0.76-2.09	1.04	0.93-1.17	1.03	0.92-1.16
Systemic hormonal preparations, excluding sex hormones and insulin H	0.83	0.46-1.48	0.81	0.45-1.48	0.94	0.82-1.07	0.93	0.82-1.07
Antiinfectives for systemic use J	1.34	0.73-2.45	1.20	0.65-2.23	0.96	0.82-1.13	0.95	0.81-1.12
Antineoplastic and immunomodulating agents L	0.86	0.18-4.13	0.86	0.18-4.25	0.79	0.53-1.13	0.78	0.53-1.13
Musculo-skeletal system M	0.93	0.58-1.48	0.91	0.56-1.47	0.99	0.88-1.12	0.99	0.88-1.12
Nervous system* N	1.53	0.93-2.51	1.44	0.87-2.39	1.41	1.24-1.60	1.41	1.24-1.60
Antiparasitic products, insecticides, and repellents P	1.08	0.66-1.78	1.00	0.59-1.68	0.93	0.81-1.06	0.92	0.80-1.06
Respiratory system R	1.26	0.82-1.95	1.19	0.76-1.86	0.99	0.89.1.11	0.99	0.88-1.11
Sensory organs S	0.86	0.56-1.34	0.81	0.51-1.27	1.02	0.91-1.14	1.01	0.90-1.13

*Dementia medication (table S1) is omitted in the conditional logistic regression

Table S9. Sensitivity analysis by sex – incidence rate ratios by overall categories

Overall category	FEMALE				MALE			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Alimentary tract and metabolism A	1.05	0.91-1.22	1.05	0.91-1.21	0.95	0.80-1.13	0.95	0.80-1.12
Blood and blood forming organs B	1.42	1.22-1.66	1.42	1.21-1.66	1.29	1.08-1.54	1.30	1.08-1.55
Cardiovascular system C	0.99	0.85-1.15	1.00	0.86-1.17	1.18	0.99-1.41	1.18	0.98-1.41
Dermatologicals D	0.95	0.82-1.10	0.95	0.82-1.10	1.41	0.89-1.24	1.04	0.88-1.24
Genito urinary system and sex hormones G	1.05	0.91-1.22	1.07	0.92-1.23	1.04	0.87-1.26	1.01	0.84-1.22
Systemic hormonal preparations, excluding sex hormones and insulin H	0.95	0.80-1.11	0.94	0.80-1.11	0.91	0.74-1.13	0.91	0.74-1.12
Antiinfectives for systemic use J	0.95	0.75-1.20	0.96	0.76-1.21	1.02	0.82-1.27	0.98	0.79-1.22
Antineoplastic and immunomodulating agents L	0.85	0.54-1.31	0.85	0.54-1.32	0.68	0.35-1.32	0.67	0.34-1.29
Musculo-skeletal system M	0.95	0.81-1.10	0.95	0.81-1.11	1.05	0.88-1.26	1.03	0.86-1.23
Nervous system* N	1.46	1.23-1.73	1.44	1.22-1.71	1.37	1.15-1.64	1.37	1.14-1.65
Antiparasitic products, insecticides, and repellents P	0.99	0.84-1.16	0.98	0.83-1.15	0.85	0.67-1.06	0.83	0.66-1.05
Respiratory system R	0.98	0.84-1.13	0.98	0.85-1.13	1.05	0.89-1.25	1.04	0.88-1.24
Sensory organs S	1.03	0.89-1.19	1.04	0.90-1.20	0.97	0.82-1.15	0.95	0.80-1.13

*Dementia medication (table S1) is omitted in the conditional logistic regression

Table S10. Sensitivity analysis, censoring MCI

Overall category	MILD DEMENTIA/MODERATE/SEVERE DEMENTIA			
	Unadjusted		Adjusted	
	IRR	95% CI	IRR	95% CI
Alimentary tract and metabolism **A**	1.01	0.90-1.13	1.00	0.90-1.12
Blood and blood forming organs B	1.38	1.22-1.55	1.38	1.22-1.55
Cardiovascular system **C**	1.06	0.94-1.19	1.05	0.93-1.19
Dermatologicals D	1.00	0.89-1.12	1.00	0.89-1.12
Genito urinary system and sex hormones G	1.02	0.91-1.15	1.02	0.91-1.14
Systemic hormonal preparations, excluding sex hormones and insulin H	0.92	0.81-1.06	0.91	0.80-1.04
Antiinfectives for systemic use J	0.97	0.83-1.14	0.97	0.82-1.1.3
Antineoplastic and immunomodulating agents L	0.80	0.55-1.17	0.80	0.55-1.16
Musculo-skeletal system M	0.98	0.87-1.10	0.98	0.87-1.10
Nervous system* N	1.42	1.25-1.61	1.41	1.24-1.61
Antiparasitic products, insecticides, and repellents P	0.93	0.81-1.06	0.92	0.80-1.06
Respiratory system R	0.99	0.88-1.10	0.99	0.88-1.10
Sensory organs S	0.99	0.88-1.11	0.99	0.88-1.11

*Dementia medication (table S1) is omitted in the conditional logistic regression

Table S11. Sensitivity analysis, censoring prescription medication use 6 months prior to index date

Overall category	Time-interval	Unadjusted		Adjusted	
		IRR	95% CI	IRR	95% CI
Alimentary tract and metabolism	**Overall**	1.01	0.90-1.13	1.04	0.90-1.12
A	10->5 years prior to index date	0.98	0.88-1.10	0.98	0.87-1.09
	5->1 years prior to index date	0.96	0.86-1.07	0.96	0.86-1.07
	≤1 year-6 months prior to index date	0.90	0.78-1.4	0.90	0.78-1.04
Blood and blood forming organs	**Overall**	1.36	1.21-1.53	1.37	1.24-1.54
B	10->5 years prior to index date	0.99	0.86-1.14	0.99	0.86-1.14
	5->1 years prior to index date	1.28	1.12-1.45	1.27	1.12-1.45
	≤1 year-6 months prior to index date	1.44	1.23-1.67	1.44	1.24-1.68
Cardiovascular system	**Overall**	1.07	0.95-1.20	1.07	0.95-1.20
C	10->5 years prior to index date	1.04	0.93-1.16	1.05	0.94-1.17
	5->1 years prior to index date	1.06	0.95-1.18	1.07	0.95-1.19
	≤1 year-6 months prior to index date	1.00	0.89-1.14	1.01	0.90-1.15
Dermatologicals	**Overall**	0.99	0.89-1.11	0.99	0.89-1.11
D	10->5 years prior to index date	1.06	0.95-1.18	1.06	0.95-1.18
	5->1 years prior to index date	0.89	0.80-0.99	0.89	0.79-0.99
	≤1 year-6 months prior to index date	0.93	0.77-1.13	0.92	0.76-1.12
Genito urinary system and sex hormones	**Overall**	1.05	0.94-1.18	1.05	0.93-1.17
G	10->5 years prior to index date	1.06	0.94-1.20	1.06	0.94-1.20
	5->1 years prior to index date	1.05	0.93-1.18	1.04	0.92-1.18
	≤1 year-6 months prior to index date	0.76	0.63-0.92	0.75	0.63-0.91
Systemic hormonal preparations, excluding sex hormones and insulin	**Overall**	0.93	0.82-1.06	0.93	0.82-1.06
	10->5 years prior to index date	1.00	0.87-1.17	1.00	0.86-1.16
H	5->1 years prior to index date	0.93	0.78-1.08	0.91	0.79-1.07
	≤1 year-6 months prior to index date	0.92	0.73-1.16	0.92	0.73-1.16
Antiinfectives for systemic use	**Overall**	0.99	0.84-1.16	0.98	0.84-1.14
J	10->5 years prior to index date	1.04	0.92-1.18	1.04	0.91-1.17
	5->1 years prior to index date	0.86	0.77-0.96	0.85	0.76-0.96
	≤1 year-6 months prior to index date	0.99	0.84-1.16	0.99	0.84-1.16
Antineoplastic and immunomodulating agents	**Overall**	0.79	0.55-1.14	0.78	0.51-1.13
L	10->5 years prior to index date	0.60	0.38-0.96	0.60	0.38-0.97
	5->1 years prior to index date	1.01	0.65-1.57	1.00	0.65-1.56
	≤1 year-6 months prior to index date	1.00	0.52-1.93	1.00	0.52.1.93
Musculo-skeletal system	**Overall**	0.99	0.88-1.11	0.99	0.88-1.11
M	10->5 years prior to index date	1.03	0.92-1.14	1.03	0.92-1.15
	5->1 years prior to index date	0.95	0.85-1.06	0.95	0.85-1.06
	≤1 year-6 months prior to index date	0.81	0.68-0.96	0.80	0.67-0.95

Nervous system*	**Overall**	1.42	1.25-1.60	1.41	1.25-1.60
N	10->5 years prior to index date	1.18	1.06-1.31	1.17	1.05-1.31
	5->1 years prior to index date	1.21	1.08-1.35	1.20	1.07-1.34
	≤1 year-6 months prior to index date	1.41	1.24-1.60	1.40	1.24-1.59
Antiparasitic products, insecticides, and repellents	**Overall**	0.94	0.82-1.07	0.93	0.81-1.06
P	10->5 years prior to index date	1.02	0.87-1.19	1.01	0.87-1.19
	5->1 years prior to index date	0.86	0.72-1.03	0.85	0.71-1.02
	≤1 year-6 months prior to index date	0.89	0.57-1.40	0.88	0.56-1.39
Respiratory system	**Overall**	1.01	0.90-1.13	1.01	0.90-1.12
R	10->5 years prior to index date	1.01	0.90-1.13	1.01	0.90-1.13
	5->1 years prior to index date	0.92	0.82-1.03	0.92	0.82-1.03
	≤1 year-6 months prior to index date	0.61	0.51-0.74	0.61	0.51-0.73
Sensory organs	**Overall**	1.01	0.90-1.12	1.00	0.90-1-12
S	10->5 years prior to index date	1.12	1.00-1.25	1.12	1.00-1.25
	5->1 years prior to index date	0.87	0.77-0.98	0.87	0.77-0.98
	≤1 year-6 months prior to index date	0.77	0.61-0.97	0.77	0.61-0.97

*Dementia medication (table S1) is omitted in the conditional logistic regression

Supplementary figures

Figure S1. Incidence rate ratios for medication use in *nervous system* subcategory in time intervals (first prescriptions only)

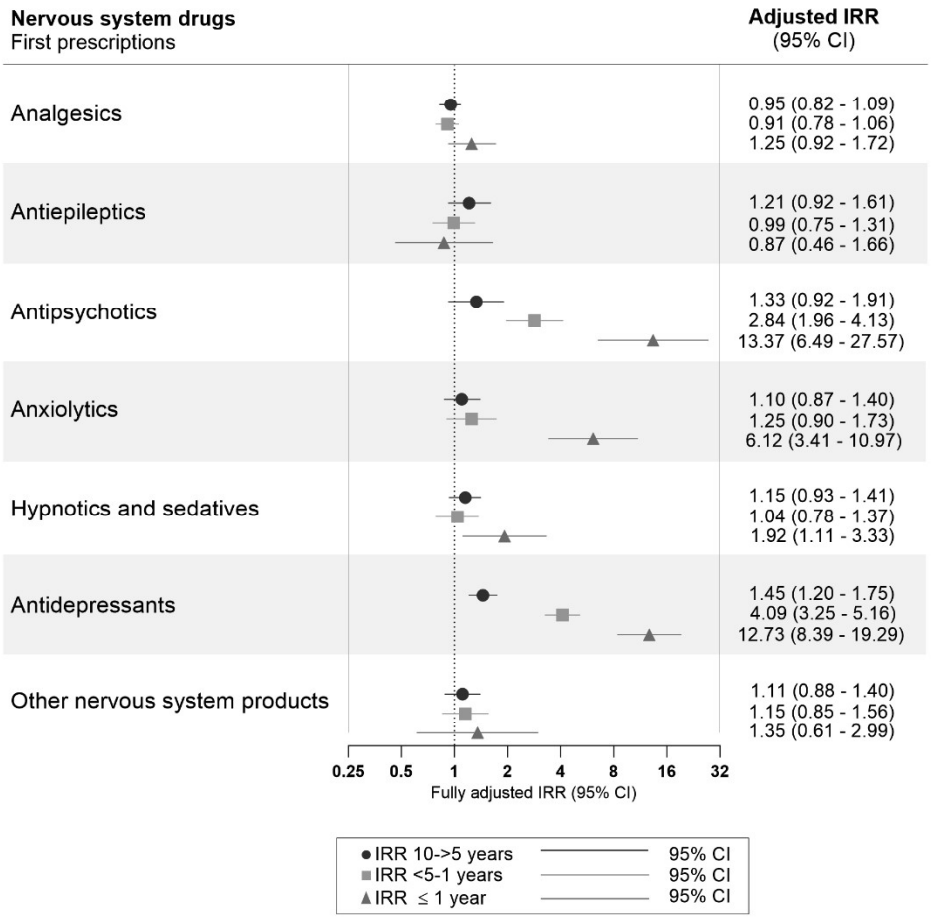

Figure S1 legend: Incidence rate ratios (IRRs) for young onset Alzheimer's disease are plotted by first-ever prescriptions, compared to no prescriptions, in the *nervous system* subcategories in the 10-year retrospective study period and in three time-intervals prior to diagnosis. Conditional logistic regression analyses produced odds ratios, which given the use of incidence-density matching is interpretable as IRRs. For the refence group (dementia-free controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals (CI). The IRRs presented are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis if age at diagnosis <40 years), and civil status at index date. Unadjusted estimates are presented in table S6.

Figure S2. Sensitivity analysis: Incidence rate ratios by overall medication category in the 10-year study period, for the entire study population and divided by disease severity at time of diagnosis.

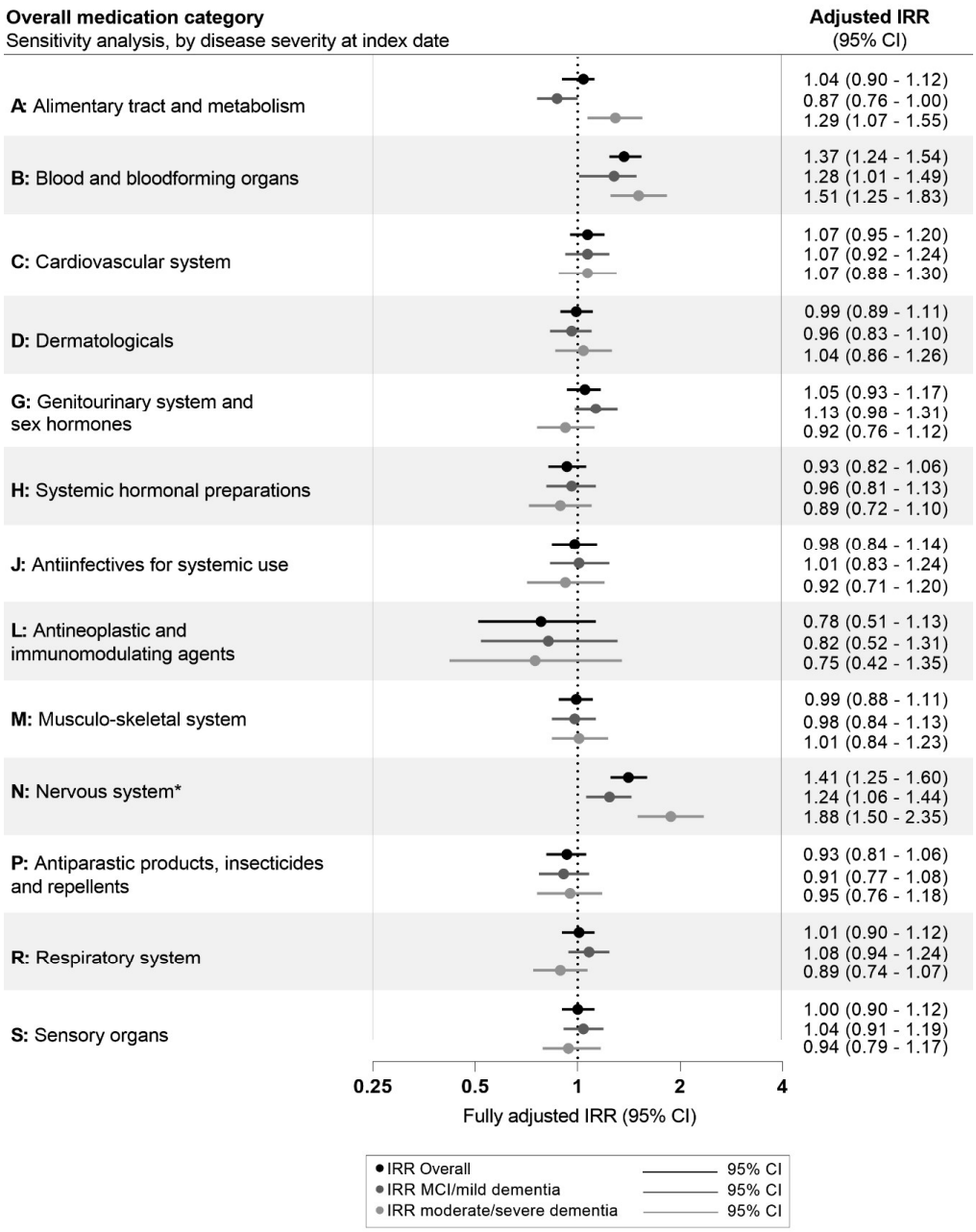

Figure S2 legend: Incidence rate ratios (IRRs) for young onset Alzheimer's disease are plotted by overall medication categories in the 10-year retrospective study period and in three time-intervals prior to diagnosis for the entire study population and divided by disease severity at time of diagnosis. Conditional logistic regression analyses produced odds ratios, which given the use of incidence-density matching is interpretable as IRRs. For the refence group (dementia-free controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals (CI). The IRRs presented are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis if age at diagnosis <40 years), and civil status at index date. Unadjusted estimates are presented in table S7. * Not including dementia medication (see ATC-codes used in table S2).

Figure S3. Sensitivity analysis: Incidence rate ratios by overall medication category in the 10-year study period and in time intervals – for the entire study population and stratified by age.

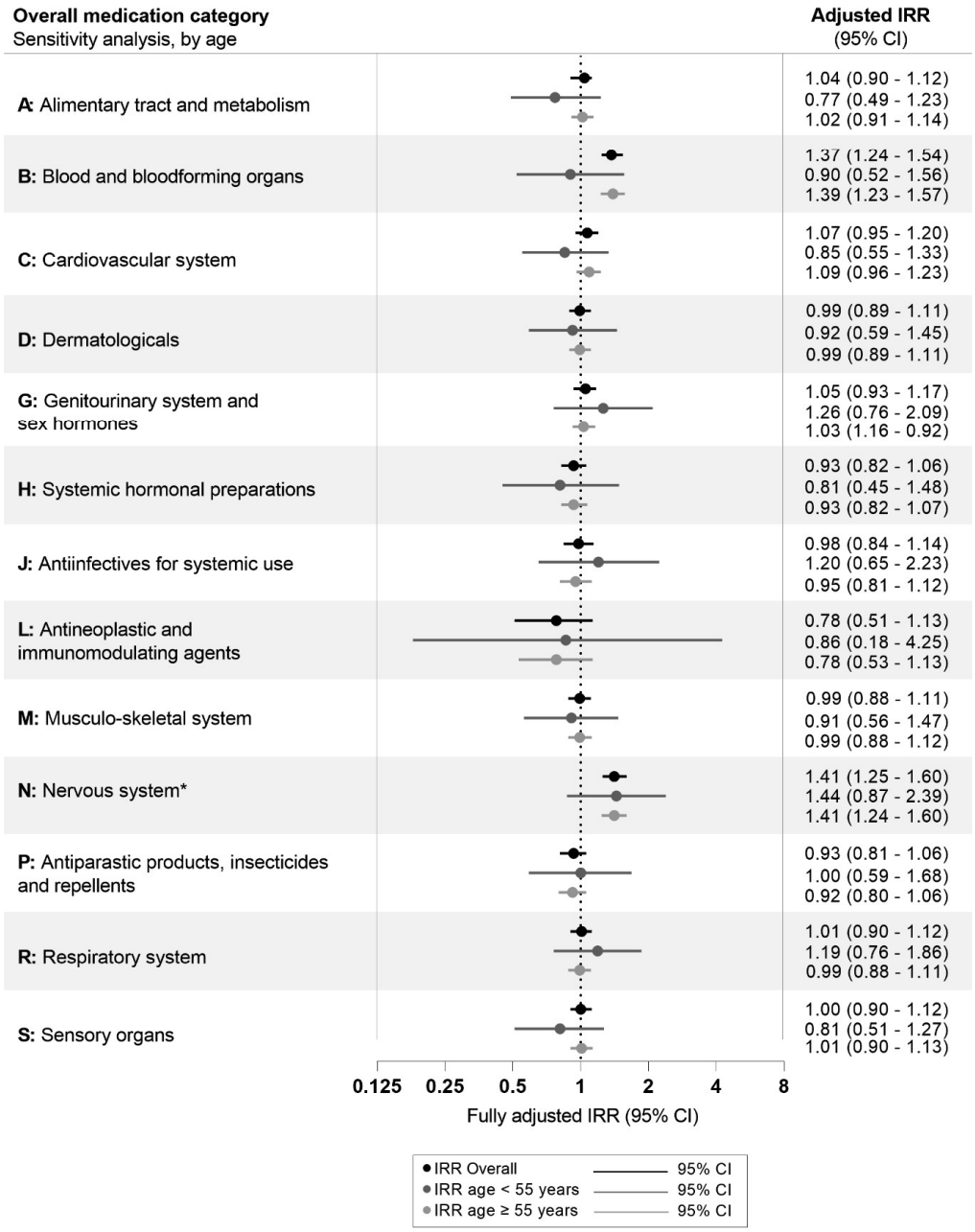

Figure S3 legend: Incidence rate ratios (IRRs) for young onset Alzheimer's disease are plotted by overall medication categories in the 10-year retrospective study period and in three time-intervals prior to diagnosis for the entire study population and stratified by age. Conditional logistic regression analyses produced odds ratios, which given the use of incidence-density matching is interpretable as IRRs. For the refence group (dementia-free controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals (CI). The IRRs presented are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis if age at diagnosis <40 years), and civil status at index date. Unadjusted estimates are presented in table S8. * Not including dementia medication (see ATC-codes used in table S2).

Figure S4. Sensitivity analysis: Incidence rate ratios by overall medication category in the 10-year study period and in time intervals – for the entire study population and divided by sex.

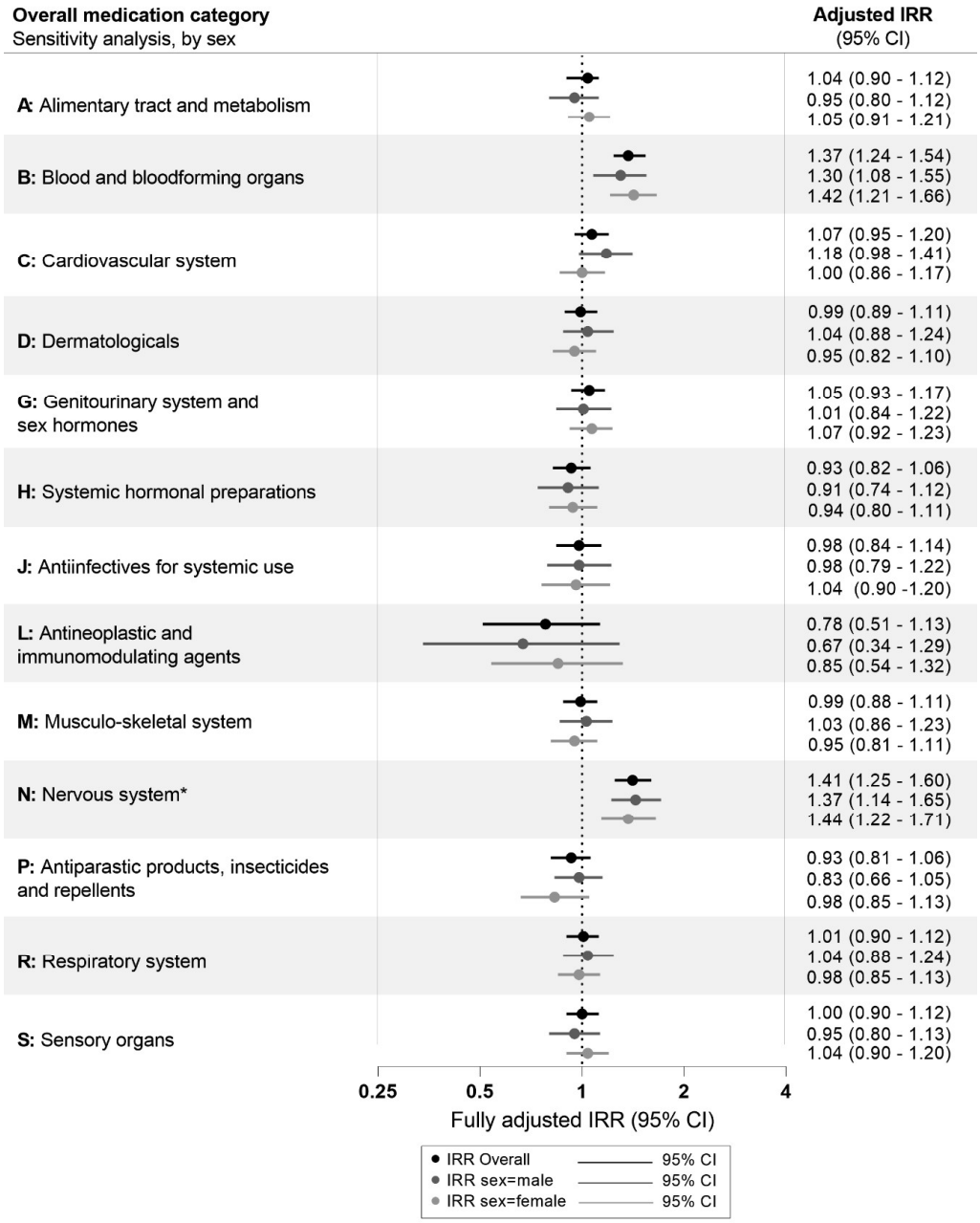

Figure S4 legend: Incidence rate ratios (IRRs) for young onset Alzheimer's disease are plotted by overall medication categories in the 10-year retrospective study period and in three time-intervals prior to diagnosis for the entire study population and divided by sex. Conditional logistic regression analyses produced odds ratios, which given the use of incidence-density matching is interpretable as IRRs. For the refence group (dementia-free controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals (CI). The IRRs presented are adjusted for age, highest attained educational level at age 40 years (or at time of diagnosis if age at diagnosis <40 years), and civil status at index date. Unadjusted estimates are presented in table S9. * Not including dementia medication (see ATC-codes used in table S2).

8.4 Study 4

STUDY 4

Patterns of sick leave and unemployment prior to a diagnosis of young onset Alzheimer's disease

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Abstract

INTRODUCTION: Early symptoms in young onset Alzheimer's disease (YOAD) may be misinterpreted, causing delayed diagnosis. This population-based study aimed to map adverse occupational events preceding YOAD diagnosis as potential prodromal signs.

METHODS: In a register-based, incidence-density-matched nested case-control study, we examined unemployment and long-term sick leave among individuals diagnosed with YOAD in Danish memory clinics during 2016-2022 compared with controls over a 13-year period. Conditional logistic regression produced incidence rate ratios (IRRs).

RESULTS: The study included 2434 cases and 12,170 controls. YOAD patients had higher rates of adverse occupational events, particularly long-term sick leave, starting from 8 years before diagnosis (IRR 1.41, 95% CI 1.08-1.85) and increasing to an IRR of 29.59 (95% CI 18.97-46.14) in the year before diagnosis.

DISCUSSION: Adverse occupational events may serve as early markers of YOAD. Timely diagnosis could facilitate restructuring the remaining working life to accommodate cognitive deficits, or in seeking disability pension.

Keywords: Young onset dementia; Alzheimer's disease; Occupation; Early warning signs; Registry-based; Epidemiology

1. Background

While late onset dementia has been the subject of intense research there has been far less focus on young onset dementia, defined as dementia debuting before age 65 years[1]. Patients with young onset dementia are often part of the active workforce when symptoms arise, whereas those with late onset dementia are most often retired. In our prior research, we have demonstrated that patients who are diagnosed with young onset Alzheimer's disease (YOAD) have increased healthcare utilization up to 10 years prior to Alzheimer's disease (AD) diagnosis[2]. In line with this, we also found increased psychiatric morbidity and medication use prior to diagnosis, which was evident up to 10 years before YOAD diagnosis[3,4]. This points to a prolonged period of vulnerability prior to diagnosis, which may also affect workforce participation, resulting in sick leave or unemployment. Decreasing abilities to perform work tasks as usual may lead to conflicts, termination of employment, or feelings of inadequacy[5], and extra care should be taken to ensure a timely diagnosis in individuals with young onset dementia.

Qualitative studies have shown that for those in paid employment, the workplace was often the first place where patients became aware of cognitive problems[6], and reduced capacity to carry out habituated routines would lead to an initiation of medical investigation or to termination of the employment for those later diagnosed with dementia[7].

While there are multiple qualitative studies that explored the challenges around working life and dementia, there is a dearth of quantitative research examining occupational changes as possible early markers of the YOAD prodrome. Such occupational changes could include unemployment, sick leave, early retirement, frequent job changes, or other adverse occupational events. A long diagnostic delay has been described for YOAD patients[8], and as many are still in paid employment as cognitive symptoms emerge and progress, the likelihood of experiencing adverse occupational events increases. This can lead to significant financial strain, highlighting the critical need for a timely diagnosis. Adverse occupational events could potentially constitute early signs of YOAD, thus aiding in the increased knowledge on the earliest signs and symptoms of YOAD necessary to ensure a timely diagnosis.

The aim of this study was to explore patterns of long-term sick leave and unemployment in patients with YOAD compared with cognitively healthy, matched adults.

2. Methods

We conducted a nationwide, retrospective nested case-control study including all Danish YOAD patients, following similar methodology as in our prior studies of this study population[2–4]. YOAD cases

and matched controls were identified in the years 2016-2022, and exposure status was assessed on a yearly basis from January 1st, 2009, allowing for 8-13 years of retrospective follow-up.

2.1 Data sources

The study was conducted using Danish nationwide registers[9]. The Civil Registration System contains general population data and was used for linkage across the different registers through each resident's unique identifier[10]. Cases were defined based on data from the Danish Dementia Quality Database (DanDem). Occupational information was drawn from the Labour Market Accounts Register[11]. Information on diagnoses and medication used in the selection of cases and controls was drawn from the Danish National Patient Register[12,13], the Danish Psychiatric Central Research Register[14], and the Danish National Prescription Registry[15]. Information on covariates came from the Population Education Register[16] and the Civil Registration System[17].

2.2 Study population

2.2.1 Case definition: Cases were identified from DanDem. All Danish healthcare facilities that accept referrals for diagnostic evaluation of dementia and cognitive impairment must enter information such as etiology, severity of the dementia syndrome at time of diagnosis (if applicable), and diagnostic investigations performed including results of selected cognitive tests, upon completion of diagnostic evaluation. The database contains information on all patients seen at Danish memory clinics from establishment of the database in 2016 onwards. By convention, YOAD is defined as dementia due to AD with symptom onset before age 65 years[1]. As time of symptom onset is not available in our data, this was approximated using date of diagnosis assuming a 5-year time lag between symptom onset and final diagnosis, as prior research has shown mean time to diagnosis around 5 years for YOAD patients[8,18]. Therefore, we included all patients with a first diagnosis of MCI or dementia due to AD from start of register (2016) through 2022 aged <70 years at time of diagnosis. Index time was set to date of diagnosis in DanDem.

2.2.2 Control definition: Each case was matched to five controls drawn from the full risk set, i.e., the entire Danish population[19]. Each control was at risk for first YOAD at matching date. Thus, incidence density sampling was used to draw controls, allowing the odds ratios from the conditional logistic regression to be interpreted as incidence rate ratios (IRRs)[20,21]. Exclusion criteria for controls were a prior dementia diagnosis in the Danish National Patient Register or the Danish Psychiatric Central Research Register, having received at least one antidementia medication in the Danish National

Prescription Registry, or visits to a memory clinic before index date (codes for identification of exclusion criteria: Table S1).

2.2.3 Exclusions: Individuals with a primary/secondary diagnostic code indicating Down syndrome (ICD-8: 759.3, ICD-10: Q90) and Mental Retardation (ICD-8: 311-315, ICD-10: F70-F79) were excluded from the study population on the date of first occurrence. To ensure completeness of data, cases and controls must have lived in Denmark in the entire retrospective period. All exclusion criteria can be seen in Table S1.

2.3 Exposures, censoring, and covariates

Exposure data were extracted from the Labor Market Accounts Register and were examined in yearly time-intervals corresponding to years before index date.

2.3.1 Unemployment (exposure 1): Defined as having a registration of any social benefit relating to unemployment, such as unemployment benefits provided to members of an unemployment insurance fund, or social assistance (a financial support system for basic living expenses for those not eligible for unemployment benefits).

2.3.2 Long-term sick leave (exposure 2): Defined as a registration of sick leave for more than 30 consecutive days. This time limit was chosen due to data availability, as sick leave absence of ≤30 consecutive days is in most cases paid by the employer and therefore not registered in public databases.

2.3.3 Part of the active workforce (reference group for exposures): The reference group included all those who were continuously part of the active work force in a given time interval, i.e., those with a registration of paid employment, not exposed (i.e., not unemployed and not on sick leave), and not censored (as detailed next).

2.3.4 Censoring events: We censored individuals from the date that they were not at risk for the exposures, either temporarily or permanently. Individuals outside of the active workforce due to education or (parental) leave were temporarily censored in the given time intervals with the possibility of re-entering the active study population upon termination of the education or leave period. Furthermore, those with both exposures in a given interval were included in both analyses, whereas those with only one of the two exposures under examination were included as exposed in the relevant

analysis and censored in the other. Likewise, individuals with missing data or for whom the interval was before study start (January 1st, 2009) were temporarily censored in the given intervals.

Those working in a "flex job" (a specific type of employment, the right to which can be awarded due to diminished work ability due to health conditions), those receiving disability pension, and retired individuals were permanently censored starting from the interval in which the censoring event first occurred.

For detailed descriptions of the labor market affiliations used in the study, see supplementary methods section 2.3S Labor market affiliations).

2.3.5 Covariates: We included the following covariates: age, sex, highest attained educational level at age 40 years (or at time of diagnosis, whichever came first), and civil status at index date.

2.4 Data analysis

2.4.2 Main analyses: For each of the two exposures, we used a conditional logistic regression model to investigate the association between having at least one period of either long-term sick leave or unemployment [yes/no] in the given time interval and subsequent YOAD compared with those working throughout the entire interval, yielding IRRs. The two exposures were examined in yearly time-intervals corresponding to years before index date (12-<13 years, 11-<12 years, …, <1 year). Exposure events were assigned to intervals based on the starting date and were further included in all intervals they spanned (see supplementary methods 2.4S for further details on assignment of exposures to time-intervals). Thus, individuals under study were those with the exposure and those continuously part of the active workforce (reference group) in each interval and were followed until censoring or index date. Each matched case-control set served as a stratum in the regression model.

For long-term sick leave, we further wanted to quantify the amount of time spent on long-term sick leave. We therefore calculated the percentage of cases and controls with either 0, 1, 2-3, 4-6 or >6 months of long-term sick leave with a starting date in the given interval, until censoring or index date (see supplementary methods 2.4S for further details on quantification of sick leave periods).

2.4.3 Sensitivity analysis

We analyzed the association between the two exposures and YOAD stratified by sex and by disease severity (MCI/mild dementia or moderate/severe dementia). As the COVID-19 pandemic may have impacted patterns in both healthcare utilization[22] and labor market affiliation[23], we also conducted a sensitivity analysis limiting the study population to only include those with index date before March 1st, 2020.

All results are presented with 95% confidence intervals (CI), corresponding to a 5% significance level. Results of analyses are presented unadjusted as well as adjusted for the covariates listed in 2.3.5. Statistical analyses were performed with SAS 9.4 software using PROC logistic. This research project is approved by the Danish Data Protection Agency, Statistics Denmark, and the Danish Health Data Authority. Danish law does not require ethics committee approval or informed patient consent.

3. Results

Out of 24,900 individuals diagnosed with AD in a Danish memory clinic in the years 2016-2022, 2567 were diagnosed before the age of 70. Following the application of exclusion criteria, the study population comprised 2434 YOAD cases and 12,170 controls. The mean age at diagnosis was 64.4 years, and 59% were female (Table 1). At the time of diagnosis, 64% of cases had either MCI or mild dementia, while 36% had moderate to severe dementia. Educational attainment and civil status at index date were similarly distributed among cases and controls.

Table 1. Baseline characteristics of study population

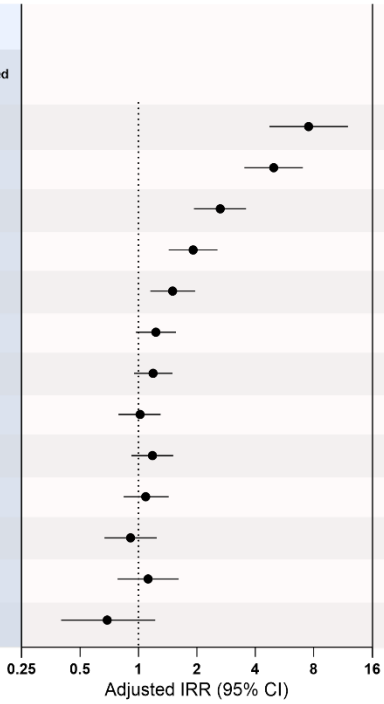
	CASES N=2434	CONTROLS N=12,170
Age at index date, mean years (sd)	64.4 (5.0)	64.4 (5.0)
Sex, male/female, n (%)	1010 (41%) / 1424 (59%)	6060 (41%) / 8544 (59%)
Dementia syndrome severity at time of diagnosis, n (%)		
Mild cognitive impairment	139 (6%)	-
Mild dementia	1421 (58%)	-
Moderate dementia	723 (30%)	-
Severe dementia	151 (6%)	-
Cognitive examination scores at first visit*, mean (sd)		
MMSE	21.2 (5.5)	-
ACE	65.6 (15.3)	-
Educational attainment at age 40, n (%)		
Low	1658 (68%)	8325 (68%)
Medium	527 (22%)	2579 (21%)
High	149 (6%)	775 (6%)
Unknown	100 (4%)	491 (4%)
Civil status at index date, n (%)		
Married	1496 (61%)	7620 (63%)
Divorced	474 (19%)	2190 (18%)
Widowed	177 (7%)	847 (7%)
Never married	261 (11%)	1426 (12%)
Unknown	26 (1%)	87 (1%)

*__MMSE__: Mini-Mental State Examination (reliable information for 2213 YOAD patients). **ACE**: Addenbrooke's Cognitive Examination (reliable information for 1780 YOAD patients). **Sd**: standard deviation. Note: Where percentages do not add up to 100%, this is due to rounding up/down.

Figure 1 shows the association between having a period of unemployment and subsequent YOAD compared with those continuously part of the active workforce. Significant differences in the rate of unemployment were seen from the time-interval 4-<5 years prior to index date. Among non-censored individuals, 11% of cases and 8% of controls had at least one period of unemployment five years prior to diagnosis, yielding an IRR of 1.50 (95% CI 1.15-1.96). The proportion of controls with periods of unemployment was relatively steady across time intervals, whereas for cases, 40% had periods of unemployment in the year immediately prior to diagnosis. This resulted in progressively increasing IRRs nearing index date, with a 7.5-fold increase in unemployment rate for YOAD cases in the <1 year prior to diagnosis.

Figure 1. Incidence rate ratios for unemployment and young onset Alzheimer's disease

Unemployment	Cases			Controls			
Time interval	Unemployed n (%)	Active workforce n (%)	Censored n	Unemployed n (%)	Active workforce n (%)	Censored n	Adjusted IRR (95% CI)
< 1 year prior to index date	84 (40%)	125 (60%)	2225	251 (8%)	3039 (92%)	8880	7.52 (4.72 - 11.98)
1 - <2 years prior to index date	102 (23%)	349 (77%)	1983	261 (7%)	3489 (93%)	8420	4.97 (3.51 - 7.04)
2 - <3 years prior to index date	94 (15%)	514 (85%)	1826	292 (7%)	3948 (93%)	7930	2.64 (1.93 - 3.59)
3 - <4 years prior to index date	94 (13%)	651 (87%)	1689	339 (7%)	4436 (93%)	7395	1.91 (1.43 - 2.55)
4 - <5 years prior to index date	99 (11%)	813 (89%)	1522	425 (8%)	5062 (92%)	6683	1.50 (1.15 - 1.96)
5 - <6 years prior to index date	118 (11%)	992 (89%)	1324	504 (8%)	5720 (92%)	5946	1.23 (0.97 - 1.56)
6 - <7 years prior to index date	120 (10%)	1105 (90%)	1209	515 (8%)	6157 (92%)	5498	1.19 (0.95 - 1.50)
7 - <8 years prior to index date	98 (8%)	1066 (92%)	1270	484 (8%)	5722 (92%)	5964	1.02 (0.79 - 1.30)
8 - <9 years prior to index date	102 (10%)	946 (90%)	1386	453 (8%)	5052 (92%)	6665	1.18 (0.92 - 1.51)
9 - <10 years prior to index date	86 (10%)	784 (90%)	1564	403 (8%)	4203 (91%)	7564	1.09 (0.84 - 1.43)
10 - <11 years prior to index date	59 (9%)	630 (91%)	1745	337 (9%)	3304 (91%)	8529	0.91 (0.67 - 1.24)
11 - <12 years prior to index date	44 (9%)	427 (91%)	1963	227 (9%)	2258 (91%)	9685	1.12 (0.78 - 1.61)
12 - <13 years prior to index date	17 (7%)	239 (93%)	2178	114 (9%)	1124 (91%)	10932	0.69 (0.40 - 1.22)



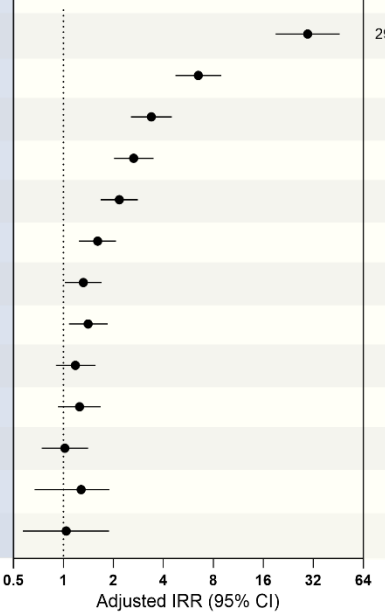
Incidence rate ratios (**IRRs**) for unemployment and young onset Alzheimer's disease are plotted in time intervals prior to index date. For the refence group (dementia-free controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals (**CI**). The IRRs presented are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis, whichever came first), and civil status at index date. A breakdown of the censored population can be found in Table S2. Unadjusted estimates are presented in Table S4.

The same tendency can be seen for long-term sick leave (Figure 2). Here, significant differences were observed from 7-<8 years prior to index date. In this time interval, 7% of cases and 6% of controls had at least one period of long-term sick leave, yielding an IRR of 1.41 (95% CI 1.08-1.85). This steadily increased to an IRR of 29.59 (95% CI 18.97-46.14) in the year immediately prior to diagnosis, corresponding to a near 30-fold increased likelihood that those later diagnosed with YOAD had at least

one period of long-term sick leave in the year before diagnosis, compared with controls. In the year prior to index date, 67% of cases had at least one period of long-term sick leave, as opposed to 7% of controls.

Figure 2. Incidence rate ratios for long-term sick leave and young onset Alzheimer's disease

Long-term sick leave	Cases			Controls			
Time interval	Sick leave n (%)	Active workforce n (%)	Censored n	Sick leave n (%)	Active workforce n (%)	Censored n	Adjusted IRR (95% CI)
< 1 year prior to index date	253 (67%)	125 (33%)	2054	224 (7%)	3039 (93%)	8907	29.59 (18.97 - 46.14)
1 - <2 years prior to index date	139 (28%)	346 (72%)	1944	238 (6%)	3489 (94%)	8443	6.50 (4.73 - 8.94)
2 - <3 years prior to index date	118 (19%)	514 (81%)	1800	263 (6%)	3948 (94%)	7959	3.39 (2.55 - 4.50)
3 - <4 years prior to index date	119 (15%)	651 (85%)	1662	310 (7%)	4436 (93%)	7424	2.65 (2.02 - 3.49)
4 - <5 years prior to index date	115 (12%)	813 (88%)	1504	326 (6%)	5062 (94%)	6782	2.17 (1.67 - 2.81)
5 - <6 years prior to index date	103 (9%)	992 (91%)	1337	375 (6%)	5720 (94%)	6075	1.61 (1.24 - 2.07)
6 - <7 years prior to index date	101 (8%)	1105 (92%)	1226	416 (6%)	6157 (94%)	5597	1.32 (1.02 - 1.70)
7 - <8 years prior to index date	84 (7%)	1066 (93%)	1282	356 (6%)	5722 (94%)	6092	1.41 (1.08 - 1.85)
8 - <9 years prior to index date	77 (8%)	946 (92%)	1409	337 (6%)	5052 (94%)	6781	1.18 (0.90 - 1.56)
9 - <10 years prior to index date	70 (8%)	784 (92%)	1578	289 (6%)	4203 (94%)	7678	1.25 (0.93 - 1.67)
10 - <11 years prior to index date	53 (8%)	630 (92%)	1749	264 (7%)	3304 (93%)	8602	1.02 (0.74 - 1.41)
11 - <12 years prior to index date	40 (9%)	427 (91%)	1965	177 (7%)	2258 (93%)	9735	1.28 (0.67 - 1.89)
12 - <13 years prior to index date	17 (7%)	239 (93%)	2176	80 (7%)	1124 (93%)	10966	1.04 (0.57 - 1.88)



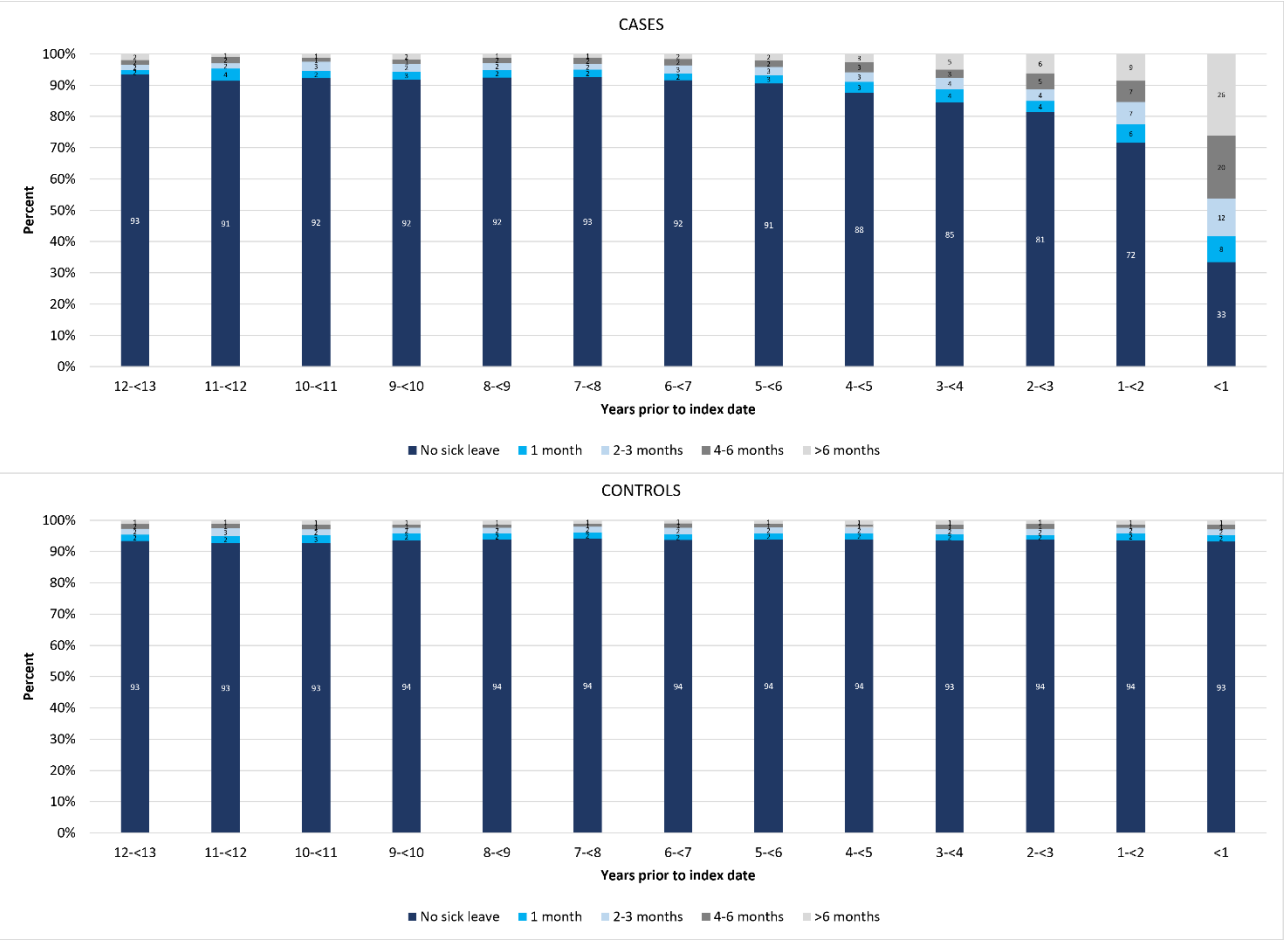
Incidence rate ratios (**IRR**s) for long-term sick leave and young onset Alzheimer's disease are plotted in time intervals prior to index date. For the refence group (dementia-free controls), the IRR is equal to 1 (as indicated by the dotted vertical line). Error bars represent 95% confidence intervals (**CI**). The IRRs presented are adjusted for age, sex, highest attained educational level at age 40 years (or at time of diagnosis, whichever came first), and civil status at index date. A breakdown of the censored population can be found in Table S3. Unadjusted estimates are presented in Table S5.

In all time intervals, some individuals were censored either temporarily or permanently due to not being at risk for the exposures (Table S2-S3). The number of individuals who were censored increased yearly nearing index date, as the population grew older and thus more individuals retired, with 62% of cases and 58% of controls, being retired in the <1 year prior to index date. A larger number of cases than controls were on leave or disability pension in this time interval (Table S2-S3). Unadjusted estimates can be found in table S4-S5.

Figure 3 shows the distribution of the study population by the annual number of months on long-term sick leave for cases (top) and controls (bottom). A noticeable difference began to appear around 4-<5 years prior to index date, with more months of sick leave observed amongst cases. In the year

immediately prior to diagnosis, 46% of cases had over 4 months of long-term sick leave; for controls, this was only 2%.

Figure 3 – Annual months of long-term sick leave



Yearly number months of long-term sick leave starting in a given interval. The figure shows percentages of the non-censored population with either 0, 1, 2-3, 3-4, 4-6 or >6 months of long-term sick leave, divided by cases (top) and controls (bottom).

We conducted sensitivity analyses stratifying by dementia syndrome severity at time of diagnosis, and on sex (Tables S6-S13). The tendencies were overall the same as observed in the main analysis, though significant increases in IRR were seen slightly earlier for those with moderate/severe dementia than for those with MCI/mild dementia, and slightly higher estimates for women than men in the year prior to diagnosis for both exposures. However, these stratifications resulted in small numbers in the outmost intervals and hence, very large CIs. A sensitivity analysis limiting the time-period under study to only include patients diagnosed before the onset of the COVID-19 pandemic did not alter the findings (Table S14-S15).

4. Discussion

In this nationwide, nested case-control study, we found that patients diagnosed with YOAD were more likely to be unemployed or have periods of long-term sick leave in the years leading up to diagnosis, as compared to controls. Notably, we found significant differences in unemployment rates already in the five years prior to diagnosis, with unemployment 7.5 times more likely among cases in the year immediately preceding diagnosis. Long-term sick leave rates increased earlier, peaking at a near 30-fold increase in the year prior to diagnosis. Furthermore, cases had more annual periods of long-term sick leave, with almost half of the cases having had four or more months of sick leave in the year prior to diagnosis, vs 2% of controls. Thus, YOAD patients are not only more likely to have long-term sick leave, but they also have more months of annual sick leave than controls.

To our knowledge, no prior studies have quantitatively examined the role of sick leave or unemployment as part of the YOAD prodrome. Prior quantitative research on workforce participation and dementia has focused predominantly on retirement age and dementia risk, with no studies found examining long-term sick leave or unemployment within the context of YOAD. However, several qualitative studies have explored related issues. Unemployment may have severe financial consequences, as highlighted in a study on the financial consequences of young onset dementia[24]. Here, several caregivers describe how challenges began before the diagnosis, with one describing how the person with young onset dementia was fired as early symptoms were misattributed to drug or alcohol abuse. A formal diagnosis of YOAD can help patients and caregivers in seeking counsel and initiating the process of applying for disability pension, helping the family maintain financial stability.

Findings from our study could reflect a long prodromal phase where cognitive demands in the workplace exceeds available cognitive resources. This is supported by two previous qualitative studies, which find that as those with YOAD are often in paid employment when symptoms arise, it is often in the workplace that demands exceed available resources, leading to symptoms often first becoming apparent at work[5,6]. Furthermore, given that the association in our study between long-term sick leave becomes apparent earlier than for unemployment, sick leave may be a driving factor in individuals with prodromal YOAD being fired or quitting their job. Thus, sick leave may be the cause of (some cases of) unemployment. There could also be a shared cause between unemployment and sick leave.

Moreover, YOAD patients face significant diagnostic delays in attaining the correct diagnosis[8]. Our prior research points towards a prolonged period of time characterized by increased healthcare utilization, seeking especially psychologists and psychiatric care, and increased psychiatric morbidity and medication use[2–4]. These findings likely point towards YOAD patients having symptoms often

misattributed to stress or depression, or that these occur comorbidly. These findings from our previous research on this YOAD population suggest that stress and depression could possibly also be major contributors to the unemployment and long-term sick leave rates found in the present study. This is consistent with results from a Danish study on labor market trajectories after long-term sick leave, where 35% of the study population self-reported the reason for sick leave as mental health reasons; of these, 71% reported stress and burnout, and 56% reported depression[25]. Adverse occupational events such as unemployment and sick leave could thus further contribute in the diagnostic pathway as early warning signs of YOAD, aiding in a timely diagnosis. Timely diagnosis could help patients restructure their remaining working life to account for cognitive deficits, or in seeking access to disability pension. This could have a positive impact not only for the individual, for whom prolonged periods of sick leave and unemployment may lead to financial ruin, but may also have significant societal impacts, as the high cost of sickness and unemployment benefits may be mitigated by an earlier, correct diagnosis. Thus, efforts in improving timely diagnosis of YOAD have substantial benefits both on an individual and on a societal level.

A strong desire to work post-diagnosis has been described among patients with young onset dementia[26]. While it may not be feasible or desirable for all YOAD patients to continue working post-diagnosis, there needs to be measures put in place to explore the possibility of keeping YOAD patients in paid employment throughout the pre- and post-diagnostic phase to the extent possible and desired by the patient, starting with measures to ensure timely diagnosis. In the present study, it was unfortunately not possible to track whether YOAD cases were transferred to less demanding tasks within the same workplace. Such measures could have helped explaining how some of the patients in the current study diagnosed at the moderate/severe dementia stages were still able to work until time of diagnosis. Thus, future studies may examine specific trajectories within YOAD patients' job tasks to identify any helpful strategies in maintaining a meaningful working life for as long as possible.

4.1 Strengths and limitations

Our study had several limitations. First, while we attempted to ensure that controls are cognitively healthy by applying wide exclusion criteria (no prior dementia diagnosis, no DanDem entry and no dementia-specific medication), it is not possible to completely rule out cognitive decline in the control group. However, the 1:5 ratio of cases to controls ensures that any undiagnosed dementia among controls would have a minimal effect on the overall estimation. Second, the results are likely influenced by at least some degree of healthy worker bias; that is, if individuals with cognitive problems are more likely to be on disability pension, or more likely to choose to go on early retirement pension if eligible,

this could have censored some of those most likely to receive a YOAD diagnosis, possibly leading to analysis of only individuals affected to a lesser degree. While the direction of bias is difficult to ascertain with certainty, we speculate that the selection of healthier individuals would primarily affect the case population, potentially leading to an underestimation of the magnitude of the association. Consequently, it is important to bear in mind that these results are generalizable primarily to individuals who remain part of the active workforce.

Third, due to data limitations, short-term sick leave was not possible to examine. While the main objective of the current study was to examine the association between long-term sick leave and YOAD, as we hypothesize that long-term sick leave is more likely to occur as a result of cognitive symptoms or comorbid or misattributed stress and depression, it would have been interesting to see how this would compare to shorter-term sick leave. Furthermore, using unemployment benefits as a proxy for measuring unemployment may cause us to inadvertently censor some individuals who are actually unemployed. While most Danish residents are eligible for unemployment benefits, some may choose not to apply or be unable to due to cognitive impairment. These individuals would thus be censored in our analysis due to missing data, and as we speculate difficulties in applying for unemployment benefits may disproportionally affect cases this could potentially lead to underestimation of unemployment rates. Nevertheless, given that most unemployed individuals are eligible for some form of financial support, we consider unemployment benefits a reasonably robust proxy. Future research could aim to incorporate more comprehensive measures of adverse occupational events to mitigate this limitation.

Finally, as the at-risk study population grows smaller closer to index date due to censoring on retirement, statistical uncertainty increases even further when stratifying by disease severity and sex in our sensitivity analyses. Thus, some estimates closest to index date produced too few discordant pairs for reasonable analysis and meaningful interpretation.

This study constitutes the first nationwide, quantitative study to examine occupational instability as part of the YOAD prodrome. A major strength of the study is the use of the high-quality, nationwide Danish registers, which ensures precise data collection with virtually full coverage and minimizes problems with selection bias. Additionally, the availability of long-term data allowed us to explore trajectories over time, tracing individuals for more than a decade. Using the quality registry DanDem, which includes all patients diagnosed with YOAD in Danish memory clinics, further strengthens the study by ensuring accurate case finding and diagnoses made by specialists. This allowed us to establish a large case cohort, which is often difficult given the relative rarity of YOAD compared to late onset AD.

4.2 Conclusions

In conclusion, this study demonstrated that those diagnosed with YOAD are more likely to have been unemployed up to five years prior to diagnosis, and on long-term sick leave up to as much as eight years prior to diagnosis. Furthermore, those with YOAD had more annual sick leave periods than controls. This highlights the need for timely diagnosis in YOAD, as consequences for the individual even before diagnosis are showcased. Repeated episodes of long-term sick leave or unemployment could thus potentially be one of several early warning signs of YOAD and may aid in establishing a timely diagnosis by guiding physicians in determining who to refer to a memory clinic for cognitive assessment.

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Conflicts of interest / declaration of interest

All authors declare no conflicts of interest.

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Consent statement

This research project was approved by the Danish Data Protection Agency, Statistics Denmark, and the Danish Health Data Authority. Danish law does not require ethics committee approval or informed patient consent.

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Supplementary - Association of occupational changes with a diagnosis of young onset Alzheimer's disease: A nationwide nested case-control study

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Contents:

Supplementary methods:

2.3S Labor market affiliations

The labor market affiliations used in the present study are described here in greater detail:

2.3S.1 Part of the active workforce (reference group for exposures): Included all those part of the active work force (salary workers, self-employed, etc.).

2.3S.2 Exposures:

Long term sick-leave: Includes those with sick leave for more 30 consecutive weeks. This time limit is chosen due to data availability, as short-term sick-leave is paid by the employer and is not registered in the public registers.

Unemployment: Included those receiving any social benefit relating to unemployment, such as unemployment benefits provided to members of an unemployment insurance fund, or social assistance (in Danish: *kontanthjælp*) which is a financial support system for basic living expenses for those not eligible for unemployment benefits.

2.3S.4 Temporarily outside of workforce: Those not included in categories 2.5S.1-3 (and not censored) and temporarily outside of the active workforce, for example due to parental leave, education, or other types of leave.

2.3S.5 Censoring events

Flex job: Included those on a specific type of employment, the right to which can be awarded due to diminished work ability due to health conditions. Tasks and working hours are adjusted based on what is manageable. To be eligible, the municipality must assess that work capacity is significantly and permanently reduced, and all possibilities for obtaining regular employment, such as through reassignment, must be explored. As there are different criteria for payouts of sick leave benefits, and therefore a difference in how sick leave is registered for those working in a flex job, they were not included in the analyses but were censored on the day of starting a flex job.

Retirement: All individuals were censored on the first day of any type of retirement. In Denmark, there are different kinds of retirement and pension schemes with differing criteria for eligibility. They are briefly described in the following:

Disability pension: This includes individuals who have been assessed to qualify for disability pension after thorough assessment. This is an early retirement pension provided to individuals who, due to health issues or disabilities, are unable to continue working until the regular retirement age. It is granted to those whose work capacity is permanently and significantly reduced and who, as a result, are unable to support themselves through regular employment.

Early retirement: Early retirement pension (in Danish: *efterløn*) is a voluntary early retirement scheme in Denmark, providing financial support to individuals who choose to retire before reaching the state pension age. There are several rules and eligibility criteria for this early retirement.

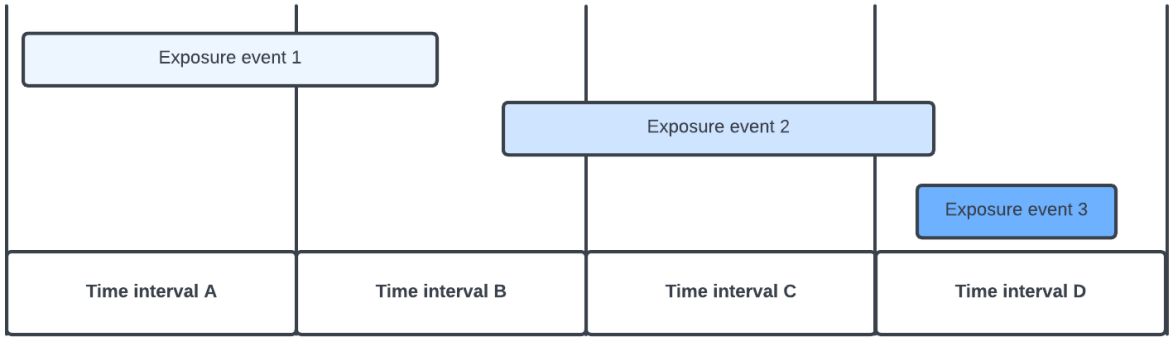
Pension: The state pension is a universal, publicly funded pension scheme available to all residents of Denmark. The age of retirement is around age 67 years but varies slightly according to birth year. This groups also includes Civil Servant Pension (in Danish: tjenestemandspension), specifically designed for public sector employees, where retirement age is not as easily defined, hindering meaningful determination of expected versus actual retirement age.

2.4S Placement of exposures into time intervals

For the main analysis:

The two exposures were analyzed in yearly intervals corresponding to the years preceding the index date (e.g., from 13->12 years before, 12->11 years, before, and so on, up to <1 year before). Each exposure was assigned to an interval based on its starting date. If a registration of sick leave or unemployment began in one interval and continued into the subsequent interval, it was included in the data for both intervals only if it continued throughout the entire interval, thus only if the exposure had a length of >365 days. This approach ensures comprehensive tracking of exposures that span multiple time periods.

The following figure illustrates this concept with three hypothetical exposure events tracked across four year-long intervals:



- Exposure event 1 starts in time interval A. It continues into time interval B but does not continue throughout the interval. *Exposure event 1 is counted only in interval A.*
- Exposure event 2 starts in time interval B, and continues throughout all of time interval C and into time interval D. *Exposure event 2 is counted in time interval B and C.*
- Exposure event 3 starts and ends in time interval D. *Exposure event 3 is only counted in time interval D.*

For quantifying long-term sick leave periods:

As reliable data on long-term sick leave is available for periods >30 days, a period of 31 days was used to approximate a month on long-term sick leave. We therefore split all periods of long-term sick leave into 31-day periods, loosely corresponding to months, and calculated the percentage of cases and controls with either 0, 1, 2-3, 4-6 or >6 "months" of long-term sick leave on a yearly basis. Months of long-term sick leave were placed into intervals based on the starting date of the sick leave period.

Supplementary tables

Table S1. Exclusion criteria

	Cases	Controls
Developmental disorders and mental retardation ICD-8: 311-315, 759.3, ICD-10: DF70-DF79, DQ90	X	X
Not living in Denmark in entire retrospective period	X	X
Dementia or mild cognitive impairment diagnosis ICD-8: 290.09-11, 290.18-19, 293.09-19, ICD 10: F00.0-00.9, F01.0-01.9, F02.0-F02.8, F03.9, F04.0-F04.9, F06.7 G30.0-G30.9, G31.0A, G31.0B, G31.8, G31.8E, G31.9		X
Dementia medication ATC code N06DA02-4, N06DX01		X
Entry in DanDem		X

ICD: International classification of diseases, ATC: Anatomical therapeutic chemical code, DanDem: Danish Quality Database for Dementia

Table S2. Breakdown of censored population for analysis of association between unemployment and YOAD

	CASES N=2434						CONTROLS N=12,170					
	Temporarily censored			Permanently censored			Temporarily censored			Permanently censored		
	LMA status missing*	Censored to sick leave	Leave/ education	Flex job	Disability pension	Retired	LMA status missing*	Censored to Sick leave	Leave/ education	Flex job	Disability pension	Retired
<1 year prior to ID	28	218 (9%)	250 (10%)	61 (3%)	212 (9%)	1486 (62%)	143	198 (2%)	513 (4%)	267 (2%)	822 (7%)	6957 (58%)
1-<2 years prior to ID	20	106 (4%)	230 (10%)	84 (3%)	224 (9%)	1377 (57%)	113	211 (2%)	562 (5%)	305 (3%)	918 (8%)	6456 (54%)
2-<3 years prior to ID	17	95 (4%)	244 (10%)	93 (4%)	243 (10%)	1213 (50%)	114	232 (2%)	680 (6%)	334 (3%)	1031 (9%)	5749 (48%)
3-<4 years prior to ID	20	100 (4%)	229 (9%)	100 (4%)	276 (11%)	1032 (43%)	124	271 (2%)	812 (7%)	371 (3%)	1162 (10%)	4933 (41%)
4-<5 years prior to ID	21	95 (4%)	252 (10%)	106 (4%)	321 (13%)	815 (34%)	129	282 (2%)	918 (8%)	422 (4%)	1377 (11%)	3898 (32%)
5-<6 years prior to ID	20	88 (4%)	253 (10%)	113 (5%)	361 (15%)	577 (24%)	131	319 3%)	1050 (9%)	472 (4%)	1624 (13%)	2691 (22%)
6-<7 years prior to ID	22	92 (4%)	259 (11%)	112 (5%)	342 (14%)	457 (19%)	135	355 (3%)	1192 (10%)	459 (4%)	1585 (13%)	2160 (18%)
7-<8 years prior to ID	369	67 (3%)	229 (11%)	94 (5%)	303 (15%)	277 (13%)	1857	301 (3%)	1048 (10%)	388 (4%)	1326 (13%)	1303 (13%)
8-<9 years prior to ID	746	65 (4%)	179 (11%)	71 (4%)	242 (14%)	117 (7%)	3718	287 (3%)	852 (10%)	317 (4%)	1061 (13%)	604 (7%)
9-<10 years prior to ID	1096	60 (4%)	138 (10%)	60 (4%)	190 (14%)	38 (3%)	5465	244 (4%)	671 (10%)	237 (4%)	810 (12%)	228 (3%)
10-<11 years prior to ID	1418	45 (4%)	107 (11%)	47 (5%)	132 (13%)	<10	7077	220 (4%)	508 (10%)	192 (4%)	550 (11%)	<10
11-<12 years prior to ID	1747	31 (5%)	68 (10%)	58 (8%)	90 (13%)	<10	8737	149 (4%)	330 (10%)	265 (8%)	362 (11%)	<10
12-<13 years prior to ID	2087	15 (4%)	29 (8%)	28 (8%)	35 (10%)	<10	10469	66 (4%)	175 (10%)	145 (9%)	174 (10%)	<10

Table S2 legend:
Censored to sick leave includes those with long-term sick leave and no unemployment during the interval. Some individuals have both exposures in a given time interval and are thus part of both exposure groups. For cells with numbers under 10, exact numbers could not be presented due to registry data regulations. *Labor market affiliation (LMA) status unknown due to missing data or individuals having not yet entered the study population (as some intervals for some individuals is before study start on January 1st, 2009). Shown percentage are of all those with a registered LMA status.
YOAD: young onset Alzheimer's disease, ID: index date

Table S3. Breakdown of censored population for analysis of association between long-term sick leave and YOAD

	CASES N=2434						CONTROLS N=12,170					
	Temporarily censored			Permanently censored			Temporarily censored			Permanently censored		
	LMA status missing*	Censored to unemployment	Leave/ education	Flex job	Disability pension	Retired	LMA status missing*	Censored to unemployment	Leave/ education	Flex job	Disability pension	Retired
<1 year prior to ID	28	49 (2%)	250 (10%)	61 (3%)	212 (9%)	1486 (62%)	143	225 (2%)	513 (4%)	267 (2%)	822 (7%)	6957 (58%)
1-<2 years prior to ID	20	69 (3%)	230 (10%)	84 (3%)	224 (9%)	1377 (57%)	113	234 (2%)	562 (5%)	305 (3%)	918 (8%)	6456 (54%)
2-<3 years prior to ID	17	71 (3%)	244 (10%)	93 (4%)	243 (10%)	1213 (50%)	114	261 (2%)	680 (6%)	334 (3%)	1031 (9%)	5749 (48%)
3-<4 years prior to ID	20	75 (3%)	229 (9%)	100 (4%)	276 (11%)	1032 (43%)	124	300 (2%)	812 (7%)	371 (3%)	1162 (10%)	4933 (41%)
4-<5 years prior to ID	21	79 (3%)	252 (10%)	106 (4%)	321 (13%)	815 (34%)	129	381 (3%)	918 (8%)	422 (4%)	1377 (11%)	3898 (32%)
5-<6 years prior to ID	20	103 (4%)	253 (10%)	113 (5%)	361 (15%)	577 (24%)	131	448 (4%)	1050 (9%)	472 (4%)	1624 (13%)	2691 (22%)
6-<7 years prior to ID	22	111 (5%)	259 (11%)	112 (5%)	342 (14%)	457 (19%)	135	454 (4%)	1192 (10%)	459 (4%)	1585 (13%)	2160 (18%)
7-<8 years prior to ID	369	81 (4%)	229 (11%)	94 (5%)	303 (15%)	277 (13%)	1857	429 (4%)	1048 (10%)	388 (4%)	1326 (13%)	1303 (13%)
8-<9 years prior to ID	746	90 (5%)	179 (11%)	71 (4%)	242 (14%)	117 (7%)	3718	403 (5%)	852 (10%)	317 (4%)	1061 (13%)	604 (7%)
9-<10 years prior to ID	1096	76 (6%)	138 (10%)	60 (4%)	190 (14%)	38 (3%)	5465	358 (5%)	671 (10%)	237 (4%)	810 (12%)	228 (3%)
10-<11 years prior to ID	1418	51 (5%)	107 (11%)	47 (5%)	132 (13%)	<10	7077	293 (6%)	508 (10%)	192 (4%)	550 (11%)	<10
11-<12 years prior to ID	1747	35 (5%)	68 (10%)	58 (8%)	90 (13%)	<10	8737	199 (6%)	330 (10%)	265 (8%)	362 (11%)	<10
12-<13 years prior to ID	2087	15 (4%)	29 (8%)	28 (8%)	35 (10%)	<10	10469	100 (6%)	175 (10%)	145 (9%)	174 (10%)	<10

Table S3 legend:
Censored to unemployment includes those with long-term sick leave and no unemployment during the interval. Some individuals have both exposures in a given time interval and are thus part of both exposure groups. For cells with numbers under 10, exact numbers could not be presented due to registry data regulations. *Labor market affiliation (LMA) status unknown due to missing data or individuals having not yet entered the study population (as some intervals for some individuals is before study start on January 1st, 2009). YOAD: young onset Alzheimer's disease, ID: index date

Table S4. Incidence rate ratios for unemployment and YOAD

	CASES N=2434					CONTROLS N=12,170					INCIDENCE RATE RATIOS AND CONFIDENCE INTERVALS			
	Unemployment		Work		Censored	Unemployment		Work		Censored	Unadjusted IRR	95% CI	Adjusted IRR	95% CI
	N	%*	N	%*	N	N	%*	N	%*	N				
<1 year prior to ID	84	(40%)	125	(60%)	2225	251	(8%)	3039	(92%)	8880	6.91	4.49 - 10.63	7.52	4.72 - 11.98
1-<2 years prior to ID	102	(23%)	349	(77%)	1983	261	(7%)	3489	(93%)	8420	4.63	3.33 - 6.44	4.97	3.51 - 7.04
2-<3 years prior to ID	94	(15%)	514	(85%)	1826	292	(7%)	3948	(93%)	7930	2.62	1.94 - 3.54	2.64	1.93 - 3.59
3-<4 years prior to ID	94	(13%)	651	(87%)	1689	339	(7%)	4436	(93%)	7395	1.93	1.49 - 2.55	1.91	1.43 - 2.55
4-<5 years prior to ID	99	(11%)	813	(89%)	1522	425	(8%)	5062	(92%)	6683	1.54	1.19 - 1.99	1.50	1.15 - 1.96
5-<6 years prior to ID	118	(11%)	992	(89%)	1324	504	(8%)	5720	(92%)	5946	1.25	0.99 - 1.58	1.23	0.97 - 1.56
6-<7 years prior to ID	120	(10%)	1105	(90%)	1209	515	(8%)	6157	(92%)	5498	1.21	0.97 - 1.52	1.19	0.95 - 1.50
7-<8 years prior to ID	98	(8%)	1066	(92%)	1270	484	(8%)	5722	(92%)	5964	1.05	0.82 - 1.34	1.02	0.79 - 1.30
8-<9 years prior to ID	102	(10%)	946	(90%)	1386	453	(8%)	5052	(92%)	6665	1.22	0.96 - 1.54	1.18	0.92 - 1.51
9-<10 years prior to ID	86	(10%)	784	(90%)	1564	403	(9%)	4203	(91%)	7564	1.14	0.88 - 1.47	1.09	0.84 - 1.43
10-<11 years prior to ID	59	(9%)	630	(91%)	1745	337	(9%)	3304	(91%)	8529	0.90	0.66 - 1.22	0.91	0.67 - 1.24
11-<12 years prior to ID	44	(9%)	427	(91%)	1963	227	(9%)	2258	(91%)	9685	1.06	0.74 - 1.51	1.12	0.78 - 1.61
12-<13 years prior to ID	17	(7%)	239	(93%)	2178	114	(9%)	1124	(91%)	10932	0.69	0.40 - 1.19	0.69	0.40 - 1.22

Table S4 legend:
* Percentage of those under analysis (all non-censored individuals).
YOAD: young onset Alzheimer's disease, ID: index date, IRR: incidence rate ratio, CI: confidence interval.

Table S5. Incidence rate ratios for long-term sick leave and YOAD

	CASES N=2434					CONTROLS N=12,170					INCIDENCE RATE RATIOS AND CONFIDENCE INTERVALS			
	Sick leave		Work		Censored	Sick leave		Work		Censored	Unadjusted IRR	95% CI	Adjusted IRR	95% CI
	N	%*	N	%*	N	N	%*	N	%*	N				
<1 year prior to ID	253	(67%)	125	(33%)	2054	224	(7%)	3039	(93%)	8907	27.57	17.90 - 42.46	29.59	18.97 - 46.14
1-<2 years prior to ID	139	(28%)	349	(72%)	1944	238	(6%)	3489	(94%)	8443	6.40	4.68 - 8.75	6.50	4.73 - 8.94
2-<3 years prior to ID	118	(19%)	514	(81%)	1800	263	(6%)	3948	(94%)	7959	3.32	2.51 - 4.40	3.39	2.55 - 4.50
3-<4 years prior to ID	119	(15%)	651	(85%)	1662	310	(7%)	4436	(93%)	7424	2.67	2.05 - 3.53	2.65	2.02 - 3.49
4-<5 years prior to ID	115	(12%)	813	(88%)	1504	326	(6%)	5062	(94%)	6782	2.17	1.67 - 2.81	2.17	1.67 - 2.81
5-<6 years prior to ID	103	(9%)	992	(91%)	1337	375	(6%)	5720	(94%)	6075	1.61	1.25 - 2.07	1.61	1.24 - 2.07
6-<7 years prior to ID	101	(8%)	1105	(92%)	1226	416	(6%)	6157	(94%)	5597	1.34	1.04 - 1.73	1.32	1.02 - 1.70
7-<8 years prior to ID	84	(7%)	1066	(93%)	1282	356	(6%)	5722	(94%)	6092	1.44	1.10 - 1.88	1.41	1.08 - 1.85
8-<9 years prior to ID	77	(8%)	946	(92%)	1409	337	(6%)	5052	(94%)	6781	1.18	0.90 - 1.55	1.18	0.90 - 1.56
9-<10 years prior to ID	70	(8%)	784	(92%)	1578	289	(6%)	4203	(94%)	7678	1.25	0.93 - 1.67	1.25	0.93 - 1.67
10-<11 years prior to ID	53	(8%)	630	(92%)	1749	264	(7%)	3304	(93%)	8602	1.01	0.73 - 1.39	1.02	0.74 - 1.41
11-<12 years prior to ID	40	(9%)	427	(91%)	1965	177	(7%)	2258	(93%)	9735	1.28	0.87 - 1.89	1.28	0.67 - 1.89
12-<13 years prior to ID	17	(7%)	239	(93%)	2176	80	(7%)	1124	(93%)	10966	1.10	0.62 - 1.98	1.04	0.57 - 1.88

Table S5 legend:
* Percentage of those under analysis (all non-censored individuals).
YOAD: young onset Alzheimer's disease, sick leave: long-term sick leave, ID: index date, IRR: incidence rate ratio, CI: confidence interval.

Table S6. Sensitivity analysis by dementia syndrome severity at time of diagnosis – unemployment and MCI/mild dementia

	CASES N=1560					CONTROLS N=7800					INCIDENCE RATE RATIOS AND CONFIDENCE INTERVALS			
	Sick leave		Work		Censored	Sick leave		Work		Censored	Unadjusted IRR	95% CI	Adjusted IRR	95% CI
	N	%*	N	%*	N	N	%*	N	%*	N				
<1 year prior to ID	56	(34%)	110	(66%)	1394	165	(7%)	2075	(93%)	5560	5.29	3.26 - 8.58	5.95	3.54 - 10.02
1-<2 years prior to ID	62	(18%)	283	(82%)	1215	175	(7%)	2385	(93%)	5240	3.35	2.28 - 4.94	3.92	2.59 - 5.93
2-<3 years prior to ID	62	(13%)	403	(87%)	1095	176	(6%)	2695	(94%)	4929	2.26	1.59 - 3.21	2.39	1.67 - 3.43
3-<4 years prior to ID	53	(10%)	494	(90%)	1013	218	(7%)	3003	(93%)	4579	1.40	0.98 - 1.99	1.50	1.04 - 2.15
4-<5 years prior to ID	57	(9%)	602	(91%)	901	269	(7%)	3399	(93%)	4132	1.18	0.85 - 1.64	1.22	0.87 - 1.71
5-<6 years prior to ID	74	(9%)	711	(91%)	775	337	(8%)	3784	(92%)	3679	1.07	0.80 - 1.43	1.14	0.85 - 1.53
6-<7 years prior to ID	72	(8%)	792	(92%)	696	345	(8%)	4048	(92%)	3407	1.05	0.79 - 1.39	1.10	0.83 - 1.47
7-<8 years prior to ID	63	(8%)	741	(92%)	756	323	(8%)	3750	(92%)	3727	0.98	0.72 - 1.32	1.02	0.75 - 1.38
8-<9 years prior to ID	66	(9%)	668	(91%)	826	308	(8%)	3329	(92%)	4163	1.08	0.80 - 1.44	1.12	0.83 - 1.51
9-<10 years prior to ID	61	(10%)	556	(90%)	943	276	(9%)	2839	(91%)	4685	1.09	0.80 - 1.47	1.11	0.81 - 1.51
10-<11 years prior to ID	39	(8%)	460	(92%)	1061	244	(10%)	2253	(90%)	5303	0.79	0.55 - 1.14	0.84	0.58 - 1.23
11-<12 years prior to ID	34	(10%)	304	(90%)	1222	158	(9%)	1538	(91%)	6104	1.19	0.79 - 1.80	1.39	0.91 - 2.12
12-<13 years prior to ID	13	(7%)	168	(93%)	1379	72	(8%)	777	(92%)	6951	0.80	0.42 - 1.52	0.90	0.47 - 1.75

Table S6 legend:
* Percentage of those under analysis (all non-censored individuals).
YOAD: young onset Alzheimer's disease, ID: index date, IRR: incidence rate ratio, CI: confidence interval.

Table S7. Sensitivity analysis by dementia syndrome severity at time of diagnosis – long-term sick leave and MCI/mild dementia

	CASES N=1560					CONTROLS N=7800					INCIDENCE RATE RATIOS AND CONFIDENCE INTERVALS			
	Sick leave		Work		Censored	Sick leave		Work		Censored	Unadjusted IRR	95% CI	Adjusted IRR	95% CI
	N	%*	N	%*	N	N	%*	N	%*	N				
<1 year prior to ID	161	(59%)	110	(41%)	1289	137	(6%)	2075	(94%)	5588	22.46	14.36 - 35.13	24.76	15.53 -39.52
1-<2 years prior to ID	79	(22%)	283	(78%)	1198	144	(6%)	2385	(94%)	5271	5.03	3.54 - 7.14	5.41	3.77 - 7.75
2-<3 years prior to ID	55	(12%)	403	(88%)	1102	155	(5%)	2695	(95%)	4950	2.51	1.79 - 3.51	2.59	1.84 - 3.64
3-<4 years prior to ID	63	(11%)	494	(89%)	1003	175	(6%)	3003	(94%)	4622	2.38	1.69 - 3.34	2.43	1.73 - 3.43
4-<5 years prior to ID	60	(9%)	602	(91%)	898	184	(5%)	3399	(95%)	4217	1.77	1.28 - 2.44	1.82	1.32 - 2.52
5-<6 years prior to ID	62	(8%)	711	(92%)	787	223	(6%)	3784	(94%)	3793	1.46	1.08 - 1.97	1.49	1.10 - 2.01
6-<7 years prior to ID	55	(6%)	792	(94%)	713	217	(5%)	4048	(95%)	3535	1.19	0.86 - 1.64	1.20	0.87 - 1.67
7-<8 years prior to ID	50	(6%)	741	(94%)	769	196	(5%)	3750	(95%)	3854	1.46	1.06 - 2.02	1.47	1.07 - 2.04
8-<9 years prior to ID	41	(6%)	668	(94%)	851	196	(6%)	3329	(94%)	4275	1.04	0.74 - 1.47	1.07	0.76 - 1.50
9-<10 years prior to ID	38	(6%)	556	(94%)	966	170	(6%)	2839	(94%)	4791	1.14	0.80 - 1.62	1.14	0.80 - 1.63
10-<11 years prior to ID	31	(6%)	460	(94%)	1069	147	(6%)	2253	(94%)	5400	1.00	0.68 - 1.47	1.04	0.70 - 1.53
11-<12 years prior to ID	19	(6%)	304	(94%)	1237	95	(6%)	1538	(94%)	6167	1.22	0.77 - 1.95	1.27	0.79 - 2.03
12-<13 years prior to ID	11	(6%)	168	(94%)	1381	42	(5%)	777	(95%)	6981	1.12	0.56 - 2.27	1.13	0.55 - 2.32

Table S7 legend:
* Percentage of those under analysis (all non-censored individuals).
YOAD: young onset Alzheimer's disease, sick leave: long-term sick leave, ID: index date, IRR: incidence rate ratio, CI: confidence interval.

Table S8. Sensitivity analysis by dementia syndrome severity at time of diagnosis – unemployment and moderate/severe dementia

	CASES N=874					CONTROLS N=4370					INCIDENCE RATE RATIOS AND CONFIDENCE INTERVALS			
	Sick leave		Work		Censored	Sick leave		Work		Censored	Unadjusted IRR	95% CI	Adjusted IRR	95% CI
	N	%*	N	%*	N	N	%*	N	%*	N				
<1 year prior to ID	28	(65%)	15	(35%)	831	86	(8%)	964	(92%)	3320	17.46	6.01 - 50.73	16.73	5.02 - 55.80
1-<2 years prior to ID	40	(38%)	66	(62%)	768	86	(7%)	1104	(93%)	3180	11.02	5.43 - 22.38	10.11	4.85 - 21.06
2-<3 years prior to ID	32	(22%)	111	(78%)	731	116	(8%)	1253	(92%)	3001	4.07	2.20 - 7.53	3.44	1.79 - 6.58
3-<4 years prior to ID	41	(21%)	157	(79%)	676	121	(8%)	1433	(92%)	2816	3.84	2.31 - 6.39	3.12	1.83 - 5.31
4-<5 years prior to ID	42	(17%)	211	(83%)	621	156	(9%)	1663	(91%)	2551	2.60	1.67 - 4.06	2.17	1.36 - 3.45
5-<6 years prior to ID	44	(14%)	281	(86%)	549	167	(8%)	1936	(92%)	2267	1.72	1.15 - 2.57	1.42	0.93 - 2.15
6-<7 years prior to ID	48	(13%)	313	(87%)	513	170	(7%)	2109	(93%)	2091	1.62	1.11 - 2.37	1.39	0.94 - 2.06
7-<8 years prior to ID	35	(10%)	325	(90%)	514	161	(8%)	1972	(92%)	2237	1.20	0.80 - 1.82	1.04	0.68 - 1.60
8-<9 years prior to ID	36	(11%)	278	(89%)	560	145	(8%)	1723	(92%)	2502	1.60	1.05 - 2.43	1.33	0.86 - 2.07
9-<10 years prior to ID	25	(10%)	218	(90%)	631	127	(9%)	1364	(91%)	2879	1.29	0.78 - 2.11	1.03	0.61 - 1.72
10-<11 years prior to ID	20	(11%)	170	(89%)	684	93	(8%)	1051	(92%)	3226	1.21	0.70 - 2.09	1.04	0.59 - 1.83
11-<12 years prior to ID	10	(8%)	123	(92%)	741	69	(9%)	720	(91%)	3581	0.77	0.38 - 1.58	0.61	0.28 - 1.30
12-<13 years prior to ID														

Table S8 legend:
* Percentage of those under analysis (all non-censored individuals). For cells with numbers under 10, exact numbers could not be presented due to registry data regulations. As stratification in some intervals resulted in too few individuals for meaningful analyses, some cells are left blank.
YOAD: young onset Alzheimer's disease, ID: index date, IRR: incidence rate ratio, CI: confidence interval.

Table S9. Sensitivity analysis by dementia syndrome severity at time of diagnosis – long-term sick leave and moderate/severe dementia

	CASES N=874					CONTROLS N=4370					INCIDENCE RATE RATIOS AND CONFIDENCE INTERVALS			
	Sick leave		Work		Censored	Sick leave		Work		Censored	Unadjusted IRR	95% CI	Adjusted IRR	95% CI
	N	%*	N	%*	N	N	%*	N	%*	N				
<1 year prior to ID	57	(79%)	15	(21%)	802	61	(6%)	964	(94%)	3345				
1-<2 years prior to ID	27	(29%)	66	(71%)	781	67	(6%)	1104	(94%)	3199	15.16	7.05 - 32.60	15.08	6.78 - 33.51
2-<3 years prior to ID	40	(26%)	111	(74%)	723	77	(6%)	1253	(94%)	3040	6.77	3.87 - 11.85	7.00	3.96 - 12.37
3-<4 years prior to ID	37	(19%)	157	(81%)	680	96	(6%)	1433	(94%)	2841	3.36	2.12 - 5.33	3.27	2.05 - 5.22
4-<5 years prior to ID	35	(14%)	211	(86%)	628	98	(6%)	1663	(94%)	2609	3.27	2.08 - 5.13	3.24	2.05 - 5.11
5-<6 years prior to ID	26	(8%)	281	(92%)	567	96	(5%)	1936	(95%)	2338	2.06	1.29 - 3.30	2.01	1.24 - 3.24
6-<7 years prior to ID	37	(11%)	313	(89%)	524	138	(6%)	2109	(94%)	2123	1.65	1.10 - 2.48	1.52	1.00 - 2.31
7-<8 years prior to ID	17	(5%)	325	(95%)	532	105	(5%)	1972	(95%)	2293	1.40	0.86 - 2.27	1.35	0.82 - 2.21
8-<9 years prior to ID	24	(8%)	278	(92%)	572	91	(5%)	1723	(95%)	2556	1.50	0.94 - 2.39	1.44	0.89 - 2.31
9-<10 years prior to ID	22	(9%)	218	(91%)	634	74	(5%)	1364	(95%)	2932	1.54	0.92 - 2.57	1.54	0.91 - 2.58
10-<11 years prior to ID	14	(8%)	170	(92%)	690	73	(6%)	1051	(94%)	3246	1.03	0.57 - 1.87	1.02	0.56 - 1.86
11-<12 years prior to ID	12	(9%)	123	(91%)	739	54	(7%)	720	(93%)	3596	1.44	0.72 - 2.87	1.35	0.67 - 2.74
12-<13 years prior to ID														

Table S9 legend:
* Percentage of those under analysis (all non-censored individuals). For cells with numbers under 10, exact numbers could not be presented due to registry data regulations. As stratification in some intervals resulted in too few discordant pairs for meaningful analyses, some cells are left blank.
YOAD: young onset Alzheimer's disease, sick leave: long-term sick leave, ID: index date, IRR: incidence rate ratio, CI: confidence interval.

Table S10. Sensitivity analysis by sex – unemployment and YOAD, men

	CASES N=1010					CONTROLS N=12,170					INCIDENCE RATE RATIOS AND CONFIDENCE INTERVALS			
	Sick leave		Work		Censored	Sick leave		Work		Censored	Unadjusted IRR	95% CI	Adjusted IRR	95% CI
	N	%*	N	%*	N	N	%*	N	%*	N				
<1 year prior to ID	32	(30%)	75	(70%)	903	101	(7%)	1437	(93%)	3512	3.88	2.18 - 6.89	4.38	2.35 - 8.15
1-<2 years prior to ID	47	(20%)	194	(80%)	769	101	(6%)	1642	(94%)	3307	4.53	2.83 - 7.26	5.29	3.17 - 8.84
2-<3 years prior to ID	45	(14%)	273	(86%)	692	119	(6%)	1843	(94%)	3088	2.62	1.70 - 4.03	2.64	1.69 - 4.11
3-<4 years prior to ID	41	(11%)	327	(89%)	642	147	(7%)	2065	(93%)	2838	1.52	1.00 - 2.30	1.61	1.05 - 2.49
4-<5 years prior to ID	42	(9%)	402	(91%)	566	190	(7%)	2344	(93%)	2516	1.39	0.94 - 2.05	1.43	0.96 - 2.14
5-<6 years prior to ID	55	(10%)	474	(90%)	481	236	(8%)	2623	(92%)	2191	1.17	0.84 - 1.64	1.81	0.84 - 1.67
6-<7 years prior to ID	60	(10%)	523	(90%)	427	239	(8%)	2793	(92%)	2018	1.20	0.87 - 1.66	1.22	0.88 - 1.69
7-<8 years prior to ID	47	(9%)	487	(91%)	476	216	(8%)	2520	(92%)	2314	1.07	0.76 - 1.53	1.08	0.75 - 1.55
8-<9 years prior to ID	60	(12%)	426	(88%)	524	207	(9%)	2217	(91%)	2626	1.41	1.03 - 1.94	1.38	0.99 - 1.92
9-<10 years prior to ID	36	(9%)	344	(91%)	630	189	(9%)	1811	(91%)	3050	1.04	0.70 - 1.54	1.02	0.68 - 1.53
10-<11 years prior to ID	25	(8%)	271	(92%)	714	155	(10%)	1395	(90%)	3500	0.87	0.55 - 1.37	0.92	0.57 - 1.47
11-<12 years prior to ID	17	(8%)	185	(92%)	808	111	(10%)	957	(90%)	3982	0.79	0.45 - 1.37	0.90	0.51 - 1.59
12-<13 years prior to ID														

Table 10 legend:
* Percentage of those under analysis (all non-censored individuals). For cells with numbers under 10, exact numbers could not be presented due to registry data regulations. As stratification in some intervals resulted in too few individuals for meaningful analyses, some cells are left blank.
YOAD: young onset Alzheimer's disease, ID: index date, IRR: incidence rate ratio, CI: confidence interval.

Table S11. Sensitivity analysis by sex – long-term sick leave and YOAD, men

	CASES N=1010					CONTROLS N=6060					INCIDENCE RATE RATIOS AND CONFIDENCE INTERVALS			
	Sick leave		Work		Censored	Sick leave		Work		Censored	Unadjusted IRR	95% CI	Adjusted IRR	95% CI
	N	%*	N	%*	N	N	%*	N	%*	N				
<1 year prior to ID	90	(55%)	75	(45%)	845	65	(4%)	1437	(96%)	3548	25.26	13.48 - 47.34	28.23	14.60 - 54.60
1-<2 years prior to ID	38	(16%)	194	(84%)	778	81	(5%)	1642	(95%)	3327	5.73	3.52 - 9.32	5.16	3.40 - 9.26
2-<3 years prior to ID	32	(10%)	273	(90%)	705	87	(5%)	1843	(95%)	3120	2.64	1.70 - 4.11	2.66	1.70 - 4.16
3-<4 years prior to ID	33	(9%)	327	(91%)	650	110	(5%)	2065	(95%)	2875	2.10	1.34 - 3.28	2.12	1.35 - 3.35
4-<5 years prior to ID	33	(8%)	402	(92%)	575	124	(5%)	2344	(95%)	2582	1.37	0.90 - 2.09	1.42	0.93 - 2.18
5-<6 years prior to ID	34	(7%)	474	(93%)	502	129	(5%)	2623	(95%)	2298	1.36	0.91 - 2.04	1.35	0.90 - 2.02
6-<7 years prior to ID	32	(6%)	523	(94%)	455	147	(5%)	2793	(95%)	2110	1.05	0.96 - 1.58	1.03	0.68 - 1.56
7-<8 years prior to ID	27	(5%)	487	(95%)	496	239	(9%)	2520	(91%)	2291	1.78	1.17 - 2.73	1.75	1.14 - 2.68
8-<9 years prior to ID	21	(5%)	426	(95%)	563	116	(5%)	2217	(95%)	2717	1.06	0.67 - 1.66	1.09	0.69 - 1.71
9-<10 years prior to ID	22	(6%)	344	(94%)	644	89	(5%)	1811	(95%)	3150	1.39	0.84 - 2.28	1.34	0.81 - 2.21
10-<11 years prior to ID	10	(4%)	271	(96%)	729	69	(5%)	1395	(95%)	3586	0.89	0.50 - 1.60	0.92	0.51 - 1.67
11-<12 years prior to ID	12	(6%)	185	(94%)	813	51	(5%)	957	(95%)	4042	1.35	0.74 - 2.46	1.26	0.68 - 2.31
12-<13 years prior to ID														

Table S11 legend:
* Percentage of those under analysis (all non-censored individuals). For cells with numbers under 10, exact numbers could not be presented due to registry data regulations. As stratification in some intervals resulted in too few individuals for meaningful analyses, some cells are left blank.
YOAD: young onset Alzheimer's disease, sick leave: long-term sick leave, ID: index date, IRR: incidence rate ratio, CI: confidence interval.

Table S12. Sensitivity analysis by sex – unemployment and YOAD, women

	CASES N=1424					CONTROLS N=8544					INCIDENCE RATE RATIOS AND CONFIDENCE INTERVALS			
	Sick leave		Work		Censored	Sick leave		Work		Censored	Unadjusted IRR	95% CI	Adjusted IRR	95% CI
	N	%*	N	%*	N	N	%*	N	%*	N				
<1 year prior to ID	52	(51%)	50	(49%)	1322	150	(9%)	1602	(91%)	5368	13.86	6.73 - 28.54	14.31	6.65 - 30.82
1-<2 years prior to ID	55	(26%)	155	(74%)	1214	160	(8%)	1847	(92%)	5113	4.72	2.98 - 7.49	4.87	3.02 - 7.86
2-<3 years prior to ID	49	(17%)	241	(83%)	1134	173	(8%)	2105	(92%)	4842	2.63	1.73 - 3.99	2.63	1.70 - 4.06
3-<4 years prior to ID	53	(14%)	324	(86%)	1047	192	(7%)	2371	(93%)	4557	2.39	1.63 - 3.51	2.21	1.48 - 3.28
4-<5 years prior to ID	57	(12%)	411	(88%)	956	235	(8%)	2718	(92%)	4167	1.67	1.18 - 2.36	1.58	1.11 - 2.27
5-<6 years prior to ID	63	(11%)	518	(89%)	843	268	(8%)	3097	(92%)	3755	1.33	0.96 - 1.84	1.28	0.92 - 1.79
6-<7 years prior to ID	60	(9%)	582	(91%)	782	276	(8%)	3364	(92%)	3480	1.22	0.89 - 1.69	1.16	0.84 - 1.61
7-<8 years prior to ID	51	(8%)	579	(92%)	794	268	(8%)	3202	(92%)	3650	1.03	0.74 - 1.44	0.98	0.70 - 1.38
8-<9 years prior to ID	42	(7%)	520	(93%)	862	246	(8%)	2835	(92%)	4039	1.01	0.70 - 1.45	0.95	0.65 - 1.38
9-<10 years prior to ID	50	(10%)	440	(90%)	934	214	(8%)	2392	(92%)	4514	1.22	0.87 - 1.72	1.15	0.81 - 1.64
10-<11 years prior to ID	34	(9%)	359	(91%)	1031	182	(9%)	1909	(91%)	5029	0.93	0.62 - 1.39	0.90	0.60 - 1.36
11-<12 years prior to ID	27	(10%)	242	(90%)	1155	116	(8%)	1301	(92%)	5703	1.35	0.85 - 2.15	1.33	0.82 - 2.14
12-<13 years prior to ID	12	(8%)	145	(92%)	1267	59	(8%)	692	(92%)	6369	0.99	0.50 - 1.94	0.93	0.47 - 1.85

Table S12 legend:
* Percentage of those under analysis (all non-censored individuals).
YOAD: young onset Alzheimer's disease, ID: index date, IRR: incidence rate ratio, CI: confidence interval.

Table S13. Sensitivity analysis by sex – long-term sick leave and YOAD, women

	CASES N=1424					CONTROLS N=8544					INCIDENCE RATE RATIOS AND CONFIDENCE INTERVALS			
	Sick leave		Work		Censored	Sick leave		Work		Censored	Unadjusted IRR	95% CI	Adjusted IRR	95% CI
	N	%*	N	%*	N	N	%*	N	%*	N				
<1 year prior to ID	128	(72%)	50	(28%)	1246	133	(8%)	1602	(92%)	5385	29.69	16.37 - 53.82	30.89	16.84 - 56.65
1-<2 years prior to ID	68	(30%)	155	(70%)	1201	130	(7%)	1847	(93%)	5143	6.91	4.58 - 10.41	7.18	4.73 - 10.90
2-<3 years prior to ID	63	(21%)	241	(79%)	1120	145	(6%)	2105	(94%)	4870	3.90	2.70 - 5.63	3.92	2.70 - 5.68
3-<4 years prior to ID	67	(17%)	324	(83%)	1033	161	(6%)	2371	(94%)	4588	3.12	2.21 - 4.40	3.03	2.14 - 4.30
4-<5 years prior to ID	62	(13%)	411	(87%)	951	158	(5%)	2718	(95%)	4244	2.96	2.11 - 4.15	2.91	2.08 - 4.09
5-<6 years prior to ID	54	(9%)	518	(91%)	852	190	(6%)	3097	(94%)	3833	1.80	1.30 - 2.50	1.79	1.28 - 2.49
6-<7 years prior to ID	60	(9%)	582	(91%)	782	208	(6%)	3364	(94%)	3548	1.59	1.15 - 2.19	1.57	1.13 - 2.17
7-<8 years prior to ID	40	(6%)	579	(94%)	805	188	(6%)	3202	(94%)	3730	1.26	0.89 - 1.78	1.22	0.86 - 1.73
8-<9 years prior to ID	44	(8%)	520	(92%)	860	171	(6%)	2835	(94%)	4114	1.26	0.89 - 1.78	1.25	0.88 - 1.77
9-<10 years prior to ID	38	(8%)	440	(92%)	946	155	(6%)	2392	(94%)	4573	1.19	0.83 - 1.70	1.17	0.82 - 1.69
10-<11 years prior to ID	35	(9%)	359	(91%)	1030	151	(7%)	1909	(93%)	5060	1.07	0.73 - 1.57	1.06	0.72 - 1.57
11-<12 years prior to ID	19	(7%)	242	(93%)	1163	98	(7%)	1301	(93%)	5721	1.24	0.75 - 2.05	1.22	0.73 - 2.04
12-<13 years prior to ID	12	(8%)	145	(92%)	1267	50	(7%)	692	(93%)	6378	1.34	0.70 - 2.57	1.24	0.63 - 2.42

Table S13 legend:
* Percentage of those under analysis (all non-censored individuals).
YOAD: young onset Alzheimer's disease, sick leave: long-term sick leave, ID: index date, IRR: incidence rate ratio, CI: confidence interval.

Table S14. Sensitivity analysis limiting to pre-COVID-19 years – unemployment and YOAD

	CASES N=1453					CONTROLS N=7625					INCIDENCE RATE RATIOS AND CONFIDENCE INTERVALS			
	Sick leave		Work		Censored	Sick leave		Work		Censored	Unadjusted IRR	95% CI	Adjusted IRR	95% CI
	N	%*	N	%*	N	N	%*	N	%*	N				
<1 year prior to ID	51	(44%)	65	(56%)	1337	142	(8%)	1715	(92%)	5408	7.47	4.35 - 12.83	9.01	4.85 - 16.72
1-<2 years prior to ID	57	(23%)	189	(77%)	1207	142	(7%)	1940	(93%)	5183	4.48	2.91 - 6.89	4.61	2.93 - 7.25
2-<3 years prior to ID	59	(17%)	288	(83%)	1106	166	(7%)	2214	(93%)	4885	2.80	1.91 - 4.13	2.78	1.87 - 4.14
3-<4 years prior to ID	53	(13%)	365	(87%)	1035	190	(7%)	2492	(93%)	4583	1.97	1.36 - 2.86	1.92	1.30 - 2.83
4-<5 years prior to ID	49	(9%)	467	(91%)	937	230	(7%)	2889	(93%)	4146	1.47	1.03 - 2.14	1.38	0.95 - 2.02
5-<6 years prior to ID	59	(9%)	573	(91%)	821	283	(8%)	3294	(92%)	3688	1.09	0.79 - 1.51	1.06	0.76 - 1.48
6-<7 years prior to ID	69	(10%)	643	(90%)	741	290	(7%)	3583	(93%)	3392	1.23	0.91 - 1.66	1.19	0.87 - 1.62
7-<8 years prior to ID	50	(8%)	562	(92%)	841	240	(7%)	3004	(93%)	4021	1.06	0.75 - 1.50	1.01	0.71 - 1.43
8-<9 years prior to ID	44	(10%)	399	(90%)	1010	164	(7%)	2146	(93%)	4955	1.44	1.00 - 2.08	1.33	0.91 - 1.94
9-<10 years prior to ID	17	(7%)	216	(93%)	1220	100	(8%)	1189	(92%)	5976	1.09	0.62 - 1.93	0.97	0.54 - 1.75

Table S14 legend:
* Percentage of those under analysis (all non-censored individuals).
YOAD: young onset Alzheimer's disease, ID: index date, IRR: incidence rate ratio, CI: confidence interval.

Table S15. Sensitivity analysis limiting to pre-COVID-19 years – long-term sick leave and YOAD

	CASES N=1453					CONTROLS N=7265					INCIDENCE RATE RATIOS AND CONFIDENCE INTERVALS			
	Sick leave		Work		Censored	Sick leave		Work		Censored	Unadjusted IRR	95% CI	Adjusted IRR	95% CI
	N	%*	N	%*	N	N	%*	N	%*	N				
<1 year prior to ID	107	(62%)	65	(38%)	1281	102	(6%)	1715	(94%)	5448	26.07	14.64 - 46.42	29.21	16.00 - 53.33
1-<2 years prior to ID	54	(22%)	189	(78%)	1210	118	(6%)	1940	(94%)	5207	6.24	4.12 - 9.44	6.46	4.23 - 9.85
2-<3 years prior to ID	45	(14%)	288	(86%)	1120	116	(5%)	2214	(95%)	4935	3.04	2.08 - 4.43	3.13	2.14 - 4.59
3-<4 years prior to ID	55	(13%)	365	(87%)	1033	140	(5%)	2492	(95%)	4633	3.00	2.04 - 4.42	2.97	2.01 - 4.39
4-<5 years prior to ID	53	(10%)	467	(90%)	933	138	(5%)	2889	(95%)	4238	2.16	1.50 - 3.10	2.15	1.49 - 3.09
5-<6 years prior to ID	44	(7%)	573	(93%)	836	170	(5%)	3294	(95%)	3801	1.52	1.05 - 2.20	1.53	1.05 - 2.21
6-<7 years prior to ID	53	(8%)	643	(92%)	757	191	(5%)	3583	(95%)	3491	1.36	0.98 - 1.90	1.33	0.96 - 1.86
7-<8 years prior to ID	32	(5%)	562	(95%)	859	156	(5%)	3004	(95%)	4105	1.50	1.03 - 2.20	1.47	1.01 - 2.14
8-<9 years prior to ID	29	(7%)	399	(93%)	1025	127	(6%)	2146	(94%)	4992	1.26	0.83 - 1.92	1.27	0.83 - 1.93
9-<10 years prior to ID	14	(6%)	216	(94%)	1223	61	(5%)	1189	(95%)	6015	1.19	0.64 - 2.12	1.18	0.63 - 2.12

Table S15 legend:
* Percentage of those under analysis (all non-censored individuals).
YOAD: young onset Alzheimer's disease, sick leave: long-term sick leave, ID: index date, IRR: incidence rate ratio, CI: confidence interval.

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