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DIABETES MELLITUS IN PATIENTS WITH DEMENTIA - CLINICAL CARE AND PHARMACOLOGICAL TREATMENT

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Stockholm 2021

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2021

ISBN 978-91-8016-021-6
Cover illustration: Brain and neurons surrounded by the blue circle of diabetes, signifying the relationship between diabetes and dementia. Illustration by Iveta Kaczarová. Permission to use the Blue Circle symbol was obtained from the International Diabetes Federation.

Diabetes Mellitus in Patients with Dementia – Clinical Care and Pharmacological Treatment
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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The thesis will be defended in public at room Gene, floor 5 at NEO building, Huddinge on January 29th, 2021 at 9.30 am

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Dedicated to My Family and Ms. Kačur

POPULAR SCIENCE SUMMARY OF THE THESIS

As the population grows older, people endure more and more long-term health problems acquired throughout their lives. This presence of multiple chronic disorders in an individual – "multimorbidity" poses a significant problem, as the interaction between the disorders makes treatment and care more difficult. One of the most serious chronic conditions is dementia, a heterogeneous group of disorders affecting the brain and leading to dependency on caregivers. More than 50 million people suffer from dementia today, most commonly due to Alzheimer's disease. Currently, the available medications do not stop the progress of dementia, thus the management of risk factors and improving the clinical care becomes crucial.

Importantly, diabetes mellitus (DM) is among the most significant risk factors for dementia. DM is typically recognized by its cardinal sign – high blood sugar, however it is a complex disorder, affecting the whole body including the brain. There are approximately 460 million patients living with DM worldwide, which leaves a huge number of people at increased risk of dementia. Indeed, a large proportion of patients suffering from dementia have concurrent diagnosis of DM, however we do not have a clear understanding what constitutes the best practice for these patients.

In this thesis, we focus on the clinical and pharmacological care patients who suffer from both DM and dementia receive in Sweden.
In the **studies 1** and **2,** we found that the symptomatic medications used in dementia help in prolonging survival, however they are prescribed less frequently in patients who suffer from both DM and dementia. In **study 3**, we conclude that the presence of dementia diagnosis may modify how DM is treated, which was reflected in more frequent use of insulin. Additionally, in **study 4** we found that certain DM medications, like sodium-glucose cotransporter-2 inhibitors are associated with better survival in patients with dementia. Finally, in **study 5** we concluded that DM medications metformin and dipeptidyl-peptidase-4 inhibitors can be cognitively protective in patients with dementia.

In summary, we found that the patients who suffer from both DM and dementia are a unique group that can benefit from the symptomatic medications used for dementia. Furthermore, we suggest which treatments for DM can have a positive impact on survival and cognition in patients with dementia diagnosis.

ABSTRACT

Diabetes mellitus (DM) and dementia are frequent chronic disorders in the older population, however their relationship is complex - while DM is an established risk factor for dementia, cognitive symptoms in dementia may hinder the self-management essential in DM care. Importantly, the co-occurrence of DM and dementia is common in clinical practice, however the research examining patients suffering from both disorders is scarce. This thesis analyzes the bidirectional associations between DM and dementia in patients with both disorders in Sweden, with specific focus on pharmacological care.

The thesis is based on the merged data from the Swedish Dementia Registry and the Swedish Prescribed Drug Register, Swedish National Patient Register, Swedish Cause of Death Register, Total Population Register and the Longitudinal Integrated Database for Health Insurance and Labour Market Studies. All included studies were observational, study 1 was cross-sectional and in studies 2-5 longitudinal open-cohort design was used.

Study 1 compares the characteristics of patients with DM and dementia to patients without DM. We show that DM is prevalent in 16.5% of patients with dementia, and that DM is associated with diagnosis at younger age, vascular dementia and mixed-pathology dementia (MixDem), and less frequent use of cholinesterase inhibitors (ChEI) and memantine. In **study 2** we analyze the association between ChEI and mortality in patients with DM and Alzheimer's disease (AD) or MixDem. We show that the initiation of ChEI class, donepezil and galantamine is associated with lower all-cause mortality, and the direction and strength of the association is comparable to DM-free patients.
Study 3 explores the changes in long-term utilization of antidiabetic medication in patients with type 2 DM or other/unspecified DM with and without dementia. We conclude that utilization as well as new dispensation of insulin is significantly higher among patients with dementia, while the newer antidiabetic drugs are less commonly prescribed.
Study 4 compares the mortality risk associated with six major antidiabetic drugs in patients with type 2 DM or other/unspecified DM and with and without dementia diagnosis. Overall, the initiation of insulin in patients with type 2 DM or other/unspecified DM is associated with higher mortality, regardless of dementia status. Additionally, we observe lower mortality in patients with dementia who used sodium-glucose cotransporter-2 inhibitors (SGLT-2i). Lastly, **study 5** examines whether the use of antidiabetic medications is associated with longitudinal changes in Mini-Mental State Examination (MMSE) scores in patients with AD or MixDem. Importantly, we conclude slower decline in MMSE scores among users of metformin and dipeptidyl-peptidase-4 inhibitors.

In conclusion, the patients with DM and dementia constitute a unique cohort less likely to receive treatment with ChEI despite the observed lower mortality associated with ChEI in our and previous studies. Moreover, we describe higher utilization of insulin and lower use of newer antidiabetic medications in patients with dementia, reflecting the Swedish clinical approach. Furthermore, we suggest that antidiabetic medications may provide cognitive benefit in patients with AD or MixDem. Additional studies focusing on optimization of antidiabetic and dementia medication, glycemic control as well as cognitive changes are needed to disentangle the role of DM in patients with manifest dementia.

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I. **Secnik J**, Cermakova P, Fereshtehnejad SM, Dannberg P, Johnell K, Fastbom J, et al. Diabetes in a Large Dementia Cohort: Clinical Characteristics and Treatment From the Swedish Dementia Registry. Diabetes Care. 2017;40(9):1159-66.

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IV. **Secnik J**, Xu H, Schwertner E, Hammar N, Alvarsson M, Winblad B, et al. Glucose-lowering medications and post-dementia survival in patients with diabetes and dementia. *Manuscript.*

V. **Secnik J**, Xu H, Schwertner E, Hammar N, Alvarsson M, Winblad B, et al. Antidiabetic medications affect Mini-Mental State Examination scores in patients with diabetes and dementia. *Manuscript.*

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VII. Xu H, Garcia-Ptacek S, **Secnik** J, Edlund A-K, Westling K, Hoang MT, et al. Changes in Drug Prescribing Practices Are Associated With Improved Outcomes in Patients With Dementia in Sweden: Experience From the Swedish Dementia Registry 2008–2017. Journal of the American Medical Directors Association.

CONTENTS

LIST OF ABBREVIATIONS

AD	Alzheimer's disease
AT	As-treated
ATC	Anatomical Therapeutic Chemical
ChEI	Cholinesterase inhibitors
CODR	Swedish Cause of Death Register
CCI	Charlson Comorbidity Index
CV	Cardiovascular/cerebrovascular
DLB	Dementia with Lewy bodies
DM	Diabetes mellitus
DPP-4i	Dipeptidyl-peptidase-4 inhibitors
FTD	Frontotemporal dementia
GLP-1a	Glucagon-like peptide-1 analogues
HR	Hazard ratio
ITT	Intention-to-treat
IPW	Inverse-probability weighting
LISA	Longitudinal integrated database for health insurance and labour market studies
MCI	Mild cognitive impairment
MixDem	Mixed-pathology dementia
MMSE	Mini-Mental State Examination
NPR	Swedish National Patient Register
OR	Odds ratio
PS	Propensity score
SGLT-2i	Sodium-glucose cotransporter-2 inhibitors
SPDR	Swedish Prescribed Drug Register
SveDem	Swedish Dementia Registry
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TPR	Total Population Register
TZD	Thiazolidinediones
VaD	Vascular dementia

1 INTRODUCTION

1.1 DEMENTIA AND DIABETES – PARTNERS IN CRIME

More than 100 years have passed since Alois Alzheimer described the characteristics of the most common dementia type worldwide[1], while the first mention of diabetes mellitus (DM) may reach as far as 1500 BC[2]. Despite such extensive history, the notion that DM and dementia may be connected has only developed in the last three decades. Since, DM has been recognized as an independent risk factor for dementia[3], while cognitive impairment has major influence on the patients' ability to manage DM[4]. Moreover, the rise in life-expectancy[5], the obesity epidemic[6] and improvements in the treatments of chronic disorders all contribute to the increasing co-occurence of both disorders in one patient[7]. However, there is insufficient knowledge to guide clinical reasoning in such situation.
In this thesis, we focus on the clinical and pharmacological management of DM and dementia in patients living with both disorders in Sweden.

2 LITERATURE REVIEW

2.1 DEMENTIA

Dementia comprises heterogeneous group of disorders, and is best characterized by cognitive or behavioral impairment of such extent, that it interferes with daily activities[8-11]. According to the NIA-AA criteria[11], impairment must involve minimum two of the following domains:

1. Impaired ability to acquire new information (memory impairment)
2. Impaired reasoning and handling of complex tasks, poor judgment
3. Impaired visuospatial ability
4. Impaired language functions (speaking, reading, writing)
5. Changes in personality, behaviour or comportment

When the impairment does not interfere with daily activities, but the cognitive performance is objectively lower than is appropriate for the patient's age and education, there a diagnosis of mild cognitive impairment (MCI) is suitable[12]. Risk factors for different disorders are often overlapping, suggesting common pathological pathways between dementia types[3, 13].

Some classifications introduced new nomenclature for dementia (e.g. DSM-V), however we keep the current wording in line with previous studies and current International Classification of Disorders, while acknowledging that the word "dementia" has negative connotation and may lead to stigma[14].

The review is focused on the main types included in the thesis' studies and does not comprise relatively newer LATE[15] or less common dementia types.

2.1.1 Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with heterogeneous etiology and the most frequent dementia disorder responsible for 60-70% of all dementia cases[9]. Age is the most important risk factor for AD, however there is a plethora of genetic, sociodemographic, vascular / metabolic and lifestyle factors that contribute to AD risk[9, 16].

AD is typically divided by the age of onset into early-onset (≤65 years) and late-onset (>65 years) AD. Late-onset AD (sporadic AD) constitutes the majority of AD cases, with the most important genetic risk factor being the epsilon-4 allele of the apolipoprotein-E[17], particularly in homozygous constellation. On the other hand, several genetic risk factors have been

identified for early-onset AD (<10% of cases), while heredity and family clustering are more frequent in this AD type[18]. The main AD-relevant genes include APP, PSEN1 and PSEN2 [18].

The clinical criteria for probable AD[11] include the impairment in cognition and behaviour as described in the section on dementia, with additional conditions including:

1. Insidious onset (months to years)
2. Clear-cut history of cognitive worsening
3. Cognitive deficits most prominent either in learning and recall of recently learned information (amnestic presentation) or
4. Cognitive deficits in language, visuospatial domain or executive functioning (non-amnestic presentations)
5. No evidence of other disorders that have a substantial effect on cognition

The main pathological hallmarks of AD include the accumulation of the toxic β-amyloid fibrils (intracellular and extracellular) and hyperphosphorylation of τ-protein (intracellular), which lead to progressive neurodegeneration with loss of synaptic function, neuronal loss, clinical dementia and disability. The predominant amyloid cascade hypothesis[19] sets the aggregation and deposition of β-amyloid in plaques as the primary event which subsequently leads to neurofibrillary tangles (constituting the hyperphosphorylated τ-protein) and neurodegeneration. The current research framework for AD diagnosis [the AT(N)] also stressed the role of abnormal amyloid metabolism at the beginning of the pathological process of neurodegeneration and dementia due to AD[20].

However, amyloid deposition may be present even in patients without cognitive symptoms[21] and the temporal relationship between β-amyloid deposition and neurofibrillary tangles has not always been observed[22].

The pathological process of neurodegeneration very likely begins decades prior to the onset of clinical symptoms, with first detectable biomarkers of β-amyloid deposition, followed by biomarkers of τ hyperphosphorylation, brain structure changes and neurodegeneration and finally, objective decline in cognitive functioning[23].

The complexity of the disease, combined with long preclinical stage has contributed to the unprecedented failure in pharmacological research[24], and no disease-modifying treatments exist for patients with AD.
Currently, the cognitive symptoms are treated with cholinesterase inhibitors (ChEI) in mild-to-moderate AD, while NMDA-receptor antagonist memantine is used in moderate-to-severe

AD, alone or in combination with ChEI[25]. Moreover, their effect is only symptomatic, and the strength of the cognitive stabilization is modest [26].

However, improvements in the diagnostic process, including positron-emission tomography, advanced magnetic-resonance imaging techniques and recent findings on blood-based biomarkers of β-amyloid metabolism[27] are encouraging and will contribute to higher precision of patient sampling for randomized clinical trials.

2.1.2 Vascular dementia

Vascular dementia (VaD) is commonly mentioned as the second most frequent dementia disorder with increasing prevalence with advancing age[28], however pure vascular phenotype is present only in less than <10% of cases[13] and mixed pathologies are more common[13, 29]. Moreover, VaD represents only the end of the pathogenetical continuum, thus the term vascular cognitive impairment was coined to reflect the whole process from preclinical stages to VaD ("major vascular cognitive impairment" is also used as synonym for VaD)[13].

The main risk factors for VaD include sociodemographic characteristics (higher age, female sex, lower education), chronic disorders (e.g. hypertension, dyslipidaemia, DM, stroke) and genetic and lifestyle factors (smoking, physical inactivity)[13]. The common presence of both AD and vascular pathologies is also reflected in the communality of risk factors for AD and VaD[3, 13].

The clinical picture is much more variable than in AD, as the impairment depends on the affected brain substrate. Typically, impairments in attention, information processing, executive function and memory are present[29]. In addition, the behavioural symptoms including apathy, anxiety and depression are common, as well as other neurological deficits - parkinsonism, urinary incontinence and language impairment[13]. The overall survival in VaD is lower compared to AD and varies between 3-5 years[29, 30].

Magnetic resonance imaging constitutes the gold standard in diagnosis vascular cognitive impairment[13, 29] and both cerebral large vessel and small vessel diseases are observed in VaD [13].

The AHA/ASA[13] criteria for VaD comprise:

1. Observed decline in cognitive functioning in at least two cognitive domains sufficient to affect individual's activities of daily living.

2. Executive function, memory, attention, language and visuospatial functioning should be assessed before establishing VaD diagnosis.
3. Deficits in activities of daily living are independent of the motoric and sensory symptoms of the vascular event.

The management of VaD is mostly focused on primary and secondary cardiovascular and cerebrovascular prevention[25]. Moreover, some degree of evidence suggests the use of ChEI mainly in patients with specific MRI findings and concurrent AD[13]. Multidisciplinary patient-approach is often necessary due to varying clinical features.

2.1.3 Mixed-pathology dementia

Mixed-pathology dementia (MixDem) is not universally recognized as a specific dementia type, however the presence of multiple pathologies is very common in the older population[31]. For the purpose of this thesis, we considered MixDem as the combination of AD and vascular pathology[32] and such combination may be responsbile for up to 20% of dementia cases[33].

2.1.4 Lewy body dementias

Lewy body dementias is an umbrella term for two dementia types - dementia in Parkinson's disease (PDD) and dementia with Lewy bodies (DLB). which are common in patients >65 years of age[34]. The main difference between PDD and DLB lies in the onset of symptomatology, where PDD presents first with motor symptoms (bradykinesia, tremor, rigidity) whereas dementia develops before or within 1 year of parkinsonism onset in DLB[34, 35]. The main connecting pathology is the presence of alfa-synuclein inclusions in the neurons, accompanied by neuronal death[34].

DLB: This specific dementia type is considered the third most common after AD and vascular dementia[36] and is commonly underdiagnosed in clinical practice[34]. One of the common traits with AD is the increased risk of DLB in Apo-E epsilon-4 carriers[34, 37], and the overlap with AD in pathogenesis and co-occurence is large overall[37]. Clinically, it may be difficult to distinguish between DLB and AD[37], however the presence of visuospatial deficits or visual hallucinations is highly indicative of DLB [34].

Diagnostic features of DLB:

1. **Central feature** – dementia presenting by deficit in attention and executive function.

2. **Core features** – fluctuating cognition, recurrent visual hallucinations, spontaneous features of parkinsonism.
3. **Suggestive features** – REM sleep behaviour disorder, low dopamine transporter uptake in basal ganglia, neuroleptic sensitivity.
4. **Supported features** (not considered in diagnosis) – depression, systematized desillusions, repeated falls and syncope.

PDD: Patients with PD commonly present with cognitive symptoms, and it is estimated that up to 80% progress to dementia[38]. For diagnosis of PDD, the onset of dementia has to occur in a patient with established PD, minimum 1 year after the onset of parkinsonian symptoms[38].

Diagnostic features of PDD:

1. **Core feature** – diagnosis of PD and dementia in context of established PD.
2. **Associated features** – impairment in attention, executive and visuospatial function, free recall; Presence of apathy, depression, halucinations and delusions support PDD diagnosis.
3. **Exclusion** of vascular or cognitive/behavioural symptoms in context of another systemic disease.

No disease-modifying treatments are available, but ChEI and memantine may provide cognitive alleviation in DLB and PDD[25].On the other hand, antipsychotic treatment to manage visuospatial deficits / hallucinations should be closely monitored and doses should be titrated due to worsening of parkinsonism, while L-dopa may exacerbate psychosis[25, 34, 39].

2.1.5 Frontotemporal dementia

Frontotemporal dementia (FTD) is the second most common dementia in patients below the age of 65[40]. Behavioral changes and symptom resemblance with other disorders may lead to missclassification and the real prevalence is underestimated [40]. FTD shows signs of heredity, 40% of all cases have positive history among first-line family members[41], thus family history is an important step in clinical investigation. Diagnosis is supported by evidence of frontal and anterior temporal atrophy on neuroimaging or neuropathological investigation[40]. FTD is acompanied by neuropsychiatric symptoms and difficulties in language and speech[41]. Average life expectancy after symptom onset varies between 6-11 years, however the survival is substantially shorter in the behavioural variant - approximately 3 years[42].

Behavioural variant of FTD: characterized by early behavioural and executive deficits leading to personality changes. Typical signs include: apathy, stereotypical and compulsive

acting, hyperorality, executive deficits, loss of empathy, personal neglect, often inappropriate and offensive actions, eating disorders.

Primary progressive aphasia: indicated by language dysfunction in early stages.

1. *Semantic variant* – impairment in semantic knowledge, naming of objects and persons, word comprehension, surface dyslexia and dysgraphia.
2. *Non-fluent variant* – speech apraxia, agrammatism, lingual errors

No drug treatments are currently available for FTD, and focus lies on the management of behavioural symptoms[40].

2.2 DIABETES

DM constitutes a cluster of metabolic disorders connected by a common biochemical disturbance – hyperglycaemia. DM is a heterogeneous disorder, comprising four distinct types[43] – type 1 DM (T1DM), type 2 DM (T2DM), gestational DM and specific DM. The main characteristics of T1DM and T2DM are summarized in **Table 1.**

Table 1. Characteristics of the two main DM types

Type 1 DM[43]	**Type 2 DM[43]**
Autoimmune or idiopathic disorder (destruction of β-cells in pancreas)	Peripheral insulin resistance & β-cell dysfunction
Absolute insulin deficiency	Relative insulin deficiency
Present autoantibodies (most cases)	No autoimmune reaction
Diabetic ketoacidosis common	Obesity & overweight common
5-10% of cases	90-95% of cases
Insulin treatment essential	Insulin treatment optional

T1DM and T2DM are responsible for most cases (prevalent and incident) of DM, while the gestational DM (diagnosed during pregnancy) and specific DM (e.g. after cystic fibrosis) are less common. The diagnosis of DM is based on the evaluation of glucose metabolism, either using concentration of venous glucose or proportion of haemoglobin A1c in blood[43]. **DM** is confirmed in patient with:

1. Fasting glucose of >7.0 mmol/l or
2. Glucose >11.1 mmol/l at 2 hours during the oral glucose tolerance test or

3. Haemoglobin A1c concentration >48 mmol/mol or
4. Random plasma glucose >11.1 mmol/l in patient with typical DM symptoms.

Prediabetes is a term used in patients without normal glycaemia who do not fulfil the criteria for DM. **Prediabetes** is identified in patients with[43]:

1. Fasting glucose between 5.6 - 6.9 mmol/l or
2. Glucose between 7.8 - 11.0 mmol/l at 2 hours during the oral glucose tolerance test or
3. Hemoglobin A1c concentration 39-47 mmol/mol

The onset of DM is often insidious (particularly in T2DM), with long prediabetes period, and patients with prediabetes have a higher risk of DM diagnosis[43]. Additionally, the presence of DM is associated with substantial microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications (accelerated atherosclerosis, heart failure, myocardial infarction, peripheral arterial disease)[44, 45], primarily depending on the level of control and duration of the disease. The treatment of DM varies between types, with insulin being the essential drug for T1DM patients, while lifestyle and diet adaptations, with or without medication therapy is used for T2DM treatment[46]. Importantly, DM is a common comorbidity in the older population, with approximately 25% of the population >65 years old affected[4].

2.3 EPIDEMIOLOGICAL LINKS BETWEEN DIABETES AND DEMENTIA

2.3.1 Type 1 diabetes

Compared to T2DM, T1DM is much less prevalent among patients with dementia, however with increasing life-expectancy of patients with T1DM[47], the clinical co-occurrence of T1DM and dementia diagnosis will become more frequent. T1DM has been associated with specific deficits in cognitive domains (sparing memory)[48], higher overall risk of dementia[49] and multiple mechanisms linked with cognitive decline[49, 50].
While a small percentage of patients included in the thesis' studies likely had T1DM, the patients were not analysed separately and studies 3-5 excluded patients with T1DM, making the generalisations to T1DM difficult. Consequently, in the subsequent sections, we describe primarily the relationships between T2DM or overall DM and dementia.

2.3.2 Type 2 diabetes

T2DM is considered a modifiable risk factor for dementia, but the nature of the relationship varies between the different dementia disorders.

Overall dementia, Alzheimer's disease, vascular dementia: The connection between T2DM and the most common dementia types has been first notioned in the late 90's with cross-sectional studies[51, 52], and the Rotterdam cohort study reporting twice the risk of dementia, AD and VaD in T2DM patients[53]. Luchsinger and colleagues corroborated the increased risk of AD in DM[54]. Conversely, the Swedish Kungsholmen study found no significant risk increase for AD[55], but later evaulation found even the prediabetic stages indicative of AD and dementia[56]. The Honolulu-Asia Aging Study observed the interaction between T2DM and apolipoprotein E genotype, a separate link between T2DM and AD[57]. Subsequently, the review of 14 cohorts by Biessels and colleagues has provided a reasonable indication on how strong the pooled dementia risk is in T2DM patients, with twice the risk for incident dementia, approximately 75% increase in risk for AD and 125% increase for VaD[58]. These estimates were further updated by Chatterjee and colleagues who concluded 68% increase in overall dementia risk, and differentially higher VaD risk in women (134% higher) than in men (73% higher)[59]. Further research by Kloppenborg and colleagues showed that 1 in 10-15 cases of dementia could be attributable to T2DM[60]. This was updated by Livingston and colleauges, who described 12 modifiable factors (**Table 2)** responsible for 40% of dementia cases, with T2DM independently responsible for every 100th case of dementia[3].

Table 2. Modifiable risk factors for dementia in different ages

	Relative risk for dementia	**Communality**	**Weighted population attributable fraction**
Early life (<45 years)			
Less education	1.6 (1.3-2.0)	61.2%	7.1%
Mid-life (45-65 years)			
Hearing loss	1.9 (1.4-2.7)	45.6%	8.2%
Traumatic brain injury	1.8 (1.5-2.2)	55.2%	3.4%
Hypertension	1.6 (1.2-2.2)	68.3%)	1.9%
Alcohol intake	1.2 (1.1-1.3)	73.3%	0.8%
Obesity	1.6 (1.3-1.9)	58.5%	0.7%
Later life (>65 years)			
Smoking	1.6 (1.2-2.2)	62.3%	5.2%
Depression	1.9 (1.6-2.3)	69.8%	3.9%
Social isolation	1.6 (1.3-1.9)	28.1%	3.5%
Physical inactivity	1.4 (1.2-1.7)	55.2%)	1.6%
DM	***1.5 (1.3-1.8)***	***71.4%***	***1.1%***
Air pollution	1.1 (1.1-1.1)	13.3%	2.3%

Communality refers to clustering of risk factors; Weighted population atributable fraction refers to the proportion of cases attributable to the specific factor adjusted for communality; Adapted from Livingston et al. Lancet (2020)[3], for full table see reference.

Overall, T2DM is a strong risk factor for dementia, AD and VaD, however the mechanistic relationships are not completely explained.

Mixed-pathology dementia: Patients with T2DM suffer from higher cardio- and cerebrovascular burden, and the presence of both cerebral AD and vascular pathologies is common in this group[61, 62].

Dementia in Parkinson's disease: Multiple studies have found T2DM to be connected to higher risk for Parkinson's disease (PD)[63, 64], on the other hand the connection to the cognitive decline associated with PD is not completely elucidated. Importantly, larger cognitive decrements were previously observed in DM patients with PD[65, 66] and a lower prevalence of DM was found in patients with PDD[67], possibly due to survivor bias. Consequently, a meta-analysis of case-control and cohort studies by Xu and colleagues found no association between T2DM and PDD[68]. The links between T2DM and PD are multidirectional, including insulin resistance, autophagy and inflammatory pathways[69].

Dementia with Lewy bodies: The connection between DLB and T2DM is not conclusive. T2DM was not associated with DLB in two studies from the United States[70, 71], and one Swedish study found DM to be less prevalent in DLB when compared to AD[67] - similar finding as for PDD, corroborating the communality between these two dementia types[37]. Moreover, Javanshiri concluded lower DM prevalence in the autopsy reports of patients with Lewy body dementias compared to other dementias, but the data were not distinguished between DLB and PDD[72].

Frontotemporal dementia: Due to lower overall frequency of this particular dementia type, few studies were performed in T2DM patients. An Argentinian case-control study of 100 FTD patients found almost 4-fold increase in odds of FTD in T2DM subgroup[73], and an Australian cohort found higher prevalence of T2DM in the behavioural variant of FTD, as well as multiple biochemical abnormalities consistent with T2DM[74]. Conversely, a Swedish registry study found no association between the two disorders[67]. Larger cohorts are needed to conclude the link.

2.4 BIOLOGICAL CONNECTIONS

We focus on the main connections between T2DM and different dementia types. The comprehensive review of the mechanisms is beyond the scope of this review.

Alzheimer's disease: Compared to periphery, where insulin's main role is the utilization of glucose by peripheral tissues, the cerebral insulin serves a different function. Specifically, insulin affects neuronal survival by inhibiting apoptosis, modulates long-term potentiation and depression, synaptic health, influences the neuronal glucose uptake, modulates the astrocyte-neuron lactate exchange and more[75, 76]. There is increasing evidence of cerebral insulin resistance in T2DM – a parallel to the systemic insensitivity of end-organ cells to insulin[75]. Consequently, Steen and colleagues have floated the name "type 3 diabetes" for AD to reflect the observed changes in insulin and insulin growth factor expressions[77], however some authors dispute the term due to lack of hyperglycorrhachia in AD[78]. The circumstances and exact pathological mechanisms of the brain insulin resistance are not clear, as T2DM seems to disrupt the levels of cerebral insulin in both directions (increased permeability of the blood-brain barrier vs. downregulation of insulin receptors due to hyperinsulinemia)[75]. The dysfunction of insulin's natural function leads to plethora of subtle changes significantly affecting neuronal and glial health[75]. Importantly, several antidiabetic medications have been connected to alleviating brain insulin resistance[79, 80].

Inflammatory response constitutes a further link between T2DM and AD. Overall, T2DM is associated with higher levels of circulating cytokines, e.g. interleukin-6 or C-reactive protein[81], and these circulating pro-inflammatory mediators in combination with hyperglycaemia may disrupt the blood-brain barrier[82, 83]. In addition, the activation of receptors for advanced-glycation products generated through hyperglycaemia may lead to release of inflammatory cytokines, endothelial dysfunction and cerebral ischemia[76]. Moreover, the increase in proinflammatory cytokines was also observed in hippocampi of DM animals[84]. One of the key contributing mechanisms in AD pathogenesis is the over-activation of microglial and astroglial inflammatory reaction[85, 86]. Thus, it is likely that T2DM-AD connection includes pathological immune response.

Additional link constitutes the Apo-E ε4 allele – most important genetic risk factor in late-onset AD[3] - considered to reduce the β-amyloid clearance and decrease the protection against reactive oxygen species[87]**.** Importantly, the cognitive effects of antidiabetic medications [e.g. metformin and dipeptidyl-peptidase-4 inhibitors (DPP-4i)] may be contingent on the ε4 genotype[88]. Moreover, higher rate and amount of β-amyloid was found in T2DM-AD carriers of the ε4 genotype compared to non-carriers[57, 89]. These suggest specific T2DM links to AD.

Multiple additional connections exist, such as oxidative stress and neuronal enzymatic deficiencies[80], adenosin-monophosphate kinase pathway (metformin acts as an activator)[90] or the mediation of cognitive impairment in T2DM patients through depression[91].

Controversially, the findings from neuropathological and biomarker studies did not find T2DM to increase the burden of the hallmark AD pathologies (β-amyloid accumulation and τ-protein hyperfosforylation), and the heightened AD risk probably stems from multiple interplaying processes, such as the amylin dyshomeostasis, proteotoxicity and post-translational changes[75, 82, 92]. Such connection, if true, would suggest that AD due to T2DM might be a unique phenotype of dementia.

Vascular dementia: The connection with T2DM and VaD include several mechanisms. First, the accelerated macrovascular atherosclerosis in T2DM doubles the risk for ischemic stroke[93] and worsens the mortality rates after stroke[94], while stroke is a major contributing factor to VaD onset[29]. Additionally, T2DM is typically associated with lacunar infarcts, an acute small subcortical infarcts in the region of one arteriole[82]. Importantly, both macrovascular and microvascular changes in T2DM contribute to increased risk of VaD[58, 95], however T2DM contributes significant risk to the overall vascular cognitive impairment[96], not just VaD. In addition, the MRI studies have identified cerebral small-vessel disease (white matter hyperintensities, cerebral microbleeds, enlarged perivascular spaces and microinfarcts) a likely factor in mediating the risk of cognitive damage in T2DM[82]. The volume of white matter hyperintensities was moderately increased in T2DM patients[97], with less consistent association found in cerebral microbleeds[98]. Currently, there is insufficient data for the other small-vessel changes.

Moreover, the mixed AD-vascular dementia is also common in T2DM, therefore it is likely that T2DM may accelerate both pathologies, and the resulting course of dementia may depend on supplementary factors, such as apo E genotype, or inflammation.

Lewy body dementias: Multiple connections between PD and T2DM have been suggested, such as the nigrostriatal damage due to hyperglycemia, mitochondrial dysfunction and disturbances in insulin signalling[69, 99]. Mitochondrial damage seems to be the most consistent link, with changes in gene expression (e.g. PGC-1a) and associations with hyperinsulinemia and insulin resistance[99]. Reduction in insulin-like growth factor signalling and their receptor binding has also been suggested as a putative mechanism between Lewy body dementias and T2DM[35]. However, it is not clear whether and how T2DM disrupts cognitive function in PDD and DLB patients. There could be parallels with AD, however, as the inefficient action of insulin can alter the cognitive functioning. A separate but interesting connection is the possible treatment of PD using the T2DM medication (e.g. exenatide)[100].

Frontotemporal dementia: Golimstok and colleagues have suggested several mutual pathways between FTD and T2DM. Specifically, the metabolic dysruptions in the insulin-receptor rich areas in the temporal lobes, generation of τ-protein hyperfosforylation due to advanced glycation end-products, and bidirectional changes in glycogen synthase kinase-3 activity[73]. Moreover, Ahmed and colleagues have found increased lipid markers in both semantic and behavioral form of FTD, as well as increased insulin levels. T2DM and FTD also might be connected by the aberrant eating behavior and carbohydrate consumption[74]. Additional studies should evaluate whether antidiabetic treatment affects the clinical course of FTD.

2.5 ANTIDIABETIC MEDICATION AND DEMENTIA

Pharmacological treatment is a major part of DM management. Interestingly, there are multiple studies suggesting that antidiabetic medications are associated with changes in cognitive functioning.

Insulin: Insulin is an endogenous peptide hormone responsible for maintaining basal and post-prandial glycaemia. While patients with T1DM depend on exogenous insulin, it is not the first choice in T2DM treatment[46]. Importantly, insulin is the most potent antidiabetic drug, with high clearance of blood glycemia after injection[101]. Insulin's potency might be a double-edged sword in dementia patients, where hypoglycemic episodes depend on cognitive function[102, 103]. Older insulin formulations have reduced microvascular complications and all-cause mortality in general DM population[46].

Insulin has pleiotropic action in neurons and glia[75], however systemic insulin administration has not been associated with improvements in cognitive functioning[104-106]. Additionally, intranasal insulin administration has been evaluated for AD, however Craft and colleagues concluded lack of cognitive benefit[79] despite no safety issues and improvement on MRI markers[107-109].

Biguanides: Metformin is the first-line therapy for T2DM, functioning as an insulin senzitizer, with additional pleiotropic effects dependent on the adenosin monophosphate-kinase pathway[110]. Metformin reduces weight and cardiovascular mortality in T2DM[46] and is considered safe to use in the elderly population without major decrease in glomerulal filtration rates[4]. Preclinical studies suggest neuroprotective properties in metformin[111]. On the other hand, studies in humans on dementia and cognition are controversial. Taiwanese cohort study found reductions in incident dementia in metformin users[112], however a case-control study by Imfeld and colleagues reported 70% increase in odds of AD in long-term metformin

users with large number of prescriptions[113]. On the other hand, Orkaby and colleagues compared sulfonylurea treatment to metformin in the US veterans and found lower hazard of dementia in metformin users in the <75 years old subgroup[114]. In addition, the 2016 meta-analysis concluded lower risk of incident dementia in insulin senzitizers, but the effect was borderline insignificant[115].

Furthermore, Dominguez and colleagues have shown some cognitive benefit of metformin use in a small sample of AD patients[116]. In addition, metformin has been evaluated in MCI, with divergent results on the two cognitive outcomes[117]. The authors stated that a multi-centered trial might be necessary to enable faster recruitment and better stratification of patients.

Sulfonylurea derivates: Sulfonylureas lower blood glucose by increasing pancreatic production of insulin[118], however the current clinical guidelines warn of possible hypoglycemic risk associated with their use in the elderly T2DM patients[4]. Moreover a study from the United States reported a high prevalence of sulfonylurea and / or insulin treatment in patients with tight glycemic control and dementia[119]. Some observational studies found increased all-cause and specific-cause mortality rates in sulfonylurea and insulin treatment, however this was not confirmed in high-quality clinical trials[120]. Similarly, Hsu and colleagues reported reduction in dementia risk in sulfonylurea users[112], but the connection was not confirmed in the randomized setting[106]. The use of sulfonylurea derivates in T2DM elderly patients seem warranted, however its use might be restricted where hypoglycemic episodes are a possibility[120] and short-term agents such as glipizide are preferred[4].

Thiazolidinediones: Thiazolidinediones (TZD) are insulin sensitizers, and act through the activation of peroxisome proliferator-activated receptor-gamma (PPAR-gamma). Currently, the only TZD approved is pioglitazone, however its use in the elderly is questionable, mainly due to the higher risk of myocardial infarction, congestive heart failure and falls[4, 46].

Similarly to metformin, TZD were associated with lower risk of overall dementia in a 2016 meta-analysis[115]. Moreover, the PPAR-gamma activation in TZD, its relation to the transcriptional factor PGC-1a (mitochondrial dysfunction in PD) and protection against neurodegeneration in animal studies[99] led to a well-designed, but unsuccesful clinical trial of pioglitazone vs placebo in early PD[121].

Incretin system: This group comprises the glucagon-like peptide-1 receptor agonists (GLP-1a) and dipeptidyl-peptidase-4 inhibitors (DPP-4i). They function either through direct activation of the GLP-1 receptor (GLP-1a) or inhibition of the dipeptidyl-peptidase-4 - the

enzyme that inactivates GLP-1 (DPP-4i). GLP-1's primary role is the food intake-related enhancement of insulin secretion, thus these drugs do not increase the risk of hypoglycemia [122].

GLP-1 receptors are located in multiple organs, including the brain[122], and GLP-1a are known to pass the blood-brain barrier[111]. They are currently one of the most promising T2DM treatments displaying good glycemic control, with multiple beneficial supplementary effects, such as weight loss, no risk of hypoglycemia and protection in atherosclerotic cardiovascular disease[46]. Moreover, neuroprotective, anti-inflammatory and prosurvival effects were observed in animal studies[111, 123, 124]. This resulted in the 6-month clinical trial of liraglutide in 38 AD patients, that has shown stabilisation of glucose metabolism in multiple brain regions compared to placebo[125], however the study could not evaluate AD biomarkers. Currently, the ELAD clinical trial on 12-month treatment with liraglutide is in the analytical stage, with cognitive and AD-pathognomical markers as primary outcomes[126]. Moreover, the results of a 60-week clinical trial with exenatide in PD were published, concluding modest but significant long-term improvement of PD symptoms, potentially marking a new era in PD treatment (the trial is continuing in phase 3)[127].
The use of GLP-1a is generally tolerated, however the adverse reactions (vomiting, diarrhea) and their dependence on good visual and motor functions due to subcutaneous application might be a problem for patients with moderate and severe cognitive impairment. The oral form of semaglutide may provide an efficacous alternative[128].

DPP-4i prolong the activity of endogenous GLP-1, stabilizing glycemic level similarly to GLP-1a[122]. However, they have smaller glucose-lowering efficacy, and were not found to exhibit cardiovascular protection[46]. In addition they seem to increase the propensity of sulfonylurea medication to cause hypoglycemia, thus closer monitoring is necessary[46]. On the other hand, DPP-4i are applied orally and have fewer side effects compared to GLP-1a, which might benefit the elderly and cognitively frail patients.
Similarly to GLP-1a, DPP-4i – sitagliptin and linagliptin were found to provide cognitive benefit in both animal and observational studies[129], however the CARMELINA-COG trial has not concluded any difference in cognitive functioning of linagliptin compared to placebo over 2.5 years[130].

Sodium-glucose cotransporter-2 inhibitors: One of the latest additions to T2DM drug arsenal are the sodium-glucose cotransporter-2 inhibitors (SGLT-2i), which enhance urinary excretion of glucose. SGLT-2i are completely dependent on kidney function, thus intermittent renal monitoring is necessary[46]. Empagliflozin and canagliflozin are highly

efficient in lowering glycemia, and provide multiple additional benefits, including weight loss, reductions in blood pressure and mortality, renal protection, and cardiovascular protection[46, 131-133]. These do not seem to be mediated through endotelial function[134]. Conversely, the adverse effects of mycotic urinary infections, reports of diabetic ketoacidosis, dehydration and limb amputations (in canagliflozin)[46] have somewhat counterbalanced the success of SGLT-2i therapy. In addition, long-term monitoring of SGLT-2i will provide data whether their efficacy is present also in the elderly or dementia populations. However, the SGLT-2i dependence on kidney function and tendencies towards dehydration might predispose them to healthier patient population.
Animal studies of empagliflozin have suggested improvements in cognitive functioning by reduction of cerebral oxidative stress, brain atrophy and BDNF increase[135, 136]. Moreover, in a small randomized-controlled trial, SGLT-2i were comparably effective to incretins in cognitive performance during 12 months[137]. Empagliflozin's cerebral metabolism effect is being evaluated in a phase 1 trial concentrating on ketone generation (NCT0385290).

2.6 ANTI-DEMENTIA MEDICATION AND DIABETES

Currently, no disease-modifying treatment is available for cognitive decline in AD, and the only approved pharmacological therapy is symptomatic and limited to ChEI (donepezil, rivastigmine and galantamine) used in mild-to-moderate dementia[26] and the NMDA-antagonist memantine used in moderate-to-severe dementia[138]. Where recognized as a separate dementia type (e.g. Sweden), MixDem can be treated with ChEI and memantine due to the present AD pathology. The treatment of VaD mainly focuses on the proper treatment of cerebro- and cardiovascular risk factors, such as hypertension, and hypercholesterolemia[29], however some authors suggest donepezil even in VaD[139]. Due to its multifaceted symptomatology including neurocognitive, parkinsonian and psychiatric symptoms, DLB requires a careful approach[39]. Donepezil and rivastigmine have been suggested to ameliorate cognitive functioning, however the results for memantine are less encouraging[25, 39]. Similarly, rivastigmine seems to be beneficial in mild-to-moderate PDD, both in the capsule and patch form[138]. There is no approved treatment for cognitive symptoms in FTD[140].

It is unclear whether ChEI use provides specific benefit to DM patients, as they were not independently assessed in the DM subgroup. On the other hand, certain characteristics of DM patients and ChEI provide an insight into possible patient-specific ChEI benefit and risks. Specifically, cognitive deterioration impedes the proper self-management of DM[141], therefore the ChEI's cognitive stabilisation might provide temporary benefits for DM patients' ability

to administer their medication. However, it is unknown whether ChEI help achieve the hemoglobin A1c targets.
Second, DM predisposes patients to higher likelihood of institutionalization[142, 143], and the additional benefit of ChEI use in T2DM patients may lie in the observed delay in nursing home admissions[144, 145].
Third, ChEI treatment was associated with lower probability of antipsychotic prescription[146, 147], which may be particularly valuable for DM patients where managing behavioural and psychological symptoms (e.g. with atypical antipsychotics) can worsen DM control[148]. Furthermore, there have been several epidemiological studies reporting reduced mortality, cardiovascular and cerebrovascular protection associated with ChEI use[149-151], primarily in higher doses[150, 151]. These findings are not completely understood, however it is reasonable to assume such medication effect extends to DM patients, as the mortality rates and cardiovascular health are generally worse in this group. On the other hand the shorter exposure to ChEI due to higher mortality might preclude DM patients to fully experience the protection, as one of the factors associated with ChEI benefit is the duration of treatment[152].

In addition, despite similar mechanism of action[26], differences exist between the individual drugs. Donepezil is a selective and reversible ChEI with favourable safety profile[153], while rivastigmine inhibits both acetyl- and butyrylcholinesterase, is slowly-reversible and exists as a capsule and transdermal patch[154]. Galantamine is rapidly-reversible and selective, and acts further as an allosteric potentiator on alpha-7 nicotinic receptors, connected to the cholinergic anti-inflammatory pathway[155]. Neuroinflammation has been linked to T2DM[156] and galantamine's modulation of the microglia[157] could act as an additional protective factor in these patients. In fact, a similar anti-inflammatory modulation can be observed in donepezil, however the dose necessary to obtain such effect is much higher than used in clinical practice[158].
Conversely, adverse effects such as syncope, diarrhea and weight loss are common in all ChEI[153]. This might be detrimental especially in the very old where a degree of overweight might be beneficial[159], however a more complicated situation may arise in T2DM patients where the balance between upholding glycemic control[160] and increasing the risk of hypoglycemia[161] needs to be carefully managed. The potential DM-specific benefits are summarized in **Figure 1.**

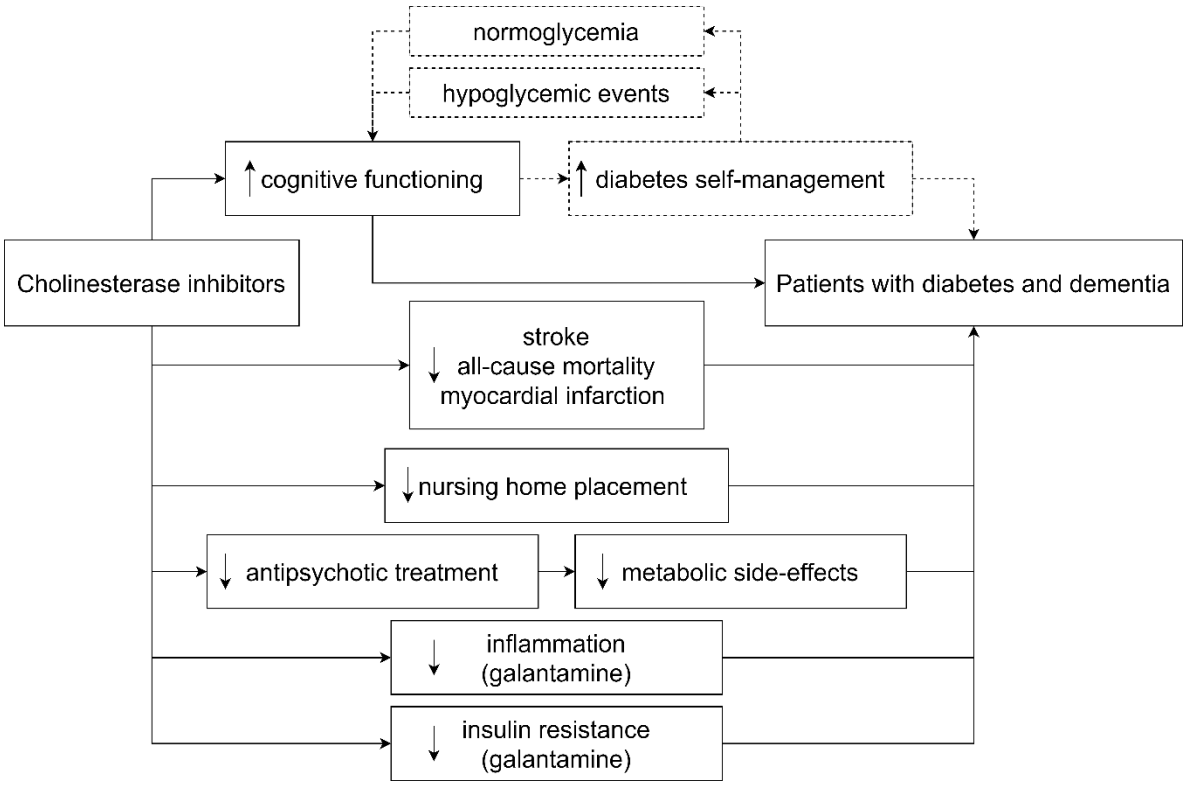

Figure 1. Suggested benefits of ChEI in patients with DM and dementia.

Full lines and boxes depict relationships where some evidence exists; dashed lines and boxes show hypothesized relationship. The figure is based on multiple studies[144, 146, 148, 150, 151, 155, 157, 162, 163].

There is limited information on the efficacy of memantine, currently the only medication used in moderate-to-severe AD as an addition to ChEI therapy[25]. Memantine has generally better safety profile compared to ChEI and provides small degree of cognitive stabilisation[164], but its action is not long-lasting[26]. No studies have evaluated its long-term effect specifically in patients with DM.

Possibly, the concerns of polypharmacy and adverse effects combined with the general knowledge of the symptomatic effect of AD medication may hinder their prescription in DM patients. Moreover, due to concerns of limited efficacy, the support for continued use of ChEI is decreasing in some countries[165]. The observational evidence of non-cognitive benefits in ChEI users suggests such approach may be premature.

2.7 CLINICAL CARE OF PATIENTS WITH DIABETES AND DEMENTIA

Both DM and dementia are connected to massive worldwide economic expenditures, 760 billion and 1 trillion, respectively[166, 167]. The average survival rate of dementia patients is estimated between 2-7 years[168, 169], and the majority of dementia-related costs are generated in this period due to the disease‘s progressive nature.

In Sweden, the long-term trend in new cases of dementia is declining[170] however there are still approximately 130-160,000 patients living currently with dementia[171, 172]. Moreover, the last decade shows temporal improvements in mortality and risk of cardiovascular events in Swedish patients with dementia, probably connected to higher utilization of cardiovascular medication[173]. Additionally, there are close to 500,000 patients with DM in Sweden[174, 175], however the research focusing on evidence-based care for patients with both DM and dementia is scarce.

Multimorbidity (the presence of at least two non-communicable diseases)[176] is almost ubiquitous in patients with dementia. Poblador-Plou and colleagues have found that dementia patients live with 3 additional comorbidites on average, the most common being hypertension and DM[177]. Moreover, a scoping review of 12 studies by Bunn and colleagues estimated that 6-39% of patients with dementia have comorbid DM, with the majority of studies reporting the proportion between 10-20%[7]. When applied to the current epidemiological trend[14], this suggests approximately 5-10 million patients live with DM and dementia worldwide.

The current diabetes care standards consider good neurocognitive performance a significant prerequisite for succesful self-management of DM[4]. One of the major challenges in the elderly population with DM is hypoglycemia – the result of inadequate DM treatment. This can be particularly important for dementia patients, as cognitive impairment can increase the risk for hypoglycemia[102, 178], and severe hypoglycemia predisposes patients to worse cognitive functioning[179, 180], enclosing a vicious circle. In addition, the stringent adherence to glycaemic targets in the elderly has not produced cognitive benefit[105] and was even associated with higher mortality[181]. Therefore the HbA1c target levels are currently adjusted and tailored to the functional status of the older patient[4, 182]. However, the standards do not provide advice on DM treatment as dementia advances, citing “individual re-evaluation” of glycaemic and cognitive outcomes.

The progression of dementia poses a significant problem, as the recognition of hypoglycemia significantly decreases with advancing age[183], which may be even more pronounced in severe stages of cognitive impairment. In addition, the capability to administer e.g. insulin or injectable GLP-1 agonists depends on the visual, cognitive and motor skills of the patient[4]. This might lead to lower prescription of the agents that are associated with cardiovascular protection[46].

Furthermore, the limited experience with the use of SGLT-2 inhibitors precludes from any conclusions, however their favourable cardiovascular profile[131], and oral administration could be an advantage for T2DM treatment in dementia patients.

Importantly, there are substantial obstacles when recruiting dementia patients for randomized control trails[184], which contribute to problems when extrapolating results from the elderly dementia-free cohorts, or dementia patients unrepresentative of the general dementia population. Additionally, with no major breakthroughs in pharmacological treatment of dementia, the optimal management of comorbidities gains an important role in dementia care. Therefore, the contributions from observational studies can fill important knowledge gaps on patient outcomes in an understudied population.

To conclude, managing DM in patients with dementia is a major challenge, and the clinicians would benefit from tailored guidelines for DM in specific dementia types and stages.

3 RESEARCH AIMS

Overall aim

The overall aim of the thesis is to determine the specific traits of patients with diabetes and dementia and provide longitudinal pharmacoepidemiologic evidence for the use of anti-dementia and antidiabetic medication in this patient group.

Specific aims

1. To decribe the sociodemographic, clinical and pharmacological characteristics of patients who were diagnosed with DM and seven dementia disorders and compare the findings to DM-free patients (**Study 1**).

2. To analyze the all-cause, CV and DM-related mortality associated with the use of overall and specific ChEI in patients with AD or MixDem dementia with or without concurrent diagnosis of DM (**Study 2**).

3. To determine whether and how dementia diagnosis affects the dispensation of antidiabetic medication and compare the findings to patients without dementia (**Study 3**).

4. To examine the differences in all-cause mortality associated with the initiation of six antidiabetic medications in patients with different dementia types as well as dementia-free subjects (**Study 4**).

5. To compare the annual changes in MMSE scores among new and all users of antidiabetic medication in patients with DM and AD or MixDem dementia types (**Study 5**).

4 MATERIALS AND METHODS

The thesis comprises one cross-sectional and four open-cohort observational studies, based on the merged data from five Swedish registers and one database, specifically the Swedish Dementia Registry (SveDem), Swedish Prescribed Drug Register (SPDR), Swedish National Patient Register (NPR), Swedish Cause of Death Register (CODR), Total Population Register (TPR) and the Longitudinal integrated database for health insurance and labour market studies (LISA). Personal identity number (personnummer)[185] was used to identify patients across sources and to merge data. The data sources and covered time intervals for each study are summarized in **Figure 2**.

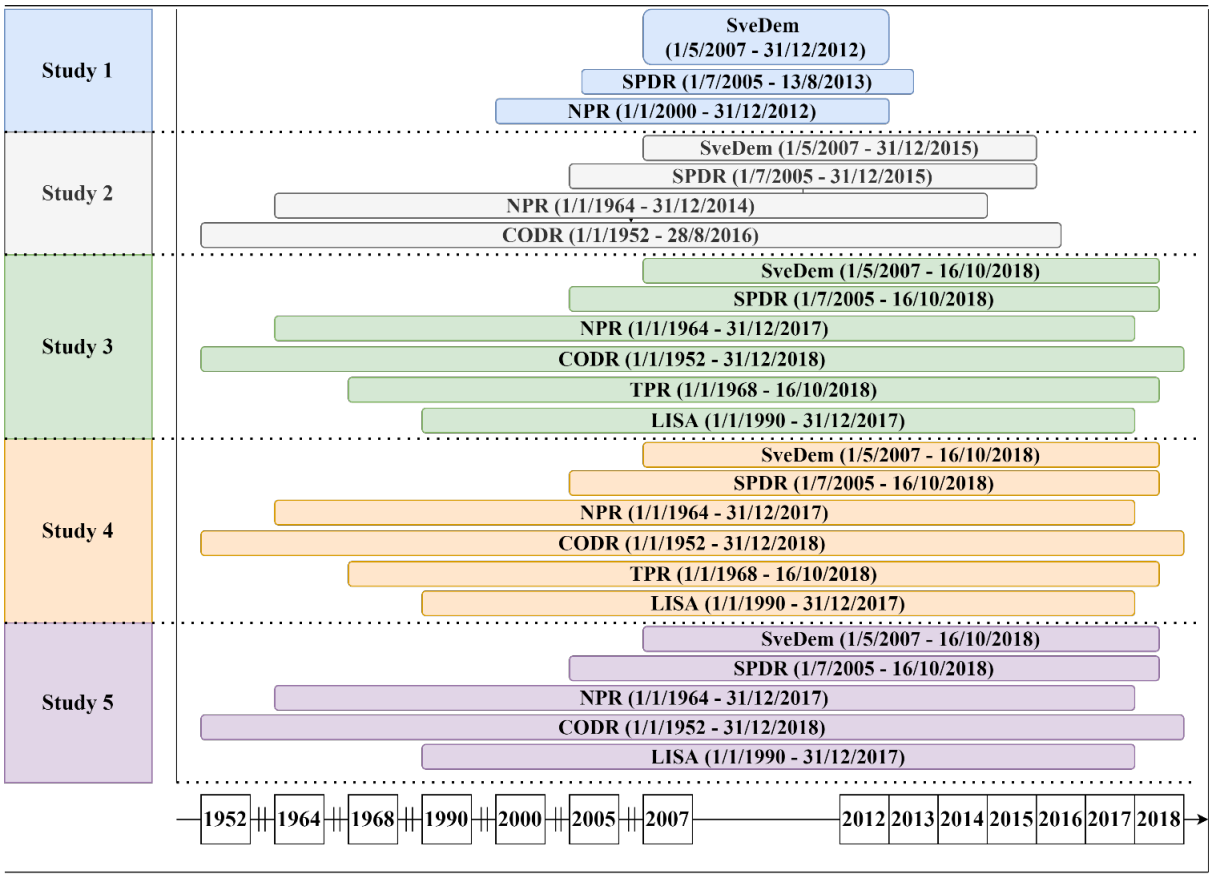

Figure 2. Registers and database used – time extent of data extracted for individual studies. Distances on the x axis (calendar years) are used for orientation and are only approximate

A brief explanation of the data sources, main variable definitions, study samples and the statistical methods utilized are included below. For further description, please refer to the individual manuscripts, relevant data reports[172] and publications[186-192].

4.1 SWEDISH DEMENTIA REGISTRY

SveDem is a Swedish national quality-of-care register established in 2007 with the aim to register all patients with diagnosis of dementia in Sweden[186].

Patients are registered to SveDem either from primary care, specialist memory clinic or nursing homes, with 78% of all primary care centers, 100% of memory clinics and 82 municipalities covered by SveDem[172]. The register contains information on patients' sociodemographic characteristics (e.g. age, sex), diagnostic variables [type of dementia, measures of cognitive functioning (e.g. MMSE scores)][193] and pharmacological treatment (e.g. cardiovascular medication, antidepressant use, ChEI use). Information at baseline registration and follow-ups (in approximately yearly intervals) is recorded[186]. In the end of 2019, 91,000 unique patients were registered to SveDem[172].

Dementia diagnoses in SveDem comprise early- and late-onset AD, MixDem, VaD, DLB, PDD, FTD, unspecified (clinical examination to determine dementia type was not carried out) and other dementia types (e.g. corticobasal degeneration, normal pressure hydrocephalus). Diagnoses are classified according to the ICD-10, while McKeith criteria, Lund-Manchester criteria and Movement Disorder Society criteria were used for DLB, FTD and PDD diagnoses, respectively[186].

4.2 SWEDISH PRESCRIBED DRUG REGISTER

SPDR was established in 2005 and stores data on dispensation of medications from pharmacies for the whole Swedish population[188]. SPDR contains basic sociodemographic data (age, sex, PIN), type of practice and profession of prescriber, and detailed information on the dispensation (substance name, ATC code, date of prescribing and dispensing), formulation and package, as well as dosage and expenditures[188]. Over-the-counter and inpatient dispensations are not included. SPDR is one of the primary sources for pharmacoepidemiologic studies in Sweden[189].

4.3 SWEDISH NATIONAL PATIENT REGISTER

NPR has been operating since 1964 collecting data on inpatient somatic and psychiatric care, with specialized (hospital-based) outpatient care being covered since 2001[187]. Registration to NPR is obligatory, and four categories of variables are stored: patient-related data (e.g. age, sex); caregiver data (hospital and department); administrative data (admission and discharge date); medical data (diagnoses according to the ICD system)[187]. The inpatient records cover the whole Swedish population since 1987, while the coverage of specialized outpatient care approaches 80%, and the primary care is not included[187].

4.4 SWEDISH CAUSE OF DEATH REGISTER

CODR is available in electronic format since 1952 and is used primarily for determining overall and specific mortality statistics in Sweden. CODR data originate from the medical death certificates which have to be made by the responsible physician within 3 weeks of the patient's death[190]. Apart from the patient identifiers, the register stores data on the date and place of death, the underlying cause and up to 48 contributing causes of death according to the latest ICD coding. CODR has complete coverage for the Swedish population[190].

4.5 TOTAL POPULATION REGISTER

TPR has been operating since 1968 and provides population statistics in Sweden, including births, immigration - emigration, divorce, civil status, place of residence and change of citizenship[191]. TPR is updated regularly and commonly utilized by both scientific and non-scientific personnel[191].

4.6 LONGITUDINAL INTEGRATED DATABASE FOR HEALTH INSURANCE AND LABOUR MARKET STUDIES

LISA is an annually-updated administrative database established in 1990 as a tool for determining changes in the labour market[192]. LISA comprises work-related and socioeconomic characteristics of the whole Swedish population older than 15 years of age. Information on sick leave, disability pensions, attained education, income statistics, and overall socioeconomic position are included[192].

4.7 DEFINITIONS AND VARIABLE TRANSFORMATIONS

4.7.1 Diabetes

DM variables (diagnosis, type and duration) were extracted from the NPR and SPDR.

In study 1, DM was defined as either having a record of ICD-10 code E10-E13 in the NPR or a record of ATC code A10 in the SPDR from up to 3 years prior and up to 3 years after dementia. In studies 2-5, DM was present if either the ICD-10 code E10-E14 or dispensation of ATC code A10 were present prior to and including the study baseline.

In studies 3-5, we devised an algorithm using NPR and SPDR to distinguish between T1DM, T2DM and other/unspecified DM. The process is summarized in **Figure 3.**

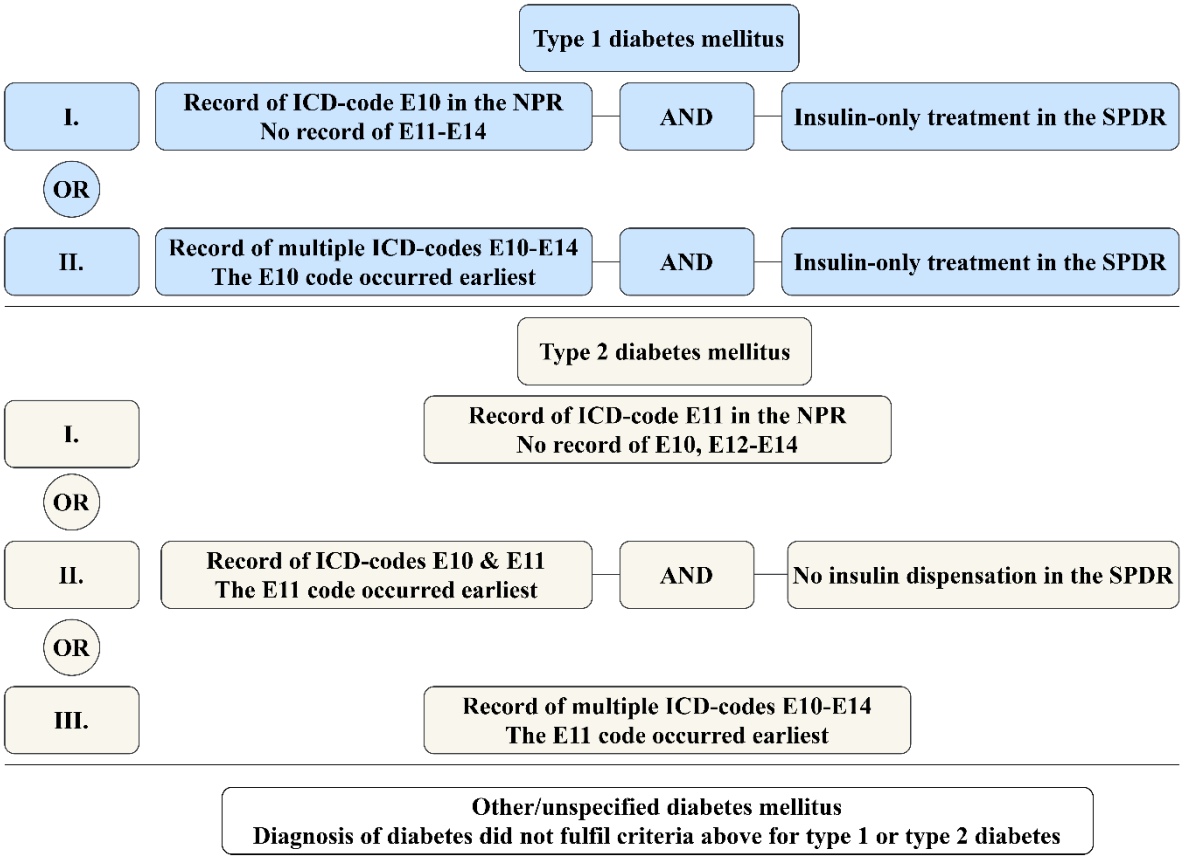

Figure 3. DM types according to the NPR and SPDR records. The "AND" and "OR" annotations describe the logical operations performed between the set conditions (I., II. & III.) for diagnosis of type 1, type 2 or other/unspecified diabetes; E10 – ICD-10 type 1 diabetes mellitus; E-11 – ICD-10 code for type 2 diabetes mellitus; E12-E14, ICD-10 code for other / unspecified diabetes.

DM duration was determined in studies 2-5 as the date difference between the earliest record of DM in the NPR (E10-E14) or SPDR (A10) and the study baseline.

4.7.2 Dementia

In study 1, all dementia diagnoses except for "other dementia" were included as registered by SveDem at the time of diagnosis. In studies 2 and 5, only patients with AD or MixDem were analyzed and in studies 3 and 4, all dementia types were included. Early- and late-onset AD were categorized as one group "Alzheimer's disease" in all studies and in study 4, patients diagnosed with DLB and PDD were grouped together into "Lewy body dementia". Additionally, MMSE scores recorded in SveDem were extracted at dementia diagnosis (all studies) and during follow-ups (study 5).

Furthermore, studies 3 and 4 utilized samples of dementia-free subjects which were extracted from the TPR. The samples were part of a larger data extraction of subjects with dementia and matched dementia-free controls (original data comprised 424,624 subjects with dementia and 1,328,035 dementia-free subjects). The exclusion criteria for dementia-free subjects

(=inclusion criteria for patients with dementia) were as follows: a) diagnosis of dementia in SveDem or b) record of ICD-10 codes F00-F03, G30, G31 in the NPR or CODR or c) record of ATC code N06D (anti-dementia drugs) in the SPDR; Subjects with codes F05-F09 and G32 were excluded from the population completely.
From the TPR, up to four dementia-free controls were matched to subjects with dementia (424,624 dementia to 1,328,035 dementia-free) on birth year (± 3 years), sex, and the county of residence and were assigned an index date matching with the date of dementia diagnosis. Out of this original extraction, we included only patients with DM diagnosis (up to and including the study baseline) with dementia (as recorded by SveDem) or without dementia.

4.7.3 Medication

SPDR provided data on medication dispensation at study baseline as well as during the follow-up. Study baseline refers either to date of dementia diagnosis or index date in dementia-free subjects. SPDR comprises only filled prescriptions, thus we used the terms "prescription" and "dispensation" interchangeably.

The record of ATC code and dispensation date of antidiabetic (ATC code A10), insulin (A10A), oral antidiabetic drugs (A10B), metformin (A10BA02), sulfonylurea (A10BB), TZD (A10BG), DPP-4i (A10BH), GLP-1a (A10BJ), SGLT-2i (A10BK), ChEI (N06DA – ChEI class, N06DA02 – donepezil, N06DA03 – rivastigmine, N06D04 - galantamine), memantine (N06DX01), antithrombotic (B01 and N02BA), cardiovascular (C1-C10), antipsychotic (N05A), antidepressant (N06A), anxiolytic (N05B) and hypnotic/sedative drugs (N05C) were extracted for the individual studies.

The use of medication was binarily defined into users and non-users (study 1-5) as well as into users of one drug and users of other drug (studies 4 and 5). In addition, the studies 2-5 distinguished between new users (called "incident" or "naïve" in different studies) and all users ("prevalent users"). Generally, the new users had no or short history of medication use prior to baseline, while all users could have been exposed to medication long before study baseline.
Medication dispensation was the primary outcome in study 3.

Study 1 included medication data extracted at seven time points – at the time of dementia diagnosis, and up to three years prior and three years after dementia diagnosis. Patients were considered users if a dispensation record was present at least once in any time point. Total number of medications at dementia diagnosis was considered a proxy for comorbidity.

The use of ChEI in study 2 was considered at study baseline and during follow-up. At baseline, patients were ChEI users if they had a record of dispensation at the time of dementia diagnosis (incident users) but did not have medication dispensation prior to dementia diagnosis - prevalent users were excluded. ChEI use was also updated on annual basis throughout the study follow-up (time-varying exposure) and ChEI users could transfer between specific ChEI. Corresponding baseline non-users were patients who were never prescribed medication prior to study baseline.
Furthermore, the dose-response was analyzed using the prescribed daily doses and categorizing patients into low- and high-dose groups by splitting on the median prescribed daily dose.
Supplementary medication (e.g. cardiovascular, antithrombotic) used in PS-matching and covariate adjustment was extracted between date of dementia diagnosis and three years prior.

In study 3, medication data functioned both to determine the outcome as well as a predictor and matching variables. The main outcome in study 3 was the dispensation of antidiabetic medication, which was defined in two ways. First, we analyzed the change in proportion of specific medication users (e.g. insulin, metformin) out of all antidiabetic drug users on an annual basis before and after the study baseline. Patients were considered users in the yearly period if a dispensation occurred at least once in that period. Second, in patients never prescribed medication prior to and including the study baseline (naïve patients), the first date of drug dispensation after the study baseline was of interest.
Supplementary medications used as predictor/matching variables were extracted up to three years prior and including the study baseline.

The exposure to antidiabetic drugs in study 4 was determined at baseline and during follow-up (**Figure 4**). Only baseline incident users (with the first record of medication dispensation in the one-year period prior to and including the baseline) were included. Non-users were subjects without medication dispensation prior to and including the study baseline. The exposure was updated during follow-up in the process identical as in study 2. In addition, baseline users of different non-metformin medications were directly compared. For example, patients who were incident users of sulfonylurea, and had no history of insulin dispensation were compared to patients who were incident insulin users and had no history of sulfonylurea dispensation.
Supplementary medications were extracted at baseline (the same way as in study 3), but the use was also updated on annual basis during the follow-up.

Finally, in study 5, both baseline incident and prevalent users of antidiabetic drugs were analyzed, and the definition of incident user was the same as in study 2 and 4. Non-users were subjects without medication dispensation prior to the baseline. Moreover, the prevalent baseline users of different antidiabetic medications were directly compared. Specifically, patients with insulin dispensation at least once prior to and including the baseline with no record of sulfonylurea dispensation were compared to prevalent sulfonylurea users who had no record of insulin dispensation. Supplementary medication was extracted the same way as in study 3. Medication exposure was analyzed as time-constant through the follow-up.

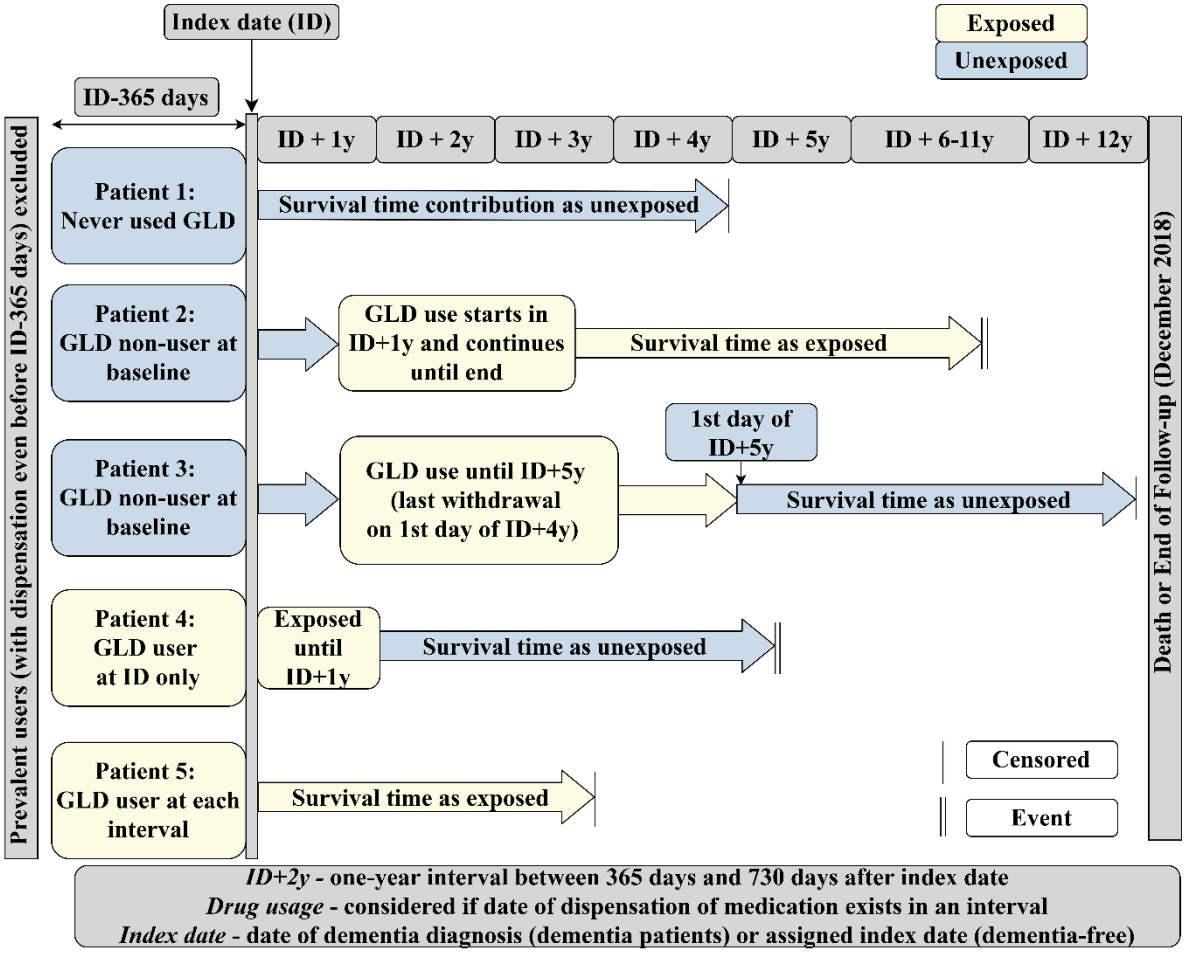

Figure 4. Exposure-time assignment of the antidiabetic drug usage in study 4. GLD, glucose-lowering drug = antidiabetic drug.

4.7.4 Other covariates

Age, sex and living arrangements (living alone, cohabitating, long-term care facility) were obtained from SveDem for patients with dementia and TPR (dementia-free subjects).

Chronic disorders other than DM and dementia were extracted from the NPR using ICD-10 coding. Study 1 included diagnosis of hypertension (I10), obesity (E66) and dyslipidemia (E78). In studies 2-5, the comorbidities were summarized as the Charlson Comorbidity Index

(CCI)[194], using a coding algorithm defined by Quan and colleagues[195]. CCI comprised the weighted sum of medical diagnoses up to and including the baseline (studies 2, 3 and 5) as well as after the baseline (study 4). Diagnosis of kidney disease was not included in the index in studies 3-5 and was analyzed separately.

For study 3, the highest education attained up to the study baseline was extracted in seven categories from the lowest (<9 years of compulsory education completed) to the highest (doctoral education). Additionally, disposable individual income in Swedish Krona at study baseline inflated to the 2019 value using Consumer Price Index was extracted for studies 3-5 and divided according to terciles into low, middle- and high-income categories.

4.7.5 All-cause and specific-cause mortality

Mortality as expressed by the record in the CODR was used to define the outcomes (studies 2 and 4), specify competing events (study 3) and determine the range of follow-up and censoring (studies 2-5).

Patient death was counted if a valid record existed in the CODR (date of death dated after the study baseline). For all-cause mortality statistics (studies 2-5), no distinction was made between underlying or contributing causes of death. In study 2, cardiovascular/cerebrovascular (CV) and DM-related mortality were determined if ICD-10 codes I00-I79 and E10-E14, respectively were recorded as underlying causes of death in CODR.

4.8 STUDY SAMPLES

Study 1 and 2 focused on patients with dementia, with or without DM diagnosis. Studies 3 and 4 comprised patients with DM, with or without dementia diagnosis. Study 5 comprised only patients with DM and dementia diagnosis. The study sample selection is summarized in **Figure 5**.

The main data source in study 1 – SveDem (36,433 patients registered until December 31st, 2013) was merged with NPR and SPDR records (**Figure 2**). After applying the exclusion criteria (**Figure 5**), 29,630 patients with dementia diagnosis from SveDem until December 31st, 2012 were analyzed. In this cohort, 4,881 (16.5%) patients had diagnosis of DM and 24,749 (83.5%) were DM-free.

In study 2, data from SveDem (58,412 patients registered until December 31st, 2015) were merged with NPR, SPDR and CODR (**Figure 2**) and exclusion criteria were applied (**Figure**

5). In the final sample of 22,660 patients with dementia, 3,176 (14.0%) patients were diagnosed with DM and 19,484 (86.0%) were diabetes-free.

Studies 3 and 4 used a subsample from a larger data extraction where both patients with dementia (from SveDem, NPR, CODR and SPDR) and dementia-free subjects (TPR) were included (**Figures 2 & 5**, section 4.5 on TPR). The subsample (n=138,900) comprised only patients with DM diagnosis who either had diagnosis of dementia from SveDem (n=13,580) or were dementia-free (n=171,052). Afterwards, patients with T1DM were excluded, and in study 4 patients with missing prognostic variables (e.g. living arrangement, dementia diagnosis) were also excluded. In the final sample, the study 3 comprised 133,318 patients and study 4 comprised 132,402 patients with T2DM or other/unspecified DM (**Figure 5**).

Furthermore, in study 4, patients without history of individual antidiabetic drug use were first PS-matched on dementia status, then the dementia and dementia-free cohorts were analyzed separately. **Figure 6** summarizes the study design in study 4 with sulfonylurea as example.

In study 5, the core sample comprised patients who were diagnosed with dementia and were registered to SveDem until October 16th, 2018 (n=80,004). The SveDem data were merged with the NPR, SPDR, CODR and LISA and exclusion criteria were applied (**Figure 5**). We analyzed only patients with T2DM or other/unspecified DM who were also diagnosed with AD or MixDem and had at least one annual follow-up (1,873 patients, 4,732 total observations).

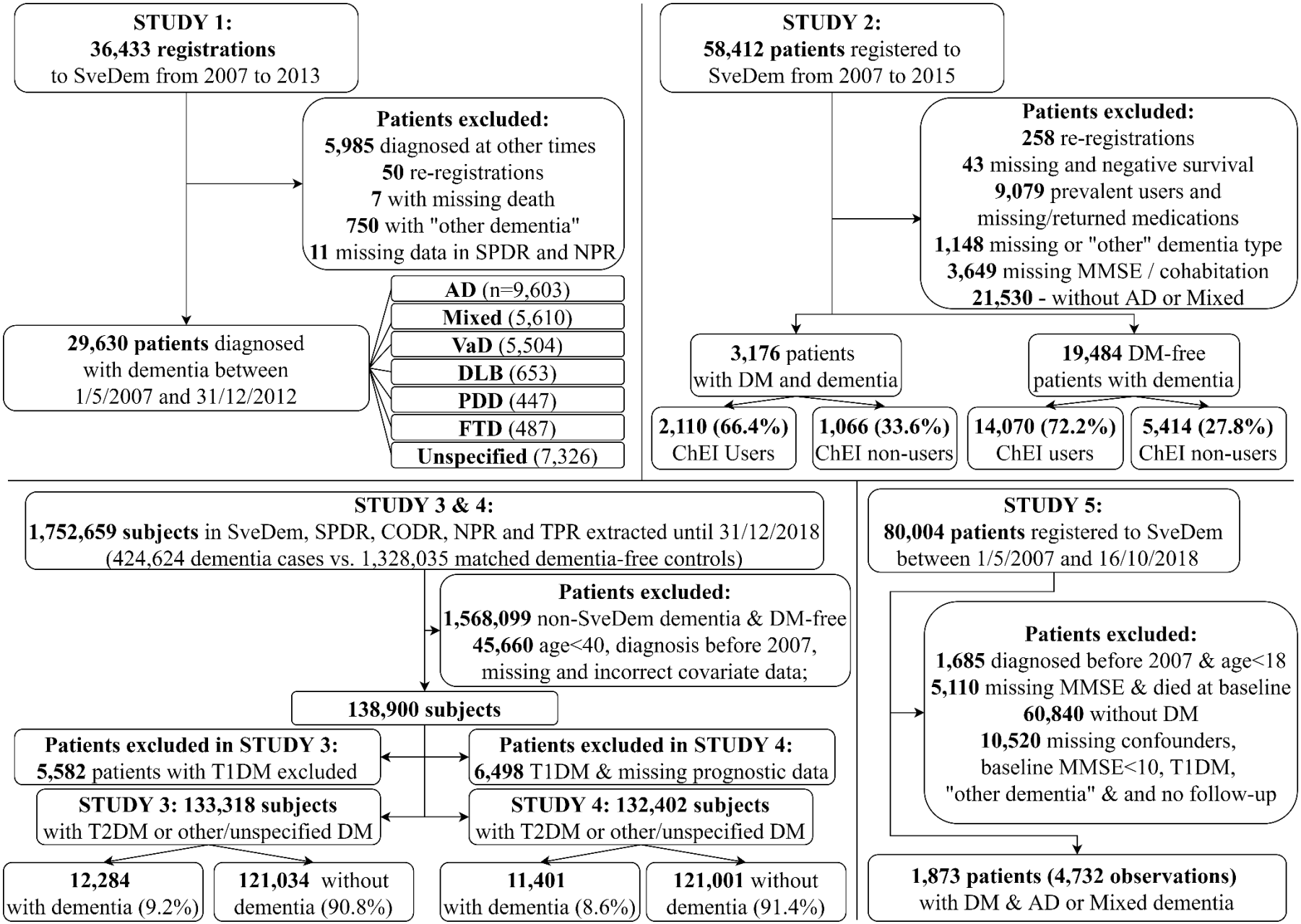

Figure 5. The analytical samples extracted for the thesis studies.

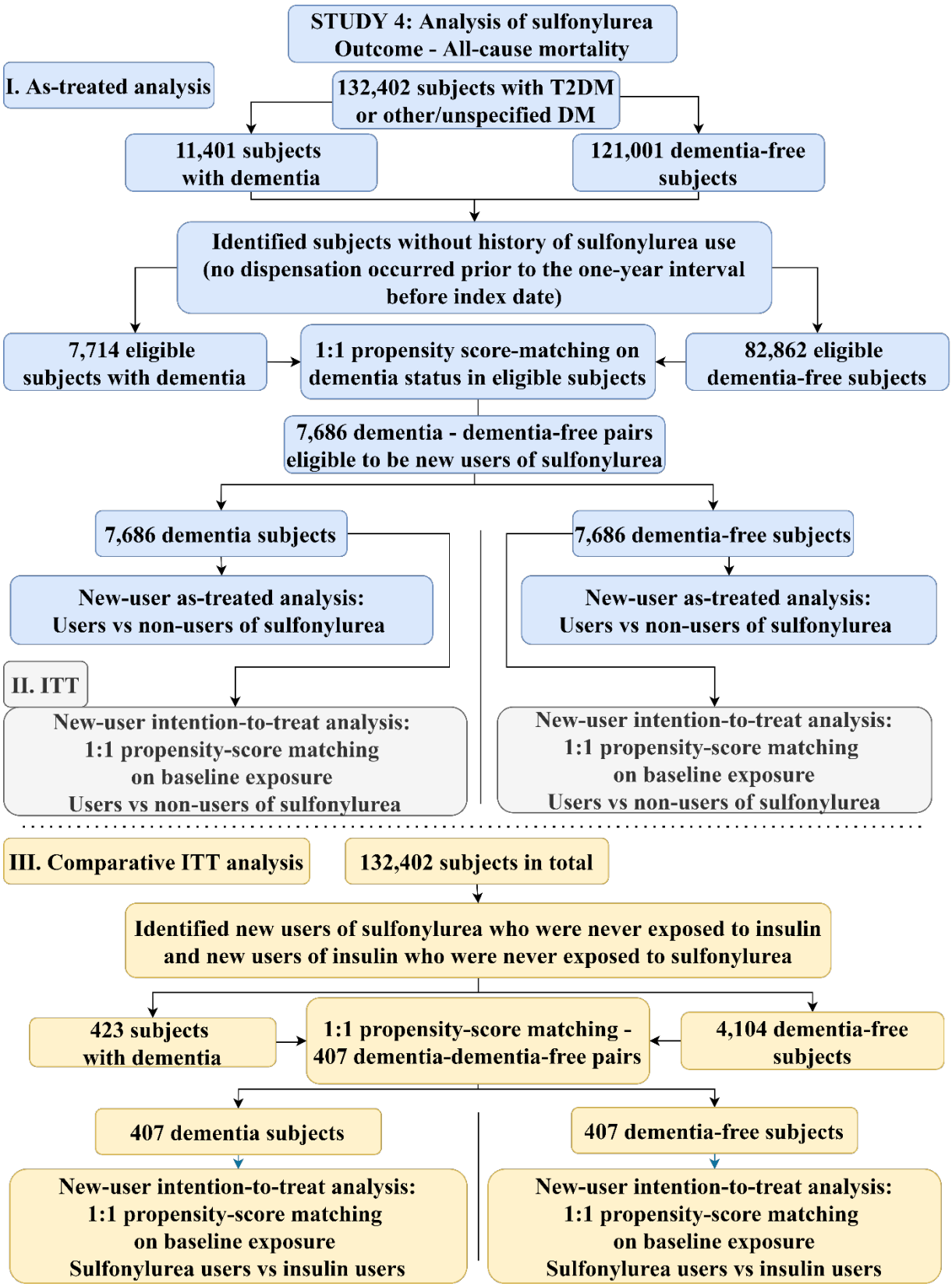

Figure 6. Analytical algorithm in study 4 with sulfonylurea as example.

4.9 STATISTICAL METHODS

Data were analyzed using IBM Statistical Package for Social Sciences (SPSS) version 23 (IBM Corporation, Armonk NY), Stata version 16 (Stata Statistical Software: Release 16.

StataCorp LLC, College Station, TX), SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.5.1 and 4.0.0[196] using the packages MatchIt[197] and rstpm2[198].

In all studies, continuous variables were summarized as mean [standard deviation (SD)] or median (interquartile range) and categorical variables as number of subjects (%). Independent-samples t-test, Mann-Whitney U-test and one-way ANOVA were used to compare continuous variables, and Fisher-exact and χ^2 test were used for categorical variables in univariate comparisons. In addition, standardized mean differences were used to determine significant differences in the PS-matched cohorts. Specific methods used in individual studies are described below and in **Table 3**. For study 1, different p-value levels were used to determine statistical significance, between <0.05 (corresponding to 95% CI) and <0.002 (corresponding to 99% CI). P-value <0.05 was considered statistically significant in studies 2-5. Both time-constant and time-varying exposure models were used (depending on whether the exposure could change during follow-up). Study baseline refers either to date of dementia diagnosis or index date in dementia-free subjects.

Study 1: Binary logistic regression was applied with DM as dependent variable and use of ChEI and memantine as the main explanatory variables, while stepwise adjusting for sociodemographic, clinical and pharmacological confounders. Odds ratios (OR) with 95% to 99% confidence intervals marked significant associations, and the significance threshold was adjusted for the number of predictors/variables entered in the models (Bonferroni correction).

Study 2: The differences among users and non-users of ChEI class and specific ChEI medications were balanced using propensity-score (PS) matching[199] as well as regression covariate adjustment. Specifically, nearest-neighbor 1:1 PS-matching with caliper of 0.2 SD of the logit of PS was used to match on exposure status. For the survival analysis, Cox proportional hazard regression[200] and competing risk regression[201] models were used in the whole and matched cohorts to determine the hazard ratios (HR) with 95% CI for the association between use of ChEI class, donepezil, rivastigmine and galantamine and all-cause, CV and DM-related mortality. In the competing risk regression models, other-cause mortality was the competing event. Time since entry was the model time scale. Time-varying and time-constant exposure models were used in the whole-cohort and PS-matched analysis, respectively. In dose-response analyses, low-dose ChEI users were the reference category. End of study follow-up was on August 28th, 2016.

Study 3: Two datasets were analysed in study 3. First, a summary dataset was created where the proportion of antidiabetic drug dispensation among all subjects within each year relative

to the study baseline was recorded. As subjects' diagnosis of dementia or index date varied between years 2007-2018 and the SPDR records started in 2005, the range of dispensations allowed for extraction of 14 years prior to the latest diagnosis/index date and 12 years after the earliest diagnosis/index date. In the summary datasert, the β coefficients with 95% CI from the linear regression analysis in the whole and PS-matched cohorts determined the changes in antidiabetic drug dispensation with yearly increments. Dementia was the main predictor in the model and the outcome was the change in dispensation proportion of specific antidiabetic drugs out of all antidiabetic drugs in the annual intervals before and after the index date or dementia diagnosis.
Second, the dataset with patient-level data was analyzed. In naïve patients and in patients who were users of metformin in the period one-year prior to study baseline, the HR and 95% CI of first antidiabetic drug dispensation after study baseline was compared between dementia and dementia-free subjects using proportional hazards regression and competing risk regression models (all-cause mortality as competing event). Attained age (all main analyses) and time since entry (supplementary stratified analysis) were used as time scale. PS-matching was done using 1:1 ratio and 0.1 caliper, and exact matching was performed on the calendar year at dementia diagnosis / index date. Patients were followed-up until December 31st, 2018.

Study 4: The use of antidiabetic medication and the risk of all-cause mortality was determined using a flexible parametric survival model[202] with attained age as time scale in the whole and PS-matched cohorts. PS-matching was performed using 1:1 and 1:4 matching ratios with 0.1 caliper. Patients with and without dementia were analyzed in separate analytical cohorts and not directly compared (**Figure 6)**. Time-varying and time-constant exposure approaches were used in whole and PS-matched cohorts, respectively. Additionally, the presence of time-dependent confounding[203] was corrected by inverse-probability weighting (IPW) on treatment and censoring using stabilized subject-specific time-varying weights – a marginal structural model was specified following a process by Fewell and colleagues[204]. Antidiabetic drug efficacy was compared in users vs non-users as well as between users of one drug vs users of other drug. For example, incident insulin users who were never exposed to sulfonylurea prior to index date were compared to new users of sulfonylurea who were never exposed to insulin. The study follow-up ended on December 31st, 2018.

Study 5: Linear mixed-effects models were applied to determine the changes in MMSE scores between annual follow-ups associated with the use of antidiabetic medications.

Analyses were done in 1:1 and 1:4 PS-matched cohorts (0.1 caliper) with the drug exposure as the fixed effect and the subject and follow-up time as random effects (random intercept and slope). Users vs non-users as well as users of one drug vs users of other drug were compared. Both incident- and prevalent-user analysis were performed. Last follow-up occurred on October 16th, 2018.

In a sensitivity analysis, MMSE scores missing between the observed follow-ups were imputed using multivariate multiple imputation with chained equations based on the slope between observed MMSE measurements and time from baseline. Furthermore, due to presence of selective dropout in the source registry (SveDem), we weighted the analyses using IPW of remaining in the study based on MMSE in the previous observation and time since baseline, as described by Handels et al. [205]. Follow-up time extended until October 16th, 2018.

Table 3. Summary of exposures, outcomes and statistical methods applied in the thesis' studies.

	Main exposures (independent variables)	Outcomes (dependent variables)	Main statistical tools	Bias handling (e.g. confounding, selection bias)	Specific study characteristics
Study 1	ChEI and memantine (user / non-user)	Presence of diabetes (yes / no)	Binary logistic regression	Regression adjustment	Cross-sectional 7 dementia types Diabetes vs diabetes-free
Study 2	ChEI class & specific, ChEI dose-response (user / non-user)	All-cause mortality Cardiovascular mortality Diabetes-related mortality	Cox regression Competing-risk regression	Propensity-score matching Regression adjustment	Cohort (time-to-event) AD or MixDem Diabetes vs diabetes-free Time-varying exposure
Study 3	Presence of dementia (yes / no)	Probability and % change of antidiabetic drug dispensation	Linear regression Cox regression Competing-risk regression	Propensity-score matching Regression adjustment	Cohort (time-to-event) All patients with diabetes Dementia and dementia-free
Study 4	Antidiabetic drugs Incident users (user / non-user / other user)	All-cause mortality	Flexible parametric survival model (survival analysis)	Propensity-score matching Regression adjustment IPW – marginal structural model	Cohort (time-to-event) Dementia and dementia-free Time-varying exposure
Study 5	Antidiabetic drugs Incident & prevalent users (user / non-user / other user)	Change in MMSE scores during follow-up	Linear mixed-effects model	Propensity-score matching IPW – selective dropout	Cohort (repeated-measures) AD or MixDem Multiple imputation

4.10 ETHICAL CONSIDERATIONS

Ethical approval was obtained for each project and the studies were permitted and approved by the regional ethical committee in Stockholm, Sweden (Paper 1: dnr 2013/147-31/2 & 2016/178-32; Paper 2: 2015/743-31/4 & 2015/1313-32; Paper 3-5: 2017/501-31). All studies comply with the Declaration of Helsinki[206].

The notable ethical issue includes the fact that informed consent is not necessary for register-based research in Sweden. According to the Law on Ethical Review of Research Involving Humans (SFS 2003:460), the research in patients with illness, psychiatric disorder or worsened health conditions may be performed under the condition that the research can lead to patient benefit and does not cause significant discomfort[207]. Importantly, the ethical aspects of individual projects are considered in detail by the regional ethical committee and the potential requirement of informed consent is at the committee's discretion (i.e. the committee acts as ethical representative for the patients). Thus, the overall risks for the patient are low. Furthermore, the advantages of the register-based research (e.g. low financial demands, wide coverage, longitudinal data, linkage with other sources) are substantial[208]. In addition, it would be practically impossible to acquire informed consent from all subjects in the registers as significant proportion of high-risk patients would decline participation or would have already died[208]. Moreover, the register data are unique, and an argument could be made that not analyzing them may be considered unethical as the research aims to improve patient care and the risks are low. Additionally, the patients by law receive information about their registration. In SveDem, the principal register in the thesis, the patients and their relatives are informed orally about the registration and can decline participation. Moreover, a patient can ask for an excerpt of the data stored in SveDem and have their data removed from the register[186].

Another ethical issue arises from extent of the merged register-based datasets, that comprise thousands of patients and plethora of variables, which may potentially lead to patient identification if misused[208]. To this end, the anonymized data were provided to the vetted researchers only after the ethical application for a specific project was approved by the ethical committee and the possibility to reverse the anonymization was not possible. Second, the data were analyzed only on a group level, and no subject-level analyses were performed. Moreover, the data were stored and analyzed on encrypted drives managed by the central information-technology center at Karolinska Institutet, with restricted and password-protected access. Therefore, the possibility for security breach was very limited.

5 RESULTS

5.1 PATIENTS WITH DIABETES AND DEMENTIA ARE LESS LIKELY TO RECEIVE CHOLINESTERASE INHIBITORS AND MEMANTINE (STUDY 1)

Among 29,630 patients with dementia diagnosed until December 31st, 2015, 4,881 (16.5%) were also diagnosed with DM. In the fully adjusted binary logistic regression model, presence of DM was associated with lower age (OR 0.97, 95% CI 0.97-0.98), lower MMSE (0.98, 0.97-0.99) and when compared to AD, more frequent MixDem (1.21, 1.06-1.39) and VaD (1.17, 1.01-1.36) diagnoses, while DLB (0.64, 0.44-0.94) and PDD (0.46, 0.28-0.75) were less frequent among DM patients (**Table 4**). ChEI and memantine use was less frequent in patients with DM (ChEI 0.77, 0.69-0.85; memantine 0.78-0.68-0.89).

Table 4. The associations of patient characteristics with the presence of DM.

Characteristics		**Dependent variable: Diabetes mellitus** (4,881 DM vs 24,749 DM-free)	
		Model 0; OR (95% CI)	**Model 2; OR (99% CI)**
Sociodemographic variables			
Age at diagnosis, years		0.99 (0.96-0.99)*	0.97 (0.97-0.98)*
Male sex		1.47 (1.38-1.56)*	1.41 (1.27-1.55)*
Institutional living		1.15 (1.05-1.30)*	0.93 (0.74-1.18)
Living alone		0.91 (0.85-0.97)*	1.10 (0.99-1.22)
Clinical determinants			
Registered at memory clinic		0.90 (0.85-0.96)*	0.94 (0.84-1.05)
Total number of drugs, n		1.18 (1.17-1.19)*	1.15 (1.13-1.17)*
MMSE at diagnosis, points		0.99 (0.98-0.99)*	0.98 (0.97-0.99)*
Dementia type	AD	Reference	Reference
	MixDem	1.62 (1.48-1.78)*	1.21 (1.06-1.39)*
	VaD	2.31 (2.11-2.52)*	1.17 (1.01-1.36)*
	DLB	0.80 (0.61-1.04)	0.64 (0.44-0.94)*
	FTD	1.43 (1.11-1.83)*	1.12 (0.76-1.65)
	PDD	0.82 (0.60-1.13)	0.46 (0.28-0.75)*
	Unspecified	1.47 (1.35-1.61)*	1.08 (0.93-1.25)
Medication use			
Antithrombotics		2.53 (2.36-2.72)*	1.18 (1.05-1.33)*
Cardiac drugs		1.76 (1.64-1.89)*	0.92 (0.82-1.03)
Antihypertensives		3.64 (3.32-4.00)*	1.96 (1.67-2.27)*
Statins		3.56 (3.34-3.80)*	2.29 (2.07-2.54)*
Antipsychotics		1.09 (1.01-1.19)*	1.08 (0.93-1.24)
Anxiolytics		1.10 (1.03-1.18)*	1.03 (0.91-1.15)
Hypnotics/sedatives		1.08 (1.01-1.15)*	0.82 (0.73-0.91)*
Antidepressants		1.03 (0.97-1.09)	0.85 (0.77-0.94)*
ChEI		0.65 (0.61-0.70)*	0.77 (0.69-0.85)*
Memantine		0.73 (0.67-0.80)*	0.78 (0.68-0.89)*

Based on binary logistic regression; In the model 0, variables were entered into the model separately; Model 2 was adjusted for sociodemographic variables, clinical determinants, cardiovascular,

psychotropic and dementia medication; Dementia was entered into the model as multi-categorical variable; The threshold for statistical significance was corrected for the number of independent variables entered in model 2; p-value of 0.05 was considered significant for Model 0; p-value of 0.002 was considered significant for Model 2; *p-value <0.05 (Model 0); *p-value <0.002 (Model 2).

In the fully adjusted model stratified by diagnosis of dementia (**Table 5)**, DM diagnosis was associated with lower odds of ChEI and memantine use among AD patients (ChEI 0.78, 0.63-0.95; memantine 0.68, 0.54-0.85). In MixDem and VaD patients, the negative association with DM was observed only for ChEI (MixDem 0.69, 0.56-0.85; VaD 0.68, 0.49-0.95).

Table 5. Association of DM and anti-dementia drug dispensation stratified by dementia type.

Dementia type	**Dependent variable: Diabetes mellitus**	
	Model 0; (OR 95% CI)	**Model 2; OR (99%CI)**
AD (n=9,603)		
ChEI	0.80 (0.70-0.91)*	0.78 (0.63-0.95)†
Memantine	0.70 (0.60-0.81)†	0.68 (0.54-0.85)†
MixDem (n=5,610)		
ChEI	0.76 (0.66-0.87)†	0.69 (0.56-0.85)†
Memantine	0.96 (0.82-1.12)	0.86 (0.69-1.09)
VaD (n=5,504)		
ChEI	0.68 (0.55-0.86)*	0.68 (0.49-0.95)†
Memantine	1.02 (0.80-1.30)	0.99 (0.69-1.43)
DLB (n=653)		
ChEI	1.37 (0.75-2.51)	1.49 (0.56-3.98)
Memantine	0.79 (0.44-1.37)	0.71 (0.29-1.72)
FTD (n=487)		
ChEI	0.40 (0.14-1.15)	0.50 (0.11-2.16)
Memantine	0.63 (0.21-1.84)	0.36 (0.06-2.10)
PDD (n=447)		
ChEI	0.71 (0.38-1.33)	0.75 (0.27-2.10)
Memantine	0.96 (0.47-1.96)	0.84 (0.26-2.72)
Unspecified (n=7,326)		
ChEI	0.90 (0.79-1.03)	0.87 (0.71-1.08)
Memantine	0.74 (0.60-0.91)*	0.70 (0.50-0.97)†

Binary logistic regression was used with diabetes as dependent variable and dispensation of dementia drugs as the main predictor; Model 0 was unadjusted; Model 2 was adjusted for sociodemographic characteristics, clinical characteristics (excluding dementia type), cardiovascular and psychotropic medication; The threshold for significance was corrected for the number of independent variables entered in model 2; *p-value <0.05, †p-value <0.003.

5.2 CHOLINESTERASE INHIBITORS ARE ASSOCIATED WITH SURVIVAL BENEFIT IN PATIENTS WITH DIABETES AND DEMENTIA (STUDY 2)

In this study of 22,660 patients with AD or MixDem, 3,176 patients had diagnosis of DM (14%) and 19,484 were DM-free (86%). Within patients with DM 2,110 (66.4%) patients were ChEI users and 1,066 (33.6%) were non-users, while among DM-free 14,070 (72.2%) were ChEI users and 5,414 (27.8%) had no ChEI prescription at baseline.
The use of ChEI was associated with lower all-cause mortality among both DM and DM-free patients with AD or MixDem in the fully adjusted whole-cohort analyses (HR 0.70, 95% CI 0.62-0.79; DM subjects; 0.68, 0.65-0.72; DM-free subjects) and PS-matched analyses (0.76, 0.67-0.86; DM; 0.80, 0.75-0.84; DM-free).
In addition, only donepezil and galantamine were consistently associated with significantly lower all-cause mortality among patients with DM (**Table 6**).

Table 6. All-cause mortality associated with ChEI use in patients with and without DM.

	Outcome: All-cause mortality – HR (95% CI)	
ChEI (user vs non-user)	**Patients with diabetes & dementia**	
	Model 1; whole-cohort analyses	**PS-matched analyses**
ChEI class	0.70 (0.62-0.79)†	0.76 (0.67-0.86)†
Donepezil	0.76 (0.66-0.88)†	0.84 (0.74-0.96)*
Rivastigmine	0.88 (0.72-1.07)	0.97 (0.79-1.20)
Galantamine	0.68 (0.57-0.81)†	0.80 (0.66-0.97)*
	Diabetes-free patients with dementia	
	Model 1; whole-cohort analysis	**PS-matched analyses**
ChEI class	0.68 (0.65-0.72)†	0.80 (0.75-0.84)†
Donepezil	0.69 (0.65-0.73)†	0.85 (0.80-0.90)†
Rivastigmine	0.82 (0.75-0.89)†	1.03 (0.95-1.12)
Galantamine	0.74 (0.69-0.80)†	0.93 (0.86-0.99)*

Cox-regression in the whole-cohort analyses (Model 1) was adjusted for age, sex, dementia type, cohabitation, MMSE score, CCI, antipsychotics, hypnotics/sedatives, cardiovascular and antithrombotic medication, and in patients with diabetes the model was further adjusted for use of antidiabetic medication and diabetes duration; In PS-matched cohorts, patients were 1:1 matched using the same variables as in adjustment; The ChEI exposure was considered a time-varying covariate in adjusted model and as time-constant covariate in PS-matched analyses; *p-value <0.05; †p-value <0.001.

Additionally, higher doses were not associated with additional protective effect (PS-matched analysis - high-dose vs low-dose ChEI 0.84, 0.63-1.12 DM; 1.17, 1.04-1.32; DM-free).

In the whole-cohort fully adjusted analyses of specific mortality, ChEI use was associated with lower CV mortality, however the association was limited to DM-free patients (ChEI 0.77, 0.69-0.85; donepezil 0.73, 0.65-0.82; rivastigmine 0.78, 0.65-0.93). Moreover, the PS-matched analyses only confirmed the protective association in donepezil users without dementia (0.84, 0.75-0.94). Finally, ChEI use was associated with lower risk of diabetes-related mortality (0.52, 0.32-0.87; DM subjects), however the association was not confirmed in PS-matched analyses (0.87, 0.54-1.39). The cause-specific mortality risk among ChEI users is summarized in **Table 7**.

Table 7. CV and DM-related mortality associated with the use of ChEI.

	Whole-cohort analyses – model 1		
	DM & Dementia sHR (95% CI)		**DM-free & Dementia sHR (95% CI)**
	CV mortality	**DM-related mortality**	**CV mortality**
ChEI class	0.87 (0.69-1.08)	0.52 (0.32-0.87)*	0.77 (0.69-0.85)†
Donepezil	0.84 (0.65-1.08)	0.56 (0.30-1.05)	0.73 (0.65-0.82)†
Rivastigmine	0.83 (0.57-1.22)	0.46 (0.16-1.30)	0.78 (0.65-0.93)*
Galantamine	1.11 (0.83-1.49)	0.81 (0.42-1.58)	0.98 (0.86-1.13)

	PS-matched cohorts		
	DM & Dementia sHR (95% CI)		**DM-free & Dementia sHR (95% CI)**
	CV mortality	**DM-related mortality**	**CV mortality**
ChEI class	1.02 (0.80-1.30)	0.87 (0.54-1.39)	0.92 (0.81-1.02)
Donepezil	0.89 (0.69-1.14)	0.77 (0.47 -1.27)	0.84 (0.75-0.94)*
Rivastigmine	0.83 (0.56 -1.24)	0.92 (0.36 -2.32)	1.06 (0.88 -1.26)
Galantamine	1.10 (0.79 -1.54)	0.89 (0.44 -1.80)	1.05 (0.90 -1.23)

sHR, subdistribution hazard ratio; Competing risk regression with other-cause mortality as competing event was used; Model 1 was adjusted for age at dementia diagnosis, sex, dementia type, cohabitation, Mini-Mental State Examination score, antipsychotics, hypnotics/sedatives, cardiovascular and antithrombotic medication and Charlson comorbidity index; Model 1 for the analysis in DM & dementia patients was additionally adjusted for the use of antidiabetic medication and diabetes duration; PS-matched analysis of ChEI was adjusted for age and MMSE in the DM-free cohort, and age and dementia type in the DM cohort due to residual differences in the matched cohorts; Use of ChEI class and specific medications were entered as time-varying exposure in whole-cohort analyses, and time-constant exposure in PS-matched cohorts; *p-value <0.05; †p-value <0.001.

5.3 PATIENTS WITH DIABETES AND DEMENTIA ARE COMMONLY TREATED WITH INSULIN AND LESS COMMONLY WITH NEWER DRUGS (STUDY 3)

The third study comprised 133,318 patients with type 2 or other/unspecified DM, among which 12,284 (9.2%) had dementia diagnosis and 121,034 (90.8%) were dementia-free. In the PS-matched analyses the annual proportion of insulin use out of all antidiabetic drugs was more pronounced in patients with dementia compared to dementia-free subjects (1.96% vs 0.99%, 0.97% absolute difference). On the other hand, DPP-4i (0.56% vs 1.14%, 0.58% difference), GLP-1a (0.13% vs 0.26%, 0.13% difference) and SGLT-2i (0.07% vs 0.28%, 0.21%) dispensations increased, albeit less steeply in patients with dementia (**Table 8, Figure 7**)**.** The annual dispensation proportion of metformin (-1.33% vs -1.06%, 0.27% difference) and sulfonylurea (-1.34% vs. -1.04%, 0.30% difference) decreased more steeply in patients with dementia. Results were similar in the cohort using metformin in the one-year prior to study baseline (not shown).

Table 8. Antidiabetic drug dispensation changes in patients with and without dementia.

Antidiabetic drug	**Change in % of annual antidiabetic drug dispensation**		
	Dementia; β (95% CI)	**Dementia-free; β (95% CI)**	**Absolute difference**
Insulin	1.96% (1.61-2.31)*	0.99% (0.82-1.15)*	0.97% (D↑)
Metformin	-1.33% (-1.64;-1.02)*	-1.06% (-1.23;-0.89)*	0.27% (D↓)
Sulfonylureas	-1.34% (-1.55;-1.13)*	-1.04% (-1.24; -0.84)*	0.30% (D↓)
TZD	-0.21% (-0.24;-0.17)*	-0.22% (-0.25;-0.18)*	0.01 (ND↓)
DPP-4i	0.56% (0.49; 0.64)*	1.14% (1.00-1.29)*	0.58% (ND↑)
GLP-1a	0.13% (0.07-0.19)*	0.26% (0.17-0.35)*	0.13% (ND↑)
SGLT-2i	0.07% (0.01-0.12)*	0.28% (0.13-0.43)*	0.21% (ND↑)

Linear regression was used to obtain the β coefficients represent slope of change in antidiabetic drug usage with advancing time (one-year increments); D↑ larger percentual dispensation increase in the dementia cohort; D↓ larger percentual decrease in the dementia cohort; ND↑ larger percentual increase in dementia-free cohort; ND↓ larger percentual decrease in dementia-free cohort; Based on summary data from the propensity-score matched cohorts; *p-value<0.001.

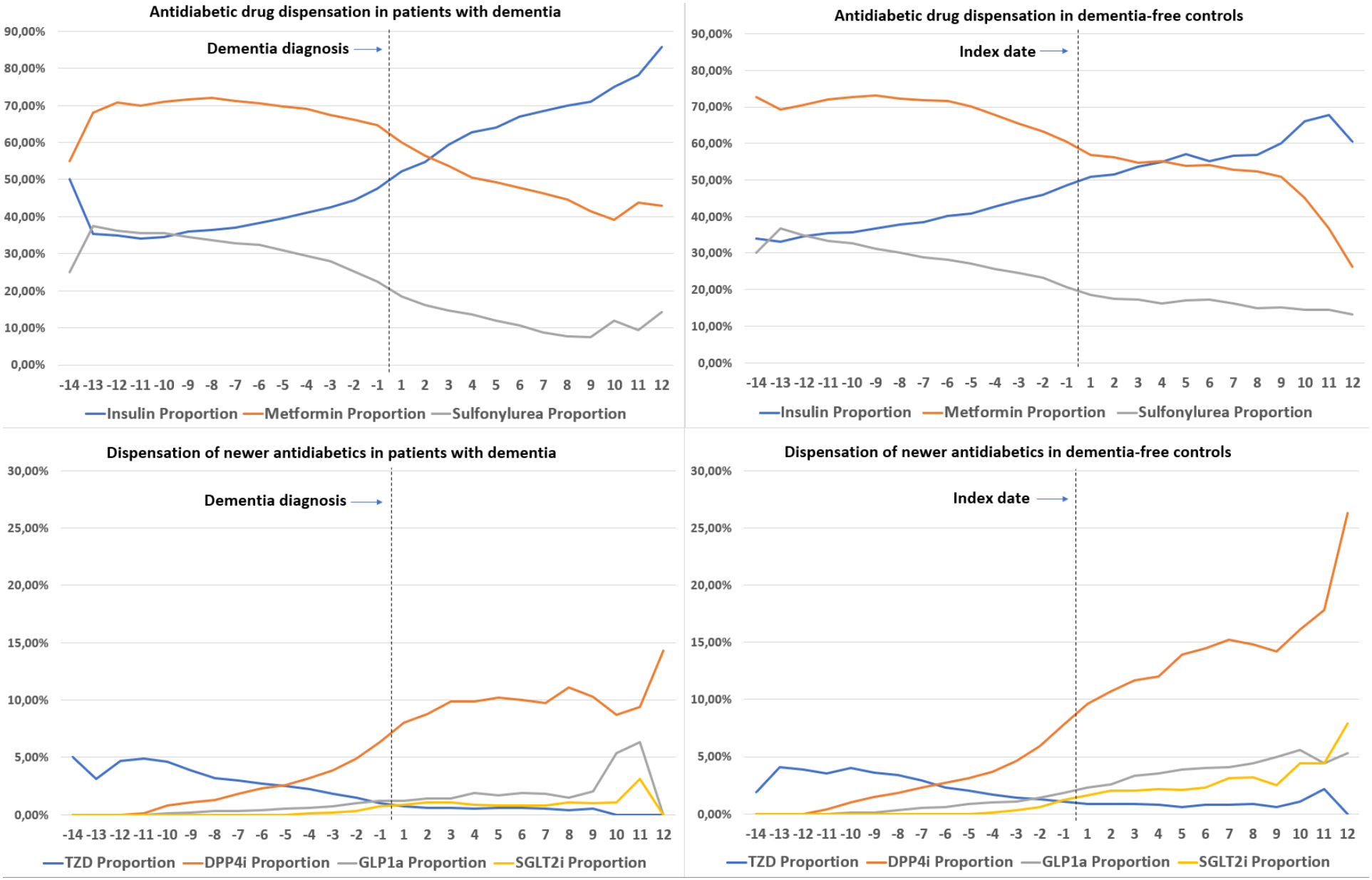

Figure 7. Long-term changes in antidiabetic drug dispensation in patients with diabetes and with and without dementia.

Based on propensity score matched cohorts; The x axis - annual interval relative to dementia / index date; The y axis - proportion of specific drug users out of all antidiabetic drug users within the specified annual period.

Furthermore, in the PS-matched cohorts of naïve patients (without history of medication use) new dispensation of insulin was more likely among patients with dementia compared to dementia-free (subdistribution HR 1.21, 1.11-1.31), while DPP-4i (0.72, 0.66-0.79), GLP-1a (0.51; 0.41-0.63) and SGLT-2i (0.44, 0.36-0.54) were less commonly prescribed to patients with dementia (**Figure 8)**. Furthermore, the probabilities of new metformin (0.88, 0.77-1.02) and sulfonylurea dispensation (0.90, 0.76-1.07) were not significantly different among patients with and without dementia.

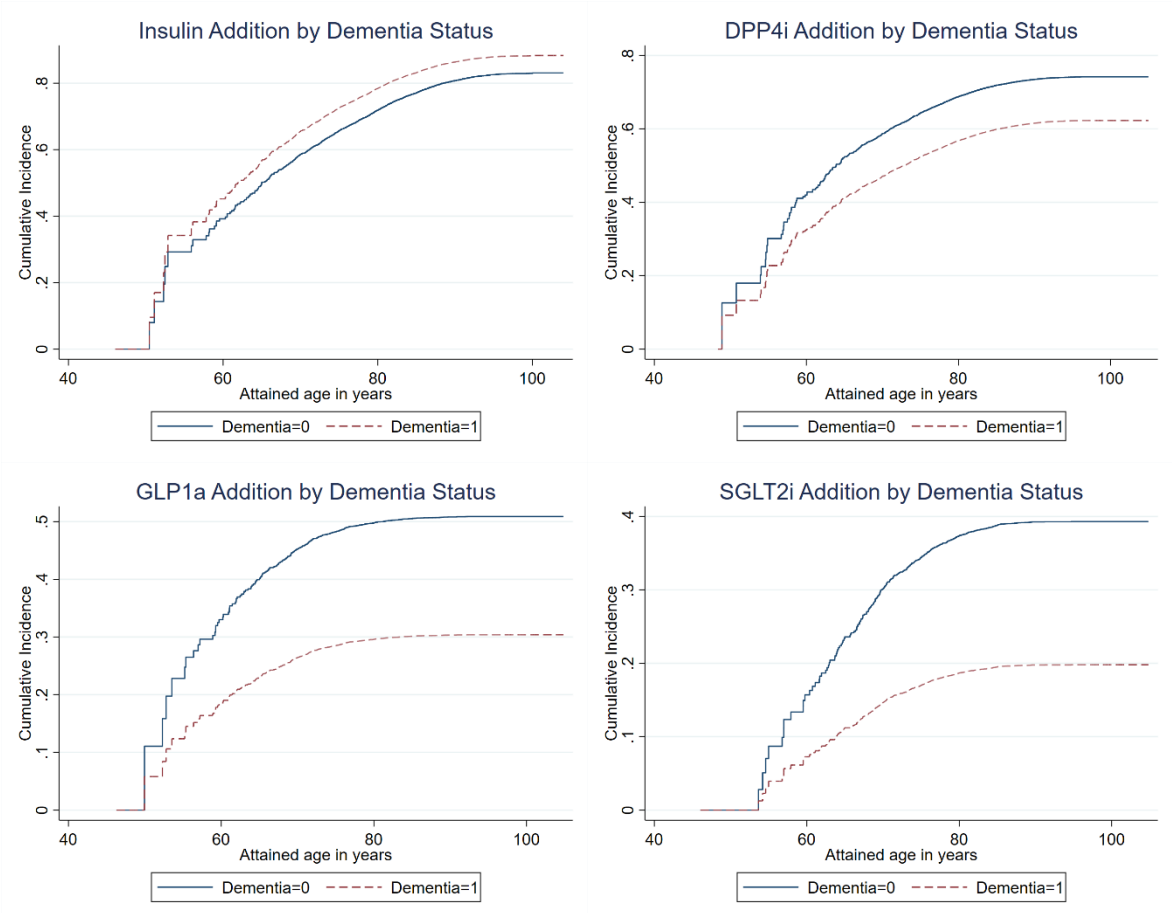

Figure 8. Cumulative incidence functions of antidiabetic drug dispensation by dementia status in naïve patients (without previous drug dispensation). Figure is based on the competing risk regression models, with all-cause mortality as competing risk; Attained age was the time-scale and first dispensation of medication after study baseline was the outcome; The patients with and without dementia were PS-matched on age, sex, Charlson comorbidity index, renal disease, diabetes type, diabetes duration, attained education, income category, and use of cardiovascular, antithrombotic, antipsychotic, antidepressant, hypnotic/sedative, anxiolytic drugs and other antidiabetic drugs.

5.4 ANTIDIABETIC MEDICATION IS ASSOCIATED WITH DIFFERENT SURVIVAL IN PATIENTS WITH AND WITHOUT DEMENTIA (STUDY 4)

In total, 132,402 subjects with type 2 DM or other/unspecified DM were included in the fourth study, where 11,401 (8.6%) were diagnosed with dementia and 121,001 (91.4%) were dementia free.

In the flexible parametric survival model using as-treated exposure, both the patients with dementia (HR 1.34, 95% CI 1.23-1.45) and dementia-free subjects using insulin (1.54, 1.39-1.71) had similarly higher risk of mortality compared to non-users (**Figure 9, Table 9)**.

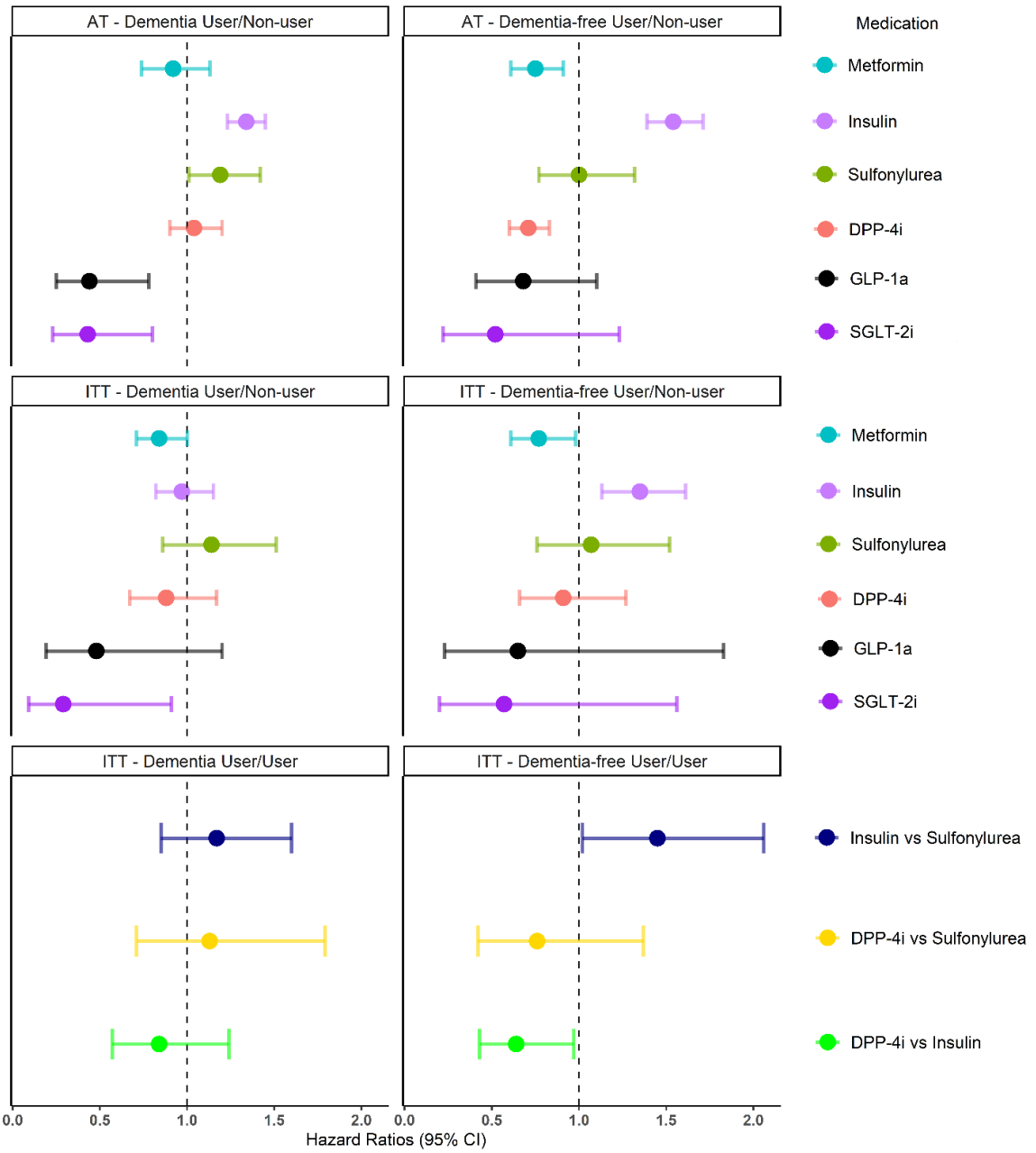

Figure 9. Antidiabetic medications and all-cause mortality by dementia status and analysis. In the as-treated (AT) models, use of medication was entered as time-varying exposure, while in the intention-to-treat (ITT) models, the exposure was time-constant.

Conversely, DPP-4i use was associated with lower mortality only in dementia-free subjects (0.71, 0.60-0.83), while no effect was observed in dementia patients (1.04, 0.90-1.20). Higher mortality risk was also observed among sulfonylurea users with dementia (1.19, 1.01-1.42). In addition, lower mortality risk was observed in GLP-1a (0.44, 0.25-0.78) and SGLT-2i users (0.43, 0.23-0.80) with dementia. The association in dementia-free was similar in strength (GLP-1a 0.68, 0.41-1.10; SGLT-2i 0.52, 0.22-1.23), however it did not reach statistical significance (**Figure 9**).

Lastly, in the comparative drug-drug analyses, insulin was associated with higher mortality compared to sulfonylurea among dementia-free subjects (1.45, 1.02-2.06), but not in patients with dementia (1.17, 0.85-1.60). On the other hand, DPP-4i use exhibited lower mortality risk than insulin in dementia-free (0.64, 0.43-0.97), while the effect was not significant in patients with dementia (0.84, 0.57-1.24) (**Figure 9, Table 9).**

Table 9. All-cause mortality associated with the use of antidiabetic drugs in patients with and without dementia.

Antidiabetic medication		Crude & weighted as-treated analyses	Adjusted & weighted as-treated analyses	PS-matched intention-to-treat analyses
			Dementia patients, HR (95% CI)	
User vs non-user	**Metformin**	0.80 (0.63-1.01)	0.92 (0.74-1.13)	0.84 (0.71-1.00)
	Insulin	1.32 (1.22-1.42)†	1.34 (1.23-1.45)†	0.97 (0.82-1.15)
	SU	1.11 (0.93-1.33)	1.19 (1.01-1.42)*	1.14 (0.86-1.51)
	DPP-4i	1.05 (0.92-1.20)	1.04 (0.90-1.20)	0.88 (0.67-1.17)
	GLP-1a	0.48 (0.27-0.86)*	0.44 (0.25-0.78)*	0.48 (0.19-1.20)
	SGLT-2i	0.36 (0.19-0.71)*	0.43 (0.23-0.80)*	0.29 (0.09-0.91)*
User vs user	**Insulin vs Sulfonylurea**			1.17 (0.85-1.60)
	DPP-4i vs Sulfonylurea			1.13 (0.71-1.79)
	DPP-4i vs Insulin			0.84 (0.57-1.24)
			Dementia-free subjects, HR (95% CI)	
User vs non-user	**Metformin**	0.59 (0.49-0.71)†	0.75 (0.61-0.91)*	0.77 (0.61-0.98)*
	Insulin	1.54 (1.39-1.70)†	1.54 (1.39-1.71)†	1.35 (1.13-1.61)*
	Sulfonylurea	0.88 (0.67-1.15)	1.00 (0.77-1.32)	1.07 (0.76-1.52)
	DPP-4i	0.64 (0.54-0.75)†	0.71 (0.60-0.83)†	0.91 (0.66-1.27)
	GLP-1a	0.59 (0.36-0.97)*	0.68 (0.41-1.10)	0.65 (0.23-1.83)
	SGLT-2i	0.46 (0.20-1.05)	0.52 (0.22-1.23)	0.57 (0.20-1.56)
User vs user	**Insulin vs Sulfonylurea**			1.45 (1.02-2.06)*
	DPP-4i vs Sulfonylurea			0.76 (0.42-1.37)
	DPP-4i vs Insulin			0.64 (0.43-0.97)*

Based on flexible parametric survival models with attained age as time-scale; As-treated models were weighted using inverse-probability stabilized treatment and censoring weights derived from the baseline and time-updated confounders; Crude analyses were weighted but not adjusted; Adjusted analyses in the dementia-free group included baseline sex, comorbidity index, renal disease, diabetes type & duration, cardiovascular, antithrombotic, psychotropic and dementia medication, income and other antidiabetic medications; Analyses in dementia patients were further adjusted for cohabitation, dementia type and MMSE; Intention-to-treat analyses were PS-matched on baseline covariates; Medication exposure was analyzed as time-varying covariate in as-treated models, and as time-constant in intention-to-treat analyses; *p-value <0.05; †p-value <0.001.

5.5 USE OF METFORMIN AND DPP-4I IS CONNECTED TO SLOWER DECLINE IN MMSE SCORES AFTER DEMENTIA DIAGNOSIS (STUDY 5)

In total, the study included 1,873 patients (4,732 observations) with DM diagnosis and AD or MixDem, who had at least one follow-up after dementia diagnosis. After applying weighting for dropout, the prevalent use of metformin (β 0.89, 95% CI 0.44-1.33) and DPP-4i (0.72, 0.06-1.37) were associated with slower decline in MMSE scores compared to non-users (**Figure 10, Table 10**). In addition, insulin and sulfonylurea users experienced significantly faster decline in MMSE compared to DPP-4i users (insulin vs DPP-4i -1.00, -1.95 to -0.04), (sulfonylurea vs DPP-4i -1.19, -2.33 to -0.04). Supplementary analyses with imputed missing MMSE scores between the observed follow-ups were consistent with the main analyses (**Table 10**).

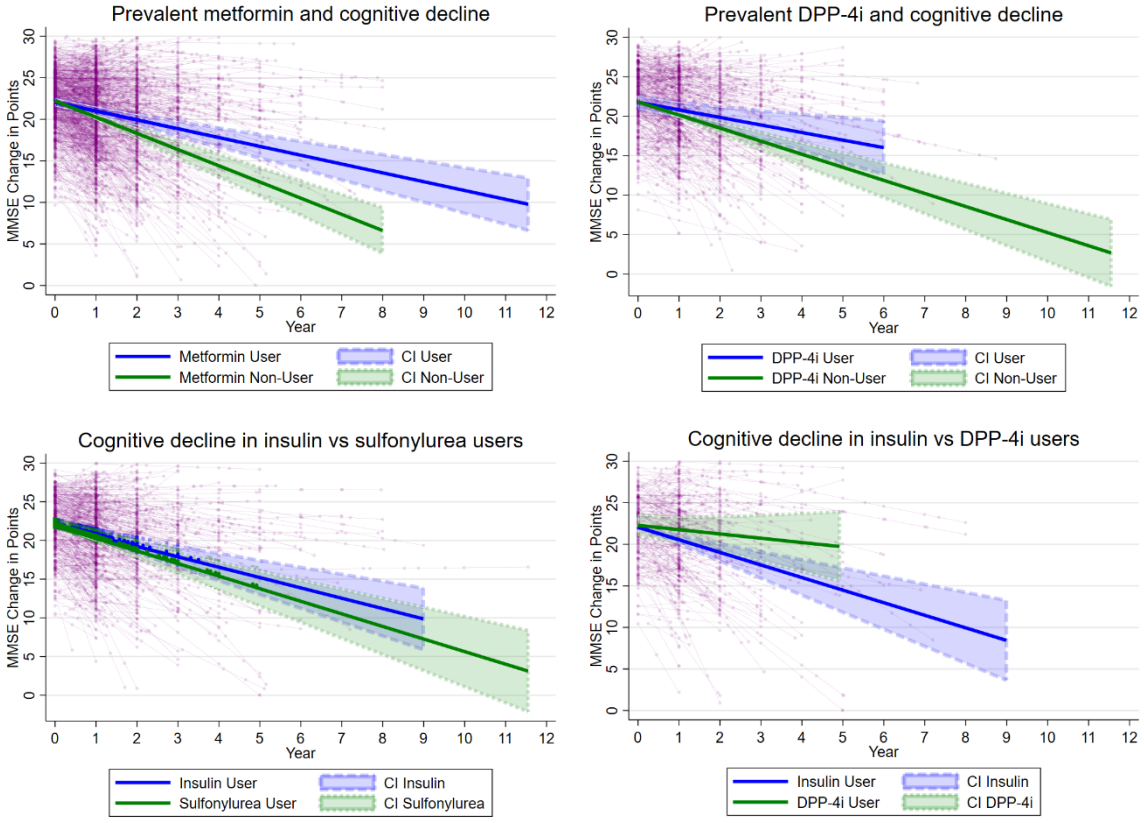

Figure 10. Changes in MMSE scores in users of antidiabetic medications. Based on weighted prevalent-user mixed-effect models analyses in propensity-score matched cohorts; Year represents follow-up time after baseline; Thin lines represent MMSE change in individual subjects (circles) with time, thick lines represent estimated MMSE change derived from the mixed-effect models and begin at the model intercept (start at the y axis); Shaded area represents confidence intervals.

Table 10. Annual point changes in post-dementia MMSE scores in incident and prevalent users of antidiabetic medication.

Antidiabetic medication		Weighted mixed-effect model			Imputed weighted mixed-effect model		
		MMSE point change with annual intervals					
		β (95% CI)	Z	p	β (95% CI)	Z	p
Prevalent users	**Metformin x Time** (514 user / non-user pairs)	0.89 (0.44; 1.33)	3.93	<0.001	0.88 (0.44; 1.32)	3.91	<0.001
	Insulin x Time (543 pairs)	-0.03 (-0.48; 0.42)	-0.13	0.90	-0.12 (-0.56; 0.32)	-0.54	0.59
	SU x Time (640 pairs)	-0.11 (-0.53; 0.31)	-0.52	0.60	-0.13 (-0.56; 0.29)	-0.62	0.53
	TZD x Time (67 users vs 260 non-users)	0.14 (-0.76; 1.04)	0.30	0.76	0.04 (-0.91; 0.98)	0.07	0.94
	DPP-4i x Time (103 vs 389)	0.72 (0.06; 1.37)	2.14	0.032	0.70 (0.03; 1.37)	2.04	0.041
Incident users	**Metformin x Time** (101 vs 277)	0.70 (-0.16; 1.56)	1.59	0.11	0.53 (-0.31; 1.37)	1.23	0.22
	Insulin x Time (66 vs 263)	-0.28 (-1.22; 0.67)	-0.57	0.57	-0.37 (-1.34; 0.60)	-0.74	0.46
	Sulfonylurea x Time (37 vs 147)	-0.10 (-1.38; 1.17)	-0.16	0.87	-0.19 (-1.48; 1.11)	-0.28	0.78

p, p-value; Z, standard score; β=beta coefficients (unstandardized coefficients) acquired from linear mixed-effects models with random intercept and slope; Time expressed in years of follow-up; Analyses were weighted for the inverse-probability of remaining in the study; Table summarizes incident (without history) and prevalent users (with and without history of medication use) who were 1:1 PS-matched with non-users in prevalent-user metformin, insulin and sulfonylurea analyses; Other cohorts were matched using 1:1 ratio; Matching criteria included age, sex, cohabitation, dementia type, Charlson comorbidity score, renal disease, diabetes type & duration, income category, use of statins, antihypertensive, antithrombotic, antipsychotic, antidepressant drugs, cholinesterase inhibitors, use of other oral antidiabetic drugs (as a summary measure user/non-user) and use of insulin (omitted in insulin analyses).

6 DISCUSSION

6.1 CHARACTERISTICS OF DIABETES IN DEMENTIA

Study 1 described the patients diagnosed with dementia in Sweden between 2007-2012, among which 16.5% had comorbid DM. The prevalence concurs with the proportion of DM in >65 year-old Swedish population[209] as well as other studies from Sweden[67] and Europe[7, 210, 211]. The results confirm DM as one of the most common comorbidities in patients with dementia. Further, the presence of DM was independently associated with lower age at dementia diagnosis, which is likely due to either overall higher risk of dementia in patients with DM[3], or more frequent utilization of care leading to earlier dementia diagnosis[212]. DM patients had 21% and 17% higher probability of MixDem and VaD compared to AD, respectively, reflecting the overall higher cerebrovascular burden, and common combination of AD and vascular pathology in patients with DM[61, 62]. On the other hand, Lewy body dementias were negatively associated with DM. There is discordant evidence on DM and Lewy body dementias, where both negative association[67, 72] and no connection[68, 213] were observed. Conversely, DM is a risk factor for PD[64], and the presence of PDD as well as combination of PDD and DM are associated with significantly higher mortality[67, 214]. Thus, while the lower activity of sympathetic nervous system may play some role[215], it is more likely that our sample comprised significantly less patients with DM who survived until diagnosis of Lewy body dementia, compared to AD.

Finally, patients with DM were 23% and 22% less likely to be prescribed ChEI and memantine, respectively. While the overall difference could be explained by a larger prevalence of VaD in DM patients where these drugs are not indicated[25, 216], the results were confirmed in the analyses stratified by dementia type. Importantly, frailty and level of dependence may play a large role (rather than age or polypharmacy) in ChEI non-prescription[217]. True, patients with DM were more commonly institutionalized (12.0% vs 10.6%), but nursing home placement was not independently associated with DM in the multivariate models. Importantly, we had no measure of frailty or the activities of daily living to confirm the proposed hypothesis. In conclusion, the ChEI and memantine bring only modest improvements in cognitive functioning[26], however the appropriateness of ChEI under-prescription in patients with DM should be further evaluated to as multiple non-cognitive benefits were observed in ChEI users[144, 146, 150, 151, 163].

6.2 CHOLINESTERASE INHIBITORS AND MORTALITY

In study 2 we followed-up the findings from study 1 and analyzed the survival associated with the use of ChEI, comparing patients with AD or MixDem who had or had not concurrent DM. ChEI were associated with 20-30% mortality risk reduction irrespective of DM status, suggesting similar overall effect across DM strata. Importantly, the findings were concordant with previous research[149-151], however we have not observed a clear dose-response, likely due to different dose categorization (median split) and using low-dose group as reference. In the analysis of specific ChEI agents, only donepezil and galantamine exhibited mortality reduction, however the effect of galantamine was moderately stronger in patients with DM (up to 32% lower mortality risk, vs 26% in DM-free). Galantamine may have specific benefits for patients with DM, mediated through the cholinergic anti-inflammatory pathway[155-157] or improving insulin sensitivity[162]. On the other hand, donepezil – the ChEI with lowest propensity for side effects[153], was also associated with lower mortality, albeit to a lesser degree in patients with DM (up to 24%, vs 31% in DM-free). Furthermore, we found no association with mortality among rivastigmine users, likely due to inability to differentiate between the oral and transdermal application forms[218, 219]. In the whole-cohort analysis, ChEI as a class reduced the risk of DM-related mortality, suggesting that ChEI may reduce the risk of complications of DM that lead directly to patient death. The association was not consistent across all analyses; however, it supports the hypothesis that ChEI may help with maintaining glycemic targets. Whether such association may be mediated via cognitive stabilization and better self-management of DM remains to be elucidated[141].
The findings should be confirmed in different national cohorts, as the prescription in Sweden is quite frequent (~70% for ChEI, 20% for memantine)[172, 173] and the utilization has been lower in the other European countries (3-20%)[220], but is increasing[221-223].

6.3 CHANGES IN ANTIDIABETIC DRUG DISPENSATION

In study 3, patients with dementia experienced a more substantial increase in insulin dispensation simultaneous with decrease in utilization of metformin and sulfonylurea. Overall, deprescribing is common among patients with dementia[224, 225], and the decreasing metformin utilization correlates to the higher prevalence of renal failure in the older population[226] - a major contraindication for metformin treatment[227]. Secondly, the risk of hypoglycemia associated with sulfonylurea[4, 228] may constitute non-negligible risk of further cognitive decrements in patients with dementia[179, 180] and sulfonylurea deprescription may be advised in patients with advanced age[119]. Hypoglycemia is an even larger concern in insulin[46] and Weiner and colleagues reported poorer health among insulin-treated older adults in the

US[229]. However, insulin has a specific position as second-line therapy in Sweden[230], where the patients with dementia receive further nursing support with insulin injections, constituting a major differentiating factor. Furthermore, an insulin-specific benefit may be related to weight gain, as modest overweight may be protective in frail patients[231, 232].

Within the newer antidiabetic medications (DPP-4i, GLP-1a, SGLT-2i), both the overall use and initiation therapy were less common among patients with dementia. The preference of DPP-4i over GLP-1a may reflect higher tolerability of oral agents compared to subcutaneous injections and possible avoidance of further weight loss, which is a common symptom in patients at risk of cognitive impairment[46, 233].
These results suggest a Sweden-specific preference for insulin treatment in clinical management of T2DM or other/unspecified DM when cognitive impairment is present. Further clarification is needed, whether the lower utilization of incretin and SGLT-2i therapy in patients with dementia leads to "missing the benefits" of these medications[234-236]. Overall, our results reflect more conservative pharmacological management of T2DM in Swedish patients with dementia, however the assessment of glycemic targets and cognitive changes as well as comparisons with other national cohorts is necessary to determine the effectiveness of this approach.

6.4 ANTIDIABETIC MEDICATIONS AND MORTALITY

In the large cohort of patients with T2DM or other/unspecified DM and dementia, the use of insulin was associated with higher mortality, however the risk-increase was not consistent across analyses. Importantly, the discordant findings from the observational studies (higher risk)[237, 238] and randomized studies (no risk increase)[239] should be clarified. Gamble suggested, that the absence of variables on weight and glycemia in observational settings skew the results towards higher risk, which also extends to our findings[240]. Conversely, the lack of major difference in the mortality risk between dementia and dementia-free strata corroborates the major role of insulin in Sweden[230] and may reflect well-managed insulin-treated DM in patients with dementia. This is further supported by the comparative analyses in patients with dementia, where we found no mortality increase among insulin users compared to sulfonylurea or DPP-4i. However, higher hypoglycemia risk may have played a role in the 19% higher mortality among sulfonylurea-treated patients with dementia[4, 228], as this was not observed in other studies[239, 241].

Furthermore, the first-line medication metformin was not associated with improved survival in patients with dementia, which was discordant to the dementia-free cohort (25% lower

mortality risk) and the meta-analysis by Campbell and colleagues (28% lower risk)[242]. The patients with dementia using metformin were commonly co-treated with insulin during the follow-up (70% vs 52% in dementia-free), however it is unclear how would insulin mediate higher mortality risk among metformin users with dementia, as generally neutral[239] or lower risk[243] were found previously. Crucially, we lacked glycemic and biometric data, which may have confounded the relationship[240].

In the as-treated models, both GLP-1a (56% lower risk) and SGLT-2i (57% lower risk) were associated with lower mortality in patients with dementia, however no association was observed in DPP-4i users. In the observational studies of all-cause mortality, GLP-1a and SGLT-2i were comparable[244], while lower mortality in GLP-1a users was reported compared to DPP-4i[245]. Moreover, Nyström and colleagues found larger mortality reduction in DPP-4i vs insulin users[246], which our data corroborated only in the dementia-free cohort. On the other hand, the randomized trials have not concluded any significant difference in all-cause mortality reduction between the antidiabetic drugs[239].
The combined findings from studies 3 and 4 suggest, that the lack of DPP-4i effect in patients with dementia is a correlate to the late addition of DPP-4i, as insulin was more commonly prescribed in patients with dementia. On the other hand, the GLP-1a and SGLT-2i may have been utilized in a specific cohort of patients who benefitted from the weight-reduction[46] and cardiovascular protection[247] observed in these medications, respectively. Further, we had limited sample size of new users for some drug-to-drug analyses, and comparisons to non-users may skew the results[248], thus the findings should be confirmed in a population with higher dispensation of GLP-1a and SGLT-2i.

6.5 ANTIDIABETIC MEDICATIONS AND MMSE CHANGE

Study 5 evaluated changes in MMSE in patients with T2DM or other/unspecified DM and concurrent AD or MixDem.
Firstly, we observed significantly slower decline in MMSE scores among the prevalent users of metformin. Metformin's role in cognitive functioning in AD is complex, where both neuroprotective[249-251] and pathology-accelerating properties[252, 253] were noted in preclinical research. In clinical data, lower risk of dementia was observed in several studies[114, 254, 255], however no association with MMSE was concluded in a recent meta-analysis[256]. Conversely, metformin was recently connected to slower decline in global cognition and executive function[257] and another study concluded slower immediate and delayed memory decline, however only in patients with normal cognition and without ApoE-ε4 genotype[88]. Wu and colleagues have suggested differential cognitive properties of metformin through the

preclinical-MCI-AD continuum, with benefit limited to early stages[88]. The lack of effect in metformin initiators in our study corroborates such hypothesis, however the absence of genotypical and preclinical and MCI cohorts makes the comparison difficult. On the other hand, the slower MMSE change in the prevalent users speaks against metformin-associated cognitive damage in patients with AD or MixDem.

Secondly, the prevalent users of DPP-4i experienced slower decline in MMSE compared to non-users. In observational setting, DPP-4i were associated with lower dementia risk[235, 258], higher MMSE scores[259-261] and slower memory decline in AD[88]. Conversely, the data from randomized studies are not encouraging[106] and a recent clinical trial with linagliptin concluded no cognitive benefit among high-risk T2DM patients[130]. The discrepancy in cognitive findings may be related to timing of DPP-4i therapy in the AD continuum, similarly to metformin. Moreover, the comparison to non-users in observational studies may be too unspecific, however we reported slower MMSE decline in DPP-4i users even when compared to insulin and sulfonylurea. Conceptually, the greater risk of hypoglycemia in sulfonylurea and insulin[46] may explain the negative association, however some findings in dementia-free patients dispute the link between hypoglycemia and cognitive dysfunction[262]. We had insufficient number of GLP-1a users, and further research on GLP-1a may provide different results even in randomized trials, as their potency and transport through blood-brain barrier is higher than DPP-4i[263, 264] and the preclinical studies suggest amelioration in several AD-related pathways[265].

The metformin and DPP-4i findings are encouraging, however the difference in MMSE change was approximately 1 point, while the minimal clinically important decline in MMSE is estimated at 2-3 points[266]. Despite the rather modest differences, any preservation in cognitive functioning should be considered important, particularly when no disease-modifying treatments are available.

Thirdly, TZD, sulfonylurea or insulin use were not associated with significant change in MMSE decline compared to non-users. The TZD findings are in line with randomized clinical trials[267, 268] and the observational data[88]. Study 3 corroborates general decrease in TZD utilization in patients with dementia, likely due to higher risk of cardiovascular and geriatric complications in TZD[46].
Our results do not suggest sulfonylurea use significantly affects MMSE scores compared to non-users, corroborating other studies concluding no effect on memory or global cognition[88, 269]. Lastly, while some studies on insulin have concluded modest increase in dementia risk and larger decline in global cognitive functioning[269], our results corroborate the

observational[258] and randomized data[79, 270] stating overall cognitive neutrality of insulin. The finding is important, as the insulin utilization in Sweden is particularly frequent.

In conclusion, our results show that metformin and DPP-4i may be beneficial for overall cognitive functioning, while other medications have not affected a change in MMSE. A life-course approach with analyses of specific cognitive domains should supplement our data to deconstruct the cognitive properties of antidiabetic medications.

6.6 METHODOLOGICAL LIMITATIONS AND BIAS

Study accuracy is determined by its precision (lack of random error – "how sure we are of the results?") and validity (lack of systematic error – "do the results reflect truth?")[271, 272]. The main sources of possible error in the thesis are described below.

6.6.1 Selection bias

Selection bias refers to the situation when the study participation is related to both the exposure and the outcome. Typically, selection bias occurs in the initial study phases where patients are recruited, or during the study course where patients may be lost during follow-up.

The SveDem coverage of incident dementia cases was estimated at 36%[186], however it is unlikely that due to nature of the disorder, the coverage will ever be complete. It is unknown how the patients participating in SveDem differ to the non-registered patients. However, the subjects included in quality registers generally tend to be healthier, male and in a higher socioeconomic position[273], skewing the generalizability towards this population.

In study 5 we analyzed MMSE change during follow-up, where a significant non-random dropout ("loss to follow-up") occurs. This would constitute selection bias as patients with significantly different level of dementia severity were less likely to return for follow-up. Moreover, the irregularity of patients' visits resulted in a dataset where some follow-ups were missing, however were preceded and followed with observed follow-ups. We addressed these issues using IPW for remaining in the study and imputation for in-between MMSE scores[205] and obtained reasonable estimates for the exposed and unexposed subjects.

In studies 2-4, the outcomes (mortality and drug dispensation) were based on nationwide registers, reducing the possibility of selection bias due to loss to follow-up. However, the results still apply to a healthier cohort of patients with dementia, due to SveDem coverage.

6.6.2 Information bias

Information bias primarily comprises measurement error leading to misclassification of exposure, outcome or other covariates[271].

SveDem provided diagnosis of dementia based on clinical criteria. The clinical diagnosis has overall lower sensitivity (~80% in AD, 20-70% VaD) compared to the gold standard – neuropathological examination[274, 275], conversely the diagnoses set at baseline in SveDem are rarely changed (<5% of cases receive different dementia diagnosis during follow-up)[172].

We combined the records from the NPR and SPDR to define DM, as the inpatient NPR has generally high positive predictive value, but low sensitivity for DM diagnosis[187]. However, while combining the registers increased the proportion of DM coverage, the absence of information from primary care probably underestimated the prevalence of patients with lifestyle-only DM management. Moreover, we had no information on glycemic markers that would confirm the diagnoses. An ideal solution would be to merge SveDem with the National Diabetes Register, where the overall DM coverage is close to 90%[175]. In addition, the algorithm we used to categorize DM was based on the temporal relationships between the diagnoses (the earlier diagnosis considered correct) in combination with antidiabetic drug usage. In conflicting cases we grouped the patients into other/unspecified category, to increase the precision of T1DM and T2DM groups. It is very unlikely, that the algorithm misclassified patients with T1DM due to dependence on insulin dispensation. Moreover, the possible misclassification of T2DM and other/unspecified DM can be considered non-differential due to equal sources and criteria used in all subjects. The algorithm's predictive properties should be validated against the National Diabetes Register.

Medication exposure was defined by the SPDR records, which reflect the medications dispensed from the pharmacy[188]. Importantly, SPDR does not allow for compliance analyses as the prescription-dispensation discordance is not recorded[188]. The national coverage and dispensation data contribute to high overall precision of the medication exposure. For higher-quality information, observing the actual medication use or measuring drug concentrations in blood samples would be necessary.
Distinction between new and all medication users was done in studies 2-5, as the inclusion of prevalent users can lead to bias (surviving on treatment)[276]. However, excluding prevalent users was not always possible due to low sample size of some medication users (studies 4 and 5), therefore the results should be reproduced in a larger study. The one-year period prior to

study baseline for defining baseline incident exposure was deemed a reasonable compromise between sample size reduction and bias avoidance.

Immortal-time bias describes a situation where during a period of the study follow-up, an outcome or an event that signifies censoring cannot occur. Usually, the distortion happens in pharmacoepidemiology when the period between study entry and medication initiation is misclassified or excluded from the analyses[271, 277]. In the studies 2 and 4, we have applied models with time-varying exposure, thus avoiding the immortal-time bias. Studies 3 and 5 utilized only baseline drug exposure and time-constant modelling.

Outcome misclassification may have occurred in study 2, where cause-specific mortality was explored. While we allowed for wide definition of DM-related mortality (E10-E14), it is possible that DM codes were less frequently denoted as the underlying cause[190], thus underestimating the total number of DM-related deaths. On the other hand, there is no reason to suspect differential misclassification of the DM-related mortality among the ChEI exposed or unexposed patients.

Information on other covariates was not conditional on the exposure or outcome categories, (e.g. duration of diabetes was extracted from the NPR in the same way for exposed, unexposed, patients who died and who survived), thus we consider the potential misclassification as non-differential, skewing the results predictably towards the null.

6.6.3 Confounding

Confounders are factors independently associated with both the exposure and the outcome and are not on the causal pathway between the exposure and the outcome. Thus, they can distort the analyzed relationships if not accounted for ("adjusted for")[271].

A specific type of confounding present in non-randomized pharmacological studies is confounding by indication. It occurs when the study design cannot account for the decision-making behind the initiation of certain treatment, and the decision-making is also related to the outcome[278]. Typical example is the spurious relationship between initiation of a more intensive treatment and worse outcomes, which is confounded by the severity of the patient condition[279]. It is likely that this type of confounding may bias our results to a certain degree, as we had no direct measure of the clinical reasoning, however we utilized several methods (e.g. covariate adjustment, PS-matching, IPW) to balance the characteristics between the exposed and unexposed.

Moreover, all thesis' studies are affected by unmeasured variables, mainly the biochemical markers (e.g. hemoglobin A1c, kidney function, amyloid and τ markers), genotype (apolipoprotein-E ε4 allele) and lifestyle factors (exercise, smoking), and it is likely that we were not able to remove such confounding by adjusting for the observed variables. However, some degree of residual confounding can be expected in the absence of randomization.

7 CONCLUSIONS

7.1 GENERAL CONCLUSIONS

Subjects with DM constitute a distinct cohort among dementia patients, with earlier diagnosis of dementia and higher probability of VaD and MixDem dementia types. The prescription of symptomatic dementia medication is associated with longer survival in patients with DM and AD or MixDem, however these drugs are less commonly prescribed to this patient group. Moreover, the patients with dementia receive more conservative treatment for DM, reflected in the higher utilization of insulin after dementia diagnosis. Furthermore, the newer antidiabetic medications are associated with both lower mortality as well as slower global cognitive decline, while their prescription rate is lower in patients with dementia.

7.2 SPECIFIC CONCLUSIONS

1. The prevalence of DM in Swedish patients with dementia diagnosis is 16.5%.
2. Compared to AD, the diagnosis of DLB and PDD is 34% and 56% less common, respectively, among patients with DM.
3. ChEI class as well as donepezil and galantamine are associated with lower all-cause mortality among patients with DM and AD or MixDem dementia, however the association does not extend to CV mortality. ChEI use is associated with inconsistent decrease in DM-related mortality.
4. Patients with dementia and T2DM or other/unspecified DM experience more frequent insulin usage, while the use of DPP-4i, GLP-1a and SGLT-2i increased less steeply in patients with dementia.
5. Initiation of newer antidiabetic medication is less common in patients with dementia compared to dementia-free subjects.
6. Insulin use in patients with dementia and T2DM or other/unspecified DM is associated with higher mortality, however the association is comparable to dementia-free subjects.
7. New users of sulfonylurea with dementia experience higher mortality compared to non-users, while the SGLT-2i are associated with protective effect on survival in this patient group.
8. In patients with AD or MixDem with concurrent diagnosis of T2DM or other/unspecified DM, overall use of DPP-4i and metformin was associated with slower decline in MMSE scores compared to non-users.
9. Compared to DPP-4i users, patients using sulfonylurea and insulin experienced faster decline in MMSE scores.

8 POINTS OF PERSPECTIVE

The findings in this thesis support the role of diabetes mellitus as a major comorbidity in dementia. We observed a similar prevalence of DM in dementia patients as other studies, where approximately every 6th person with dementia is co-diagnosed with DM[7]. However, there is a large proportion of patients not included in SveDem, where the proportion of DM cannot be predicted. Secondly, while we focused mainly on the role of pharmacological treatments, there is an urgent need to develop comprehensive guidelines tailored for the clinical co-occurrence of DM and dementia. Furthermore, the thesis studies did not focus on T1DM in dementia, however T1DM is also associated with cognitive impairment[48-50], and more research is needed on the care and clinical management in patients who have diagnosis of both dementia and T1DM.

Our studies contribute to the observational evidence[146, 147, 150, 151], that ChEI exhibit benefits beyond symptomatic cognitive improvement. Unfortunately, we had no information on markers of glucose metabolism, thus further studies should explore whether the survival benefit in DM patients may be due to better glycemic control and whether cognitive improvement mediates such association. Furthermore, the differences between ChEI utilization suggest care inequality between DM and DM-free patients, and the reasons for this difference should be clarified. Overall, our studies support ChEI prescription for patients with DM and AD or MixDem, with specific survival benefit with donepezil and galantamine.

Further research avenues should include the role of insulin in patients with DM and already manifest dementia. Our studies reflect the Swedish approach to dementia care where insulin use in T2DM patients is more pronounced, however the patients receive nursing assistance with insulin injections, thus the results should be reproduced in other populations. Importantly, we observed no additional global cognitive decline in insulin users with AD or MixDem. Furthermore, the patients with dementia using insulin experienced moderate mortality increase, but comparable to the patients who were dementia-free. On the other hand, it is unclear how frequently the subclinical hypoglycemic events occur in patients with dementia, and whether these contribute to subtle changes unmeasurable by a cognitive screening test – such as MMSE. Additional studies into specific insulin regimens – short-acting vs long-acting agents may clarify the relationship.

The use of newer antidiabetic medications, such as DPP-4i, GLP-1a and SGLT-2i was associated with some survival and cognitive benefit, however the studies were limited by the sample size of users and the observed lower prescription among patients with DM and

dementia. Our results may contribute to more frequent utilization of these medications, however there are multiple research gaps that need to be filled. For example, the biological connections between the incretin system, SGLT-2i and AD pathogenesis should be clarified and the specific timing of the individual T2DM medications in the preclinical stages – MCI - AD continuum should be examined. We hypothesize, that such inquiry may result in a treatment of both T2DM and AD with one pharmacological agent – providing individualized care. The results from the ongoing randomized controlled trials will hopefully confirm this hypothesis.

9 ACKNOWLEDGEMENTS

This doctoral thesis has been conducted at **the Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society**. I would like to express my gratitude to everybody that contributed to this work, specifically:

My main supervisor Professor **Dorota Religa** for giving me a chance to work at Karolinska Institutet and sharing your extensive clinical and research experience in the dementia field. I am very grateful for the responsibility and challenges you allowed me to handle, which made me a competent researcher. I wish you all the best in the clinical, research and personal life.

Professor **Bengt Winblad** for your endless support throughout my PhD, connecting me with the right people to collaborate with and always pushing me to be better and work harder. You are a true legend of the dementia field and it was a privilege to work and discuss science with you.

Professor **Maria Eriksdotter** for welcoming me into the SveDem group and showing me the value of the registry-based research. Your on-point comments and the tough but honest discussions we had were very valuable to my scientific growth.

Professor **Niklas Hammar,** for sharing your incredible command of epidemiology, and the hours we spent discussing all the epidemiological problems, biases and misclassifications. I am looking forward to our continued collaboration on the AMORIS-SveDem merge.

Associate Professor **Michael Alvarsson,** for providing your extensive knowledge on endocrinology and helping me comprehend the clinical and societal aspects of diabetes.

My mentor, Professor **Fredrik Piehl** for spending time with me in the neurology department and advising on clinical work.

Maria Ankarcrona and **Eric Westman** for the great working environment at NVS and the division of Clinical Geriatrics. **Gunilla Johannson, Erika Bereczki, Kristina Johnell, Johan Fastbom, Mats Talbäck, Håkan Malmström** and **Dan Hedlin,** for all your help throughout my studies.

Anette Eidehall, **Catarina Cleveson, Sofia Fridén** and **Camille Birgegård** for all the administrative support during my doctoral education.

Karin Westling, **Ann-Katrin Edlund** and **Emma Timerdal**, for your kind advice on the organisation and content of the Swedish Dementia Registry.

Pavla, for introducing me into the KI world and your valuable advice on the project. **Emilia**, for being a great office mate and enduring these four years side by side with me. **Sara**, for your passion for dementia research and training me how to write exciting grant applications. **Hong**, for all the help and a very similar opinion on the Swedish PM exam. **Tuan,** for your quick advice whenever I needed. **Una** and **Dario** for your friendship and confirming that Croatian and Slovakian are practically siblings. **Ipsit,** for being a friend and the "Cave" jokes. **Konstantinos**, for your statistical mind and Swedish banter. **Azadeh**, **Gustav**, **Chenhong** (the basket queen!), **Dani**, **Laetitia**, **Joana**, **Axel**, **Médoune**, **Elena**, **Mona-Lisa**, **Sathya**, and everyone in Neo and Bioclinicum for making this a great working environment. **Seyed-Mohammad Fereshtehnejad, Soheil Damangir, Farshad Falahati, Alexandra Lebedeva** and **Daniela Enache** for guidance in the early years of my studies.

The Slovenian neurology gang that I had the pleasure to work with - **Eva Zupanic, Irena Kalar, Ana Subic** and **Bojana Petek**.

Marloes for teaching me that all good inventions come from the Netherlands and **Luca** for sharing the clinical history and pure Italian spirit. To **Julen, Eva, Andrea and Paulina** for being great office mates in Novum.

Everybody at the department of Neurobiology, Care Sciences and Society and **the divisions of Clinical Geriatrics and Neurogeriatrics –** you all create a very friendly and productive workplace.

The students – **Pontus Dannberg, Abbe Ullgren, Hamsah Al-Qashqri, Hugo Söderström, Oliver Edner, Filippa Martinsson, Sofia Lim, Ramin Sasani, Sara Fadhil and Alexander Rytarowski** – you helped me develop both in the Swedish language and as a teacher, explaining statistics in Swedish was one of the biggest challenges of my PhD.

The partners who provided funding and made the research possible - **the Swedish Research Council**, **FORTE**, **the Stockholm University**, **the Stockholm County Council (ALF project)**, **Alzheimerfonden**, **the Old Servants Foundation**, **the Margaretha af Ugglas Foundation**, **the Swedish Society for Medicine, the Swedish Associations of Local Authorities and Regions, the Swedish Stroke Association** and **the Order of Saint John.**

My partner **Iveta Kaczarová**, for 11 years filled with love, respect, humour and very specific sneezing. You have always believed and supported me and the whole journey would not have happened without you.

My family, specifically my parents **Peter Sečník** and **Adelhaida Sečníková,** my brother **Peter Sečník** and sister in-law **Zuzana Sečníková**, for your support even from thousands of kilometres away. **Vojtech Parrák** for encouraging and supporting my research at Karolinska Institutet.

Finally, I would like to thank **the Patients** who have provided their information to the registers, I hope that my work provides some benefit to Your lives.

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