From Department of Neurobiology, Care Sciences and Society
Karolinska Institutet, Stockholm, Sweden

DEPRESSION IN ALZHEIMER'S DISEASE:
BIOMARKERS AND TREATMENT

Daniela Enache

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Depression in Alzheimer's Disease: Biomarkers and Treatment

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By

Daniela Enache

Principal Supervisor:
Professor Dag Aarsland
Karolinska Institutet
Department of Neurobiology, Care Sciences and Society
Division of Neurogeriatrics

Co-supervisor(s):
M.D. Ph.D. Vesna Jelic
Karolinska Institutet
Department of Neurobiology, Care Sciences and Society
Division of Clinical Geriatrics

Professor Maria Eriksdotter
Karolinska Institutet
Department of Neurobiology, Care Sciences and Society
Division of Clinical Geriatrics

Professor Bengt Winblad
Karolinska Institutet
Department of Neurobiology, Care Sciences and Society
Division of Neurogeriatrics

Opponent:
Professor Frank Jessen
University of Cologne, Medical Faculty
Department of Psychiatry
German Center for Neurodegenerative Disorders

Examination Board:
Docent Åke Rundgren
Gothenburg University
Institute of Medicine
Sahlgrenska Academy Sweden

Professor Ingrid Agartz
Oslo University and Diakonhjemmet Hospital
Norwegian Centre for Mental Disorders Research
KG Jebsen Centre for Psychosis Research
Division of Mental Health and Addiction

Professor Steen G. Hasselbalch
Copenhagen University Hospital
Danish Dementia Research Centre
Department of Neurology

Dedicated to the patients and their carers

“Everything makes sense a bit at a time. But when you try to think of it all at once, it comes out wrong“ Sir. Terry Pratchett, Only you can save mankind

ABSTRACT

Depression and Alzheimer's disease (AD) are among the most common clinical diagnosis in older people. The relation between depression and AD is complex: depression has been shown to be a risk factor, prodromal symptom and a consequence of AD. Increased understanding of the underlying mechanisms of depression in AD may lead to early detection and differential diagnosis, and is crucial for development of novel and mechanism-based treatments

The first two studies of this doctoral thesis are exploring the associations between depressive symptoms and biomarkers of amyloid deposition and neuronal injury in patients with subjective cognitive impairment (SCI), mild cognitive impairment (MCI) and AD. The aims of the third study were to describe the use of antidepressants in patients with dementia and to explore the association between mortality risk and the use of antidepressants 3 years before the dementia diagnosis.

CAIDE Dementia Risk Score is taking into account midlife risk and protective factors; age, educational level, gender, systolic blood pressure, body mass index, cholesterol level and physical activity and APOE genotyping, and can predict dementia over 20 years. The last study was focused on exploring the associations between CAIDE Dementia Risk Score and biomarkers of amyloid deposition, neuronal injury and small vessel pathology in SCI and MCI patients. Additionally we explored the capacity of CAIDE Dementia Risk Score to predict dementia in a memory clinic population.

Data were obtained from Memory Clinic Karolinska University Hospital Huddinge Sweden (Study I, II and IV). In study III, two large national registries were merged: the Swedish Dementia Registry (SveDem) and the Swedish Prescribed Drug Register.

In study I, analysis of the three different cerebrospinal fluid biomarkers; amyloid beta (CSF Aβ), total-tau (CSF t-tau), and phosphorylated-tau did not support the hypothesis that more severe amyloid or tau pathologies are associated with more severe depressive symptoms. In contrast, SCI and AD patients with depressive symptoms tended to have lower CSF p-tau levels and, in particular, lower CSF t-tau levels than those without depression, indicating less severe neuronal injury. In study II, we used two different analysis methods of MRI to measure medial temporal lobe atrophy and hippocampus volume. Using manual tracing of the hippocampi we found smaller left hippocampus volume in SCI patients with depressive symptoms compared to those without depressive symptoms. In contrast, AD patients with depressive symptoms had less medial temporal lobe atrophy compared with those without depressive symptoms.

In study III, 20,050 patients with incident dementia diagnosed in memory clinics and registered in SveDem were included. Information on the total number of medication and all antidepressants dispensed at the time of dementia diagnosis and at the first, the second and the third year prior to dementia diagnosis was obtained from the Swedish Prescribed Drug Register. During a median follow up of 2 years, 5168 (25.8%) dementia patients died. At the time of dementia diagnosis, 5,004 (25.0%) patients were on antidepressant treatment. Use of antidepressant treatment for 3 consecutive years prior to a dementia diagnosis was associated with a lower mortality risk for all dementia disorders in general and particularly in AD.

In study IV, a higher CAIDE Dementia Risk Score was associated with higher CSF t-tau levels, more severe medial temporal lobe atrophy and more severe white matter changes. For the CAIDE score including APOE, a score above 9 points was associated with lower CSF Aβ, more severe medial temporal lobe atrophy and more severe white matter changes. CAIDE Dementia Risk Score (version with APOE) performed better at predicting AD compared with CAIDE Dementia Risk Score without APOE.

Conclusion: We found that depressive symptoms in patients with AD and SCI are not associated with more amyloid deposition nor more neuronal injury compared with AD and SCI patients without depressive symptoms. Thus our results are consistent with the hypothesis that the mechanisms underlying depression differ between older people with and without AD. Our results have shown that use of antidepressants in prodromal AD stages is associated with a lower mortality risk. Further longitudinal studies are needed to better understand the associations between the use of antidepressants and mortality risk in dementia.

LIST OF SCIENTIFIC PAPERS

I. Kramberger MG, Jelic V, Kareholt I, **Enache D**, Eriksdotter Jönhagen M, Winblad B, Aarsland D. Cerebrospinal Fluid Alzheimer Markers in Depressed Elderly Subjects with and without Alzheimer's Disease. Dement Geriatr Cogn Dis Extra. 2012, 2:48-56

II. **Enache D**, Cavallin L, Lindberg O, Farahmand B, Kramberger MG, Westman E, Jelic V, Eriksdotter M, Ballard C, Winblad B, Wahlund L-O, Aarsland D. Medial Temporal Lobe Atrophy and Depressive Symptoms in Elderly Patients With and Without Alzheimer Disease. Journal of Geriatric Psychiatry and Neurology 2014;

III. **Enache D**, Fereshtehnejad SM, Cermakova P, Garcia-Ptacek S, Kåreholt I, Johnell K, Religa D, Jelic V, Winblad B, Ballard C, Aarsland D, Fastbom J, Eriksdotter M. Antidepressants and mortality risk in a dementia cohort- data from SveDem, the Swedish Dementia Registry, submitted

IV. **Enache D,** Solomon A, Cavallin L, Kåreholt I, Kramberger MG, Aarslad D, Kivipelto M, Eriksdotter M, Winblad B, Jelic V. CAIDE Dementia Risk Score and biomarkers of neurodegeneration in memory clinic patients without dementia, submitted

CONTENTS

LIST OF ABBREVIATIONS

Aβ	amyloid beta
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADL	Activities of daily living
APOE	Apolipoprotein E genotype
BDNF	Brain Derived Neurotrophic Factor
CSDD	Cornell Scale for Depression in Dementia
CSF	Cerebrospinal fluid
DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD	The Manual of the International Statistical Classification of Diseases Injuries and Causes of Death
MCI	Mild cognitive impairment
MDD	Major Depressive Disorder
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
MTA	Medial temporal lobe atrophy
PET	Positron emission tomography
p-tau	Phosphorylated tau at threonine 181
t-tau	Total tau
SCI	Subjective Cognitive Impairment
SSRI	Selective Serotonin Reuptake Inhibitors
vaMTL	Visual assessment of the medial temporal lobe
WMC	White matter changes

1 INTRODUCTION

1.1 ALZHEIMER'S DISEASE

Major neurocognitive disorder or dementia existed long time before Alois Alzheimer described the most common form, Alzheimer's disease (AD) in 1907 [1] . Alzheimer Disease International defines the word "dementia" as a general term for progressive degenerative syndromes which "affect memory, thinking, behavior and emotions" severely enough to interfere with daily life [2].

In Diagnostic and Statistical Manual of Mental Disorders – fifth edition (DSM-5) the term "dementia" was replaced with major neurocognitive disorder. The new term emphasizes the evolution of the cognitive decline as a continuum from subjective and mild cognitive impairment to severe cognitive impairment [3,4]. It is suggested that the word "dementia" expresses a stigmatizing attitude towards older people with cognitive disorders [4].

Stigma associated with major neurocognitive disorder (dementia) has an important impact on quality of life, psychological and social well-being [5]. A higher level of perceived stigma is associated with: more depressive and anxiety symptoms, lower self –esteem, avoidance, isolation, reduced social supports and increased dependence [5]. Health care professionals have also been shown to contribute to stigma [6]. Recent studies report that patients with major neurocognitive disorder (dementia) are facing structural discrimination within the health service; lack of time for patients and being treated by medical doctors with little experience [6].

Throughout this thesis we will consistently use the term "dementia" as in our studies the diagnosis of AD were according to The Manual of the International Statistical Classification of Diseases Injuries and Causes of Death 10 (ICD 10), which use the terminology of dementia.

1.1.1 Epidemiology

Dementia is not a normal part of normal aging, although it is very common in the elderly. In 2015 the number of people living with dementia worldwide was estimated to 46.8 million[7] and there are around 9,9 million new cases each year [7].

AD and vascular dementia are the most common causes of dementia accounting for 50-75% and respectively 20-30% of all cases. All other forms account for less than 10-15% of all cases[2]. Around 5-7% of individuals younger than 60, are suffering from a form of dementia. By age 85 the prevalence increases to more than 50% [7,8].

A large population based study from the UK has shown a significant reduction in the

prevalence of dementia during 20 years of follow up[9], while a study conducted in Spain found a reduction of dementia prevalence in men [10]. The incidence of dementia in a large observational study from the Netherlands found no significant reduction in dementia occurrence during a 10-year period [10], while a study from Sweden suggested that the incidence may have decreased during a 20-year period[11].

- *Causes of dementia:*

Various disorders cause dementia. Mixed forms of dementia often co-exist, as the clinical and pathological boundaries between different forms are sometimes indistinct.

Types of dementia disorders according to ICD 10 dementia in Alzheimer's disease, mixed dementia (vascular and Alzheimer), vascular dementia, dementia in Pick disease, Dementia in Creutzfeldt-Jakob disease, Dementia in Huntington's Disease, Dementia in Parkinson's disease, Dementia in human immunodeficiency virus (HIV) disease, unspecified dementia and other dementia (dementia in cerebral lipidosis, epilepsy, hepatolenticular degeneration, hypercalcaemia, acquired hypothyroidism, intoxications, Lewy body (disease), multiple sclerosis, neurosyphilis, niacin deficiency [pellagra], polyarteritis nodosa, systemic lupus erythematosus, trypanosomiasis, uraemia, vitamin B_{12} deficiency)[12].

1.1.2 Risk factors

Several risk and protective factors for AD and dementia have been identified. Most of them are discussed and presented on http://www.alzrisk.org/. The greatest risk factor is age[13].

Table 1: Most common risk and protective factors for dementia

Risk factors	Protective factors
Age	
Genetic	**Genetic**
APOE ε 4	
Different genes CR1, PICALM, CLU, TREM2, TOMM40) www.alzgene.org	Different genes (APP, APOE ε2) www.alzgene.org
Familial aggregation	
Down Syndrome	
Lifestyle	**Lifestyle**
Smoking	Physical activity
High alcohol intake	Moderate alcohol intake
	Caffeine[14]
Diet	**Diet**
Saturated fats	Mediterranean diet
Low B vitamins/ high homocysteine	PUFAs and fish related fats
High sodium intake [15]	Vitamins B6, B12 and folate

Vascular and metabolic	Antioxidant vitamins (A,C, E)
Cerebrovascular lesions	Vitamin D
Cardiovascular disease	**Psychosocial factors**
Diabetes mellitus and pre-diabetes	High levels of education
Midlife hypertension	High socioeconomic status
Midlife high BMI (overweight and obesity)	High level of complexity of work
Midlife hypercholesterol	Rich social network and social engagement
Others	Mentally stimulating activities
Depression	**Drugs**
Coronary artery bypass surgery	Antihypertensive drugs
Traumatic brain injuries	Statins
Occupational exposure (heavy metals –ELF-EMFs)	Hormone replacement therapy
Infectious agents (herpes simplex virus type 1, *chlamydophila pneumonia*, spirochetes)	Non steroid anti-inflammatory drugs

APP: amyloid precursor protein, APOE: Apolipoprotein E, BMI: Body mass index, CR1: complement component receptor, PICALM: phosphatidylinositol binding clathrin assembly protein, CLU: clusterin, TOMM40: translocase of outer mitochondrial membrane 40 homolog, TREM2: triggering receptor expressed on myeloid cells 2, ELF-EMFs: extremely low frequency electromagnetic fields, PUFA: polyunsaturated fatty acid. (adapted from Solomon et al [16])

1.1.2.1 Genetic risk factors: APOE genotype

APOE ε4 genotype is the strongest and most studied genetic risk factor for sporadic AD. Allele ε4 increases the risk while ε2 has been shown to be protective [17]. Individuals with *APOE ε4* genotype present an increased vulnerability for other vascular and metabolic risk factors like smoking, alcohol, physical inactivity and high intake of saturated fatty acids [18].

APOE ε4 allele increases the risk in an amyloid beta (Aβ) dependent and independent manner. Several mechanisms involving amyloid deposition, tau pathology, neuro inflammation, lipid metabolism, neurotoxicity, mitochondrial dysfunction have been associated with *APOE ε4* allele[17]. *APOE ε4* allele increases brain amyloid β burden and decreases the amyloid β clearance[17,18].

APOE ε4 carriers are constantly found with increased PET Aβ deposition and lower CSF levels of $A\beta_{1\text{-}42.}$ It has been reported that *APOE ε4* allele carriers present higher phosphorylated and total tau levels in cerebrospinal fluid[18,19], more severe synaptic loss and neuroinflammation[17]. A recent study reports that *APOE ε4* carriers have increased Aβ deposition independently of their cognitive performance (e.g normal cognitive performance or with MCI) [20].

1.1.2.2 Environmental risk factors

Several modifiable risk factors have been associated with AD: lifestyle, diet, vascular and metabolic, depression (table1).

Several cardiovascular diseases like midlife hypertension, midlife obesity, midlife dyslipidemia[21], diabetes, stroke [22], late life heart disease[23] have been shown to increase the risk for AD and dementia.

Studies like Cardiovascular Risk Factors Ageing and Dementia (CAIDE), the Framingham Heart Study, Honolulu Asia Aging Study (HAAS) have contributed to increased awareness on the importance of midlife vascular risk factors for AD and dementia[2]

1.1.2.3 Risk scores

There are several risk scores for estimating the risk to develop dementia and research is focusing now on validating them in different populations[24].

CAIDE Dementia Risk Score is a tool for estimating the risk of dementia in the general population. The score has the ability to predict dementia over 20 years (Table 2). There are two versions of CAIDE Dementia Risk Score one which takes into account the following midlife risk/protective factors: age, education levels, gender, systolic blood pressure, body mass index, cholesterol levels and physical activities and another which include APOE genotyping. Total maximum points for the version without APOE is 15 and for the version with APOE is 18[21]. However, by adding APOE ε4 allele the score's capacity to predict dementia did not improve in the original population[21].

CAIDE Dementia Risk Score was developed in a Finish population and externally validated in a population from the USA[25]. Exalto *et al.*[25] added to the score other midlife risk factors including central obesity, depressed mood, diabetes mellitus, head trauma and smoking. Enriching CAIDE Dementia Risk Score with depressed mood the score 's capacity to predict dementia was not improved [25].

Other risk scores taking into account late life risk factors have included depressive symptoms with a good predictive capacity in community-based or primary care settings[24]. Some examples include: Australian National University- Alzheimer's disease Risk Index[26], Dementia Risk Score in type 2 Diabetes, Brief Dementia Indicator for Primary Care[24].

Table 2: CAIDE Dementia Risk Score in the original publication [21]

CAIDE Dementia Risk Score		Version without APOE genotype	Version with APOE genotype
Age	<47 years	0	0
	47-53 years	3	3
	>53 years	4	5
Education	≥10 years	0	0
	7-9 years	2	3
	0-6 years	3	4
Sex	Women	0	0
	Men	1	1
SBP	≤140 mmHg	0	0
	>140 mmHg	2	2
BMI	≤30 kg/m^2	0	0
	>30 kg/m^2	2	2
Cholesterol	≤6.5 mmol/l	0	0
	>6.5 mmol/l	2	1
Physical activity	Active	0	0
	Inactive	1	1
APOE ε4 status	Non-carrier	-	0
	Carrier	-	2
Points, total		Max. 15	Max. 18

CAIDE: Cardiovascular Risk Factors, Aging and Dementia Study, BMI: body mass index, SBP: systolic blood pressure, APOE: apolipoprotein E genotype, (courtesy Dr. Miia Kivipelto)

1.1.3 Neuropathology

Alois Alzheimer described the major neuropathological features of the disease in 1907: amyloid plaques and neurofibrillary tangles in addition to neuronal loss and brain atrophy[1].

At a macroscopic examination it can be observed that brains of patients with AD are bilaterally symmetrically atrophic with widened sulci, narrowed gyri of all lobes and enlargement of the vernicles[27]. A more extensive and severe atrophy can be observed in anteromedial regions of frontal and temporal lobe[27] (Figure 1).

Anatomically, the medial temporal lobe structures include: the hippocampus, parahippocampal cortex, entorhinal cortex, perirhinal cortex[28]. The hippocampus is formed by three major units: the dentate fascia, the Ammon's horn with its 4 subfields Cornu Ammonis 1- 4 (CA1 - CA4) and subiculum[27]. It has complex connectivity with other brain regions such as the thalamus, hypothalamus, amygdala, entorhinal cortex, frontal, temporal and parietal lobes[29]. The hippocampus play a crucial role in memories processes and it is particularly vulnerable in early AD stages[30].

The neuropathological hallmarks of AD- associated pathology are aggregates of abnormal proteins. Intraneuronal neurofibrillary tangles consist of hyperphosphorilated tau protein, whereas amyloid plaques are extracellular and consist mainly of amyloid beta (Aβ) peptide[1] (Figure 1). These protein accumulations have different predilection for different regions in the brain. According to Braak stages neurofibrillary tangles appear first in the allocortex (entorhinal cortex and hippocampus)[31], while Aβ accumulates mainly in the isocortex[31]. The spatial and temporal pattern of amyloid deposition is less predictable than that for neurofibrillary tangles[32,33]. During the course of the pathological process, both types of pathologies spread out systematically throughout the brain, increasing in severity[27]. Earliest changes may begin at least 20 years before a clinical diagnosis of AD[34].

In the APOE *ε4* carriers an accumulation of Aβ plaques is reported[18]. Microvascular changes are common in patients with AD, although they are not considered neuropathological hallmarks of AD[31].

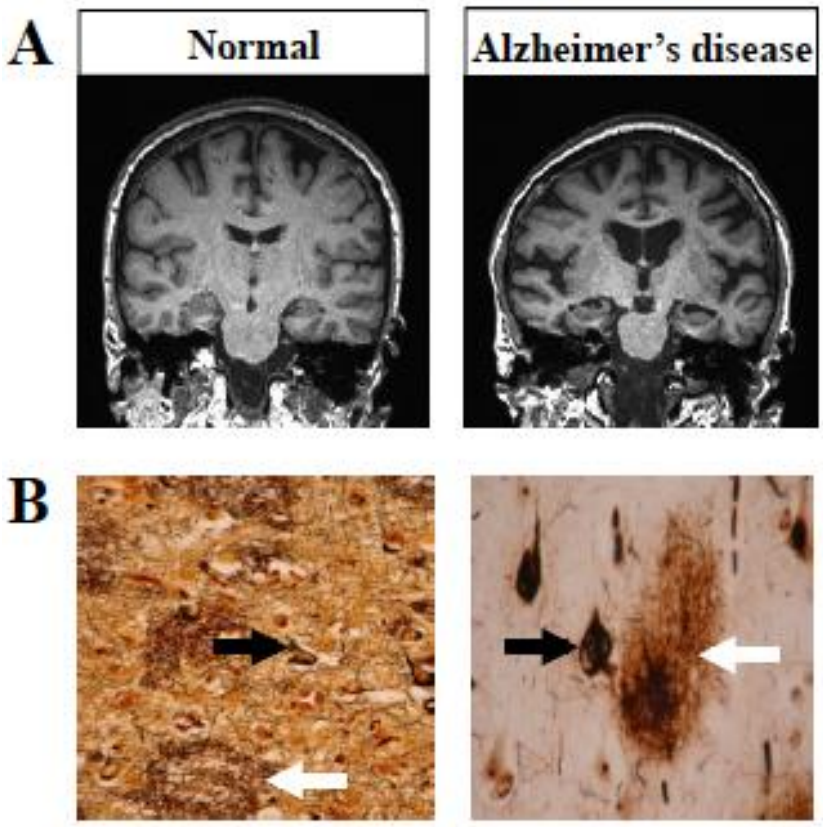

Figure 1: Characteristic AD type pathology: (A) brain atrophy- magnetic resonance imaging (MRI). MRI imaging from a 66-years old healthy control and MRI imaging from a 66 years old patient with sporadic Alzheimer's disease. (B) Bielschowski silver stain highlights both plaques (white arrow) and neurofibrillary tangles (black arrow). Magnetic Resonance Images courtesy Dr. Xiaozhen Li, Karolinska University Stockholm; Microscopy images courtesy Dr. Nenad Bogdanovic, University Hospital Oslo.

1.1.4 Diagnosis

1.1.4.1 Clinical features

- *Cognitive impairment*

Cognitive profiles in patients with subjective cognitive impairment (SCI), mild cognitive impairment (MCI) and AD are very heterogeneous[35]. Identifying the affected domains is helpful to establish the aetiology and the severity of the cognitive impairment. In patients with MCI due to AD the primary neurocognitive feature is decline in memory and learning early in the course of the disease; mainly decline in the ability to learn and retain new information[36,37]. However impairment in other domains such as executive function, attention, language and visuospatial abilities is common in patients with MCI and mild AD[35].

Atypical presentations are usually rare; they appear in younger patients (below 65 years of age) and other cognitive domains are dominating the clinical picture. [38] Posterior cortical atrophy (PCA) variant presents with a major impairment in visuospatial (perceptual-motor function). A "language" and a "frontal" AD variant have been described with progressive aphasia or fontal and behavioural symptoms and relatively preserved memory initially[38,39].

DSM 5 recommends assessment of 6 key neurocognitive domains: learning and memory, language, perceptual motor function, executive function, complex attention and social cognition (Figure 2)[3,4].

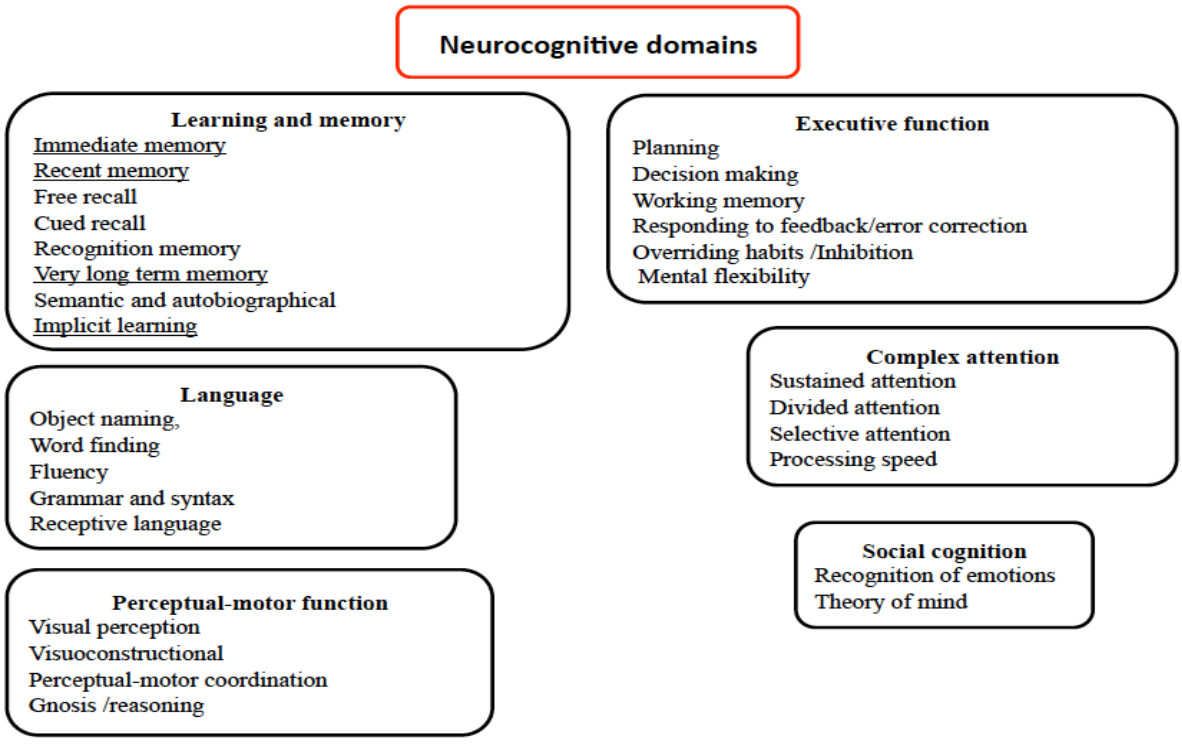

Figure 2: Neurocognitive domains and subdomains proposed by DSM 5 (adapted from Sachdev *et al.*, 2014)[4]

- *Behavioural impairment*

Behavioural symptoms are non-cognitive symptoms in patients with AD. Several neuropsychiatric symptoms such as depression and apathy occur in MCI and mild AD[40,41]. Recently, provisional criteria for "mild behavioural impairment" have been recently proposed [41].

The most common behavioural symptoms include: depression/dysphoria, anxiety, apathy, sleep disturbance, disinhibited behaviour, verbal and physical aggression, agitation, delusion, hallucinations. Behavioural symptoms' severity is associated with severity of cognitive impairment, caregiver burden, increased disability, lower quality of life, earlier institutionalization and increased mortality rate[42]. Moreover, behavioural symptoms such as psychosis, agitation/ aggression and affective symptoms in incident AD can predict progression to more severe AD dementia and death[42].

- Functional impairment

Cognitive and behavioural impairment leads to functional impairment. In patients with SCI and MCI the cognitive symptoms do not interfere with instrumental activities of daily living, although a functional decline can be observed in patients with MCI[43].

The patients' abilities decline from deterioration in instrumental activities of daily living in mild AD to impairment in basic activities of daily living in moderate AD and total dependence and institutionalization in severe AD stages[44].

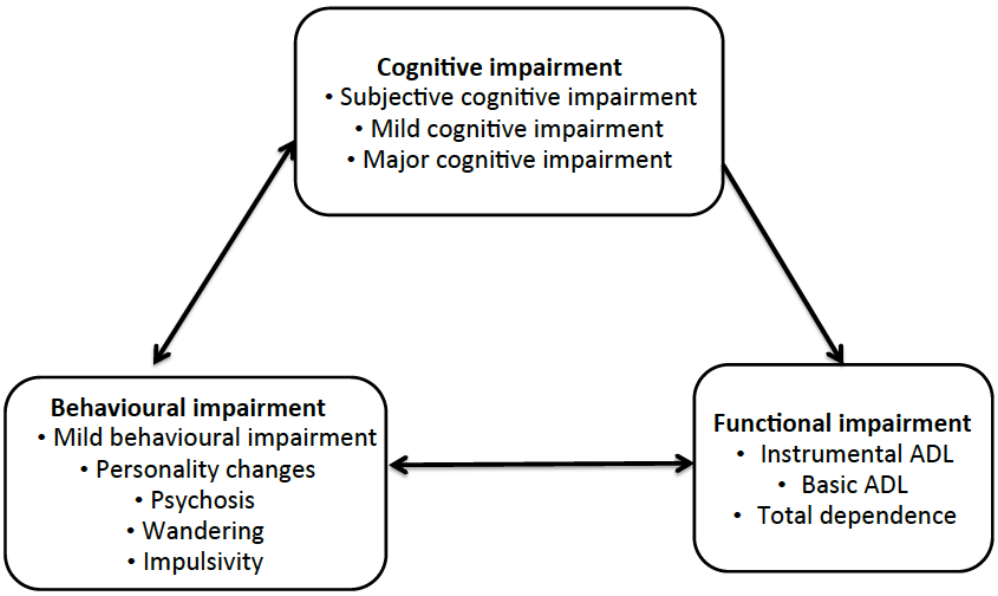

Figure 3: Clinical features of Alzheimer's disease. ADL: activities of daily living

Several scales have been developed to assess the basic and instrumental activities of daily living[43]. In patients with AD some of the most used instruments are: Alzheimer's Disease Cooperative Study– Activities of Daily Living (ADCS-ADL) inventory[45] the Disability Assessment for Dementia (DAD) scale[46], The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[47]. For patients with MCI have been developed new ways to assess functional decline; instruments which are assessing speed and accuracy to perform activities of daily living or financial capacity[43].

1.1.4.2 Diagnostic criteria

Progression of AD symptomatology occurs on a spectrum from preclinical-asymptomatic AD, symptomatic-prodromal AD to clinically manifest AD[48]. Cognitive impairment evolves in this time interval from subjective cognitive impairment (SCI), mild cognitive impairment (MCI) and dementia (Figure 4). Preclinical AD includes 2 stages an "asymptomatic at-risk stage" - individuals without clinical symptoms, but positive biomarkers – and a "presymptomatic AD stage" when an individual experience subjective cognitive impairment and biomarkers can be positive. Prodromal AD stage includes mainly patients with MCI objectively measured and subjectively observed by a knowledgeable informant or clinician[39].

Improved diagnostic techniques and criteria allow a better clinical diagnoses of SCI, MCI and AD. However, a diagnosis of definite AD can only be established post-mortem[34].The assessment procedure should take into account different treatable conditions which may contribute to cognitive impairment such as depression, hypothyroidism, vitamin deficits and alcohol abuse[34].

1.1.4.2.1 Subjective cognitive impairment (SCI)

Individuals with SCI describe a subjective decline in their cognitive function and have normal performance on cognitive testing. It is associated with an increased risk for developing dementia and several biomarkers of amyloid deposition and neuronal injury can be present at this stage[48].

SCI is a heterogeneous clinical entity, being present in different other medical condition or as a side effect of treatment and it can be influenced by personal traits [49,50]. Nowadays there are many international efforts to identify SCI due to AD. Subjective Cognitive Decline Initiative (SCD-I) Working group proposed recently research criteria for pre-MCI subjective cognitive decline[49]. The criteria requires persistent subjective decline in cognitive functioning and

normal cognition at tests used for MCI. The symptoms should not be explained by an acute event, MCI, dementia or by another psychiatric and neurologic disease[49].

The risk for converting to dementia from SCI has been estimated to 10% in studies with more than 4 year follow up; reported conversion rates depend on study design, duration of the follow up, and population type (clinic-based or general population)[51,52]. The annual conversion rate from SCI to MCI is estimated to 6.6% and from SCI to dementia is 2.3% [51].

A recent meta-analysis found that patients with SCI had a similar prevalence of PET amyloid burden as cognitively normal subjects, suggesting that SCI may not have an increased risk for AD than cognitively normal individuals[53]. Obviously, future research focusing on associations between SCI and biomarkers of amyloid deposition and neuronal injury are needed.

1.1.4.2.2 Mild Cognitive Impairment (MCI)

MCI criteria have gone through several revisions after the introduction of the concept by Mayo Clinic group [54]. Most used criteria are:

- Mayo Clinic MCI criteria proposed originally by Petersen *et al.* in 1999[54], are able to diagnose mainly patients with amnestic MCI. These criteria require a cognitive decline from a previous performance level in memory and learning domain objectively measured, subjective cognitive impairment, preserved general cognitive function, preserved independence in performing activities of daily living and no dementia disorder [55].
- International Working Group (IWG) criteria [56] are a broad conceptualization of the Mayo Clinic criteria. It require cognitive decline from a previous performance level in one or several cognitive domains objectively measured, subjective cognitive impairment, preserved independence in activities of daily living, no dementia disorder. The International Working Group criteria are used throughout this thesis.
- DSM5 criteria for mild neurocognitive disease are relatively similar with the International Working Group criteria for MCI. In addition it requires that the cognitive impairment does not occur in the context of delirium or another mental disorder as for example major depression [3,4]
- National Institute on Aging-Alzheimer's Association (NIA-AA) [36] clinical criteria are similar with the International Working Group criteria. NIA-AA research criteria for MCI due to AD, proposed use of biomarkers of amyloid deposition or/and neuronal injury to diagnose MCI due to AD [36]. Patients with MCI due to AD intermediate

likelihood fulfil clinical criteria of MCI and present at least one positive biomarker for amyloid deposition or neuronal injury. MCI due to AD high likelihood is diagnosed when both biomarkers for amyloid deposition and neuronal injury are positive. MCI unlikely due to AD is considered when none of the biomarkers are positive.

Recently, the prevalence of MCI diagnosed according with the DSM-5 criteria was half than using Petersen criteria [57]. One of the explanation is that patients with MCI associated with other mental disorders as major depression for example do not fulfil the DSM-5 criteria[57].

The risk for conversion from MCI to dementia has been estimated to 30-40% and annual conversion rates have varied between 5-10% depending on study design, duration of the follow up, and population type (clinic-based or general population) [52,58]Similarly the risk for conversion from MCI to AD has been estimated to 30% with annual conversion rates of 7% depending on study design[58].

1.1.4.2.3 Dementia in Alzheimer's disease

According with ICD 10 a diagnosis of dementia requires decline in both memory (typically registration, storage and retrieval of new information) and thinking that leads to deterioration from previous level of daily life functioning. Symptoms duration should have been evident for at least 6 months. A diagnosis of dementia in AD according to ICD 10 criteria requires presence of dementia, insidious deterioration which interferes with activities of daily living and do not occur in the context of other brain disease that can induce dementia or of a sudden onset or of neurological symptoms of focal damage[12].

The DSM 5 criteria for major neurocognitive disorder require a significant cognitive decline from a previous performance level in one or several cognitive domains measured objectively by the neuropsychological tests and reported subjectively. The cognitive impairment interferes with instrumental activity of daily living and do not occur in the context of delirium or others mental disorders. Major cognitive impairment can be with or without behavioural impairment [3,4].

There are no studies to compare those two concepts "dementia" and "major neurocognitive disorder". It has been suggest that the concept of¨ " major neurocognitive disorder" may be broader than concept of "dementia". A diagnosis of "dementia" requires memory impairment while a diagnosis of "major neurocognitive disorder" is more flexible and requires impairment in any neurocognitive domain. DSM 5 recommendations for clinicians are to

establish first a diagnosis of neurocognitive disorder and later on the severity of the disorder: minor or major [3,4].

The diagnosis of AD is made based on the NIA-AA criteria[37] according to which the diagnosed is classified as:

1. Probable AD (typical clinical presentation)
2. Probable AD with an increased level of certainty (patients with documented cognitive decline over time, patients with an autosomal genetic mutation for AD)
3. Probable AD with positive biomarkers of amyloid deposition or /and neuronal injury
4. Possible AD (atypical clinical presentation or etiologically mixed presentation)
5. Possible AD with positive biomarkers of amyloid deposition or/and neuronal injury

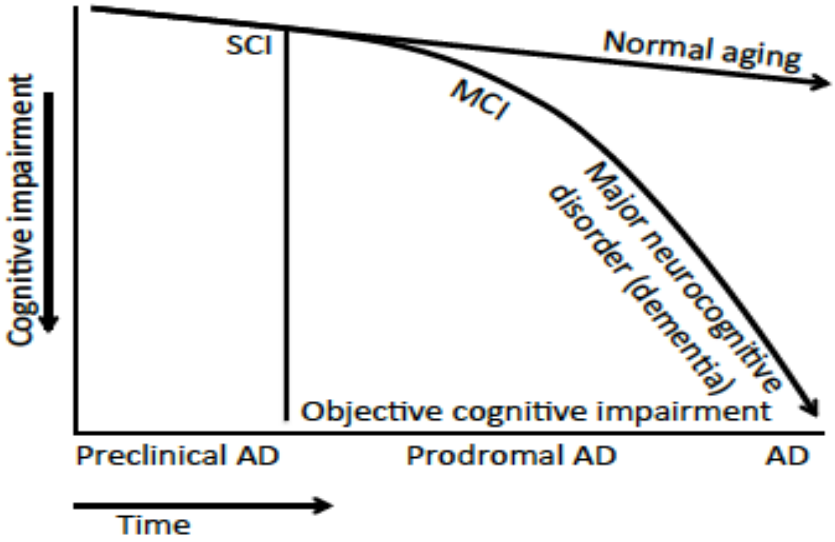

Figure 4: Cognitive decline in different stages of AD: preclinical AD, prodromal AD and AD-dementia. Presence of SCI may indicate late stage of preclinical AD. MCI and dementia present objective cognitive impairment. Not all patients with SCI and MCI develop AD-dementia, many of them will evolve towards normal aging. AD: Alzheimer's disease, SCI: subjective cognitive impairment, MCI: mild cognitive

1.1.4.3 Biomarkers

A biological marker or a "biomarker" is defined by National Institutes of Health (NIH)-Biomarkers definition working group as " a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention"[59].

Most of the current biomarkers for AD are diagnostic biomarkers; are used to increase diagnostic accuracy and for risk assessment in prodromal stages of AD. In clinical practice

none of the current biomarkers are used for staging AD, measuring progression of AD or predicting response to treatment [60].

A good diagnostic biomarker should be able to [39,61].

- Detect AD pathology
- Be validated in post-mortem confirmed AD cases
- Is present in all stages of AD
- Detect early pathological changes of AD (even in asymptomatic stages)
- Distinguish AD pathological changes from other pathologies involved in other dementia disorders
- Be reliable
- Be non-invasive
- Be easy to perform
- Be economically affordable

1.1.4.3.1 Markers of amyloid deposition:

- Cerebrospinal fluid- amyloid beta (CSF Aβ)

Different Aβ isoforms such as Aβ 40 and Aβ 42 can be measured in the cerebrospinal fluid (CSF). CSF Aβ42 levels and Aβ 42:Aβ40 ratio are decreased in patients with AD[62]. Post mortem studies have shown that lower levels of CSF Aβ correlate with cortical amyloid β plaques and can distinguish between AD and healthy controls and AD and other dementia diagnosis[63]. The CSF levels of Aβ42 are decreasing relatively early in the course of the disease[64]. Recently, CSF Aβ42 levels have been found to decrease slowly in some cognitively normal middle aged people, and this pattern was more accentuated in APOE4 ε4 carriers[65]. It is considered a reliable biomarker. However, a large variability in the results obtained with the same method across different laboratories has been reported. Several cut-offs have been proposed for CSF-Aβ42[66]. It is a relatively invasive procedure as a lumbar puncture is required to collect CSF, but it is among the cheapest diagnostic biomarkers of AD and it is used in specialized units.

- Amyloid -Positron emission tomography (Amyloid-PET)

Pittsburgh compound B (PiB) was the first PET tracer used to measure fibrillary amyloid *in vivo* and since then different other PET-tracers have been developed [62]. Detection of amyloid with PET was validated with neuropathologically confirmed cases of AD. A higher uptake of

amyloid tracer on PET scans correlates with lower CSF $A\beta_{1-42}$ [67]. Amyloid PET is a reliable method and can detect early AD changes. In preclinical stages of AD prevalence of amyloid positive on PET scans is associated with age and APOE ε4 status[53]. It is useful for differential diagnosis of early onset dementia [68]. An intravenous injection is needed to deliver the radioactive substance. The patient is exposed to a higher amount of radiation when a computer tomography (CT) scan is performed comparing to a magnetic resonance imaging (MRI) scan. The high costs makes PET mainly used for research purposes. [62]

1.1.4.3.2 Markers of neuronal injury:

- Cerebrospinal fluid- total tau (CSF t-tau) and phosphorylated tau (CSF p-tau)

CSF t-tau and p-tau are relatively a reliable measures of tau pathology. Increased CSF t-tau and p-tau have been observed in patients with AD and are correlated with neurofibrillary tangles in post-mortem studies of confirmed AD cases[69]. A large variability and several cut-off points have been proposed by different laboratories using same measuring techniques[66]. CSF t-tau levels are not specific for AD as it increases in different other neurodegenerative disease[70], however the addition of p-tau levels increased the specificity for the disease[71]. Some studies suggested that CSF tau correlates with cognitive progression[60].

- Hippocampal atrophy or medial temporal lobe atrophy

Hippocampal atrophy and medial temporal lobe atrophy on structural MRI scans correlates with tau pathology[72] and cognitive impairment[60]. Hippocampal atrophy can distinguish with a good accuracy between patients with AD and healthy controls and is used in risk assessment in patients with MCI and SCI[73]. In population based studies hippocampal volume decrease gradually from the age of 30-40 until 60 years when the shrinkage becomes more severe[74,75]. Hippocampal atrophy can occur in other dementia, while patients with atypical AD presentations can depict parietal or frontal lobe atrophy mainly with no involvement of the hippocampus[38]. Hippocampus region present relatively small anatomical variability compared with other cortical regions and several methods have been developed to measure it[76]. Manual delineation of hippocampal volume is a method with high accuracy, but it is time consuming and mainly used for research purposes. Visual assessment of the medial temporal lobe atrophy is a method used in clinical practice, but it is less accurate for detecting subtle variation[77]. Visual assessment correlates well with the manual delineation of the hippocampal volume[78] and can predict conversion to AD in patients with MCI[77,79]. Automated methods are now developed and have potential to be used in clinical practice[80]. Hippocampal and medial

temporal lobe atrophy measured on MRI are non-invasive and relatively inexpensive biomarkers[76].

Apart from hippocampus, other brain regions are atrophied in patients with AD. An index of AD-like patterns of atrophy based on structural MRI have been shown to predict conversion from MCI to AD[81].

- Tau Positron Emision tomography (Tau-PET)

Different tracers for tau are underdevelopment and used for research proposes. Imaging tau in vivo will facilitate research into underlying mechanism in AD[70].

1.1.4.3.3 White matter lesions (WML) or white matter changes (WMC)

WML are attributed to small vessel chronic ischemia[82] and affects executive function (planning, organizing)[82]. Prevalence of WML in population-based studies varies between 45-95%[83]. WML are common in prodromal stages of AD and more severe parietal WML can predict conversion to AD in patients with hippocampal atrophy or pathological CSF levels of t-tau[84,85]. WML are very common in patients with AD and prevalence is higher in vascular dementia[86] . A recent study have shown that alterations in white matter integrity measured with diffusion tensor MRI (DTI-MRI) precede gray matter atrophy in patients with MCI and pathological CSF Aβ levels[87].

1.1.4.3.4 Interaction between the biomarkers

Understanding the particular sequence and evolution in time of biomarkers abnormalities is essential in staging the disease in presymptomatic stages and evaluating the patient state and disease prognosis [88]. Several models that estimate biomarker dynamics have been proposed, most of them assume a single progression pattern. The first model proposed by Jack *et al*. in 2010 suggest that markers of amyloid deposition (CSF Aβ and Amyloid PET) occur first, followed by biomarkers of neuronal injury (^{18}F-fluordeoxyglucose PET (FDG-PET), CSF t-tau, CSF p-tau and hippocampal atrophy) and later on clinical symptoms as cognitive impairment, neuropsychiatric symptoms and functional impairment appear[60].

More recently, hypothetical model of dynamic biomarkers proposed by Jack *et al.* in 2013 suggests that amyloid and tau pathology can begin independently one from another and both pathologies are necessary but not sufficient to produce clinical symptoms of AD[88]. Other pathologies like small vessel disease, inflammation, Lewy bodies, TDP-43 inclusions[69], genetic factors and brain cognitive reserve may also play a role.

1.1.5 Treatment of Alzheimer's disease

The approved treatment for AD is symptomatic. Acetylcholinesterase inhibitors (AChEI) as donepezil, rivastigmine and galantamine inhibit acetylcholinesterase and enhance acetylcholine in the synaptic cleft. Apart from AChEI memantine is licensed for moderate to severe AD, it is a partial antagonist of N-Methyl-D-aspartic acid (NMDA) -receptor[34].

No disease modifying therapy is approved for clinical use. Many trials targeting Aβ plaques in patients with early or moderate AD have been more or less unsuccessful[89].However, new promising Aβ antibodies are in early phase trials[89]. One of the possible explanations for the unsuccessful trials was that the intervention was too late in the course of the AD. Secondary prevention trials are on going to intervene with disease modifying drugs in asymptomatic individuals with pathological biomarkers. One of these trials is the A4 trial (Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease); it will test the hypothesis that decreasing amyloid burden will prevent or slow the occurrence of the clinical symptoms of AD [90].

Recent studies have shown that life style interventions could improve or maintain cognitive functioning in individuals at risk to develop dementia [91,92]

The treatment of choice for the behavioural and psychological symptoms in AD is non pharmacological; psychological treatment, music therapy, aromatherapy, physical exercise are useful in treating agitation/aggression and depressive symptoms[93,94]. Medication should be reserved for extreme cases. Atypical antipsychotics as risperidone, olanzapine and aripiprazole show modest benefits for treating psychotic symptoms, aggression or agitation in patients with AD for a short period of time (12 weeks). Antipsychotics have severe side effects as sedation, gait disturbance, prolonged QTc, thromboembolic, cerebrovascular events and increased mortality [94,95] . A recent trial suggest that atypical antipsychotics can have a modest benefit on psychotic symptom for long term use (more than 24 weeks)[96].

Use of antidepressant treatment for treatment of depressive symptoms will be discussed late on in the thesis (treatment of depression in AD). It has been suggested that citalopram may reduce agitation/aggression[94].

1.1.6 Life expectancy with Alzheimer's disease

AD has a long asymptomatic stage and can go under diagnosed for several years. The average length of time between the occurrence of the mild cognitive impairment and diagnosis of AD is estimated to 3 years[97]. Life expectancy in patients with AD varies largely, the average life

expectancy after diagnosis is 7 to 10 years[98] but it can varies between 3 years or up to 20 years depending on study design , age of the studied population [99,100].

1.1.6.1 Factors associated with increased mortality risk in AD

Life expectancy after a diagnosis of AD depends on numerous factors and their complex interactions. Several of them have been identified:

- Age at onset is the main predictor of the life expectancy, older people having a higher mortality rate[100]
- Male Gender has higher mortality rates after the initial AD diagnosis[101]
- Severity of the cognitive impairment at diagnosis[101]
- Behavioural symptoms at the time of AD diagnosis was associated with increased mortality rate[102].
- Comorbidities:

In the elderly population over 67 years of age life expectancy decrease with each additional chronic condition[103]. Patients with AD and cardiovascular disease, diabetes, genitourinary diseases and chronic obstructive pulmonary disease have a shorter life span than AD patients without these comorbidities[104,105].

- Medication:

Intake of a high number of medications reflects a high number of chronic comorbidities and is associated with a higher mortality risk[101]. Use of cholinesterase inhibitors in patients with AD can reduce the mortality risk and slow the disease progression[106].

Psychotropic medication is often used in the elderly with AD. Use of antipsychotic medication has been associated with increased mortality risk in elderly with AD and dementia[95,107].

The evidence however is conflicting regarding use of antidepressant medication and mortality rate. Recently, a large retrospective case-control study reported a small but increased mortality risk in patients with AD or dementia using antidepressants [95]. Meanwhile, studies conducted in nursing homes have reported decreased mortality rates in patients using antidepressants with an increased protective effect in those who used antidepressant treatment more than one year[108,109]. Moreover, effective treatment of behavioural symptoms in AD with antidepressants was associated with lower mortality rate in nursing home patients with AD and other forms of dementia[109].

1.2 LATE LIFE DEPRESSION

Depression is an important cause of years lived with disabilities worldwide[110]. It is also the leading cause of disease burden for women[111]. Depression and depressive symptoms are often under-diagnosed in older people [112].

1.2.1 Epidemiology

Depression is a common condition throughout the life span, with important clinical consequences such as functional impairment, reduced quality of life, and increased mortality [113]. The prevalence and incidence varies largely across studies depending on study design, criteria used to assess depression and settings. Lifetime prevalence of major depressive disorder varies between 3% in Japan and 16.9 % in the USA, with the majority of countries reporting a range between 8% to 12%[114]. The gender ratio shows a lifetime prevalence estimated at 20.4% in women and 9.6% in men[115].

The overall prevalence of depressive disorders in older adults varies between 10-20% [116]. In elderly population the prevalence of major depressive disorder decreases with age [115] , while the prevalence of depressive symptoms increases with age [117]. Prevalence of major depressive disorder varies between settings: 1-6.3% in the community, 4-10% in primary care units, 15-30 % in clinical in-patient units and 6-24% in long term care units [113]

In older adults prevalence of minor depressive disorder varies between settings: 1.4-23% in the community, 5-20% in primary care units, 10-30 % in clinical in-patient units and 10-30% in long term care units [113,118]. Patients with minor depression have an increased risk to develop dementia [113].

1.2.2 Diagnosis

1.2.2.1 Depressive symptoms in late life

Late life depression (over 60 years) is considered to have a more chronic course with a higher relapse rate compared with depression in younger patients [119]. Depression in late life is associated with female gender, low socio-economic status, reduced social support and an increased sense of loneliness, recent adverse life events (e.g. bereavement) and coexisting medical illnesses[112].

Depression is very frequent among older people with associated comorbidities, like AD, Parkinson disease, stroke, diabetes [120,121]. Co-occurrence of depression and another medical illnesses is strongly associated with poor self-management, substance abuse, poor adherence

to treatment[122], increased use of health services with early institutionalization and increased mortality[123].

The clinical presentation of depression in older people has some particularities when compared to depression in younger people[124]. In a meta-analysis of 11 studies, patients suffering from late life depression were found to have more psychomotor agitation, somatic symptoms and hypochondriasis, less guilt and less sexual interest [124].

The core symptom, depressed mood, may be less common in late life depression compared with depression early in life[120]. More unspecific symptoms such as anxiety, social withdrawal, psychomotor agitation, irritability, sleeping problems, pain and somatic symptoms may be more common in late life depression than in younger patients with depression[119,124].

Psychotic symptoms as delusional ideation regarding poverty, physical illness or with nihilistic content are common in late life depression [125]. Recognition of depression in older people is a priority as elderly suffering from depression have a higher suicide risk[126]. However, recognition of depression in older adults may be difficult due to increased tendency to alexithymia and somatisation[127], which sometimes could dominate the clinical picture[112].

1.2.2.2 Cognitive impairment in late life depression

Cognitive profile in late life depression is very heterogeneous[128]. Decline in executive function is common in both acute and euthymic states and it can be associated with difficulties in verbal and non-verbal learning and recall. Retention, recognition memory, implicit learning and language fluency are relatively intact in late life depression[128]. Difficulties in recall tasks support the implication of frontostriatal pathways in late life depression[129]. These cognitive symptoms may be reversible during successful antidepressant treatment. In some cases, symptoms may persist and even progress to dementia.

Patients with depression in AD have a more severe impairment in several cognitive domains such as complex attention, executive function, verbal fluency and memory [130,131]. In patients with dementia, depression may aggravates the rates of cognitive decline[132].

1.2.2.3 Diagnostic criteria

Diagnosis of depression is purely clinical, as no diagnostic biomarker for depression has been approved for clinical practice. National Institute of Mental Health has launched the Research Domain Criteria project (RDoC) to “create a framework for research on pathophysiology

especially for genomics and neuroscience, which ultimately will inform future classification schemes"[133,134].

DSM-5 criteria for major depressive disorder require the presence of a minimum 5 symptoms (at least one core symptom) over a 2-week period. Core symptoms are depressive mood or anhedonia. Additional symptoms are: increased or decreased appetite, clinically significant weight gain or loss, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, loss of energy, loss of concentration, difficulties in taking decisions, feelings of worthlessness or excessive or inappropriate guilt, and suicidal ideation[112,125,135]. DSM 5 introduced the concept of depression without sadness acknowledging that elderly complain more of loss of motivation, lack of energy, withdrawal and physical complains. Therefore DSM5 criteria are more likely to identify depression in older people compared to previous DSM criteria for major depressive disorder [125].

ICD criteria are frequently used in Europe and those criteria for depressive disorders are mainly similar to DSM criteria[12].

Sub-threshold depression or subsyndromal symptomatic depression refers to clinically symptoms of major depression without fulfilling all criteria that leads to reduction in social function. Several criteria have been proposed for sub-threshold depression in younger patients[136] and in older people[137,138]. Lyness *et al.* 2007 showed that there are many similarities among the criteria[138]. Judd *et al.* criteria require more than 2 depressive symptoms at a threshold level and one of the symptoms is either anhedonia or depressive mood[136]. Lyness *et al.* require more than 2 depressive symptoms at a threshold or sub-threshold level, when one of the symptoms is either anhedonia or depressive mood [138]. For both criteria depressive symptoms should be for more than 2 weeks[136,138] . Several studies defined sub-threshold depression as scoring above an established cut-off point on depression rating scale (e.g. Hamilton rating scale for depression (HAM-D) $\geq$ 10 [138] or Geriatric Depression scale (GDS) $\geq$12[137]).

Depressive symptoms are included as diagnostic criteria for several affective disorders (see list below of several DSM 5 diagnoses). In clinical practice it is important for the patient to get an accurate diagnosis and appropriate treatment.[135 125]

- Major Depressive Disorder
- Persistent Depressive Disorder which replace the dysthymic disorder from DSM IV
- Disruptive Mood Dysregulation Disorder
- Premenstrual Dysphonic Disorder

- Substance/Medication-Induced Depressive Disorder

  Depressive Disorder Due to Another Medical Condition (following stroke, with Huntington's disease, with Parkinson Disease, hypothyroidism)
- Other Specified Depressive Disorder (recurrent brief depression, short-duration depressive episode: 4-13 days, depressive episode with insufficient symptoms)
- Bipolar Affective Disorder
- Cyclothymic Disorder
- Unspecified Depressive Disorder
- Complicated bereavement have been excluded from DSM 5, but is often used in clinical practice

1.2.3 Relationship between depression and Alzheimer's disease

The relation between depression and cognitive impairment is complex; major depression in late-life is often accompanied by cognitive impairment. Additionally, depression has been shown to be a risk factor, a prodromal symptom and a consequence of AD [139] [121].

- *Depression as a risk factor for AD*

Epidemiological studies suggest that depression/ depressive symptoms are a risk factor for AD. The evidence however is inconclusive regarding the risk associated with early-life depression (before 60 years of age) and late-life depression (after 60 years of age). Studies with long follow up periods report that patients with recurrent depression earlier in life have a high risk for AD [140–143] . Other studies did not find this association despite relatively long follow up periods[144,145].

The majority of epidemiological studies reports late life depression as a risk factor for AD[146] [144]. However, the several studies designed in clinical settings found no association between depression in patients with MCI and risk of progression to AD[147,148]. These studies suggest that late life depression is an early symptom of AD rather than a risk factor [144].

- *Depression as a prodromal symptom of Alzheimer's disease*

Differentiating between depression as a behavioural symptom of AD and depression with cognitive impairment is challenging in clinical practice. Depression is very common in prodromal stages of AD[117] and in the same time it is a treatable cause of subjective or mild cognitive impairment[149].

Amyloid deposition and tau pathology occur at least 20 years before the occurrence of clinical symptoms of AD[88] . Therefore depression (late life or late onset depression) in preclinical or prodromal stages of AD can be considered as an early behavioural symptom of AD. Depression or depressive symptoms coexist with cognitive impairment in patients with prodromal AD (10 -20% of cases of AD are preceded by depression[121]) and are associated with increased risk of progression to AD[150].
However, studies in cognitively normal individuals have shown that depressive symptoms do not differ between patients who developed subsequent cognitive impairment and those who remain cognitively normal[117].

- *Depression in Alzheimer's disease*

The prevalence of depression in AD varies across studies[121]. Around 20-30% patients with AD suffer from depression or sub-threshold depression[121]. Population based studies report a prevalence of depression/depressive symptoms between 5% and 35%[151]. Clinic-based studies report relatively similar frequencies when depressive symptoms are measured[152], while the frequencies are much lower (0.9%-4.8%) when more strict criteria for major depression were used[153]. Few studies have reported on incidence of depression in AD, but an incidence of 2% per year has been reported for major depressive disorder[153].

A major depressive episode in AD usually includes less severe symptoms and its duration is usually shorter than major depressive episode in younger patients. Symptoms such as dysphoria, anhedonia, social isolation or irritability are most common in depression in AD [154]. Prevalence and incidence of depression increase in early stages and decrease in late stages of AD[155,156]. Decline in cognitive performance including language abilities can make depression difficult to assess in late stages of AD[157]. However, studies conducted in nursing homes reported a relatively high prevalence (21.2%), incidence (15%) and persistence (45%) of depressive symptoms in dementia [158].

Younger age, increased number of comorbidities, bereavement, greater impairment in activities of daily living and previous depression have been associated with an increased risk for occurrence and persistence of depression in AD [152,159]. The evidence remains inconclusive regarding the association between severity of depression and severity of cognitive impairment [160]. However, in a longitudinal study major depression was found to accelerate the cognitive decline in AD and dementia [132]. Mood symptoms defined as depression, anxiety and apathy measured with neuropsychiatric inventory have been associated with increased severity of

impairment in executive function, visual memory and working memory in patients with AD[161].

1.2.4 Mechanisms of depression in Alzheimer's disease

The mechanisms underlying depression in older people are only partially known, and are likely heterogeneous, involving a number of different pathophysiological changes, several of which are shared with AD.

- *Genetics*

Several genetic factors have been associated with late life depression and neuropsychiatric symptoms in AD. APOE ε4 allele is a risk factor for AD and a recent study reported an association between APOE ε4 allele and late life depression[162]. Prevalence of APOE ε4 allele is higher in AD patients with depressive symptoms compared with AD patients without depressive symptoms[163]. APOE ε4 allele and depressive symptoms in cognitively normal, SCI and MCI individuals are strongly associated with conversion to AD or dementia[164,165].

Serotonin system is affected in both AD and depression[166]. Some studies found associations between polymorphisms in serotonin transporter gene (SLC6A4) and serotonin receptor 2A gene (HTR2A) and depressive symptoms in AD patients [167], while other studies did not found such associations[168]. Response to selective serotonin reuptake inhibitors (SSRI) in patients with late life depression is influenced by polymorphism in serotonin 1B (HTR1B) and 1A (HTR1A) receptor genes[169].

Symptoms of anhedonia in major depression [170] and apathy in AD have been associated with deregulation in dopamine system[171]. A study from the UK found that higher scores on NPI depression and anxiety items were associated with dopamine receptor D4 (DRD4) 2R allele[172]. The role of genes related to other systems of neurotransmitters with potential relevance for depression in AD needs to be evaluated.

Finally, the brain derived neurotrophic factor (BDNF) Val66Met polymorphism may increase susceptibility for depression in AD[173].

- *Cerebrovascular mechanisms: "vascular depression" hypothesis*

The link between late life depression and cerebrovascular disease is well established. "Vascular depression"[174] describes a subtype of late life depression[175] where

"cerebrovascular disease may predispose, precipitate or perpetuate some geriatric depressive syndromes"[176].

Patients with depression and cerebrovascular disease often have ischemic lesions and small regions of hypoperfusion leading to disruption of the frontolimbic and frontostriatal circuits [174]. Periventricular and frontal white matter hyperintensities on MRI reflect small vessel pathology[86]. These vascular lesions are associated with higher score for depression in patients with late life depression [177] and depression in AD [178].

- *Hypothalamic-pituitary-adrenal (HPA) axis and hippocampal atrophy*

Corticotrophin release factor, in chronic depression and AD, activates the hypothalamic-pituitary-adrenal (HPA) axis and increases release of stress hormones including glucocorticoids.

Hippocampus, cornu ammonis 1- 3 (CA1-CA3) subfields and subiculum in particular are very sensitive to increased cortisol levels, reduced levels of serotonin and BDNF occurring in depression and AD[29,179]. Hippocampal atrophy, accordingly, is commonly found in AD and depression.

The association between late life depression and reduced hippocampal volume is conflicting as several cross-sectional and longitudinal studies report such an association[180,181], while no other studies do [180,182]. Some studies suggest that hippocampal atrophy is a temporary state in the evolution of depression since no significant difference could be observed between patients with depression in remission and healthy controls[183]. Hippocampal atrophy in late life depression is associated with poor response to antidepressant treatment[184] and can be considered a predictive marker of response to treatment[184].

Increased levels of glucocorticoids promote Aβ formation[139,185] and suppress hippocampal neurogenesis [186] in patients with late life depression and AD [185].
However, there is inconclusive evidence supporting the major role of HPA axis activation in late life depression [177] and in depression in AD[139,185]. In a recent study increased cortisol levels in cerebrospinal fluid (CSF) were associated with cognitive impairment in MCI due to AD and in AD patients, but no significant associations were found with depression scores[187].

- *Amyloid β plaques formation and neurodegenerative processes*

Processes of abnormal protein accumulation in AD lead to neurobiological changes that can impair networks implicated in depression[188]. Therefore patients with depression in AD have a poor response to classical antidepressant treatment[189].

Studies using biomarkers of Aβ deposition and neuronal injury and studies of neuropathology have tried to explain the underlying mechanisms in late life depression and depression in AD.

◊ *PET:* Several studies using PET to visualize Aβ plaques in vivo suggest an association between increased amyloid deposition and late life depression[190–193] while other studies did not find such association[194,195]. Moreover depressive symptoms in patients with MCI and PET Aβ positive are associated with higher amyloid load compared with non depressed Aβ positive MCI patients[196].

◊ *CSF:* Several studies suggest an association between lower CSF $A\beta_{1-42}$ levels and late life depression[197], while others found increased levels or no significant association between CSF $A\beta_{1-42}$ levels and late life depression[198–200]. In patients with AD and depressive symptoms $A\beta_{1-42}$ was found not significantly different than in patients with AD and without depression[200,201].

Most of the studies reported no associations between CSF t-tau or p-tau and late life depression[188,202] and depression in AD[201].

◊ *Structural MRI: MRI* studies have shown associations between late life depression and brain atrophy. Hippocampal[180], entorhinal cortex[203] and orbitofrontal cortex atrophy have been consistently reported in late life depression[180]. Depressive symptoms in AD patients are associated with cortical thinning in temporal and parietal regions[204,205] compared with AD patients without depressive symptoms. Moreover, more severe cortical thinning have been associated with higher CSF t-tau levels in AD patients with depressed symptoms[204].

◊ *Neuropathology:* Studies on postmortem patients' brains with late life depression failed to show an association between depressive symptoms and amyloid plaques and neurofibrillary tangles[206]. Meanwhile patients with AD and depressive symptoms present more amyloid plaques and neurofibrilary tangles than AD patients without depressive symptoms[207,208].

- *Neuroinflammatory changes*

Chronic inflammation has been implicated in both depression[209] and AD[210]. Some researchers propose that activation of inflammatory pathways in late life depression increase vulnerability for vascular events and amyloid accumulation[211].

Few studies addressed the role of inflammation in AD depression. In recent studies lower levels of anti inflammatory interleukin 10 in the CSF[212] and raised serum levels of pro inflammatory tumor necrosis factor were associated with depressive symptoms in AD[213].

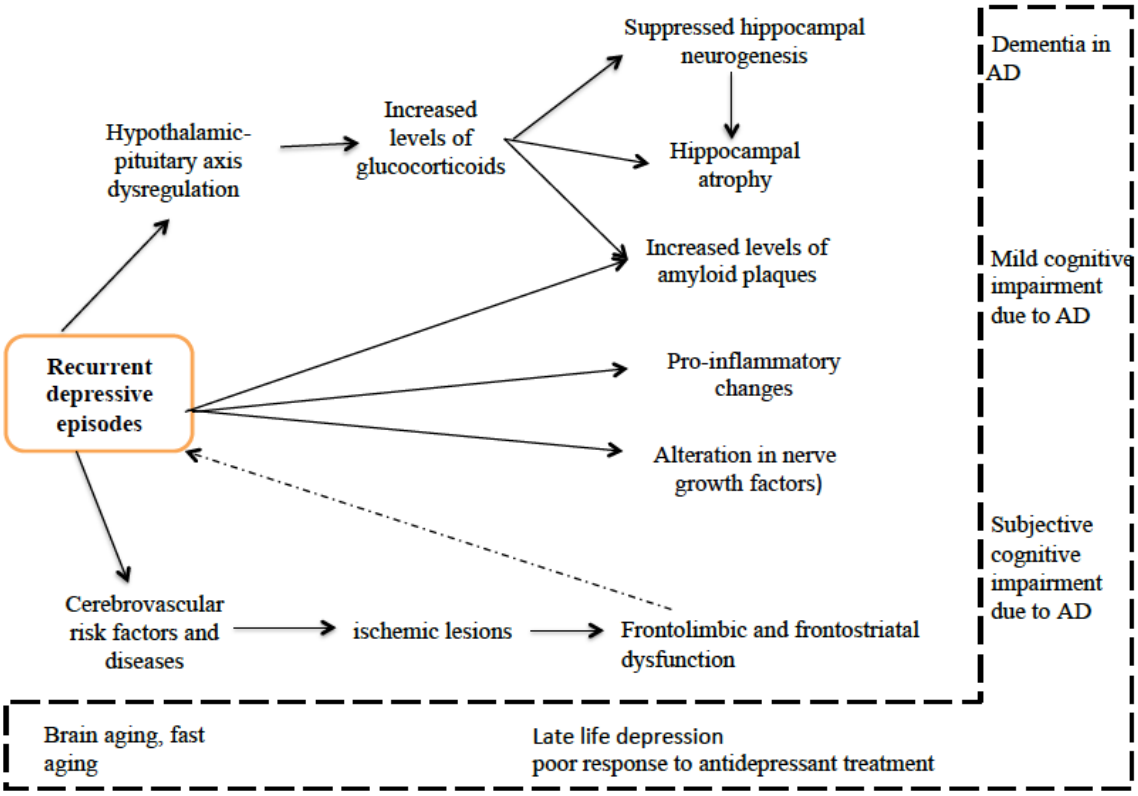

Figure 5: Potential mechanism involved in depression that can increase the risk for AD Chronic depression (with severe recurrent depressive episodes) is associated with hyperactivity of hypothalamic-pituitray axis which leads to increased secretion of stress hormones like glucocorticoids contributing to the pro-inflammatory environment, hippocampal atrophy, increased levels of amyloid plaques and alteration in growth factors (brain-derived neurotrophic factor). Proinfalmmatory processes increase brain vulnerability for cerebrovascular disease particulary in middle age individuals; ischemic leasions have been involved in dysruption of the frontolimbic and frontostriatal connectivity. Presence of the ischemic lesions and hypoperfusion processes in late life depression are associated with a poor respons to antidepressant treatment and increase the number of recurrent depressive episodes. All these processes increase the risk for brain aging and development of cognitive impairment, Alzheimer's disease.

- *Nerve growth factors*

Decreased levels of BDNF have been involved in late life depression and AD. BDNF has an important role in maintaining the integrity of the hippocampus [214]. A recent study, has shown that patients with late life depression and MCI have lower CSF- BDNF levels compared with MCI patients without depression[215] . The role of BDNF and other nerve growth factors in depression in AD needs to be further explored.

1.2.5 Assessment of depression in Alzheimer's disease

Several scales are used to screen for depressive symptoms or to measure severity of depressive symptoms in older people with and without AD. None of the following scales is a diagnostic tool for depression in AD. Some examples of the most commonly used scales for clinical and research purposes:

- *Cornell Scale for Depression in Dementia (CSDD):*

The scale was developed initially to screen for depressive symptoms among elderly with dementia [216], but it can be applied in elderly without dementia [217]. It consists of two semi-structured interviews where both patient and caregiver are interviewed. It takes around 25 minutes to administer the scale.

The scale shows a good reliability, sensitivity and validity for measuring depressive symptoms in older people with AD[216] from hospital[218] and nursing homes[159]. The scale is widely used. Other versions have been translated from English, culturally adapted and validated[219].

The scale has 19 items assessing different depressive symptoms. Each item ranges from 0 to 2 (0-the symptom is not present, 1 – the symptom is present intermittently, 2 the symptom is constantly present; a- the symptom can not be assess). It equally assesses psychological and physical symptoms associated often with depression in AD. The total score ranges from 0 to a maximum of 38 points [216].

Different cut-off points have been proposed for measuring depression in patients with and without dementia. In the original publication a total score above 7/8 has been suggested as cut-off, but no sensitivity, specificity, positive and negative likelihood ratios and accuracy values were calculated for that cut-off point or other cut-off points [216]. Cut-off points with the best sensitivity, specificity and accuracy vary among patient populations, cultural differences and study designs[220]. For example in a nursing home Norwegian population a cut-off 8/9 has

the best accuracy for diagnosing ICD-10 major depression, a cut-off 10/11 has the best accuracy for DSM-IV-TR major depression while a cut-off 6/7 has the best accuracy for diagnosing depression in AD using the Provisional Criteria for Depression in Alzheimer's Disease[221]. Kørner *et al.* found the best accuracy for a cut-off 6/7 in a Danish out –patient population with and without dementia[218]. Knapskog *et al.* proposed several cut-off points for patients with and without dementia in a memory clinic cohort[222]. They suggested that the cut-off with the best sensitivity and specificity is 5/6; while the cut-off 7/8, which is widely used in clinical practice has good psychometric properties (sensitivity 60, specificity 79 and accuracy 72) for diagnosing ICD-10 major depression[222].

It is very important that the staff is trained to use CSDD. A study in nursing home population found a relatively low recognition of depressive symptoms when the CSDD was administrated by the staff in nursing homes compared with trained psychiatrists[223].

CSDD have 6 subscales and the assessed symptoms are:

A. Mood Related Signs (anxiety, sadness, lack of reactivity to pleasant events, irritability)

B. Behavioural Disturbance (agitation, retardation, multiple physical complaints, acute loss of interest)

C. Physical Signs (appetite loss, weight loss, lack of energy)

D. Cyclic Functions (diurnal variation of mood, difficulty falling asleep, multiple awakenings during sleep, early morning awakenings)

E. Ideational Disturbance (suicide, self-depreciation, pessimism, mood congruent delusions)

- Geriatric Depression Scale (GDS)[224]

This was designed mainly to assess depressive symptoms in older people. It is relatively easy to use and it takes around 5-10 minutes to administer. The original version includes 30 items, but short versions like GDS-15, GDS-10 and GDS-4 have been developed[225]. There is also a self-administrated version. It focuses only on affective symptoms of depression. A Swedish version; GDS-20 has been developed by adding 5 items about somatic symptoms of depression to the GDS-15 version[226].

- Montgomery Asberg Depression Rating scale (MADRS).[227]

MADRS is one of the most used scales for assessing depression. It takes around 15-20 minute to administer. Items focusing on the affective and psychological symptoms have an increased preponderance than items focusing on somatic symptoms; thus it can be less useful in assessing depression in dementia. It is, however preferred in interventional research for its sensitivity to changes in depressive symptoms.

- Hamilton Depression Rating Scale (HAM-D)[228]

It is a useful scale in assessing the severity of depression symptom. It is a semi-structured interview based on self-reported symptoms. It takes around 20-30 minutes to administer. Like MADRS, it is less useful in assessing depression in dementia.

- Neuropsychiatric inventory (NPI)[229]

NPI assesses frequency and severity of behavioural symptoms in AD and major dementia. A question about depressive symptoms is included. It takes around 10 minutes to administer it to a carer.

- Behavioural pathology in Alzheimer's disease (BEHAVE-AD).[230]

This scale is designed to assess the presence of neuropsychological symptoms in AD. As NPI it takes around 10 minutes to administer to a caregiver or an informant and a question about presence of depressive symptoms is included.

Scales assessing more affective symptoms as MADRS, HAM-D and GDS-15, GDS-10, GDS-4 are better correlated among themselves[225 231], while a relatively poor correlation had been recently reported between CSDD and MADRS[220]. Moreover, use of MADRS had a better accuracy in predicting major depression assessed by ICD-10 in a memory clinic population[222].

In AD, the scoring of scales based on self-reported depressive symptoms such as MADRS, GDS and HAM-D can be influenced by the patient's communication skills, insight, and ability to abstract thinking. Scales as NPI and BEHAVE-AD mainly based on carer reports may be influenced by carer's mood and perceived burden[232]. Scales as NPI and BEHAVE-AD assess mainly mood symptoms as sadness, while CSDD includes other depressive symptoms[233].

1.2.6 Diagnosis of depression in Alzheimer's disease

Symptoms of depression and AD overlap, therefore diagnosis of depression in AD may be challenging. In prodromal AD cognitive symptoms coexist with neuropsychiatric symptoms such as depressive mood, social withdrawal, apathy etc[234].

It was suggested that DSM criteria for major depressive disorder are not useful to diagnose depression in AD[154], but are used to diagnose depression in prodromal AD[235]. In DSM 5 no criteria for depression in AD have been proposed.

In 2002 Olin JT *et al.* proposed clinical diagnostic criteria for depression of AD: National Institute of Mental Health provisional diagnostic criteria for depression in AD (PDC-dAD)[154]. The proposed criteria are based on the DSM IV criteria for major depression. The authors reduce emphasis on verbal communication and include new criteria as irritability and social isolation. To meet these criteria, a patient with AD must have a change in functioning for 2 or more weeks characterized by 3 or more of the following symptoms, either depression or anhedonia must be one of the symptoms[154].

1. Depressed mood (sad, hopeless, discouraged, tearful)
2. Anhedonia: Decreased positive affect or pleasure in response to social contacts and activities
3. Social isolation or withdrawal
4. Disruption in appetite
5. Disruption in sleep
6. Psychomotor agitation or retardation
7. Irritability.
8. Fatigue or loss of energy
9. Worthlessness, hopelessness or excessive guilt
10. Recurrent thoughts of death or suicidal ideation

The PDC-dAD correlates well with DSM IV criteria and has a good sensitivity and specificity. However the prevalence of depression in AD was found higher when using the PDC-dAD compared to DSM IV criteria for major depression[236]. In a population of 112 AD patients with different degrees of cognitive impairment, proportion of depression was 53.5% for PDC-dAD, 47.3% for ICD-10 and 34.8% for DSM-IV-TR criteria[237].

Scales as CSDD that use a combination of patient and caregiver interviews are more useful for measuring the severity of the depressive symptoms in AD. Scales based only on self-

reported symptoms as MADRS, HAM-D, HADS can be used in assessing depressive symptoms in patients with subjective and mild cognitive impairment[238]. CSDD and GDS are more commonly used in assessing depression in AD[238]. BEHAVE-D and NPI can be used in more severe stages of AD [239].

1.2.7 Treatment of late life depression

There is a lack of evidence-based treatment recommendations for late life depression[240]. In clinical practice the preferred strategy is an antidepressant treatment[241] and rarely psychotherapy[242].

Several studies suggest that antidepressant drugs and lithium are neuroprotective[184,243] and can induce neurogenesis in mice and increase BDNF signalling[244,245]. Other studies have found that antidepressants are associated with reduced hippocampal volume[246]. Antidepressant treatment as by citalopram has been found to reduce CSF Aβ levels [247] and delay onset of dementia and increase life span in patients with Down syndrome[248]. In contrast, a recent retrospective cohort study reported that antidepressant treatment might increase the risk for developing AD[249].

Several studies suggested that hippocampal atrophy, severe white matter lesions and severe cognitive impairment are associated with poor response to antidepressant treatment in patients with late-life depression[184].

Antidepressants are generally considered safe. However, several severe side effects have been reported. Short-term use of has been associated with syndrome of inappropriate antidiuretic hormone secretion, occurrence of sinus bradycardia, and increased incidence of torsade de pointes cardiac arrhythmias (citalopram)[250]. Long-term use increases the risk for osteopenia/osteoporosis and falls (for SSRI)[251,252] and cardiovascular toxicity and confusion (for tricyclic antidepressants)[250].

Although all classes of antidepressant treatment are equally efficacious in treating late life depression[253], SSRIs, venlafaxine or mirtazapine are most commonly used[241]. On the other hand use of other antidepressant treatments as duloxetine and vortioxetine can improve working memory and delayed recall in older people with major depressive disorder over 65 years of age[254,255]; vortioxetine having the advantage of improving the executive functioning[255]. Citalopram, otherwise a commonly used antidepressant, does not improve executive functioning associated with major depression disorder in older people over 75 years of age[256].

A randomized double placebo trial on late life depression and cognitive impairment suggested that augmentation of an antidepressant treatment with AChEI can be beneficial[257].

In older people depression is frequently co-occurring with anxiety and sleeping problems and therefore anxiolytic and sedative-hypnotic medication (including benzodiazepines) are often concomitantly prescribed with antidepressant therapy[258].

1.2.7.1 Treatment of depression in Alzheimer's disease

There is evidence that psychosocial interventions are significantly beneficial in preventing[259] and treating depression in MCI and AD [94,121]. Such interventions can be problem adaptation therapy and supportive therapy for cognitively impaired patients[260]. Other interventions such as music and reminiscence therapy, cognitive stimulation, conversation and physical activity may also reduce severity of depressive symptoms in AD [94,121]. However, a randomized intervention study found that early psychosocial interventions in AD such as counselling, education and social support had little effect on patients' well-being and did not delay institutionalization[261].

Although non-pharmacological interventions have been found useful in treating depression in AD, antidepressant treatment remains the first choice therapy in clinical practice.

A Finish registry-based study found that use of antidepressant treatment in community dwelling patients with AD is three times that used in community dwelling individuals without AD (29.4% versus 10.7%)[262]. The evidence is weak for use of antidepressant treatment for depression in AD. Several studies reported benefit of antidepressant treatment[263–267], while more recent studies did not support such benefit[189,268–271]. A Cochrane meta-analysis concluded that there are no benefits from use of antidepressant treatment in people with established AD and depression[189,272]. The most prescribed antidepressants are SSRI and mirtazapine [262,273]. Little is known about use of antidepressant treatment in preclinical stages of AD.

Electroconvulsive therapy is considered efficacious in treatment of major depression in older people. However its effects on depression in AD patients are less well understood. It has been suggested that electroconvulsive therapy can be beneficial in treating major depressive disorder in patients with AD; in most of the cases the associated memory impairment being transitory[274].

Table 3: Depression and the risk for conversion from Mild Cognitive Impairment to Alzheimer's disease or dementia

	Number MCI	Convertors to AD or dementia	Depressed patients (baseline)	Definition depression	Age	Duration follow up (years)	Source	Depression risk factor
Modrego *et al.* 2004 [235]	114	AD:59 (51.7%)	41 (36%)	DSM IV (≥5 symptoms	72.8	3	MC	**Yes (**RR:2.6, 95%CI: 1.8-3.6)
Gabryelewicz *et al.* 2007[275]	105	Dementia:23 (21.9%) AD :19 (18.1%)	Mean MADRS=9.8	MADRS MDD excluded	69.3	3	clinic	**Yes** (higher MADRS baseline scores among convertors)
van der Mussele 2014[150]	193	AD:109	Mean CSDD 14.3	CSDD GDS-30	74.9	3.8	MC	**Yes** (HR: 2.06; 95% CI:1.2–3.4)
Teng *et al.* 2007[276]	51	AD:12 (23.5%)	20 (39%)	dNPI	73.8	2	MC	**Yes** (67% of convertors and 31% non convertors had depression)
Devier *et al.* 2010[277]	148	AD: 39 (26.4%)	Mean HAM-D: 4.7	HAMD-17 MDD excluded	67.1	5.1	MC	**No** (RR: 0.99; p:0.8)
Ramakers *et al* 2009[148]	263	AD:79 (30%) Other dementia 11	Mean HAMD-17: 9.0	HAMD 17	69.9	5.4	MC	**No** (OR 0.62, 95% CI 0.38–1.03)
Vicini Chilovi *et al* .2009[278]	124	AD:23 Other dementia 5	38 (30.7)	DSM IV	71.2	2	MC	**No (**OR:0.10; 95% CI 0.02-0.4)
Gallagher *et al.* 2011[279]	161	AD: 69 (42.8%)	41 (25.5%)	BEVAHE-AD [b]	73.7	2.2	MC	**No**(19% of convertors and 30% non convertors had depression)
Mackin *et al.* 2012[280]	405	Dementia 103 (45.3)	223 (55%) SSD	GDS-15	74.8	3	MC	**No (**βyears:converter = 0.09, p = 0.2)
Chan *et al.* 2010[281]	321	Dementia: 51 (15.9%)	54 (16.8%)	dNPI	77.5	2	PB	**Yes** (OR:2.40 95%CI: 1.05–5.5)
Richard *et al.* 2013 [282]	320	AD: 54 (17%) Other dementia 13	96 (23.1%)	CES-D	77.2	5.1	PB	**Yes (**HR:1.9, 95%CI:1.0-3.6**)**
Artero *et al.* 2008[283]	2879	AD:122 (4.23) Other dementia 67 (2.32)	Depressive symptoms16% MDD:2.4%	CES-D and DSMIV	74.6	4	PB	**Yes** (OR = 2.0, 95% CI 1.1 -3.6)

MC: memory clinic, PB: population based, MDD major depression disorder, SSD: subsyndromal depression, NS not specified, RR: risk ratio, OR: odds ratios, HR hazard ratio, p: p-value, DSM: Diagnostic and Statistical Manual of Mental Disorders GDS: geriatric depression scale, CSDD: Cornell Scale for Depression in Dementia, MADRS: Montgomery Åsberg depression rating scale, CES-D Center for epidemiologic studies depression scale

Table 4: Associations between CSF biomarkers and depression

Reference	CSF	Population	Age	Depression measures	Depression associated with	Design
Skogseth *et al.* 2008 [201]	t-tau, p-tau, $A\beta_{1-42}$	AD:32	74.0	MADRS	No associations with CSF t-tau, p-tau, $A\beta_{1-42}$ (**AD patients**)	Clinic, cross sectioal
Kramberger *et al.* 2012[200]	t-tau, p-tau, $A\beta_{1-42}$	AD:90 SCI:92	67.6	CSDD	Lower CSF t-tau **(AD patients)** Lower CSF t-tau and p-tau **(SCI patients)**	Clinic, cross sectioal
Auning *et al.* 2015[284]	t-tau, p-tau, $A\beta_{1-42}$	SCI:22 MCI:38	60.0	GDS-15items	No associations with CSF t-tau, p-tau, $A\beta_{1-42}$ **(SCI and MCI patients)**	Clinic, cross sectional
Reis *et al.* 2012[199]	t-tau, p-tau, $A\beta_{1-42}$	Cognitively normal: 28	71	DSM IV	No associations with CSF t-tau, p-tau, $A\beta_{1-42}$ (**cognitively normal subjects**)	Clinic, cross sectional
Gudmundsson *et al.* 2007 [198]	t-tau, $A\beta_{1-42}$, CSF/serum albumin ratio	Cognitively normal: 84	72.6 (only women)	DSM III-R	Higher CSF $A\beta_{1-42}$ levels Higher CSF /serum albumin ratios **(cognitively normal subjects)**	Population based, cross sectional
Pomara *et al.* 2011[197]	t-tau, p-tau, $A\beta_{1-42}$, F2-isoprostane	Cognitively normal: 47	67.3	DSM IV	Lower CSF $A\beta_{1-42}$ levels Higher CSF F2-isoprostane No associations with CSF t-tau, p-tau **(cognitively normal subjects)**	Volunteers, cross sectional
Diniz *et al.* 2014[215]	t-tau, p-tau, $A\beta_{1-42}$, BDNF	MCI :10 Cognitively normal: 40	69.7	DSM IV-TR	Lower CSF BDNF levels No associations with CSF t-tau, p-tau, $A\beta_{1-42}$ (**MCI with depression versus cognitively normal with and without depression**)	Clinic, cross sectional
Vermeiren *et al.* 2013 [285]	aspartate, glutamate, glutamine, glycine, taurine, proline	AD:202	80.4	CSDD	Lower CSF taurine levels No associations with other CSF amino acids (**AD patients**)	Clinic, cross sectional

AD: Alzheimer's disease, SCI: Subjective cognitive impairment, MCI: mild cognitive impairment, t-tau: total tau, p:tau : phosphorylated tau, $A\beta_{1-42}$: Amyloid beta, DSM: Diagnostic and Statistical Manual of Mental Disorders GDS: geriatric depression scale, CSDD: Cornell Scale for Depression in Dementia, MADRS: Montgomery Åsberg depression rating scale, MDD major depressive disorder.

Table 5: Neuroimaging of depression in AD

Reference	Imaging modalities	Population	Age	Depression measures	Depression associated with	Design
Lebedeva *et al.* 2014[286]	MRI cortical thickness	AD:148 (ADNI cohort) AD:41 (KI cohort)	76.0 (ADNI cohort) 66.0 (KI cohort)	GDS (ADNI cohort) CSDD (KI cohort)	Cortical thinning in temporal and parietal regions Negative correlation between cortical thickness and CSF total tau (**AD patients**)	Clinic, Cross sectional
Lebedev *et al.* 2014 [205]	MRI cortical thickness	AD:30	76.5	MADRS	Cortical thinning in prefrontal and temporal areas. **(AD patients)**	Clinic, cross sectional
Zahodne *et al.* 2013[203]	MRI cortical thickness	MCI: 334 (ADNI cohort)	74.9	NPI-Q	Reduced entorhinal thickness at baseline Accelerated atrophy in anterior cingulate cortex at follow-up (**MCI patients**)	Clinic, Prospective 30.5 months follow up
Hu *et al.* 2015[287]	MRI: GM volumes, cortical thickness	MCI: 202 AD: 85 (ADNI cohort)	74.8	NPI-Q	Decreased gray matter volumes in left middle frontal cortex (**AD and MCI patients**)	Clinic, Cross sectional
Auning *et al.* 2015[284]	MRI: GM volumes, cortical thickness DTI, FDG-PET	SCI: 22 MCI: 38	60.0	GDS	No associations with pathological imaging (**SCI and MCI patients)**	Clinic, cross sectional
Enache *et al.* 2015 [288]	MRI visual assessment, hippocampal volume	SCI:139 MCI:130 AD:99	64.6	CSDD	Smaller right and left hippocampi **(SCI patients)** Less atrophic right and medial temporal lobe **(AD patients)**	Clinic, cross sectional
Lee *et al.* 2015[289]	MRI: WMH volumes	AD: 93	76.1	DSM IV GDS	Frontal WMH (**AD patients**)	Clinic and community based, cross sectional

Soennesyn *et al.* 2012[290]	MRI: WMH volumes	AD:59	77	MADRS	Higher volumes of total and frontal deep WMH (**AD patients**)	Clinic, prospective
Tsai *et al.* 2013[291]	MRI spectroscopy	AD: 26	75	GDS	Higher choline/creatine ratio in the left dorsolateral prefrontal cortex Higher myo-inositol/creatine ratio in the left and right cingulate gyri (**AD patients**)	Clinic, cross sectional
Chung *et al.* 2015[292]	^{18}F-florbetapir-PET	MCI+Lifetime Depression: 39 (ADNI cohort)	70.5	GDS, NPI	Increased Aβ deposition bilateral frontal cortex (**amnestic MCI patients with lifetime depression**)	Clinic, cross sectional
Donovan *et al.* 2015 [195]	MRI: GM volumes FDG-PET ^{11}C PiB-PET	Healthy controls 248	74.0	GDS Depressive symptoms	Lower hippocampal volume No associations with Aβ deposition **(healthy controls with depressive symptoms)**	Community based, cross sectional
Madsen *et al.* 2012[194]	^{11}C PiB-PET	LLD:28 (moderate to severe)	61.3	HAM-D<8, GDS<5 no current episode	No associations with Aβ deposition (**LLD patients, no current episode**)	Clinical, cross sectional

AD: Alzheimer's disease, MCI: mild cognitive impairment, LLD: late life depression, ADNI : cohort from Alzheimer's Disease Neuroimaging Initiative; KI: cohort from Karolinska University Hospital cohort; GDS: geriatric depression scale, CSDD: Cornell Scale for Depression in Dementia, HAM-D: Hamilton rating scale for depression, GM volumes: gray matter, DTI: Diffusion tensor imaging , WMH: white matter hyperintensities, WML:white matter lesions, PET: positron emission tomography, FDG-PET: fluoro-deoxy- glucose positron emission tomography, PiB: [11C] Pittsburgh Compound B, NPI Neuropsychiatric Inventory, NPI-d Neuropsychiatric Inventory-depression question , Aβ: amyloid beta

2 AIMS

General aims:

To explore the associations between depressive symptoms and biomarkers of amyloid deposition and neuronal injury in older people with and without AD.

To explore the associations between antidepressant treatment in pre-dementia stages and mortality risk after a dementia diagnosis.

To explore the associations between CAIDE Dementia Risk Score and biomarkers of amyloid deposition, neuronal injury and small vessel disease. To evaluate the role of CAIDE Dementia Risk Score to predict dementia in a memory clinic population.

Specific aims:

Study I:

- To explore the associations between depressive symptoms and CSF biomarkers of amyloid deposition, tau pathology in older people with and without AD

Study II:

- To explore the associations between depressive symptoms and medial temporal lobe atrophy and hippocampus atrophy in older people with and without AD

Study III:

- To describe the use of antidepressant treatment in patients with dementia
- To explore the association between mortality risk and use of antidepressants three years before diagnosis of dementia

Study IV:

- To explore the associations between CAIDE Dementia Risk score and biomarkers of amyloid deposition, neuronal injury, small vessel pathology
- To evaluate capacity of CAIDE Demntia Risk Score to predict dementia in a memory clinic cohort

Supplementary analysis:

- To explore the risk of developing dementia in patients with depressive symptoms and in patients on antidepressant treatment in a memory clinic cohort

3 MATERIAL AND METHODS

Data used for this thesis is derived from 2 projects: a large memory clinic database from Karolinska University Hospital Huddinge and Swedish Dementia Registry (SveDem).

3.1 MEMORY CLINIC KAROLINSKA UNIVERSITY HOSPITAL HUDDINGE SWEDEN

Patients at risk to develop dementia are referred from general practitioners and other specialties to the Memory Clinic Karolinska University Hospital Huddinge. Patients younger than 65 years of age are referred from the whole Stockholm's area. Approximately 550 new patients are seen in the clinic every year with a total number of approximately 3500 follow up visits per year.

Our database includes a total of 1760 patients: 1588 new patients referred consecutively between 2007-2010 and additional 172 patients referred between 2001-2004, 2011-2012 and from 2 imaging studies.

3.1.1 Study population

3.1.1.1 Inclusion and exclusion criteria

The base population for study I consisted of 1,154 outpatients referred to the Memory Clinic between 2007 and 2009. For study II, 57 patients from another imaging study referred between 2001 and 2004 were added. New data had been collected and the base population for study IV consisted 1,703 outpatients referred between 2007-2012. Figure 6 presents a flow chart of the whole cohort included and excluded in each study.

Inclusion and exclusion criteria for study I, II and IV are described in Table 6.

Table 6: Inclusion and exclusion criteria for studies I, II and IV.

	Inclusion criteria	**Exclusion criteria**
Study I	1. Age 60 years or older 2. Complete data on CSDD 3. CSF biomarkers: $A\beta_{1-42}$, t-tau, p-tau_{181} 4. Diagnosis of AD and SCI	1. Diagnosis of MCI or other dementia 2. Disease with expected reduced survival time
Study II	1. Age 55 years or older 2. Complete data on CSDD and use of antidepressant treatment (yes/no) 3. MRI or CT available coronar section	1. Diagnosis of other dementia 2. Disease with expected reduced survival time 3. Psychiatric disorders or brain injuries significantly affecting

	4. Diagnosis of AD, MCI and SCI	cognitive performance
Study IV and Supplementary analysis	1. Age 40 years or older 2. Complete data on CAIDE Dementia Risk Score 3. CSF biomarkers: $A\beta_{1-42}$, t-tau, p-tau_{181} 4. Diagnosis of AD, MCI and SCI	1. Dementia 2. Development of dementia within one year from baseline 3. Medical condition affecting CSF and MRI assessment (multiple sclerosis, large strokes, hydrocephalus, brain tumors)

SCI: subjective cognitive impairment, MCI: Mild Cognitive impairment, AD: Alzheimer's disease, CSDD: Cornell Scale for Depression in Dementia, CSF: Cerebrospinal Fluid, MRI magnetic resonance imaging

3.1.1.2 Follow up (Study IV)

SCI and MCI patients with high risk for cognitive decline as judged on multidisciplinary diagnostic rounds are invited for follow-up visits after the initial assessment. The planned follow up is according to the protocol at the Memory Clinic.

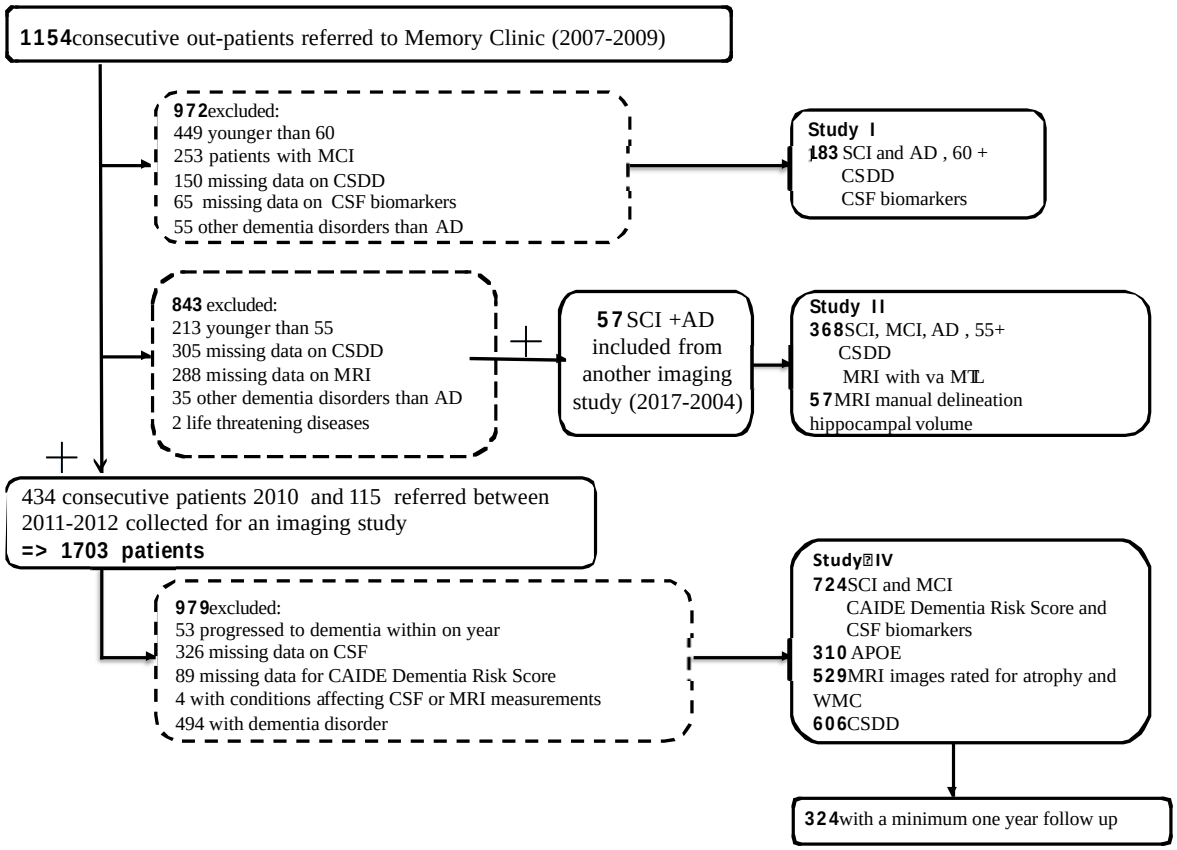

Figure 6: Flow chart presenting the memory clinic sample included and excluded in Studies I, II, IV. SCI: subjective cognitive impairment, MCI: Mild Cognitive impairment, AD: Alzheimer's disease, CSDD: Cornell Scale for Depression in Dementia, WMC: white matter changes, CSF: Cerebrospinal Fluid, MRI magnetic resonance imaging,

In study IV, follow up data were collected in March 2015. Altogether, 324 (44.8%) patients out of 724 were followed-up for at least one year (mean ± SD: 2.9 ± 11.6 years). At the end of the follow up, 100 (30.9%) patients progressed to dementia (78 (24.1%) patients progressed to AD and 22 (6.8%) patients progressed to other dementia disorders). 110 out of the 324 patients had SCI at baseline and at the end of the follow up 72 (65.5%) remained as SCI, 24 (21.8%) progressed to MCI, 14 (12.7%) progressed to dementia disorders (10 patients with AD and 4 patients with other dementia disorders). 214 out of the 324 patients had MCI at baseline and at the end of the follow up 15 (7.0%) converted to SCI, 113 (52.8%) remained as MCI, 86 (40.2%) progressed to dementia disorders (68 patients with AD and 18 patients with other dementia).

3.1.2 Assessment program

Participants in studies I, II and IV underwent a standard protocol that included:

1. General Demographic information (age, gender, mother language, occupation and socioeconomic status)
2. Complete medical examination including:
    - Interview performed by a physician with the patient and informant
    - Neurological examination
    - Vascular risk profile
    - Information on previous depression and current use of antidepressants
    - Depressive symptoms measured with severity scales: CSDD or GDS
    - Functional status by proxy (Informant Questionnaire on Cognitive Decline in the Elderly-IQCODE)[47 293]
    - Neuropsychological tests
    - Speech pathologist assessment*
    - Routine blood chemistry (Thyroid hormones, homocysteine, vitamin B12)
    - APOE genotype
    - CSF (Aβ 42_{1-42}, t-tau, p-tau_{181}) values
    - EEG*
    - MRI: (visual assessment of brain atrophy)
    - FDG-PET*
    - Amyloid-PET*
    - DaT SCAN*

*Performed for particular clinical indication

3.1.2.1 Diagnostic criteria for Alzheimer's disease (AD), mild cognitive impairment (MCI) and subjective cognitive impairment (SCI)

Diagnoses of AD, MCI and SCI were established after a consensus meeting with specialists in neurology, geriatric medicine and psychiatry, nurses, neuropsychologists and speech therapist taking into account all available information.

Patients were diagnosed with dementia disorders (AD and other types) according to the International Classification of Diseases –Tenth (ICD-10).

Patients were diagnosed as MCI according to the revised International Working Group criteria[56]. Patients were diagnosed as SCI if neither dementia disorder nor MCI criteria were fulfilled. In patients classified as SCI, neuropsychological tests did not show evidence of cognitive impairment although the patients and their informant reported some degree of impairment in the patients' cognitive performance compared to the premorbid level.

3.1.2.2 Assessments of cognitive function

1. Global cognition (Mini Mental State examination -MMSE[294]- and Full Scale IQ - FSIQ*)
2. Language (Similarities*, Information* and Vocabulary*)
3. Perceptual motor function (Rey complex figure copying[295], Block design*, Matrix*)
4. Short-term memory (Digit span*) and Episodic memory (Rey auditory verbal learning test learning and retention after 30 minutes, Rey complex figure immediate retention[295])
5. Executive function and complex attention (Trail making test A and B[295] and Digit symbol*)

* Wechsler Adult Intelligence Scale revised version (WAIS -R)[296] for patients referred in 2007, and Wechsler Adult Intelligence Scale III version (WAIS-III)[297] for patients referred between 2008-2010.

3.1.2.3 Depressive symptoms

Depressive symptoms were assessed using Cornell Scale of Depression in Dementia (CSDD), which has good psychometric properties in both individuals with and without dementia[216 217]. The CSDD was completed by a licensed geriatrician or psychiatrist, or a trained geriatric nurse specialist.

Data on antidepressant treatment at the clinic assessment was collected retrospectively from patients' records. History of depression is self reported or documented by a physician and coded as depression, using ICD-10 codes for depression.

We defined depressive symptoms using recommended cut-offs:

- CSDD ≥ 7 [218] –study I
- CSDD ≥ 8 [216]- study II and supplementary analysis (when calculating associations between depression and risk to develop dementia)
- CSDD ≥ 8 or antidepressant therapy [298]- study II. It have been suggested that information on use of antidepressant treatment can improve the classification accuracy [298].

3.1.2.4 Assessment of CAIDE Dementia Risk Score

For study IV we used a modified version of the CAIDE Dementia Risk Score relatively similar with the version used in the validation study by Exalto et al[25]. Variables "cholesterol levels and systolic blood pressure" were replaced with diagnosis of hyperlipidaemia or hypertension. Physical activity was excluded due to lack of systematic recoded data. The total maximum points for CAIDE Dementia Risk Score version without APOE was 14 points and version with APOE was17 points[25] (Annex). CAIDE Dementia Risk Score was scored retrospectively by an experienced research clinician based on available data, blind to CSF and MRI results.

3.1.2.5 Cerebrospial fluid (CSF) analyses

CSF was obtained by lumbar puncture. CSF $A\beta_{1-42}$, t-tau and p-tau_{181} were measured using procedures previously described for $A\beta_{1-42}$[299] and for t-tau and p-tau_{181}[300].

3.1.2.6 APOE genotype

APOE genotype was analyzed from blood leucocytes using polymerase chain reaction and HhaI digestion[301].

3.1.2.7 Image acquisition

The neuroradiologic investigations used for these studies were performed as part of the dementia assessment. Magnetic resonance imaging (MRI) and computer tomography (CT) scans are performed at the Department of Radiology, Karolinska University Hospital or in other different radiology departments and hospitals in Stockholm and neighbouring counties,

with different equipment and protocols. All images were collected in a common electronic database at the Department of Radiology, Karolinska University Hospital-Huddinge.

- Visual assessment of the medial temporal lobe (vaMTL)(fig 1) (study II and Study IV)

Medial temporal lobe was visually assessed on T1 weighted oblique coronal sections of MRI and CT images, since a good intra-observer agreement had been shown between multi-detector row CT and 1.5 Tesla MRI for vaMTL on the left and right hemisphere[302]. Medial temporal lobe was rated using Scheltens scale[77], which is based on a visual estimation of volume of the medial temporal lobe. The visual assessment includes hippocampus, dentate gyrus, subiculum, parahippocampal gyrus, entorhinal cortex and surrounding CSF spaces such as the temporal horns and choroid fissure. This is a 5-point scale, which ranges from 0 (no atrophy) to 4 (end stage) and it is applied to the right and left hemispheres separately.

In study II medial temporal lobe was visually assessed on 295 (80.16%) MRI and 73 (19.84%) CT scans. Medial temporal lobe volume is age dependent; we considered as normal vaMTL scores 0-1 in persons less than 70 years, vaMTL ≤ 2 between 70-80 and vaMTL ≤ 3 over the age of 80 according to the findings from our group[303]. Medial temporal lobe atrophy (MTA) was defined as vaMTL scores above the age reference values.

In study IV 529 MRI scans were rated for medial temporal lobe atrophy, parietal atrophy, global cortical atrophy- frontal subscale and white matter changes. No cut off points on the Scheltens scale were used in study IV. MTA was obtained by calculating the average score on Scheltens scale [304], and mean scores 2.5, 3 and 4 were grouped together.

- Manual tracing : hippocampal volume (study II)

Manual tracing of hippocampal volumes was performed on MRI scans following the protocol proposed by Malykhin et al.[305]. Manual tracing of hippocampal volume has a high reliability and is considered the gold standard method for measuring hippocampal volume. The total intracranial volume (TICV) was obtained using a stereologic point-counting technique, consisting of normal tracing of the TICV on every forth section, following the landmarks proposed by Eritaia et al[306] image with the manual tracing technique. Right and left hippocampal volumes (cm3) were separately delineated and normalized by TICV using Jack CR Jr et al[307] method:

Volume (adjusted) = Volume (observed) – β [slope of the regression line of hippocampal volume regressed on TICV]*(TICV the subject TICV – TICV sample mean)

In study II hippocampus was manually delineated on 57 MRI scans.

- Visual assessment of parietal lobe atrophy (study IV)

Parietal atrophy (PA) was visually assessed by combining T1 weighted axial, T1 weighted coronal and axial FLAIR sequences using Koedam score[308]. Koedam score is a 4-point scale, which ranges from 0 (no atrophy) to 3 (severe atrophy).

- Visual assessment of frontal atrophy (study IV)

Frontal atrophy was visually assessed on a FLAIR sequence using a subscale of global cortical atrophy –frontal region (GCA-F)[309]. GCA-F is a 4-point scale, which ranges from 0 (no cortical atrophy) to 3 (severe atrophy).

- Visual assessment of white matter changes (WMC) (study IV)

WMC were visually assessed on transverse FLAIR images using the Fazekas scale[310]. The scale provides an overall impression of the presence of WMC in cerebrum. Fazekas scale is a 4-point scale, which ranges from 0 (no white mater hyperintensity changes) to 3 (large confluent white matter hyperintensity changes).

Experienced raters (Lena Cavallin and Bram B. Zandbelt) performed the manual tracing of hippocampal volume and visual assessment of vaMTL, parietal, frontal atrophy and WMC. Both raters were blinded to clinical diagnosis, CSDD scores, antidepressant therapy and CAIDE Dementia Risk Score. Intrarater reliability was assessed for vaMTL, was 0.81 on right side and 0.78 on left side[76] and intraclass correlation coefficient for manual hippocampus tracing was 0.91[311].

3.2 SWEDISH DEMENTIA REGISTRY AND SWEDISH PRESCRIBED DRUG REGISTRY

In study III the cohort included was based on data from two national registries: Swedish Dementia Registry (SveDem) and the Swedish Prescribed Drug Register. The databases were merged using the unique social security number assigned to each Swedish citizen. Information on deaths occurring within the cohort during the study period was obtained through record linkage with the national patient registry. The end of follow up for the outcome was the date of death or 31 October 2013.

SveDem, Swedish Dementia Registry was established in May 2007 with the aim to ensure the quality of the diagnostic workup, treatment and care of patients with dementia disorders

in Sweden [312]. Age, gender, demographic data, Body Mass Index, MMSE scores, diagnostic procedures, type of dementia disease and treatment are recorded at the time of dementia diagnosis in primary or specialist care. SveDem covers almost 60% of primary cares and almost 90% of memory clinics across Sweden[312]. Information on death is collected from the national population registry. Diagnoses of dementia diseases are coded as AD, mixed dementia (MixedD- vascular and Alzheimer), vascular dementia (VaD), frontotemporal lobe dementia, Dementia with Lewy bodies, Parkinson's disease dementia, unspecified dementia (Unspecified) and other dementia (Others). Although the diagnoses of dementia disorders registered in SweDem are not neuropathologically validated, in a random sample of patients registered in memory clinics the diagnoses were in good agreement with medical records[313].

The Swedish Prescribed Drug Register was established in 2005 and contains information on all drugs prescribed in ambulatory care and dispensed (i.e. drugs were collected by the patient at the pharmacy) at Swedish pharmacies to the entire Swedish population. It is administrated by Centre for Epidemiology at the National Board of Heath and Welfare in Sweden. The register contains the following data: personal identification number, age, gender, address, substance, brand name, formulation and package; dispensed amount, dosage, expenditure and reimbursement, date of prescribing and dispensing, the practice (primary Health care center or hospital clinic) that has issued the prescription and the prescriber's profession[314]. All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system[314].

3.2.1 Subjects

Data from The Swedish Prescribed Drug Register was available between 1st July 2005 and 31st August 2013. We used information on the total number of medication and all antidepressants dispensed at four specific time points: at the time of a diagnosis of dementia disorder and inclusion in SveDem, at the first, second and third year prior to the date of diagnosis of dementia and inclusion in SveDem.

We used the following ATC codes for antidepressant and other drug classes approved in Sweden in 2014 (see http://www.whocc.no/atc_ddd_index): N05A Antipsychotics, N05B Anxiolytics, N05C Hypnotics and sedatives, N06A Antidepressants (N06A A Non-selective monoamine reuptake inhibitors, N06A B Selective serotonin reuptake inhibitor, N06A X Other antidepressants), N06D A Cholinesterase inhibitors, N06D X01 Memantine: N-methyl D-aspartate (NMDA) antagonist, Cardiovascular medication (B01

Antithrombotic agents, C01 Cardiac therapy, C02 Antihypertensive, C03 diuretics, C07 Beta blocking agents, C08 Calcium channel blockers, C08 agents acting on the renin-angiotensin system , C10 Lipid modifying agents).

The study sample includes patients referred to memory clinics and registered in SveDem with a diagnosis of dementia disorders during 1st May 2007 – 31st October 2013 (Figure 7). Patients diagnosed in primary care settings were excluded due to inconsistency in diagnostic procedures for dementia disorders as compared to specialist units and due to a lower coverage of these units in the registry. Out of 21,991 patients in SveDem with a complete data set at diagnosis of dementia disease, 1941 patients registered in SveDem in 2007 were excluded due to missing or incomplete data on antidepressant use 3 years prior to dementia diagnosis, thus 20,050 patients were included.

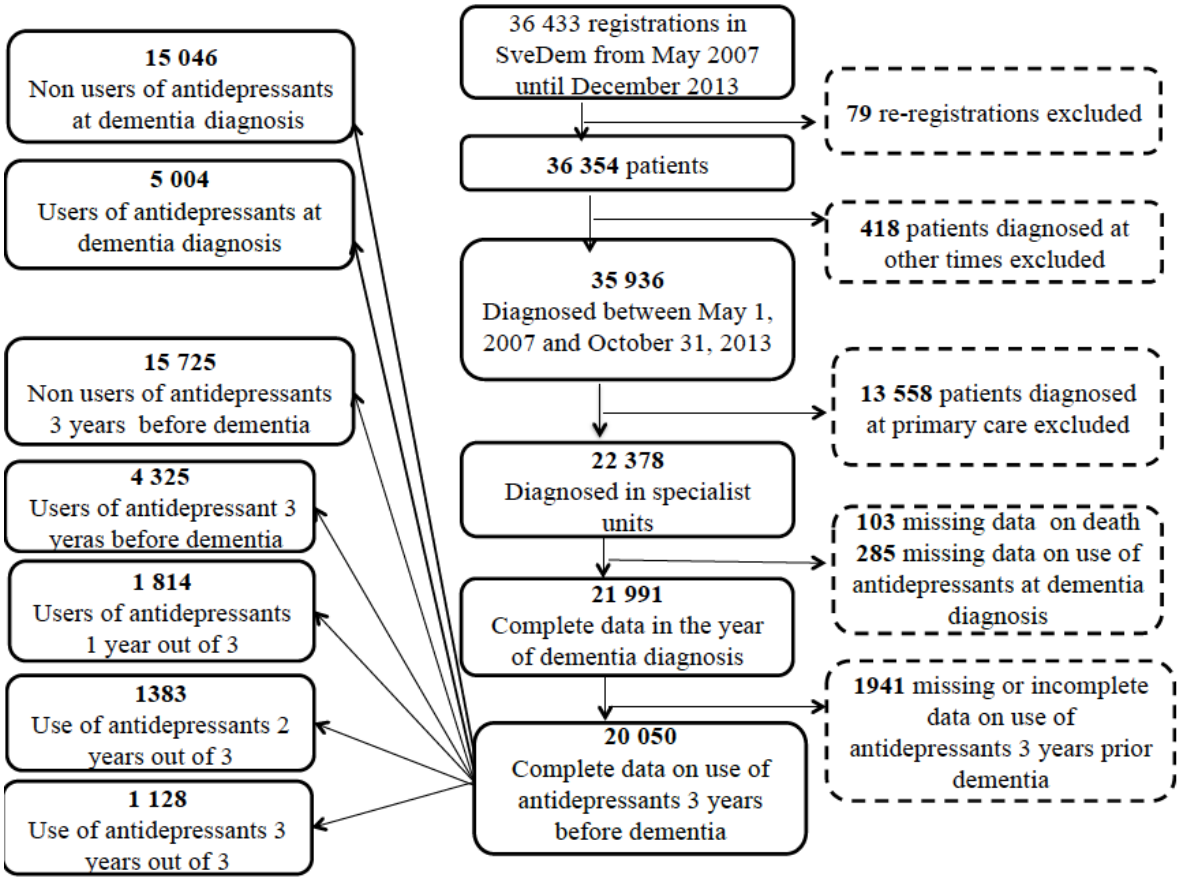

Figure 7: Flowchart with study population in study III

3.3 STATISTICAL METHODS

Statistical analyses were performed with Statistical Package for the Social Science (SPSS Inc., Chicago, IL, USA) software versions 20.0 and 22.0 for Windows and Stata software version 13 (diagt command was used in study IV). The level of statistical significance was set

to $p<0.05$ in all analyses. Several statistical analyses were used throughout all 4 studies; Table 4 summarizes the outcome variables and the determinants for each study.

3.3.1 Specific analyses for each study

Study I

Patients with SCI and AD were divided into 4 groups based on presence or absence of depressive symptoms. Between-group comparisons were made using parametric (Student-t test) and non-parametric (chi-square tests, Mann-Whitney) tests as appropriate. Simple logistic regression was used to compare the CSF-$A\beta_{1-42}$, t-tau and p-tau_{181} values between patients with and without depressive symptoms in each diagnostic group.

To explore the association between CSF-$A\beta_{1-42}$, t-tau and p-tau_{181} values and CSDD total scores, regression models were built using ordered logistic regression, adjusting for cofounders. Model 1 adjusting for age and gender and model 2 adjusting for age, gender and MMSE score.

Study II

Patients with SCI, MCI and AD were divided in 6 groups based on presence and absence of depressive symptoms. Between-group comparisons were made using parametric (Student-t test) and non-parametric (chi-square tests, Mann-Whitney, Kruskal Wallis) tests as appropriate in each diagnostic group.

To explore the associations between MTA and depressive symptoms, regression models were built using simple logistic regression (MTA yes/no) or ordered logistic regression (taking into account the scale for visual assessment of the medial temporal lobe). Odds ratios (OR) and 95% confidence intervals (95%CI) were estimated between MTA or vaMTL and depressive symptoms. All analyses were adjusted for gender, MMSE and years of education.

To explore the associations between hippocampal volumes manually delineated and depressive symptoms, regression models were built using generalized linear model (depressive symptoms yes/no) and linear regression (taking into account the whole CSDD) scale. Generalized linear model estimated mean and mean differences between hippocampal volume in patients with and without depressive symptoms. Linear regression estimated standardized beta-coefficients and p-values between hippocampal volume and CSDD. All models were adjusted for age, gender, MMSE and years of education.

Study III

Cross sectional data on dispensed antidepressants (yes/no) were available at the third, the second and the first year prior to a diagnosis of dementia (e.g. a patient received a diagnosis of dementia on 11/11/2011, we have data on use of antidepressant (yes/no) on that day, 11/11/2011 and on the same day in the first 11.11.2010, second 11.11.2009 and third 11.11.2008 year prior to a diagnosis of dementia). Summing up our cross-sectional data we obtained a dichotomous variable of users and non-users of antidepressants at any time during the three-year period prior to a diagnosis of dementia. In addition we classified patients as users of antidepressants one, two, or three years out of 3.

The study cohort was divided in 2 groups: users of antidepressants and non-users of antidepressants at the time of diagnosis of dementia disorder, and during the 3 years prior to a diagnosis of dementia. Between-group comparisons were made using parametric (Student-t test) and non-parametric (chi-square tests, Mann-Whitney, binary logistic regression) tests as appropriate in each diagnostic group. Means, standard deviations (SD), total numbers and percentages were reported. Person-years (PY) at risk were calculated from dementia diagnosis to date of death or end of follow-up, on October 31st, 2013.

To explore the associations between use of antidepressants and time to death, regression models were built using Cox regression. Hazard ratios (HR) of death and 95%CI were estimated. The analysis was adjusted for average age, average number of medication taken during the 3 years prior to a diagnosis of dementia, gender, MMSE at time of diagnosis of dementia and living conditions at time of diagnosis of dementia (home or nursing home). The analyses performed in the whole cohort included additionally "type of dementia" as a categorical covariate in each model.

Study IV

CAIDE Dementia Risk Score was categorized into three groups of relatively similar sample size: 0-5 points (lower risk, n=301 patients), 6-7 points (intermediate risk, n=214) and 8-14 points (higher risk, n=209) for the version without APOE; and 0-6 points (lower risk, n=81 patients), 7-8 points (intermediate risk, n=98) and 9-17 points (higher risk, n=131) for the version with APOE. The lower risk category was used as reference in all analyses.

Based on recent studies suggesting that combinations of CSF biomarkers may be more accurate indicators of Alzheimer's disease than each marker separately[315], the $A\beta_{1-42}$/t-tau and

$A\beta_{1-42}$/p-tau_{181} ratios were calculated. Zero-skewness log-transformation was applied to $A\beta_{1-42}$, t-tau, p-tau_{181}, and $A\beta_{1-42}$/t-tau and $A\beta_{1-42}$/p-tau_{181} ratios.

Comparisons between included and excluded patients were made using parametric (Student-t test) and non-parametric (chi-square tests, Mann-Whitney, Kruskal Wallis) tests as appropriate.

To explore the associations between CSF $A\beta_{1-42}$, t-tau and p-tau_{181} values and CAIDE Dementia Risk Score regression models were built using linear regression. Standardized beta-coefficients and p-values were estimated.

To explore associations between visual assessment scales on MRI (MTA, parietal atrophy, frontal atrophy and WMC) and CAIDE Dementia Risk Score, regression models were built using ordinal regression. OR and 95%CI were estimated. Stratified analyses were conducted according to diagnosis (SCI or MCI).

We evaluated the performance of CAIDE Dementia Risk Score (version with and without APOE) to predict dementia in patients with available follow up (n=324). Area under the receiver operating characteristics curve (AUC) and 95% CI, sensitivity, specificity, likelihood ratios for positive and negative tests were calculated. We conducted additional analyses to account for missing follow up data: 1) assuming that patients without planned follow-up did not develop dementia; and 2) assuming that MCI patients without planned follow-up developed dementia.

Supplementary results

We used clinical follow up data from study IV to explore the associations between depressive symptoms and risk to develop dementia. Additionally we explored the associations between use of antidepressant treatment and risk to develop dementia. At baseline 606 patients had available data on CSDD and all patients had data on use of antidepressants. The study cohort was divided into: patients with and without depressive symptoms. Additionally the sample was divided into: users and non-users of antidepressants.

Between-group comparisons were made using parametric (Student-t test) and non-parametric (chi-square tests, Mann-Whitney) tests as appropriate in each diagnostic group. Means, SD, total numbers and percentages were reported.

To explore the associations between depressive symptoms and time to end of the follow up, regression models were built using Cox regression. HR and 95%CI were estimated. Similarly cox regression models were built to assess the associations between use of

antidepressant treatment and time to end of the follow up. Crude and adjusted models for age, gender, education, CSF $A\beta_{1-42}$, t-tau and p-tau_{181} were made. We present the results from the adjusted analysis.

Table 7: Statistical analyses used throughout the four studies

Study	Aims	Outcome	Main covariates	Other covariates	Main statistical procedure
Study I	Associations: depression and CSF biomarkers	Constinuous variable CSF $A\beta_{1-42}$ CSF t-tau CSF p-tau_{181}	Depressive symptoms (yes /no)	M1: age, gender M2 age, gender, MMSE	Ordinal regression
Study II	Associations: depression and MTA	MTA yes /no vaMTL(scale0-5)	Depressive symptoms (yes/no) CSDD score	Gender, MMSE years of education	Logistic regression Ordinal regression
	Associations: depression and hippocampal volume	Hippocampal volume		Age, gender, MMSE years of education	Generalized linear model Linear regression
Study III	Associations: use of antidepressant treatment and mortality risk	Number of days until death or end of follow up	Antidepressants (yes/no) Antidepressants 3 years before dementia (3 groups)	Age, gender, total number of medication, MMSE, living conditions, use of antipsychotics	Survival analysis (Cox regression)
Study IV	Associations: CAIDE Demntia Risk Score and CSF biomarkers, MTA, WMC, PA, GFA, CAIDE LR+LR-	Continuous variable: CSF Abtea42, T-tau, p-tau_{181}	CAIDE Dementia Risk Score (3 groups)	-	Linear regression Ordinal regression Receiver operating characteristic (ROC)
Supplementary	Associations: Depressive symptoms/ antidepressant treatment and risk to develop dementia	Number of days until conversion to dementia or end of follow up	Depressive symptoms (yes/no) Antidepressants (yes/no)	Age, gender, education, CSF Aβ, t-tau and p-tau_{181}	Survival analysis (Cox regression)

CSDD:Cornell Scale for Depression in Dementia, M1: model 1, M2: model 2, vaMTL: visual assessment of the medial temporal lobe, APOE: apolipoprotein E genotype, $A\beta_{1-42}$: amyloid β_{1-42}, t-tau: total tau, p-tau_{181}: phosphorylated tau at threonine 181, MTA: medial temporal lobe atrophy (mean MTA scores of both hemispheres) , GCA-F : global cortical atrophy frontal subscale, WMC: white matter changes measured with Fazekas scale for white matter changes, CAIDE: Cardiovascular Risk Factors, Aging and Dementia Study, LR+: likelihood ratio for positive test, LR-: likelihood ratio for negative test

4 ETHICAL CONSIDERATIONS

Study I, II and IV were approved by the Ethical Committee at Karolinska University Hospital in Huddinge and by the Regional Ethical Review Board in Stockholm (DNR: 2010/1817-31/2, 2011/1987 31/4). All patients provided written consent to use clinical information for research.

Study III was approved by the regional ethical review board in Stockholm (Dnr: 2013/147-31/2). An additional amendment facilitating the use of both registry and the data related to antidepressant treatment was approved (Dnr: 2014/2029-3 2). The data were anonymized before statistical analysis. Patients and their relatives were informed orally and in writing about SveDem and could decline participation.

5 RESULTS

5.1 BIOMARKERS OF AMYLOID DEPOSITION, NEURONAL INJURY IN DEPRESSION IN ALZHEIMER'S DISEASE

5.1.1 Cerebrospinal fluid biomarkers

We found no significant associations between CSDD scores and CSF-Aβ_{1-42} in our memory clinic cohort of 183 patients with SCI (n=92) and AD (n=91) (Figure 8).

In AD group we found that patients with depressive symptoms have lower CSF t-tau levels (p=0.03) than those without depressive symptoms. No significant differences in CSF p-tau$_{181}$ or Aβ_{1-42} levels were found between the groups of AD patients with and without depressive symptoms. In the SCI group depressive symptoms were associated with lower CSF t-tau (p=0.02) and p-tau$_{181}$ (p=0.04) levels; No associations were found with levels of CSF Aβ_{1-42}.

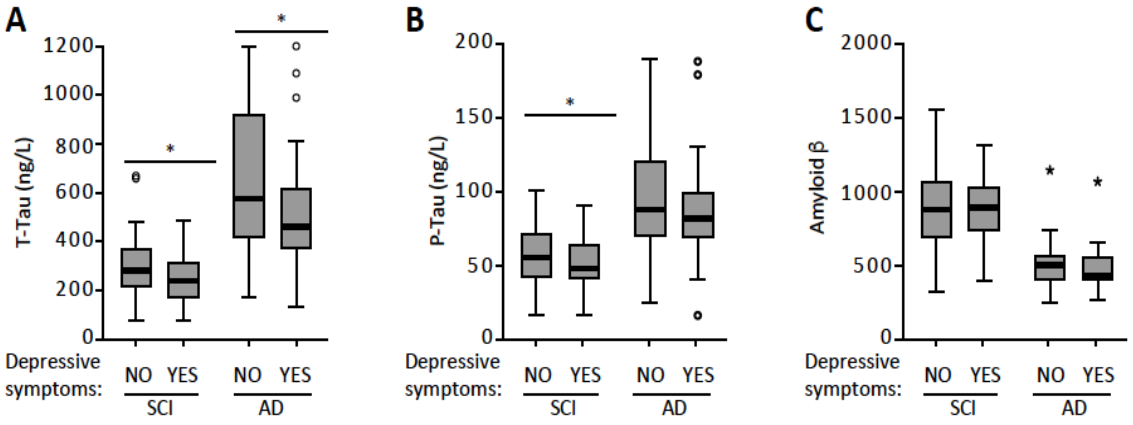

Figure 8. Associations between levels of CSF-Aβ_{1-42} (A) and CSF t-tau (B) and depressive symptoms in patients with subjective cognitive impairment and Alzheimer's disease. SCI: subjective cognitive impairment, AD: Alzheimer's disease.

5.1.2 Imaging biomarkers

The studied sample included 368 patients with SCI (n=139), MCI (n= 130) and AD (n=99). We found that in patients with AD, right MTA was associated with decreased OR of depressive symptoms (adjusted OR: 0.39 95%CI: 0.16-0.99). Moreover using the score of the whole Scheltens scale we found in the AD group decreased OR for having depressive symptoms for each increase of 1 point on Scheltens scale (adjusted OR: 0.43 95%CI: 0.19-0.96) (Figure 9).

We stratified the analysis based on the age of onset of AD, 47 had an early onset before 65 years. Patients with early onset AD and depressive symptoms had 0.79 times decreased likelihood to present right MTA (OR 0.21; 95% CI 0.05-0.95), while in patients with late

onset AD the association between depressive symptoms and MTA was not significant (OR 0.53; 95% CI 0.15-1.99).

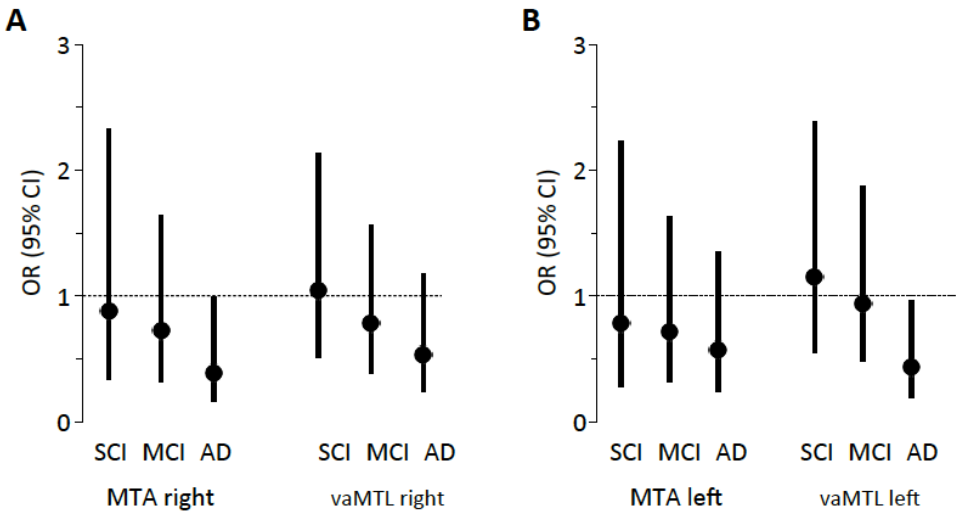

Figure 9. Associations between medial temporal atrophy and depressive symptoms in patients with subjective cognitive impairment (SCI), mild cognitive impairment (MCI) and Alzheimer's disease (AD); data presented as Odds ratios (OR) and 95% CI, MTA: medial temporal atrophy (yes/no), vaMTL: visual assessment of the medial temporal lobe (Schelten's scale); A: Right medial temporal lobe; B: left medial temporal lobe.

For 57 patients with SCI (n=32) and AD (n=25), hippocampal volume was manually delineated. Patients with SCI and depressive symptoms had more atrophic hippocampal volumes (mean values for right 2.60 cm^3 and left 2.45 cm^3 hippocampus) compared to SCI patients without depressive symptoms (mean values for right 2.88 cm^3 and left 2.77cm^3 hippocampus). Mean difference and (p value) were -0.28 cm^3 (p=0.005) for the right hippocampal volume and -0.32 cm^3 (p=0.002) for left hippocampal volume (Figure 10). In AD, there were no significant association between depressive symptoms and hippocampal

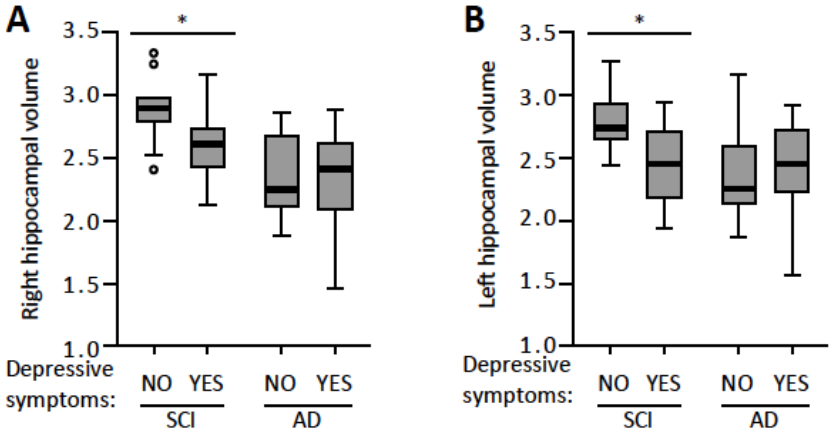

Figure 10. Associations between right (A) and left (B) hippocampal volume and depressive symptoms in patients with Subjective cognitive impairment (SCI) and Alzheimer's disease (AD).

volume

5.2 USE OF ANTIDEPRESSANT TREATMENT IN ALZHEIMER'S DISEASE AND MORTALITY RISK

In a large memory clinic cohort of 20,050 patients registered in SveDem with incident dementia we found that 25% (n=5,004) were on antidepressant treatment at the time of diagnosis. Antidepressants were less commonly prescribed among patients with AD (22.7%) and mixed dementia (21.5%), and more commonly in patients with Parkinson Disease Dementia (31.7%) and frontotemporal lobe dementia (30.3%). In our study, almost one fourth of the patients on antidepressants were prescribed anxiolytic or sedative-hypnotic medication at the time of dementia diagnosis and in the three-year period prior to dementia.

In total 5,168 (25.8%) patients with dementia died during a median follow-up after the dementia diagnosis of 2 years (range: 0-5 years).

We explored the associations between use of antidepressant treatment 3 years prior to a dementia diagnosis and mortality risk after diagnosis. Use of antidepressants at any time during three-year period in pre-dementia stage was associated with reduced mortality risk in the whole cohort (adjusted HR =0.87, 95%CI= 0.80-0.93) and in patients with AD (adjusted HR= 0.75, 95%CI= 0.64-0.88). We observed an association between longer duration of antidepressant use and lower mortality risk. In the whole cohort we found that patients with 2 and 3 years use of antidepressants prior to a diagnosis of dementia had a lower mortality risk comparing with non-users of antidepressant treatment (adjusted HR and 95%CI for 2 years use were HR:0.83, 95% CI: 0.73-0.93 and for 3 years use were HR:0.82, 95%CI: 0.72-0.94) (Table 6). Similarly, we found lower mortality risk (adjusted HR 0.61, 95%CI: 0.45-0.83) for using antidepressants 3 consecutive years in prodromal AD stage. Use of SSRIs at any time during the three-year interval in pre-dementia stage was significantly associated with lower mortality rate in the whole cohort and in patients with AD (Table 8). We found no associations between use of antidepressant treatment at the time of dementia diagnosis and mortality risk in a median of 2 years follow up.

Table 8: Cox proportional hazard models for mortality risk associated with antidepressant use among elderly with dementia

	Total N= 20,050	AD N=7,201 (35.9%)	MixedD N=5,052 (25.2%)	VaD N=3,821 (19.1%)	Others N=3,976 (19.8%)
Antidepressant use					
At diagnosis	0.98 (0.92-1.04)	0.98 (0.87-1.11)	1.05 (0.93-1.19)	0.99 (0.87-1.12)	0.95 (0.83-1.10)
3 years prior to dementia (yes/no) n=4,325	**0.87 (0.80-0.93)**	**0.75 (0.64-0.88)**	0.94 (0.81-1.10)	0.91 (0.79-1.05)	0.87 (0.74-1.02)
1 year out of 3 prior to dementia n=1814	0.93 (0.83-1.03)	**0.77 (0.62-0.96)**	0.97 (0.80-1.20)	1.02 (0.84-1.25)	0.90 (0.72-1.13)
2 years out of 3 prior to dementia n=1383	**0.83 (0.73-0.93)**	0.84 (0.66-1.08)	0.78 (0.60-1.01)	0.75 (0.60-0.95)	0.95 (0.72-1.20)
3 years out of 3 prior to dementia n=1128	**0.82 (0.72-0.94)**	**0.61 (0.45-0.83)**	1.10 (0.86-1.41)	0.95 (0.75-1.21)	**0.74 (0.57-0.96)**
Antidepressant class- use any of the 3 years prior to dementia					
MAOI n=417	0.87 (0.70-1.07)	0.68 (0.43-1.06)	1.06 (0.73-1.55)	0.77 (0.50-1.20)	0.92 (0.84-1.00)
SSRI n=3261	**0.89 (0.82-0.96)**	**0.81 (0.68-0.96)**	0.92 (0.78-1.08)	0.94 (0.81-1.10)	0.95 (0.77-1.18)
Other antidepressants n=1222	0.88 (0.78-1.00)	**0.73 (0.55-0.96)**	0.97 (0.75-1.26)	0.91 (0.71-1.17)	0.97 (0.86-1.09)

Statistically significant hazard ratios (HR) and 95% confidence interval (95%CI) are shown in bold font (*p*-value <0.05). AD, Alzheimer's disease; MixedD, mixed dementia; VaD, vascular dementia; Other includes Parkinson Dementia, dementia with Lewy body; frontotemporal dementia, diagnosis of dementia not specified or unknown and any other established diagnosis other than AD, mixed Dementia, VaD, dementia with Lewy body, dementia in Parkinson disease. MAOI, Non-selective monoamine reuptake inhibitors, SSRI Selective serotonin reuptake inhibitors

5.3 RISK TO DEVELOP DEMENTIA

5.3.1 CAIDE Dementia Risk Score: mechanisms and progression to dementia

CAIDE Dementia Risk Score version without APOE genotype was calculated for 724 patients and 209 (28.9%) had a score indicating higher risk for dementia (8-14 points). CAIDE Dementia Risk Score version with APOE genotype was calculated for 310 patients and 131 (42.3%) patients had a score indicating higher risk for dementia (9-17 points). The baseline demographic data are shown in Table 9.

Higher scores on CAIDE Dementia Risk Score version without APOE were associated with higher CSF t-tau levels (β=0.09, p=0.04), more severe MTA (OR=1.47, 95%CI= 1.01-2.15), frontal lobe atrophy (OR= 2.40 95%CI=1.11-5.10) and more severe WMC (OR= 3.41, 95%CI= 2.20-5.27). Higher scores on CAIDE Dementia Risk Score version with APOE were associated with lower CSF-$A\beta_{1-42}$ (β=-0.27, p= <0.001), more severe MTA (OR=2.71 95%CI=1.48-5.95) and more severe WMC (OR= 3.91, 95%CI=1.93-7.92) **(**Table 10).

324 patients were followed up for 1.36 ± 1.7 years. Progression to dementia occurred in 23.8% (n=100). 27.6% (n=86) patients with MCI and 3.4% (n=14) patients with SCI progressed to dementia. CAIDE Dementia Risk Score version with APOE (AUC 0.64, 95%CI 0.56-0.73) performed better in predicting dementia than version without APOE (AUC 0.58, 95%CI 0.56-0.73) and APOE alone (AUC 0.61, 95%CI 0.53-0.68). CAIDE Dementia Risk Score version with APOE had a relatively good sensitivity, but poor specificity in predicting dementia (Table 11).

Table 9. Baseline characteristics of the study sample

	All (n=724)	**SCI (N=412)**	**MCI (N=312)**
Age, years*	60.8 (8.5)	58.5 (7.3)	64.0 (8.9) *
Women, n (%)	417 (57.6)	254 (61.7)	163 (52.2)*
Education, years*	12.5 (3.7)	13.1 (3.7)	11.8 (3.7) *
CAIDE Dementia Risk Score	6 (0-14)	6 (0-14)	6.5 (0-14) *
Hyperlipidaemia, n(%)	201 (27.8)	98 (23.8)	103 (33.0) *
Hypertension, n(%)	246 (34.0)	111 (26.9)	135 (43.3) *
BMI, kg/m2*	26.2 (4.1)	26.3 (4.2)	26.1 (4.0)
MMSE*	27.7 (2.6)	28.3 (2.2)	26.9 (2.9) *
APOE ε4 carrier, n(%)	156 (21.5)	76 (18.4)	80 (25.6)
Cornell Depression Scale	6 (0-26)	6 (0-26)	5 (0-24)
Antidepressant treatment, n (%)	192 (26.5)	114 (27.7)	78 (25.0)
History of depression, n (%)	261 (36.0)	157 (38.1)	104 (33.3)
CSF markers			
$A\beta_{1-42}$, ng/L	855 (56-1920)	910 (286-1920)	718,5 (56-1640) *
t-tau, ng/L	240.5 (41-1030)	222 (43-689)	273 (41-1030) *
p-tau_{181}, ng/L	51 (16-183)	49 (16-183)	56 (16-175) *
MRI visual ratings	*n=529*		

MTA	1 (0-4)	1 (0-3)	1 (0-4) *
GCA-F	0 (0-1)	0 (0-1)	0 (0-1) *
Parietal atrophy	0 (0-2)	0 (0-1)	0 (0-2) *
WMC	1 (0-3)	1 (0-3)	1 (0-3) *
Progression to dementia			
Follow-up, n (%)	324(44.8)	112 (27.2)	222 (71.2) *
Follow up years mean (SD)	2.90 (1.6)	1.00 (1.5)	2.1 (1.8) *
Conversion to dementia n (%)	100 (13.8)	14 (3.4)	86 (27.6) *

Values are medians (range) unless otherwise specified. *Values are means (SD). CAIDE: Cardiovascular Risk Factors, Aging and Dementia Study, BMI: body mass index, SCI: subjective cognitive impairment, MCI: mild cognitive impairment, MMSE: Mini-mental State Examination, APOE: apolipoprotein E genotype, $A\beta_{1-42}$: amyloid β_{1-42}, t-tau: total tau, p-tau_{181}: phosphorylated tau at threonine 181, MTA: medial temporal lobe atrophy (mean MTA scores of both hemispheres) , GCA-F : global cortical atrophy frontal subscale, parietal atrophy: Koedam score for parietal atrophy, WMC: white matter changes measured with Fazekas scale for white matter changes

Table 10. Associations of CAIDE Dementia Risk Score with CSF and MRI markers at baseline

	CAIDE risk score (without APOE)		**CAIDE risk score (with APOE)**	
CSF markers, standardized beta-coefficients (p-values)				
$A\beta_{1-42}$, ng/L	0-5 points (n=301)	Ref	0-6 points (n=81)	Ref
	6-7 points (n=214)	-0.04 (0.37)	7-8 points (n=98)	**-0.22 (0.002)**
	8-14 points (n=209)	-0.07 (0.10)	9-17 points (n=131)	**-0.27 (<0.001)**
t-tau, ng/L	0-5 points (n=301)	Ref	0-6 points (n=81)	Ref
	6-7 points (n=214)	0.08 (0.06)	7-8 points (n=98)	**0.14 (0.04)**
	8-14 points (n=209)	**0.09 (0.04)**	9-17 points (n=131)	0.10 (0.17)
p-tau_{181}, ng/L	0-5 points (n=301)	Ref	0-6 points (n=81)	Ref
	6-7 points (n=214)	0.06 (0.17)	7-8 points (n=98)	0.05 (0.49)
	8-14 points (n=209)	0.05 (0.22)	9-17 points (n=131)	0.05 (0.43)
MRI visual ratings, OR (95%CI)				
MTA	0-5 points (n=226)	Ref	0-6 points (n=57)	ref
	6-7 points (n= 150)	1.11 (0.76-1.62)	7-8 points (n=78)	1.50 (0.80-2.78)
	8-14 points (n=153)	**1.47 (1.01-2.15)**	9-17 points (n=100)	**2.71 (1.48-5.95)**
WMC	0-5 points (n=226)	Ref	0-6 points (n=57)	Ref
	6-7 points (n= 150)	**1.80 (1.16-2.77)**	7-8 points (n=78)	1.78 (0.87-3.65)
	8-14 points (n=153)	**3.41 (2.20-5.27)**	9-17 points (n=100)	**3.91 (1.93-7.92)**
GCA-F	0-5 points (n=226)	Ref	0-6 points (n=57)	Ref
	6-7 points (n= 150)	1.14 (0.47-2.73)	7-8 points (n=78)	1.48 (0.26-8.40)
	8-14 points (n=153)	**2.40 (1.11-5.10)**	9-17 points (n=100)	4.47 (0.99-20.5)
Parietal atrophy	0-5 points (n=226)	Ref	0-6 points (n=57)	Ref
	6-7 points (n= 150)	0.88 (0.52-1.49)	7-8 points (n=78)	0.81 (0.36-1.84)
	8-14 points (n=153)	1.36 (0.84-2.20)	9-17 points (n=100)	1.46 (0.70-3.05)

*p<0.05, Standardized beta-coefficients (p-values) are from linear regression with $A\beta_{1-42}$, t-tau and p- tau as dependent variable. Odds Ratios and 95% Confidence interval (OR and 95% CI) are from ordinal logistic regression with MTA, WMC, CGA-F and parietal atrophy as dependent variable. CAIDE: Cardiovascular Risk Factors, Aging and Dementia Study, $A\beta_{1-42}$: amyloid β_{1-42}, t-tau: total tau, p-tau_{181}: phosphorylated tau at threonine 181 MTA: medial temporal lobe atrophy (mean MTA scores of both hemispheres), GCA-F global cortical atrophy frontal subscale, parietal atrophy – Koedam score for parietal

atrophy, WMC: white matter changes measured with Fazekas scale for white matter changes, APOE: apolipoprotein E genotype

Table 11. Performance of the CAIDE Dementia Risk Score in predicting dementia

Cut-off	Sensitivity (95%CI)	Specificity (95%CI)	LR + (95%CI)	LR- (95%CI)	AUC (95%CI)
CAIDE Dementia Risk Score (version without APOE)					
6/7	51.0 (40.8-61.1)	60.3 (53.5-66.7)	1.28 (1.00-1.65)	0.81 (0.65-1.02)	0.58 (0.51-0.65)
7/8	39.0 (29.4-49.3)	72.8 (66.4-78.5)	1.43 (1.03-1.98)	0.84 (0.70-1.00)	
CAIDE Dementia Risk Score (version with APOE)					
7/8	83.6 (71.2-92.2)	42.5 (33.2-51.2)	1.45 (1.19-1.77)	0.39 (0.20-0.73)	0.64 (0.56-0.73)
8/9	60.0 (45.9-73.0)	61.1 (51.4-70.1)	1.54 (1.12-2.11)	0.66 (0.46-0.93)	
APOE alone					
0/1	69.1 (55.2-80.9)	52.2 (42.6-61.7)	1.45 (1.11-1.88)	0.59 (0.38-0.91)	0.61 (0.53-0.68)

CAIDE: Cardiovascular Risk Factors, Aging and Dementia Study, LR+: likelihood ratio for positive test, LR-: likelihood ratio for negative test, APOE: apolipoprotein E genotype

5.3.2 Depressive symptoms and risk to develop dementia

In addition to the published and submitted to publication data, we wanted to use our available memory clinic database to explore the association between depressive symptoms and risk to develop dementia. Among patients with SCI and MCI, CSDD scores were available for 606 patients, while information about use of antidepressant treatment was available for all 724.

At baseline 235 (38.8%) had depressive symptoms (CSDD ≥8) and 192 (26.5%) were on antidepressant treatment. The characteristics of the group are shown in Table 12. Patients with depressive symptoms at baseline had a lower educational level, and lower MMSE, used more antidepressants and more often had a history of depression compared to patients without depressive symptoms. Patients using antidepressant treatment at baseline were more commonly women, have lower MMSE, more depressive symptoms and a history of depression compared to patients without use of antidepressant treatment. After a mean follow up time of 2.9 years, 100 (13.8%) patients had developed dementia. Fewer patients with depressive symptoms and use of antidepressant treatment at baseline were followed up compared to patients without depressive symptoms and use of antidepressants at baseline

We found that patients with depressive symptoms have a lower risk to develop dementia compared to those without (adjusted, HR:0.53, 95%CI: 0.30-0.96), after adjusting for age, gender, education, CSF $A\beta_{1-42}$, t-tau and p-tau_{181}. Similarly depressive symptoms were associated with a lower risk to develop AD (adjusted, HR:0.43, 95%CI: 0.20-0.94). No significant associations were observed between use of antidepressant treatment and risk to develop dementia (adjusted, HR:1.2, 95%CI: 0.71-1.97).

Table 12: Characteristics of the subgroup used for supplementary analysis

	No Depressive symptoms N=371	**Depressive symptoms N=235**	**Antidepressants Non-users N=532**	**Antidepressants Users N=192**
Age men (SD)	62.1 (8.4)	58.7 (8.1)	61.3 (8.4)	59.5(8.5)
Women #	209 (56.5)	149 (63.4)	293 (55.1)	124 (64.6) *
Education years men (SD)	12.6 (3.4)	12.2 (4.1)*	12.7 (3.6)	12.0 (4.1)
Antidepressant treatment #	54 (14.6)	106 (45.1)*	-	192
History of depression #	80 (21.6)	144 (61.3)*	87 (16.4)	174 (90.6)*
MMSE mean (SD)	28.1 (1.9)	27.03 (3.1)*	28.0 (2.3)	27.0 (3.2)*
Cornell median (range)	3 (0-7)	12 (8-26)*	5 (0-24)	10 (0-26)*
SCI #	169 (52.3)	175 (61.8)*	298 (56.0)	114 (59.4)
MCI #	154 (47.7)	108 (32.8)*	234 (44.0)	78 (40.6)
Progression to dementia	***N=272***		***N=324***	
Follow-up, #	191(62.9)	101 (37.1%)*	251 (77.5)	73 (22.5)*
Follow up years men (SD)	2.8(1.6)	3.1 (1.6)	2.9 (1.6)	2.9 (1.7)
Conversion to dementia #	68 (35.6)	15 (18.5)*	80 (32%)	20 (27.4)

*p<0.05, # Values are numbers (percentages) unless otherwise specified. SD: standard deviation, SCI: Subjective cognitive impairment, MCI: Mild cognitive impairment, MMSE: Mini Mental State Examination

6 DISCUSSSION

6.1 BIOMARKERS OF AMYLOID DEPOSITION AND NEURONAL INJURY IN DEPRESSION IN ALZHEIMER'S DISEASE

We found that AD patients with depressive symptoms had less abnormal biomarkers of neuronal injury (lower CSF tau levels and less severe MTA) as compared to AD patients without depressive symptoms. SCI patients with depressive symptoms had lower CSF t-tau and p-tau$_{181}$, but more hippocampal atrophy compared to SCI patients without depressive symptoms. No significant association was found between the biomarker of amyloid deposition (CSF Aβ_{1-42} levels) and depressive symptoms in SCI or AD. Aβ accumulation occurs early in the course of the AD and is considered to be relatively stable at symptomatic stages; tau accumulation is more a marker of neuronal injury, which may reflect the progressive neurodegeneration and associated cognitive decline [316].

We could not confirm a positive association between biomarkers of amyloid deposition and neuronal injury with depressive symptoms. To the contrary, AD patients with depressed symptoms seem to have less severe neurodegenerative changes than those without. One possible explanation is that AD patients with depressive symptoms seek medical care at earlier stages of AD as they have less abnormal biomarkers of neuronal injury. Depression and AD are both associated with cognitive impairment. In our study AD patients with and without depressive symptoms had a similar overall cognitive performance. AD patients without depressive symptoms may have more severe tau and amyloid pathology, since the overall cognitive impairment in AD patients with depressive symptoms might be caused by a combination of AD pathology and depression associated pathology such as inflammation and small vessel pathologies [139]. Our data did not allow a more detailed cognitive profile, which might have informed on this hypothesis.

On the other hand, another study performed in our memory clinic cohort Lebedeva *et al.*[204] found that depressive symptoms in AD are associated with more severe bilateral superior temporal and parietal thinning compared to AD patients without depressive symptoms; but no associations were found between hippocampus and depressive symptoms in AD patients. Moreover, a significant negative correlation was observed between CSF t-tau levels and cortical thickness in the parietal lobe in AD patients with depressive symptoms compare with those without[204]. They included a highly selected small cohort of AD patients (n=41) from our memory clinic, many of whom had an early onset AD where parietal lobe are known to be more atrophic compared to late onset AD[317]. In our study we found a strong association between less severe MTA and depressive symptoms in patients with early onset AD, while no

such associations were found in late onset AD. One possible explanation may be that in patients with early onset AD depressive symptoms do not accelerate the atrophy of the medial temporal lobe, but may increase the atrophy of the parietal lobe which is a more specific pattern of atrophy in early onset AD. Although depression is a common neuropsychiatric symptom in patients with early onset AD, further depression-associated atrophy is not well studied[318].

In Lebedeva *et al.* study depressive symptoms had relatively low scores on CSDD (maximum CSDD score was 8 points), and in another cohort, the maximum score on GDS 15 was 3 points. Some of the CSDD and GDS items overlap with apathy and it has been shown that apathy is more related to neuronal injury [201]. Another possible explanation for the apparent different findings may be that in our study we defined depressive symptoms using also antidepressant treatment, which has been shown to have a protective role for hippocampus[319]. Thus, different regimes of antidepressant treatment may have influenced the findings. Several definitions for depressive symptoms were used in study II but only depressive symptoms defined as "CSDD $\geq$ 8 or uses of antidepressants" were associated with less atrophic MTA.

In contrast, SCI patients without depressive symptoms had more pathological levels of CSF t-tau and p-tau$_{181}$ and less hippocampal atrophy. These patients can be considered elderly patients with depressive symptoms and subjective cognitive complaints. Biological processes associated with late life depression, such as inflammation and small vessel disease[139], may contribute to the increased hippocampal atrophy[320]. Another possible explanation is that more severe hippocampal atrophy in SCI patients with depressive symptoms reflects early neurodegenerative changes due to AD in SCI. However, our findings that depressive symptoms were not associated with low CSF A$\beta_{1\text{-}42}$ or high CSF t-tau or p-tau$_{181}$ levels, argue against this possible explanation.

However depressive symptoms co-occur with cognitive impairment and are likely related to pathological processes leading to hippocampal atrophy[320]. Depressive symptoms may thus represent brain changes that together increase the risk for subsequent development of AD. Longitudinal studies are needed to explore the mechanisms underlying this association and the observed smaller hippocampi in patients with late life depression[321].

6.2 USE OF ANTIDEPRESSANTS IN ALZHEIMER'S DISEASE AND MORTALITY RISK

Depression is often under-diagnosed in older people and antidepressants are the most commonly used treatment of depression in patients with and without AD[94].

We found that 25% of dementia patients are on antidepressant treatment at the time of dementia diagnosis. Citalopram and mirtazapine were the most frequently prescribed antidepressant treatments for the patients with dementia, which were registered in SveDem. Our results are similar to a Finnish register-based study where 29% of patients with AD used antidepressant treatment and citalopram and mirtazapine were the most commonly prescribed drugs[262].

To our knowledge, this is the first study exploring the associations between the use of antidepressants in pre-dementia stages and mortality risk. The results suggest that use of antidepressant treatment in pre-dementia stages reduces mortality in patients with AD. One possible explanation is that patients receiving antidepressant treatment for depression or another medical condition in pre-dementia stages have a regular contact with a physician allowing an earlier diagnosis of dementia; implying a better treatment and care for dementia and other diseases which may reduce mortality. A higher mortality rate is associated with a late diagnosis of AD on the trajectory of the disease[322]. The results support the findings from Study I and II which suggest that patients with AD and depression are in earlier stages of AD at the time of diagnosis and therefore may have lower mortality rate.

Behavioural symptoms are associated with increased mortality risk in patients with dementia [102]. Another possible explanation is that antidepressant treatment may be useful in treating these symptoms including depression in AD and dementia[323] and therefore decreases mortality rate[109].

Antidepressants may have biological effects, which lead to reduced mortality in patients with AD. We found an association between longer duration of antidepressant treatment and lower mortality risk. Some studies have found that use of antidepressants like citalopram reduces Aβ production[247] and that use of antidepressants can delay onset of dementia and increase longevity in patients with Down syndrome[248]. Meanwhile other studies reported that antidepressants are associated with hippocampal atrophy[246] and increased risk for dementia[249].

Antidepressants have been previously found to reduce mortality risk in the elderly with late life depression[123]. Most of the studies conducted in nursing homes on individuals with different degrees of cognitive impairment found an association between use of antidepressants and reduced mortality risk[108,109]. Additionally one study from nursing homes found that use of antidepressant treatment more than one year is associated with lower

mortality risk[108]. In contrast, a study that included outpatients found a small but significant increased in mortality risk in patients with AD on antidepressants[95].

6.3 RISK TO DEVELOP DEMENTIA

6.3.1 CAIDE Dementia Risk Score: mechanisms and progression to dementia

We found that CAIDE Dementia Risk Score was associated with biomarkers of amyloid deposition, neuronal injury and small vessel pathology, and a higher risk of progression to dementia.

Several risk scores for dementia have been developed taking into account modifiable vascular and lifestyle-related risk factors[21,324–327] .CAIDE Dementia Risk Score is one of the scores developed in the general population with a high potential to be used in clinical practice in dementia risk assessment[21]. The risk of cognitive disorders increases with age[149]. Risk scores like CAIDE Dementia Risk Score can select individuals at risk to develop dementia and who can benefit from lifestyle interventions[91]. Currently, there are no pharmacological therapies approved for patients with subjective or mild cognitive impairment.

This is the first study that assesses the associations between CAIDE Dementia Risk Score and biomarkers of amyloid deposition, neuronal injury and small vessel disease, as well as the score performance to predict dementia in patients with SCI and MCI from a memory clinic. These findings thus support the validity of the score and its clinical relevance. Aβ and tau pathologies often coexist and interact with cerebrovascular pathology, particularly small vessel disease [86,328]. CSF t-tau and p-tau$_{181}$, and MTA on MRI are considered to reflect the burden of neurofibrillary tangles [72], while WMC are found in AD[86], and potentiate the effects of cortical atrophy on cognitive impairment [329].

The association between CAIDE Dementia Risk Score and WMC is expected as the score is mainly based on cerebrovascular risk factors[21], and the risk factors included in the score such as midlife hypertension[330], hypercholesterolemia[331] and obesity[332] have already been associated with pathological biomarkers for neuronal injury or amyloid deposition.

Our results support previous reports from a population-based study where CAIDE Dementia Risk Score was associated with more severe hippocampal atrophy and WMC up to 30 years later[333]. In addition to their findings, we found that the score correlates with CSF t- tau levels.

A memory clinic sample is a selected cohort at risk to develop dementia, thus high numbers of APOE ε4 carriers (50.3%) is expected. We found that higher CAIDE Dementia Risk Score

including APOE was associated with reduced CSF $A\beta_{1-42}$ levels, suggesting accumulation of Aβ in the brain.

In the original publication, including APOE genotype in CAIDE Dementia Risk Score did not improve the score's capacity to predict dementia 20 years later in the general population[21]. However, adding APOE genotype to CAIDE Dementia Risk Score improved the score's capacity to predict dementia a few years later in memory clinic patients already at risk to develop dementia. CAIDE Dementia Risk Score version with APOE has a good sensitivity, but low specificity at a cut-off ≥ 8. The risk score may thus be useful for identifying individuals at risk to develop dementia and who could therefore benefit more from lifestyle interventions and vascular and metabolic risk management [91].

6.3.2 Depressive symptoms and risk to develop dementia

In our memory clinic database, we found that SCI and MCI patients with depressive symptoms have a lower risk to develop dementia during a short follow up period. We found no associations between antidepressant treatment and risk to develop dementia. There is a lot of evidence from community based studies that depression is a risk factor for dementia and predicts conversion from MCI to dementia[147]. The evidence is inconsistent in clinical studies as a large amount of clinical based studies could not confirm the associations found in epidemiological studies[147]. Our results are similar with the results from a memory clinic study that reported MCI patients with depressive symptoms have a lower likelihood to convert to dementia after 2 years of follow up[278]. Our findings support the results reported in study I and II, that suggest that patients with depressive symptoms seek medical help in earlier stages of the disease. Depressive symptoms can lead to memory complains and personality changes that are observed in early stages of MCI and dementia[50]. However, fewer patients with depressive symptoms or using antidepressants were followed up, and this may have influenced the findings.

6.4 METHODOLOGICAL LIMITATIONS

The present studies have a number of methodological limitations. All studies used a retrospective design, using already collected data. Studies I, II, IV have a cross-sectional design and thus assumptions regarding causality cannot be made. Studies III and IV used a retrospective design, but included longitudinal data of progression to dementia, drug use and survival. Only patients referred to memory clinics were included and thus generalisations to the population are not possible. The naturalistic design inevitable leads to some missing data.

The cohorts for studies I, II and IV included patients from one university memory clinic and no inter-rater reliability studies are available. Although regular attempts are made to enhance standardization and harmonization of the procedures, no formal reliability studies of the diagnostic procedures and clinical rating scales have been performed. However, the use of standardized procedures, validated clinical rating scales including neuropsychological testing, extensive biomarker assessment, longitudinal follow-up of many patients, and a final diagnosis based on a consensus meeting suggest that the diagnoses are accurate. However, since there was no autopsy confirmation the diagnostic accuracy is not known.

Patients with SCI and MCI have and increased risk to develop dementia and as a group have more advanced stage of Aβ pathology, neuronal injuries, or small vessel pathology, and an increased prevalence of the APOE ε4 allele compared to the general population[334]. For the first two studies the comparison group consisted of patients with SCI, with a high risk of developing AD and increased proportion of pathological CSF and MRI findings[334] . Thus, this is not a "healthy" control group and thus extrapolation to elderly without AD suffering from depression cannot be made.

In study III patients were included from several memory clinics across Sweden using different assessment protocols and neuropsychological test batteries. The data obtained did not contain information on cognitive performance in preclinical stages of dementia and patients with SCI and MCI are not included in SveDem. The accuracy of diagnoses of dementia in SveDem are not validated independently with autopsy records. Patients suffering from dementia with Lewy bodies, Parkinson's disease dementia and vascular dementia may not be representative for the population of these diagnoses since a large proportion are likely to be seen by neurologist or other clinics and only a selection of those with early, severe, or atypical cognitive impairment may be referred to memory clinics and registered in SveDem [335]. However, experienced specialists using clinical information and several biomarkers in order to increase the diagnostic accuracy established the diagnoses. Detailed analyses have shown that in SveDem less than 5% of the diagnoses are changed after the yearly follow-up[101].

Another limitation is that patients were considered to have depressive symptoms based on CSDD scores and not on a structured diagnosis interview. Trained nurses and clinicians were applying the scale but no data on intra- and inter-rater reliability were available. Moreover, the Swedish version of the scale used for this study is not validated in a Swedish population, most of the validation studies were in culturally similar populations from Norway[220] and Denmark[218]. However, the CSDD is the recommended tool for assessing depressive

symptoms in people with cognitive impairment[238], and has been shown good psychometric properties[220]. Throughout the thesis we used several cut-off points on CSDD to define depressive symptoms. We used 2 cut-off points, which are validated in a Danish (6/7)[218], and a Norwegian (7/8) cohort of out patients[220]. In study II we defined depressive symptoms as a CSDD score more and equal 8 or use of antidepressant treatment[140], as it have been suggested that information on use of antidepressant treatment can improve the classification accuracy[140].

The patients were referred for memory rather than mood problems, and thus the depressive symptoms were usually of mild and sometimes moderate severity. Thus, although our findings are relevant for memory clinic cohorts, they may not be valid for patients with dementia and clinically significant depression. Data on clinical features such as history of depression (age at onset, number and severity of episodes) and on duration and indication of antidepressant treatment were not available.

In study III we used data on antidepressant treatment from the Swedish Prescribing Drug Register, which covers dispensation of all dugs in all Swedish pharmacies, but does not contain information on prescriptions during hospitalization, indication of, or adherence to treatment.

In study II we assessed the medial temporal lobe structures using two methods well correlated with each other [303]: visual assessment of the medial temporal lobe and manual delineation of the hippocampal volume. Differences between these 2 methods can explain the different results in patients with SCI and AD. The visual assessment is an approximate measure of the medial temporal lobe, which includes other brain structures such as the entorhinal cortex that is affected in both late life depression [336] and AD [27]. We limited our research to medial lobe structures, although there are other brain changes such as atrophy of frontal lobe[337] and more severe white matter changes[338], which might have influenced the findings.

The visual assessment was performed on T1 weighted MRI images with different protocols of acquisition, and in study II we used both CT and T1 weighted MRI scans. However, a good intra-observer agreement had been shown between multi-detector row CT and 1.5 Tesla MRI for vaMTL on the left and right hemisphere[302]

Another methodological limitation of study II is that the results were not corrected for multiple statistical comparisons. Thus, there is a risk for false-positive findings.

In study IV CAIDE Dementia Risk Score was not calculated according to the original version

as data on physical activity were not available[21]. However, we used the same version of CAIDE Dementia Risk Score used in the validation study, which did not include physical activity[25]. Furthermore, follow up data are available only for patients considered with a high risk to develop dementia at baseline. Additional analyses were conducted to address the missing data (see statistics study IV). However, in a small intern study 30 randomly selected patients with SCI without follow up were invited to a new neurocognitive assessment after 5 years, and none of them developed dementia in this period[339].

7 CONCLUDING REMARKS AND FUTURE PERSPECTIVES

7.1 GENERAL CONCLUSIONS

Our findings do not support the hypothesis that depressive symptoms are associated with more severe amyloid deposition and neuronal injury in patients with AD. Antidepressants are used by a quarter of newly diagnosed patients with dementia at the time of diagnosis. Use of antidepressant treatment in prodromal stages of AD is associated with lower mortality risk.

In a memory clinic cohort, CAIDE Dementia Risk Score was associated with biomarkers of amyloid deposition, neuronal injury, and can predict development of dementia.

7.2 SPECIFIC CONCLUSIONS

- Patients with AD and depressive symptoms have lower pathological levels of the CSF t-tau and less atrophy of the medial temporal lobe than AD patients without depressive symptoms.
- Patients with SCI and depressive symptoms have less pathological CSF t-tau and p-tau$_{181}$, but more severe hippocampal atrophy compared to SCI patients without depressive symptoms
- 25% of patients newly diagnosed with dementia use antidepressant treatment at the time of diagnosis.
- Citalopram and mirtazapine are the most commonly used antidepressants at the time of dementia diagnosis
- Use of antidepressant treatment for 3 consecutive years in prodromal stages of AD is associated with a lower mortality rate after AD diagnosis
- In a memory clinic cohort of patients with SCI and MCI, higher CAIDE Dementia Risk Score version with APOE genotype is associated with biomarkers of amyloid deposition, neuronal injury and small vessel pathology.
- In a memory clinic cohort of patients with SCI and MCI, CAIDE Dementia Risk Score version with APOE genotype predicts better dementia up to 7 years later.

- In a memory clinic cohort of CAIDE Dementia Risk Score has a low specificity, but a good sensitivity to predict dementia in 2.9 year follow up period.

7.3 FUTURE DIRECTIONS

In order to understand the mechanisms implicated in depression in AD further longitudinal studies are necessary. This may help clarify the relationship between depressive symptoms, psychological factors and biomarkers of amyloid deposition, neuronal injury, small vessel disease, neuroinflammation as well. Future studies will benefit from the use of recently proposed research criteria for subjective cognitive decline[49] which were not available when the thesis was planned.

Our findings that antidepressants can reduce mortality in AD needs to be replicated in a prospective study. More evidence is needed to understand the mechanisms underlying antidepressants' effect on mortality in AD and other dementia disorders. A key future question is to explore whether use of antidepressants can reduce the risk for developing AD or can delay onset of AD. Further studies need to address the safety of specific antidepressants in prodromal stages of AD. Finally, since available antidepressants do not seem to be effective in people with AD, it will be important to develop novel treatments.

A further research question is, can CAIDE Dementia Risk Score predict brain pathology and what type of pathology? Future studies should be prospective and formulate an adapted version of CAIDE Dementia Risk Score for use in memory clinic patients with SCI and MCI. Behavioural symptoms and other biomarkers can be included to improve the score's performance in a memory clinic cohort with a high risk to develop dementia.

Our studies have several implications for clinical practice. We have confirmed other findings that depressive symptoms and use of antidepressants are common among memory clinic patients. Accordingly, in memory clinics screening for depressive symptoms and a critical review of psychopharmacological treatment is important. Effective multimodal management strategies are needed. Our findings that antidepressants do not increase mortality in patients with early AD, and might even reduce mortality, are re-assuring, and suggest that antidepressants are safe in these patients. CAIDE Dementia Risk Score can aid in the dementia risk assessment of patients with SCI and MCI, which may be particularly useful in centres with less resources for more sophisticated biomarker analyses. The score may also be used to recruit patients who can benefit from life style or other management interventions as well as for inclusion in clinical trials.

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Annex: CAIDE Dementia Risk Score version used in study IV.

CAIDE Dementia Risk Score		**Version without APOE genotype**	**Version with APOE genotype**
Age, years	<47	0	0
	47-53	3	3
	>53	4	5
Education, years	≥10	0	0
	7-9	2	3
	0-6	3	4
Sex	Women	0	0
	Men	1	1
Hypertension	No	0	0
	Yes	2	2
BMI, kg/m^2	≤30	0	0
	>30	2	2
Hyperlipidemia	No	0	0
	Yes	2	1
APOE ε4	Non-carrier	-	0
	Carrier	-	2
Total points		**Max 14 p**	**Max 17 p**

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