Subjective cognitive decline in memory clinic patients – characteristics and clinical relevance

Results from Sahlgrenska University Hospital Memory Clinic in Mölndal

Doctoral thesis

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Cover illustration: 'I väntan på' by Lars Magnusson

"Innerst inne i mig står en sliten, vanvårdad filmprojektor. Kuggar har lossnat, dreven hackar, motorn slirar, den stora filmrullen är skev, celluloiden har brustit. Men för något flyktigt ögonblick fungerar allt som det ska och en bildruta, en enda, blir synlig. Sedan rasslar den trasiga projektorn vidare."

Ur Minnen av Torgny Lindgren

"No matter how you feel: get up, dress up, show up, and never give up."

Regina Brett

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ABSTRACT

Subjective cognitive decline (SCD) refers to concerns – symptoms - regarding one's cognitive functioning, in the absence of objective evidence of impairment. SCD has been described as a possible stage preceding mild cognitive impairment (MCI) and dementia. The characteristics and clinical relevance in relation to subsequent objective cognitive decline is however still unclear.

We developed a patient-based comprehensive questionnaire on everyday cognitive difficulties. Patients with SCD were followed over time, to analyze the associations between SCD and cognitive outcome. Furthermore, we investigated the associations between SCD and stress, depressive symptoms and CSF AD profiles, and evaluated newly published international criteria for SCD, 'preclinical AD' and subcategories, involving both clinical features and neurochemical biomarkers. All participants in the current thesis were patients or healthy volunteers at the Sahlgrenska memory clinic in Mölndal.

We identified specific SCD symptoms that were more frequently reported by subjectively impaired patients seeking help for cognitive problems, compared to healthy elderly. The self-report instrument SASCI-Q is a useful research tool to investigate cognitive symptoms further. SCD patients were characterized by relatively young age, high educational attainment, high prevalence of stress conditions and depressive symptoms, and a family history of dementia. About 40 % of patients with SCD declined cognitively over 4±2.9 years – one fourth of them converted to dementia. When CSF biomarkers were added, the ability to predict MCI, dementia and AD dementia clearly increased. A specific profile of subjective cognitive symptoms could not be associated with cognitive decline in a mixed SCD+MCI patient sample. However, when groups were analysed separately, reporting more symptoms was associated with subsequent decline in the SCD group whilst reporting less symptoms was associated with subsequent decline in the MCI group.

Cognitive symptoms reported by the patient may signify many different conditions, and their associations with subsequent dementia should not be overstated when there are no objective signs present.

1 SAMMANFATTNING PÅ SVENSKA

"Vad heter hon nu, hon i den där filmen…?"
"Vad var det jag skulle hämta i förrådet…?"
"Va, har jag redan berättat det?"
Minnesproblem är något de flesta av oss kan känna igen oss i. Hjärnan verkar inte alltid vara med på noterna, och dagligen märker vi dess begränsningar. Förutom minnesbesvär kan vi exempelvis uppleva svårigheter att koncentrera oss, planera, lösa problem, hitta ord eller följa en karta – alla dessa funktioner och många fler kan samlas under begreppet 'kognitiva funktioner'. För en del personer blir problemen så oroande att de bestämmer sig för att söka sig till sjukvården, ofta av rädsla för demenssjukdom. Alzheimers sjukdom är den vanligaste orsaken till demens, och innebär en gradvis försämring av kognitiva funktioner, orsakade av skadade eller döda hjärnceller.

På minnesmottagningar utreds personer som söker hjälp för kognitiva svårigheter, där det bedöms finnas en risk för begynnande demenssjukdom, t.ex. om personen är äldre och upplever en försämring jämfört med tidigare. Undersökningen består oftast av samtal/intervju, skattningsskalor, hjärnavbildning med t.ex. magnetkamera, och bedömning av kognitiv funktion med neuropsykologiska tester. Ofta görs ett ryggvätskeprov, som möjliggör en undersökning av tecken på Alzheimers sjukdom i ryggvätskan, som står i direkt kontakt med hjärnan. Ryggvätskeprov och hjärnavbildning är exempel på 'biomarkörer' för demens – objektiva indikationer på en sjukdomsprocess i hjärnan. Inga idag tillgängliga metoder kan dock ge ett helt säkert svar på om en person är på väg att utveckla demens.

Oftast är personer som söker hjälp på en minnesmottagning någonstans mellan friskt åldrande och demens. En kognitiv nedsättning som kan bekräftas med standardiserade kognitiva tester, men som ändå inte är på demensnivå, kallar vi 'lindrig kognitiv störning', på engelska mild cognitive impairment (MCI), vilket passar in på de flesta personer som utreds på en minnesmottagning. Men hos en relativt stor andel av hjälpsökande personer hittar vi inga nedsatta testresultat. 'Subjektiv kognitiv försämring', på engelska subjective cognitive decline (SCD), är en term som används inom bland annat demensforskning för att beskriva detta tillstånd – vilket alltså innebär att en person har kognitiva problem (symptom) som inte kan bekräftas med tester trots omfattande undersökning.

Huvudsyftet för denna avhandling är att undersöka om subjektiv kognitiv försämring är kliniskt relevant som en tidig indikator på demenssjukdom. Vad karaktäriserar patienter med SCD, jämfört med patienter med MCI och friska

äldre? Vilken typ av symptom har personer med SCD? I hur hög utsträckning ökar möjligheten att identifiera demens i tidigt skede när personer med SCD också har avvikande biomarkörer? Finns det ett samband mellan specifika kognitiva symptom vid första undersökningen och demens flera år senare? Deltagarna i de fyra studierna är patienter och friska frivilliga som har undersökts på minnesmottagningen i Mölndal, vid Sahlgrenska universitets-sjukhuset.

Först utvecklade vi ett frågeformulär (studie I). Vi hittade symptom som tycks vara mer frekventa hos de som söker sjukvård för sina kognitiva besvär, än hos 'normalbefolkningen'. I studie II fann vi att patienter med SCD ofta har haft, och har, stressproblematik. Patienter med SCD hade också ofta depressiva symptom, högre utbildning än övriga patienter, och var förhållandevis unga. I studie III utvärderade vi internationella forskningskriterier för SCD, och fann att möjligheten att förutsäga MCI och demens tydligt ökar hos patienter med SCD om också biomarkörer från ryggvätska är avvikande. På basen av endast SCD var risken att utveckla demens förhållandevis liten, även om den var större än vad som skulle förväntas i motsvarande åldersgrupp i befolkningen. I studie IV fann vi att mycket få specifika kognitiva symptom kan relateras till framtida demenssjukdom. Men hos personer som bara hade SCD var kopplingen mellan subjektiva symptom och framtida objektiv försämring tydligare än hos personer med MCI, som tenderade att underrapportera symptom – troligtvis på grund av försämrad insikt.

På basen av de fyra studierna och andra internationella forskningsresultat dras slutsatsen att subjektiva kognitiva symptom hos äldre personer på en minnesmottagning överlag är mer relaterade till depressivitet, ångest och stress än till framtida demenssjukdom. Dessa personer kan behöva andra insatser för att bättre förstå och förbättra sina kognitiva funktioner. För en mindre andel av personer med SCD, 10%, kunde vid dock se demensutveckling vid en uppföljning efter fyra år. Särskilt personer med SCD som också har avvikande biomarkörer bör därför följas upp vidare på minnesmottagning, eftersom risken för en underliggande demenssjukdom då är tydligt större. Vi drar också slutsatsen att möjligheten att förutsäga MCI och demenssjukdom på basen av en viss profil av symptom tycks vara liten. Insikten i svårigheter kan vara nedsatt redan vid MCI, och SCD bör därför inte vara ett krav för att diagnostisera MCI. Trots sina brister har subjektiva kognitiva symptom en viktig roll eftersom det endast är genom symptom som patienter söker sig till sjukvården, där man sedan tar ställning till vidare utredning.

LIST OF STUDIES

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I.   Eckerström M, Skoogh J, Rolstad S, Göthlin M, Steineck G, Johansson B, Wallin A. *Sahlgrenska Academy Self-reported Cognitive Impairment Questionnaire (SASCI-Q) – a research tool discriminating between subjectively cognitively impaired patients and healthy controls.* International Psychogeriatrics, 2013, 25 (3): 420-30.

II.   Eckerström M, Berg A I, Nordlund, A, Rolstad S, Sacuiu S, Wallin A. *High Prevalence of Stress and Low Prevalence of Alzheimer Disease CSF Biomarkers in a Clinical Sample with Subjective Cognitive Impairment.* Dementia and Geriatric Cognitive Disorders, 2016, 42: 93–105.

III.   Eckerström M, Göthlin M, Rolstad S, Hessen E, Eckerström C, Nordlund A, Johansson B, Svensson J, Jonsson M, Sacuiu S, Wallin A. *Longitudinal evaluation of criteria for subjective cognitive decline and preclinical AD in a memory clinic sample.* Manuscript accepted for publication in Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, April 2017.

IV.   Eckerström M, Eckerström C, Göthlin M, Rolstad S, Wallin A. *Subjective cognitive symptoms in progressing vs. non-progressing memory clinic patients – a five year follow-up.* Manuscript.

CONTENT

ABBREVIATIONS

Aβ	Amyloid beta peptide
AD	Alzheimer's disease
ADNI	Alzheimer's disease neuro-imaging initiative
AIBL	The Australian imaging, biomarkers and lifestyle flagship study of aging
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APOE	Apolipoprotein E
APP	Amyloid precursor protein
CDR	Clinical dementia rating
CDQ	Cognitive dysfunction questionnaire
CFQ	Cognitive failures questionnaire
CIMP-QUEST	Cognitive impairment questionnaire
CSF	Cerebrospinal fluid
DESCRIPA	Development of screening guidelines and criteria for predementia Alzheimer's disease
DSM	Diagnostic and statistical manual of mental disorders
ECog	Everyday cognition questionnaire
ELISA	Enzyme-linked immunosorbent assay
FMD	Functional memory disorder
GDS	Global deterioration scale

HADS	Hospital anxiety and depression scale
HBM	Health belief model
ICD	International classification of diseases
I-FLEX	Short version of the executive interview
LADIS	Leukoaraiosis and disability
LR	Logistic regression
MAC-Q	Memory assessment complaint questionnaire
MCI	Mild Cognitive Impairment
MMSE	Mini mental state examination
MFQ	Memory functioning questionnaire
MRI	Magnetic resonance imaging
MQ	Metamemory questionnaire
NIA-AA	National institute on aging – Alzheimer's Association
NINCDS-ADRDA	National institute of neurological and communicative disorders and stroke and the Alzheimer's disease and related disorders association
NINDS-AIREN	National institute of neurological disorders and stroke and the association internationale pour la recherche et l'enseignement en neurosciences
NP	Neuropsychological
NUD	Non ultra descriptum
PET	Positron emission tomography

PiB   Pittsburgh compound B

PROCOG   Patient-reported outcomes in cognitive impairment
                   questionnaire

P-tau   Phosphorylated tau

SASCI-Q   Sahlgrenska academy self-reported cognitive
                   impairment questionnaire

SCC   Subjective cognitive complaints

SCCQ   Subjective cognitive complaints questionnaire

SCD   Subjective cognitive decline

SCD-I   Subjective cognitive decline initiative

SCD-Q   Subjective cognitive decline questionnaire

SCI   Subjective cognitive impairment

SD   Standard deviation

SMC   Subjective memory complaints

SMC scale   Subjective memory complaints scale

SMI   Subjective memory impairment

SNAP   Suspected Non-Amyloid Pathology

SPECT   Single photon emission computed tomography

SPSS   Statistical package for social sciences

STEP   Stepwise comparative status analysis

T-tau   Total tau

UNS   Utan närmare specification (=unspecified)

VaD   Vascular dementia

DEFINITIONS IN SHORT

Alzheimer's disease

A neurodegenerative disease characterized by certain neuropathological changes and a gradual progression of cognitive and eventually functional impairment. Alzheimer's disease is considered the most common cause of dementia.

Awareness

The ability to accurately appraise aspects of one's own situation or functioning. In this thesis primarily used in relation to cognitive functioning.

Biomarker

A characteristic that is objectively measured and evaluated as an indication of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Dementia

A wide range of progressing cognitive and functional symptoms, caused by disease or injury in the brain. Impairment is severe enough to interfere with daily functioning.

Depressive symptoms

Continuous and troubling symptoms corresponding to, but milder than, criteria for major depressive disorder, such as depressed mood, decreased interest in activities, feelings of worthlessness, changed activity level, changed sleep patterns, changed weight or

	appetite, reduced energy, pessimistic thoughts and reduced self-esteem.
Mild cognitive impairment	A term aimed at describing an intermediate stage between healthy cognitive aging and dementia, characterized by a limited, but test detectable, cognitive decline compared to previously, not severe enough to interfere with basic activities of daily life.
Objective cognitive impairment	Cognitive impairment that may be verified by clinical assessment or standardized neuropsychological assessment, e.g. MCI.
Preclinical AD	A stage preceding MCI, including the spectrum of pre-symptomatic autosomal dominant mutation carriers, asymptomatic biomarker-positive older individuals at risk for progression to MCI due to AD and AD dementia, as well as biomarker-positive individuals demonstrating only subtle cognitive decline.
Stress	A state of mental or emotional strain or tension resulting from adverse or demanding circumstances.
Subjective cognitive decline	Self-perceived decline in any cognitive domain over time. The category SCD does not require cognitive testing or confirmation of cognitive decline by an informant.

SCD is not associated with a particular disease or disease state per se. When reporting on SCD, the specific disease condition to which it refers in the particular context should be added (e.g. SCD in pre-clinical AD).

Symptom

A subjective evidence of disease or physical disturbance observed by the patient.

2 INTRODUCTION

2.1 Short description of the research topic

Subjective cognitive decline (SCD) refers to concerns regarding one's cognitive functioning, in the absence of objective evidence of impairment [1]. In the memory clinic setting, it refers to those patients who are worried for dementia development and seek consultation for cognitive decline, although their scores on cognitive tests turn out to be in the normal range. Gradual decline and a continuous erosion of the brain and functions characterize most dementia disorders, which leads to the puzzling question of how the first symptoms manifest themselves and if they are possible to measure. This thesis deals with the role of SCD in relation to the dementia continuum and strives to contribute to answering the question of whether having self-reported cognitive difficulties is a risk factor for development of dementia.

SCD is a complex topic. Subjectively experienced cognitive symptoms are of heterogeneous origin and may follow different trajectories. SCD may progress to objectively measurable levels, possibly leading to dementia. However, SCD may also remain stable, or fluctuate. SCD may reflect actual changes in an individual's normal aging process. Furthermore, SCD may signify objective cognitive change caused by factors other than a progressing dementia disorder - such as other somatic conditions, or mood disorders. They may reflect personality traits associated with negative self-appraisal and worry. Some persons with SCD seek help while others do not. Some persons are accurate in their self-appraisal – others are not.

This complex heterogeneity makes SCD difficult to interpret, and not easy to manage in the clinic. However, patients with SCD are common help-seekers at memory clinics, and more knowledge is needed to understand the characteristics and relevance of these symptoms.

2.2 Dementia

2.2.1 Definitions and underlying diseases

Dementia is characterized by progressive loss of cognitive functions, until the individual has lost all independency and ability in daily life. The cognitive dysfunction is caused by neuronal death and deteriorating synaptic function, although the driving mechanisms involved may differ depending on etiology. Dementia is not a disease in itself – it is a description of symptoms, a syndrome, caused by a disease or injury. A disease leading to dementia may be called a 'dementia disorder'. In the revised Diagnostic and Statistical Manual of mental disorders (DSM-V) from 2013 [2], the term dementia has been replaced with 'major neurocognitive disorder'. 'Mild neurocognitive disorder' signifies earlier stages such as 'mild cognitive impairment' (MCI). However, 'dementia' is still by far the most familiar concept, and will be used throughout this thesis. A diagnosis of dementia requires that memory and at least one more cognitive domain is significantly impaired compared to previous level, which should be determined by neuropsychological assessment. Additionally, there should be changes in socioemotional functions such as emotional lability, apathy, irritability or changes in social behavior. Symptoms should have a duration of at least 6 months [3].

Alzheimer's disease (AD) is considered the most common etiology of dementia. In persons over 65 years suffering from dementia, approximately 50-60 % have AD type dementia [4]. AD is characterized by a specific pattern of brain pathology including neuritic amyloid plaques and neurofibrillary tangles [5]. Except for in more recent research criteria [6, 7], biomarkers indicating such pathology are however generally not included in clinical criteria for AD dementia or the pre-dementia stages. The diagnosis is determined primarily based on the absence of other etiologies, such as vascular factors. A typical neuropsychological profile of AD dementia starts with decline in episodic memory, followed by language (object naming, verbal fluency, semantic categorization) and executive, visuospatial, and attention dysfunction [8]. AD dementia may have early onset (before the age of 65) or late onset. There are also atypical variations and AD dementia forms concurrent with vascular pathology (mixed forms).

Vascular dementia is the second most common dementia form. The etiological overlap between AD dementia and vascular dementia forms is not fully determined. Vascular dementia presents in several different forms, such as acute onset, multi-infarct, subcortical vascular, mixed or unspecified forms [3]. The common denominator is blocked or reduced blood flow to the brain. In short, the neuropsychological profile in the subcortical vascular dementia form – which is the most frequently occurring vascular form in our sample - is more related to dysfunction within attention, speed and executive areas, and less to memory functioning, compared to AD [9, 10].

Less frequent dementia disorders include Lewy-body dementia, frontotemporal dementia (subdivided into several different variants) [8] and dementia caused by Huntington's disease, Parkinson's disease, HIV and Creutzfeldt-Jakob [3].

2.2.2   Prevalence and health care costs

The prevalence of dementia is largely related to aging. The elderly population is growing in proportion as well as absolute numbers - globally as well as nationally. In 2012, only one country (Japan) had a proportion of individuals over 60 years old that exceeded 30% of the population. Projections show that many countries e.g. almost all European countries, China and Canada will have a similar proportion of older individuals in 2050 [11]. In Sweden, it has been estimated that the number of persons over 80 years will increase from 497.000 to 810.000, from 2010 to 2030. That would mean a 2.5 times greater increase compared to the 20-year period between 1990 and 2010 (from 370.000 to 497.000) [12].

In 2015, dementia affected over 47 million people worldwide. By 2030, more than 75 million people are estimated to be living with dementia, and the number is projected to triple by 2050 [11]. In Sweden, the number of individuals with dementia was estimated to 160.000 in 2012, with approximately 26.000 new cases per year and economic societal costs estimated to 63 billion SEK yearly [12, 13]. The national board of health and welfare (Socialstyrelsen) concluded in a report from 2014 [14] that methods for examining patients with prodromal dementia varies greatly across Sweden, and that e.g. level of education and birth country influences the access to

investigation and care. More than half of patients who were diagnosed with dementia in primary care received a non-specific diagnosis ('dementia UNS'), which limits the possibilities of appropriate treatment [14]. The number of yearly dementia investigations at Swedish memory clinics were estimated to 14.000 in 2012, of which approximately 50 % resulted in a dementia diagnosis [12].

Several variables affect the prevalence of dementia, such as the age of the population and treatment of risk factors, which makes forecasting difficult. The forecasted dementia prevalence increases alongside the longer life expectancy – from 160.000 Swedish persons with dementia in 2010, to approximately 230.000 in 2030 [12]. Conditions related to elevated dementia risk - such as obesity, diabetes and hypertension – have increased in many countries during the last decades. However, the awareness of and treatments for cardiovascular risk factors have improved [15]. Additionally, level of educational attainment is increasing globally – a factor that has been hypothesized to affect dementia prevalence [15]. Thus, the number of individuals with dementia is increasing worldwide, however the risk for an individual to develop dementia seems to be declining, at least in high-income countries [15].

2.2.3 The early cognitive continuum of dementia

There is great variability between individuals regarding how cognitive functioning changes along with age. Many older adults out-perform younger people on cognitive tests, and remain cognitively preserved. However, some aspects of memory (e.g. episodic memory) and attention (e.g. dividing or shifting attention) often decline with increasing age – while others seem to be more preserved (e.g. maintaining concentration; semantic memory). Furthermore, decline in executive functions has been described as a key contributor of cognitive change in older ages [16]. Sensory changes such as visual or auditory impairment may also affect performance on cognitive tasks. Consequently, the close and complex inter-relations between aging, cognition and dementia complicates the assessment of early signs of dementia.

Research on early dementia characteristics, especially for AD dementia, focus on the cognitive syndrome parallel to the pathophysiological process [17]. The

cognitive continuum of dementia refers to the gradual change in cognitive processes alongside the neuropathological progression, from the earliest symptoms to severe dysfunction. For most dementia conditions, it is still unclear how and at which point in time the neuropathological process begins. Simply put, functional disability is a consequence of cognitive impairment, which is a consequence of neuropathological events – which is a consequence of largely unknown factors. With respect to AD dementia, mounting evidence suggests that brain pathology is present for more than 20 years before clinical diagnosis [18]. A majority of the AD treatment trials have targeted brain amyloid accumulation, and have largely failed - believed to be partly a result of treatment initiated too late in the disease process when irreversible loss of brain cells has already taken place [19] .

Diagnostic categories designated to describe potential early dementia stages have largely been based on observations of test-detectable symptoms – i.e. objective cognitive impairment. Although several similar diagnostic categories have been used (e.g. cognitive impairment no dementia – CIND [20]; 'benign senescent forgetfulness' [21]), mild cognitive impairment (MCI) is by far the most prominent one. MCI is a term to describe a possible intermediate phase between normal cognition and dementia, characterized by cognitive impairment that is more pronounced than what would be expected in 'normal aging'. The impairment in MCI is not at the level of affected basic 'activities of daily living' (e.g. self-caring, self-feeding), but the ability to perform more complex daily tasks – 'instrumental activities of daily living', such as paying bills, cooking or using technical devices, may be somewhat affected. The term was first suggested by Reisberg [22], but has since then undergone continuous development. One of the first widespread descriptions of MCI [23] entails the following criteria: (a) complaint of defective memory, (b) normal activities of daily living, (c) normal general cognitive function, (d) abnormal memory function for age, and (e) absence of dementia. In 2004, the MCI concept was subdivided into: single vs multiple domain MCI (one or more cognitive domains affected), and amnestic vs non-amnestic MCI (memory affected or not) [24, 25]. In 2011, the NIA-AA (the national institute on aging – Alzheimer's association), suggested that biomarkers should also be included in the MCI criteria [6], although purely for research purposes.

Importantly, even though most studies report that they have applied consensus MCI criteria (often referred to as the 'Petersen criteria'), there are almost as

many varying methods used to operationalize these criteria, as there are published reports. Nevertheless, numerous studies have presented support for increased risk to develop dementia in patients categorized as MCI. In a meta-analysis covering data from 41 studies, it was concluded that the annual conversion rate from MCI to dementia was 5-10% (6.5% to AD; 1.6% to vascular dementia - VaD) [26]. The cumulative proportion progressing from MCI to dementia averaged 32% across 13 studies using the 'Petersen criteria' and following over 4.300 individuals with MCI for 3-10 years. However, it was also observed that most MCI patients do not convert to dementia within a foreseeable time frame [26]. Despite that there is a problem with lack of specificity, and that risk estimates vary widely based on different methodological factors, the proportion of dementia converters from MCI are significantly higher than in the normal population [27], which makes MCI a highly relevant clinical concept.

Although MCI criteria have varied over the years, being categorized as MCI always implies a mild - but to some degree objectively detectable - cognitive impairment. During the last decade, there has been an increasing interest within symptom-based research to investigate even earlier phases of cognitive decline – characterized by merely subjective reports of difficulties. This research area has grown exponentially in the last 20 years. During the 1980's and 1990's, subjectively reported cognitive symptoms were only sporadically mentioned in scientific papers on dementia, whilst over 300 papers have been published with subjective cognitive symptoms as a key topic during the last seven years (according to a PubMed search on 20 March 2017). One of the earliest accounts was presented by Reisberg in 1986 [28], hypothesizing that - based on clinical observations - a phase characterized by only subjective cognitive difficulties would last approximately 15 years before the onset of detectable cognitive impairment (MCI). The border between subjective and objective cognitive functioning, and between subjective cognitive decline associated with disease and normal aging are obviously large challenges for this research area.

2.3 Signs, symptoms, biomarkers and risk factors

To understand and differentiate between the various methods available for assessing pre-dementia phases, it is worth-wile to consider the difference between symptoms, signs, biomarkers and risk factors. A 'symptom' is "a subjective evidence of disease or physical disturbance observed by the patient" [29]. A medical 'sign' is "an objective evidence of disease especially as observed and interpreted by the physician rather than by the patient or lay observer" [30]. A 'biomarker' has been defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [31]. Thus, 'biomarker' can be somewhat regarded as a subcategory of medical 'signs' (although it may also be used to indicate normal biological processes). A 'risk factor' is a broader concept including variables that increases risk or susceptibility to develop a condition. The overall most important risk factor for dementia is old age. For AD dementia, other known risk factors are e.g. female sex (onset > 65 years), male sex (onset < 65 years) [4] low levels of education, heredity and smoking [32], and for vascular dementia forms e.g. prior stroke episodes, elevated systolic blood pressure, and excessive alcohol consumption [33].

It should be noted that the term 'symptom' is often used interchangeably with 'sign' in the literature. For example, the preclinical stage of AD is described as a 'pre-symptomatic stage', even though this refers to an absence of test-verified signs rather than absence of experienced symptoms. Furthermore, symptoms, signs, biomarkers and risk factors should not be mistaken for clinical endpoints. The only clinical endpoint of dementia is a manifest dementia state fulfilling diagnostic criteria. Neither is any currently available symptom, sign, biomarker or risk factor consistent or accurate enough - in relation to actual dementia development – to be considered a surrogate endpoint (= a substitute for a clinically meaningful endpoint).

Most methods associated with assessing pre-dementia stages focus on early *signs*. Identification of early signs of dementia may be regarded as resting on three pillars: 1) Brain imaging, used to observe structural and functional brain changes by techniques such as magnetic resonance imaging (MRI), positron

emission tomography (PET), and single-photon emission computed tomography (SPECT) ; 2) neurochemical analyses, used to measure protein concentrations in the cerebrospinal fluid (CSF) mirroring pathogenic processes in the brain; and 3) neuropsychological assessment, used to assess cognitive functions and dysfunctions, which may be linked to central nervous system disease or injury. These three pillars are all well-established measures of pre-dementia signs, and may to a varying degree also be described as biomarkers. The term biomarker has, within AD research, often been inaccurately limited to describe neurochemical markers, although often used also for brain imaging markers [34]. Despite its strong and scientifically anchored associations with actual and specific brain changes, neuropsychological assessment usually is not described as a biomarker, even if it meets most definitions of what a biomarker is. The 'bio' in biomarker refers to that the object of measurement should be biological or intrinsic (from inside the body), but the marker itself may be intrinsic or extrinsic [35].

The differentiation between symptoms, signs, biomarkers and risk factors facilitates the understanding of assessment methods as different parts of the dementia puzzle, and clarifies the role of SCD. Regarding the neuropathological changes of dementia, there are no symptoms – only signs, such as structural, functional or neurochemical brain changes. Regarding the cognitive changes – there may be both symptoms (self-report, i.e. SCD) and signs (measured by neuropsychological assessment, or clinical assessment when signs are more manifest). The main hypothesis of the SCD research field is that clinically relevant 'cognitive symptoms' are measurable before 'cognitive signs'. Neuropsychological assessment, brain imaging and neurochemical analyses concerns signs. Figure 1 illustrates the chronological onset of symptoms and signs in relation to the pathophysiological and clinical progression ending with dementia.

Risk factors and unknown
causes of disease

*Preclinical
stage*

Pathophysiological
changes

*'Signs' measured
by e.g. brain
imaging and CSF
analysis (i.e.
'biomarkers')*

Symptoms?

(=SCD)

*'Symptoms'
measured by self-
report*

*Clinical
stage (MCI
followed by
dementia)*

Cognitive
changes

*'Signs' measured by
neuropsychological and
clinical assessment*

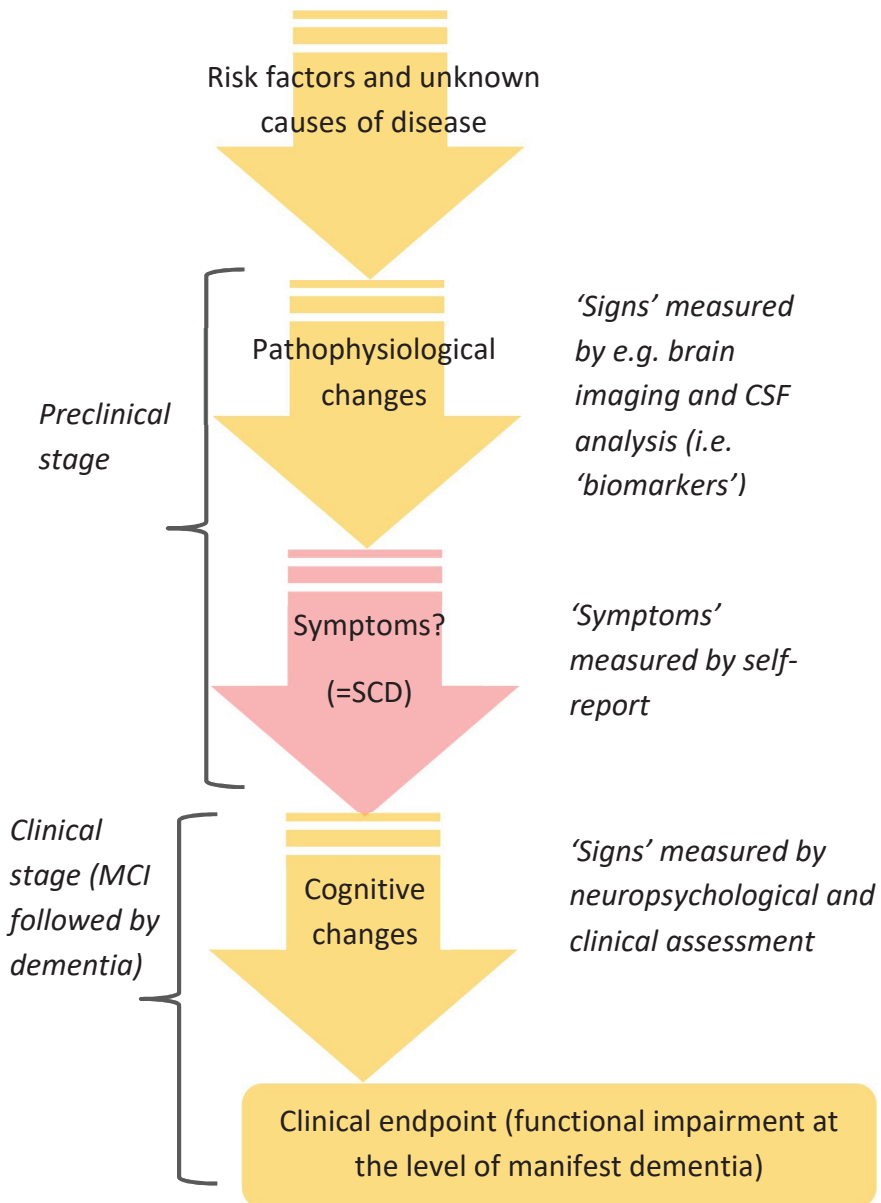Clinical endpoint (functional impairment at
the level of manifest dementia)

*Figure 1. Symptoms and signs in relation to the pathophysiological and clinical
progression ending with dementia.*

2.4 The SCD concept

2.4.1 Prevalence of SCD

Experiencing subjective cognitive difficulties – in lay-terms often referred to as 'memory problems' – is common in the general population. The prevalence rates of 'memory complaints' has been reported as 25-50% in community-based studies [36], with differing methodology being a likely cause of the large variations. Results from a large Norwegian survey reported that nearly half of the respondents had minor subjective memory problems, increasing with age [37], and the prevalence of experiencing 'forgetfulness' was 32% in a British health survey. One study compared 'memory complaints' in younger vs older healthy adults, and found that complaints about memory functioning was frequent in both age groups but had different features – e.g. older persons had more general complaints and younger person were more often told by others that they were forgetful [38].

Among persons seeking help at memory clinics (generally consisting of individuals who may be categorized as either SCD, MCI or manifest dementia), the prevalence of SCD (without MCI or dementia) has been reported to be 41% [39]; 18% [40]; 24% [41] and 55% in a younger sample [42]. At the Karolinska University hospital memory clinic, the proportion of SCD patients increased from 24% during 1999 to 38% in 2005, showing increasing rates of SCD help-seeking [43].

2.4.2 An overview of the SCD research area

Research on SCD in relation to dementia may be described in terms of four overlapping, although different, areas (Figure 2).

1) Concept development, dealing with how to define and limit the concept of SCD. This includes terminology and criteria.

2) Method development – development and evaluation of different methods to measure SCD, and investigation of how different research settings may influence findings.

Areas 1 and 2 serve as a basis for areas 3-4, which deal with the potential causes of SCD.

3) Confounders – the associations between SCD and conditions other than dementia, such as other somatic conditions, mood disorders; the influence of e.g. demographic factors and personality traits; compromised awareness of cognitive functioning; and factors associated with help seeking for cognitive symptoms.

4) Associations with dementia - dealing with the key issue of 'if and how SCD is associated with dementia', investigated both cross-sectionally and longitudinally by analyzing SCD in relation to e.g. neuropsychological tests; functional and structural brain-changes; neurochemical markers; genetic factors; and actual conversion to detectable cognitive impairment and dementia.

Obviously, SCD may to a varying degree also be present when dementia has become manifest – this theme will however not be elaborated on in this thesis as it deals only with SCD prior to manifest dementia.
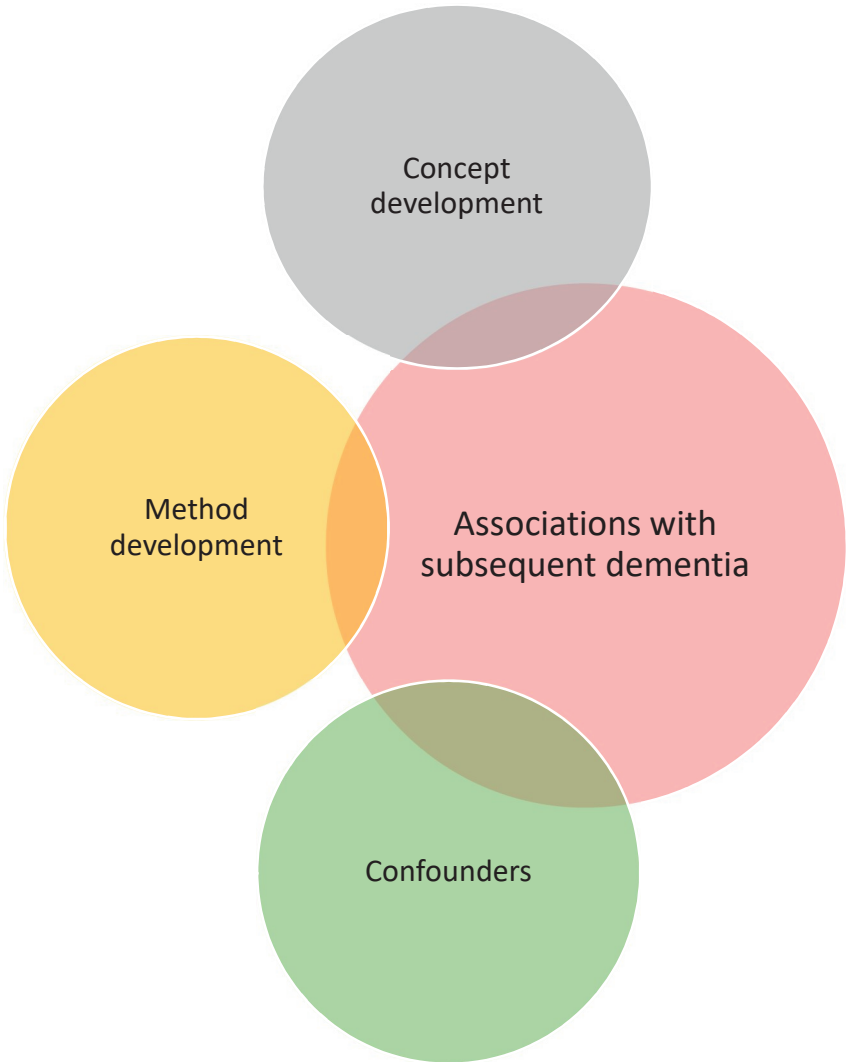
Figure 2. A brief overview of the SCD research area.

2.5   SCD - concept development

2.5.1   Terminology

Several terms have been used interchangeably in this research field: 'subjective cognitive impairment' (SCI); 'subjective memory impairment' (SMI); 'subjective memory complaints' (SMC); 'subjective cognitive complaints' (SCC), and lately 'subjective cognitive decline' (SCD), to mention the most frequently used terms. 'Forgetfulness' has sometimes been used, and 'metamemory' – the knowledge of one's own memory capacity – is also a related concept [44], however more often used in an experimental than in a clinical context. A PubMed search on 20 March 2017 using the terms subjective cognitive impairment, complaints or decline, resulted in 239 reports, and 248 reports when using subjective memory impairment, complaints or decline. Thus, both 'memory' and 'cognition' are frequently used terms in this context. Figure 3 shows the use of different terms over time, based on PubMed published reports.

'Memory' may be a preferred term when communicating with patients, because 'cognition' is a less known concept. However, the term 'memory' may attain to many different functions, both scientifically and in the common language. Health care professionals working in a memory clinic will recognize that patients refer to "memory problems" when they talk about very different types of dysfunction, such as trouble finding words, difficulties finding one's way, having a hard time focusing on a written text, or difficulties organizing an event. For neuropsychologists and other specialized health care professionals, these difficulties would translate into difficulties within

different *cognitive domains* – e.g. language; visuospatial function; speed/attention and executive function. Thus, we cannot be sure that we mean the same thing when we talk about 'memory'.

The terms 'impairment', 'decline' and 'complaint' to designate deficiency have also been debated. Stewart [45] suggested the term subjective cognitive impairment (SCI) to be used in population contexts and subjective cognitive complaints (SCC) to be used in clinical contexts, as a 'complaint' more clearly refers to an act of help-seeking. It has also been argued that 'complaints' should not be used at all, because it may come across as a condescending term [46, 47].
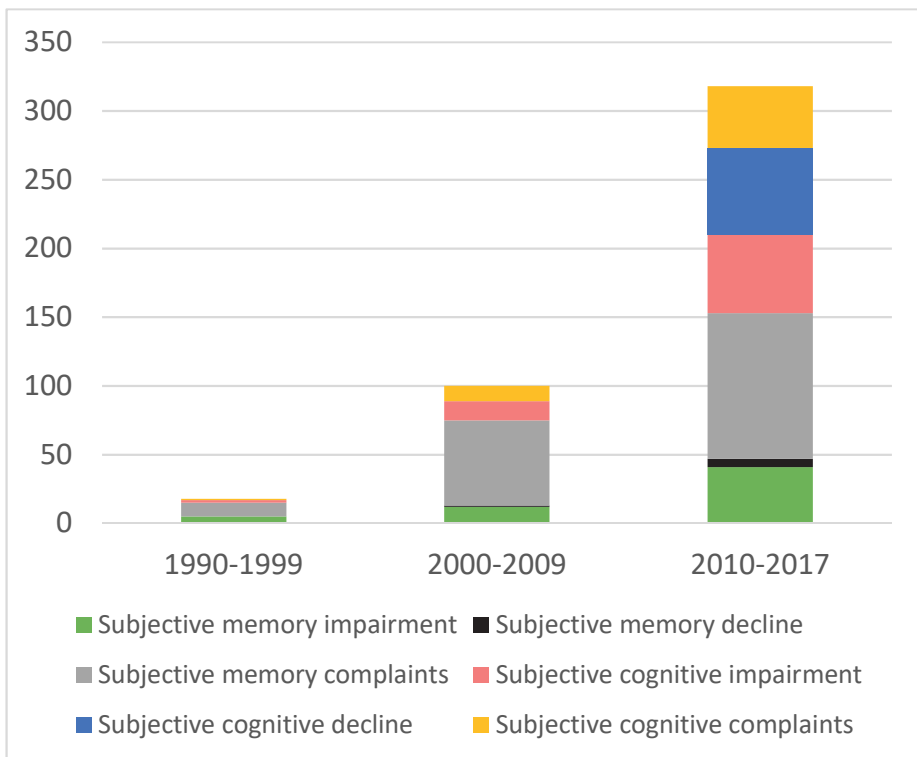

Figure 3. Number of PubMed indexed scientific articles using different terms related to subjective cognitive symptoms, between 1990 and 2017, according to a PubMed search on 20 March 2017.

2.5.2 Toward consensus criteria

Until recently, 'subjective cognitive symptoms' has been a poorly defined concept with apparent absence of consensus, which may perhaps be forgiven due to its relative novelty. When applied clinically, rather vague classifications are sometimes used such as ICD-10 R41.8A ('mild cognitive impairment, subjective') or Z03.3 ('observation for suspected nervous system disorder') [3]. In their review of 44 scientific reports in which the theme of subjective cognitive symptoms in relation to dementia was addressed, Abdulrab and Heun [48] found that no definition included a comprehensive set of criteria and that there was no overall agreement between different authors or studies.

Two sets of criteria were proposed in 2008. Abdulrab and Heun used the term 'subjective memory impairment'[48], and Reisberg *et al*. [47] used the term 'primary idiopathic subjective cognitive impairment'. Both criteria require a subjective cognitive deficit perceived by the affected individual as a decline compared to previous function, with absence of objective cognitive impairment and dementia. The criteria proposed by Abdulrab and Heun included factors such as frequency of symptoms, age at onset, and duration of symptoms. Furthermore, they suggested an additional consideration of gradual vs sudden/staggered onset, arguing that gradual onset would indicate underlying AD and sudden/staggered onset would indicate VaD. The criteria by Reisberg addressed that other conditions, possibly leading to cognitive decline, must be ruled out. The two sets of criteria account for the role of informant reports in contradictory ways. Abdulrab and Heun suggested that informant reports may be used as supportive criteria. In the criteria by Reisberg, corroboration by an informant is rather considered a potential objective sign of decline, and is thereby incompatible with the limitations of the 'subjective' patient category. Another distinction between the two sets of criteria is the use of single vs multiple domains (Abdulrab and Heun used 'memory'; Reisberg used 'cognition') [47, 48].

In 2012, the Subjective Cognitive Decline Initiative (SCD-I) was launched - an international working group with the goal of formulating a research agenda for the field [46]. The group consists of main investigators of ongoing biomarker initiatives including ADNI (Alzheimer's disease neuroimaging initiative), AIBL (Australian imaging, biomarker and lifestyle flagship study

of ageing), and DESCRIPA (Development of screening guidelines and criteria for predementia Alzheimer's disease) [46].

The SCD-I group suggests that the term Subjective cognitive decline 'SCD' should be used in future research. They argue that 'decline' is more appropriate than 'impairment', since the aim is to identify deterioration from previous functioning. Furthermore, they choose 'cognitive' over 'memory' because the first cognitive impairments of AD dementia are not limited to memory, and because of the semantic confusion concerning cognition vs memory [46]. The SCD-I definition of SCD is "self-perceived decline in any cognitive domain over time". They acknowledge that SCD is not associated with a specific disease per se, and that objective cognitive impairment (i.e. MCI) should be excluded when SCD is studied in the context of dementia. The SCD-I further suggests using an enriched category of SCD – SCDplus, including features to increase the likelihood of preclinical AD. Suggested research criteria for 'pre-MCI SCD' [46] are as follows:

- Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event
- Normal age-, gender-, and education-adjusted performance on standardized cognitive tests, which are used to classify MCI or prodromal AD

Criteria included in the enriched SCD plus category:
- Subjective decline in memory, rather than other domains of cognition
- Onset of SCD within the last 5 years
- Age at onset of SCD ≥60 years
- Concerns (worries) associated with SCD
- Feeling of worse performance than others of the same age group

If available or possible to obtain in the respective study:
- Confirmation of cognitive decline by an informant
- Presence of the apolipoprotein E (*APOE*) ε4 genotype
- Biomarker evidence for AD (defines preclinical AD)

MCI and dementia are exclusion criteria, together with presence of psychiatric or neurologic diseases (other than AD), or substance abuse, that may explain the symptoms. Individual symptoms of depression or anxiety, which do not reach the threshold of a disorder, are not considered exclusion criteria [46]. With minor exceptions, the SCD-I definition largely corresponds with the criteria previously suggested by Abdulrab and Heun [48], and Reisberg [47]. Importantly, the SCD-I emphasizes that the characteristics of SCD related to preclinical AD are probably variable and expressed heterogeneously.

Another term has been suggested to describe the stage with the earliest objective cognitive signs – 'subtle cognitive decline' [7], thus placed between SCD and MCI on the cognitive continuum. The criteria for 'subtle cognitive decline' are not clearly formulated. For example, it has been suggested that the term could be used for individuals who perform within normal range on tests but demonstrate evidence of decline from their own baseline, or individuals with impaired test results only on very challenging tests [7]. The term 'subtle cognitive decline' has mostly been used in the context of preclinical AD, outlined further below.

The SCD research field would certainly gain from increased stringency regarding use of terminology and methodology, and the development of clearer criteria is highly warranted. The work on this thesis began before the term SCD was established. Nonetheless, 'SCD' is used as the key term throughout the thesis. To simplify, the term SCD is also used when referring to previous research using other but similar terms such as SMI, SCC or SCI. 'Subjective cognitive symptoms' is used interchangeably with SCD, and 'self-reported' is used interchangeably with 'subjective'.

2.5.3 'Preclinical AD'

The concept of 'preclinical AD' and similar terms may be viewed as the pathophysiological counterpart of the symptomatically based SCD concept, with respect to AD type dementia. The two concepts are interesting to compare because they both deal with the phase prior to objectively measurable cognitive decline. However, that is largely the end of the similarities. 'Preclinical AD' is

used to define several stages of different pathophysiologic changes prior to AD, characterized by different outcomes of abnormal biomarkers. SCD may "occur in the preclinical stage of AD" [46], but is not a prerequisite for preclinical AD criteria - some would describe SCD as a subcategory of 'preclinical AD'. However, 'preclinical AD' is limited to AD, while SCD is not limited to a specific etiology. Thus, the two concepts should not be regarded as competing or comparable in validity, but are potentially relevant to combine in analyses.

Jack et al [18, 49] has presented a hypothetical model illustrating the time course for five different biological markers of AD, in relation to symptom development (Figure 4). An important point of this model is that both pathologic and clinical changes occur gradually over time. As this model illustrates, pathophysiological changes are likely to occur for a long time before clinical signs become evident. A potential problem with the term 'preclinical AD' is that it may be misinterpreted as a stage inevitably leading to AD dementia. However, neuropathological abnormality may also occur without symptoms ever developing [50, 51].
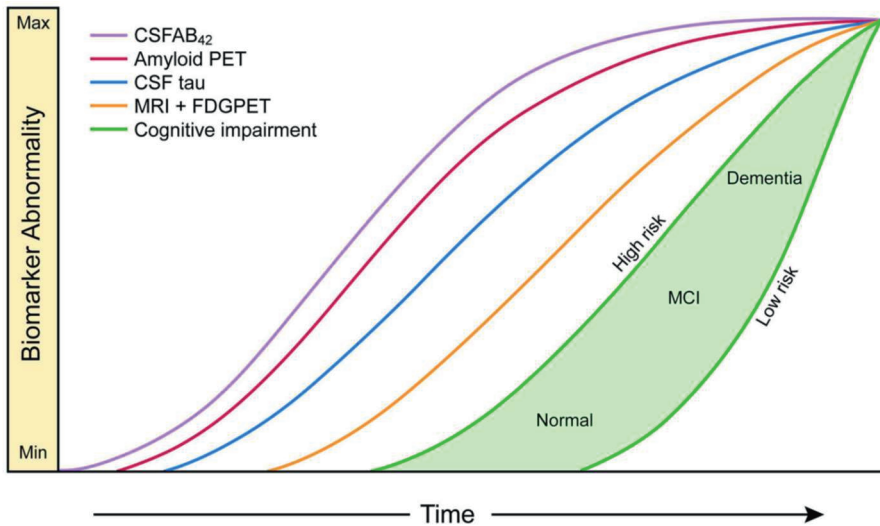
Figure 4. Revised dynamic biomarkers of the AD pathological cascade model. Reprinted from The Lancet Neurology, Vol. 12, Jack et al., Update on hypothetical model of Alzheimer's disease biomarkers, copyright (2013), with permission from Elsevier.

In 2012, an international working group convened by the NIA-AA presented a conceptual framework for preclinical AD stages, based on current evidence [7]. Table 1 outlines a summary of the recommended stages, generally based on different combinations of markers of amyloidosis and neurodegeneration. Stage 0 (no signs of pathology or cognitive decline) and SNAP ('suspected non-Alzheimer pathophysiology' = neurodegeneration, but no amyloidosis and no cognitive decline) were added to the framework in a later publication [52]. One study using the NIA-AA-stages observed an increased risk of progression to MCI and AD dementia in the third stage of 'preclinical AD' [53]. It was concluded that high-level subjective cognitive symptoms may provide a sensitive indicator of further cognitive decline in preclinical stages with abnormal biomarkers [53]. Another study reported that the greatest severity of SCD was observed at 'preclinical stage 2', thus when markers for Aβ and tau were both abnormal [54].

Table 1. Stages of 'preclinical AD' and SNAP, recommended by NIA-AA

	Amyloidosis	Neurodegeneration	Symptomatology
Stage 0	-	-	'Asymptomatic'
Stage 1	+	-	'Asymptomatic'
Stage 2	+	+	'Asymptomatic'
Stage 3	+	+	Subtle cognitive decline
SNAP	-	+	'Asymptomatic'

- /+ = negative or positive, as measured by e.g. cerebrospinal fluid (CSF). NIA-AA = national institute on aging – Alzheimer's association; SNAP = suspected non-Alzheimer pathophysiology.

2.6 SCD - method development

2.6.1 Assessing SCD

Even if clearer SCD criteria have been launched, these do not specify which methods to use for assessing specific symptoms of SCD – likely because numerous different methods, from single questions to comprehensive questionnaires, are already applied in different ongoing studies. There is currently no 'gold standard' measure to assess SCD [55]. In specialized settings such as memory clinics, patients may be categorized as having SCD because they sought help for cognitive symptoms but cognitive impairment could not be verified [55]. That is, no specific instruments or questionnaires are in such cases used to categorize an individual as SCD. One review focusing on methods used to assess subjective memory impairment identified 44 relevant studies [48]. In 39 % of the studies, subjective memory impairment was determined by asking a single question with a yes/no response, often a variation of *"do you have trouble with your memory?"* The authors criticized this method as likely too unspecific and over-inclusive. An additional five papers (11 %) used a single question with a graded response. Another 14% used sets of questions (scales) with no/yes responses. In 20% of the studies, a questionnaire or subscale with scored responses was used [48].

Several questionnaires exist, varying greatly considering number of items, target population, scope, development method, and established properties pertaining to validity and reliability. A review of self-report instruments used within the 19 studies under the SCD-I umbrella identified 34 self-report measures comprising 640 cognitive self-report items [56]. MAC-Q (Memory assessment complaint questionnaire) and ECog (Everyday cognition questionnaire) were the most commonly used instruments. The ECog is a 39-

item instrument for informant-report (although used as a self-report measure in the ADNI study), with questions related to several cognitive domains [57]. The MAC-Q was developed in 1992, with six items selected based on clinical experience and on empirical evidence regarding patterns of age-related memory loss. It was designed to quantify presence and severity of memory complaints in the elderly [58]. These and other questionnaires that stand out as frequently used in the literature and/or otherwise of potential interest are presented in Table 2.

Table 2. List of frequently used instruments to measure subjective cognitive decline

Name Year Country	Features	Participants assessed for instrument development	Scale development	Example studies
CFQ [59] **1982** **UK**	25 items multi-domain	Community-based sample	Expert panel	US community-based study [60]
MFQ [61] **1990** **USA**	25 items memory domain	Healthy volunteers	Based on previous instrument	Australian community-based study [62]
MAC-Q [58] **1992** **USA**	6 items memory domain	Patients with AAMI (=MCI)	Experts	Danish memory clinic study [63]
SMC scale [64] **1996** **The Netherlands**	10 items multi-domain	Community-based sample, later evaluated for differences between healthy controls and SCD patients.	Based on previous instrument	AMSTEL study [64]; Lisbon memory clinic study [65]
PROCOG [66] **2006** **USA**	55 items multi-domain	MCI and mild AD	Patients in focus groups, experts	-

Table 2 continued. List of frequently used instruments to measure subjective cognitive decline

Name Year Country	Features	Participants assessed for instrument development	Scale development	Example studies
SCCQ [67] 2006 Australia	60 items multi-domain	Healthy volunteers	Experts (unclear)	-
ECog [57] 2008 USA	39 items, multi-domain	Originally intended for informant reporting. Based on mixed clinical/population sample	Survey of existing measures, literature review, experts	ADNI [68]
CDQ [69] 2011 Sweden	20 items, multi-domain	Community-based sample (Betula study)	Experts, statistical analysis	-
SASCI-Q [70] 2013 Sweden	45 items, multi-domain	Memory clinic patients with SCD, healthy volunteers	Patient interviews, experts	Gothenburg MCI study [71]
SCD-Q [72] 2014 Spain	24 items, multi-domain	Healthy volunteers, patients with SCD, MCI, dementia	Survey of existing measures, literature review, experts	Barcelona Memory clinic study [73]

AAMI = age-associated memory impairment; ADNI = Alzheimer's disease neuroimaging initiative; AMSTEL = Amsterdam study of the elderly; CDQ = cognitive dysfunction questionnaire; CFQ = Cognitive failures questionnaire; ECog = Everyday Cognition questionnaire; MAC-Q = Memory assessment complaint questionnaire; MFQ = Memory functioning questionnaire; PROCOG = Patient-reported outcomes in cognitive impairment questionnaire; SASCI-Q = Sahlgrenska academy self-reported cognitive impairment questionnaire; SCCQ = Subjective cognitive complaints questionnaire; SCD-Q = Subjective cognitive decline questionnaire; SMC scale = Subjective Memory Complaints scale

Many of the frequently used questionnaires were developed about 20-30 years ago. A general tendency for instruments developed in later years is that more specific clinical populations are targeted. There is also a tendency to widen the object of assessment from 'memory' to 'cognition', which is in line with current evidence that multiple cognitive domains, and not just memory, are affected also early on the dementia continuum [74]. Two questionnaires (other than the instrument presented in this thesis study I) has been developed or subsequently validated to assess differences between healthy controls and patients with SCD (the subjective memory complaints scale – SMC scale, and the subjective cognitive decline questionnaire - SCD-Q, both presented about concurrently with our instrument Sahlgrenska academy self-reported cognitive impairment questionnaire - SASCI-Q) [65, 70, 72]. Another recent study used advanced statistical methods, such as item response theory, to identify a subset of relevant SCD questions [75]. By this statistical approach, questions were grouped into other themes (e.g. global memory functioning and temporal comparisons) than the traditional cognitive domains [75].

2.6.2 SCD in different research settings

A distinction needs to be made between SCD in community/general population contexts vs clinical contexts. Early studies (during 1990-2005) on subjective cognitive symptoms were often large population-based studies, whilst the proportion of clinically based studies have increased in publications that are more recent. In population-based studies, subjects may be assessed as 'having SCD' by their response to a question or questionnaire about cognition or memory, and are not active help-seekers, contrary to patients in clinical settings. This distinction was acknowledged already in early research [36] and was further elaborated by Stewart [45], who suggested that the term 'complaints' therefore is more suitable for clinical research settings, and 'impairment' for epidemiologic settings. The issue is especially relevant considering the high prevalence of subjective cognitive symptoms in population-based studies. Memory complaints severe enough to trigger help seeking are likely to be of higher clinical validity than 'general comments' referring to 'poor memory' in population-based populations [76]. This was supported by a study that observed that SCD was more 'severe' in patients who sought help at a memory clinic than in subjects with SCD identified in

population-based studies [65]. The prognosis of SCD may also differ – it has been observed that memory clinic patients have a higher risk of conversion to dementia [77, 78]. However, negative findings were also reported [79]. Although clinically based studies often include smaller samples compared with population-based studies, they generally present better-characterized patient groups, e.g. separating between SCD and MCI.

Two important current studies – ADNI and AIBL - used mixed samples, consisting of both volunteers and memory clinic patients, which may be methodologically problematic [80]. The SCD-I group acknowledged sample differences and argued that "all SCD studies should explicitly describe their recruitment strategy and describe the setting" [46, 55]. Typical research settings include (1) population-based studies, (2) volunteer samples, and (3) medical help–seeking samples [46]. Epidemiological studies generally have larger samples, followed for longer time periods, compared to clinical studies, whilst clinical studies perform more detailed examinations [81], e.g. more frequently separating between SCD and MCI. More comprehensive test batteries are often used in clinical studies, thus the threshold for determining MCI is therefore likely lower in clinical settings [81].

Additionally, different paths to recruit 'normal healthy controls' or 'healthy volunteers' lead to sample differences. On average, persons volunteering through e.g. advertising or media appeals have higher education and are generally more well-functioning compared to controls randomly selected from the general population [82]. Having a family history of dementia is more frequent in volunteers compared to in the normal population [82]. This is not surprising, as individuals with a parent or sibling with dementia may be more motivated to contribute to dementia research. Thus, it should be noted that volunteering in a research study might mask an actual subjective cognitive concern, in some individuals.

Taken together, these findings suggest that there are large variations based on type of research setting and sample in this research field, and the generalizability between clinical and epidemiological studies is limited.

2.7 SCD – confounders

In this context, 'confounders' refers to variables - other than related to dementia - that may be associated with SCD.

2.7.1 Depressive and anxious symptomatology

Intuitively, an association between a negative appraisal of one's own cognitive functioning and a lowered mood, such as depressive symptomatology, seems plausible. A depressive state leads to negative self-perception, which may lead to an increased overall tendency to report various kinds of problems. This association has been thoroughly explored by researchers, likely further motivated by that the many negative findings of associations between subjective and objective cognitive functioning increases the need for alternative hypotheses.

The association between depressive symptomatology/feelings of anxiety, and SCD, has been widely supported in clinical as well as population-based studies [38, 39, 53, 83-87], most frequently focusing on subclinical affective symptoms. One large population-based study observed that this association was similar across different age groups throughout adulthood [88]. A memory clinic based study reported that young patients (< 65 years) with an affective disorder had the most subjective cognitive symptoms compared to other memory clinic groups (dementia, MCI, no cognitive impairment) [85]. Several studies, e.g. sub-studies from ADNI and AIBL, have reported findings suggesting that this association is stronger than the association between subjective and objective cognitive performance [68, 84, 89-91]. A ruminative style of thinking (the tendency to focus on negative emotions and their meaning), and a history of depression has been associated with SCD [92, 93].

A study of the specific *beliefs* related to subjective cognitive symptoms observed that depressive symptomatology was more frequent in memory clinic patients who perceived cognitive symptoms to have serious consequences and who perceived a low personal control over the symptoms [94]. In a continuation of that study, beliefs held about the symptoms were found to be stronger determinants of negative affect than coping strategy, or clinical/demographic factors [95].

Overall, the close connection between negative affect and subjective cognitive symptoms is well established and hardly surprising. However, the directionality between negative affect and cognition is unclear and represents a classic 'chicken-and-egg' problem. What comes first? Depression is sometimes part of the prodromal stage of dementia and/or an independent risk factor of dementia. Recent findings summarized by Kessing [96] suggest that some forms of a depressive disorder, such as early-onset depression before 65 years and a recurrent depression, may be long-term risk factors for subsequent dementia, whereas onset of more recent depressive symptoms may be part of a prodromal phase of dementia. Furthermore, depressive symptomatology is common in MCI [97], manifest dementia [98], especially in vascular dementia forms [99]. One study reported that in amyloid-positive healthy elderly, anxiety symptoms predicted cognitive decline [100]. The Leukoaraiosis and disability study (LADIS), a large clinical multicenter study on elderly persons with white matter changes, has reported associations between depressive symptoms and white matter changes in several cross-sectional studies [101-103]. By using a longitudinal approach they could show support for that white matter changes are likely causal in the pathogenesis of late-life depression [104]. On the contrary, one study observed that SCD was more associated with psychological distress than with vascular risk factors [105].

Results from our Oslo-based sister-study showed that depressive symptoms was common in a small sample of memory clinic patients (40% prevalence) [106]. However, the authors could not establish a significant association between depressive symptoms and AD-type brain changes such as CSF abnormal concentrations and structural/functional brain imaging markers – in neither SCD nor MCI patients [106]. Reports from the AIBL study showed that otherwise healthy volunteers with high scores on a measure of subjective cognitive symptoms exhibited significantly more depressive symptomatology

than those with low scores [53]. The results were especially pronounced for persons with non-pathological Aβ [53].

Despite the convincing associations between SCD and affective factors, it is important to note that reporting subjective cognitive symptoms may be entirely unrelated to both negative affect and disease progression, given the high prevalence of SCD in the normal aging population. Thus, the relation between negative affect and cognitive dysfunction – objective as well as subjective - is complex.

2.7.2 Psychosocial stress

'Stress' is a vague term that can be used to describe a range of phenomena – relating to physical, biological as well as psychological mechanisms. It may be defined as 'a state of mental or emotional strain or tension resulting from adverse or demanding life circumstances' [107]. There are also related concepts describing more severe states such as 'stress-related exhaustion', or the previously popular but unfortunate term 'burnout'. Both terms may be defined as a work-related chronic stress syndrome combining emotional exhaustion, depersonalization, and reduced personal accomplishment [108]. In ICD-10, stress-related exhaustion is diagnosed by code F43.8A ('utmattningssyndrom') [3]. The symptoms and signs of stress-related exhaustion overlap with depression and anxiety, but it has also been distinguished as a unique concept [109].

In this thesis, we use the term 'psychosocial stress'. 'Psychosocial' means 'relating to the interrelation of social factors and individual thought and behaviour' [110]. 'Psychosocial stress' is per definition related to life events or conditions, whilst depression may be unrelated to external events. In simple terms, a person experiencing severe stress is primarily overwhelmed, whilst a person with depression has a low mood and a person with anxiety experiences fear and worry.

Cognitive dysfunction is one of the key symptoms of stress-related exhaustion. However, psychosocial stress in relation to SCD in older adults has been the focus of few studies, compared to the large amount of studies on e.g. SCD and

depressive symptoms. Studies on patients with stress conditions have identified frequent subjective [111] as well as objective [112] cognitive impairment. One study reported that the frequency of subjective cognitive impairment was considerable, although objective cognitive impairments were only mild, in patients with work-stress induced exhaustion [113]. Considering objective cognitive impairment, studies have reported that decline in attention and memory [114, 115] as well as executive functions [116, 117] may be characteristics of stress-related exhaustion. Population-based studies have reported associations between perceived stress and SCD [105, 118], also independent of influences of depression and anxiety [119]. Stress conditions are associated with higher cortisol levels and hypothalamic-pituitary-adrenal axis dysfunction, which has also been observed as a characteristic of patients with SCD [120]. Very few studies exist on stress and SCD in memory clinic samples. A Swedish study reported a 71 % prevalence of psychosocial stress in SCD patients, defined as self-reported daily stress over the last 3 months, compared to 18 % in patients with MCI [39].

2.7.3   Somatic and other conditions

SCD has been reported in a large number of somatic and other conditions, such as traumatic brain injury, epilepsy, bipolar disease, menopause, Parkinson's disease, multiple sclerosis and cancer - just to mention a few that were summarized by Stewart [45]. A comprehensive range of conditions related to cognitive impairment is further accounted for in the text-book Kognitiv Medicin [121]. Besides clinical conditions, SCD has also been identified following different treatment interventions such as chemotherapy and radiation treatment in cancer [122], coronary artery bypass graft surgery [123] and electroconvulsive therapy [124].

2.7.4   Demographic factors

SCD is common throughout life. A large community-based study reported a 29 % prevalence of SCD in younger adults and 52 % in older adults [125]. Not surprisingly, the prevalence of SCD increases with age [37], although some

have not been able to corroborate these findings [126]. Normal aging is associated with some decline in cognitive functioning and therefore a certain presence of SCD is expected in healthy older adults. Consequently, population-based studies have found that the prevalence of SCD in older healthy adults is high - between 25 and 50 % [36]. How SCD is perceived by older adults is for example reflected by the rate of help-seeking, which is low (refer to details below, in the section on Help-seeking) and may suggest that subtle cognitive changes may be perceived as a part of normal aging by most otherwise healthy individuals. SCD has also been associated with lower educational attainment in population-based samples [37]. Considering sex, Holmen [37] found no clear differences between men and women, although men in the normal population reported slightly more difficulties.

2.7.5   Personality traits

Personality characteristics related to SCD in the absence of objective cognitive decline includes high neuroticism, low feelings of mastery and a low level of perceived self-efficacy [127]. High levels of neuroticism in SCD were also supported by a Swedish study [128], but only for female participants. Furthermore, females with SCD reported higher levels of agreeableness and lower scores on extraversion compared to a normal population sample. Another Swedish study [129] investigated differences in personality between memory clinic patients with MCI, SCD and healthy controls. SCD and MCI patients scored higher than controls on anxiety proneness and aggression-hostility, and lower on traits of extraversion. Conscientiousness is another personality trait that has been observed to influence SCD [130], suggesting that persons who are more "organized, achievement-striving and dutiful" are more likely to report and seek help for their SCD. Obviously, the 'chicken-and-egg'-problem is worth regarding also for the relationship between personality traits and SCD. Behavioral changes secondary to cognitive symptoms rather than corresponding to personality traits established previously in life, may very well affect how individuals score on personality questionnaires.

2.7.6 Awareness in relation to SCD and MCI

Awareness may be defined as the ability to accurately appraise aspects of one's own situation or functioning. In this context, awareness refers to whether self-reported cognitive symptoms accurately reflect the actual cognitive level. 'Metacognition', 'metamemory' and 'insight' are related terms, often used interchangeably in studies [131]. 'Anosognosia' generally refers to a more clinically noticeable form of impaired awareness, and is part of the more advanced dementia syndrome. Cognitive experimental studies often use standardized tests such as 'Judgment of learning' or 'Feeling of knowing', to investigate 'meta-cognition' [132] (which is the preferred term in experimental settings). In clinical settings, a common measure of awareness is to compare self-report with reports of functioning from an informant [132].

Cognitive awareness is a key issue on the borderline between subjective and objective cognitive decline. It is especially important in dementia research as awareness of cognitive functioning eventually decreases in patients with a dementia disorder. The degree of awareness has been increasingly studied lately [131], also in incipient stages of dementia such as MCI. The concept of MCI is well used and rather well defined, but also highly heterogeneous potentially including individuals with very few objective signs of cognitive decline and those who are close to a dementia diagnosis. The uncertainty about the level of awareness in MCI patients is reflected in the ambiguous role of SCD in the MCI criteria. Initially, memory complaints were included in the 'Petersen criteria' [23], but in revised criteria they were given a less prominent role as complaints should then be 'corroborated by an informant' [24]. One study found that about half of persons developing AD did not report problems with their memory three years before diagnosis [133] – i.e., when they were supposedly in an MCI phase. Based on such results, it has been suggested that memory complaints should be excluded altogether from the MCI criteria [134].

Roberts *et al*. [131] reviewed 16 studies on the topic of degree of awareness of memory functioning in MCI patients, and addressed the question whether the degree of awareness in MCI may predict future progression to dementia. Unsurprisingly, given the heterogeneity of the MCI concept, the review by Roberts *et al*. concluded that people diagnosed with MCI differ in level of awareness. Whereas some patients with MCI have a low degree of awareness, but not at the level of dementia, others tend to over-estimate dysfunction [131].

In the review, one study investigated 'unawareness' in MCI as a predictor of dementia, finding that under-reporting of functional decline compared to informant reports strongly predicted subsequent dementia (mean follow up time two years). Similar findings have been reported using ADNI data – underestimation of cognitive difficulties in patients with MCI was associated with positive AD biomarkers and progression to dementia [68].

Research concerning meta-cognition is a large separate research area, including numerous theoretical models and hypotheses about e.g. neuroanatomical correlates. A more detailed outline of this field is outside the scope of this thesis. However, it should be noted that a compromised degree of accordance between actual and self-reported level of functioning is common also in the normal population, and it has been hypothesized that impairment or 'incompetence' within an area leads to a diminished capacity to accurately appraise one's ability [135]. Translated to memory functioning: if your memory is poor, you are more likely to forget what you have forgotten.

2.7.7 Help seeking for cognitive symptoms

The implications of subjective cognitive symptoms do not only rely on an individual's identification of problems, but also on her decision and ability to seek medical help. Empirical investigations of the process or determinants of help seeking are not included in this thesis. However, to seek medical consultation is an important common characteristic of the otherwise heterogeneous memory clinic patient group. Scientific reports related to help seeking for cognitive symptoms are therefore briefly summarized below.

How common is help seeking for subjective cognitive symptoms? A Danish survey showed that less than 20 % of elderly patients who considered their memory to be impaired had consulted a physician [136]. In a large Australian survey, 26% of respondents reporting memory complaints interfering with daily life had consulted a physician. When comparing help seeking patterns associated with seventeen different symptoms such as angina, asthma, hearing problems, headaches, insomnia etcetera, subjective memory impairment was the fifth most prevalent symptom - but the least likely symptom to trigger help seeking [137].

Why do some people with subjective cognitive symptoms choose to seek professional help, while others do not? Research findings show that the tendency to seek help seems to be more influenced by factors such as perceptions, knowledge and experience, than by actual risk factors for dementia. In a study comparing persons who sought help at a memory clinic with persons who did not seek help despite subjective cognitive symptoms, there was no significant difference in objective cognitive performance [138]. A large community-based study showed no significant difference regarding presence of the *APOE* ε4 genotype, between help seekers and non-help seekers [92], and pathological levels of Aβ42 were in another study not more prevalent in help seekers compared to non-help seekers [139]. Factors that have been associated with help seeking for subjective cognitive symptoms are: perceiving that one's memory is worse than that of peers [138]; believing that the cognitive problems have a biological or medical cause [138, 140]; having a family history of dementia [138, 141, 142]; having good knowledge about dementia warning signs [143]; having poorer physical health [92]; being more concerned about the problems [140, 141]; having a good perception of medical services [140]; and experiencing more deterioration in daily functioning and lower quality of life [142]. The relationship between depressive/anxious symptomatology and help-seeking is not clear, as both positive [65] and negative associations [138, 142] have been reported.

To not seek help despite of subjective cognitive symptoms, or only seeking advice in informal settings (e.g. friends or family, internet), has been associated with perceiving memory problems to be caused by non-biological factors, not amenable to medical treatment [138]. Other studies have reported that socio-economic barriers such as low educational attainment; belonging to an ethnic minority; and low income, are factors associated with lower frequency of help seeking [144]. Furthermore, better physical health [92]; having less concern about the problems; having poor perceptions of medical services; and believing that the cause of the problems are psychosocial (e.g. stress related) or a part of normal aging [140, 144], are other factors that have been associated with not seeking help. Additionally, there may be a cohort effect in that cognitive problems may be more accepted by older individuals as a 'normal' part of aging, and therefore are tolerated for a longer time before seeking help [143].

The health belief model (HBM) can be applied to better understand the process of help seeking [145]. The model suggests that people's tendency to seek help

stems from several factors, such as how serious they perceive the health threat to be, what the benefits and barriers are to seeking help, and how susceptible to actual disease they assess themselves to be [145, 146]. In Figures 5 and 6, the HBM is applied to illustrate the process of help seeking vs non-help seeking for cognitive symptoms, based on previous research findings.

Similarly, the 'common sense model of illness perception' [147] deals with how people respond when they experience health problems. According to this model, people develop different coping strategies based on their beliefs and knowledge about e.g. the cause of the symptom, the consequences of the symptom, controllability of the symptom, and likely future duration of the symptom. The model has been used in the context of SCD [95], MCI [148] and dementia [149].

*Figure 5. The health belief model, modified to exemplify possible factors leading to **increased** help seeking tendencies for subjective cognitive symptoms.*

Modifying variables
"I'm not a worrying type of person. I don't know much about what dementia is and what signs to look for."

Perceived benefits vs perceived barriers
"There is no cure anyway. I feel ashamed to talk about these problems. It is better not to know. I generally have a low confidence in medical services."

Perceived seriousness
"My problems are just a normal part of getting older. My problems are not very serious; probably they won't get worse. It is probably just stress."

Perceived threat

Low likelihood of seeking help from medical services

Perceived susceptibility
"Dementia won't happen to me. No one in my family has had dementia. I'm too young to get dementia"

Cues to action
"I don't know where to seek help. No one is telling me to seek help. My problems don't affect my everyday life that much."
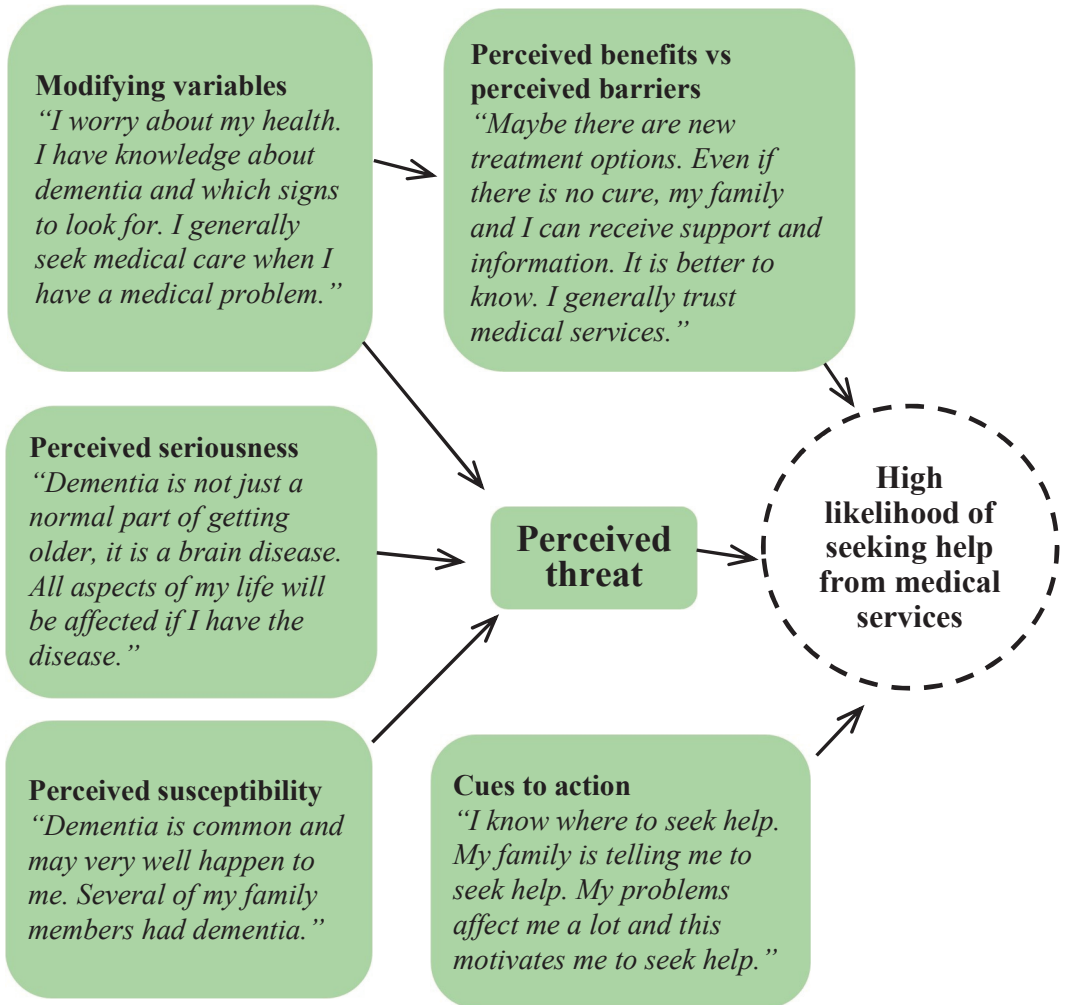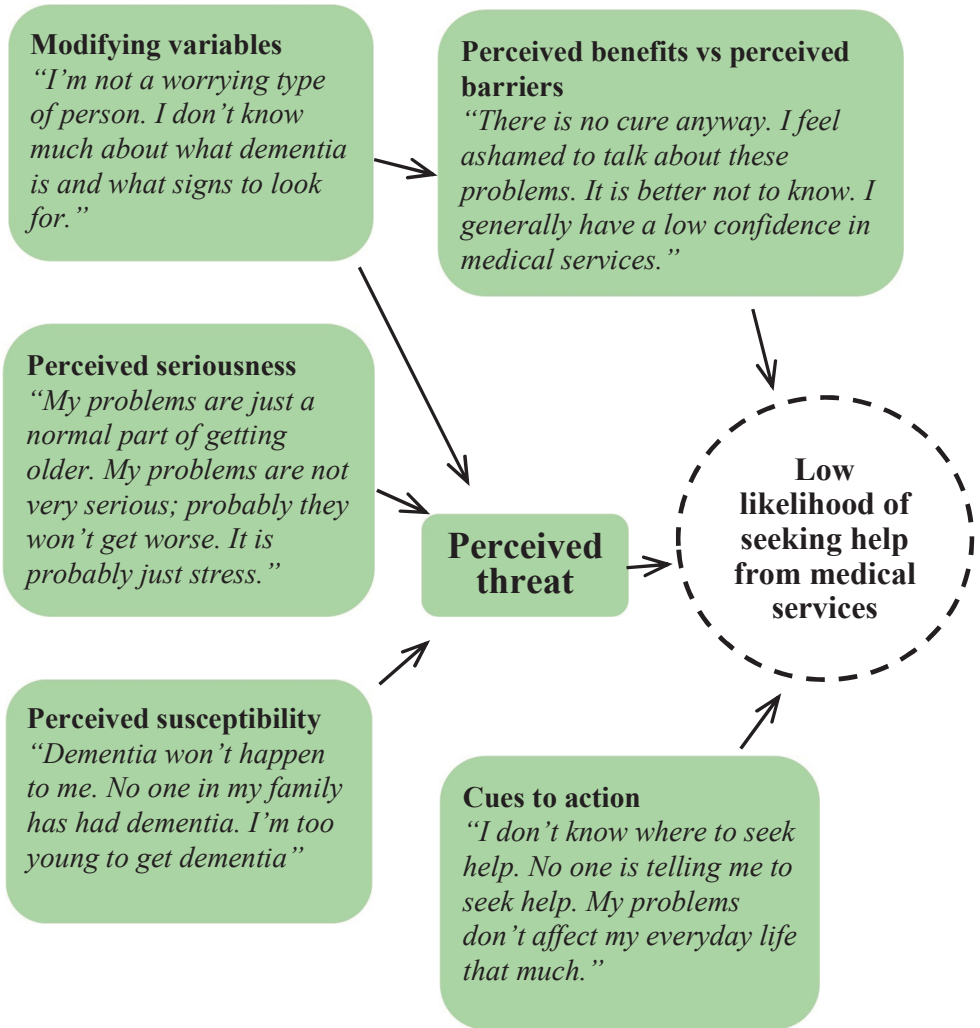
*Figure 6. The health belief model, modified to exemplify possible factors leading to **decreased** help seeking tendencies for subjective cognitive symptoms.*

2.8 Associations with dementia and related factors

This research area addresses the key question about the relationship between SCD and dementia, and involves several different lines of research. Since far from everyone with SCD will develop MCI and dementia, identifying features that are more associated with deterioration over time than others is an essential issue. This issue is approached by cross-sectional investigations associating SCD with other dementia-related factors such as brain and neurochemical changes, objective cognitive performance and functional level; as well as longitudinal studies of cognitive changes and development of dementia.

2.8.1 Objective measures of cognition in relation to SCD

'Objective' measures of cognition commonly refers to assessment using neuropsychological tests – i.e. measuring cognitive 'signs'. Sometimes the term '*cognitive* tests' is used, usually when describing a briefer assessment. Informant-reported cognitive decline is occasionally also categorized as an 'objective' measure, in the regard that it indicates signs rather than symptoms.

Neuropsychological tests are standardized tests developed to assess cognitive functions and dysfunctions, which may be linked to central nervous system disease or injury. Cognitive functions are divided into cognitive 'domains', such as the memory/learning-, attention-, language-, visuospatial- and executive domain. The borderline between domains and associated tests vary greatly throughout the literature. Validity and reliability are important

psychometric aspects of neuropsychological test development. In short, a test is valid if it successfully measures what it is intended to measure and reliable if it produces similar results under consistent conditions. Most of the more prominent neuropsychological tests have been used and further developed for decades, adding to their robustness. The associations between tests and different neurological conditions are generally well established by numerous studies. Nonetheless, the 'objectivity' of any test may certainly be discussed – the term 'objective' is however frequently used in this field of research as a natural counterpart to 'subjective'. Alternatively, in this thesis objective/subjective is sometimes replaced with 'detectable'/'not detectable' or 'test-measured'/'self-reported'.

As an assessment of validity of the SCD concept, several studies have addressed the relation between SCD and objectively measured cognitive performance, as measured with neuropsychological tests. To assess the 'validity of SCD' by comparing self-report to test results may be discussed, as it may be argued that, per definition, only the patient affected by the symptoms can validate her own symptom-status. Symptoms are just symptoms – if they can be verified by tests, they should rather be referred to as signs. Nevertheless, it is certainly of interest to investigate the associations between symptom-assessment and test-measured cognitive performance. In general, studies have reported that the associations between subjective and objective cognitive functioning have often been weak or non-existing [84, 86, 91, 150-152]. However, a few positive correlations have also been reported [153-155].

Reports from the AIBL study concluded that patients with objective cognitive impairment (MCI) reported more subjective cognitive symptoms compared to healthy controls, but there was generally no association between subjective cognitive symptoms and memory tests [84]. Similar findings were reported using ADNI data – there were no associations between subjective cognitive symptoms (measured with ECog) and a battery of six well-established neuropsychological tests [68]. Another study investigated the association with objective cognitive performance and specific items from several SCD questionnaires. They found that age-anchored questions (asking the respondent to compare with peers of the same age) reflected objective performance the most accurately [156]. In contradiction, a large population-based study reported findings that supported an association between subjective and objective cognitive functioning [153]. They also analyzed specific subjective

cognitive symptoms, finding that some symptoms (e.g. 'difficulties finding one's way around familiar streets' and 'difficulties following group conversations') were more associated with objective cognitive difficulties than others (e.g. 'forgetting things from one second to the next') [153].

Informant report refers to an assessment by a close family member or friend regarding an individual's level of functioning. As signs may present later than symptoms in the disease process, it may not be surprising that several studies have found that informant report is a better predictor of concurrent objective cognitive performance than self-report. e.g., [47, 86, 157-159]. Similar to the methods available for self-report of cognitive decline, there are numerous instrument used for informant-reported cognitive decline [160]. The perhaps most wide-spread instrument is the Informant questionnaire on cognitive decline in the elderly (IQCODE), asking the informant to rate the participants' function compared to previously [161]. Our group co-developed the Cognitive Impairment Questionnaire (CIMP-QUEST), an informant-report instrument designed to identify dementia signs related to different brain regions [162].

2.8.2   Brain changes and imaging markers in SCD

Brain changes related to dementia include both anatomical and functional changes, involving e.g. reduced volume of structures important for the forming of memory such as hippocampus; abnormal glucose metabolism in related brain areas; and changes in activation patterns measured when performing cognitive tasks. Several brain changes related to dementia have also been associated with SCD. Evidence of morphological, functional as well as metabolic changes have been observed in clinical as well as in population-based settings. More specifically, SCD has been associated with decreased volume of the hippocampus [163-165] and entorhinal cortex [163]; decreased grey matter in other areas of the medial temporal lobe and frontotemporal regions [166]; white matter lesions in the temporal region [164] and in the subcortical parieto-occipital area [167]; changes in glucose metabolism in parieto-temporal regions, especially the medial temporal lobe involving hippocampal and parahippocampal areas as well as precuneus [165, 168]; and reduced right hippocampal activation during an episodic memory task [169]. Brain activation patterns have been found to be similar in SCD and MCI

patients [170] as well as in SCD and AD patients, such as changed activation in the left medial temporal lobe, bilateral thalamus, posterior cingulate and caudate [171]. Magnetoencephalography studies have found differences in the neurophysiological profiles of SCD patients compared to healthy controls [170, 172].

However, negative findings have also been reported. One population-based study did not find any difference in hippocampal or amygdala volumes between persons with vs without SCD [92], and another study could not confirm any association between SCD and severity of white matter hyperintensities [173].

2.8.3 SCD and neurochemical biomarkers for AD

The three most well-established neurochemical biomarkers for AD are the $_{42}$ amino acid form of amyloid-β (Aβ$_{42}$), total tau (t-tau) and phosphorylated tau (p-tau). The 'amyloid cascade hypothesis' was postulated in 1991/1992, suggesting that Aβ is the driving mechanism of AD, via a defective cleavage of the amyloid precursor protein (APP) [174, 175]. When Aβ is defectively released from APP, it aggregates into 'plaques', which is one of the two hallmark pathologies of AD and leads to neuron death [176]. Aβ is increased in both familial and sporadic forms of AD. When Aβ aggregates into plaques, the concentration of Aβ in the CSF decreases, resulting in that lower levels of CSF Aβ are associated with higher risk for AD dementia. Aβ deposition may also be measured by PET imaging [177].

Tau markers are associated with the second hallmark pathology of AD – neurofibrillary tangles [178]. This pathology relates to the defective contact between neurons – loss of synapses. The normal function of tau protein is to stabilize the microtubules – the transport pathways – of the neuronal axons. In AD, this function has deteriorated, causing damage to the axons. Tau proteins that are failing to bind to the microtubule are believed to clump together, forming neurofibrillary tangles [179]. P-tau is the phosphorylated form of tau [180]. The tau markers are described as markers for brain damage, more specifically indicating axonal degeneration [181]. When tau is pathological, the concentrations in CSF t-tau and p-tau are elevated. A combination of

decreased levels of Aβ42 and increased levels of t-tau and p-tau, are sometimes described as a "CSF AD profile", e.g. [182]. Using a metaphor derived from the amyloid cascade hypothesis, Aβ can be described as the trigger of AD, and tau as the bullet – causing the damage but not acting independently from the trigger [183].

The association between Aβ, tau and AD dementia is however not that clear-cut. Significant levels of Aβ plaques have been found in the absence of symptoms [50, 51]. The prevalence of amyloid plaques has been observed to increase with age regardless of diagnosis [184]. Tau – being a marker for brain damage – is not specific for AD and is abnormal in more than 20 clinico-pathological entities [185].

The reported prevalence of pathological AD biomarkers in SCD vary across studies, which in part is related to use of different cut-offs and ratios to determine pathological levels. A memory clinic based study reported that prevalence of pathological CSF concentrations in SCD patients was 24%, 32% and 21% for Aβ42, t-tau and p-tau respectively, and 7% for a combined CSF AD profile [186]. From the memory clinic multicenter DESCRIPA study [187], it was reported that a CSF AD profile, based on an Aβ:tau ratio, was present in 52% of SCD patients, which was significantly more frequent compared to healthy controls (31%). A clinical study based on a small sample found no statistically significant differences in the three CSF AD biomarkers between subjects with and without SCD [188].

The AD CSF biomarkers have mostly been used to identify AD pathology during the MCI stage [182]. However, cross-sectional studies on CSF markers in SCD patients, and comparing SCD and MCI patients, are rapidly emerging. It would be especially interesting if an exponential increase from healthy older adults, to SCD, MCI and AD dementia could be established. A recent review [1] of 36 studies on the subject of Aβ and tau markers and their associations with SCD reported that some studies have reported significant biomarker concentration differences between SCD and MCI, whilst others reported negative findings. Overall, more studies reported differences between SCD and MCI considering Aβ (i.e. individuals with SCD had less pathological Aβ concentrations compared to individuals with MCI) than considering tau markers. Ten studies found no significant differences in t-tau and p-tau markers between SCD and MCI [1]. This result is unexpected, as it does not

correspond well with the suggested temporal order of AD, placing the presence of abnormal tau concentrations more closely in time to the onset of objective cognitive deficits compared to Aβ concentrations, which is believed to reach abnormal levels earlier. Few studies found a difference between SCD and healthy controls [1]. Nevertheless, Colijn and Grossberg concluded that there is some evidence from several studies of an exponential increase of abnormal Aβ and tau from SCD to MCI to AD dementia [1].

In a study based on ADNI data, SCD was not analyzed as a separate group, but the presence of subjective cognitive symptoms in a subgroup of the MCI cohort was investigated in relation to CSF AD biomarkers. MCI patients with positive CSF AD biomarkers tended to underestimate their cognitive difficulties compared to MCI patients with negative CSF AD biomarkers. The risk of misclassification is therefore high when using subjective cognitive symptoms, according to the authors [68]. The AIBL study [84] investigated subjective cognitive symptoms as a continuous variable in a mixed sample of volunteers and MCI patients, in relation to e.g. amyloid burden. They could not establish a direct association between subjective cognitive symptoms and AD biomarkers. However, they observed that subjective cognitive symptoms were related to mood in healthy volunteers and correlated positively to age in MCI patients [84].

One study showed that having more subjective cognitive symptoms was associated with pathological concentrations of Aβ42 in healthy community-recruited controls, while the reversed pattern was observed in MCI – less SCD was associated with pathological Aβ [189]. Using PiB-PET (Pittsburgh compound B, a PET method to measure beta-amyloid plaques in neuronal tissue), one study reported an association between Aβ burden and memory-related as well as executive-related subjective symptoms, although an association between neuropsychological test measures and amyloid burden could *not* be found [190]. Another PiB-PET study [191] showed similar results for a group of 48 cognitively normal older individuals. Subjects with a higher Aβ load tended to be less confident about their memory abilities than those with a lower Aβ load, although these were not 'complainers' but were taken from a normal community sample. Studies have shown that presence of SCD in patients with a high Aβ burden predicts faster cognitive decline [53, 100].

To summarize, the associations between SCD and concentrations of Aβ or tau markers in older adults without detectable cognitive impairment are not clear. There is some evidence of an exponential increase of abnormal biomarker concentrations from SCD to MCI to AD dementia, but less evidence of biomarker differences between SCD and healthy older adults. Findings are mixed, and several findings have been negative. SCD is considered a largely heterogeneous group, which likely affects the possibility of finding positive associations between SCD and AD biomarkers.

2.8.4   Prevalence of ApoE ε4 in SCD

For the most common form of dementia – late onset AD dementia – the ε4 variant of the gene coding for *APOE* is a well-known risk factor, possibly due to reduced neural protection and repair mechanisms which may lead to increased Aβ-deposition [168]. A memory clinic based study reported that the prevalence of the *APOE* ε4 genotype was similar in SCD patients (33%) as compared to MCI patients (32%) [186], and a second memory clinic study also reported non-significant differences in *APOE* ε4 prevalence between SCD and MCI [192]. Combining *APOE* status with amyloid/tau markers may increase the ability to predict AD dementia in patients with SCD [1]. Several recent studies have reported associations between amyloid/tau markers of AD and presence of *APOE* ε4 [168, 184, 187, 193, 194].

2.8.5   Subjective cognitive decline - longitudinal findings

Are patients with subjective cognitive symptoms at greater risk of developing dementia? This is a key issue of the SCD research field. From 1995 to 2007, several large community-based studies investigated the ability of subjective cognitive symptoms to predict cognitive decline (defined as declining test performances or conversion to dementia) among elderly people [64, 87, 133, 195-206]. Some reported positive associations [64, 87, 133, 195, 196, 200, 203, 206], whereas others reported negative findings [197, 199, 202, 205], and in a few studies findings were mixed, e.g. results changed when adjusting for

objective cognitive level at baseline [198, 201, 204]. In these early days of the SCD research field, the importance of excluding subjects with detectable cognitive impairment to investigate SCD as a separate entity, had not yet been fully emphasized. Thus, only four of the 15 community-based studies mentioned above excluded MCI or a similar category [87, 198, 201, 204]. Various methods were used to measure subjective cognitive symptoms; most frequently, participants were asked a single question about memory problems. Follow-up time of the 14 studies ranged from one to nine years, with a mean of 4.5 years, and the mean number of participants was over 1.800.

The hypothesis presented by Reisberg in 1986 [28] – that a phase characterized by subjective cognitive symptoms would last approximately 15 years before onset of MCI – was supported by a study in 2006 [207], in which patients were followed for 8.9 years. Based on the 15-year-hypothesis this would lead to a 59.3% MCI development rate. The observed rate was 61.4%, thus quite close to the estimated progression rate. In a review [208], Reid and MacLullich summarized findings from community-based studies conducted prior to 2006, and concluded that there were increasing evidence of subjective cognitive symptoms predicting subsequent cognitive decline and dementia. However, the mix of subjectively and objectively impaired samples and other methodological variations between studies made it difficult to draw firm conclusions.

A meta-analysis [79] including and comparing data from 32 community- and clinically based prospective longitudinal SCD studies, reported an annual conversion rate for individuals with SCD to dementia of 2.3 %, compared to 1 % for subjects without SCD, thus representing a twofold increase in risk of dementia when SCD is present. The cumulative proportion of individuals converting from SCD to dementia over approximately 5 years was 11%. The annual conversion rate to MCI was 6.7%, and the cumulative proportion of converters was 24.4%. The authors concluded that SCD is a clinically meaningful indicator of subsequent cognitive decline [79].

During the last decade, the number of clinically based longitudinal studies on SCD has increased. Studies range from large multicenter initiatives such as ADNI [68, 209], AIBL [53], DESCRIPA [187] and LADIS [210], to single center studies [39, 165, 211-217].

Elfgren *et al.* [39] concluded that the risk of SCD patients in their Swedish memory clinic sample (n=24) to develop MCI was small over 3 years, as 88% remained stable. A study based on a British memory clinic sample [211] followed 62 SCD patients over a mean of 3.7 years, observing that 24% declined to amnestic MCI or dementia during that time. Additionally, being over 61 years of age when seeking help, and onset of SCD at later age, were strong predictors of decline. Declining SCD patients had lower scores on cognitive tests at baseline compared to non-decliners, even though they were within normal limits. A South Korean study followed 129 SCD patients over 0.5-4.7 years, and reported that 22% declined to MCI or dementia during the study period. Higher age, lower cognitive scores at baseline, and being an *APOE* ε4 carrier predicted decline [217]. A Spanish study following 55 SCD patients reported that 25% declined to MCI or dementia over a mean follow-up time of 3 years. Only three subjects declined to dementia – all three had abnormal CSF AD biomarker ratios [216]. In a Portuguese study, not excluding detectable cognitive impairment in subjectively affected individuals, 37% of 134 patients with subjective cognitive symptoms developed dementia over the follow-up of at least 2 years [215]. This study also analyzed specific cognitive symptoms using the SMC scale, and reported that patients who did *not* convert actually reported more difficulties on several items (using notes; having difficulties finding words). Converters had fewer years of education, but age or depressive symptomatology did not differ between converters and non-converters [215]. In a German study [165], 27 SCD patients were followed for 3 years and were also examined using measures of glucose metabolism and MRI at baseline. SCD patients showed greater decline in episodic memory functions compared to healthy controls, but not in executive and speed functions. Weak associations were observed between longitudinal decline and brain imaging findings in this study.

SCD has almost exclusively been studied in relation to AD dementia, however a few longitudinal studies have also used VaD as an outcome. For example, one study reported that SCD predicted AD dementia but not VaD [218], However, it should be noted that this study did not base the diagnosis of vascular dementia on neuroimaging findings. In the European LADIS study, SCD was observed to predict AD dementia as well as AD with a vascular component (small vessel disease) [210].

Longitudinal studies including CSF AD biomarkers generally show that abnormal levels of Aβ and tau markers in individuals with SCD are associated with an increased risk of future cognitive decline [1]. In a study from our group (the Gothenburg MCI cohort), the ability of CSF AD biomarkers to predict cognitive decline in specific cognitive domains from baseline to 2-year follow-up was analysed for e.g. patients categorized as SCD [213]. It was observed that in SCD patients, t-tau predicted a significant proportion of the decline in the speed/executive functions domain, whilst Aβ was not significantly associated with any cognitive decline. In a study based partly on the same sample as the current thesis and pooled with a sister-sample from Oslo, t-tau rather than Aβ was associated with decline in memory over time in patients with SCD [214]. Autopsy studies have observed that subjective cognitive decline during the years prior to death can predict a neuropathological diagnosis of AD (plaques and tangles) in elderly persons with and without dementia during life [92, 219].

2.8.6 Foundation of thesis aims

Subjective cognitive decline is a possible early indicator of actual cognitive impairment and dementia, and is an inevitable aspect of the everyday clinical considerations regarding which patients are in need of further examination. If a firm association between SCD and subsequent dementia could be established, SCD has the potential to be useful in the early detection of neurodegenerative disease and thereby optimizing early interventions and treatment trials. SCD is, however, an elusive concept since it may reflect a pathological condition as well as normal aging. It may be affected by various aspects such as mood disorders, tendency to seek medical care and certain personality traits. SCD is, by definition, a subjective measure – but one that clinicians will have to assess and respond to when meeting the patient. Consensus definitions and criteria are emerging, but they are still 'in the bud', in need of evaluation.

When establishing the aims of this thesis, some aspects of SCD research areas in need of further contributions were identified. Firstly, there has been a lack of comprehensive instruments specifically developed to measure a broad spectrum of SCD. Many instruments might be outdated and are not based on actual patient report. When starting out this project, there were no instruments

covering a broad range of cognitive domains, based on patient input and developed with the specific population in mind. Type and frequency of SCD has not been measured in most studies as often just a single question has been used to identify and investigate SCD. Memory has often been the only assessed cognitive domain.

Secondly, the study of affective conditions in relation to SCD has mostly focused on depressive symptoms while aspects of stress are rarely studied. Clinical experience tells us that severe stress is not uncommon in this patient group and should be further studied.

Furthermore, SCD in combination with biomarkers is a natural focus point of study, since both might identify phases prior to detectable cognitive signs. Brain imaging studies on SCD patients are quite frequent but there are fewer studies of CSF AD markers in SCD, especially including longitudinal follow-up. Recent criteria for SCD and preclinical AD should be further evaluated.

Finally, there are now several longitudinal studies investigating how patients with SCD progress or not over time. However, as this is the core question of a research field complicated by heterogeneous etiologies and methodological disparities, more studies are needed – especially in memory clinic samples with comprehensive measures and long follow-up time. Indeed, very few studies have focused on specific SCD symptoms and their relation to progression in comprehensively investigated individuals.

3 AIMS

The general objective of this thesis is to investigate SCD in memory clinic patients with respect to characteristics and clinical relevance. 'Characteristics' refers to features that may characterize patients with SCD, and to the specific type of symptoms patients with SCD report. 'Clinical relevance' in this context refers to the degree of association between SCD and cognitive decline and dementia – the predictive ability of the concept. Considering the overview of SCD research (Figure 2), the separate studies included in the current thesis are related to 'concept development' (study III); 'method development' (study I), 'confounders' (study II-IV), and 'associations with dementia' (studies III-IV). The term 'SCI' is used instead of 'SCD' in studies I-II, but in the following overall description of the studies, only 'SCD' will be used.

Aim study I: To develop a patient-based comprehensive questionnaire on everyday cognition, with the ability to distinguish patients with subjective, but not objective, cognitive impairment seeking care at a memory clinic, from healthy controls. Furthermore, to examine the cognitive spectrum of subjective cognitive symptoms in patients with SCD.

Aim study II: To investigate the prevalence of stress, depressive symptoms and CSF AD profiles in memory clinic patients categorized as SCD and MCI.

Aim study III: To examine SCD, SCDplus, SCDplusbio (i.e. SCDplus + *APOE* ε4 and biomarkers), NIA-AA stages 0-3 of 'preclinical AD' and MCI in patients seeking care at a memory clinic, with respect to:

> 1) the proportion of cognitively stable and declining patients over time
>
> 2) the ability of the classifications to predict cognitive decline, dementia and AD dementia specifically
>
> 3) the individual contribution of each feature included in the classifications to predict cognitive decline and dementia

Aim study IV: To investigate potential differences in baseline subjective cognitive symptoms between progressing and non-progressing patients,

addressing possible explanatory variables such as CSF AD biomarkers and anxiety/depressive symptoms. Furthermore, to investigate differences in baseline subjective cognitive symptoms in MCI and SCD patients, in relation to cognitive outcome and CSF AD biomarkers, as an assessment of awareness in different cognitive stages.

4 PATIENTS AND METHODS

4.1 Participants

All participants were help seeking patients or healthy controls at the Sahlgrenska memory clinic, Gothenburg, Sweden. All studies included patients and healthy controls who had been previously included in the Gothenburg MCI study [71].

Study I and IV, dealing with data from SASCI-Q, also included an additional sample of other memory clinic patients ('the SASCI-Q-cohort'). Inclusion/exclusion criteria were identical, but some patients could accept participation in the shorter current study (which only entailed completing a questionnaire), but declined participation in the more comprehensive Gothenburg MCI study. In general, patients in the SASCI-Q-cohort completed similar examinations, but for analyses, data were collected from medical records and not from a previous study database.

Inclusion criteria were: age 40-79 years and subjective or informant-reported cognitive decline with a duration of at least 6 months, established through clinical interview. Healthy controls were mainly recruited from senior citizen organizations and information meetings about dementia. They were assessed by a physician and included if they had no subjective or objective cognitive impairment.

Exclusion criteria for all participants were: current severe somatic disease; current severe psychiatric disorder defined using DSM-IV criteria [220]; and current substance abuse or dependence defined using DSM-IV criteria [220]. In this thesis, patients were also excluded if they had manifest dementia at baseline.

Table 2. Brief summary of methods in study I-IV

	Study I	**Study II**	**Study III**	**Study IV**
Time period for data collection	2007-2010	2001-2011	1999-2013	2007-2016
Sample origin	Gothenburg MCI study cohort + SASCI-Q cohort	Gothenburg MCI study cohort	Gothenburg MCI study cohort	Gothenburg MCI study cohort + SASCI-Q cohort
Analysis design	Cross-sectional	Cross-sectional	Follow-up	Follow-up
Key issue	Method development	Characteristics	Criteria evaluation, prediction	Characteristics, prediction
Specific groups included	SCD Healthy controls	SCD MCI (Healthy controls)	SCD Subtle cog. decline MCI (Healthy controls)	SCD MCI (Healthy controls)
N total	143	353	336	245
N patients	93	250	235	130
N healthy controls	50	103	101	115
Role of controls	Included in main analysis	To define normal range of NP scores	To define normal range of NP scores	To define normal range of NP scores
Method to differentiate between SCD/MCI	GDS	GDS + 10 NP tests	GDS + 4 AD specific NP tests	GDS + 10 NP tests

Main measurements included

GDS	X	X	X	X
SASCI-Q	X			X
NP tests		X	X	X
CSF biomarkers		X	X	X
Affective symptoms		X	X	X
Reported stress (medical record review)		X		
Clinical interview (family history of dementia)		X		
APOE genotype			X	

APOE=apolipoprotein E; CSF=cerebrospinal fluid; GDS=global deterioration scale; NP=neuropsychological; SASCI-Q=Sahlgrenska academy self-reported cognitive impairment questionnaire.

4.2 Tests used to define SCD and MCI

To make the distinction between SCD and MCI, different methods were used in the studies. Details are specified in Table 3. In short, in study I the Global deterioration scale (GDS) [22] was used, while in study II-IV, different sets of neuropsychological (NP) tests were used. GDS was also used in study II-IV, but only to exclude patients with no subjective/objective cognitive decline (GDS stage 1) or patients with probable dementia (GDS stage 4/4+). The developed SASCI-Q instrument (described in more detail in Study I Results) was thus not used to define a group with SCD, but was used to measure *specific* subjective cognitive symptoms.

Other studies within the Gothenburg MCI study have generally used GDS, and not NP tests, as defining instrument for SCD (often called SCI) vs. MCI. The rational for this is to avoid circularity since NP tests have often been used as outcome measures. The GDS stages in the Gothenburg MCI study are determined by medical history, clinical assessment and four cognitive instruments: for assessment of basic cognitive symptoms such as memory disturbance, disorientation, reduced abstract thinking, visuospatial disturbance, poverty of language, sensory aphasia, visual agnosia and apraxia, Stepwise comparative status analysis (STEP; [221]) is used. For executive symptoms I-FLEX (a short form of the executive interview EXIT; [222]) is used. The assessment is further based on scores on the Mini-Mental State Examination (MMSE; [223]) and Clinical Dementia Rating sum of boxes (CDR; [224]). The GDS algorithm is presented in detail in study I and further in Wallin *et al.* 2016 [71], which offers a comprehensive account of methods used within the Gothenburg MCI study. GDS stage 1 means that no subjective or objective cognitive impairment is present. GDS stage 2 corresponds to what is often called 'the SCI stage' and is fulfilled if subjective cognitive complaints are present (determined through clinical interview) but only very subtle or no impairment detected by the GDS tests. GDS stage 3 corresponds to an 'MCI stage', and may include subjective cognitive complaints but more importantly is set based on that GDS tests reveal a cognitive impairment which is still mild but more impaired than expected. GDS stage 4 or more indicates probable dementia, and these patients are further assessed using standardized dementia criteria. Generally, the GDS staging procedure is clinically useful but less refined than an NP test battery. In other words, NP tests are more difficult than

cognitive screening tests. When SCD is defined as 'GDS stage 2', some patients who would have an impaired NP test profile may be included in the SCD group. When using NP tests, the exclusion of objective cognitive impairment in the SCD group is more rigorous and closer to what is used clinically in a comprehensive specialist investigation of early subtle signs of dementia. Nevertheless, both methods (and many others) are used in similar studies worldwide.

GDS was thus used in study I primarily to be consistent with previous Gothenburg MCI study publications. A comprehensive NP test battery was used in study II, to raise the threshold for SCD and avoid including patients with objective cognitive impairment in the SCD group. The specific tests were selected because they predicted dementia in a previous study. A smaller NP test battery was used in study III. That paper focused on prediction of AD dementia, which was the rational for choosing the four test variables that predicted AD dementia in a previous study. (In that previous study, more test variables predicted AD dementia, but we only selected the best predictor variable from each test.) Study IV had a broader approach to dementia conversion (not just focusing on AD dementia), and therefore a more comprehensive test battery was used, using the same number of tests as in study II. However, it was not possible to choose identical tests as in study II, due to that the samples differed somewhat and we had limited resources to carry out follow-up visits in the SASCI-Q-cohort. Also, we prioritized choosing an equal number of tests from each cognitive domain.

Some impairment in cognitive tests will be present also in normal healthy aging populations, due to normal variation. It may be argued that the important difference between healthy controls and patients in this context is therefore *not* an absolute separation when it comes to objective cognitive performance, but rather that patients experience a cognitive decline that affect their daily life enough to make them seek health care. As healthy controls are not help seeking patients, they were not classified using the GDS or NP test battery, but it was established through clinical interviews and assessment that they had no subjective or objective cognitive impairment.

4.3 Determination of cut-offs

In study I, cut-offs for GDS were determined based on the consensus classification within the Gothenburg MCI study. In study II-IV, cut-offs for NP tests were based on results from 'in-house'-healthy controls, enrolled in the Gothenburg MCI study. The control group was stratified based on age and years of education, to reduce the potential influence of these factors on the test results. Thus, when there was a significant test difference between healthy controls of high/low age and high/low education, patients were only compared to healthy controls of their own age/education group. In study II, MCI was defined as scoring at least 1.5 standard deviations (SD) below the means of controls on any of the 10 test variables. If this was not fulfilled, patients were classified as SCD. In study III, focusing on SCD and 'preclinical AD'-criteria [7], we needed to define patients with 'subtle cognitive decline' which is part of 'preclinical AD' stage 3. 'Subtle cognitive decline' is not a well-defined category, but it should be placed between SCD and MCI on the cognitive continuum. In study III, SCD, 'subtle cognitive decline', and MCI were defined as having 0; 1; or 2/2+ test scores at least 1.5 SD below the healthy control mean, respectively. In study IV, not addressing 'subtle cognitive decline', we again used the same cut-off as in study II – at least one impaired test score defined MCI, otherwise the patients were categorized as SCD. This study also included categorizing single-domain MCI (defined as 1-2 impaired tests within only one cognitive domain) and multi-domain MCI (1-2 impaired tests in at least two domains). Additionally, medical records were reviewed to establish that all SCD patients were truly help-seekers based on their own account (not just prompted to seek help by e.g. their spouse).

4.4 Depressive and anxious symptomatology

Different methods were used to determine depressive/anxious symptomatology, primarily because of varying availability of data. The Hospital anxiety and depression scale, HADS [225], was used to assess depressive symptoms (HADS-D subscale) and anxious symptoms (HADS-A subscale) in study I and IV. In study II – the one study that had greater focus on affective symptoms – we used the clinician's assessment at baseline visits as a measure, which had been registered in the fixed study protocol as 'current

symptoms' or 'previous symptoms', also specifying type of symptoms. In study III, depressive symptoms were assessed with the Montgomery-Åsberg depression scale, MADRS [226], or the 20-item Geriatric Depression Scale [227, 228]. The explanation for data from two scales is that the Gothenburg MCI study changed instruments a few years into the study.

4.5   Psychosocial stress

This variable was only considered in study II, and was assessed through a review of all medical records (blinded for other patient data, performed by M.E.), searching for entries describing stress-related conditions, which were subsequently categorized (refer to study II for details). Even though we did not have access to data from a validated instrument focusing on stress, we chose to pursue this issue based on the clinical experience that many – especially younger – patients at the memory clinic reported 'stress conditions'. Stress is a multi-faceted term, and in the context of study II we defined it as *a state of perceived mental or emotional strain or tension resulting from adverse or demanding life circumstances*.

4.6   Informant-reported cognitive function

Informant-reported cognitive function was analyzed in study II as a to measure symptom duration, development and type from the informant's perspective (data on specific features of subjective symptoms were not available for this sample). In study III, informant-reported cognitive function was part of the SCDplus criteria. We used the CIMP-QUEST, which was developed to identify signs related to dementia by informant-report [162] and was part of the Gothenburg MCI study protocol.

4.7   CSF AD biomarkers and APOE

CSF AD markers Aβ, t-tau and p-tau were included in study II-IV. The CSF samples were obtained by lumbar puncture, performed in the morning to avoid influence from possible diurnal fluctuations. CSF $A\beta_{1-42}$ concentrations were determined using the INNOTEST® ELISA assay technology (Innogenetics,

Ghent, Belgium) [229]. The axonal damage marker CSF T-tau and CSF concentrations of tau phosphorylated at threonine 181 (P-tau181) were measured using INNOTEST® ELISA assays [230, 231]. In study II and IV, a CSF AD profile was calculated using the formula ($A\beta_{42}$/p-tau $> 3.694 + 0.0105$ x t-tau), suggested by Mattsson *et al*. [182]. In study III, we needed to analyse the CSF markers separately due to the 'preclinical AD'-criteria, and therefore used separate cut-offs, previously used for prediction of AD ($A\beta \leq 482$ ng/L; t-tau ≥ 320 ng/L; p-tau ≥ 52 ng/L; [182]).

Whole blood was collected from all participants in the Gothenburg MCI study, and APOE genotyping was performed by mini-sequencing as described elsewhere [232]. Presence of the *APOE* ε4 allele was included as a variable in study III, considering SCDplus-criteria.

4.8   Determination of decline

Determination of decline was only in question for the two follow-up studies (study III-IV). In study III, 'cognitive decline' was defined as either a decline in NP test scores or a conversion to dementia. Decline in NP tests was determined using 'delta values' – the change of scores from baseline to follow-up. To calculate cut-offs for delta values, we again used data from healthy controls – for this purpose also matched considering follow-up time. For each test, delta values for the healthy controls were calculated. The mean delta value for the 25% (lowest quartile) of those controls who declined the most was used as cut-off for each test. The cut-off was set prior to any analyses. In study IV, 'progression' was defined as conversion from one cognitive stage to another – from SCD to MCI or dementia, from MCI single-domain to MCI multi-domain, or from MCI to dementia. We chose not to use delta values in study IV, primarily to simplify the description of decline. 'Decline' and 'progression' are used as interchangeable terms in study III and IV.

4.9   Dementia diagnoses

Conversion to dementia was only in question for study III and IV. In the Gothenburg MCI study, all patients that were categorized as GDS 4/4+ were further assessed by a specially trained physician, considering specific dementia

diagnostics. The assessor was blinded to NP test results, CSF and imaging results (except assessment of white matter changes), to avoid circularity. AD was diagnosed according to the NINCDS-ADRDA criteria [233] – in addition to fulfilling general dementia criteria the patient must have no or only mild white matter changes, and AD-related symptoms such as associated with memory-, language- and visuospatial domains. Vascular dementia forms were diagnosed as either subcortical vascular dementia (signified primarily by substantial white matter changes) [234] or cortical vascular (stroke-related) dementia - the NINDS-AIREN criteria [235]. A MixD diagnosis in the Gothenburg MCI study is a combination of AD/subcortical vascular dementia or AD/cortical vascular dementia. Frontotemporal dementia was diagnosed according to Neary *et al.* [236]; Lewy-body dementia according to McKeith *et al.* [237]; primary progressive aphasia according to Gorno-Tempini *et al.* [238], and dementia non ultra descriptum (unspecified dementia, NUD) diagnosis according to the ICD-10 [3].

Study IV partly included follow-up of patients who were not included in the Gothenburg MCI study. Due to limited resources, it was not possible to perform an identical diagnostic assessment as in the Gothenburg MCI study on this patient group. We instead used clinical diagnoses set in the memory clinic, retrieved from medical records, and based on ICD-10 criteria.

4.10 Procedures

4.10.1 Qualitative phase of study I

The initial and qualitative phase of the project leading to the development of SASCI-Q was completed in collaboration with researchers from the department of Oncology, Sahlgrenska university hospital. They originally initiated the project to investigate cognitive symptoms in cancer survivors [239]. The symptom assessment method developed by Steineck and colleagues [240] involves several key standpoints: a symptom is a subjective evidence of disease or physical disturbance observed by the patient [29, 30] and must, per definition, be noticed by self-assessment. When the objective is *symptom* assessment, an assessment made by a clinician or researcher is very sensitive to bias, as it is an interpretation by an external evaluator. The patient 'owns'

her own symptoms. Furthermore, validity of a symptom assessment instrument is obtained if respondents from the target group acknowledge the accuracy of the questions asked, in relation to the investigated phenomenon. This validity is obtained through 'face validation' – sitting together with respondents, observing difficulties and discussing the wording of questions to ensure that they are understood correctly. It is important that items be based on actual patient-reported symptoms, not further interpreted by the researcher or constructed based on theory about the phenomenon. The proximity to the patients' experience is ascertained through comprehensive interviews with open-ended questions, applying the groundwork for the construction of questions. Additionally, it is preferred that one symptom at a time is analyzed ('one conceptual entity'). To summarize items into scores, as is otherwise common in psychometric instrument development, is considered to result in less distinct information about the studied phenomenon. That is, a score of '10' compared to a score of '15' on a summarized symptom scale gives very little information about the actual symptoms experienced. It is preferred that the number of occasions that the symptom has been experienced is reported (incidence or prevalence), instead of symptom intensity, which is considered more arbitrary. The time frame for symptoms (e.g. 'in the last month') should be specified in the questions. [240]

In the qualitative phase of our study, memory clinic patients and cancer survivors were interviewed to generate a pool of items. Items were condensed through qualitative methodology and comments and input from patients were carefully considered in the design of the questions. Items that were specifically directed toward the cancer population were excluded in the memory clinic version, and a section on 'cognitive change' was added instead, due to the importance of 'change' for the current research. Refer to study I for more details concerning the qualitative procedure.

4.10.2 Baseline procedures

All included patients were already enrolled at the Sahlgrenska memory clinic at the time of study inclusion and baseline examinations. This is potentially important in this context due to the risk of some individuals otherwise over-reporting symptoms in order to be scheduled for further examinations. For referral acceptance at the clinic, the patient had to have undergone a CT scan,

primarily to rule out other causes of cognitive impairment such as tumors and subdural hematoma. If patients fulfilled Gothenburg MCI study criteria, at their first visit to the clinic, they were asked to participate and written informed consent was collected. The Gothenburg MCI study was designed to follow clinical routine as closely as possible. At the first visit, blood sampling, cognitive function assessment scales and cognitive screening were completed. The cognitive screening tests are later the basis of GDS staging. In following visits, lumbar puncture and NP examinations were performed. NP examinations were conducted by licensed psychologists, and consisted of approximately 20 tests during 2 visits á 1.5 - 2 hours – the test battery somewhat changed over the years of the study. The tests used for analyses in the current thesis are specified in the separate reports. Blood flow measurement (SPECT) and magnetic resonance imaging (MRI) were performed in other hospital locations – this data was not used in the current thesis. The patients referred to as the 'SASCI-Q cohort' were asked to participate by a registered nurse. The specific procedure of the SASCI-Q data collection is described in detail in study I.

4.10.3 Follow-up procedures

The aim of the Gothenburg MCI study has been to repeat examinations every two years, with some exceptions: NP examinations were not performed year 4. Patients categorized as GDS 2 year 2 were not followed up again until year 6. Follow-up rounds were conducted largely using the same procedures as at baseline. Follow-up data (NP test scores and dementia diagnoses) were analyzed in study III and IV. In study III, the average follow-up time was 4 years (± 2.9 years), and in study IV 4.9 years (± 2.1 years). In both studies, only two points of measurement were analyzed – baseline and the last available follow-up. For the SASCI-Q sample, only one follow-up round was performed, during 2015-2016. Patients were invited to the follow-up study by mail and telephone. Inclusion entailed completion of the SASCI-Q questionnaire, approving of data being collected from medical records, and a follow-up visit at the clinic. At the visit, a research assistant performed NP tests and a licensed psychologist (M.E.) subsequently reviewed the results. Based on ethical considerations, it was decided beforehand that any patient who would be identified as cognitively impaired during the testing would be offered an in-

house referral to the memory clinic. However, there were no such cases, as all patients with objective cognitive impairment already had ongoing contact with primary care or the memory clinic. As a service to the participating patients, those who inquired about test results or expressed worry about possible cognitive decline received feedback by a licensed psychologist (M.E.), by letter or telephone.

4.11 Statistical analyses

4.11.1 Statistical methods

In all studies, independent samples t-test and X^2 test were used to compare characteristics between groups, such as age and years of education.

Study I and IV dealt with items from the SASCI-Q. These were analyzed item-by-item in study I, and also dichotomized and summarized in study IV (refer to study IV for details). In both studies, parametric tests such as one-way between groups analysis of covariance (ANCOVA) were used to compare mean group scores for items. This was conducted despite of data being of ordinal rather than interval type. Refer to the next section for a discussion of parametric vs non-parametric methods.

In study I, Pearson's correlation was used to analyze the association between a single question about memory and all separate SASCI-Q items, as a measure of convergent validity. Cronbach's alpha was used to assess internal consistency reliability. Before any analyses, items were categorized by co-authors with respect to cognitive domains and considering general/specific question type and load on social functioning.

Binary logistic regression analysis was used to analyze which variables predicted SCD (cross-sectional; study II) and cognitive decline, dementia and AD dementia (longitudinal; study III).

Sensitivity, specificity and likelihood ratios were calculated to assess predictive ability of SCD criteria and 'preclinical AD' criteria (study III), in relation to cognitive decline, dementia and AD dementia.

In study IV, Pearson's correlation and partial correlation were used to analyze the relationships between subjective cognitive symptoms on the one hand, and CSF AD biomarkers and depressive/anxiety symptoms on the other hand. T-test and ANCOVA were used to analyze group differences between separate SASCI-Q items.

Covariates such as age were generally taken into account only if differences between groups were statistically significant. The alpha level for significance was $p<.05$, however Bonferroni corrected results were presented in study I and IV due to the high number of variables. SPSS was used for all statistical analyses.

4.11.2 Statistical issues

There has been controversy for decades about the practice of using parametric or non-parametric tests with ordinal and non-normally distributed data. For scientific measures, unusually harsh standpoints have sometimes been used when discussing this issue, including stern comments like "using parametric analysis for ordinal data is the first of the seven deadly sins of statistical analysis" [241], and on the other side that reviewers' seemingly automatized demand for non-parametric methods is "overvaluation of criticism for its own sake, inappropriate statistical dogmatism'' [242]. To address this controversy, Norman [243] conducted a review of the assumptions of various statistical methods and the potential problems when the assumptions are violated. He argues that it is a misconception that data needs to be normally distributed to use parametric tests. It is the *means* – not the data – that should be normally distributed. According to the central limit theorem, means are approximately normally distributed regardless of the original distribution, for sample sizes greater than 5 or 10 per group. This theorem has also been supported by empirical studies, showing that parametric tests such as ANOVA and Pearson's correlation, are highly robust to e.g. skewness and non-normality [243]. Norman concludes:

"*Parametric statistics can be used with Likert data, with small sample sizes, with unequal variances, and with non-normal distributions, with no fear of "coming to the wrong conclusion". These findings are consistent with empirical literature dating back nearly 80 years. The controversy can cease (but likely won't).*" [243]

4.12 Approvals from the ethics committee

The Gothenburg MCI study was approved by the local ethics committee (diary number: L091-99 15 March 1999/T479-11 8 June 2011). Written informed consent was obtained from all participants in the Gothenburg MCI study (study II-III, and sub-samples in study I and IV) and in the follow-up study visits of the SASCI-Q cohort (study IV). For the SASCI-Q data-collection (study I), a separate ethics approval was sought and received (2009, diary number: 649-08), in which the ethics committee deemed verbal informed consent as sufficient. An amendment to this approval was later sought and permission was received to carry through the follow-up visits presented in study IV.

5 SUMMARIZED RESULTS

5.1 Study I

Study I presents the development and initial validation of a self-assessment instrument to measure SCD – the SASCI-Q.

The main objective of the study was to develop a patient-based comprehensive instrument on everyday cognition, identifying questions which separated between SCD patients and healthy controls – in other words, designing an instrument based on cognitive symptoms more often reported by help seekers without detectable cognitive impairment, compared to healthy older adults. Another objective was to investigate the cognitive spectrum of subjective cognitive symptoms in memory clinic patients with SCD – were all cognitive domains represented or not?

The 97 original items that were generated mainly from patient and informant interviews were reduced to 45 items that separated significantly between healthy controls and SCD patients. The psychometric properties – here referring to convergent validity (level of correlation with a measurement based on the same theoretical construct) and internal consistency (level of correlation between items) - were assessed as satisfying. Considering the spectrum of cognitive domains, it was found that the majority (62%) of items separating between healthy controls and SCD patients were related to the memory domain, although the domains of speed, attention, executive functions and language functions were also represented. No items related to the visuospatial domain separated between groups and were therefore not included in the final version of the instrument.

5.2 Study II

The main objective of study II was to investigate the prevalence of considerable psychosocial stress, depressive symptoms and CSF AD profile in memory clinic patients with SCD vs MCI. In line with our hypothesis, we found that SCD patients were generally characterized by high levels of stress

– over 50% of the sample, but low occurrence of CSF AD biomarkers – 14%. The prevalence of current depressive symptoms was largely similar in SCD and MCI groups. Reporting previous depressive symptoms was however significantly more frequent in SCD compared to MCI. Simultaneous reports of both stress and depressive symptoms – implying a greater load of affective symptoms – were more than two times more frequent in SCD compared to MCI. High levels of stress, more years of education and a negative CSF AD profile predicted SCD. The odds for belonging to the SCD group rather than the MCI group were 2.5 times higher for patients who reported previous or current stress. In addition to the main findings, we observed that the prevalence of SCD in the total non-demented patient sample was 36%, and that SCD patients on average were younger and had more years of education compared to MCI patients.

5.3 Study III

The objective of study III was to examine several variants of different SCD criteria and 'preclinical AD' criteria, concerning the proportion of progressing patients, and predictive ability of the criteria – both as clustered criteria and with respect to individual criteria. In other words, which variables predict progression in patients with SCD?

We observed that 39% of the 122 SCD patients had declined cognitively between baseline and follow-up, compared to 61% in the MCI/'subtle cognitive decline'-group. As expected, only a few (10%) of the SCD patients had developed dementia (although more than what would be expected in the healthy aging population during the same amount of time) – the majority of cognitively declining patients declined only in neuropsychological scores (=converted to MCI) during the follow-up time. By adding biomarker criteria to the SCD-group, the proportion of declining patients significantly increased – especially the criteria for 'preclinical AD stage 2' (both Aβ and tau markers positive) was observed as a successful predictor of progression. In patients categorized as 'preclinical AD stage 2', 81% converted to MCI or dementia, as compared to 39% in the total SCD group. When analyzing criteria separately, CSF Aβ was the only significant predictor of progression.

5.4 Study IV

The main objective of the study was to investigate differences in baseline subjective cognitive symptoms, using SASCI-Q, between progressing and non-progressing patients. Secondly, to investigate if any differences could be observed between SCD and MCI patients, with respect to baseline subjective cognitive symptoms in MCI and SCD patients, in relation to cognitive outcome and CSF AD biomarkers. We reasoned that it could indicate poor awareness if patients with verified cognitive impairment reported low levels of subjective symptoms.

Somewhat counterintuitively, when analyzing the entire sample consisting of both SCD and MCI patients, progressing patients did *not* report more cognitive symptoms at baseline for any of the 45 SASCI-Q items, compared to patients who did not progress. However, these results changed – and were somewhat explained - when the groups were separated into SCD and MCI: progressing SCD patients reported significantly *more* cognitive symptoms at baseline compared to their non-progressing counterparts, whilst progressing MCI patients reported significantly *less* cognitive symptoms compared to their non-progressing counterparts. With respect to specific items, progressing SCD patients reported significantly more symptoms for five items, compared to non-progressing SCD patients: 'someone else said that you did something you can't remember doing'; 'difficulties learning phone numbers by heart'; 'had the feeling that you planned to do something, without remembering what it was'; 'someone else reminded you about something'; and 'difficulties findings words compared to when you were 25 years old'. However, for most items, there was no significant difference between progressing and non-progressing patients. Interestingly, in SCD patients, reporting *more* cognitive symptoms correlated with having pathological concentrations of CSF AD biomarkers. Again, the results were reversed in MCI patients – reporting *less* cognitive symptoms correlated with having pathological concentrations of CSF AD biomarkers. The associations between depressive/anxiety symptoms and subjective cognitive symptoms were generally strong, especially in non-progressing patients.

6 DISCUSSION

The objective of this thesis was to investigate SCD in memory clinic patients with respect to characteristics and clinical relevance. 'Characteristics' firstly refers to features that may characterize patients with SCD, and secondly to the specific type of symptoms reported by patients with SCD. 'Clinical relevance' refers to the degree of association between SCD and cognitive decline and dementia.

6.1 Characteristics of patients with SCD

Per definition, SCD patients scored higher on neuropsychological tests (study II-IV) and cognitive screening tests (study I). When compared with MCI patients, the patients with SCD in our studies were of younger age and had higher education (study II-IV); which is in line with other clinically based studies [192, 244] but contradicts population-based findings, showing an association between SCD and higher age/lower education [36]. As has previously been mentioned, it is important to acknowledge the differences between findings generated in different research settings.

Compared to MCI patients, SCD patients reported more psychosocial stress and more previous depressive symptoms (study II). Specific subjective cognitive symptoms were more strongly associated with anxiety/depressive symptoms than with subsequent cognitive decline (study IV). These findings correspond to previous reports, showing firm evidence of an association between affective factors and cognitive symptoms [83-87]. Additionally, not only current but also previous affective states may help explain SCD. Taken together, the complex interrelationship between cognitive and affective symptoms clearly complicates the application of SCD as a marker for objective cognitive decline, which is further discussed below.

As compared to MCI patients, SCD patients were less likely to display pathological concentrations of CSF AD biomarkers (study III; however the difference was not significant in study IV when analysing a smaller sample); less memory difficulties as reported by an informant (study III); and scored

slightly higher on the MMSE (study IV, however non-significant difference in study III). These findings were expected because MCI per definition entails more cognitive impairment. However, not all studies have been able to establish a CSF AD biomarker difference between SCD and MCI, especially not in smaller samples [1]. Features that did not differ significantly between SCD and MCI patients were current depressive symptoms or anxiety, and male vs female sex. As was further discussed in study II, depressive symptoms thus seem less specific to the SCD group, compared to stress conditions.

The differences between SCD patients and healthy controls were only analysed in study I, showing that there was an equal level of education years; that SCD patients were younger than controls; reported more depressive symptoms; and had slightly lower mean scores on MMSE (although the mean difference was only 0.3 points). The most important difference between SCD patients and healthy controls was the main result of study I – for all the 45 final items in the SASCI-Q questionnaire, SCD patients reported more frequent symptoms compared to healthy controls. This result suggests that it is possible to identify cognitive symptoms that are more frequently reported by individuals who seek help for their cognitive problems compared to 'general cognitive complaints' in healthy older adults, which is an important aspect of separating potentially clinically relevant symptoms.

Unpublished results showed that having a family history of dementia (affected parents or siblings) was more than twice as frequent in SCD (65%) as in healthy controls (29%). Furthermore, there were no significant differences regarding presence of *APOE* ε4 between SCD and MCI or between SCD and healthy controls. In my opinion, especially patients who report having a family history of dementia should be thoroughly interviewed before being enrolled as patients. To what degree have they actually experienced cognitive symptoms, and to what degree have they sought help 'just in case', or to ease worries about heredity. In my experience, many patients have misconceptions about e.g. genetic risk factors. Some are convinced that they will develop dementia if both parents had dementia, which certainly does not have to be the case. These individuals would gain from receiving more facts about prevalence, different dementia disorders, heredity and risk.

In total, the factors that we observed as typical characteristics of SCD patients correspond well with the health belief model (HBM, section 2.7.7) describing

factors associated with higher vs lower likelihood of medical help seeking. According to the HBM, perceptions about what should be regarded as 'normal' or not, are factors associated with the likelihood of help seeking. In the current studies, younger age was a characteristic of the SCD patient group. Plausibly, when cognitive symptoms are experienced before retirement age, individuals may be more likely to consider them as troubling and unexpected compared to their peers. Older individuals may be less likely to seek help for subtle cognitive difficulties if they perceive them as part of normal aging – which may be partly accurate given what is known about cognitive aging processes, but also may be affected by negative stereotypes about aging.

Knowledge about symptoms is another factor associated with help seeking in the HBM. On average, SCD patients may have a wider knowledge/interest of dementia symptoms than general, e.g. reflected by their higher education level and the frequent occurrence of a family history of dementia. 'Cues to action', such as whether an individual is prone to seek medical care or not (for any symptom), is another factor in the HBM. A higher frequency of medical help seeking has been observed in individuals with higher educational attainment [245], which may partly explain our findings. Having a family history of dementia may also be related to the factor 'perceived susceptibility' in the HBM – individuals worrying for 'inheriting dementia' may be more likely to perceive themselves as more susceptible to disease.

Younger age may also indicate that individuals are more likely to still be employed, and thereby meet more cognitive challenges in daily life – not least associated with the increasing demands of technical skills in the workplace. However, it cannot be excluded that the younger mean age of SCD patients compared to MCI patients is simply a result of dementia being associated with age.

6.2   Characteristics of specific symptoms

The other aspect of characteristics of SCD refers to which type of symptoms that are reported. In study I, we started out with a questionnaire based on interviews with patients. Thus, it was not predetermined that a certain number of items should be included for each cognitive domain. By analysing data as presented in study I, the number of items were further reduced to only include those showing a significant difference between SCD patients and healthy

controls. The final items were unevenly distributed across the cognitive domains. Most items showing a difference between SCD patients and healthy controls were clearly associated with the memory domain – with sporadic items that were considered as more associated with other cognitive domains (attention/speed-, executive-, language- or mixed domains). Obviously, this was not surprising given that the sample consisted of patients at a memory clinic. Several of the memory items phrased as "did someone else remind you/say to you…[e.g. that you have a poor memory]". Possibly, these questions have an increased clinical relevance in that they indicate that others noticed the cognitive problems. On the other hand, a previous study found that being assessed as more forgetful by others was more common in younger respondents [38]. Other memory items were mostly related to problems noticed in everyday situations, such as when talking to others, remembering what you or others have said, remembering facts and learning new things. No questions in the final version were associated with the visuospatial domain. Similar findings were reported by two previous studies [64, 65] (although contradicted by another study in which difficulties with finding one's way around familiar streets was associated with objective cognitive impairment). This finding was somewhat unexpected, as problems with spatial orientation are known as dementia related symptoms. However, other cognitive domains such as memory and language (AD dementia), or executive functions and attention (vascular forms) are typically affected prior to the visuospatial domain. Another possible explanation is that complex visuospatial tasks may be easier to avoid in daily life for those with poor visuospatial ability than, for example, verbal tasks.

The developed instrument SASCI-Q has similarities – especially considering the broad spectrum of cognitive domains – with a couple of other questionnaires developed during the same time period, such as CDQ [69], SCD-Q [72], and the items suggested by Gifford *et al*. [75], but there are also important differences. The CDQ was also developed in Swedish, but was based on a sample from the general population. It was in part developed through statistical analysis that clustered items into components. Items were validated based on their correlation to cognitive tests – with the rationale that items that maximize the coherence between self-assessment items and objective performance should be maximized – and on the negative correlation to depressive symptoms. Thus, the CDQ and the SASCI-Q are likely valid for

different populations and different research questions, given the differences in construction methods, target population, and the underlying view on symptom validity. Considering SCD-Q [72], the most important difference compared to the SASCI-Q considers the construction of items – an expert panel generated items for the SCD-Q whilst we used patient interviews in our construction phase of SASCI-Q. Other differences are that the SCD-Q includes one self-report section and one informant-report section, whilst the SASCI only includes self-assessment, and the questions in the SCD-Q are dichotomous yes/no questions, whilst questions in the SASCI-Q are formulated in terms of prevalence and incidence, to offer a more detailed report. On item-level, the SASCI-Q and the SCD-Q share several items, such as 'difficulties learning new phone numbers', 'finding personal possessions', and 'finding words in a conversation'.

6.3   Clinical relevance of SCD

Assessing pre-dementia stages is a puzzle. All currently available methods for assessing early signs of sporadic forms of dementia, even those elevated to 'biomarkers', have well-known limitations of sensitivity and specificity. As of yet, no markers perform well enough to be considered surrogates of disease. The complex nature of SCD that the current studies and many other have recounted, obviously limits the usefulness of the SCD concept as a marker for disease. Despite using a carefully developed self-report instrument, we observed only a weak association between specific subjective cognitive symptoms and subsequent cognitive decline. However, we did identify five items for which progressing SCD patients reported more frequent symptoms compared to non-progressing SCD patients, in contrary to entirely negative findings reported previously (although that study included a mixed sample of SCD and MCI patients) [215]. These items, and others showing some, but non-significant differences, may be interesting to explore further longitudinally in larger samples. Especially as very few studies so far have investigated the predictive value of specific symptoms — or perhaps, negative findings were not reported.

Relatively few individuals with SCD (10%) converted to dementia over time (mean 4 years). This number however corresponds well with the findings of a large meta-analysis, reporting a 5-year conversion rate from SCD to dementia

of 11% [79] – twice as many converters compared to individuals without SCD. Thus, as could be expected, within the heterogeneous SCD group certainly some individuals will develop dementia. It cannot be excluded that the results would have been different with longer follow up time and larger samples. However, the associations between SCD and affective factors were considerably more convincing compared to the associations between SCD and any objective sign of underlying neurodegenerative disease. That said, in my opinion SCD cannot compete in clinical relevance with e.g. the MCI concept, neuropsychological tests, brain imaging or neurochemical analysis. There is not enough evidence to support SCD as a 'fourth pillar' of pre-dementia assessment, or as of equal predictive value compared to MCI. SCD cannot stand on its own as a clinically relevant concept in relation to disease progress – it is far too lacking in specificity. However, the association between SCD and subsequent dementia becomes apparently more relevant if there are simultaneous positive objective markers for ongoing neuropathological events. We observed that 81% of SCD patients with both positive amyloid and tau markers (='preclinical AD stage 2') converted to MCI or dementia over a mean of four years, as compared to 39% in the total SCD group. Other markers – such as imaging markers – may be equally valuable, although not investigated in this thesis. However, the entire population cannot be screened by lumbar puncture. Even if markers in blood were improved, it would be highly unethical to screen the population when treatment possibilities for dementia are still lacking. That is what makes SCD important despite its 'fuzziness' - there is currently no other way to identify individuals who may benefit from dementia screening, than by symptom report. That is how patients communicate their difficulties. Thus, striving to validate subjective cognitive symptoms as markers for future dementia is likely to overstate its potential diagnostic value.

However, there are several other areas in which self-report of cognitive symptoms may be useful. Studies comparing help-seekers with individuals who choose not to seek help despite experiencing cognitive symptoms are potentially important, because they increase knowledge about which persons choose to seek help. Such studies should also investigate how cognitive symptoms may be perceived, described, and associated to help seeking differently in different demographic groups, in both clinical and population based samples. It is well known that neuropsychological assessment of persons with a different native language is a challenge. Although it needs to be

investigated, self-report of cognitive symptoms may be a more important complement to neuropsychological tests in groups that are difficult to assess using standardized neuropsychological tests and norms based on native Swedish speakers.

In patients with stress conditions, cognitive problems may be difficult to verify, due to that their problems may be mostly noted in real-life situations with overwhelming stimuli. In these patients, self-assessment of cognitive symptoms could perhaps be – and is likely already – used as a basis for interventions and therapy.

The role of subjective cognitive symptoms in MCI has been debated. In the original criteria, 'memory or other cognitive complaint' was part of the criteria [246], although later criteria include that subjective symptoms should be corroborated by an informant [24]. Some have argued that subjective symptoms should be excluded from the MCI criteria altogether, due to its complex nature and contradictory findings [68, 76]. Researchers focusing on subjective symptoms have also highlighted that studies should separate between SCD and MCI, to enable separate evaluations of the two concepts as different stages on the dementia continuum [46]. We observed a curvilinear relationship in study IV – an association between more subjectively reported cognitive symptoms at baseline and future objective cognitive decline in patients with SCD, but the opposite in patients with MCI. A similar relationship has been observed by a previous study [68]. These results indicate that the clinical value of SCD is higher before objective cognitive signs are detectable. As has been previously acknowledged [68], SCD may thus be more confusing than clarifying in patients with MCI, because of the reduced symptom awareness that seem to affect some people even before a manifest dementia state. Results from study IV indicated that, before objective cognitive signs are observable, having subjective cognitive symptoms seems to be a more reliable indicator of subsequent decline. However, the level of ability awareness or 'meta-cognition' can be compromised also in the general population. Self-assessment may be affected by many factors, and is not an objective report of the cognitive state, as it would be described when measured by tests, which should always be kept in mind.

The differences in SCD based on different research settings have been a recurring point in this thesis. Although the differences between SCD in the

population and clinical settings were not investigated in the current studies, findings from previous studies have shown that the conversion rate in SCD is higher in clinical than in population-based samples [78]. Consequently, the clinical relevance of the SCD concept is higher in clinical settings. If screenings using biomarkers are to be conducted, e.g. for medical treatment interventions, a clinical SCD sample is likely more suitable as a target group compared to a community-based SCD sample.

To summarize the theme of clinical relevance, the results from this thesis indicate that there is some clinical relevance of SCD (as a patient category as well as specific subjective cognitive symptoms) as a predictor of future cognitive decline, but it should not be overstated. However, when CSF biomarkers indicate possible pathology, there is evidence to suggest that patients with SCD should be further investigated.

6.4 Functional memory disorder (FMD) – a justified concept

It has been suggested that another term is needed to distinguish persons with cognitive symptoms that are more likely to be related to dementia, from persons with cognitive symptoms that are potentially reversible and thought to be caused by emotional or psychological factors – that is, not caused by a neurological condition [247, 248]. A proposed term is FMD – functional memory disorder. It was first presented with criteria in 2008 [249] but has received much less attention than SCD – there are only nine publications on PubMed concerning FMD (April 2017). Since SCD is primarily a concept concerning the dementia realm, there is certainly a need of a parallel concept describing another etiology and trajectory. Especially as a majority of individuals with SCD will likely not develop dementia.

FMD has often been used for younger populations, and age >70 years is considered exclusion criteria in the original FMD criteria. However, the concept may just as well be applied in the aging population. FMD has been associated with above-average education and socio-economic attainment [250, 251], and is related to depressive symptoms, a ruminative style of thinking, a perfectionist attitude toward memory, and experiencing stress-related events

such as interpersonal conflicts, overwork, and distressing life changing events [249]. Besides the age criteria, the criteria of SCD and FMD differs in that FMD includes presence of 'psychosocial burden' and absence of a recognizable organic cause of cognitive impairment. The similarity between FMD and the characteristic profile we observed in many of our SCD patients is thus apparent – high educational attainment, stress, and depressive symptoms.

Schmidtke suggested that these factors may spiral into a 'vicious cycle' of worry and cognitive failures [249]. A few studies have analysed the effects of short-time counselling with help seeking individuals categorized as FMD, focusing on e.g. reassuring that test results were normal, and educating people about stress-induced cognitive impairment [252, 253]. The studies could generally not establish sufficient evidence for such interventions, as the symptoms remained in most individuals at follow-up. Often, these individuals are referred via primary care again, after a few years, with the same non-verifiable symptoms. These findings suggest that FMD, or 'non-progressive SCD', may be more difficult to treat than what could perhaps be expected. However, it is important to develop effective counselling and therapeutic strategies, as the symptoms of these individuals are potentially reversible. Using the FMD concept would distance the symptoms from being about 'just' dementia prediction, which seems reasonable given the non-progressive nature of most patients categorized as SCD. In my opinion, FMD is therefore a potentially useful concept to use in memory clinics.

6.5   Implications for health care services

The current studies, as well as previous research, have shown that a large proportion of help seekers at memory clinics only have subjective cognitive decline, and the vast majority of them do not seem to progress to MCI or dementia. In my opinion, this finding is partly related to the organization of health care services.

About half of the patients with SCD in our study II reported current or previous prolonged severe stress, often work related. Plausibly, a non-negligible number of individuals seek consultation at memory clinics even though they are rather convinced that their cognitive difficulties stem from stressful life

circumstances rather than an underlying neurodegenerative disease. These patients should be able to receive healthcare elsewhere, from caregivers dedicated to stress-related cognitive impairment. Such medical facilities exist, but apparently not enough to meet the needs. The general aim of memory clinics is to investigate possible early signs of dementia, and to offer medical support and treatment for those who are likely to have a progressing disorder. Those who experience cognitive decline in relation to e.g. stress, depression or anxiety, are not the target group and there is often a lack of specialist clinics to refer them to. If symptoms cannot be verified by investigations, they are sent home – probably less worried about dementia, but likely still with cognitive symptoms. In my opinion, an improved availability of interventions regarding the cognitive impairment associated with e.g. stress disorders would be valuable for affected individuals as well as to make health care more efficient. Using the concept FMD is a potential way forward to categorizing these individuals more accurately.

Overall, there seems to be a need for improved information to help-seeking patients – and to society – about a number of factors that are frequently misinterpreted: what cognitive functioning is; how it may be affected by different conditions and life circumstances; what can be expected in 'normal aging'; and the hereditary and risk factors for dementia. For example, comprehensive information to adult children of patients with dementia could increase knowledge in the next generation.

The cognitive implications related to conditions other than dementia have been curiously under-explored, but are fortunately now receiving more research attention, e.g. in the areas of stress conditions, intensive care, cancer, and brain trauma. Hopefully, health care services will follow, so that individuals with cognitive symptoms – regardless of etiology – will receive appropriate investigation, information and treatment. 'Cognitive medicine' may be further developed as a useful concept for both research and health care, to describe the inter-relationship between various medical conditions and cognitive dysfunction.

6.6 Strengths and limitations

6.6.1 Strengths

The phenomena in focus, subjective cognitive symptoms, were thoroughly investigated by developing and using a comprehensive instrument. The construction of questions was largely based on actual patient-report. The questionnaire addressed difficulties related to several cognitive domains, not just memory. Questions were evaluated and further developed in discussions with patients. The integration of qualitative and quantitative methods is a benefit in that they may balance each other's strengths and weaknesses.

The follow-up time was relatively long compared to in other similar clinical studies. Patients were well-characterized and investigated with multiple measures. Overall, it is a strength that the current thesis applies a comprehensive perspective on SCD – considering potential confounders as well as the specific symptom expression and pathophysiological correlates.

Furthermore, the researchers and other professionals involved in conducting the current research were clinically experienced, and the studies reflect actual phenomena encountered in a memory clinic.

6.6.2 Limitations

The patients in the current studies were all active help seekers at a memory clinic. As has previously been discussed, SCD may denote very different things in a clinical setting compared to in a community-based setting. The findings should therefore not be generalized to experiences of cognitive symptoms in the general population. Furthermore, as participation in the current studies partly involved responding to a comprehensive questionnaire in Swedish, the sample did not reflect the ethnic diversity in society. It cannot be excluded that individuals with different cultural origins describe symptoms differently. Furthermore, the degree of help seeking is known to be affected by demographic factors.

Varying methods to distinguish SCD from MCI were used in the current studies. This may affect the possibility to compare results across studies.

However, the different classifications were occasionally cross-tested, showing similar results regardless of classification variations.

As in most single center clinical studies, the samples of the current studies were fairly small. It cannot be excluded that negative findings was partly caused by small sample size. Furthermore, there was a varying follow-up interval between patients, some being followed for 12 months and others for over 10 years. This may partly be explained by the type of research setting – patients were consecutively included during 14 years. Additionally, some patients did not continue follow-up because of e.g. dementia, severe somatic disease or death.

The possible biases involved with using healthy volunteers as controls should be acknowledged. It is well established that volunteers on average are more well-functioning than the general aging population. There is also a risk that a few volunteers are interested to participate because they are in fact worried about their cognitive functioning – it is likely less of a stigma to enrol as a 'healthy control' than to become a patient. Such issues have however been addressed in the healthy control interviews before inclusion. Furthermore, when responding to a symptom questionnaire, there is a risk that healthy controls under-report symptoms, because they know that 'their role' is to 'be healthy'. However, when analysing data we did not observe such pattern of null-responses.

6.7 Ethical issues

The increased focus in research and health care in very early phases of possible dementia may be a key to more knowledge about the origins of disease. However, there are ethical issues involved that should be accounted for. Firstly, it may be an ethical problem to endorse a patient's subjective complaints using a diagnostic label, when there are in fact no objective signs of decreased functioning. Are we then 'diagnosing' patients when categorizing them as having SCD? In many scientific reports, the term 'diagnosis of SCD' is used. If 'diagnosis' is defined as 'an analysis or description of the nature of a condition/situation', SCD may be considered to be a diagnosis. On the other hand, if 'diagnosis' is defined as 'identification of a disease from its signs and symptoms', SCD should not be considered as a diagnosis but rather a

categorization or possibly a risk factor. The essential ethical issue of the terminology is that patients may perceive SCD, MCI or preclinical AD as diagnostic labels or even as pre-dementia-states, leading to the belief that they will inevitably develop dementia. To phrase a risk factor or biomarker to sound like a disease is a 'red flag' for possible over-diagnosis [254]. The use of the term 'preclinical AD' is therefore problematic, as it is easily misinterpreted as dementia being inevitably underway. SCD may be a less controversial concept, as it is clearly addressing the subjectivity of the symptoms, but there is still a risk of misuse. As Canevelli [255] stated: "*it should not be underestimated how many times other research conditions have almost automatically acquired clinical value*", pointing to MCI as an example of a 'condition' acquiring status as a diagnostic entity even though many individuals with MCI never develop dementia.

On the other hand, labels and diagnoses may be helpful for validation of the experienced problems, confirming that clinicians take patients' concerns seriously. When a previously poorly defined concept is upgraded to a diagnostic category, it also enables a sharper definition and operationalization, which increases the possibility of equal treatment across clinics and countries. Thus, validating a patient's problems by naming them may not be wrong, but it is important that clinicians make an effort to thoroughly describe the meaning, uncertainty and limitations of the used classification concepts.

A second ethical issue is that research on SCD and similar concepts require longitudinal follow-up over many years of patients without objective signs of disease. This may prevent help seeking and worried patients from moving on psychologically, remaining in the phase of "watchful waiting" far longer than what is medically justified. On the other hand, there are also patients who feel less worried if they receive regular check-ups. Reasonably, the psychological consequences for each individual study participant should be taken into account, by not pushing for study continuation for patients who seem to be negatively affected by study participation. This may partly explain why group sizes are generally small in memory clinic studies on SCD – the value of research must be weighed against the effect participation has on individual patients.

7 CONCLUSION

The results of this thesis show that it is possible to identify specific SCD symptoms that are more frequently reported by patients seeking help for cognitive problems, compared to healthy elderly – even in patients for whom no objective cognitive impairment could be verified. The self-report instrument SASCI-Q is a useful research tool to investigate cognitive symptoms further.

SCD patients are characterized by relatively young age, high educational attainment, high prevalence of stress conditions and depressive symptoms, and a family history of dementia. Even if subjective cognitive decline can have many causes, the SCD term is primarily used to signify a possible pre-MCI and pre-dementia stage. Another term, such as FMD, may be useful to describe individuals who have SCD with plausible affective/emotional causes.

Only a small proportion of help seeking patients with SCD convert to dementia over four years, and a majority does not decline to MCI. However, when CSF biomarkers are added, the ability to predict MCI, dementia, and AD dementia increases. SCD in combination with other markers is more clinically relevant in relation to subsequent cognitive decline.

The recently recommended criteria of SCD/SCDplus is an important development to improve research quality in this area and will hopefully lead to more stringent and comparable reports. However, this thesis could not establish most SCDplus criteria as predictors of cognitive decline. It is important that SCD is not misinterpreted as a diagnosis – it should only be conceived as a concept to categorize the presence of cognitive symptoms.

It could not be established that specific subjective cognitive symptoms are associated with cognitive progression in a memory clinic sample including both SCD and MCI patients. However, the clinical relevance of subjective cognitive symptoms differed between patients with SCD and MCI, as they may convey a risk of deterioration at the SCD stage, but in MCI, symptom awareness may be reduced, and the relationship is thus reversed – less reported symptoms may indicate a higher risk of future decline.

8 FUTURE PERSPECTIVES

The recommended criteria for SCD and the enriched SCD plus category are still in need of much further evaluation, in community-based samples as well as clinical populations. The ability to predict dementia by SCD and related concepts may only be truly evaluated by following patients, compared to non-SCD controls, for 10-15 years.

The area of specific symptoms, as opposed to summarized scales, should be further investigated as studies are still scarce. When the objective is to predict cognitive decline, is it relevant to ask multiple questions about specific symptoms? Or is one general question enough?

There are possible ethical issues involved with following individuals, as patients, for many years without objective signs of any disease. These issues should be further acknowledged and investigated. Is a continuous contact with health care and related research calming for affected individuals, or does it lead to even more worry?

Traditional neuropsychological tests are the 'gold standard' of assessing cognitive function. Many of the large tests used worldwide were developed decades ago, and are 'paper-and-pen tests' performed in a strict clinical environment. There are many strengths associated with these features - neuropsychological tests are generally convincing in terms of validity and reliability. However, we observed a relatively large number of individuals with self-reported stress conditions who had subjective cognitive difficulties, but for whom we could not verify cognitive impairment even by a comprehensive neuropsychological examination. Investigating cognition related to stress conditions is thus a challenge for neuropsychological method development. It is likely time to take even more steps toward computerization of tests. For example, by virtual reality (VR) technology it is possible to create precise and controlled dynamic multi-sensory 3D stimulus environments, as well as recording behavioral responses using advanced technical methods. Collaborations involving neuropsychology and VR technology is an exciting field for the future and has begun to show promising findings, e.g. in the area of stress-related cognitive functioning [256].

The aspects of help seeking is an important area to investigate further. Research suggests that factors such as perception of symptom severity, confidence in health care, a family history of dementia, knowledge about symptoms, and perceived risk to develop disease are some of the factors that affect if individuals seek help for their cognitive symptoms or not. Are there other factors involved that are not yet recognized? How does cultural background affect patterns of help seeking and symptom reporting? Is there a risk that different patterns of help seeking and inequality of health care accessibility lead to that specialized clinics over-include individuals from 'high-income' areas with benign subjective symptoms, and under-include individuals with more severe, objective, symptoms from 'low-income' areas?

Would increased efforts of education and information about e.g. cognitive function, stress effects on the brain, dementia, genetic risk and normal aging, decrease help seeking for benign subjective cognitive changes? Would a development of more cognitively oriented health care instances relieve the burden on memory clinics of help seekers with a non-neurodegenerative cause of cognitive symptoms?

There is still no 'cure' for dementia. A breakthrough in treatment trials does currently not appear to be close, as several trials have failed in recent years. However, in the case of an effective treatment for e.g. AD, new health care strategies will have to be developed to meet a likely escalating number of help seekers. In what way these demands are going to change can only be subject to speculation, but if or when a medical breakthrough comes, the conditions for both health care services and research will likely change tremendously.
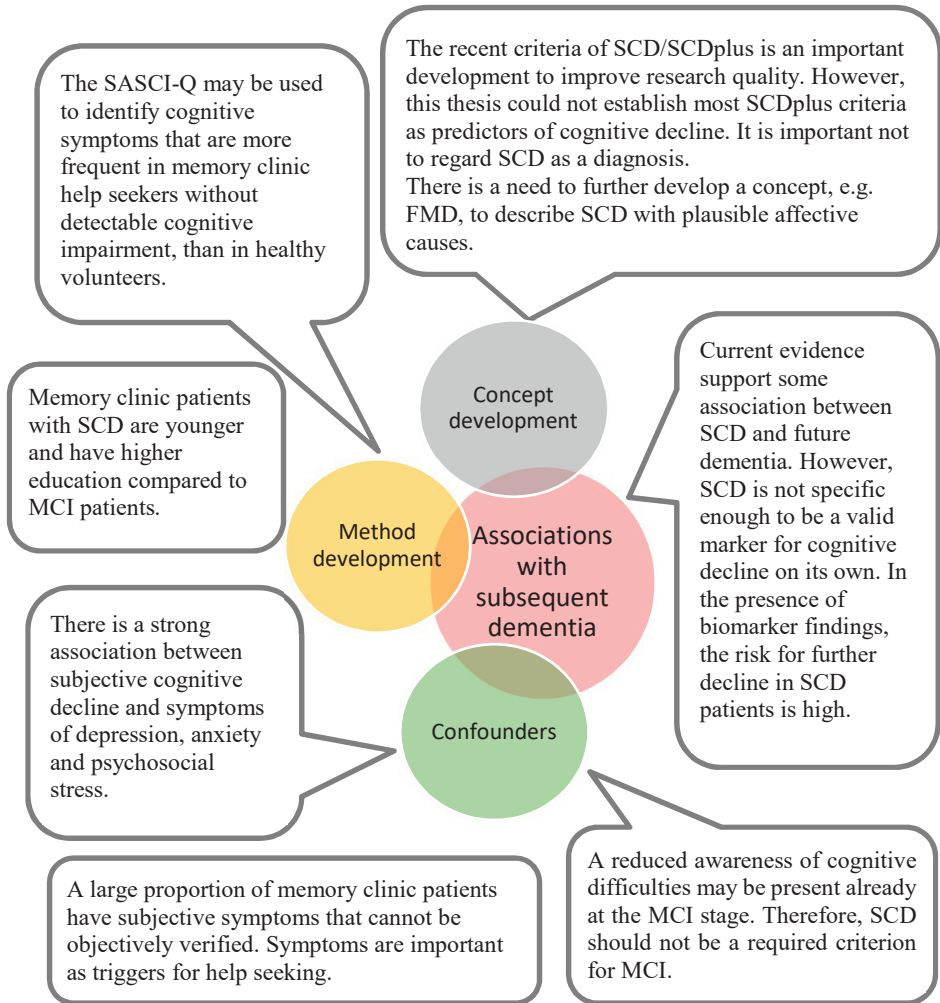
9 TAKE HOME MESSAGES

The SASCI-Q may be used to identify cognitive symptoms that are more frequent in memory clinic help seekers without detectable cognitive impairment, than in healthy volunteers.

The recent criteria of SCD/SCDplus is an important development to improve research quality. However, this thesis could not establish most SCDplus criteria as predictors of cognitive decline. It is important not to regard SCD as a diagnosis.
There is a need to further develop a concept, e.g. FMD, to describe SCD with plausible affective causes.

Memory clinic patients with SCD are younger and have higher education compared to MCI patients.

Current evidence support some association between SCD and future dementia. However, SCD is not specific enough to be a valid marker for cognitive decline on its own. In the presence of biomarker findings, the risk for further decline in SCD patients is high.

Concept development

Method development

Associations with subsequent dementia

Confounders

There is a strong association between subjective cognitive decline and symptoms of depression, anxiety and psychosocial stress.

A large proportion of memory clinic patients have subjective symptoms that cannot be objectively verified. Symptoms are important as triggers for help seeking.

A reduced awareness of cognitive difficulties may be present already at the MCI stage. Therefore, SCD should not be a required criterion for MCI.

Figure 7. Take home messages

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