

The Significance of Subjective Cognitive Decline in Primary Care and Memory Clinic Patients

Risk of Alzheimer's Dementia and Biological Correlates

Inaugural-Dissertation

zur Erlangung der Doktorwürde

der

Philosophischen Fakultät

der

Rheinischen Friedrich-Wilhelms-Universität

zu Bonn

vorgelegt von

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aus

Neuwied

Bonn 2015

Gedruckt mit der Genehmigung der Philosophischen Fakultät
der Rheinischen Friedrich-Wilhelms-Universität Bonn

Diese Dissertation ist auf dem Hochschulschriftenserver der ULB Bonn
http://hss.ulb.uni-bonn.de/diss_online elektronisch publiziert.

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Tag der mündlichen Prüfung: 05.10.2015

Note on advance publication – Hinweis auf Vorabveröffentlichung

With permission of the dean of the faculty of arts, Rheinische Friedrich-Wilhelms-Universität Bonn, the empirical part (section 3) of this dissertation has been previously published in the form of three peer-reviewed scientific articles, referenced in the following:

Study 1: Jessen, F.*, Wolfsgruber, S.*, Wiese, B., Bickel, H., Mösch, E., Kaduszkiewicz, H., Pentzek, M., Riedel-Heller, S. G., Luck, T., Fuchs, A., Weyerer, S., Werle, J., van den Bussche, H., Scherer, M., Maier, W. & Wagner, M. (2014). AD dementia risk in late MCI, in early MCI, and in subjective memory impairment. *Alzheimer's & Dementia* 10, 76–83. *shared first authorship. © 2014, reuse in this dissertation with permission by Elsevier (RightsLink Licence number: 3390241083326).

Study 2: Wolfsgruber, S., Wagner, M., Schmidtke, K., Frölich, L., Kurz, A., Schulz, S., Hampel, H., Heuser, I., Peters, O., Reischies, F. M., Jahn, H., Luckhaus, C., Hüll, M., Gertz, H.-J., Schröder, J., Pantel, J., Rienhoff, O., Rütther, E., Henn, F., Wiltfang, J., Maier, W., Kornhuber, J. & Jessen, F. (2014). Memory concerns, memory performance and risk of dementia in patients with mild cognitive impairment. *PloS one* 9, e100812. **Creative Commons Attribution (CC BY) license.**

Study 3: Wolfsgruber, S.*, Jessen, F.*, Koppa, A., Kleineidam, L., Schmidtke, K., Frölich, L., Kurz, A., Schulz, S., Hampel, H., Heuser, I., Peters, O., Reischies, F. M., Jahn, H., Luckhaus, C., Hüll, M., Gertz, H.-J., Schröder, J., Pantel, J., Rienhoff, O., Rütther, E., Henn, F., Wiltfang, J., Maier, W., Kornhuber, J. & Wagner, M. (2015). Subjective cognitive decline is related to CSF biomarkers of Alzheimer's disease in MCI patients. *Neurology* 84, 1261–1268. *shared first authorship. © 2015, reuse in this dissertation with permission by AAN Enterprises, Inc.

Acknowledgements – Danksagung

First, I would like to thank my supervisor Prof. Dr. Michael Wagner for his generous support from start to finish of this dissertation project. It is fantastic to work with a great amount of independence, while knowing that your supervisor takes his time to answer your questions, discuss results and guides you through tough peer-review processes. It is a pleasure to be a member of his working group.

I would like to give my special thanks to Prof. Dr. Frank Jessen for his enormous support and supervision over the last few years.

Further, I would like to thank Prof. Dr. Ulrich Ettinger who agreed to be second supervisor and Prof. Dr. André Beauducel who agreed to be chairman of the examination committee.

Many thanks to my (current and former) colleagues from the UKB and DZNE, Alexander Koppa, Alexandra Polcher, Katharina Heilmann, Moritz Daerr, Nadine Petrovsky, Leonard Lennertz, Ingo Fromman, Gabriele Herrmann, Sandra Röske, Dix Meiberth, Xiao-Chen Hu, Catherine N. Widman, Luca Kleineidam, and Lisa Miebach, for professional (and unprofessional) conversations, their helpful support and tons of coffee-breaks. I would further like to thank my colleague Maryse Scheller for proofreading and for her very helpful comments to this thesis.

I thank my parents, my sister, the rest of the family and my friends for their encouragement and their emotional support during the last years.

Anna, thank you for all the great moments we had during the last years and for shared suffering (including table formatting). Thank you for keeping me in line and standing by my side.

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1 Abstract

Subjective Cognitive Decline (SCD) is defined as an individual's perception of worsening cognitive function compared to his/her earlier performance level (Jessen *et al.* 2014a). SCD may often accompany regular cognitive ageing processes (Schaefer & Bäckman, 2007) given the high prevalence (25-50%) of this phenomenon in people 65 years and older (Stewart, 2012). However, during the last decade, SCD has also become an important research topic within the field of Alzheimer's disease (AD; Stewart, 2012). SCD is today considered among the earliest clinical symptoms of AD and may occur even before overt cognitive impairment objectified by neuropsychological testing. At this earliest symptomatic stage of AD, SCD may thus reflect an individual's perception of subtle intra-individual cognitive decline while cognitive performance is still within the normal range. SCD has therefore been proposed as a first clinical symptom that may emerge in the transient stage between a completely asymptomatic stage of AD and the pre-dementia clinical stage of AD which is commonly referred to as Mild Cognitive Impairment (MCI). Several studies have shown that individuals with SCD but normal objective cognitive test performance are at increased risk of future AD dementia and of having abnormal values in biomarkers indicative of AD pathology. These individuals may thus represent a particularly relevant target population for early prevention approaches as they are enriched for risk of AD dementia but are still in the earliest clinically detectable stage in which interventions might be most effective. However, the usefulness of SCD in prediction of AD has also been questioned, mainly because there is little cross-sectional correlation of SCD with objective cognitive performance and, more importantly, because SCD has consistently been related to potentially confounding factors such as depressive symptomatology and, to a lesser degree of evidence, to anxiety and personality factors.

SCD as a symptom is not limited to the pre-MCI stage of AD but rather extends into the MCI stage. In fact, SCD is part of the current MCI criteria. However, the utility of SCD as part of these criteria has also been questioned. This is because anosognosia (i.e. a patient's unawareness of his/her own disease-related deficits) as a core symptom of AD dementia might already emerge, and thereby confound the endorsement of SCD, at least in more progressed stages of MCI. This may limit the utility of SCD as a predictor of clinical progression or underlying AD pathology in the MCI stage.

Open questions remain with regard to the significance of SCD at different stages of AD. While the overall evidence shows that SCD is associated with incident AD dementia, it is unclear whether specific quantitative and/or qualitative features of SCD might be of higher predictive value than others. This question addresses the optimal operationalization and measurement of SCD. Furthermore, as mentioned above, while SCD has gained significant attention in the field of pre-clinical AD, the significance of SCD in MCI has been questioned. However, the relationship between SCD and possible confounders in MCI, such as objective memory impairment and reduced symptom insight, is not well understood. The question whether SCD has differential predictive value at different stages of objective impairment, is unclear and remains to be empirically tested.

In this thesis, the questions above have been addressed in three consecutive, previously published, empirical studies which examined the significance of SCD as a predictor of incident AD dementia and of AD biomarkers in the pre-MCI and the MCI stage. These studies are based on a multicenter primary care cohort (German study on Ageing, Cognition and Dementia (AgeCoDe study), study 1) as well as a multicenter memory clinic MCI cohort of the German Competence Network Dementia (DCN cohort, study 2 and study 3). Study 1 (Jessen *et al.* 2014b) examined the risk of incident AD dementia in individuals with and without SCD in the pre-MCI and MCI stage within a long follow-up time frame of up to six years. The main finding of that study was that cognitively normal individuals who reported SCD in the memory domain and who had concerns related to their experienced memory decline were at a significantly elevated risk to develop AD dementia over time compared to controls. Furthermore, risk of AD dementia in these individuals was similar to those who had the same memory concerns but whose memory performance was in the range of mildly impaired MCI patients (called “early MCI”). This study, thus, provides evidence that stages of very early mild cognitive impairment are not well captured by standard neuropsychological testing. It further highlights the relevance of subjective indicators of memory decline over time to predict AD dementia at this early stage of AD. Furthermore, these results suggest that concerns regarding self-experienced memory decline may be a particularly important qualitative feature of AD-related SCD.

Study 2 (Wolfsgruber *et al.* 2014b) and study 3 (Wolfsgruber *et al.* 2015) investigated the significance of SCD with regard to prediction of incident AD dementia

and biomarkers of AD in a memory clinic sample of patients with MCI. As mentioned above, the significance of SCD in the MCI population is a controversial topic. Studies 2 and 3 found quantitative and qualitative aspects (again in the form of concerns about memory decline) of SCD to be significant predictors of incident AD dementia and of abnormal AD biomarkers. Results of study 2 further suggest that the significance of SCD as a predictor of incident AD dementia may decrease with decreasing memory performance, thereby providing evidence of a dynamic interplay of SCD and objective cognitive impairment in AD dementia prediction. Both studies suggest that a refined and improved SCD assessment in the MCI stage may be warranted in order to complement the broad clinical SCD criterion in current MCI definitions. This might eventually contribute to improved prediction of AD dementia and could also be useful for enrichment of MCI samples for underlying AD pathology.

After a general introduction and the presentation of these studies, this thesis will be continued with a general discussion of the study results and their contributions to the field of AD research. Lastly, an outlook on possible directions of further research in the field of AD-related SCD will be given.

2 Introduction

The aim of this section is to give a cohesive overview on the development of Alzheimer's disease (AD) and the concept of Subjective Cognitive Decline (SCD). The section will start by providing a definition and short overview of dementia and AD dementia as its most common form (section 2.1). A description of the temporal development and the stages of AD from the preclinical phase to the dementia phase will then be given. The so called "biomarker model of AD" will be presented, which describes "the temporal evolution of AD biomarkers in relation to each other and to the onset and progression of clinical symptoms" (Jack *et al.* 2010; Jack *et al.* 2013; section 2.2). After presenting the model as a general framework, the proposed stages of AD will be outlined briefly (section 2.3). Current biomarker based criteria of preclinical AD, MCI due to AD and AD dementia will be summarized for a convenient reference. However, the informed reader may skip these passages. Next, an overview of the SCD concept will be given (section 2.4). Here, terminology, methods of assessment and the heterogeneity of the concept in the literature will be described. SCD will then be discussed in relation to the biomarker model and the different stages of AD. Similarly to the biomarker model of AD, a working model for the temporal evolution of SCD across the spectrum of AD, which served as a conceptual model for the empirical studies of this work, will be presented. The last section of the introduction (section 2.5) sums up the previous sections and leads to a short description of the goals and hypotheses of the three empirical studies presented in this thesis.

2.1 Dementia and Alzheimer's disease (AD): Definition and Overview

The term "dementia" is defined as a non-specific *syndrome* (i.e. a set of clinical symptoms) rather than a specific disease. Although there is great variation regarding its phenotypical presentation, dementia is in its core characterized by (usually progressive) loss of global cognitive functioning severe enough to cause significant impairment in daily living. Affected cognitive domains are verbal and visual memory, language, executive functions, orientation and attention, intellectual abilities and visual perception.

Impairment in memory and in at least one other domain is the minimal requirement implemented in the diagnostic algorithm for dementia according to the criteria of DSM-IV (American Psychiatric Association, 2000). In the recently published

new version of the DSM (DSM-5), the term dementia has been replaced by the terms “mild and major cognitive disorders”, respectively (American Psychiatric Association, 2013). While the mild cognitive disorder basically corresponds to the diagnosis of a Mild Cognitive Impairment (MCI; described later), the term major cognitive disorder has replaced the syndrome of dementia. An important change in DSM-5 is that memory impairment no longer poses a necessary requirement for the diagnosis of a major cognitive disorder. This amendment acknowledges that memory impairment is not the primarily affected domain in some forms of dementia (e.g. frontotemporal dementia). Furthermore, specific guidelines concerning the severity of cognitive impairment (in terms of standard deviations below test norms) are detailed in DSM-5, which, as a consequence, means that neuropsychological testing is required for the diagnosis.¹

A detailed outline of up to date general criteria for dementia and specific criteria for “dementia due to Alzheimer’s disease”, which also incorporates biomarker information in the diagnostic procedure, is given in section 2.3.3. These are the *National Institute on Aging-Alzheimer’s Association* (NIA-AA) criteria (McKhann *et al.* 2011) which represent a revised version of the older criteria set proposed in 1984 by the *National Institute of Neurological and Communicative Disorders and Stroke* (NINCDS) and the *Alzheimer’s Disease and Related Disorders Association* (ADRDA) (McKhann *et al.* 1984). The clinical Alzheimer’s disease dementia criteria of the NINCDS-ADRDA have been the research standard for the last 30 years and are also the basis for the Alzheimer’s disease dementia diagnosis in the empirical studies of this work.

While the term dementia is used to describe the clinical syndrome, “Alzheimer’s disease” (AD) is a progressive neurodegenerative disease that leads to a dementia syndrome. Besides AD, other neurodegenerative diseases such as Parkinson’s disease or Pick’s disease can lead to dementia. However, AD is by far the most common cause for the dementia syndrome, accounting for roughly 50-70% of all cases (Burns & Iliffe, 2009). Vascular dementia or “multi-infarct dementia” is the second most common cause of dementia in the elderly (ca. 25% of cases) followed by dementia with Lewy bodies (ca. 15% of cases; Burns & Iliffe, 2009). Mixed dementia describes a condition in

¹ In this manuscript the term dementia is used instead of the DSM-5 terminology as the research results presented herein are based on DSM-IV criteria for dementia and NINCDS-ADRDA criteria for AD dementia. In addition, the term dementia is still preferred in the scientific field.

which pathophysiological characteristics of more than one form of dementia are simultaneously present. The most common form of this type of dementia etiology is a combination of AD and vascular pathology (Viswanathan *et al.* 2009) which occurs in about one third of the AD and vascular dementia cases, respectively (Burns & Iliffe, 2009).²

While the definite etiological diagnosis for a patient with dementia requires a post-mortem brain autopsy, research of the last decades has made it possible to diagnose dementia due to AD and its prodromal stages with high sensitivity and specificity (Dubois *et al.* 2014). This has led to the formulation of new diagnostic criteria sets which incorporate specific *in-vivo biomarkers* that (if abnormal) increase the likelihood of AD pathology in patients with either dementia, MCI or in the preclinical stages of AD. These criteria are detailed in section 2.3 after the temporal development of AD has been outlined.

Despite major advances in the understanding of the development of AD, pharmacological and non-pharmacological treatments have only lead to a symptom relief but not to a significant prevention of disease progression (Aisen *et al.* 2011). Results of clinical trials of anti-dementia drugs in MCI patients with prominent amnesic deficits (i.e. at increased risk of subsequent AD dementia) have also shown little success (Aisen *et al.* 2011). It has therefore been acknowledged that effective pharmaceutical treatment should best be located in the earlier MCI stages or even in the pre-MCI stage, when only little brain damage has occurred (Aisen *et al.* 2010; Sperling *et al.* 2011). However, in order to achieve this, an improvement of the early detection of incipient AD and more knowledge of the cognitive decline in the early (pre-MCI) phase of AD are needed (Sperling *et al.* 2011). As will be discussed further below, the concept of SCD is important in this regard because it might be useful to define populations who are at increased risk of future AD dementia but are still in the earliest clinically detectable stage where interventions might be most effective (Sperling *et al.* 2011).

Effective prevention will be crucial in order to face the socioeconomic burden of dementia today, and even more in future generations. As a consequence of the ageing

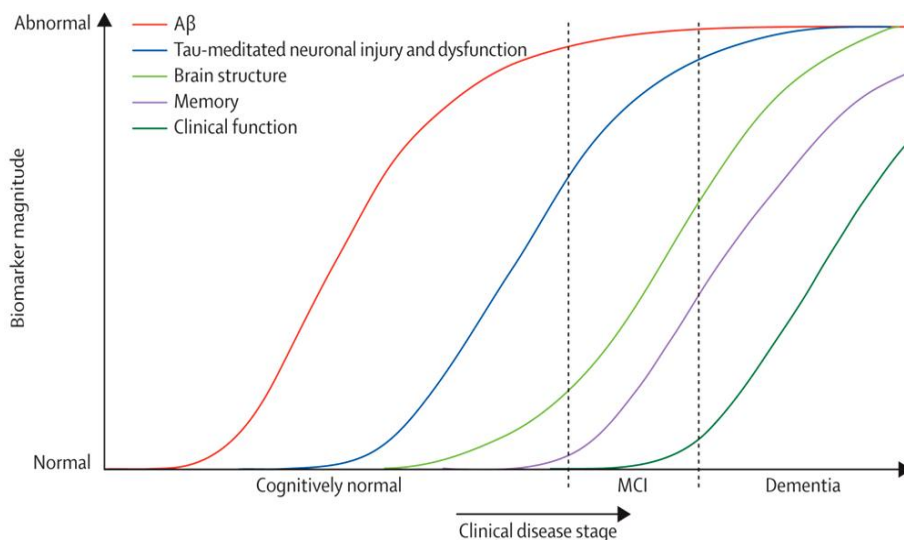
² A definite diagnosis of mixed dementia would require a brain autopsy. In empirical studies with clinical dementia diagnoses, cases of AD/vascular mixed dementia are usually included in the AD dementia group as it is the case in empirical studies 1 and 2 in this manuscript.

population, dementia prevalence is growing and will posit increasing societal costs. A study by Wimo and colleagues (Wimo *et al.* 2011) reported on 7.22 million demented people in the European Union and estimated the total costs of dementia to be €160 billion corresponding to annual costs of €22 000 per dementia case with costs of informal care (56%) exceeding direct costs (44%). In a more recent study, the worldwide costs of dementia in 2010 were estimated to US\$604 billion with 70% of these costs occurring in high-income regions of Western Europe and the USA (Wimo *et al.* 2013). For the latter, Hurd and colleagues (Hurd *et al.* 2013) have estimated that the total costs will approximately double in 2040 assuming that prevalence rates and costs per demented person remain stable. The implication of these numbers is straight forward: Improved early diagnosis and evidence based cost-effective intervention strategies need to be developed in order to relieve health care systems and improve the life of patients and their caregivers (Wimo *et al.* 2013).

2.2 Temporal development: The biomarker model of AD

This section describes the development of AD according to the “biomarker model of AD”, proposed by Jack and colleagues (Jack *et al.* 2010). The model suggests an ordered fashion in the dynamics of different markers of AD across progression from cognitively normal to dementia (see *Figure 1*).

Figure 1. The biomarker model of AD as proposed in Jack *et al.* (2010, 2013).



Note. Further information on *Figure 1* is given in the following text. Figure reused in this dissertation with permission by Elsevier (RightsLink Licence number: 3390241478378).

Figure 1 describes the temporal cascade of onset of AD pathology and clinical symptoms across the stages of Cognitively normal (preclinical AD), MCI due to AD

and AD dementia. According to the model, the level of abnormality of a disease marker for an individual at a given point in time is a function of (1) the time elapsed from onset of deviation of the marker away from normality to the point of assessment and (2) the marker's average rate of change over this period of time. The first factor can be viewed as shifting from left to right on the x-axis of the graph. The second factor can be described as the steepness of the trajectory which is not linear but varies across different intervals of the trajectory. AD is therefore viewed as an evolving process with dementia forming the clinical endpoint. Pathological changes in the brain, however, occur years to decades before the onset of overt clinical symptoms.

For the description of the temporal development of AD, the model uses the five most well established indicators of AD pathological changes, which are called *biomarkers*. According to Jack and colleagues, these biomarkers can be divided into two major categories. The first category comprises markers of brain amyloid β ($A\beta$) plaque formation which can be measured by cerebrospinal fluid (CSF) levels of $A\beta_{42}$ ³ and by brain PET $A\beta$ imaging. The second category comprises three measures of neurodegeneration, defined as progressive loss of neurons or their functioning. Increased CSF tau reflects tau pathological changes and neuronal damage which also occurs in other conditions than AD (i.e. it is non-specific for AD). ¹⁸F-fluoro-deoxy-glucose positron emission tomography (FDG-PET) is used to measure reduced brain metabolism (which indicates reduced synaptic activity). In early AD, hypometabolism can be detected in medial temporal lobes and parietotemporal posterior cortices, while other cortical areas are involved later as the disease progresses (Cason *et al.* 2011). Finally, structural magnetic resonance imaging (MRI) is used to measure brain atrophy.

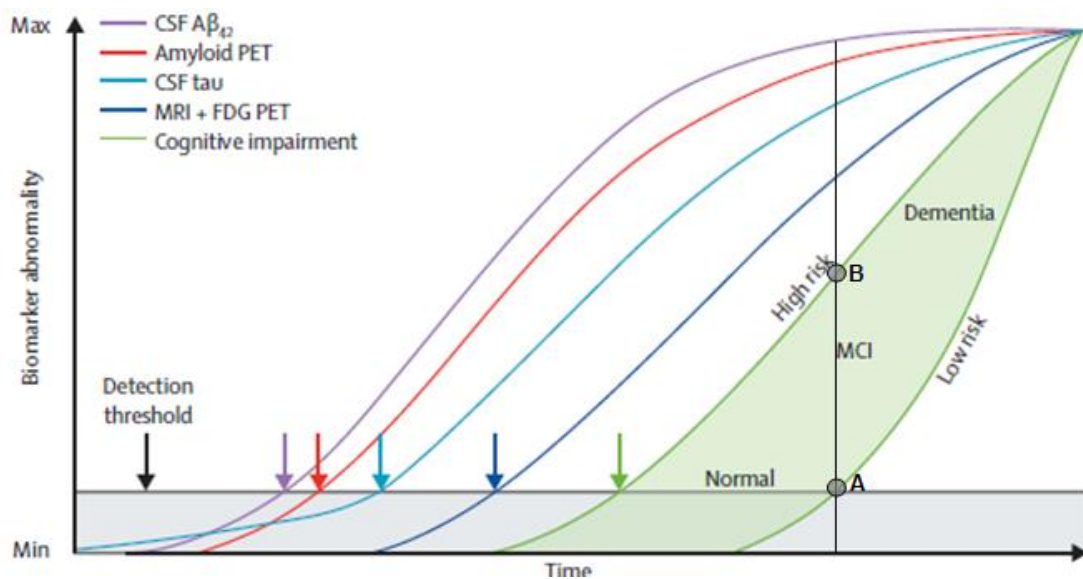
The temporal ordering of the biomarker changes depicted in *Figure 1* follows the *Amyloid Cascade Hypothesis* of AD. This widely accepted hypothesis states that AD begins with abnormal processing of the amyloid precursor protein, which then leads to excessive production or reduced clearance, and consequently plaque formation of $A\beta$ in the brain. Strong evidence for this assumption comes from genetic research on autosomal-dominant forms of (familial) *early-onset* AD (i.e. diagnosed before age of

³ $A\beta_{42}$ is an $A\beta$ -peptide consisting of 42 amino acids. $A\beta$ peptides with this length form the major part of the senile AD plaques in the brain. As $A\beta_{42}$ cumulates into plaques in the brain, *lower* concentration of $A\beta_{42}$ in the CSF indicates *more* AD pathology.

65) that is caused by genes involved in the production or cleavage of the amyloid precursor protein. Amyloid plaque formation is then supposed to lead to a downstream pathological cascade characterized by abnormal Tau protein aggregation, Tau-mediated neuronal injury and dysfunction, cell death, and atrophy of the brain. The mechanisms of this hypothetical cascade are yet not fully understood and subject to extensive research.

Since the introduction of the biomarker model in 2010, it has received great interest in the field and numerous studies have been conducted to test the model's hypotheses. In 2013, Jack and colleagues published an updated model in which this research is summarized (Jack *et al.* 2013). The accumulated evidence so far has supported the model's main assumptions. However, challenging empirical data has also led to some important modifications. *Figure 2* shows the updated biomarker model.

Figure 2. The updated biomarker model of AD (adapted from Jack *et al.* 2013).



Note. Further information on *Figure 2* is given in the following text. Figure reused in this dissertation with permission by Elsevier (RightsLink Licence number: 3390241478378).

A comparison of *Figure 1* with *Figure 2* shows that the main biomarkers of Aβ, Tau-mediated neuronal injury, and brain structure are now depicted more differentiatedly with slight reordering. In addition, a *detection threshold* has been introduced, which demarks the point where AD pathology can be detected by currently available in-vivo biomarkers. Autopsy studies (Braak & Del Tredici, 2011) have suggested that subcortical AD-like tauopathy precedes the Aβ pathology which

apparently contradicts the Amyloid Cascade Hypothesis of AD. In *Figure 2* these findings have been integrated by proposing that subcortical AD-like tauopathy starts before and independently from A β accumulation. This process lies below the detection threshold of in-vivo markers and can only be found by methods of autopsy. Pathophysiological changes in A β , by yet unknown mechanisms, then accelerate the preceding subcortical tauopathy which will now also spread to neocortical areas. This accelerated tauopathy will however reach the detection threshold after the A β changes. Besides these amendments, it is important to note that both currently available diagnostic markers of A β (CSF-A β 42 assays and A β -PET) provide evidence of *fibrillar* aggregates of A β but not of *soluble* A β oligomers. However, there is strong evidence from laboratory studies suggesting that oligomeric A β plays an important role in the AD cascade (Jack *et al.* 2013). Therefore this model might need refinement if methods to detect oligomeric forms of A β were to be developed in the future (Jack *et al.* 2013).

From a clinical perspective, the most important revision has been made to the x-axis of the model that is now labeled as “Time” rather than “Clinical disease stages”. The latter are now placed within a zone of cognitive impairment (green field in *Figure 2*) that is delimited to the left and right by a high risk and low risk cognitive impairment trajectory, respectively (green lines). This new depiction of the disease progress accounts for inter-individual variability in the response to AD pathology. This is illustrated by the two points A and B within *Figure 2* (inserted by the author of this thesis), which stand for individuals with a low risk (A) vs. high risk (B) profile, respectively. Likely modifiers of risk are genetic factors, lifestyle factors, comorbid (e.g. vascular) pathological processes, and cognitive reserve (Stern, 2012). As person A and B lie on the same point on the time-axis, they are confronted with the same level of AD pathological burden. However, while Person B will display cognitive impairment in the range of MCI, Person A will still perform within range of “normal test performance” on neuropsychological tests. Importantly, deterioration from the baseline performance has also taken place for Person A but this deterioration lies just at the border of the (cross-sectional) detection threshold of neuropsychological testing, i.e. impairment might not be detected with high diagnostic certainty.

This modification of the relationship between cognitive impairment and AD pathology has important implications for neuropsychological research and the concept of SCD. Person A is located exactly at the detection threshold of cognitive impairment.

As neuropsychological test results are usually a cross-sectional “snap-shot” of an individual’s performance, it will be difficult to classify this person either as normal or cognitively impaired (e.g. MCI) with sufficient diagnostic certainty. One possible solution to improve this dissatisfactory situation could be to apply neuropsychological tests that are optimized for detecting subtle, cognitive impairment due to AD, i.e. below the current detection threshold set by clinical standard tests. Research in this regard is undertaken (Rentz *et al.* 2013).

The concept of SCD offers a second possibility that could complement more sensitive neuropsychological testing. As stated above, Person A has already deteriorated from a higher level of cognitive performance. Hence, although clinical standard tests would show no cognitive impairment, this individual might actually have perceived the decline from his/her former baseline performance and, as a consequence, reports SCD, is concerned about his/her cognitive performance and may seek medical evaluation. If the report of SCD already reflects the longitudinal decline of an individual below the threshold level of clinical standard tests, it bears the chance to detect people at higher risk to develop AD dementia at an earlier level of the disease process. Furthermore, as biomarkers of AD pathology will, according to the biomarker model, already be above their respective detection thresholds when SCD is reported (see *Figure 2*), the diagnostic certainty of incipient AD in these individuals can be further increased by more intensive, biomarker-based diagnostic procedures. Therefore SCD has the potential to be used as an indicator of increased likelihood of AD pathology and might be used in clinical practice and research, e.g. for sample enrichment in longitudinal studies or as a pre-selection process when defining “preclinical AD” samples on the basis of biomarkers (less people need to be screened which saves time and money). Samples defined like this might then also serve to validate new neuropsychological measures in the pre-MCI stage.

2.3 Stages of AD: From preclinical AD to AD dementia

The last section has outlined the temporal development of AD biomarkers in order to provide the basic context for SCD research within the field of AD. The next subsections will briefly describe the different stages of AD. These stages have been proposed in the recent years as research results have made it possible to diagnose probable AD in vivo with high accuracy due to the incorporation of biomarkers.

Two biomarker-based research criteria sets for the definition of AD are currently in use, namely the recommendations proposed by the workgroups of the NIA-AA in 2011 (Sperling *et al.* 2011; Albert *et al.* 2011; McKhann *et al.* 2011) and those proposed by an International Working Group (IWG) in 2007 which were revised in 2010 and 2014 (Dubois *et al.* 2007; Dubois *et al.* 2010; Dubois *et al.* 2014). Both criteria sets share many similarities but differ in some points regarding cognitive criteria, the application of biomarkers and the approach to subdivide AD stages. A detailed comparison of both criteria sets would be beyond the scope of this manuscript (see Visser *et al.* 2012 for a comprehensive overview). Instead, a short outline of the rationale to use the terminology of the NIA-AA criteria for the present document will be given in the following.

Independently of specific criteria sets, AD can be divided into three stages (Visser *et al.* 2012): a pre-pathology stage (biomarkers normal, absence of cognitive impairment), an asymptomatic stage (biomarkers abnormal, absence of cognitive impairment), and a symptomatic stage (biomarkers abnormal, presence of cognitive impairment). Visser and colleagues further subdivide the symptomatic stage into pre-MCI SCD, MCI and dementia. Both the IWG and NIA-AA criteria deal with the asymptomatic and symptomatic stages of AD. The IWG criteria propose only two criteria sets, namely one for the asymptomatic stage (termed “preclinical AD” in 2007, and “asymptomatic at risk” in the 2010/2014 revised criteria) and one for the symptomatic stage, which is simply named “AD”. The latter comprises subjects with MCI (now termed “prodromal AD”) and with AD dementia. That means that the term MCI is omitted in these criteria.⁴ Concerning cognitive criteria, the IWG criteria require a specific form of memory impairment measured by a test that controls for encoding and probes response to cueing (Dubois *et al.* 2010). Importantly, despite abnormal biomarkers, subjects with SCD who have normal test performance (pre-MCI SCD) cannot be clearly classified by these criteria (Visser *et al.* 2012) because they are neither “asymptomatic” nor do they meet the objective memory impairment criterion to be classified as “prodromal AD”. In contrast to this, the NIA-AA criteria propose three criteria sets: Preclinical AD, MCI due to AD, and AD dementia. With regard to

⁴ In the IWG criteria, MCI is reserved for unclear diagnostic entities without clear cognitive criteria (i.e. the specific amnesic memory syndrome) and biomarker evidence of AD (Dubois *et al.* 2010).

cognitive criteria, (single or multiple) cognitive impairment rather than explicit memory impairment is required for diagnosis of MCI due to AD and AD dementia, respectively. Impairment in memory is considered a core feature which is seen in most (but not all) patients. However no specific memory test is required. Finally, in the NIA-AA criteria, subjects with pre-MCI SCD due to AD are part of the preclinical AD group (see section 2.3.1).

In summary, the NIA-AA criteria seem better suited as a framework for the present work as the term MCI is still used and patients presenting with pre-MCI SCD are explicitly addressed in these guidelines. Furthermore, the clinical-neuropsychological criteria for MCI due to AD resemble the MCI criteria in the present studies.

2.3.1 Preclinical AD

The stage of preclinical AD as defined in the NIA-AA criteria set comprises the asymptomatic (abnormal biomarkers, no cognitive decline) as well as the earliest symptomatic phase of AD (abnormal biomarkers, subtle cognitive decline). As such they are centered on the early biomarkers of AD as outlined in the biomarker model (see section 2.2) which means that, following the Amyloid Cascade Hypothesis, abnormality in A β biomarkers (CSF-A β 42 or A β brain PET imaging) are necessary features in these criteria. Additional markers of neurodegeneration and even subtle forms of cognitive impairment (not severe enough to warrant a diagnosis of MCI) are also part of the criteria. However, these features are complementary to the core feature of A β abnormality and are present in later sub-stages of preclinical AD (see below).

The preclinical AD stage has been deliberately proposed using the term “research recommendations” instead of “diagnostic criteria” (Sperling *et al.* 2011). This is to emphasize that the proposed research criteria for preclinical AD should not yet be used for clinical purposes as there is currently limited knowledge on the relation between preclinical biomarker evidence of AD and subsequent emergence of clinical symptoms (Sperling *et al.* 2011). Instead, the aim of these criteria is to provide a common basis for the definition of study cohorts with increased risk of future AD in order to further investigate this relationship. This comprises longitudinal observational studies to test the predictive validity of preclinical AD criteria as well as clinical trials to

test the effect of disease-modifying interventions on biomarker progression or onset of clinical symptoms (Sperling *et al.* 2011).

Sperling and colleagues have proposed a 3-stage schema to conceptualize preclinical AD as shown in *Table 1*. This staging schema describes preclinical AD as a continuum which comprises individuals with earliest detectable changes in biomarkers of A β (stage 1), individuals with additional abnormalities in markers of synaptic dysfunction and neuronal injury (stage 2) and finally those individuals who exhibit subtle cognitive decline in addition to evidence of abnormal biomarkers of both types (stage 3).

Table 1. Stages of preclinical AD according to the NIA-AA criteria (Sperling *et al.* 2011).

Preclinical AD stage	Evidence of markers of Aβ burden (CSF or PET)	Evidence of markers of neuronal injury (CSF-Tau, FDG-PET, MRI)	Evidence of subtle cognitive decline
Stage 1: Asymptomatic cerebral amyloidosis	Positive	Negative	Negative
Stage 2: Asymptomatic amyloidosis + “downstream” neuronal injury	Positive	Positive	Negative
Stage 3: Amyloidosis + neuronal injury + subtle cognitive decline	Positive	Positive	Positive

Note: Abbreviations: AD, Alzheimer’s disease; A β , amyloid beta; CSF, cerebrospinal fluid; FDG, ¹⁸F-fluoro-deoxy-glycose; MRI, (structural) magnetic resonance imaging; PET, positron emission tomography.

Stage 1 represents the earliest definable stage of AD with current diagnostic markers. Individuals in stage 1 have evidence of A β deposition (CSF-A β 42 and/or A β -PET), but neither detectable abnormality in markers of early neuronal dysfunction nor detectable cognitive decline.

Individuals in Stage 2 are considered “farther down the trajectory” of the AD pathological cascade as they show additional evidence of early neuronal injury and/or neurodegeneration (Sperling *et al.* 2011). Such evidence is defined as: (1) elevated CSF-Tau or phospho-tau, and/or (2) hypometabolism in an AD-like pattern on FDG-PET (i.e., posterior cingulate, precuneus, and/or temporoparietal cortices) and/or (3)

cortical thinning/gray matter loss in a specific anatomic distribution (i.e., lateral and medial parietal, posterior cingulate, and lateral temporal cortices) and/or hippocampal atrophy on volumetric MRI (Sperling *et al.* 2011).

Stage 3 is considered to be the last stage of preclinical AD. Individuals in this stage will show evidence of subtle cognitive decline in addition to biomarker evidence of both A β deposition and neurodegeneration. Subtle cognitive decline may be evident as a *decline from a previously higher level*, although a level of impairment that would warrant a diagnosis of MCI is not yet reached. These individuals thus can be considered as being in a transitional state between “cognitively normal” and “clinically impaired” (i.e. MCI). One major research goal is to develop sensitive and specific neuropsychological instruments to predict conversion from this state to incident MCI or dementia. Emerging evidence suggests that more challenging episodic memory tests e.g. the Face-Name-Test or tests that measure visual short-term feature binding (Rentz *et al.* 2013) might be useful in this regard. Importantly, SCD is explicitly mentioned as an alternative, potentially useful indicator of subtle cognitive decline. In addition, the emergence of behavioral symptoms might be a feature of preclinical AD stage 3. However, there is only very limited evidence to date (Duara *et al.* 2011). Importantly, classification of an individual as preclinical AD will largely depend on the cutoffs for biomarker positivity that are applied. One goal of future research is to develop the optimal combination of and cutoffs for biomarkers with regard to prediction of incident MCI and AD dementia. The same is true for the criterion of subtle cognitive decline as measured either by a challenging memory test or evidence of SCD.

2.3.2 Mild Cognitive Impairment due to AD

The syndrome of MCI is characterized by the presence of impairment in one or more cognitive domains while at the same time the patient’s functional abilities are largely preserved, not warranting a diagnosis of dementia. Neuropsychological impairment is here defined as a performance deficit which is greater than would be expected based on the patient’s age, gender and educational background. It is typically expressed in units of standard deviations (SD) below the age-, gender-, and education adjusted norm. The necessary number of domains to be impaired (single- or multi-domain MCI), the number of test scores per domain and the best threshold of impairment have constantly been debated since the introduction of the term MCI into the field and are still subject to extensive research (Bondi & Smith, 2014).

The clinical syndrome of MCI can be caused by different factors besides AD, such as head trauma, depression, substance abuse or other forms of neurodegenerative diseases. The NIA-AA criteria therefore introduce the term “MCI due to AD” (MCI-AD), in order to characterize those individuals within the MCI spectrum, whose primary underlying pathology is AD. MCI-AD is thus the first *clinical* stage of AD and considered a transitional stage between clinically normal (i.e. preclinical AD) and AD dementia.

As in the preclinical AD criteria, biomarkers are part of the MCI-AD criteria. However, again similarly to the preclinical AD criteria, it is emphasized that the biomarker based criteria should at present only be applied in research contexts and might be subject to revision (Albert *et al.* 2011). As such the MCI diagnosis is still first and foremost based on clinical/cognitive criteria which are named the “*core-clinical criteria*” within the NIA-AA framework. The clinical research criteria for MCI-AD are an extension of the core-clinical criteria and incorporate biomarkers to provide *increasing levels of certainty* that AD is the cause for a patient’s MCI syndrome (Albert *et al.* 2011).

Core-clinical criteria of MCI (NIA-AA framework)

The core-clinical criteria for MCI are defined as follows (Albert *et al.* 2011):

1. Evidence of a concern regarding a change (decline) in cognition, obtained either by the patient and/or a close informant or clinician. This criterion of self- or informant-reported cognitive change is used to infer a decline in cognitive performance in the (usual) scenario of a single objective cognitive evaluation. It is important to note here that informant reports are *equally treated* as a source of information on subjective cognitive decline.

2. Objective impairment in one or more cognitive domains. Impairment is defined as performance that is lower than would be expected based on the patient’s age and educational background. If repeated measurement is available, then there should be evidence of a decline in performance over time. No specific cutoffs for impairment are proposed, but the NIA-AA criteria state scores of *1.0-1.5SD* below the age-, (gender-) and education adjusted means in the impaired domains to be “typical” for MCI patients. By stating this, the NIA-AA take a rather liberal approach with regard to the severity of neuropsychological impairment as it may be sufficient for an individual to show scores

below 1SD in one test of one cognitive domain to be classified as MCI (providing the other criteria are met). It has been argued that such a liberal definition might enhance the number of false-positive MCI diagnoses compared to a more strict neuropsychological definition of MCI (Bondi *et al.* 2014). However, one must keep in mind that the core-clinical criteria are thought to be combined with biomarker evidence. As such, a liberal approach that, at the expense of reduced specificity, maximizes the number of potential cases with underlying AD, might be optimal when combined with a subsequent biological criterion that has the potential to significantly enhance specificity to AD.

3. Preservation of independence in functional abilities. This criterion basically distinguishes the MCI syndrome from dementia. Although individuals with MCI usually have mild problems when performing complex instrumental activities of daily living (IADL; such as performing financial transactions, shopping, preparing meals etc.), they maintain independence of function in daily life, with minimal aids or assistance.

4. Not demented. As already stated in the third criterion, the cognitive changes should be sufficiently mild that there is no interference with social or occupational functioning (which if present would warrant a diagnosis of dementia).

These four criteria together warrant a clinical diagnosis of MCI. In the next step of the diagnostic process, it must be determined whether the MCI syndrome is consistent with that typically seen in individuals who later progress to AD. Typical clinical/cognitive features of MCI patients with underlying AD pathology are a decline in *episodic memory* as the primarily affected domain (“*amnestic MCI*”). This decline is usually a *slowly progressive* rather than a rapid one. In addition, causes other than AD that could account for the decline in cognition (e.g. vascular, traumatic, medical, or other neurodegenerative factors) should be ruled out. However, this might be challenging since vascular diseases or other neurodegenerative factors might coexist with AD pathology in many individuals (Albert *et al.* 2011; Viswanathan *et al.* 2009). Lastly, the presence of one or two $\epsilon 4$ alleles in the apolipoprotein E (APOE) gene increases the likelihood of an AD etiology in a patient who meets the core clinical criteria for MCI (Albert *et al.* 2011).

MCI-AD research criteria incorporating biomarkers

Based on the core-clinical criteria, MCI-AD criteria incorporating biomarkers are proposed to provide increasing levels of certainty for underlying AD in a patient meeting the core-clinical criteria for MCI. The NIA-AA criteria employ two types of biomarkers, namely biomarkers of A β deposition and biomarkers of neuronal injury, as already outlined in the previous section on preclinical AD criteria (see section 2.3.1). CSF-A β 42 and CSF-Tau are among the best validated measures of A β deposition and of neuronal injury respectively (Albert *et al.* 2011). Based on (1) the core-clinical criteria and (2) information on biomarkers of both types named above, the terminology outlined in *Table 2* has been proposed.

Table 2. MCI due to AD according to the NIA-AA criteria (Albert *et al.* 2011).

Diagnostic category	Biomarker probability of AD pathology	Evidence of markers of A β burden (CSF or PET)	Evidence of markers of neuronal injury (e.g. CSF-Tau, FDG-PET, MRI)
MCI-core clinical criteria	Uninformative or not available	Conflicting/ indeterminate/untested	Conflicting/ indeterminate/untested
MCI due to AD – intermediate likelihood	Intermediate	Positive	Untested
		Untested	Positive
MCI due to AD – high likelihood	Highest	Positive	Positive
MCI – unlikely due to AD	Lowest	Negative	Negative

Note: Abbreviations: AD, Alzheimer’s disease; A β , amyloid beta; CSF, cerebrospinal fluid; FDG, ¹⁸F-fluoro-deoxy-glycose; MCI, Mild cognitive impairment; MRI, (structural) magnetic resonance imaging; PET, positron emission tomography. Further information is given in the following text.

As can be seen in *Table 2*, the NIA-AA proposes a probabilistic approach to diagnose MCI-AD with different levels of likelihood of an AD pathology based on the available biomarker information. The diagnostic category of *MCI-core clinical criteria* comprises patients with a syndrome of MCI that is clinically consistent with AD but for whom biomarker information is either unavailable or has been uninformative. Uninformative biomarker evidence is here defined as either an indeterminate (i.e. falling within ambiguous ranges) or a conflicting (i.e. positive A β biomarker and a negative biomarker of neuronal injury or the reverse) test result. Individuals falling in the

category of *MCI-AD with intermediate likelihood* fulfill the core-clinical criteria and have a positive biomarker result for either A β deposition or neuronal injury with the other category *untested*. With regard to the probability of AD these individuals are supposed to lie between those with conflicting evidence and those in the third category: *MCI-AD with high likelihood*. This category is defined by positivity in both types of biomarkers. Individuals in this category have the highest likelihood for underlying AD and will likely progress faster to AD dementia compared to the individuals in the intermediate and core-clinical group. Finally, there is the category of *MCI – unlikely due to AD*, defined by negative results in both types of biomarkers. In such a case, further search for biomarker evidence that suggests other etiologies may be warranted (see Albert *et al.* 2011 for details).

Further research aims to provide the necessary empirical data to prove the utility of these criteria. For the present work the following points are important. In study 1 of this work MCI is defined similar to the NIA-AA core-clinical criteria, however, with an emphasis on episodic memory decline as the defining cognitive domain. In addition, study 1 will subdivide MCI individuals according to the severity of memory impairment into “early MCI” with impairment between 1.0-1.5SD below norm and “late MCI” with performance of <1.5SD below norm.

MCI in study 2 and study 3 is defined according to criteria proposed by an International Working group in 2004 (Winblad *et al.* 2004). These are similar to the NIA-AA core-clinical criteria and employ a liberal cut-off of 1SD in one or more of the tests applied. In addition, study 3 incorporates biomarkers of CSF-A β 42 and CSF-Tau which enables the definition of a subgroup of MCI patients with increased likelihood of AD pathology (“MCI due to AD – high likelihood” in the NIA-AA or “prodromal AD” in the IWG terminology, respectively).

2.3.3 AD dementia

AD dementia describes dementia secondary to the neurodegenerative process of AD (McKhann *et al.* 1984; McKhann *et al.* 2011). Following the logic of the MCI criteria set, the NIA-AA criteria proposes *core-clinical criteria for AD dementia*, which can be applied in all clinical settings, and an additional set of criteria, incorporating biomarkers and currently intended for research settings. At this point it should be reemphasized that the criteria for AD dementia used in the empirical studies of this

thesis are not based on the newer NIA-AA criteria but on the previous version of these criteria, namely the NINCDS-ADRDA criteria for clinical AD dementia (McKhann *et al.* 1984). Since the studies presented here used clinical diagnoses as outcomes, the core-clinical criteria for probable AD in the newer NIA-AA criteria are the important equivalents. Patients diagnosed with “probable AD” by the 1984 NINCDS–ADRDA criteria would also meet the core-clinical criteria for probable AD as outlined below (McKhann *et al.* 2011). The NIA-AA first proposes criteria for all-cause dementia to characterize the general syndrome of dementia and then presents the core-clinical and biomarker-based criteria for *probable AD* dementia and *possible AD* dementia as the specific dementia syndrome secondary to AD pathology.

NIA-AA core clinical criteria: All-cause dementia

All-cause dementia is defined by presence of cognitive or neuropsychiatric symptoms that fulfill the following criteria (McKhann *et al.* 2011):

1. The symptoms interfere with the ability to function at work or at usual activities.
2. They represent a decline from previous levels of functioning and performing.
3. They are not explained by delirium or major psychiatric disorder.
4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient *and* a knowledgeable informant and (2) an objective cognitive assessment, i.e. either a “bedside” mental status examination or neuropsychological testing (to be employed if the routine history and bedside mental status examination cannot provide a confident diagnosis).
5. The cognitive or behavioral impairment involves a minimum of two of the following domains:
 - a. Impaired ability to acquire and remember new information – symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.
 - b. Impaired reasoning and handling of complex tasks, poor judgment – symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, and inability to plan complex or sequential activities.

c. Impaired visuospatial abilities – symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.

d. Impaired language functions (speaking, reading, and writing) – symptoms include: difficulty in thinking of common words while speaking, hesitations; speech, spelling, and writing errors.

e. Changes in personality, behavior, or comportsment – symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, and socially unacceptable behaviors.

NIA-AA core-clinical criteria: AD dementia

Based on the criteria for all-cause dementia, two types of clinical AD dementia diagnoses are proposed according to the level of certainty of AD as the primary cause of the dementia syndrome: probable AD and possible AD (McKhann *et al.* 2011).

Core-clinical criteria for probable AD dementia

Probable AD dementia according to the core-clinical criteria is diagnosed if the following criteria are met (McKhann *et al.* 2011):

1. The individual meets criteria for dementia described above, and in addition, has the following characteristics:

A. Insidious onset: Symptoms have a gradual onset over months to years, not sudden over hours or days;

B. Clear-cut history of worsening of cognition by report or observation; and

C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:

a. Amnesic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.

b. Nonamnesic presentations: Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present as well.

Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia (inability to perceive more than one object at a time), and alexia. Deficits in other cognitive domains should be present.

Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

D. The diagnosis of probable AD dementia should not be applied when there is evidence of one of the following aspects: (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; (b) core features of Dementia with Lewy bodies other than dementia itself; (c) prominent features of behavioral variant frontotemporal dementia; (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

In addition to these core-clinical criteria, a diagnosis of probable AD dementia *with increased level of certainty* can be coded for (a) patients in whom cognitive decline is documented on subsequent evaluations (through informant reports or neuropsychological examination), or (b) patients who are carrier of a *causative* AD genetic mutation (APP, PSEN1, or PSEN2 gene variants).

Core-clinical criteria for possible AD dementia

A diagnosis of possible AD dementia should be made when a patient meets the core-clinical criteria with regard to the nature of the cognitive deficits described above but has characteristics of either an *atypical course* or evidence of an *etiologically mixed presentation* (McKhann *et al.* 2011). An atypical course is characterized by a sudden (rather than an insidious) onset of impairment or limited information on progressive decline. An etiologically mixed presentation is characterized by: (a) concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) features of Dementia with Lewy bodies other than the dementia itself; or (c) evidence for another neurological disease or

a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition.

NIA-AA criteria for AD dementia with incorporation of biomarkers

Following the logic outlined in the criteria schemes of the preclinical AD and MCI-AD stage, biomarker information of the two major categories (A β deposition and downstream neuronal injury) is incorporated in the biomarker-based research criteria for probable and possible AD. *Table 3* summarizes these diagnostic criteria.

Table 3. Biomarker-based AD dementia diagnosis according to NIA-AA criteria (McKhann *et al.* 2011).

Diagnostic category	Biomarker probability of AD etiology	Evidence of markers of Aβ burden (CSF or PET)	Evidence of markers of neuronal injury (CSF-Tau, FDG-PET, MRI)
1. Probable AD dementia			
1.a. based on core-clinical criteria	Uninformative	Conflicting/ indeterminate/ unavailable	Conflicting/ indeterminate/ unavailable
1.b. Intermediate level of biomarker evidence	Intermediate	Positive Unavailable or indeterminate	Unavailable or indeterminate Positive
1.c. High level of biomarker evidence	Highest	Positive	Positive
2. Possible AD dementia (atypical clinical presentation)			
2.a. based on clinical criteria	Uninformative	Conflicting/ indeterminate/ unavailable	Conflicting/ indeterminate/ unavailable
2.b. with evidence for AD pathophysiological process	High but does not rule out second etiology	Positive	Positive
3. Dementia – unlikely due to AD	Lowest	Negative	Negative

Note: Abbreviations: AD, Alzheimer’s disease; A β , amyloid beta; CSF, cerebrospinal fluid; FDG, ¹⁸F-fluoro-deoxy-glycose MCI, Mild cognitive impairment; MRI, (structural) magnetic resonance imaging; PET, positron emission tomography.

2.4 Subjective Cognitive Decline (SCD) as a clinical symptom of AD

The following section deals with the concept of Subjective Cognitive Decline (SCD). Section 2.4.1 will provide an overview on the SCD concept with regard to different terminology in the literature. It will also explain the terminology used in the present manuscript. Section 2.4.2 will describe (the heterogeneous) operationalizations and assessment methods of SCD in the field of geriatrics. Section 2.4.3 will focus on previous research that addresses cross-sectional and prospective associations of SCD with other variables in the above outlined stages of AD (preclinical AD, MCI-AD and AD dementia). Based on this research overview, a hypothetical working model of the temporal development of SCD during the course of AD will be presented and its implications discussed (section 2.4.4).

2.4.1 Overview and terminology

The concept of SCD has already been introduced more than 30 years ago by Berry Reisberg and colleagues in their approach to define stages of AD with the Global Deterioration Scale (GDS; Reisberg *et al.* 1982). In fact, stage 2 of the GDS is defined as “normative cognitive functioning, with subjective cognitive impairment” corresponding well to the term “SCD in preclinical AD/pre-MCI SCD” introduced by the SCD-Initiative in 2014 (Jessen *et al.* 2014a). However, within this 30-year period, SCD has developed to a very heterogeneous concept with regard to terminology, specific criteria and assessment methods.

Heterogeneous terminology in the literature

A review of the relevant literature reveals a variety of terms to describe subjectively experienced cognitive worsening.

Table 4 shows that there are a number of different terminologies used in the field. Although these differences seem subtle at a first glance, it is important to point them out from the beginning to ensure a better understanding of the implications of each of the different wordings.

Table 4. Terms for the symptom of SCD in the scientific literature.

Term	abbreviation	Source (selected examples)	Comment
Subjective Memory Impairment	SMI	Jessen <i>et al.</i> (2010)	Preferred by the AgeCoDe study group until 2014. Used in the original publication of study 1 of this manuscript.
Subjective Memory Complaints	SMC	Schmand <i>et al.</i> (1997)	Used in many original articles and reviews
(Subjective) Memory Concerns	MC	Wolfsgruber <i>et al.</i> (2014b); Wolfsgruber <i>et al.</i> (2015)	Term describes a subgroup of patients who appraise their memory decline as worrying/concerning. Also used in Jessen <i>et al.</i> (2010) and Jessen <i>et al.</i> (2014b) as “Subjective Memory Impairment with worries” or as “Subjective Cognitive Decline with concerns (SCD+C).
Subjective Memory deterioration	–	Wang <i>et al.</i> (2004)	Seldomly used
Subjective Memory Loss	–	Sinoff & Werner (2003)	Seldomly used
Subjective Cognitive Impairment	SCI	Stewart (2012)	Used in many original articles and reviews
Subjective Cognitive Complaints	SCC	Dufouil <i>et al.</i> (2005)	Also used simply as “cognitive complaints”. Often used in other fields than Geriatrics.
Subjective Cognitive Decline	SCD	Jessen <i>et al.</i> (2014a)	Preferred term of the newly founded Subjective Cognitive Decline Initiative. Preferred term in this manuscript.

Note: The Table shows different terms used in the scientific literature for memory-related or global Subjective Cognitive Decline.

In his review on the recent literature on SCD⁵, Stewart (2012) points out two sources of variability in the nomenclature. The first refers to the cognitive domain. Some terminologies use “cognitive” while “memory” is most often used. In this regard, Stewart points out that there is a lack of research regarding the exact nature of the impairment itself and the term used to describe it. In other words it is unclear “whether persons complaining of problematic forgetfulness are truly describing their perceived memory function or whether they are experiencing impairment in a different cognitive domain (or multiple domains) for which a complaint of poor memory provides the only

⁵ Stewart actually uses the term „Subjective Cognitive Impairment” in his review.

recognizable and/or acceptable term available” (Stewart, 2012, p.445). The second aspect concerns the use of “complaints” vs. “impairment” to describe the symptom. Stewart points out that the term “complaints” implies some form of spontaneous reporting and therefore fits to clinical settings where patients actively present for memory assessment. However, “impairment” may be the more accurate term for defining the symptom on the basis of a positive response to a questionnaire, typically employed in epidemiological settings. Further differences, not mentioned by Stewart, arise from the usage of a term that directly describes a *change* in cognition (such as “loss”, “deterioration” or “decline”) in contrast to a term that is unspecific with regard to this important aspect (“impairment”, “complaints”). As AD-related cognitive deficits are slowly progressive, a term describing change seems more accurate (Jessen *et al.* 2014a; Abdulrab & Heun, 2008). Studies having used terms like complaints or impairment might actually have assessed decline, as the questions applied in the study protocols, or at least a portion of those if a summary measure was used, actually referred to a change in cognition (e.g. Geerlings *et al.* 1999). Likewise, studies in epidemiological settings have used the word “complaints” while actually measuring “impairment” (e.g. Jorm *et al.* 1997). The respective opposite holds true for some studies in clinical settings that used the term “impairment” when, precisely speaking, they measured “complaints” (e.g. Erk *et al.* 2011).

Description of a symptom vs. labeling of a diagnostic group

In addition to the above mentioned subtleties regarding SCD terminology, there is one important aspect that needs to be pointed out, namely the usage of SCD to describe a symptom vs. the usage of SCD to describe a certain group of patients. SCD and its related terms (see *Table 4*) have been used for both purposes. SCD as a symptom is not limited to a certain patient group but applies to individuals who present with SCD due to several etiologies, of which AD is but one. Even when only referring to AD-related SCD, it is not limited to a certain disease stage. In contrast to conceptualization of SCD as a symptom, the term has also been used to describe patients that present with the symptom of SCD *in the absence of a cognitive impairment*, evidenced by neuropsychological test results in the normal range.

Usage of the broad term of SCD to describe a specific group of patients must be seen critically, as it can lead to confusion with other studies that speak of SCD without exactly referring to a patient group. The SCD-Initiative has therefore decided to speak

of either “pre-MCI SCD” or “SCD in preclinical AD” to specifically address the *patient group* characterized by presence of SCD but absence of cognitive impairment on clinical standard tests which would warrant a diagnosis of MCI. The terminology of the present manuscript follows this suggestion.

Terminology used in the present work

The last section has emphasized the need for a SCD terminology that is as consistent as possible throughout the present manuscript. For the main part of the present manuscript the term SCD will be used as it is arguably the best to describe *the symptom* of AD-related subjective cognitive worsening over time, comprising both memory and non-memory domains (Jessen *et al.* 2014a). As such, SCD is used as a general term throughout the text and will also be used when referring to studies that used other terms listed in *Table 4*. However, whenever there is the need for a more precise wording, additional adjectives will be used to describe the exact form of SCD, e.g. “memory-related SCD” would specifically describe subjective cognitive decline in the memory domain. Note that, although the empirical studies presented in this thesis (section 3) focus on such memory-related SCD, the broader term of “SCD” will most often be used. This has been done to be more consistent with the most recent term introduced by the SCD-Initiative.

Further, the empirical studies presented herein partly address a specific form of memory-related SCD that can be described as “Subjective Cognitive Decline with associated concerns” (SCD+C). This term describes a subgroup of individuals who report a subjective cognitive decline (in empirical studies 1-3 referring always to the memory domain) and, in addition, appraise this self-experienced decline as particularly worrying. Individuals who only report memory decline (without associated worries) will be termed “Subjective Cognitive Decline without associated concerns” (SCD-C). Note that in *study 2 and 3* the term “memory concerns” is also used as a synonym of SCD+C to keep with the wording of the original publications of these two studies.

Finally, note that study 1 is a population based study that compares the risk of incident AD dementia in patients with MCI to that in individuals with normal cognitive test performance but presence of SCD. That means SCD is, as an exception, also used to describe a diagnostic subgroup of patients in that study. This group will be labeled with the prefix “pre-MCI” to distinguish them from the groups which exhibit SCD but have

cognitive impairment in the MCI range. For reference, *Table 5* provides an overview of the terminology used in this manuscript.

Table 5. Terminology of SCD used in the present work

Term	Abbreviation	Comment
Subjective Cognitive Decline	SCD	General term to describe the symptom of subjective cognitive decline throughout the whole manuscript.
Subjective Cognitive Decline with associated concerns	SCD+C	Describes a subgroup of individuals who appraise their subjective cognitive decline as worrying. SCD+C refers both to individuals with normal cognitive test performance and to MCI patients.
Subjective Cognitive Decline without associated concerns	SCD-C	Describes a subgroup of individuals with subjective cognitive decline but with no concerns regarding the self-experienced decline. SCD-C refers both to individuals with normal cognitive test performance and to MCI patients.
Memory Concerns	MC	Is used synonymous to “memory-related SCD+C” in empirical studies 2 and 3 and reflects the notion of worsening memory appraised as worrying.
	pre-MCI	Pre-MCI is used as a prefix to SCD. When used in conjunction with SCD it describes individuals with SCD but normal cognitive test performance (i.e. the term then describes a specific <i>patient group</i> , not the symptom per se)
pre-Mild Cognitive Impairment	pre-MCI SCD	Individuals with SCD but normal test performance
	pre-MCI SCD+C	Individuals with SCD+C but normal test performance
	pre-MCI SCD-C	Individuals with SCD-C but normal test performance
Controls	CO	Individuals without report of any subjective cognitive decline and with normal cognitive test performance.

Note: The table contains the Subjective Cognitive Decline terminology used in the different sections of the present manuscript. Further explanation of this terminology is given in section 2.4.1.

2.4.2 Operationalization and assessment of SCD

The heterogeneity of SCD with regard to terminology is paralleled by an equally heterogeneous array of operationalization and assessment methods. These range from single questions to detailed quantitative assessment with multi-factorial questionnaires. A comprehensive overview of all the different questions, scales and operationalizations

used throughout the literature would go far beyond the scope of this work. Rather, the different definitional approaches to SCD are presented together with a selection of questions and scales. The key point of this selected presentation is to show that SCD has been defined rather inconsistently in the past and that the field has just recently begun to develop a common set of research criteria.

Heterogeneous operationalization of SCD in the recent literature

Abdulrab and Heun (2008) give an overview of the various forms of operationalizations of memory-related SCD and list the following common approaches:

- Use of a single question with “yes/no” response.
- Use of a single question with “graded” (i.e. ordinal) response categories.
- Use of scales comprising a set of questions with “yes/no” responses for which
 - either a single item or
 - a minimum number of itemsmust be answered “yes” in order to categorize a subject as having SCD.
- Use of questionnaires or subscales of a questionnaire with scored responses. A *cutoff score* is then used to define SCD.

All these approaches, irrespective of number and characteristics of items, have in common that they lead to a *categorical definition* of either presence or absence of SCD. However, there is also a significant amount of papers that measured *SCD as a continuous variable* derived either from a single scale or by aggregation of multiple scales without giving a categorical SCD definition. Abdulrab and Heun (2008) identified 100 such papers but discarded them from further analysis as they focused on the categorical definition of memory-related SCD in their review. In line with this, categorical definitions will be discussed first and selected quantitative SCD scales are presented at the end of this section. Finally, SCD has also been defined by using questions from broader psychopathological symptom check lists (e.g. SCL-90-R, as in Grambaite *et al.* 2013)⁶.

⁶ Interestingly, Abdulrab and Heun excluded 12 such papers from their review without further explanation.

Single-question-operationalizations usually employ more broader questions, with regard to context and severity of the memory problems (no questions with regard to specific activities) and might not even ask for a specific course of the symptoms (example questions: “Do you have problems/trouble with your memory?”; “Do you consider yourself as being forgetful?”). Other single questions specifically ask for a change in cognitive performance with or without setting a specific time frame (e.g. “Is your memory *becoming worse*” vs. “Have you had memory *loss in the past year*?”).

Multiple-question-operationalizations usually ask for difficulties in several situations (e.g. remembering names, conversations). Some may also assess a grade of subjective severity of the experienced impairment, e.g. by asking for interference with daily activities, medical help seeking, perception by others, or associated concerns (some example questions are: “Do other people find you forgetful?”, “Are there any activities which you are prevented from participating in as a result of these memory problems?”, “Have you sought medical help or taken medication for this memory problem?”).

The number and nature of questions in the SCD definitions has varied widely and, thus, criteria across studies from different work groups have been inconsistent (Abdulrab & Heun, 2008). It is further unclear whether more general vs. specific questions, single vs. multiple questions etc. are best to define SCD. One plausible argument against single-question and a categorical operationalization is that it might be too over-inclusive, i.e. the specificity with regard to identification of subjects with underlying AD pathology is limited in this approach. It is similarly unclear whether categorical definitions of SCD are better in terms of research and clinical practice utility than treatment of SCD as a dimensional variable. A dimensional approach might be beneficial for complex statistical analyses. However some kind of cutoff on a dimensional measure to classify an individual, either as having SCD or not, is usually required for sampling purposes.

Acknowledgement of the above outlined heterogeneous definitions of SCD has recently led to the start of a research initiative to address this apparent deficiency. The SCD-Initiative has proposed a conceptual framework for research on pre-MCI SCD (Jessen *et al.* 2014a). Within this framework SCD has been defined as *symptomatically*

without recommendation of specific questions or scales.⁷ However, based on the existing small empirical basis, the SCD-Initiative has outlined some specific features associated with SCD that might increase the likelihood of underlying preclinical AD (termed as “SCD *plus*”). These features are outlined in the following together with the SCD-Initiative’s recommendation of general features to be coded in a study employing the concept of SCD (Jessen *et al.* 2014a):

- Setting in which SCD is expressed.
 - Medical environment
 - Memory clinic, memory specialist (compare empirical study 2 and 3)
 - General practitioner
 - Population sample (compare empirical study 1)
 - Volunteer sample (recruitment by advertisement)
- Association of SCD with medical help seeking (yes/no).
- Report of SCD (spontaneously/on request; relates to complaints vs. impairment in Stewart’s (2012) terminology).
- Onset of SCD (number of years) → **SCD *plus* if within last 5 years.**
- Age at onset of SCD → **SCD *plus* if age at onset ≥ 60 .**
- Subjective decline in *memory* (yes/no) → **SCD *plus* if yes.**
- Subjective decline in non-memory domains (yes/no) → if yes, specify.
- Concerns (worries) associated with SCD (yes/no) → **SCD *plus* if yes (= SCD+C).**

⁷ Rather, the SCD-Initiative has first agreed on SCD as a “best trade-off” concept: “Subjective” (i.e. no external validation by objective test or informant needed), “Cognitive” (instead of memory alone) and “Decline” (as opposed to “impairment”). The SCD-Initiative further acknowledges that any SCD definition is “a trade-off between being overinclusive and being too restrictive”. They chose a sensitive and potentially overinclusive definition as the specific features of SCD in preclinical AD are yet unclear (Jessen *et al.* 2014a).

- Feeling of worse performance than others of the same age group (yes/no) → **SCD *plus* if yes.**
- Association of SCD with experience of impairment (yes/no).
- Confirmation of cognitive decline by an informant (yes/no) → **SCD *plus* if yes.**
- Score on a depression scale, score on an anxiety scale.
- APOE genotype, if available → **SCD *plus* if carrier of one or more APOE4 alleles.**

Importantly, Jessen and colleagues highlight the caveat that these features need further validation and are subject to modifications (especially those of SCD *plus*; see Jessen *et al.* 2014a for a list of empirical evidence for each feature).

Quantitative SCD assessment and selected scales

Assessment of SCD on a quantitative scale level is nearly as heterogeneous as the reported categorical definitions of SCD. Over the last decades a variety of scales has been in use in empirical research. These scales range from ad-hoc constructed scales (taking items from different item pools; e.g. Rabin *et al.* 2012) to completely new constructed, multi-factorial scales with the specific aim of (improved) SCD assessment in mind (e.g. Eckerström *et al.* 2013). There are also several studies in which authors have constructed composite scores for SCD based on items from different questionnaires available to them (e.g. Amariglio *et al.* 2012), thereby merging items from validated scales with items not formally validated. Again, a comprehensive overview of all the different quantitative approaches would be beyond the scope of this manuscript. However, several important points should be mentioned with regard to quantitative assessment. Firstly, comparability of studies employing different quantitative assessment of SCD is thoroughly limited. This is due to a lack of comparative psychometric studies even with regard to the more common scales. The use of composite measures also hinders comparability of those studies that used partly the same scales. Secondly, the development of many scales is not well documented, their psychometric properties either not well studied or unknown. Thirdly, with regard to item development, many scales have relied on expert panels or clinical experience. However, a systematic phase of qualitative data collection (interviews with patients, subsequent qualitative analysis), although recommended as best practice, is rare (Eckerström *et al.* 2013). Fourthly, the available scales were mostly not specifically

developed to measure SCD as an early symptom of AD. For example, the “Memory Assessment Clinics Questionnaire” (MAC-Q) was initially designed to measure “Age Associated Memory Impairment” (a concept different from memory loss due to specific diseases; Crook *et al.* 1986). The MAC-Q consequently asks for change in cognition compared to performance in young age (high school) which is arguably suboptimal to capture SCD related to AD pathology. However, the MAC-Q has still been used in the field of AD-related SCD research with mixed results (Buckley *et al.* 2013).

In conclusion, there seems to be large room for improvement in the quantitative assessment of SCD which poses a major task for further research (Jessen *et al.* 2014a). To conclude this section, a selection of scales with original sources is presented in *Table 6*. The selection was made so that both more recently published scales (ECog, SCD-Q) as well as older scales (SMDS, MAC-Q, MMQ) are covered. A short comment on general and psychometric properties of each scale is given.

Table 6. Quantitative scales to measure SCD (examples).

Name of the scale	abbreviation	reference	Comment
Multifactorial Memory Questionnaire	MMQ	Troyer & Rich (2002)	Assessment of separate dimensions of self-reported memory: 1. Contentment (i.e., affect regarding one’s memory), 2. Ability (i.e., self-appraisal of one’s memory capabilities), 3. Strategy (i.e., reported frequency of memory strategy use). The scale is designed for research and <i>intervention</i> purposes. It therefore focuses on <i>problems with recent memory</i> , not decline in memory. Psychometric properties, based on a sample of 115 individuals in initial publication: very good content and construct validity, factorial validity, test-retest and intra-test reliability.
Memory Assessment Clinics Questionnaire	MAC-Q	Crook <i>et al.</i> (1992)	6 item questionnaire on a 5-point Likert Scale. Subjects are asked to rate their memory in comparison to what it was like when they were in high school. Higher scores reflect greater subjective memory impairment. 5 questions regarding specific daily activities (e.g. remembering a person’s name) and one item asking for overall comparison of current vs. earlier memory. Summary score of 0-30 points. Psychometric Properties, based on 232 subjects meeting diagnostic criteria for age-associated memory impairment: Satisfactory internal consistency and test-retest reliability. Concurrent validity supported by a significant correlation to another well-validated memory questionnaire.

Subjective Memory Decline Scale	SMDS	Jorm <i>et al.</i> (1997)	<p>This scale is used in empirical study 3. It contains four questions on self-experienced increasing difficulties in everyday memory (e.g. “Do you have more trouble remembering things that have happened recently?”; “Are you worse at remembering where belongings are kept?”). Responses to each question are rated as follows: 0, “no, not more difficult than in the past”; 1, “Yes, a bit worse than in the past” 2, “yes, much more difficult than in the past”. A summary score of 0-8 points can be derived.</p> <p>Psychometric properties: Limited data. Cronbach’s alpha of 0.71 reported in Jorm <i>et al.</i> (1997).</p>
Everyday Cognition Scale	ECog	Farias <i>et al.</i> (2008)	<p>This scale has been designed to capture subtle <i>functional</i> abilities that are, however, cognitively mediated. The ECog has originally been developed as an informant rating scale. It contains 39 items (4-point Likert scale: 1 = “better or no change to 4 = “consistently much worse”) that ask for performance compared to 10 years ago. The ECog has six domain-specific factors: Everyday Memory, Language, Visuospatial Abilities, Planning, Organization, and Divided Attention.</p> <p>Psychometric properties: The original informant rated scale has good psychometric properties (Farias <i>et al.</i> 2008). A self-rated version of the E-Cog, composed of identical questions, has been used in SCD studies but only the informant version has been formally validated (Amariglio <i>et al.</i> 2012). However, in the study of Amariglio and colleagues, ECog memory values were significantly related to brain amyloid burden in patients with pre-MCI SCD and also correlated with episodic memory performance. This speaks for good construct validity of the self-report version in pre-MCI SCD at least for the memory factor.</p>
Subjective Cognitive Decline Questionnaire	SCD-Q	Rami <i>et al.</i> (2014)	<p>New assessment tool developed by Spanish members of the SCD-Initiative. 24-item scale that assesses <i>perceived subjective decline</i> in memory, language, and executive functions <i>in the last two years</i>. Initial item-pool generated by literature review and expert consensus revision. Parallel informant version that allows for calculation of a <i>discrepancy index</i> between subject and informant. This allows for measurement of over- or underreporting of an individual’s SCD in comparison to an informant (or vice versa depending on research question).</p> <p>Psychometric properties, based on an initial validation study with 124 CO, 144 pre-MCI SCD, 83 MCI, 46 AD dementia patients, and 397 informants: Good internal consistency and discriminant validity: SCD-Q scores from SCD and MCI differed significantly from controls and differed between those SCD who sought help at a clinic compared to those who did not. Informant SCD-Q scores can differentiate between controls and patients with cognitive impairment (MCI, AD dementia) with good sensitivity and specificity.</p>

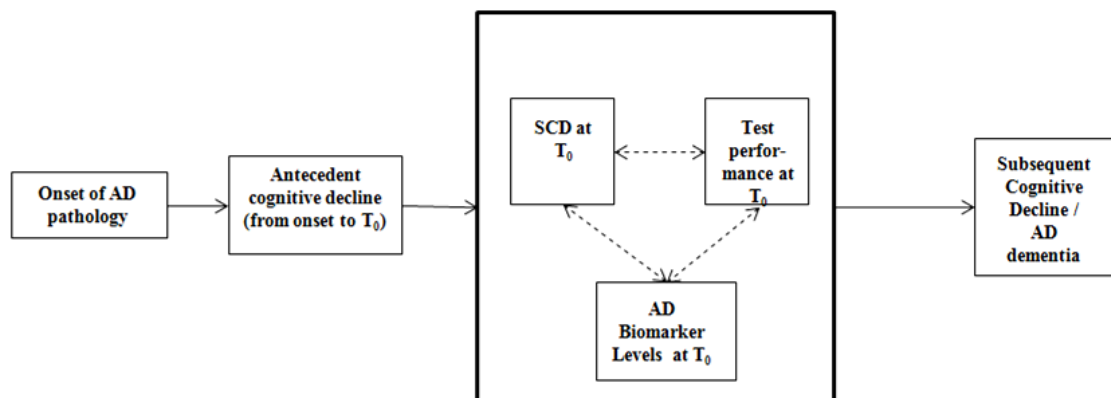
Note. The table shows a selection of scales that have been used in SCD research.

2.4.3 Cross-sectional and prospective associations of SCD across the stages of AD

This section will give a cohesive overview of the literature on associations between SCD and other variables. Again, a selection rather than a complete review of the literature will be given⁸. The overview is broken down into several subsections according to the temporal relationship (cross-sectional vs. prospective associations with subsequent outcomes) and type of variables (behavioral measures, biomarkers).

The following figure first provides a “timeline” for the antecedents, cross-sectional associations and sequelae (i.e. subsequent events) of AD-related SCD as the biomarker model of AD would suggest (see section 2.2). As it is the case with the biomarker model itself, the model in *Figure 3* is first of all hypothetical in nature. However, it may serve well as a general frame for the remainder of the section.

Figure 3. Hypothetical timeline model comprising antecedents, cross-sectional associations and sequelae of AD-related SCD.



Note. The figure displays antecedents, cross-sectional associations and sequelae (i.e. subsequent events) of AD-related SCD. Further information is given in the text.

Figure 3 is created following a visualization method typically used in structural equation modeling (SEM), i.e. unidirectional arrows represent directed regressive effects (“variable X influences variable Y”) while bidirectional arrows stand for correlations of two variables.⁹ As shown in *Figure 3*, SCD at a given cross-sectional

⁸ There are several extensive reviews on this topic (see e.g. Reid & MacLulich, 2006; Stewart, 2012; Roberts *et al.* 2009; Reisberg & Gauthier, 2008)

⁹ For clarity, variables in *Figure 3* are considered as latent variables or “constructs”, deliberately ignoring the otherwise important measurement part of an SEM model.

time of measurement (T_0) is depicted as a result of an antecedent cognitive decline from the individual's baseline cognitive performance. When speaking of AD-related SCD, this antecedent cognitive decline is itself preceded, and later accompanied, by the onset of AD pathology. The unidirectional arrows between these variables indicate that AD pathology is the etiological cause for the cognitive decline (deliberately ignoring other etiological factors for the sake of simplicity). This decline in performance is then, at some point, perceived by the individual and expressed as *SCD at T_0* . If T_0 is defined as a cross-sectional measurement point in the course of AD development then SCD at T_0 will be influenced by the perceived antecedent cognitive decline which itself is a result of AD pathology. However, it will also depend on the individual's capability to perceive and express the cognitive decline at T_0 . This capability (which relates to the term "awareness", discussed later in this section) might be limited in more progressed stages of AD such as MCI and dementia. *Objective test performance at T_0* similarly depends on the extent of preceding AD-related antecedent cognitive decline (from baseline performance to T_0). Lastly, the *biomarker levels at T_0* will depend on the time elapsed from onset of deviation of the marker away from normality to T_0 and the average rate of change of the marker over this period of time (see section 2.2). As a result, the correlations between test performance, SCD and biomarkers at T_0 will largely depend on the time elapsed from onset of AD pathology to T_0 , or, more broadly spoken, on the individual's stage of AD at T_0 measurement. As an example, in a study on individuals in the pre-MCI stage of AD, a correlation between SCD at T_0 and a biomarker of early amyloid deposition (e.g. CSF-A β 42 or brain A β PET imaging) might be observed. However, correlations between cognitive test performance and SCD or cognitive test performance and A β might be weaker or even absent (see e.g. Amariglio *et al.* 2012). The correlative pattern for a sample of MCI patients might, however, be different. Here, cognitive test performance will likely correlate well with biomarkers (especially those reflecting Tau-mediated neuronal injury and degeneration) while a correlation of SCD with objective impairment might not be observed. One reason for this absent relationship may be that two individuals with the same test performance at T_0 may have declined from different baseline levels of performance and, thus, report different levels of SCD at T_0 . This relates to the concept of cognitive reserve which describes an individual's relative ability to preserve task performance in the presence of brain pathology by use of compensatory mechanisms (Stern, 2012). A second explanation may be heterogeneity in symptom awareness among MCI patients. Awareness and

cognitive reserve may therefore be considered as influential factors with regard to the relationship between SCD and either objective performance or biomarkers of AD. This example shows that cross-sectional and prospective associations of SCD with other variables of interest (e.g. memory performance, biomarkers, incident AD dementia), as well as with possible confounders, may vary across the AD timeline. This thought will be picked up again at the end of this section where a working model on the evolution of SCD throughout the course of AD will be presented. This model served as a conceptual framework for the empirical studies of this work. It might, although hypothetical, also serve as a reasonable explanation for the rather heterogeneous findings on the cross-sectional and prospective associations of SCD which are presented in the following.

Cross-sectional associations with demographic, clinical, and personality variables

Cross-sectional studies have related SCD to a range of factors in non-demented individuals. These variables include the following demographic factors associated with SCD in large population based cohort studies of middle and old aged subjects: higher age (Holmen *et al.* 2013; Reisberg & Gauthier, 2008), lower education (Jonker *et al.* 2000; Holmen *et al.* 2013; however see also van Oijen *et al.* 2007) and female gender (Jonker *et al.* 2000; however, see also Holmen *et al.* 2013). Studies have found evidence for SCD to be associated with subjective health status, vascular risk factors like smoking and hypercholesterolemia (Paradise *et al.* 2011), and even increased mortality among middle-aged individuals after controlling for effects of depression (Singh-Manoux *et al.* 2014). Moreover, a number of affective and personality factors such as psychological distress and ineffective coping style (Steinberg *et al.* 2013; Paradise *et al.* 2011), negative affect and anxiety sensitivity (Dux *et al.* 2008), neuroticism, conscientiousness, low self-esteem (Pearman & Storandt, 2004; Steinberg *et al.* 2013), increased self-focused attention (Chin *et al.* 2014) and self-discipline (a sub-facet of conscientiousness; Pearman & Storandt, 2005), have been associated with measures of SCD.

The most robust findings, however, have been reported for the association between SCD and depressive symptomatology. Depressive symptoms have been positively associated with SCD in volunteer (e.g. Buckley *et al.* 2013), population-based (e.g. Benito-León *et al.* 2010; Paradise *et al.* 2011), and clinical samples (e.g. Erk *et al.* 2011; Chin *et al.* 2014) with varying age ranges. Some researchers have therefore argued that SCD is mainly driven by depressive symptomatology rather than being an

indicator of an underlying pathology such as AD. However, in light of the emerging evidence that SCD is associated with incident AD dementia and biomarkers of AD (reported below) this statement can today be considered as overstated. Furthermore, little is known about the temporal (and accordingly the causal) relationship between SCD and depressive symptomatology. According to Roberts and colleagues (Roberts *et al.* 2009), the relationship between SCD and depression is most likely reciprocal: One individual might endorse subjective cognitive deficits during the course of a depressive episode while another individual might develop depression and anxiety due to recognition of subjectively worsening cognitive performance. In a novel study, Buckley and colleagues found some evidence that depressive symptomatology might contribute stronger to SCD symptomatology in individuals with normal test performance than in those with MCI (Buckley *et al.* 2014a). Despite these unresolved issues, depressive symptomatology is certainly an important variable that should be recorded and controlled for in any SCD study (Jessen *et al.* 2014a). The same might, for a lesser degree of evidence, be true for anxiety and other personality factors.

Cross-sectional associations with objective cognitive performance, informant reports and the potential role of confounding/moderating factors: Awareness, affect and cognitive reserve.

In contrast to the robust findings regarding SCD and depressive symptomatology, studies on the association between SCD and concurrent cognitive performance have produced inconsistent results. Some studies have reported, albeit modest, associations between SCD and objective cognitive performance measures after accounting for effects of age and depressive symptomatology (e.g. Jonker *et al.* 2000; Jessen *et al.* 2007; Snitz *et al.* 2008; Pearman & Storandt, 2004; Amariglio *et al.* 2011). Other studies, however, have found no such association (Reid & MacLulich, 2006; Minett *et al.* 2008; Lenehan *et al.* 2012). Lastly, there are studies with findings of an association which, however, did not hold up after adjustment for multiple testing and/or covariate effects of depressive/affective symptoms (Benito-León *et al.* 2010; Steinberg *et al.* 2013).

Empirical evidence concerning associations between self- and informant-reported SCD have further shown that correlations between the two sources of information are rather poor (Caselli *et al.* 2014; Jorm *et al.* 1994; Edmonds *et al.* 2014). Informant reports seem to correlate more consistently with the subject's cognitive test

performance (Rami *et al.* 2014; Jorm *et al.* 1994). However, it is also worth mentioning that informant reports seem to be equally influenced by affective states of either the subject itself or the informant (Rami *et al.* 2014; Jorm *et al.* 1994; Caselli *et al.* 2014). The question whether self- vs. informant-reported decline is more predictive of prevalent and incident AD dementia is still controversial. For prevalent dementia it seems clear that only informant-reported SCD has diagnostic value (Carr *et al.* 2000). The evidence with regard to incident dementia is less clear. Overall, there are few studies that specifically compared self- vs. informant reports with consistent methodology (i.e. parallel patient-informant questionnaires). Two studies with incident dementia as outcome found informant reports to be more predictive (Rabin *et al.* 2012; Tierney *et al.* 1996). However, in these samples individuals with MCI were included and measures were not parallelized. On the contrary, a new study on cognitively normal individuals with incident *MCI* as outcome showed that those who converted to MCI self-endorsed decline *earlier* than informants (Caselli *et al.* 2014). These seemingly inconsistent findings might, as suggested above, be based on the fact that associations between SCD and different outcomes depend on the stage of AD in which the individual is situated at the time of measurement.

Potential confounding factors

Before coming back to the idea of AD stage dependence, other potential confounders, leading to inconsistent results across studies, are briefly mentioned in the following. The heterogeneity in SCD assessment (the same is true for informant reports) is a confounding factor in itself. Further, there might be, according to Vestergren and colleagues (Vestergren *et al.* 2012), other psychometrical factors to name here: methodological differences between questionnaires and neuropsychological tests, the (memory) introspection paradox¹⁰, influence from social desirability, and individual differences in interpretation and use of self-rating scales.

Symptom awareness, anosognosia and SCD

A look back to the ideas outlined with regard to *Figure 3* might also help to understand the heterogeneous findings. As discussed above, associations between SCD and other variables on the individual level may vary across the AD timeline and

¹⁰ „The paradox of introspection stems from the fact that personal experience corresponds to that which we know best subjectively, yet least empirically” (Schooler & Schreiber, 2004).

therefore depend on the stage of AD in which the individual is situated at the time of measurement. An important variable that comes into play as AD progresses is the tendency of the affected individual to inadequately judge his/her own memory capacity. This is commonly referred to as symptom unawareness or “anosognosia”. Reduced awareness and anosognosia are common in individuals with AD dementia (Galeone *et al.* 2011) but have also been observed in individuals with MCI (Galeone *et al.* 2011; Vogel *et al.* 2004; Vogel *et al.* 2005; Nobili *et al.* 2010). However, in MCI, awareness of memory deficits is more heterogeneous (Kalbe *et al.* 2005; Roberts *et al.* 2009), i.e. some patients have reduced insight while others seem to have preserved introspective capacity. Importantly, there is evidence of a link between reduced symptom awareness and lower concurrent cognitive performance (Grambaite *et al.* 2013; Vogel *et al.* 2005; Snitz *et al.* 2008). Furthermore, studies have reported that anosognosia in MCI patients is associated with functional and structural brain changes consistent with more progressed AD pathology (Nobili *et al.* 2010; Ries *et al.* 2007; Vogel *et al.* 2005; Chételat *et al.* 2009), with positive AD CSF biomarkers (Edmonds *et al.* 2014) and with more rapid conversion to dementia (Chételat *et al.* 2009; Edmonds *et al.* 2014). In summary, this evidence suggests two important aspects: First, reduced awareness is an important determinant of whether individuals who truly have objective cognitive deficits will report SCD or not. Second, reduced awareness seems to evolve with progression of AD and might emerge first in the transitional stage between MCI and AD dementia. This might not only contribute to the heterogeneous findings regarding the relationship between SCD and other variables. It also has implications for the usefulness of SCD as a diagnostic criterion and predictor: The predictive value of SCD seems temporally limited across the AD timeline.

Associations with biomarkers

Evidence that SCD correlates with biomarkers of AD pathology mostly comes from studies that have investigated this relationship in individuals with normal cognition, i.e. in the presumed preclinical/pre-MCI stage of AD. Here, different qualitative and quantitative operationalizations of SCD have been associated with different biomarkers of AD pathology such as brain amyloid burden (Chételat *et al.* 2010; Perrotin *et al.* 2012; Amariglio *et al.* 2012; Merrill *et al.* 2012), AD typical CSF biomarkers (Visser *et al.* 2009; Mosconi *et al.* 2008), as well as AD-related hypometabolism and structural brain changes (Saykin *et al.* 2006; Scheef *et al.* 2012;

Mosconi *et al.* 2008). Recently, it has also been reported that SCD correlates with post mortem amyloid brain pathology in subjects with initial pre-MCI SCD who, however, had not progressed to a clinical diagnosis of either MCI or dementia before death (Kryscio *et al.* 2014). Furthermore, functional MRI studies provide evidence that, during the performance of cognitive tasks, individuals with SCD show brain activations consistent with employment of compensatory strategies of neural networks in order to deal with the functional brain changes of early AD (Rodda *et al.* 2011; Erk *et al.* 2011). Importantly, studies in which SCD has been measured more differentiatedly, found that *memory-related* cognitive complaints/decline had the strongest association to biomarkers of AD (Amariglio *et al.* 2012; Perrotin *et al.* 2012). To summarize, although negative findings have also been reported (e.g. Buckley *et al.* 2013; Grambaite *et al.* 2013), evidence that SCD is related to early AD pathology is growing.

Importantly, the referenced studies above are based on individuals in the pre-MCI stage. As suggested by the model in *Figure 3*, results from these studies are inconclusive regarding associations of A β biomarkers with objective cognitive performance. This indeed suggests that, at the pre-MCI stage, SCD might reflect subtle decline which is induced by AD pathology, but is partly compensable and hardly detectable on standard tests designed to measure cognitive impairment in MCI. On the contrary, there is a lack of studies investigating associations of SCD and AD biomarkers within MCI patients. One study (Grambaite *et al.* 2013) found no association between SCD measures and CSF-A β 42 (or CSF-Tau). However, small sample size (n = 47 MCI) was acknowledged as a limitation in this study. Also, the authors of this study operationalized SCD with two single items from a scale designed to assess *current* psychopathological symptoms rather than employing a measure specifically designed to capture subjective decline in cognition. In a recent and considerably more robust study (Edmonds *et al.* 2014), Edmonds and colleagues reclassified the Alzheimer's Disease Neuroimaging Initiative (ADNI) MCI sample based on cluster-analysis-derived neuropsychological profiles into amnesic MCI, "mixed MCI" (with most prominent impairment in executive functions and language but also mild memory impairment) and a "cluster-derived normal" MCI group whose neuropsychological test scores in all domains were, on average, not different from normal controls of the ADNI sample. Importantly, the memory test used to define MCI in ADNI (story A of the Logical Memory test of the Wechsler Memory Scales) was not part of this cluster analysis. All

patients (as well as one informant per patient) were also administered the ECoG as a measure of SCD (see *Table 6*). Edmonds and colleagues found that patients in the amnesic and mixed MCI groups with lower ECoG scores compared to their informant's rating (i.e. those that presumably "underestimated" their cognitive deficits relative to their informant) were more likely to have an AD like CSF biomarker profile and were more likely to develop incident AD dementia. On the contrary, subjects in the "cluster-derived normal" group overestimated their deficits relative to informants. Importantly, the amnesic and mixed MCI groups in this study consisted of MCI patients defined by a conservative method, i.e. they can be considered as patients with robust cognitive impairment and presumably in a more progressed stage along the continuum of AD. Edmonds and colleagues' results, thus, fit well with the idea that unawareness of symptoms is associated with more progressed AD pathology. However, the authors' conclusion that SCD generally contributes to a misdiagnosis of MCI must be seen critical, as this result deserves replication in an independent memory clinic sample, and, furthermore, the meaningfulness of this statement might depend on how strict the neuropsychological criteria of MCI are defined.

Prospective associations with adverse outcomes

Similarly to the current state of studies on SCD and biomarkers of AD, most studies that found a relationship between SCD and subsequent adverse outcomes are based on studies on mostly cognitively unimpaired individuals with long follow-up intervals. Overall, compared to the weak associations with concurrent memory performance, the literature is far more consistent regarding the relationship between SCD and incident AD dementia. Several large cohort studies have demonstrated that individuals endorsing SCD while having cognitively normal performance are at an increased risk of incident MCI and/or AD dementia (e.g. Geerlings *et al.* 1999; Reisberg *et al.* 2010; Jessen *et al.* 2011; Waldorff *et al.* 2012; see Stewart, 2012 or Jessen *et al.* 2014a for a summary of studies). There is also emerging evidence linking SCD to future cognitive decline in cohort studies (e.g. Dufouil *et al.* 2005; Glodzik-Sobanska *et al.* 2007; Hohman *et al.* 2011; Samieri *et al.* 2014). However, negative results have also been reported (e.g. Tierney *et al.* 1996; Jorm *et al.* 1997; Reid & MacLulich, 2006; Hollands *et al.* 2014). While estimates for excess in risk differ between the studies, a recent meta-analysis has reported that, across all included studies, individuals with pre-MCI SCD are at a two-fold increased risk to develop dementia over time (Mitchell *et al.*

2014). An analogous meta-analysis with rate of decline as the variable of interest has not been published yet.

One cohort study of elderly with white matter changes (LADIS study; Verdelho *et al.* 2011) found SCD predictive for incident AD dementia but not for vascular dementia. There has also been evidence that the relationship between SCD and increased risk of incident AD dementia is moderated by education (van Oijen *et al.* 2007). Other studies found a moderating role of ApoE4 status (Samieri *et al.* 2014) on the relationship between SCD and subsequent cognitive decline. Finally, van Harten and colleagues demonstrated that the best predictor of memory decline and clinical progression in subjects with pre-MCI SCD is a positive AD biomarker profile, which provides evidence for SCD as a phenotypic feature of preclinical AD (van Harten *et al.* 2013a; van Harten *et al.* 2013b).

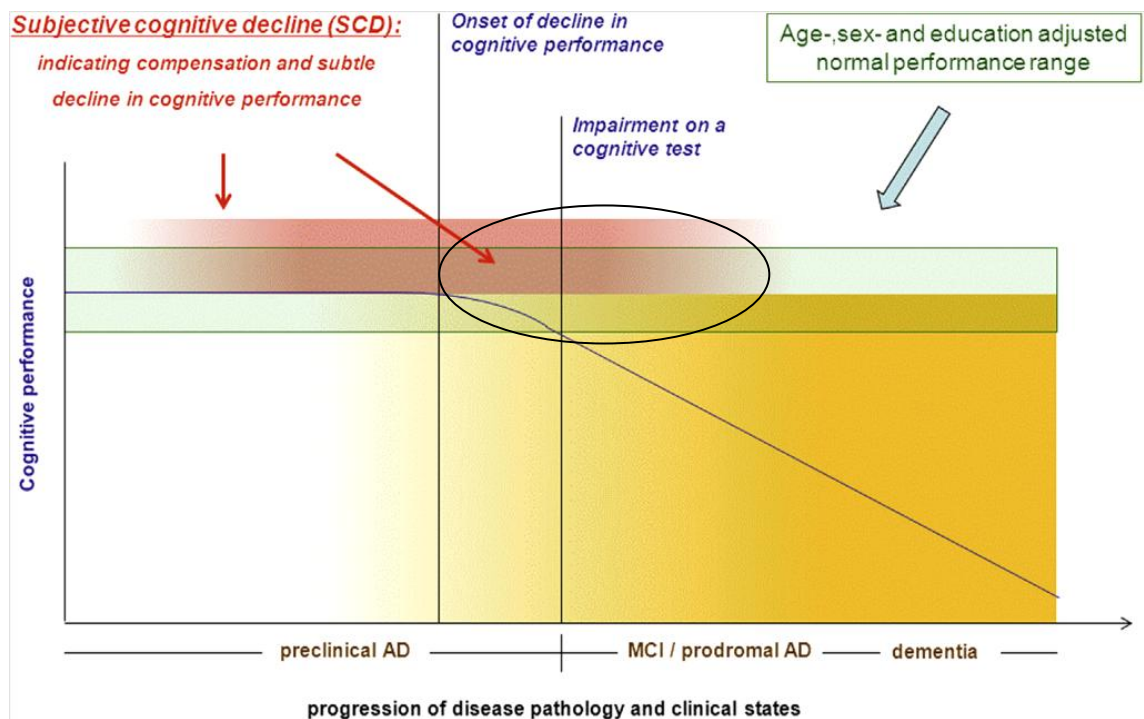
Again, studies of SCD as a predictor of incident AD dementia or future cognitive decline in subjects with cognitive impairment at the MCI level are rare (Edmonds *et al.* 2014). There are some older longitudinal studies that did not explicitly exclude MCI patients as the MCI concept was not yet developed at that time (Tierney *et al.* 1996; Jorm *et al.* 1997; Schmand *et al.* 1997). It would be hard to retrospectively determine which participants of the sample would receive a diagnosis of MCI and often no subgroup analysis has been conducted. Geerlings and colleagues (Geerlings *et al.* 1999), however, excluded demented individuals from their study and classified participants based on the MMSE score as either “normal” (≥ 26 points) or “borderline/impaired” (≤ 25 points). The authors found SCD associated with incident AD dementia but this effect was modified by cognitive baseline level, such that SCD predicted incident AD only in those with normal cognition but not in those with borderline/impaired cognition. This may again speak towards the hypothesis that the predictive value of SCD may level off in samples of more progressed individuals.

Another moderator of the relationship between SCD and future cognitive decline in MCI may be depressive symptoms as suggested by a population-based cohort study with psychometrically defined amnesic MCI (Crowe *et al.* 2006). This study found an association of SCD with steeper cognitive decline over time in MCI subjects with lower depressive symptoms but not in those with higher depressive symptoms (the sample was divided via median split on a self-report depression scale).

2.4.4 Relationship of objective and subjective cognitive decline across the time line of AD progression: A working model for the present studies

This section will sum up empirical evidence and ideas already discussed in the last section by presenting a working model on the temporal development of SCD and its interaction with objective cognitive decline across the timeline of AD progression. Implications of this model for prediction of AD biomarker pathology and future AD dementia will then be given. The model is depicted in *Figure 4*.

Figure 4. Working model for the temporal development of SCD across progression of AD (adapted from Jessen *et al.* 2014a)



Note. The figure depicts the evolvement of SCD and its relation to objective cognitive decline in the course of AD progression from preclinical AD to AD dementia. Further information is given in the text. Figure reused in this dissertation with permission by Elsevier (RightsLink Licence number: 3512451165092).

Depicted on the y-axis in *Figure 4* is the presumed trajectory of objective cognitive decline in relation to the progression of AD pathology. Progression of AD is projected on the x-axis and broadly segmented in the three clinical stages outlined earlier, i.e. preclinical AD, MCI-AD/prodromal AD and AD dementia. It is assumed that after a phase of stable cognitive performance in the presence of increasing AD pathology (i.e. preclinical AD stage 1 and 2 according to NIA-AA criteria), cognitive decline occurs in the late preclinical stage of AD (NIA-AA preclinical AD stage 3). The

trajectory for cognitive decline in *Figure 4* represents that of an average performing individual, as it lies in the middle of the green-shaded bar representing the range of age-, sex- and education adjusted normal performance. Risk- or protective factors like cognitive reserve, genetic factors, comorbid conditions, or lifestyle factors will likely moderate both the intercept and slope of this trajectory. After falling below the threshold of normal age-, sex-, and education-adjusted performance, the MCI-AD/prodromal AD stage with measurable cognitive deficits is reached. Cognitive decline then progresses onward and, in addition, functional decline (not shown in this figure) will evolve as a consequence of increased cognitive impairment. Once functional decline has reached a level of impairment that significantly interferes with the ability to function at work or in usual activities, the stage of dementia is reached.

The evolvement of SCD is depicted by a bar that is shaded from white (absence of SCD) to red (presence of SCD) across the disease stages. According to *Figure 4*, it is assumed that SCD occurs first as a symptom of the late stage of preclinical AD (NIA-AA preclinical AD stage 3), reflecting the individual's notion of subtle cognitive decline and increasing compensatory cognitive efforts. This is illustrated by the bar having the most strong red shade in the zone where objective cognitive performance deviates from baseline but is still within normal limits. SCD is, thus, proposed as a key feature of the late preclinical AD stage when the cognitive impairment threshold of MCI has not yet been reached. However, as cognitive impairment progresses into MCI, the red bar slowly fades out and turns into a white shade again. This represents that the subjective experience of cognitive impairment may vanish as disease progresses into the more advanced stage of MCI and finally dementia.

Implications for the significance of SCD and objective cognitive impairment with regard to prediction of AD arise from the differential temporal involvement of both symptoms and their relation to each other across the progression of AD. The working model proposes that the predictive power of SCD is most valuable at the late preclinical stage of AD when SCD is not influenced by anosognosia and the validity of detecting *objective* cognitive impairment is low due to limited sensitivity of standard cognitive tests. However, on the other hand, the validity of SCD might decrease as AD progresses due to evolvement of anosognosia which itself is related to progression of objective cognitive impairment. In addition, the validity to detect objective cognitive impairment increases with progression of AD into the MCI stage and is high at more advanced

stages. This increasing predictive validity of objectively measured cognitive impairment is indicated by the yellow shaded area that fades in from white to yellow as AD progresses¹¹. The increasing validity of the standard cognitive tests is a result of lower false-negative and false-positive classification compared to cognitive testing at earlier stages. This has direct implications for definition of cognitive impairment thresholds in the MCI diagnosis illustrated by the right vertical bar in *Figure 4*. The more left the bar is placed, i.e. the more liberal the cognitive impairment threshold, the more red shade (i.e. more predictive value) has the bar representing SCD and the less yellow shade (less accuracy) has the area representing objective cognitive impairment. If the cognitive impairment threshold is, however, shifted to the right side of the picture, SCD fades out and objectively measured cognitive impairment becomes a valid predictor for AD dementia. In conclusion, according to the model, there is a “time window” (encircled by the ellipse in *Figure 4*), expanding from the NIA-AA stage 3 of preclinical AD to the MCI stage, where both SCD and objective cognitive impairment may complement each other as predictors of incident AD dementia or underlying AD biomarker pathology. The relative importance of the two predictors, however, shifts from SCD to objective cognitive impairment as AD progresses. Importantly, although the existing literature, outlined in the previous sections, might partly support the general principles of this model, its implications for AD dementia prediction have not yet been formally tested. The empirical studies presented in the present thesis were conceptually based on this proposed working model and aim to provide further empirical evidence for it.

2.5 Conclusions and hypotheses addressed in the present studies

In the previous sections, a general framework for the development of AD was outlined and stages of AD from preclinical AD to AD dementia were described. SCD was then defined for the present work and a comprehensive overview of the rather heterogeneous literature on SCD was given. Finally, a working model, describing how SCD might evolve and interact with objective cognitive decline throughout the course of AD, was presented. Implications from this working model for SCD as a predictor of either future AD dementia or higher likelihood of AD pathology were briefly discussed.

¹¹This is the interpretation of the author and not explicitly mentioned in the original paper of Jessen *et al.* (2014a).

Based on the present literature it can be cautiously concluded that SCD is associated with future cognitive decline, higher risk of AD dementia, and higher likelihood of AD pathology. Thus, it is potentially useful as an indicator of incipient AD with implications both for clinical practice and research. However, although there is a growing body of evidence, there are also studies that have not found associations with longitudinal outcomes or biomarker profiles. Furthermore, there has been a wide heterogeneity both in the samples studied (preclinical AD, MCI, mixed samples) and in the definition of SCD (see section 2.4.2). This two-fold heterogeneity (samples and assessment) might explain some of the equivocal findings in the research literature (section 2.4.3), especially as the validity of SCD may vary depending on the stage of AD, as outlined above (section 2.4.4.). The aspects just mentioned pose a serious difficulty to compare results across studies and there are many questions not fully answered yet. These questions refer to the proposed working model in section 2.4.4 and to the measurement aspect of SCD outlined in section 2.4.2. Such questions may be:

- Is SCD a valid feature specifically in the early clinical phase of AD?
- How strong is the predictive validity of SCD in subjects with MCI? Does it vary across different levels of objective cognitive impairment?
- What factors influence SCD and/or moderate its association to incident AD dementia or biomarkers of AD pathology?
- Are there certain aspects of SCD which are more closely related to AD and thus of a higher predictive value than others? If yes, are these aspects the same for different stages of AD?

Section 3 of this thesis contains empirical research that addresses some of these questions. In the following subsections, the study aims and hypotheses of the three empirical studies presented herein are described. Study 1 is based on a population based sample of the German “Study on Ageing, Cognition and Dementia (AgeCoDe)” while study 2 and 3 are based on a memory-clinic MCI sample of the German Competence Network for dementia (DCN).

2.5.1 Study 1 (longitudinal study, AgeCoDe sample): Memory-related SCD (with vs. without concerns) as a predictor of AD dementia in individuals with normal cognition, early and late MCI.

Building on previous research that showed associations of SCD with higher risk of future AD dementia, study 1 (previously published; Jessen *et al.* 2014b) addresses two aspects. First, it compares the AD dementia risk of subjects with pure memory-related SCD (but no cognitive impairment; i.e. pre-MCI SCD) to that of patients with either early or late MCI. Early MCI comprises patients with evidence of very mild objective memory impairment on neuropsychological tests (memory performance between 1.0 to 1.5 SD below the norm) while late MCI patients are more advanced in their objective memory impairment (more than 1.5 SD below the norm). Both MCI groups have SCD as defined in the MCI criteria. Second, the study evaluates whether SCD with concerns/worries (SCD+C) is associated with a higher risk of developing incident AD dementia compared to SCD without concerns (SCD-C). It is hypothesized that the qualitative appraisal of a self-experienced cognitive decline as worrisome (i.e. SCD+C) is important and might further elevate the risk of AD compared to SCD-C.

2.5.2 Study 2: (longitudinal study, DCN sample): Significance of memory-related SCD in a clinical sample of MCI patients: Interaction with objective memory impairment.

Study 2 (previously published; Wolfsgruber *et al.* 2014b) deals with a key aspect of the working model presented in the previous section. The model stated that, during the early course of symptomatic AD, SCD might evolve as a result of self-perceived, intra-individual decline that is difficult to detect on cross-sectional neuropsychological tests. However, with the evolvement of more severe cognitive impairment, SCD might wane as a result of reduced insight into symptoms. If these assumptions from the working model were true, then the predictive value of SCD should be most predictive in very mildly impaired MCI patients and then decrease with increasing levels of memory impairment. Study 2 tests this hypothesis derived from the working model by examining the risk of incident AD dementia by SCD+C, objective memory performance and the proposed interaction of both factors in a large sample of memory clinic MCI patients with different levels of cognitive impairment. Some of these patients could be considered as early MCI patients (see definition in 2.5.1.) while others have more advanced, multi-domain cognitive impairment in the range of late MCI.

2.5.3 Study 3 (cross-sectional biomarker study, DCN sample): Biomarker correlates of memory-related SCD in MCI patients.

Study 3 (Wolfsgruber *et al.* 2015) finally addresses an under-researched topic, namely the relationship between measures of SCD and biomarkers of AD in the stage of MCI. While most research on SCD and biomarkers has focused on the pre-MCI stage, the MCI stage has been somewhat overlooked presumably due to the equivocal findings regarding the presence or absence of SCD in this patient group and the importance of objective cognitive testing in MCI. SCD might be influenced by several confounding factors in MCI: depressive symptoms, objective impairment level (interaction hypothesis proposed in section 2.5.2 applies here too) and education (as a cognitive reserve proxy). This study examines whether measures of SCD may predict abnormal CSF biomarkers of AD in a sample of MCI patients while taking into account the aforementioned factors as covariates.

3 Empirical Studies

3.1 Study 1: AD dementia risk in late MCI, in early MCI, and in pre-MCI SCD (Jessen *et al.* 2014b)

3.1.1 Abstract

Objective

To compare the risk of developing Alzheimer's disease (AD) dementia in late mild cognitive impairment (LMCI), early MCI (EMCI), and subjective cognitive decline with normal test performance (pre-MCI SCD).

Methods

The baseline sample (n = 2892) of a prospective cohort study in non-demented individuals (German Study on Aging, Cognition and Dementia in Primary Care Patients) was divided into LMCI, EMCI, pre-MCI SCD, and control subjects by delayed recall performance. These groups were subdivided by the presence of self-reported concerns associated with experienced memory decline. AD dementia risk was assessed over 6 years.

Results

Across all groups, risk of AD dementia was greatest in LMCI. In those with self-reported concerns regarding their memory decline, pre-MCI SCD and EMCI were associated with a similarly increased risk of AD dementia. In those subgroups without concerns, pre-MCI SCD was not associated with increased risk of AD dementia, but EMCI remained an at-risk condition.

Conclusions

Pre-MCI SCD and EMCI with self-reported concerns were associated with the same risk of AD dementia, suggesting that risk conditions earlier than LMCI should be extended to pre-MCI SCD with concerns.

3.1.2 Introduction

Defining at-risk stages of dementia resulting from Alzheimer's disease (AD) is crucial for biomarker-based predementia AD detection, which in turn is the requirement for future predementia AD treatment (Aisen *et al.* 2011; Hampel *et al.* 2010). The

Alzheimer's Disease Neuroimaging Initiative (ADNI) and other large-scale multicenter studies have demonstrated that individuals with mild cognitive impairment (MCI) are at increased risk of developing AD dementia, particularly if they display biomarker evidence of AD (Buchhave *et al.* 2012; Koivunen *et al.* 2011; Mitchell, 2009). MCI in these studies is defined as amnesic MCI by reported memory concerns, memory impairment on standard tests, absence of significant impairment in activities of daily living, and the absence of dementia (Winblad *et al.* 2004). Impairment on cognitive testing is usually defined as performance below 1.5 standard deviations (SD) of the age-, sex- and education-adjusted normative mean in a standardized test. In the attempt to define an even earlier point in time for disease detection, the recent extensions of ADNI (ADNI go, ADNI 2) have introduced the distinction of MCI into early and late MCI. Late MCI (LMCI) refers to the original definition (performance of 1.5 SD below the normative mean), whereas in early MCI (EMCI), impairment is defined as performance between 1.0 SD and 1.5 SD below the normative mean on a standard test (Aisen *et al.* 2011).

Epidemiologic studies further propose that the pure report of memory decline with normal cognitive performance (subjective cognitive decline [pre-MCI SCD]) is an at-risk condition of developing AD (Geerlings *et al.* 1999; Jessen *et al.* 2010; Reisberg *et al.* 2010). It has been shown that SCD with self-reported concerns/worries (SCD+C) is associated with a two-fold risk of AD dementia in comparison with SCD without concerns (SCD-C; Jessen *et al.* 2010).

In the study presented here, we investigate the risk of AD dementia over 6 years for the three categories LMCI, EMCI, and pre-MCI SCD. In addition, we tested the risk of AD dementia in these groups after subdivision based on the presence of self-reported concerns associated with experienced memory decline. The investigation was performed within the German study on Aging, Cognition and Dementia in primary care patients (AgeCoDe).

3.1.3 Methods

Participants

The AgeCoDe study is a general practice (GP) registry-based longitudinal study in elderly individuals designed to identify predictors of cognitive decline and dementia (Jessen *et al.* 2007; Luck *et al.* 2007). The study recruitment was undertaken in six

German cities (Bonn, Düsseldorf, Hamburg, Leipzig, Mannheim, and Munich) with a total of 138 GPs connected to the study sites. The inclusion criteria for this study were an age of 75 years and older, absence of dementia according to GP judgment, and at least one contact with the GP within the past 12 months. Exclusion criteria were GP consultations by home visits only, living in a nursing home, severe illness with an anticipated fatal outcome within 3 months, language barrier, deafness or blindness, and lack of ability to provide informed consent. Baseline recruitment was performed in 2002 and 2003.

The study was approved by the local ethical committees of the Universities of Bonn, Hamburg, Düsseldorf, Heidelberg/Mannheim, and Leipzig, and the Technical University of Munich.

A total of 3327 subjects provided informed consent for participation after being provided with a complete description of the study protocol. The study assessments were performed by trained interviewers at the subjects' home. Seventy individuals were excluded after baseline interview because of the presence of dementia according to standard assessment, and 40 subjects were excluded for age less than 75 years. For the current analysis, 16 subjects were excluded as a result of a lack of follow-up information on conversion to dementia, and 171 subjects were excluded as a result of conversion to non-AD dementia because the focus of the current analysis was on AD dementia only. In addition, 24 subjects were excluded because of incomplete neuropsychological test data for classification into subgroups of pre-MCI SCD and EMCI and LMCI. Because we also included the apolipoprotein E genotype (ApoE) in the analyses, another 114 subjects without information on ApoE status were excluded. After exclusion of these subjects, 2892 individuals remained in the database for analysis.

Four follow-up visits with 18-month intervals were the basis for the analyses. The personal interview rates and the rates of informant-only information (described later), respectively, at follow-up were 2503 and 389 at follow-up 1 (100% total), 2215 and 286 at follow-up 2 (86.5% total), 1797 and 409 at follow-up 3 (76.3% total), and 1509 and 225 (60.0% total) at follow-up 4. The main reasons for lack of follow-up and informant-only information were incident dementia and death. Also, those subjects with

only informant-based information at one follow-up were excluded from further follow-ups.

Assessment Procedures

SCD was assessed by the question: “Do you feel like your memory is becoming worse?” Possible answers were “no”; “yes, but this does not worry me”; and “yes, this worries me”. The expression of worries was rated as self-reported concerns (SCD+C) to stay in accordance with the nomenclature of the current MCI definition.

Neuropsychological assessment included the Structured Interview for Diagnosis of Dementia of Alzheimer type, Multi-infarct Dementia and Dementia of other Aetiology according to the Diagnostic and Statistical Manual of Mental Disorders, version IV (DSM-IV) and the International Classification of Diseases, version 10 (ICD-10) (SIDAM; Zaudig *et al.* 1996). The SIDAM is specifically designed to diagnose dementia according to the named criteria. It contains a 55-item neuropsychological test battery, a 14-item scale for the assessment of activities of daily living (ADL; SIDAM-ADL scale), and the Hachinski Rosen Scale. The neuropsychological battery includes the Mini-Mental State Examination.

The verbal memory test of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD; Morris *et al.* 1989) neuropsychological battery (10-item word list, three presentations, delayed recall after 10 minutes) was administered during all assessments. Subjects also performed the semantic verbal fluency task of the CERAD battery. Depressive symptoms were assessed with the 15-item version of the Geriatric Depression Scale (Yesavage *et al.* 1982).

Level of education was classified by the Comparative Analysis of Social Mobility in Industrial Nations classification system into low, middle, and high (König *et al.* 1988).

For those subjects, who could not be interviewed in person at follow-up, the Global Deterioration Scale (Reisberg *et al.* 1982) and the Blessed Dementia Rating Scale (Blessed *et al.* 1968) were completed by the interviewer with an informant and with the GP.

Definition of LMCI, EMCI and pre-MCI SCD at baseline

The CERAD verbal memory delayed recall performance was used to define the level of impairment at baseline. Independent age-, sex-, and education-adjusted German normative data for this test are available (www.memoryclinic.ch). The groups were classified as follows: LMCI, reported memory decline (memory has become worse) and performance on the CERAD delayed recall task of more than 1.5 SD below the normative mean; EMCI, between 1.5 SD and 1.0 SD below the normative mean; or pre-MCI SCD, less than 1.0 SD below the normative mean. In addition, all groups were subdivided by the association of self-reported concerns (worries) with regard to the reported memory decline. Individuals without the report of memory decline and with a performance of less than 1.0 SD below the normative mean on the CERAD delayed verbal recall task served as the reference group (control subjects; CO group). Subjects without the report of memory decline but with a performance below 1.0 SD of the normative mean on the CERAD delayed verbal recall task (n = 359) were not considered for the primary analyses because they neither met the criteria of MCI or pre-MCI SCD nor of the CO. They were only included in a secondary exploratory analysis (discussed later).

Applying these classification rules, 358 subjects were classified as having LMCI; 251 subjects, EMCI; 1061 subjects, pre-MCI SCD; and 863, CO (total, 2533). Subgroup classification was performed post hoc during data analysis and was not fed back to interviewers. Interviewers thus were unaware of group membership, ruling out surveillance bias in the detection of incident dementia across the groups.

Definition of dementia at follow-up

Dementia was diagnosed in a consensus conference with the interviewer and an experienced geriatrician or geriatric psychiatrist according to the criteria set of DSM-IV, which is implemented as a diagnostic algorithm in the SIDAM. The etiological diagnosis of dementia due to in AD was established according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD (McKhann *et al.* 1984). Mixed dementia was diagnosed in cases of cerebrovascular events without temporal relationship to cognitive decline. For all analyses, mixed dementia and dementia in AD were combined. Dementia diagnosis in subjects who were not interviewed personally was based on the Global Deterioration Scale (score ≥ 4 points).

In these cases, an etiological diagnosis was established if the information provided was sufficient to judge etiology according to the criteria just described.

Statistical Analyses

Multivariate Cox proportional hazard regression analyses were performed to evaluate the influence of selected predictors on the time to onset of AD dementia. The predictors were group membership (LMCI, EMCI, pre-MCI SCD, or CO), age, sex, education (low, medium, high), depressive symptoms (Geriatric Depression Scale scores <6 points or \geq 6 points), and ApoE4-status.

We performed three separate analyses. The first analysis was performed with the total sample ($n = 2533$). During the second analysis, we restricted the sample to the LMCI, EMCI, and pre-MCI SCD groups with self-reported concerns plus the CO group ($n = 1327$). The third analysis was performed in the LMCI, EMCI, and pre-MCI SCD groups without concerns plus the CO group ($n = 2069$). For the exploratory assessment of the difference in risk between the pre-MCI SCD group and the other two groups of interest (LMCI, EMCI) all analyses were also performed with the pre-MCI SCD group as the reference instead of the CO group.

To describe further the relevance of the subjective report, an exploratory analysis was performed in which subjects without report of impairment, but below normal performance on verbal delayed recall (EMCI–noSCD, between 1.0 SD and 1.5 SD below the normative mean; LMCI–noSCD, below 1.5 SD of the normative mean) were integrated in the model of the second analysis (subjects with SCD+C). We chose the model of the second analysis to include both “ends” of subjective report (i.e., no SCD and SCD+C).

3.1.4 Results

The number of subjects excluded at follow-up 1, followup 2, follow-up 3, and follow-up 4, respectively, were 0, 125, 82, and 143 ($n = 350$) in the CO group; 0, 111, 99, and 160 ($n = 370$) in the pre-MCI SCD group; 0, 33, 27, and 40 ($n = 100$) in the EMCI group; 0, 57, 43, and 69 ($n = 169$) in the LMCI group; 0, 34, 17, and 19 ($n = 70$) in the EMCI–noSCD group; and 0, 31, 27, and 41 ($n = 99$) in the LMCI–noSCD group. The number of conversions to AD dementia at follow-up 1, follow-up 2, follow-up 3, and follow-up 4, respectively, were in 0, 6, 15, and 11 ($n = 32$; rate of conversion, 3.7%) in the CO group; 4, 17, 22, and 23 ($n = 66$; rate of conversion, 6.2%) in the pre-

MCI SCD group, 2, 7, 11, and 7 (n = 27; rate of conversion, 10.8%) in the EMCI group; 26, 24, 24, and 15 (n = 89; rate of conversion, 24.9%) in the LMCI group; 0, 2, 1, and 1 (n = 4; rate of conversion, 2.5%) in the EMCI–noSCD group; and 7, 4, 5, and 8 (n = 24; rate of conversion, 12.1%) in the LMCI–noSCD group.

The descriptive data of the analyses are listed in *Table 7*. The number of incident AD cases with respective hazard ratio (HR) for each group throughout the course of the study are listed in *Table 8*. For the entire sample, the AD dementia risk in subjects with LMCI was increased (HR = 7.27; $p < .001$). The risk was increased also in subjects with EMCI (HR = 3.10; $p < .001$) and with pre-MCI SCD (HR = 1.55; $p = .04$) in comparison with the control subjects. *Figure 5A* shows the survival curves. In addition, age (HR = 1.13; $p < .001$) and positive ApoE4 carrier status (HR = 1.88; $p < .001$) were associated with an increased risk of AD dementia. With the pre-MCI SCD group as the reference group, both LMCI (HR = 4.69; $p < .001$) and EMCI (HR = 2.0; $p = .003$) were associated with a significantly greater risk of AD dementia.

In the second analysis, all three categories were restricted to those participants reporting concerns regarding their memory decline (SCD+C). In this analysis, the risk of AD dementia was increased in the LMCI group (HR = 11.13; $p < .001$). The EMCI group (HR = 2.46; $p = .06$) and the pre-MCI SCD group (HR = 2.44; $p < .001$) showed a very similar increase in risk. The increase in risk in the EMCI group did not reach significance, most likely because of the limited size of the group (*Figure 5B*). In this analysis there was also an increased risk of AD dementia associated with greater age (HR = 1.15; $p < .001$) and with positive ApoE4 carrier status (HR = 2.2; $p < .001$). Compared with the pre-MCI SCD group, there was a difference in risk of incident AD dementia in the LMCI group (HR = 4.56; $p < .001$), but not in the EMCI group (HR = 1.01; $p = .99$).

In the third analysis, all three categories were restricted to subjects who reported no concerns regarding their memory decline (SCD-C). Here, the risk of incident AD was increased in LMCI (HR = 5.64; $p < .001$) and EMCI (HR = 3.35; $p < .001$), but not significantly in the pre-MCI SCD group (HR = 1.25; $p = .343$; *Figure 5C*). Age (HR = 1.14; $p < .001$) and positive ApoE4 carrier status (HR = 1.72; $p = .004$) were also associated with a greater risk of incident AD dementia. In addition, depressive symptoms (HR = 1.81; $p = .025$) were associated with increased risk of incident AD

dementia in this analysis. When the pre-MCI SCD group was treated as the reference group, both LMCI (HR = 4.51; $p < .001$) and EMCI (HR = 2.67; $p < .001$) were associated with a greater risk of incident AD dementia.

In an exploratory analysis, we included the groups of EMCI-noSCD and LMCI-noSCD in the second model (individuals with SCD+C). Four subjects (2.5%) in the EMCI-noSCD group and 24 subjects (12.1%) in the LMCI-noSCD group converted to AD dementia. In comparison with the CO group, the risk of AD dementia for EMCI-noSCD was not increased (HR = 0.85; $p = .765$), whereas the risk for LMCI-noSCD was increased (HR = 3.87; $p < .001$).

Table 7. Study 1: Sample description for all groups.

		CO	pre-MCI SCD	Early MCI	Late MCI	all
total sample	N	863	1061	251	358	2533
	age: years (mean, SD)	79.7 (3.47)	79.8 (3.48)	79.4 (3.79)	79.9 (3.93)	79.7 (3.58)
	female: n (%)	584 (67.7)	618 (58.3)	162 (64.5)	277 (77.4)	1641 (64.8)
	<i>level of education</i>					
	low: n (%)	530 (61.4)	604 (56.9)	167 (66.5)	229 (64)	1530 (60.4)
	middle: n (%)	249 (28.9)	308 (29)	60 (23.9)	96 (26.8)	713 (28.1)
	high: n (%)	84 (9.7)	149 (14)	24 (9.6)	33 (9.2)	290 (11.4)
	depressive *: n (%)	41 (4.8)	98 (9.2)	24 (9.6%)	58 (16.2)	221 (8.7)
ApoE4+: n (%)	163 (18.9)	210 (19.8)	44 (17.5)	100 (27.9)	517 (20.4)	
subjects with concerns only	N	863	261	70	133	1327
	age: years (mean, SD)	79.7 (3.47)	79.6 (3.42)	78.7 (3.05)	79.7 (4.22)	79.6 (3.52)
	female: n (%)	584 (67.7)	180 (69.0)	46 (65.7)	110 (82.7)	920 (69.3)
	<i>level of education</i>					
	low: n (%)	530 (61.4)	162 (62.1)	50 (71.4)	86 (64.7)	828 (62.4)
	middle: n (%)	249 (28.9)	61 (23.4)	15 (21.4)	33 (24.8)	358 (27.0)
	high: n (%)	84 (9.7)	38 (14.6)	5 (7.1)	14 (10.5)	141 (10.6)
	depressive *: n (%)	41 (4.8%)	49 (18.8)	13 (18.6)	30 (22.6)	133 (10.0)
ApoE4+: n (%)	163 (18.9)	54 (20.7)	10 (14.3)	40 (30.1)	267 (20.1)	
subjects without concerns only	N	863	800	181	225	2069
	age: years (mean, SD)	79.7 (3.47)	79.8 (3.5)	79.7 (4.02)	80.0 (3.76)	79.8 (3.56)
	female: n (%)	584 (67.7)	438 (54.8)	116 (64.1)	167 (74.2)	1305 (63.1)
	<i>level of education</i>					
	low: n (%)	530 (61.4)	442 (55.3)	117 (64.6)	143 (63.6)	1232 (59.5)
	middle: n (%)	249 (28.9)	247 (30.9)	45 (24.9)	63 (28.0)	604 (29.2)
	high: n (%)	84 (9.7)	111 (13.9)	19 (10.5)	19 (8.4)	233 (11.3)
	depressive *: n (%)	41 (4.8%)	49 (6.1)	11 (6.1)	28 (12.4)	129 (6.2)
ApoE4+: n (%)	163 (18.9)	156 (19.5)	34 (18.8)	60 (26.7)	413 (20.0)	

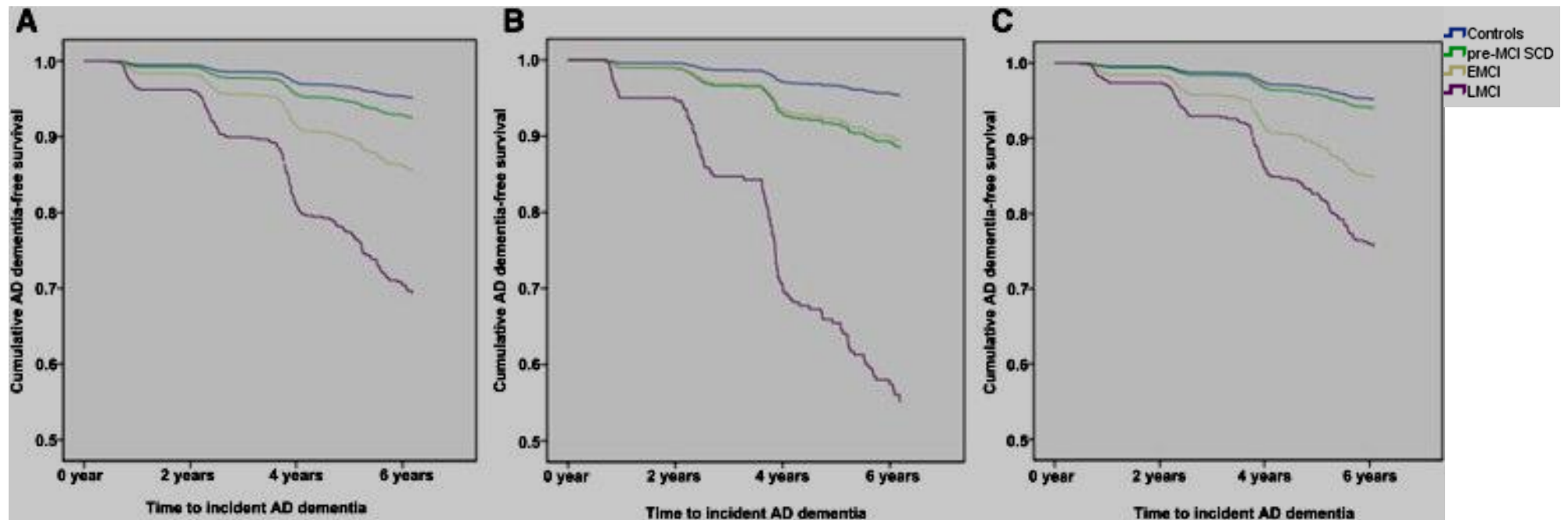
Note. *depressive symptoms were defined as a score of 6 or higher on the Geriatric-Depression-Scale. CO, control subjects group; pre-MCI SCD, group with subjective cognitive decline but normal test performance; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment.

Table 8. Conversion to AD dementia for different risk groups.

		CO	pre-MCI SCD	EMCI	LMCI	All
total sample	conversion to AD dementia (n, %)	32 (3.7)	66 (6.2)	27 (10.8)	89 (24.9)	214 (8.4)
(first analysis)	risk* (Hazard-Ratio, CI)	1.0	1.55 (1.02-2.37)	3.1 (1.86-5.18)	7.27 (4.82-10.97)	-
subjects with concerns only	conversion to AD dementia (n, %)	32 (3.7)	25 (9.6)	5 (7.1)	45 (33.8)	107 (8.1)
(second analysis)	risk* (Hazard-Ratio, CI)	1.0	2.44 (1.44-4.14)	2.46 (0.95-6.36)	11.13 (6.92-17.89)	-
subjects without concerns only	conversion to AD dementia (n, %)	32 (3.7)	41 (5.1)	22 (12.2)	44 (19.6)	139 (6.7)
(third analysis)	risk* (Hazard-Ratio, CI)	1.0	1.25 (0.786-2.0)	3.35 (1.94-5.77)	5.64 (3.55-8.97)	-

Note. CO, control subjects group; pre-MCI SCD, group with subjective cognitive decline but normal test performance; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease; CI, confidence interval. *Risk in comparison with CO. Covariates: age, sex, education (low, medium, high), depressive symptoms (Geriatric Depression Scale scores < 6 points or >= 6 points), and apolipoprotein E4 status.

Figure 5. Survival Curves across late MCI, early MCI and pre-MCI SCD groups with and without concerns respectively.



Note. Survival curve (A) across all subjects, (B) across all subjects with concerns regarding their experienced memory decline, and (C) across all subjects without concerns regarding their experienced memory decline. AD, Alzheimer’s disease; pre-MCI SCD, individuals with experienced memory decline but normal test performance; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment.

3.1.5 Discussion

We tested the risk of AD dementia in a large sample of dementia-free elderly subjects who were categorized into three groups according to their baseline report on memory-related SCD and their performance in a verbal memory task. These categories were (1) LMCI defined by the report on memory-related SCD and performance on delayed verbal recall below 1.5 SD of the norm, (2) EMCI defined by the report on memory-related SCD and performance on delayed verbal recall between 1.0 SD and 1.5 SD below the norm, and (3) pre-MCI SCD defined by the report on memory-related SCD with performance on delayed verbal recall within the norm (better than 1.0 SD below the normative mean). The distinction of LMCI and EMCI was made specifically because these two stages of MCI have recently been proposed, and EMCI is now used as an inclusion criterion in early AD recognition studies (e.g. ADNI; Aisen *et al.* 2010). The rationale for this approach is to move the biomarker-based identification of AD in individuals to an even earlier point in time before the originally used definition of MCI, which is now termed LMCI. The reference in our analysis was individuals who reported no memory-related SCD and who performed within the unimpaired range (better than 1.0 SD below the normative mean) on delayed verbal recall.

Across all individuals, we observed increasing risk of AD dementia in an ordered fashion, with highest risk in LMCI followed by EMCI and pre-MCI SCD. This result substantiates the concept of MCI as a risk factor of AD and shows that risk increases with increasing levels of impairment (Gomar *et al.* 2011).

In a second analysis, we restricted the groups to those who reported memory-related SCD associated with self-reported concerns (SCD+C). This approach was chosen because LMCI and EMCI are defined by the presence of impairment on tests and by reported concerns regarding memory impairment (<http://adni.loni.ucla.edu/>) (Winblad *et al.* 2004). The second reason for restricting the analysis to subjects with SCD+C relates to the finding of a doubling in risk of AD dementia in SCD+C compared with SCD without concerns (Jessen *et al.* 2010). In this analysis, subjects with LMCI had a very high risk of incident AD dementia. Subjects with pre-MCI SCD, however, had the same risk of incident AD dementia as subjects with EMCI. Thus, if both the pre-MCI SCD and EMCI groups report memory-related SCD with concerns, the fact that the subjects with EMCI performed between 1.0 SD and 1.5 SD below the norm on verbal delayed recall had no additional effect on the risk of AD dementia in our data.

This suggests that a categorical definition of minimal impairment (EMCI) is of limited sensitivity and specificity to detect individuals at the earliest disease stages. The lack of sensitivity is most likely associated with misclassification of high-performing subjects as normal. The lack of specificity is caused by false classification of actually unimpaired subjects as impaired, who perform poorly in a particular testing situation. To the contrary, the subjective report on decline, which is present in both pre-MCI SCD and EMCI, reflects the overall longitudinal development of cognitive performance within the recent time and may be a more robust indicator of minor changes than a single time point measurement.

In the third analysis, which was restricted to individuals who report memory-related SCD but not associated concerns, the effect was different. Here, individuals with pre-MCI SCD were only at a mild, non-significant increased risk of AD dementia compared with the CO group. In contrast, individuals with LMCI and EMCI were still at increased risk of AD dementia. It needs to be pointed out that, in this case, LMCI and EMCI definitions differed from the currently proposed MCI definitions (<http://adni.loni.ucla.edu/>; Winblad *et al.* 2004) because those require concerns associated with experienced memory impairment.

The second and third analyses show that pre-MCI SCD becomes predictive only if the self-evaluation of the experienced impairment causes concerns. If the experienced impairment was evaluated by the individuals as being of no concern, there was no prediction of dementia. This suggests that SCD without concerns may actually correspond to normal age-associated decline (Burke & Barnes, 2006) rather than to the first manifestation of AD. The concept of concerns regarding the experienced decline is most likely different from an increased intensity of perceived decline. One study found that subjective impairment was associated with cognitive decline; the increasing intensity of the experienced impairment assessed through a self-report questionnaire, however, did not contribute further to the prediction of decline (Glodzik-Sobanska *et al.* 2007). The presence of concerns was not assessed explicitly in this study.

The results of our study suggest that explicitly assessed self-reported concerns have predictive value. This suggests that if SCD corresponds to initial disease manifestation, the specific characteristic of experienced memory impairment might be different from normal aging and therefore cause such concerns. If this assumption was

true, it might explain the discrepant findings in SCD in the prediction of cognitive decline and dementia across studies (prediction or no prediction; Reid & MacLullich, 2006) because most studies do not address the specific self-evaluation of SCD (e.g. association with concerns), but address SCD in general (Abdulrab & Heun, 2008).

We found a higher rate of depressive symptoms in all groups with concerns associated with SCD compared with those with no concerns associated with SCD or without SCD at all. We accounted for this statistically in the analyses and it did not change the effects of SCD on prediction of AD dementia. However, the slightly increased level of depressive symptoms may also represent a very early sign of AD (Barnes *et al.* 2012).

Conceptually, our data strengthen the importance of the subjective experience of memory decline in dementia prediction. As pointed out earlier, the subjective experience and evaluation of memory decline (concerns) may actually be an indicator of early disease-related impairment. As an indicator of longitudinal change, it adds information to the cross-sectional measures of performance obtained by tests. Accordingly, it has been shown that SCD and objective measures of cognitive performance both contribute independently to dementia prediction, and that the prediction is improved by the combination of both rather than either one alone (Jessen *et al.* 2011). This is of particular importance for prediction models because not all individuals with cognitive impairment report SCD (Mitchell, 2008). It can be speculated that the predictive power of the subjective report increases, and the predictive power of objective cognitive test performance decreases, as prediction moves to the earliest disease stages. This assumption is supported by the lack of risk increase of AD dementia in individuals with very mild performance impairment (1.0–1.5 SD below the norm), but without the report on memory impairment (EMCI-noSCD) in opposition to the risk increase in subjects with SCD and concerns but normal performance on testing. The greater relevance of subjective report rather than of test measures at the earliest symptomatic stage of AD may be related to effects of compensation. At this early disease stage, increased compensatory neuronal effort may facilitate still normal performance on tests, but may be experienced subjectively and interpreted as evidence for impairment (Erk *et al.* 2011).

Obviously, SCD with concerns alone or in combination with cognitive testing is not sufficient for individual prediction of AD dementia. It has, however, great heuristic value for identification of subjects, which may undergo biomarker-based predementia AD detection (Scheef *et al.* 2012).

On a practical level, our data suggest that current biomarker-based early disease recognition research (such as ADNI) should consider expansion from EMCI to pre-MCI SCD with concerns because these subjects carry a similar risk of AD dementia as subjects with EMCI. By keeping the requirement for minor cross-sectional impairment on tests (EMCI), those subjects who are classified falsely as not impaired will be missed (e.g. those with high premorbid performance levels or with very effective compensatory mechanisms). For these individuals, however, early disease recognition may be of the highest value because they are still at a largely normal level of function.

Our exploratory analysis also showed that individuals with slight memory impairment without subjective report (EMCI-noSCD) had no increased risk of future AD dementia, but those with more severe impairment and no subjective report (LMCI-noSCD) were at increased risk. The LMCI-noSCD individuals may represent a group with cognitive decline resulting from AD pathology, but lack of awareness. One recent FDG-PET study found evidence that LMCI patients who were unaware of their memory deficits exhibited a more severe and AD-typical hypometabolic pattern than LMCI individuals who were aware of their deficits (Nobili *et al.* 2010).

This study has limitations. The design of this study is not identical to biomarker-based studies that focus on MCI (e.g. ADNI). The participants in our study are not seen in specialist centers, but rather resemble a population-based sample. In addition, the neuropsychological and clinical assessments were not extensive. It has been demonstrated in other studies that the stage of pre-MCI may also be associated with very mild impairment in executive function and increased apathy scores (Duara *et al.* 2011), which were not addressed specifically in this study.

One potential confound may be related to the inclusion criterion of at least one visit in the GP office within the past 12 months. This may exclude very healthy subjects or those who do not go to a GP office. In Germany, however, the vast majority of persons older than 75 years of age visit the GP regularly. Thus, we consider the data externally valid. The high age at entry in the study (average, 80 years) does not allow

generalization to younger subjects with SCD, in whom other factors such as psychosocial distress may be of great relevance for the presence of SCD (Paradise *et al.* 2011). Because we did not use biomarkers, we applied the NINCDS-ADRDA (McKhann *et al.* 1984) and DSM-IV criteria for AD dementia rather than recently proposed criteria that involve biomarkers (McKhann *et al.* 2011). Also, our definition of MCI was restricted to amnesic MCI. It is uncertain how subjective report and performance impairment in other cognitive domains are related to dementia prediction. In a number of cases, only informant-based information could be obtained, mostly because of death or morbidity-related reasons. In an exploratory analysis, we recalculated the models after exclusion of those with informant-based information only. The prediction results were similar across the entire sample (data not shown). Thus, we think that the results are not biased by this approach.

Residual confounding of the data is unlikely because we used well-defined categories for level of education and ApoE4 status. Depressive symptoms were dichotomized according to an established cutoff (Gauggel & Birkner, 1999). In addition, we have also repeated our analyses with the Geriatric Depression Scale as a continuous predictor with similar results (data not shown). Last, the subjective report was based on interview with the participants only. Reports from informants were not considered for classification of SCD.

Overall, our data provide evidence that stages of very mild impairment may not be well captured by standard neuropsychological testing and also highlight the relevance of subjective reports as an indicator of individual change over time and predictor of AD dementia.

3.2 Study 2: Memory concerns, memory performance and risk of dementia in patients with MCI (Wolfsgruber *et al.* 2014b)

3.2.1 Abstract

Background

Concerns about worsening memory (“memory concerns”; MC) and impairment in memory performance are both predictors of Alzheimer’s disease (AD) dementia. The relationship of both in dementia prediction at the pre-dementia disease stage, however, is not well explored. Refined understanding of the contribution of both MC and memory performance in dementia prediction is crucial for defining at-risk populations. We examined the risk of incident AD dementia by MC and memory performance in patients with mild cognitive impairment (MCI).

Methods

We analyzed data of 417 MCI patients from a longitudinal multicenter observational study. Patients were classified based on presence ($n = 305$) vs. absence ($n = 112$) of MC. Risk of incident AD dementia was estimated with Cox Proportional-Hazards regression models.

Results

Risk of incident AD dementia was increased by MC (HR = 2.55, 95%CI: 1.33 – 4.89), lower memory performance (HR = 0.63, 95%CI: 0.56 – 0.71) and ApoE4-genotype (HR = 1.89, 95%CI: 1.18 – 3.02). An interaction effect between MC and memory performance was observed. The predictive power of MC was greatest for patients with very mild memory impairment and decreased with increasing memory impairment.

Conclusions

Our data suggest that the power of MC as a predictor of future dementia at the MCI stage varies with the patients’ level of cognitive impairment. While MC are predictive at early stage MCI, their predictive value at more advanced stages of MCI is reduced. This suggests that loss of insight related to AD may occur at the late stage of MCI.

3.2.2 Introduction

The syndrome of mild cognitive impairment (MCI; Petersen, 2004) has been established as a risk state for Alzheimer's disease (AD) dementia. Patients with MCI show cognitive impairment objectified by neuropsychological testing while their functional activities are largely intact. In addition, current criteria for MCI (Petersen, 2004; Winblad *et al.* 2004; Albert *et al.* 2011) require report on cognitive decline, provided either by the patient and/or by an informant or clinician who knows the patient well.

Compared to the current knowledge and standards of neuropsychological testing, the criterion of subjective report about cognitive decline in the definition of MCI is less elaborated. It is unknown whether more precise operationalization (either quantitatively or qualitatively) of this criterion may increase the predictive accuracy for AD dementia in MCI patients. In fact, in everyday clinical practice, the criterion of experienced or observed cognitive decline might often be considered fulfilled by the fact that a patient consults the medical system for diagnostic workup of cognitive impairment. Studies that investigated the role of individual and informant reports for the prediction of AD dementia in MCI are rare. One early study (Tierney *et al.* 1996) found informant reports but not the individual's memory complaints associated with future AD dementia in memory impaired patients. A recent study (Rabin *et al.* 2012) in a non-demented elderly community sample found both self and informant reports to be predictive, while in a combined predictive model only informant reports together with neuropsychological tests remained a significant predictor.

Other studies, based on pre-MCI samples, showed elevated risk of future AD dementia (Geerlings *et al.* 1999; Reisberg *et al.* 2010; Jessen *et al.* 2011) as well as associations with biomarkers of AD in individuals who report self-experienced cognitive decline (Saykin *et al.* 2006; Mosconi *et al.* 2008; Visser *et al.* 2009; Chételat *et al.* 2010; Scheef *et al.* 2012; Amariglio *et al.* 2012; Mielke *et al.* 2012). However, there are also studies that did not find associations of self-reported cognitive decline with either incident AD dementia (Reid & Maclullich, 2006) or biomarkers of AD (Buckley *et al.* 2013; Grambaite *et al.* 2013) in pre-MCI samples. Importantly, comparability of results across studies is limited due to heterogeneity of samples and assessment of self-experienced cognitive decline. Further, it was recently reported that, in individuals with normal cognitive test performance (pre-MCI), those who are

particularly concerned about their experienced memory decline have a higher risk of developing AD dementia, as compared to those who report a self-experienced memory decline without concerns (Jessen *et al.* 2010; Jessen *et al.* 2014b). Thus, the appraisal of the experienced decline as worrying may be of specific predictive value when assessing an individual's report.

Based on the existing data, the significance of self-reported concerns about worsening memory (hereafter: "memory concerns" (MC)) in MCI is yet unclear and it is largely unknown what factors might influence the report or denial of MC in MCI patients (Mitchell, 2008). Reduced self-awareness is one factor that might influence the report of MC in this patient group (Roberts *et al.* 2009). Self-awareness often becomes impaired during the progression of AD. Hence, unawareness (also termed anosognosia) concerning the memory impairment is frequently observed in AD dementia (Vogel *et al.* 2004). Reduced self-awareness and anosognosia are also observed in MCI patients (Vogel *et al.* 2004; Vogel *et al.* 2005; Galeone *et al.* 2011). However, levels of awareness are heterogeneous among these patients (Roberts *et al.* 2009). This might contribute to the fact that MC are not consistently present in patients with MCI (Vogel *et al.* 2004; Vogel *et al.* 2005; Kalbe *et al.* 2005).

The heterogeneity in self-awareness may originate from the fact that anosognosia as a core symptom of AD dementia manifests at the stage of MCI and that the likelihood of its occurrence rises with increasing cognitive impairment. Evidence for this assumption comes from studies that investigated self-awareness in patients with AD dementia and patients with amnesic MCI (i.e. with clinical impairment in the memory domain, evidenced by neuropsychological testing (Petersen, 2004; Winblad *et al.* 2004). Patients with advanced amnesic MCI, scoring lower than two standard deviations (SD) below age-corrected norms on a memory test (Vogel *et al.* 2005), showed symptoms of anosognosia similarly severe compared to the AD dementia group. In a study on amnesic MCI patients, Nobili and colleagues found that low awareness of memory deficits was associated with more progressed AD pathology (Nobili *et al.* 2010). Moreover, results from a recent study showed that cognitive complaints decreased with decreasing cognitive performance in MCI patients, while the relationship was opposite (i.e. reported complaints increased with decreasing memory performance) in individuals with only subjective memory impairment but no MCI (Grambaite *et al.* 2013). These

results suggest that, within the stage of MCI, those patients with more severe cognitive impairment tend to have reduced insight into their cognitive deficits.

Based on the empirical evidence a hypothetical model of AD dementia prediction in MCI can be formulated: At the earliest stage of impairment (early MCI) self-awareness of the patient is mostly unaffected. Here, MC should reflect the true self-perceived, longitudinal intra-individual decline and should contribute to AD dementia prediction in addition to cross-sectional impairment on tests. At later stages of MCI, self-awareness is waning and the predictive value of MC is declining. MC as defined in this model comprises two important aspects, i.e. the specific notion of (1) a decline in memory performance and (2) the appraisal of this self-perceived decline as worrying. The appraisal as worrying extends beyond the subjective report about cognitive decline as part of the general MCI criteria and has been found to be of higher predictive value than the notion of a worsening memory without worries (Jessen *et al.* 2010; Jessen *et al.* 2014b). This clearly separates the definition of memory concerns in our study from subjective memory decline in general.

In the present study, we tested the proposed model in a sample of MCI patients whose memory impairment ranged from very mild to advanced severity.

3.2.3 Methods

Ethics Statement

The protocol of the study was approved by the Institutional Review Board (IRB) of the Medical Faculty, University of Erlangen (coordinating study center) and by IRBs at each individual participating study center, listed in the following: IRB Medical Faculty, University of Hamburg; IRB Charité – University Medicine Berlin; IRB Medical Faculty, University of Göttingen; IRB Medical Faculty, University of Düsseldorf; IRB Medical Faculty, University of Bonn; IRB Medical Faculty, University of Leipzig; IRB Medical Faculty, University of Frankfurt (am Main); IRB Medical Faculty, University of Heidelberg; IRB Medical Faculty, Saarland University; IRB Medical Faculty, University of Mannheim; IRB Medical Faculty, University of Freiburg; IRB Medical Faculty, Ludwig Maximilian University Munich; IRB Medical Faculty, Technical University Munich.

The study was conducted in accordance with the Declaration of Helsinki. After complete description of the study to the patients, written informed consent was obtained.

Participants

Subjects were recruited between 2003 and 2007 at 14 specialized university memory clinics collaborating within the German Dementia Competence Network (DCN). The general procedures for assessment and selection of subjects have been reported in detail previously (Kornhuber *et al.* 2009). Briefly, patients over 50 years of age who were referred to or sought help at one of the participating memory clinics underwent a clinical, neuropsychological and laboratory assessment and brain imaging. Patients with either MCI or mild dementia were asked to participate in this longitudinal observational study.

Clinical and neuropsychological assessment

Patients were assessed annually by experienced physicians and neuropsychologists for up to three years with standardized diagnostic procedures as described in detail previously (Kornhuber *et al.* 2009). This assessment included the neuropsychological test battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-NP; Morris *et al.* 1989). The CERAD-NP consists of various subtests, including the Mini-Mental State Examination (MMSE) (Folstein *et al.* 1975), and is specifically designed to assess the cognitive domains most commonly affected in AD. The subtests are (in order of administration) (1) Verbal Fluency, (2) modified Boston Naming Test (15 item version), (3) the MMSE, (4) Word List Learning of a 10-item word list (sum of three learning trials; maximum score of 30), (5) Figure Copying (maximum score of 11), (6) Word List Delayed Recall (maximum score of 10), (7) Word List Recognition (maximum score of 10 or 100%), and (8) Figure Recall (maximum score of 11). We used the Word List Delayed Recall subtest (CERAD-DR) as a measure of objective memory impairment as delayed recall of word lists is considered among the tests that are most sensitive to incipient AD (Albert *et al.* 2001). In addition, high levels of diagnostic accuracy for the CERAD-DR have been reported regarding cross-sectional detection (Sotaniemi *et al.* 2012) and prediction of AD dementia (Wolfsgruber *et al.* 2014a).

Depressive symptoms were rated by the interviewer with the Montgomery Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979). The MADRS consists of 10 items which are scored from 0 to 6 after a clinical interview. It is well established in psychogeriatric and AD studies (Müller-Thomsen *et al.* 2005). A cutoff score of 13 points is suggested for mild depression. Instrumental activities of daily living were assessed with the Bayer-Activities of Daily Living Scale (BADL), a 25-item, informant-rated questionnaire developed to assess deficits in the performance of everyday activities in patients with MCI or mild-to-moderate dementia (Hindmarch *et al.* 1998).

Definition of MCI and incident AD dementia

All diagnoses were established in a consensus conference between physicians and neuropsychologists at each site. The diagnosis of MCI was made according to the consensus criteria proposed in 2004 by the International Working Group on MCI (Winblad *et al.* 2004): (1) subjective and/or informant report about cognitive decline, (2) evidence of an impairment on objective cognitive test, (3) no or only minor impairments in instrumental activities of daily living (BADL score < 4), and (4) not demented. Criterion (2) was met if patients showed a cognitive deficit of more than 1SD below age- and education-adjusted norms in at least one subtest of the CERAD-NP battery or in the Wechsler-Memory-Scales Logical Memory II subtest. The diagnosis of incident AD dementia was made according to the NINCDS/ADRDA criteria for probable AD (McKhann *et al.* 1984).

Classification of participants into “MCI with memory concerns” vs. “MCI without memory concerns”

Patients were classified as “MCI with memory concerns” (MC+) or “MCI without memory concerns” (MC-) according to their response to the following standardized question (Geerlings *et al.* 1999): “Do you feel like your memory has become worse”. Possible answers were: (1) “No”, (2) “Sometimes, but this does not worry me”, (3) “Yes, that worries me”, (4) “Yes, that worries me seriously”. Answers (1) and (2) were combined to the MC- and answers (3) and (4) to the MC+ group, respectively.

The question and response categories were read aloud to patients by the interviewer as part of the initial assessment prior to neuropsychological testing. Duration of MC was not assessed in this study.

The standardized question on memory concerns was not used for the initial diagnosis of MCI but only for division into groups of MC+ and MC- patients respectively. The criterion of subjective report on cognitive decline required for the diagnosis of MCI could be provided either by the subject and/or by an informant according to the criteria of the International Working Group on MCI (Winblad *et al.* 2004). Thus the MC+ group constitutes a subgroup of MCI patients who themselves, when questioned in person with a standardized item, report memory decline which they appraise as particularly worrying. MC as operationalized here thus extend beyond the subjective report about cognitive decline as part of the general MCI criteria. Patients in the second response category “sometimes, but this does not worry me” were therefore assigned to the MC- group. We also refrained from keeping the four categories separate as this would have prevented the detailed analysis and straightforward interpretation of moderating effects between categorical (MC+ vs. MC-) and continuous (memory performance) variables, also due to limited number of participants answering “No” to the question on experienced memory decline. However, we report descriptive statistics of interest (conversion rates and memory performance) for all subgroups.

Statistical analysis

Differences between groups were evaluated using independent sample t-tests for continuous and Chi²-test for categorical variables, respectively. Risk of incident AD dementia was evaluated using stepwise Cox Proportional-Hazards regression analyses (SPSS-Version-20). Hazard Ratios (HR) with corresponding 95% Confidence Intervals (CI) are reported. Continuous predictors were age, years of education and the CERAD-NP delayed recall score (CERAD-DR). These were mean-centered prior to analysis by subtracting the respective sample mean from each observed value. Categorical predictors were gender, ApoE4-status (no E4 allele vs. presence of one or two E4 alleles) and group-status (MC- vs. MC+ group). In step 1 we entered age, gender, education, ApoE4 plus the CERAD-DR in the model. In step 2 we added group-status as an additional variable, to test the hypothesis that MC contribute to the risk of incident AD dementia over time after controlling for objective memory impairment. In step 3 we added the linear interaction term of group-status and memory performance (group-

status*CERAD-DR) to the model to test the hypothesis that the impact of MC on risk of future AD dementia is moderated by the level of objective memory impairment. In an additional analysis we added the MADRS score in step 1 to control for depressive symptoms as a possible confounder.

Eight hundred and thirteen MCI patients were included at baseline in the longitudinal observational study. For the present analyses we included patients with a MMSE score between 24 and 30 (inclusive) and excluded patients with incomplete clinical or neuropsychological data required for the classification of subgroups and for statistical analysis. We further excluded those without information on ApoE4 genotype and those who withdrew early from the study without at least one follow-up visit at 12 months after baseline. Application of these criteria resulted in a sample of 454 MCI patients eligible for the present analyses. Thirty-seven patients (8.1%) converted to dementia other than AD during follow-up. We excluded these cases for the present analysis as our focus was on the impact of MC on incident AD dementia. The final sample had a size of $n = 417$ MCI patients. Dropout analysis revealed that the group of patients excluded due to missing baseline data or lack of follow-up were older on average ($M_{\text{excluded}} = 68.8$, $SD = 8.73$; $M_{\text{included}} = 65.6$, $SD = 7.93$; $p < 0.05$) but had only slightly lower MMSE mean scores ($M_{\text{excluded}} = 27.3$, $SD = 1.72$; $M_{\text{included}} = 27.7$, $SD = 1.66$; $p < 0.05$). The two groups did not differ regarding years of education, gender distribution and expression of memory concerns (i.e. distribution of MC+ vs. MC-).

3.2.4 Results

Descriptive statistics of the sample

Of the 417 included patients, 19 patients (4.6%) responded “No” to the question on experienced memory decline, 93 (22.3%) answered “Sometimes, but this does not worry me”, 211 (50.6%) answered “Yes, that worries me” and 94 (22.5%) answered “Yes, that worries me seriously”. Thus, 112 (26.9%) patients were classified as MC- and 305 (73.1%) as MC+. The two groups did not differ in demographical variables, frequency of ApoE4 status, MMSE score, memory- or overall cognitive impairment on the CERAD-NP and mean follow-up time. MC+ patients showed higher scores on the MADRS scale and slightly higher BADL scores (*Table 9*).

Table 9. Study 2: Sample description.

	Total Sample (n = 417 MCI subjects)		MC- group (n = 112 MCI subjects)		MC+ group (n = 305 MCI subjects)		Group comparison	
	M	(SD)	M	(SD)	M	(SD)	MC- vs. MC+ group	
							Cohen's d	p-value
Age (years)	65.6	7.93	66.3	8.70	65.4	7.63	0.11	0.341
Education (years)	12.6	2.84	12.8	2.81	12.5	2.85	0.12	0.270
MMSE-Score	27.6	1.66	27.6	1.62	27.7	1.67	-0.06	0.617
CERAD								
Delayed Recall	5.3	2.21	5.3	2.15	5.4	2.23	-0.03	0.766
CERAD								
Total Score	73.3	10.8	73.4	10.9	73.2	10.7	0.02	0.888
MADRAS	7.93	6.34	5.13	5.01	8.95	6.47	-0.63	< 0.001
B-ADL-Score	2.16	1.29	1.96	1.37	2.23	1.26	-0.21	0.061
Follow-Up time (months)	27.6	9.85	28.5	10.5	27.3	9.61	0.12	0.304
Time to Conversion (months)	19.1	7.80	20.8	7.42	18.8	7.87	0.27	0.422
	n	%	n	%	N	%	Chi²	p-value
Female gender	170	40.8	42	37.5	128	42.0	0.68	0.411
Positive								
ApoE4-status	158	37.9	44	39.3	114	37.4	0.13	0.722
Conversion to AD dementia	74	17.7	11	9.8	63	20.7	6.59	0.010

Note. P-values are derived from independent sample t-tests (2-sided) for comparison of continuous variables, and from Chi²-tests for categorical variables. AD, Alzheimer's disease; BADL, Bayer-Activities of Daily Living Scale; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; M, Mean; MADRS, Montgomery Asberg Depression Rating Scale; MMSE, Mini-Mental State Examination; MCI, Mild Cognitive Impairment; MC-, MCI patients without Memory Concerns; MC+, MCI patients with Memory Concerns; SD, Standard deviation.

Risk of AD dementia

Seventy-four patients (17.7%) developed incident AD dementia within a mean follow-up time of 27.6 months. The incidence rate differed significantly between groups (9.8% vs. 20.7% for the MC- and MC+ group respectively). Incidence rates according to the individual response categories of the question on experienced memory decline were 6 out of 19 (31.6%) in the “No” category, 5 out of 93 (5.4%) in the category “Sometimes, but this does not worry me”, 42 out of 211 (19.9%) in the category “Yes, that worries me”, and 21 out of 94 (22.3%) in the category “Yes, that worries me seriously”. With regard to memory performance, the patients answering “No” had the lowest mean CERAD-DR scores ($M = 4.37$, $SD = 2.63$) while patients in the other categories displayed better and similar mean CERAD-DR scores (category “Sometimes, but this does not worry me”: $M = 5.48$, $SD = 2.01$; category “Yes, that worries me”: $M = 5.29$, $SD = 2.16$; category “Yes, that worries me seriously”: $M = 5.53$, $SD = 2.21$). Mean CERAD-DR performance in the group of patients answering “No” was significantly lower compared to that of patients in the other three response categories ($t = 1.99$, $df = 415$, $p = 0.048$).

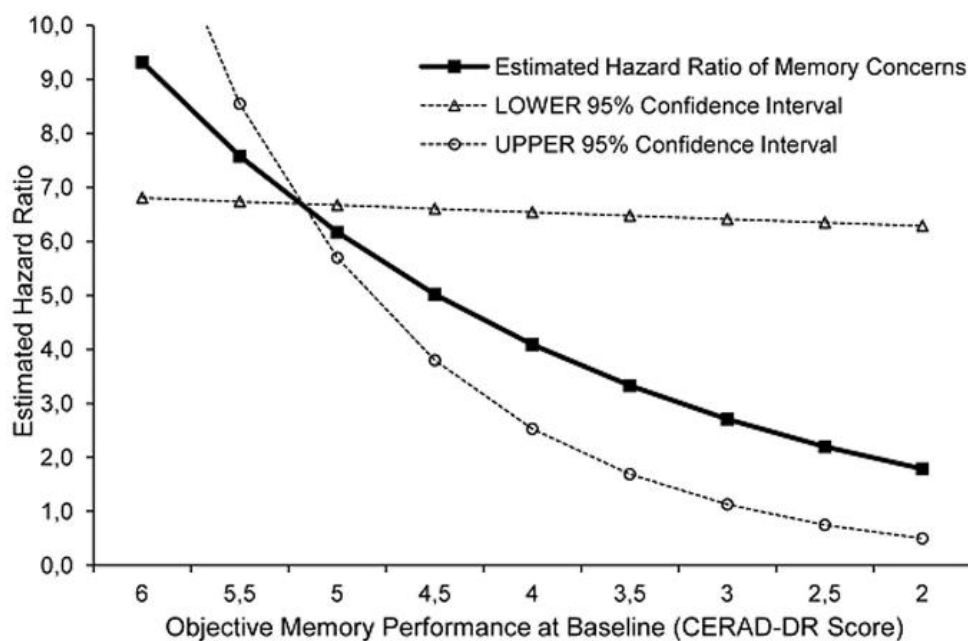
Results of the Cox Proportional-Hazards regression models are presented in *Table 10*. In step 1, positive ApoE4 status ($HR = 1.89$, 95% CI: 1.18 – 3.02) and lower CERAD-DR performance ($HR = 0.63$, 95% CI: 0.56 – 0.71) were associated with higher risk of developing incident AD, yielding acceptable model fit (Nagelkerkes $R^2 = 0.262$). Group-status (MC- vs. MC+) was entered in step 2 of the analysis. In addition to CERAD-DR and ApoE4, presence of MC (i.e. belonging to the MC+ group) was also associated with an increased risk of future AD ($HR = 2.55$, 95% CI: 1.33 – 4.89) and significantly increased model fit ($\Delta\text{-Chi}^2 = 9.5$, $df = 1$, $p = 0.002$, change in Nagelkerke’s $R^2 = 2.1\%$). Thus, the hypothesis that presence of MC does individually contribute to the risk of future AD dementia after controlling for objective memory impairment, was supported by the results of the regression analyses.

The third step of the regression model included the interaction term of group-status and CERAD-DR. The overall model fit was again improved by inclusion of the interaction term ($\Delta\text{-Chi}^2 = 4.8$, $df = 1$, $p = 0.028$, change in Nagelkerke’s $R^2 = 1\%$), supporting the hypothesis that the impact of MC on risk of future AD varies with the severity of objective memory impairment. The HR-value of the interaction term is greater than one ($HR = 1.51$, 95% CI: 1.01 – 2.25), which means that the impact of MC

on the risk of future AD increases with higher memory performance and decreases with lower memory performance with an estimated factor of 1.5 per word. This moderating effect is depicted in *Figure 6* (black solid line) where on the y-axis the estimated HR of MC is plotted as a function of memory performance (CERAD-DR). As can be seen here, the HR of MC decreases with decreasing memory performance, i.e. when moving from left to right along the x-axis.

The additional analysis with the MADRS score as a predictor added in step 1 of the modelling process revealed that depressive symptoms were not associated with risk of future AD dementia ($p = 0.56$) and did not alter the results reported above.

Figure 6. The impact of memory concerns on the risk of future AD dementia is moderated by objective memory performance at baseline.



Note. The impact of memory concerns on the risk of future AD dementia, expressed in terms of the Hazard Ratio (HR) for the predictor “memory concerns”, is plotted as a function of objective memory performance at baseline, i.e. the interaction effect between memory concerns and objective memory performance is depicted. Values are derived from the multivariate Cox-proportional Hazard Regression analysis (see *Table 10*, model step 3: HR of the interaction-term = 1.51, 95% Confidence Interval: 1.01–2.25). The black solid line corresponds to the estimated HR-value = 1.51 of the interaction effect. The two dotted lines represent the functional curves that result when the boundary HR-values of the lower 95% Confidence Interval (= 1.01) or upper 95% Confidence Interval (= 2.25) respectively, are inserted as numbers to plot the interaction effect. CERAD-DR, Delayed Recall of the Consortium to Establish a Registry for Alzheimer’s Disease Neuropsychological Assessment Battery.

Table 10. Differential risk for incident AD dementia across follow-up time (Results of Cox proportional hazard regression models).

		Model Statistics				Predictor Statistics						
		M2LL Chi ²	Δ-Chi ² (df)	p- value	Nagelkerke R ² (%)	B	SE	Wald-Chi ²	p-value	HR	95% C.I. for HR	
											Lower	Upper
Model variables		723.5	107.2 (5)	0.000	26.2							
Step 1: Model with covariates and CERAD-DR as predictors	Age					0.03	0.02	2.33	0.127	1.03	0.99	1.06
	Female gender					0.26	0.24	1.17	0.279	1.29	0.81	2.05
	Education					-0.05	0.04	1.52	0.218	0.95	0.88	1.03
	Positive ApoE4 status					0.63	0.24	6.95	0.008	1.89	1.18	3.02
	CERAD-DR					-0.47	0.06	56.1	< 0.001	0.63	0.56	0.71
Model variables		713.9	9.5 (1)	0.002	28.3							
Step 2: MC added as predictor	Age					0.03	0.02	3.34	0.068	1.03	1.00	1.07
	Female gender					0.11	0.24	0.22	0.641	1.12	0.70	1.80
	Education					-0.05	0.04	1.77	0.183	0.95	0.88	1.03
	Positive ApoE4 status					0.61	0.24	6.39	0.011	1.85	1.15	2.97
	CERAD-DR					-0.46	0.06	55.9	< 0.001	0.63	0.56	0.71
	Presence of MC					0.93	0.33	7.87	0.005	2.55	1.33	4.89
Model variables		709.1	4.8 (1)	0.028	29.3							
Step 3: added Interaction between CERAD-DR and MC	Age					0.03	0.02	2.97	0.085	1.03	1.00	1.07
	Female gender					0.16	0.24	0.44	0.506	1.18	0.73	1.90
	Education					-0.05	0.04	1.31	0.252	0.95	0.88	1.03
	Positive ApoE4 status					0.64	0.24	6.95	0.008	1.89	1.18	3.05
	CERAD-DR					-0.83	0.20	17.4	< 0.001	0.44	0.30	0.65
	Presence of MC					1.95	0.70	7.73	0.005	7.01	1.78	27.7
Linear Interaction: CERAD-DR * MC						0.41	0.21	4.00	0.046	1.51	1.01	2.25

Note. M2LL of the Intercept model = 830.6. Details of the modeling process are given in the methods section. The HR for the CERAD-DR is below one as it represents the HR for a one unit increase in CERAD-DR scores (i.e. for better memory performance). Lower CERAD-DR scores are therefore associated with a higher risk for developing incident AD dementia. B, Beta-Coefficient of the predictor; C.I., Confidence Interval; CERAD-DR, Delayed Recall of the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery; HR, Hazard Ratio; M2LL, Minus-Two-Log-Likelihood; SE, Standard Error for B; MC, Memory Concerns.

3.2.5 Discussion

In the present study we found that MC, which extend beyond the subjectively experienced memory decline that is part of the general MCI criteria set, were associated with an increased risk of incident AD dementia. This main effect of MC is of importance as it suggests that reported concerns regarding self-perceived memory decline (rather than just self-report without associated concerns) are predictive for future AD dementia in the MCI stage. We suggest that the magnitude of this main effect (about two-fold increased risk in the MC+ group) is of clinical relevance. Our findings are in line with results from an independent population-based study which found that self-perceived memory decline with reported concerns is associated with a higher risk of incident AD dementia than the mere notion of worsening memory without concerns (Jessen *et al.* 2010; Jessen *et al.* 2014b). These results also suggest that AD-related memory decline might be experienced in a different quality (i.e. as more serious and therefore worrying) compared to memory decline related to other factors such as normal aging. As an alternative hypothesis, proneness to psychological distress, a trait which has been reported as a risk factor for AD dementia (Wilson *et al.* 2003), might also be associated with a higher proneness to worry about self-perceived memory decline. If true, this could also explain the higher risk of incident AD dementia associated with endorsing worries about worsening memory. We also stress that the main effect of MC does not imply that MCI patients without concerns about worsening memory are of no risk of future AD dementia, but our data suggest that their risk is lower at a group level. Interestingly, in the small patient group who answered “No” to the question on experienced memory decline the conversion rate was highest and the memory performance level was lowest.

We also observed an interaction effect between MC and objective memory performance. The impact of MC on risk of future AD dementia was highest for patients with very mild memory impairment and decreased with increasing memory impairment. Compared to the main effect of MC, this interaction effect was less strong. While this impedes a direct clinical applicability (e.g. for prediction in the individual case), it still highlights that at a group level MC and objective memory impairment interact in the course of AD. We suggest that this interaction between MC and memory performance is meaningful in several ways. Firstly, at the stage of very mild memory impairment, the assessment of self-perceived and worrying intra-individual decline might further

contribute to AD dementia prediction in addition to cross-sectional impairment on tests. This is of relevance as it highlights the particular value of self-reported memory decline with associated worries at the stage of very mild impairment (Jessen *et al.* 2014b).

Secondly, the effect of decreasing predictive validity of MC with increasing memory impairment may be caused by the reduction of self-perceived insight into symptoms at later stages of MCI. In this regard, we observed the highest conversion rate (31.6%) in the group answering “No” to the MC question, i.e. in those patients who were neither concerned about worsening memory nor reported any experienced memory decline at all. These patients also had the lowest CERAD-DR performance in the studied sample which is consistent with this potential explanation. Our observation is in line with results from a recent brain FDG-PET imaging study in a sample of single- and multidomain amnesic MCI patients (memory performance of < 1.5 SD below norm), which also included an assessment of awareness (Nobili *et al.* 2010). Patients with poor awareness of their memory deficits showed a hypometabolic pattern similar to that of patients with early AD dementia, suggesting that unawareness of memory deficits in MCI is linked to a more progressed pathology. Vogel and colleagues (Vogel *et al.* 2004) studied a group of amnesic MCI patients with more severe memory impairment (< 2 SD below norm). They found similar levels of reduced awareness for this MCI group compared to a group of AD dementia patients and observed lower MMSE scores to be associated with lower levels of awareness. Furthermore, one recent study has shown that, in the group of MCI patients, subjective cognitive complaints decreased with increasing cognitive impairment (Grambaite *et al.* 2013). Based on these empirical data, we propose that anosognosia, which is a well-known clinical sign of AD dementia, might occur at the stage of late MCI. At the stage of very mild MCI, before this loss of valid self-perception, the presence of MC is predictive of future AD dementia. This is in agreement with several studies showing that subjective memory decline in individuals with normal cognitive function is also predictive for AD dementia (Geerlings *et al.* 1999; Reisberg *et al.* 2010; Jessen *et al.* 2011; Jessen *et al.* 2010; Jessen *et al.* 2014b).

Depressive symptoms did not predict risk of future AD dementia in the present study and inclusion of depressive symptoms as a possible confounding variable did not alter the effects for objective memory impairment and MC. It is important to note, that although the MC+ group scored higher on the MADRS, their mean MADRS score reflected only very mild depressive symptoms and did not correspond to the clinical

diagnosis of a major depression. ApoE4 status was associated with a higher risk of incident AD dementia which is in line with recent studies (Xu *et al.* 2013; Espinosa *et al.* 2013). However, frequencies of ApoE4 did not differ between the MC+ and MC- group. Results remained similar when ApoE4 was not accounted for in the models and we did not observe an interaction between MC and ApoE4 with regard to risk of incident AD dementia in additional post-hoc analyses (data not shown). ApoE4 and MC thus independently contributed to risk of AD dementia in the present sample. We also controlled for level of education in our analysis. Regarding the interplay of education and memory concerns, results from a large population based cohort study of non-demented elderly suggest that the clinical relevance of subjective memory complaints might be higher in individuals with higher educational background (van Oijen *et al.* 2007). We also tested for an interaction between memory concerns and level of education in our analysis but did not find such an effect (data not shown). Differences in samples and design (i.e. community based cohort of non-demented elderly vs. memory clinic MCI sample in our study) might have contributed to these discrepant findings.

Our results are different to those of other studies which did not find a clear association between self-reports of memory decline and incident AD dementia (Tierney *et al.* 1996; Rabin *et al.* 2012). However, besides differences regarding samples and assessment of self-reported memory decline, these studies did also include informant reports in their predictive models. Therefore the comparability of our results to these studies is limited and we acknowledge the lack of informant reports in our study as a limitation.

A strength of the present study is the large number of neuropsychologically well characterized patients who met criteria for MCI (Winblad *et al.* 2004). Within these criteria we set the cutoff for cognitive impairment at 1.0SD below the normative mean. This procedure is in line with recently established study protocols of large studies, e.g. ADNI-2 where recruitment was extended to early (amnestic) MCI patients with very mild memory impairment (< 1.0 SD below the norm; Aisen *et al.* 2010). The present sample therefore enabled us to test the specific contribution of MC for risk of AD dementia at different stages of memory impairment within the MCI spectrum.

This study has limitations. The present sample reflects MCI patients with at least very mild impairment in one cognitive domain. Therefore the present results concerning

the prognostic value of MC at different levels of memory impairment only refer to the MCI spectrum and not to cognitively unimpaired individuals (pre-MCI). Secondly, we focused on memory concerns only (rather than concerns about other cognitive domains or cognition in general) and on AD dementia as the outcome. It is important to note that other cognitive domains beyond memory can also be affected in MCI due to AD (Albert *et al.* 2011). Thirdly, data on duration of MC and on discrepancies between the informant and the patient regarding the report of MC was not available to us. Finally, our sample reflects a memory clinic population and the transfer to population-based cohort or volunteer samples may not be valid. Dropout analysis also revealed that the patients included in this study were three years younger on average compared to those excluded due to baseline missing data or lack of follow-up. However the two groups differed only slightly regarding baseline cognitive functioning and, more importantly, the groups did not differ in the expression of MC (73.1% MC+ in the study sample vs. 74.8% MC+ in those excluded from the analysis; $p = 0.661$). Thus, although a small selection bias was observed in our data, we consider the main results of our study not confounded by this bias.

In conclusion, the present study highlights a dynamic of the impact of MC as a predictor for incident AD dementia in MCI patients. The results may have implications for clinicians working with elderly patients at risk of AD dementia, but also for the design of early intervention trials in AD. MC should be taken seriously as a risk indicator for future AD dementia, especially in cases where neuropsychological test results are at the border between normal and impaired.

3.3 Study 3: SCD is related to CSF biomarkers of AD in MCI patients (Wolfsgruber *et al.* 2015)

3.3.1 Abstract

Objective

To test whether, in individuals with mild cognitive impairment (MCI), different measures of subjective cognitive decline (SCD) in the memory domain predict abnormal CSF biomarkers of Alzheimer's disease (AD).

Methods

We analyzed the multi-center baseline (cross-sectional) data of 245 MCI patients. SCD was measured quantitatively with the Subjective-Memory-Degradation-Scale (SMDS) and qualitatively by assessing particular concerns associated with self-experienced worsening of memory. Logistic regression models were used to examine associations between SCD and abnormal CSF biomarkers, taking into account objective memory impairment, depressive symptoms and education as covariates.

Results

Abnormal CSF-A β 42 and more depressive symptoms were associated with higher SMDS scores and with the report of memory concerns. Risk of abnormal CSF-A β 42 increased by an estimated 57% for a one standard deviation increase in SMDS scores and was doubled in patients who had SMDS scores > 4 or who reported memory concerns, respectively. In addition, both SCD measures predicted risk of having a biomarker signature indicative of prodromal AD defined as presence of low CSF-A β 42 together with either high CSF-Tau or CSF-pTau181 levels.

Conclusions

In MCI, specific aspects of SCD severity and quality are related to CSF biomarkers indicative of AD. This extends findings in pre-MCI samples and calls for an improved operational assessment of SCD in MCI. This might be useful for sample enrichment strategies for increased likelihood of AD pathology.

3.3.2 Introduction

The subjective report of cognitive decline is part of the mild cognitive impairment (MCI) diagnostic criteria (Winblad *et al.* 2004) and can be provided, unstandardized, either by the patient and/or by a close informant, or by a clinician familiar with the patient. However, *self-reported* subjective cognitive decline (SCD) is neither a mandatory criterion nor is there a standardized SCD assessment in current MCI criteria sets (Winblad *et al.* 2004; Petersen, 2004; Albert *et al.* 2011). It has been established that specific qualitative and quantitative neuropsychological deficits (e.g. marked episodic memory deficits) increase the likelihood of Alzheimer's disease (AD) in MCI (Albert *et al.* 2011; Wagner *et al.* 2012; Dubois *et al.* 2014).

It is yet unclear whether quantitative and qualitative features of self-reported SCD may also improve the prediction of underlying AD pathology in MCI patients, however, studies in the presumed preclinical stage of AD (Sperling *et al.* 2011) suggest that this may well be the case. These studies have associated various measures of SCD with increased likelihood of abnormality in biomarkers of AD pathology (Visser *et al.* 2009; Mosconi *et al.* 2008; Amariglio *et al.* 2012; Mielke *et al.* 2012; Saykin *et al.* 2006; Rami *et al.* 2014) including CSF biomarkers. Thus, SCD measures may serve as indicators of AD pathology in the stage of preclinical AD (Jessen *et al.* 2014a).

The present study examines whether this association of SCD with AD biomarkers extends into the stage of MCI. We tested whether different measures of SCD in the memory domain predict CSF biomarker abnormality indicative of AD. We took several factors into account which could affect this association: objective memory performance (because in advanced MCI awareness of own cognitive deficits may vanish; Roberts *et al.* 2009; Vogel *et al.* 2004; Snitz *et al.* 2008; Grambaite *et al.* 2013), depressive symptoms (because they may relate to SCD independent of AD pathology; Roberts *et al.* 2009; Reid & MacLulich, 2006) and education (as a cognitive reserve proxy; Stern, 2012).

3.3.3 Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by Institutional Review Boards of all participating study centers of the German Dementia Competence Network (DCN; Kornhuber *et al.* 2009). All patients provided written informed consent.

Participants

We analyzed data from a multi-center longitudinal observational study of the German DCN. Sample selection and assessment procedures of this study have been reported in detail previously (Kornhuber *et al.* 2009). Eight hundred and thirteen MCI patients were included at baseline of which 702 had complete clinical and neuropsychological data. For the present analyses we used cross-sectional baseline data from a subsample of 245 of these patients with available biomarker data.

We investigated missing data pattern by comparing the study sample with the group of patients excluded due to missing CSF, clinical, or neuropsychological data. The two groups did not differ regarding age, education, Mini-Mental State Examination (MMSE) score, gender or APOE4 status, suggesting that the assumption of a missing at random data pattern was not violated.

CSF measures

We collected CSF according to previously described standard operating procedures (Lewczuk *et al.* 2006) by lumbar puncture from the L3/L4 or L4/L5 intervertebral region, into polypropylene test tubes with intermediate storage at site (-80°C). Samples were then shipped to a central biobank without undergoing any thawing/re-freezing cycles. We measured CSF-A β 42, CSF-Tau and CSF-pTau181 (Innogenetics, Ghent, Belgium) with ELISA (Lewczuk *et al.* 2004) in an ISO 9001-certified laboratory under routine quality control regime (intra-assay coefficients of variation: 2.3–5.9%; inter-assay coefficients of variation: 9.8–13.7%). We performed all analyses in duplicate and used the mean of the two.

We defined abnormally low CSF-A β 42 (< 600 pg/ml), abnormally high CSF-Tau (> 300 pg/ml) and abnormally high CSF-pTau181 (> 60 pg/ml) based on our own, previously published cutoff values (Lewczuk *et al.* 2006; Lewczuk *et al.* 2004), as is currently best practice. We defined a biomarker signature indicative of AD pathology (hereafter: “CSF-AD signature”) as presence of low CSF-A β 42 together with either high CSF-Tau or CSF-pTau181 levels (Dubois *et al.* 2014).

Clinical, neuropsychological assessment

Standardized diagnostic procedures have been described previously (Kornhuber *et al.* 2009). Assessment included the German version of the neuropsychological assessment battery of the Consortium to Establish a Registry for Alzheimer's Disease

(CERAD; Morris *et al.* 1989), which contains the MMSE and is extended with the Trail-Making-Test (TMT) A and TMT-B (Reitan, 1958). Additional memory tests administered were the Wechsler-Memory-Scale Logical Memory II (WMS-LM-II; Wechsler, 1987) and the Free and Cued Selective Reminding Test (FCSRT; Buschke, 1984). We used the CERAD Word List Delayed Recall subtest (CERAD-DR), to quantify objective memory performance in our main analysis. This free delayed recall measure has good diagnostic accuracy for prevalent and incident AD dementia (Wolfsgruber *et al.* 2014a). We assessed depressive symptomatology with the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) consisting of 10 items scored from 0 to 6 based on a clinical interview. A score ≥ 13 suggests at least mild depression (Müller *et al.* 2003). We assessed instrumental activities of daily living (IADL) with the Bayer-Activities of Daily Living Scale (BADL; Hindmarch *et al.* 1998).

Definition of MCI

MCI diagnosis was made according to criteria proposed by Winblad *et al.* (2004): (1) subjective and/or informant report about cognitive decline (2) evidence of objective cognitive impairment (3) no or only minor IADL impairment (BADL score < 4), and (4) not demented. Criterion (2) was met if patients' test scores (cognitive domains in parentheses) fell more than 1SD below age- and education-adjusted norms on the WMS-LM-II (verbal memory) or on one or more of the following subtests of the CERAD battery: Word List Immediate Recall, Word List Delayed Recall (both verbal memory); Figure Copying (visuoconstruction); Verbal Fluency, Boston Naming Test (both language); Figure Recall (visual memory); TMT-A (processing speed); TMT-B (executive functions). We considered MCI patients with deficits in one of the verbal memory tests as amnesic MCI and those without deficits in verbal memory as non-amnesic MCI. We will further report on a subgroup of patients who met amnesic impairment at a more conservative cutoff ($< -1.5SD$ below norm) in at least one of the verbal memory tests.

SCD assessment

The quantitative and qualitative SCD assessment outlined below was not used for initial MCI diagnosis. Rather, the diagnosis of MCI required "evidence of cognitive decline measured either by self- and/or informant report in conjunction with deficits on objective cognitive tasks" according to the applied MCI criteria (Winblad *et al.* 2004).

Thus, the operational SCD assessment as outlined below extends beyond the general (self- or informant-based) SCD report required by the MCI criteria.

We assessed SCD quantitatively with the Subjective-Memory-Division-Scale (SMDS; Jorm *et al.* 1997) which contains four questions related to self-experienced, increasing difficulties in everyday memory (e.g. “Do you have more trouble remembering things that have happened recently?”; “Are you worse at remembering where belongings are kept?”). Responses to each question were rated as follows: 0, “no, not more difficult than in the past”; 1, “Yes, a bit worse than in the past” 2, “yes, much more difficult than in the past”. We summed item ratings to obtain a score from 0 to 8.

In addition, we assessed particular concerns regarding self-experienced memory decline. This qualitative aspect of SCD might be associated with higher risk to develop AD dementia compared to report of self-experienced memory decline without concerns (Jessen *et al.* 2014b). We classified subjects as “MCI with memory concerns” (MC+) or “MCI without memory concerns” (MC-) according to their response to the following standardized question: “Do you feel like your memory has become worse”. Possible answers were: 1, “No”; 2, “Sometimes, but this does not worry me”; 3, “Yes, that worries me”; 4, “Yes, that worries me seriously”. We classified patients who did not specifically endorse memory concerns (response category 1 and 2) as MC- and those in categories 3 and 4 as MC+.

Statistical analysis

Descriptive statistics of the sample

Statistical analyses were conducted with SPSS-Version-20. As part of descriptive sample statistics we examined relationships between CSF measures, objective memory performance, depressive symptoms and both SCD measures. We conducted Pearson correlations for quantitatively measured SCD (SMDS scale), while performing independent sample t-tests and Chi² tests for the categorical memory concerns measure (MC+ vs. MC- group).

Prediction of abnormal CSF biomarkers: Main analysis

We conducted a series of stepwise logistic regression analyses with abnormality in CSF-A β 42 and CSF-AD signature (Dubois *et al.* 2014) as dependent variables in separate models. We performed separate analyses for both SCD measures. In step 1, we

entered one of the SCD measures as a single predictor. In step 2 we then adjusted for covariates, by adding the terms age, gender, education, memory performance (CERAD-DR score), MADRS depression score, and dropped insignificant terms from the model.

Prediction of abnormal CSF biomarkers: Additional analyses

After this main analysis, we conducted a series of additional analyses. Firstly, we added both the SMDS scale and the predictor “memory concerns” together in a single model in step 1 of the modeling process to check for additional effects of both SCD measures. Secondly, we included APOE4 status as an additional predictor (n = 26 cases with missing APOE4 data). Thirdly, we repeated the main analysis but substituted the CERAD-DR with the Total Recall score of the FCSRT, which we previously found to be most closely related with AD biomarkers (Wagner *et al.* 2012). Fourthly, we extended the main analysis by adding an interaction term of CERAD-DR and either SCD measure in a separate analysis. With this analysis we tested whether the predictive power of the SCD measures might decrease with increasing memory impairment as reported recently for incident AD dementia as an outcome (Wolfsgruber *et al.* 2014b). As an alternative approach to the interaction analysis, we repeated the main analysis but restricted the sample to patients with more pronounced amnesic impairment at the < -1.5SD cutoff. Lastly, we modeled an interaction effect between SCD measures and education to check for a moderating effect of education (as a proxy for cognitive reserve) on the relationship between SCD measures and abnormal CSF biomarkers.

3.3.4 Results

Descriptive statistics of the sample

Table 11 contains descriptive statistics of the whole sample, the number of patients classified as “MCI without memory concerns” (MC-) vs. those classified as “MCI with memory concerns” (MC+), and results of group comparison of these subgroups. MC+ patients showed higher MMSE, CERAD total score (Chandler *et al.* 2005), MADRS and SMDS mean values. Individuals with higher SMDS scores showed more depressive symptomatology and lower CSF-A β 42 values while SMDS was uncorrelated to objective memory performance, CSF-Tau and CSF-pTau181 levels (*Table 12*).

Prediction of abnormal CSF biomarkers: Main analysis

Both measures of SCD were significant predictors of abnormal CSF-A β 42 and of a CSF-AD signature according to IWG2 criteria when treated in separate models (*Table 13*). Lower memory performance also predicted abnormal CSF biomarkers and was the strongest predictor for abnormal CSF in terms of p-value and relative contribution to the R² of the covariate adjusted models. In addition, more years of education were slightly associated with higher likelihood of abnormal CSF biomarkers. The likelihood of abnormal CSF biomarkers was increased by 57% (CSF-A β 42) to 73% (CSF-AD signature) for patients scoring 1SD above the sample mean in SMDS scores. Risk of abnormal CSF-A β 42 or CSF-AD signature was about two times higher in patients who reported memory concerns.

Prediction of abnormal CSF biomarkers: Additional analyses (not shown in *Table 13*).

When both measures of SCD were added simultaneously, only the SMDS remained a significant predictor of abnormal CSF-A β 42 and of a CSF-AD signature together with objective memory performance and education.

Inclusion of APOE4 status or substitution of the CERAD-DR with a measure of cued recall (FCSRT Total Recall score) did not alter the results reported above. SCD measures remained significant predictors with similar ORs. As expected, APOE4 carriers had higher risk of abnormal CSF-A β 42 (OR = 2.34, 95%CI: 1.28-4.29) and CSF-AD signature (OR = 3.05, 95%CI: 1.57-5.91). There was no interaction of APOE4 and SCD measures.

There were no significant interaction effects between CERAD-DR and SCD measures. SCD measures remained significant predictors with similar ORs when only the subgroup of patients with amnesic impairment at the < -1.5SD cutoff was analyzed. The same was true when an even more conservative amnesic MCI subsample with impairment at the < -1.5SD cutoff in at least two of the three verbal memory tests was selected (n = 116, 47.3% of the sample, prevalence of CSF-AD signature = 42.2%).

Lastly, there was no moderating effect of education on the association between SCD measures and abnormal CSF biomarkers.

Table 11. Study 3: Sample description of demographical, clinical and biomarker data.

	Total Sample (n = 245)		MCI without memory concerns (MC-, n = 53, 21.6%)		MCI with memory concerns (MC+, n = 192, 78.4%)		Group comparison		
	M	(SD)	M	(SD)	M	(SD)	MC- vs. MC+		
							Cohen's d	T-value	p
Age (years)	66.8	8.32	68.3	9.20	66.3	8.03	0.24	1.52	0.130
Education (years)	12.4	3.00	12.4	3.31	12.5	2.92	-0.01	-0.08	0.935
MMSE-Score	27.4	1.73	27.0	1.52	27.5	1.78	-0.29	-2.05	0.043
CERAD Delayed Recall	4.9	2.26	4.4	2.27	5.03	2.25	-0.27	-1.71	0.089
CERAD Total Score	70.8	11.2	68.1	10.9	71.5	11.2	-0.31	-1.99	0.048
MADRAS	8.30	6.37	6.57	4.92	8.77	6.64	-0.35	-2.25	0.025
SMDS-Score	4.29	2.29	2.47	2.05	4.80	2.09	-1.12	-7.20	< 0.001
B-ADL-Score	2.51	1.48	2.69	1.71	2.46	1.41	0.16	0.98	0.330
CSF Aβ42 (pg/ml)	777	338	840	329	759	340	0.24	1.54	0.125
CSF Tau (pg/ml)	420	257	428	234	418	263	0.04	0.23	0.814
CSF pTau181 (pg/ml)	62.5	30.0	62.7	30.0	62.4	30.1	0.01	0.24	0.954
	n	%	n	%	n	%		Chi²	p
Female Gender	100	40.8	18	34.0	82	42.7		1.32	0.251
APOE4+ (n = 26 missing)	89	36.3	22	41.5	67	34.9		0.94	0.331
MADRAS >= 13	54	22.0	7	13.2	47	24.5		3.02	0.080
Amnestic MCI (< -1.0SD cutoff)	217	88.6	48	90.6	169	88.0		0.26	0.606
Non amnestic MCI	28	11.4	5	9.4	23	12.0			
Amnestic MCI (< -1.5 SD cutoff)	188	76.7	44	83.0	144	75.0		1.5	0.221
Low CSF Aβ42 (< 600pg/ml)	91	37.1	13	24.5	78	40.6		4.61	0.032
High CSF Tau (> 300pg/ml)	148	60.4	36	67.9	112	58.3		1.60	0.206
High CSF pTau181 (> 60pg/ml)	105	42.9	22	41.5	83	43.2		0.05	0.823
CSF-AD signature*	71	29.0	11	20.8	60	31.3		2.22	0.136

Note: *CSF-AD signature (biomarker signature indicative of AD pathology) defined as presence of low CSF-Aβ42 together with either high CSF-Tau or CSF-pTau181 levels (Dubois *et al.* 2014). Group comparison statistics are derived from independent sample t-tests (2-sided p-value). Definition of amnestic and non-amnestic MCI is given in the method section. M, Mean; B-ADL, Bayer Activities of Daily Living Scale; CERAD, Consortium to Establish a Registry for Alzheimer's Disease neuropsychological assessment battery; MADRS, Montgomery Asberg Depression Rating Scale; MC-, "MCI without memory concerns"; MC+, "MCI with memory concerns". SMDS, Subjective-Memory-Decline-Scale.

Table 12. Correlation-Matrix of predictor variables for the whole study sample.

	SMDS	Age	Education (years)	MADRS score	CERAD-DR	CSF-Aβ42	CSF-Tau
Age	.044						
Education (years)	-.108	-.017					
MADRS score	.228**	-.172**	-.117				
CERAD-DR	-.012	-.438**	.087	.062			
CSF-Aβ42	-.209**	-.212**	-.047	.126*	.258**		
CSF-Tau	.091	.320**	-.005	-.066	-.307**	-.375**	
CSF-pTau181	.080	.299**	.022	-.050	-.305**	-.310**	.880**

Note: * ≤ 0.05 ** ≤ 0.01 2-sided p-value. CERAD-DR, Delayed recall task of the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological assessment battery; MADRS, Montgomery Asberg Depression Rating Scale; SMDS, Subjective Memory Decline Scale.

Table 13. Prediction of abnormal CSF biomarkers in MCI patients by measures of objective memory performance and SCD.

	Abnormal CSF-Abeta42 (< 600pg/ml)			AD typical CSF signature*		
	OR (95% C.I.)	p-value	R ² †	OR (95% C.I.)	p-value	R ²
Model 1: with SMDS scale as a predictor						
Unadjusted model			.045			.059
SMDS scale (per one standard deviation increase)	1.47 (1.12 - 1.93)	0.006		1.61 (1.19 - 2.14)	0.002	
Covariate adjusted model			.168			.221
SMDS scale (per one standard deviation increase)	1.57 (1.17 - 2.10)	0.002	.045	1.73 (1.26 - 2.37)	0.001	.059
CERAD-DR (per one standard deviation decrease)	1.92 (1.43 - 2.60)	< 0.001	.098	2.36 (1.66 - 3.28)	< 0.001	.143
Education (1 year increase)	1.11 (1.01 - 1.22)	0.027	.025	1.10 (.998 - 1.22)	0.056	.019
Model 2: with Presence of memory concerns as a predictor						
Unadjusted model			.026			.028
Presence of memory concerns	2.08 (1.05 - 4.16)	0.037		1.79 (.861 - 3.72)	0.119	
Covariate adjusted model			.157			.185
Presence of memory concerns	2.69 (1.29 - 5.63)	0.009	.026	2.42 (1.10 - 5.37)	0.028	.028
CERAD-DR (per one standard deviation decrease)	2.00 (1.48 - 2.72)	< 0.001	.113	2.38 (1.69 - 3.33)	< 0.001	.145
Education (1 year increase)	1.09 (.997 - 1.20)	0.058	.018	1.08 (.980 - 1.19)	0.118	.012

Note: SMDS and CERAD-DR raw scores were rescaled as z-scores on the basis of mean and SD of the whole sample. Thus, the odds ratios for these predictors correspond to one SD increase (SMDS) or decrease (CERAD-DR) in the z-score. * defined as low CSF-Abeta42 together with either high CSF-Tau or high CSF-pTau181 (see Dubois *et al.* 2014 and method section), † numbers in bold are R² values for the whole model, values in the predictor lines are each predictor's relative contribution of R² to the R² of the whole model, C.I., Confidence Interval; CERAD-DR, delayed recall task of the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological assessment battery; OR, Odds Ratio; SMDS, Subjective-Memory-Decline-Scale.

3.3.5 Discussion

In patients with MCI, we found that quantitative and qualitative aspects of SCD significantly predicted abnormal CSF-A β 42 levels, as well as a CSF biomarker signature indicative of prodromal AD (Dubois *et al.* 2014), in addition to the prediction possible with objective memory performance. This complements other findings which related subjective memory decline in MCI patients to increased risk of incident AD dementia (Wolfsgruber *et al.* 2014b) and future cognitive decline (Crowe *et al.* 2006).

Memory performance was not consistently related to measures of SCD, in line with previous findings (Snitz *et al.* 2008; Reid & MacLulich, 2006). While there was no correlation of memory performance with SMDS scores, we found that patients who did not report memory concerns (MC- group) performed worse on cognitive measures than those who reported concerns. This counter-intuitive observation is in line with the hypothesized link between lower memory performance, reduced awareness and lower probability of self-reported SCD in the MCI stage (Vogel *et al.* 2004; Snitz *et al.* 2008; Grambaite *et al.* 2013; Wolfsgruber *et al.* 2014b). Reduced insight in more severely impaired MCI patients might limit the significance of SCD as a predictor of underlying AD pathology. In the present study we found no evidence that SCD was less predictive for AD biomarkers in those patients with more severe memory impairment. However, this could be due to limited statistical power as we previously found, in a larger sample of the DCN MCI cohort, that the predictive power of SCD for incident AD dementia decreased with decreasing memory performance (Wolfsgruber *et al.* 2014b).

We observed a small effect of higher education being associated with higher risk of CSF pathology. This might reflect that patients with higher education can tolerate more AD pathology due to higher cognitive reserve (Stern, 2012; Dumurgier *et al.* 2010). We did, however, not observe a moderating effect of education on the relationship between SCD measures and abnormal CSF biomarkers.

The prevalence of abnormal CSF-A β 42 and CSF-AD signature in our sample seems lower than in other MCI samples (Visser *et al.* 2009), however, it was higher than in cognitively normal individuals with SCD (van Harten *et al.* 2013b). Differences in cutoffs for biomarker abnormality and algorithms to define a CSF-AD signature are likely sources of prevalence variability across samples. The lower prevalence in our sample might also originate from inclusion of non-amnesic MCI and from setting the

cognitive impairment cutoff at 1SD below the normative mean. The present sample, thus, contains a broad spectrum of (early and late) memory clinic MCI patients which is important both in terms of external validity and as a comparison to other well established MCI samples, such as the ADNI sample, which included early (amnestic) MCI patients characterized by very mild memory impairment (Aisen *et al.* 2010).

This study has limitations. We did not explicitly measure cognitive reserve (although education is a reasonable proxy; Stern, 2012) and a direct measure of awareness was unavailable to us. We had to focus on subjective decline in the memory domain due to lack of questionnaire data measuring subjective decline in other cognitive domains. Executive dysfunctions also evolve early in the process of AD and are predictive of future AD dementia (Dickerson *et al.* 2007). SCD regarding executive functioning therefore might also be related to amyloid pathology in MCI, as has been found in cognitively normal elderly (Amariglio *et al.* 2012). Finally, while our multi-center sample reflects a large memory clinic population, the results might not be generalizable to population-based cohorts or volunteer samples.

We here demonstrated that SCD is related to AD biomarkers in MCI, thereby extending findings in pre-MCI samples (Amariglio *et al.* 2012; Mielke *et al.* 2012). At the pre-MCI stage, SCD might reflect A β induced subtle impairment that is partly compensable and hardly detectable on standard tests (Amariglio *et al.* 2012). However, this does not imply a reduced significance of SCD at the MCI stage, where the emergence of objectively measurable cognitive deficits offers additional predictive value. In fact, effect sizes of the association between SCD and amyloid pathology were very similar in our MCI sample as compared to those reported in a pre-MCI sample (Mielke *et al.* 2012). This suggests that SCD remains an equally strong predictor of AD pathology in the MCI stage irrespective of the increasing predictive validity of objective memory performance from pre-MCI to MCI samples.

In sum, our results show that specific aspects of SCD severity and quality are related to CSF biomarkers indicative of AD pathology in MCI. This calls for a refined and improved SCD assessment to complement the broad clinical SCD criterion in current MCI definitions. This might eventually contribute to improved prediction of AD and could also be useful for enrichment of MCI samples regarding underlying AD pathology. Steps towards improved SCD assessment have recently been taken in the

context of preclinical AD (Jessen *et al.* 2014a) including research on qualitative features of SCD (Buckley *et al.* 2014a). Our results suggest that further research on refinement and validation of SCD in preclinical AD might also improve the assessment of SCD in the MCI stage. This is especially true as the border between the late preclinical AD stage, where individuals might experience SCD (Sperling *et al.* 2011), and the early MCI stage of AD, as regards neuropsychology, depends on how the threshold of cognitive impairment is defined. Thus, as the field strives to better identify and ultimately treat individuals at the earliest clinical stages of AD, we believe that research aimed at improving the understanding and assessment of AD-related SCD can make significant contributions. Our findings suggest that self-reported subjective memory decline and associated concerns are important features to consider for SCD assessment.

4 General Discussion

In the course of normal aging processes, development of cognitive performance in most domains, including memory, follows a descending trajectory already beginning from middle age (Schaefer & Bäckman, 2007). Thus, it is not surprising that reports of SCD are quite common in the elderly general population. SCD can be defined as an individual's perception of worsening cognitive function compared to his/her earlier performance level (Jessen *et al.* 2014a). Depending on assessment methods and sample characteristics, the prevalence of SCD in elderly people of 65 years and older is about 25-50%, increases with age, and may reach values over 80% in persons aged 80 years and older (Stewart, 2012). Considering these numbers, subjective reports on cognitive decline in the elderly may often represent the subjective notions of declining cognitive performance due to normal aging processes.

However, SCD can also be associated with significant concerns about cognitive functioning in daily life and is then often the reason for consulting a general practitioner or a specialized memory clinic for diagnostic evaluation of possible causes for the subjectively experienced symptoms. The perceived cognitive deterioration may also be corroborated by family members and physicians and/or the concurrent performance on objective neuropsychological tests is below what would be expected according to the individual's age, gender and level of education. In the latter case, a diagnosis of mild cognitive impairment (MCI) is justified, provided that daily function and independence is still largely preserved, i.e. a dementia diagnosis can initially be ruled out (Winblad *et al.* 2004).

MCI, especially with amnesic deficits, is considered a well-established risk stage for AD dementia (Petersen, 2004). Recent research criteria for AD include the MCI spectrum and speak of "MCI due to AD" or "prodromal AD" if, in addition to the clinical phenotype of MCI, biochemical or imaging diagnostics are positive for AD pathology. SCD is part of the MCI criteria to further characterize the clinical phenotype of cognitive deficits. As there is usually only one measurement point at the time of diagnosis, SCD provides information about a previous deterioration of cognitive performance, i.e. presence of SCD supports that the cross-sectionally measured cognitive deficit is the result of a decline from higher performance (instead of being a life-long existing deficit). Within the MCI criteria this information can be obtained

either from the patient and/or from a close informant or a clinician familiar with the patient. The usefulness of the criterion of (self-reported) SCD has been questioned in the literature (Edmonds *et al.* 2014), not least because symptoms of *reduced insight* into cognitive deficits, a typical characteristic of the dementia stage of AD, can already occur in more progressed stages of MCI (Galeone *et al.* 2011) and will then reduce the reliability and validity of self-reported SCD (Roberts *et al.* 2009). Furthermore, the lack of operationalization of this criterion has been criticized (Abdulrab & Heun, 2008) and there are currently no common standards for the assessment of SCD. It therefore remains to be determined to what extent the phenomenon of SCD is adequately captured by today's approaches and whether its full potential in terms of diagnosis and prognosis in the context of AD is utilized.

Research on SCD has gained new impetus in recent years in the field of early diagnosis of AD. Since many pharmacological intervention studies for the prevention of AD in the MCI stage showed no significant effects, the scientific field now endeavors to detect incipient AD before the MCI stage (Sperling *et al.* 2011). Several large studies have shown that people with SCD but objective cognitive performance in the normal range, have significantly increased risk of incident AD dementia and biomarker abnormality indicative of AD (Jessen *et al.* 2014a). SCD could therefore be considered as a very early symptom of incipient AD and offer a starting point for risk enrichment of samples or as a dependent measure over time for intervention studies and naturalistic observational studies. Because of these recent findings, SCD has been taken into account as an early clinical symptom in the research criteria of the final stages of preclinical AD (Sperling *et al.* 2011). This last phase of preclinical AD marks the transition from the preclinical phase to the early clinical phase of MCI. However, also for this transitional stage, the optimal characterization and measurement methods of SCD are still insufficiently determined.

This thesis presented three empirical studies that addressed aspects of characterization and measurement of SCD in individuals with objectively normal cognitive function and MCI patients. These studies were conceptually based on a current working model for the temporal development of SCD in the course of AD (Jessen *et al.* 2014a). This model assumes that the predictive power of SCD is most valuable at the late preclinical stage of AD when SCD is not influenced by reduced insight as a confounding factor and, at the same time, the validity of detecting *objective*

cognitive impairment is low due to limited sensitivity of standard cognitive tests. However, as AD progresses, the validity of SCD might decrease due to involvement of reduced symptom insight which itself is related to progression of objective cognitive impairment. At the same time the validity to detect objective cognitive impairment increases with progression into the MCI stage and is high at more advanced MCI stages.

In the remainder of this section, a brief summary of the results of the three studies is given and their contributions to the field of AD research are discussed (section 4.1). In section 4.2, further thoughts regarding limitations, implications and directions for future research on AD-related SCD are outlined.

4.1 Contributions of the presented studies to the field of AD research

The present studies have made a number of contributions to the field of AD-related SCD research. Study 1 has highlighted the fact that cognitively unimpaired elderly General Practice patients, a sample highly relevant to the health care sector, who report SCD with associated concerns (SCD+C) are of a 2.5-fold increased risk to develop AD dementia over a period of 6 years compared to individuals with normal cognition and without SCD. Study 1, thus, suggests that SCD in the memory domain might be useful as a predictor of incident AD dementia, even in the absence of overt neuropsychological testing deficits. This finding confirmed earlier findings of the AgeCoDe study with shorter follow-up time (Jessen *et al.* 2010) and is in line with recent findings from other epidemiologic studies investigating SCD as a risk factor for dementia (Mitchell *et al.* 2014).

Beyond these confirmatory results, study 1 suggested that the qualitative feature of *concerns/worries* about the self-perceived memory decline might be of specific predictive value as the risk in the SCD+C group was also significantly increased compared to those individuals with SCD but without associated concerns. Study 1, thus, provided strong evidence for the recent inclusion of concerns regarding experienced cognitive decline, especially in the memory domain, as one of several features that may increase the likelihood of underlying AD in subjects with SCD (Jessen *et al.* 2014a). As an open question for future research it remains to be determined *why* the appraisal of self-experienced cognitive decline as worrying is associated with such an elevated risk of AD dementia compared to SCD without concerns. The results suggest that AD-related memory decline is experienced in a different quality (i.e. as more serious and

therefore worrying) compared to memory decline related to other factors such as normal aging. Following this idea, further research should try to determine what specific qualitative aspects of the self-experienced cognitive decline (and what other factors) may determine the emergence of patients' concerns. Research in this regard will contribute to better operationalization and measurement of AD-related SCD.

Importantly, in study 1 the AD dementia risk in individuals with SCD+C was not substantially different from those individuals whose memory performance fell in the range of early amnesic MCI (risk of AD dementia in this group was also about 2.5-fold increased compared to the cognitively normal control group). It, thus, seems that the transition of pre-MCI SCD to early MCI is fluent and the definition of a strict border between these two stages is arbitrary. This clearly highlights the problems associated with neuropsychological cutoffs to define, and differentiate from one another, the presumed late preclinical stage of AD (clinically manifesting as "only SCD") and the early MCI stage.

Study 2 focused on the interplay between objective and subjective cognitive decline with regard to risk of AD dementia in a large memory clinic sample and was the first study to directly test a prediction hypothesis derived from the recently proposed working model of the temporal evolution of SCD in the course of AD (Jessen *et al.* 2014a). From a statistical point of view, the assumptions on the interplay between objective memory performance and SCD outlined above can be modeled by a moderating effect of objective memory performance on the relationship between SCD and incident AD dementia: The predictive value of SCD for incident AD dementia should be highest at subtle memory impairment and should decrease as memory impairment progresses. Results of study 2 showed a significant main effect of SCD+C on incident AD dementia. Across the whole sample MCI patients with memory concerns were of 2.5-fold increased risk to convert to AD dementia compared to those MCI patients without concerns about their experienced memory decline. The hypothesized relationship between objective and subjective cognitive decline with regard to risk of AD dementia could also be demonstrated by a significant moderating effect as proposed above. This finding has also relevance for the widely received dynamic biomarker model for the development of AD (Jack *et al.* 2013). In this model, biomarkers of AD pathology as well as cognitive and functional performance are modeled as sigmoid-shaped, ascending curves of pathology/impairment. However, the

development of AD-related SCD seems to markedly differ from these trajectories. The SCD trajectory may rather divert from the trajectory of objective impairment in the stage of late MCI/early AD dementia and may be better modeled as an inverse U-shaped function. Thus, the association of SCD with biomarkers and cognitive/functional status is variable throughout the course of AD. Since SCD is gaining even further interest in the scientific field of AD, a revised biomarker model of AD should incorporate the aforementioned diverging trajectory of SCD and support this hypothesized trajectory with empirical, longitudinal data on *intra*-individual changes in SCD.

Study 3 demonstrated that, in a memory clinic sample, specific aspects of SCD quantity and quality were predictive of a CSF profile indicating AD pathology, i.e. presence of “prodromal AD” according to the IWG2 (Dubois *et al.* 2014) and NIA-AA (Albert *et al.* 2011) criteria. Risk of a prodromal AD CSF profile increased by 73% for a one standard deviation increase in scores on a quantitative SCD scale and was approximately doubled in those MCI patients that reported memory concerns, respectively. These results, thus, highlighted, together with the longitudinal findings of study 2, the usefulness of SCD operationalizations that extend beyond the broad clinical SCD criterion as part of the general MCI diagnostic procedures. This argues for a refined SCD assessment in MCI and might again be especially important in the early stage of MCI.

In practice, clinicians are indeed often confronted with cases that fall on the border between normal test performance and early mild cognitive impairment. The DCN memory clinic cohort, initially drawn from patients that actively sought evaluation at one of the DCN memory clinics, contains a substantial number of such mildly impaired patients. Therefore, not only has the DCN MCI sample a high external validity. It follows from this that the diagnostic entity of SCD without clearly determinable cognitive impairment is highly relevant for memory clinic routine practice. While such patients have long been considered “the worried well” or those with depression related complaints, the recent literature provides growing evidence that this clinical entity of pre-MCI SCD should be taken seriously and better characterized in future studies (Jessen *et al.* 2014a).

This, however, also implies that the definition of *objective impairment at the MCI level*, which will serve as an exclusion criterion for studies on pre-MCI SCD,

needs to be sharpened as well as harmonized across those studies. It can be argued here that, for the purpose of distinguishing a group of individuals with pre-MCI SCD from those with MCI, a more robust neuropsychological MCI definition, compared to that applied in studies such as the DCN cohort should be chosen (Edmonds *et al.* 2014; Bondi *et al.* 2014). Recently proposed neuropsychological MCI criteria which balance reliability (i.e. stability of the MCI diagnosis across time) and sensitivity to incipient AD (Jak *et al.* 2009; Bondi *et al.* 2014) could be used to define such a robust MCI group from which a pre-MCI SCD group could then be distinguished by not meeting these neuropsychological MCI criteria.

Following the logic from the working model outlined above, in such a pre-MCI SCD patient group, measures of SCD should be predictive of incident AD dementia and of biomarker abnormality indicative of AD while associations between memory performance and these outcomes should be weak or even absent. Indeed, application of the proposed neuropsychological MCI criteria of Jak and colleagues (2009) to the DCN MCI sample leads to 39% patients not meeting these more robust criteria, i.e. they would be classified as pre-MCI SCD. In these patients, short term rate of conversion to incident AD dementia, within the average 28 months follow-up interval of the DCN study, is low in (only 4%). However, a substantial number (30%) of these patients have a CSF profile indicative of AD suggesting that, given a longer follow-up, a high number of these will eventually develop robust MCI or AD dementia. In addition, as proposed above, presence of an AD biomarker signature in these patients is predicted by SCD measures while both neuropsychological measures and informant reports are not predictive (unpublished data).

An implication of these results is that new studies with longer follow-up intervals and a more extensive SCD assessment are needed to contribute further to the characterization of the pre-MCI SCD stage. In these new prospective studies it could then be examined whether more precise SCD operationalizations together with innovative objective tests (Rentz *et al.* 2013) can help to detect those individuals among the pre-MCI SCD patient group who have truly underlying AD pathology and will later convert to AD dementia. Such studies have only recently been set up (e.g. DELCODE or the ADNI-2 cohort), so there is only limited data today.

4.2 Limitations of today's SCD studies and future directions

Over the course of the present work it became clear that the nature of SCD is extremely complex, both in regard to its phenomenology, its determinants, its evolution over time and finally the subsequent outcomes it is associated with. The empirical studies here, thus, only focused on small aspects of the whole SCD picture.

One limitation of all studies is that, while study 1 and 2 deal with longitudinal data on the level of outcome (incident AD dementia), the symptom of SCD itself was always measured on a single time point. In general, there is still a lack of empirical data on the longitudinal evolution of SCD over the course of AD. It needs to be acknowledged that the hypothesized temporal evolution of SCD in the working model outlined above is based on inference from cross-sectional data across studies of individuals situated at different time points along the AD continuum (stages of pre-MCI, MCI, AD dementia). In addition, these studies have rarely employed the same measures of SCD. Hypotheses can be derived and empirically tested from the proposed working model based on cross-sectional SCD measurement, as was done in study 2 and 3 of this work. However, a more refined understanding of the development of SCD in relation to objective cognitive decline (and biomarkers of AD) will certainly require large longitudinal data on *intra*-individual change in self- and informant reported SCD¹², objective cognitive performance, and biomarkers. A long follow-up time frame is needed to monitor the trajectories of these AD-related variables from the earliest symptoms to overt dementia. As a consequence, such data is both difficult and expensive to collect. Further, to effectively monitor SCD longitudinally, reliable and change-sensitive SCD scales are needed. However, the existing scales have not been thoroughly evaluated in this regard. It should also be mentioned that even the assessment of change in *objective* cognitive performance at the earliest AD stages is, at the current state of knowledge, not optimal and therefore subject to extensive research (e.g. Ayutyanont *et al.* 2014). It would, thus, be helpful to connect the research on longitudinal assessment at both levels (subjective and objective) of cognition.

¹² The degree of discrepancy between both sources of information might serve as a measure of over- or underestimation of SCD by the patient relative to his/her informant. An underestimation could be interpreted as a sign of a patient's reduced insight into his/her own cognitive deficits (Edmonds *et al.* 2014).

Good news is that, from a statistical point of view, powerful techniques for the analysis of complex longitudinal data have recently been developed, are continuously advanced and have been made more accessible to applied researchers (Duncan *et al.* 2013). These structural equation modeling techniques for longitudinal data are commonly referred to as Growth Curve Modeling (GCM) or Latent Growth Curve Modeling (LGCM; Duncan *et al.* 2013). They allow to model longitudinal trajectories of phenomena on the basis of single test scores (GCM) or latent constructs (LGCM). Furthermore, it is possible to model trajectories of different constructs simultaneously and test hypotheses on the relationship between those trajectories. Such models, commonly referred to as “Parallel Process GCM”, could be used to simultaneously study the trajectories of the above named, AD-related variables. It is further possible to incorporate categorical outcomes (“sequelae of change”; Duncan *et al.* 2013) in these modeling approaches and to adjust them to non-ignorable, “not at random” missing data patterns that are often present in longitudinal studies on neurodegenerative diseases (Gottfredson *et al.* 2014).

With regard to the aim of optimized SCD assessment, future research will also have to focus on a better phenomenological characterization of, and distinction between, AD-related vs. non-AD-related SCD. One can assume that there will be overlap between both types of SCD but also distinctive features pertaining more to one or the other. There are generally two possible approaches to this goal, a quantitative and a qualitative approach. Optimally, both should inform each other (Buckley *et al.* 2014a; Buckley *et al.* 2014b).

The quantitative approach may employ advanced statistical and psychometric methods, such as item response theory (IRT) and co-calibration techniques, with the aim to identify those SCD items most closely related to AD and to make currently available SCD measures more comparable (see Crane *et al.* 2008 for an analogous IRT example with *objective* cognitive test data). Such techniques can rely on existing data sets that can be merged together for a simultaneous psychometric analysis. Latent Class Analysis (LCA) could be used as an alternative quantitative approach to a better characterization of SCD. LCA is a structural equation modeling technique that can be used to find distinct classes of individuals based on a set of multivariate variables. In the field of AD, LCA has been used for empirically driven subtyping of samples of individuals with dementia (Libon *et al.* 2014) and AD dementia (Davidson *et al.* 2010)

according to their neuropsychological test performance, or presence of neuropsychiatric symptoms (Lyketsos *et al.* 2001). The same approach has also been applied to non-demented memory clinic patients at risk for incident dementia. Köhler and colleagues (Köhler *et al.* 2013) submitted the neuropsychological data of a large memory clinic sample to LCA and extracted distinct neuropsychological profiles that were differentially associated with clinical progression to dementia. Similar to its application to neuropsychological test score data, LCA could also be applied to rich SCD questionnaire data, e.g. in a sample of patients with SCD and normal cognition. It could, thus, be used to find possible subtypes within the heterogeneous phenotypic presentation of individuals with SCD. Linked with association analyses on multiple levels (e.g. depressive symptoms, biomarkers, risk factors, clinical progression) it might be possible to further describe the characteristics of potential SCD subtypes and test whether certain types might be more closely associated than others with AD-related risk factors and outcomes such as ApoE4 genotype, abnormal biomarkers and subsequent decline/clinical progression to MCI and dementia. It would then be of further interest which SCD items best characterize these subtypes.

Besides those quantitative approaches mentioned above, there are also efforts to employ qualitative research strategies for the refinement of the SCD concept (Buckley *et al.* 2014a). The main idea behind the qualitative research approach is that the experience of the working mind is inherently subjective and of a high phenomenological complexity. An entirely quantitative approach to characterize such experiences of mental function will, thus, inevitably result in loss of useful information. In other words: "not everything that counts can be counted" (Cameron, 1963). Qualitative research could help to characterize different phenomenological profiles of SCD that relate to different conditions underlying the subjective experience of cognitive decline. This idea is similar to LCA, however, the type of data is different. LCA requires numerical data of preferably interval or ordinal scale type (i.e, questionnaire data in case of SCD). This kind of data has already been reduced in its informative value due to the act of quantification of a subjective experience into numerical values representing the item responses of the questionnaire. In contrast, qualitative research will deal with less reduced data in form of directly communicated experiences of the individual under study. The idea now is that, although the subjective experience of cognitive decline and its communication is certainly subject to variable factors (such as

personality traits or intercultural differences), there will likely be an overlap of phenomenological experience (a “phenomenological profile”) that may be more closely related to a condition such as AD than to other conditions, e.g. depressive symptoms.

Phenomenological profiling is in fact well established in clinical psychiatry, e.g. in differential diagnosis of different psychiatric disorders. For example a patient with obsessive compulsive disorder and a schizophrenic patient may both experience recurring, intrusive and obsessive thoughts which are experienced as uncontrollable (American Psychiatric Association, 2013). Both patients might further engage in compulsive behavior. Patients with obsessive compulsive disorder generally recognize there obsessive thoughts and compulsive behavior as their own and judge them as irrational. However, a schizophrenic patient might experience the intrusive thoughts as not of his own but rather to be induced by some external power (e.g. by way of “brain manipulation” in paranoid psychosis). In this example, a *qualitative* difference in the experience of the source of origin of the intrusive thoughts distinguishes different psychiatric phenotypes. In principle, this qualitative information could be obtained via questionnaire. However, this is only possible due to the established knowledge about qualitative similarities and differences (i.e. a phenomenological profile) of both disorders that has been gathered by clinicians by observation of and communication with patients, i.e. a qualitative research approach was the starting point.

With regard to SCD assessment, development of most items and questionnaires was based on expert panels or clinical experience. A formal phase of qualitative data collection, although recommended as best practice, has usually not been conducted (Eckerström *et al.* 2013). A notable exception constitutes the development of the Sahlgrenska Academy Self-reported Cognitive Impairment Questionnaire (SASCI-Q; Eckerström *et al.* 2013) which had a qualitative open format interview phase with MCI patients, their relatives as well as a third group of surviving cancer patients as a starting point for item generation. The initial open format interview was centered on questions about various functional difficulties experienced in participants’ everyday lives. Importantly, the authors took care that questions were “not limited to the interviewees’ personal understandings of cognition or memory”. Rather, they were “deliberately designed to address everyday activities and behaviors instead of referring to specific cognitive domains” (Eckerström *et al.* 2013). The first interview phase was then followed by transcription of the interview material and a content analysis with focus on

identifying those everyday difficulties that could be related to cognition. These interview aspects were then categorized into meaningful concepts (e.g. “forgetfulness”), rephrased into questions with selection of an appropriate response scale (yes/no vs. Likert scale etc.), revisited and subject to a face validation phase with practitioners and patients of a memory clinic. Results of this phase lead to cancellation of further items as well as to addition of new ones. In a final development phase, around 100 remaining items were administered to healthy individuals and to individuals who attended a memory clinic for diagnostic work-up but for whom cognitive impairment could not be objectified. The authors then examined which items were most capable of distinguishing between those diagnostic groups. As expected, many items that distinguished well were related to decline in memory. However, a rather interesting finding for the authors was that also items related to social activities and social communication were among the distinguishing ones. One possible explanation for this finding is that social activities are omnipresent in everyday life and, therefore, hardly avoidable by the patient without consequences. Thus, items, which relate to difficulties in performing these activities, may be more salient and thereby “more useful as indicators when investigating subjective cognitive impairment and compromised functioning in a clinical sample” (Eckerström *et al.* 2013). This study example demonstrates how qualitative and quantitative approaches to item and questionnaire development can work hand-in-hand to derive a well thought out SCD questionnaire.

In conclusion, much work remains to develop the SCD concept and its optimal assessment. However, fortunately, international research groups are now combining their efforts to take up this challenge.

Finally, it should be noted that the concept of SCD is one out of several possible approaches to better study the characteristics of (and possible interventions in) the preclinical AD stage. It may well be the case that one day, if highly accurate biomarkers of preclinical AD were easily available and early symptomatic treatments were developed, the assessment of SCD would no longer be necessary. Thus, the SCD concept may be seen as a temporarily limited research approach to study preclinical AD and may be abandoned once better objective markers of preclinical AD are at hand. However, today, in a state where there is a lack of objective markers that are both easily accessible *and* reliable in predicting disease risk (Henriksen *et al.* 2014), SCD may prove as useful a research approach to preclinical AD as has the MCI concept been to

generate knowledge on the earliest *clinical* features of AD (Petersen *et al.* 2009). SCD as a research approach to preclinical AD has several key advantages. Firstly, assessment of SCD is very feasible, cost-effective and non-invasive. Secondly, due to the non-invasiveness but also because individuals with SCD are often *actively* help-seeking, it is less hampered by ethical consideration and very relevant to the health care system. This sets it apart from other current approaches to study preclinical AD which either rely on extensive biomarker assessment to enrich samples for risk of AD (e.g. A4-Trial, Sperling *et al.* 2014) or study preclinical AD in dominantly inherited *early-onset* AD samples (e.g. the DIAN study, Morris *et al.* 2012). The combined advantages of low costs, non-invasiveness and high relevance to care make enrichment via SCD especially appealing for low-cost/low-risk intervention approaches, e.g. concerning nutritional behavior, physical/cognitive activity and other lifestyle factors. However, more invasive, e.g. pharmacological treatments should better be studied in more thoroughly enriched (biomarker-defined) preclinical AD samples bearing more clearly increased risk of cognitive decline and incident AD dementia (Sperling *et al.* 2011; Sperling *et al.* 2014). Importantly, as long as biomarker assessment is not widely available, SCD may complement biomarker-based enrichment strategies as a pre-selection criterion due to its positive association to biomarker abnormality in cognitively normal individuals (Mielke *et al.* 2012). In a similar way, assessment of SCD may help to enrich samples for studies on new objective markers of preclinical AD, such as blood-based biomarkers (Henriksen *et al.* 2014) or more sensitive neuropsychological tests (Rentz *et al.* 2013).

5 German Summary (Deutsche Zusammenfassung)

Die Leistungsfähigkeit in den meisten kognitiven Domänen, insbesondere auch im Gedächtnis, zeigt im Zuge normaler Alterungsprozesse bereits ab dem mittleren Erwachsenenalter einen abfallenden Verlauf (Schaefer & Bäckman, 2007). Aus diesem Grund verwundert es nicht, dass Berichte über Subjektive Kognitive Verschlechterungen (engl. "Subjective Cognitive Decline", SCD) in der älteren Allgemeinbevölkerung durchaus häufig anzutreffen sind. Als SCD bezeichnet man dabei die subjektive Wahrnehmung sich verschlechternder kognitiver Leistungsfähigkeit einer Person in Bezug auf ein früheres Leistungslevel (Jessen *et al.* 2014a). Je nach Art der Erfassung und der untersuchten Stichproben liegt die Prävalenz von SCD im Bereich des Gedächtnisses bei älteren Menschen ab dem 65ten Lebensjahr bei ca. 25-50% (Stewart, 2012). Die Prävalenz solcher Beschwerden steigt mit dem Alter an und erreicht Werte über 80% bei Personen von 80 Jahren und älter (Stewart, 2012).

Diese Zahlen verdeutlichen zunächst, dass subjektive Empfindungen über nachlassende kognitive Leistungsfähigkeit zu Phänomenen des regulären kognitiven Alterungsprozesses gehören können. Dennoch kann eine solche Wahrnehmung auch mit ausgeprägten Sorgen um die kognitive Leistungsfähigkeit einhergehen und ist dann meist Anlass für das Aufsuchen eines Allgemeinarztes oder einer Fachambulanz zur Abklärung möglicher Ursachen für die subjektiv erlebten Symptome. Häufig, aber nicht immer, wird die wahrgenommene Verschlechterung auch von Angehörigen und behandelnden Ärzten berichtet und/oder es zeigt sich bei Abklärung der Leistungsfähigkeit mittels objektiver neuropsychologischer Testverfahren auch ein tatsächlich bestehendes Defizit, d.h. eine Leistung, die unterhalb des aufgrund von Alter, Geschlecht und Bildung der Person zu erwartenden Niveaus liegt. In einem solchen Fall ist die Diagnose einer leichten kognitiven Einschränkung (engl. „Mild Cognitive Impairment“, MCI) gerechtfertigt, sofern Alltagsfunktion und Unabhängigkeit der Lebensführung noch weitgehend erhalten ist, d.h. eine Demenzdiagnose zunächst ausgeschlossen werden kann (Winblad *et al.* 2004).

MCI gilt als gut etabliertes Risikostadium für eine später eintretende Demenz, zumeist aufgrund der Alzheimer Krankheit und dies besonders wenn es sich um amnestische Defizite (amnesic MCI) handelt (Dubois *et al.* 2014). Personen mit MCI weisen ein deutlich erhöhtes Risiko für inzidente Alzheimer Demenz auf, mit jährlichen

Übergangsraten von ca. 10-15% (Petersen, 2004). Neuere Forschungskriterien für die Alzheimer Krankheit umfassen auch das MCI Spektrum und sprechen von „MCI aufgrund Alzheimer Krankheit“ oder „prodromaler Alzheimer Krankheit“ wenn neben dem klinischen Phänotyp des MCI zusätzlich biochemische oder Bildgebungsdiagnostik („Biomarker“ Diagnostik) positiv für eine ursächliche Alzheimer Krankheit sprechen (Albert *et al.* 2011; Dubois *et al.* 2014). SCD ist Teil der MCI Kriterien um den klinischen Phänotyp des kognitiven Defizits näher zu charakterisieren. Da für gewöhnlich nur ein Messzeitpunkt zum Zeitpunkt der Diagnose vorliegt, gibt SCD Information über eine vorangegangene Verschlechterung und erhärtet damit den Befund, dass die objektiv defizitäre Leistung Ursache einer neurodegenerativen Erkrankung (anstatt eines lebenslang bestehenden Defizits) ist. Innerhalb der MCI Kriterien kann diese Information entweder vom Betroffenen selbst, einem Angehörigen oder einem mit dem Patienten vertrauten Kliniker gegeben werden.

Die Nützlichkeit des Kriteriums der (selbst-berichteten) subjektiven Gedächtnisbeschwerden wurde in der Literatur mehrfach in Frage gestellt (Edmonds *et al.* 2014), nicht zuletzt deshalb, weil bereits im MCI Stadium Symptome von reduzierter Einsichtsfähigkeit, wie sie für das Stadium der Alzheimer Demenz charakteristisch sind, auftreten können (Galeone *et al.* 2011). Das Auftreten dieser Symptome kann die Verlässlichkeit subjektiver Information hinsichtlich einer kognitiven Verschlechterung negativ beeinflussen (Roberts *et al.* 2009). Weiterhin wurde die mangelhafte Operationalisierung von SCD kritisiert (Abdulrab & Heun, 2008) und es gibt derzeit noch keine einheitlichen Standards zur Erfassung selbstberichteter subjektiver kognitiver Verschlechterung. Es stellt sich daher für die Forschung die Frage, in wie weit das Phänomen des SCD adäquat erfasst ist und seine Informationskraft in Hinblick auf Diagnostik und Prognostik im Rahmen der Alzheimer Krankheit ausgeschöpft wurde.

Neuen Auftrieb hat die Forschung um das Phänomen der subjektiven Gedächtnisbeschwerden in den letzten Jahren im Bereich der Frühdiagnostik der Alzheimer Krankheit erfahren. Da viele pharmakologische Interventionsstudien zur Prävention von Alzheimer Demenz im MCI Bereich keine durchschlagenden signifikanten Effekte zeigten, ist das wissenschaftliche Feld darum bemüht, die Alzheimer Krankheit noch vor dem MCI Stadium zu detektieren (Sperling *et al.* 2011). Mehrere große Studien konnten zeigen, dass Personen mit SCD aber objektiver

kognitiver Leistung im Normalbereich ein signifikant erhöhtes Risiko für inzidente Alzheimer Demenz und Biomarkerpositivität für die Alzheimer Krankheit aufweisen (Jessen *et al.* 2014a). SCD könnte daher als ein frühes Symptom einer sich anbahnenden Alzheimer Demenz gelten und bietet Ansatzpunkte für die Risikoanreicherung von Stichproben oder als abhängiges Maß über die Zeit für Interventionsstudien und naturalistische Beobachtungsstudien. Aufgrund dieser neueren Befundlage ist SCD im Sinne eines klinischen Frühsymptoms auch in den Forschungskriterien der letzten Phase der präklinischen Alzheimer Krankheit aufgenommen wurden („preclinical AD stage 3“; Sperling *et al.* 2011). Diese letzte Phase markiert den Übergang von stummer präklinischer zur frühen klinischen Phase des MCI. Auch für diesen Übergangsbereich gilt jedoch, dass die genaue Charakterisierung von SCD, der Verlauf über die Zeit und die Messmethoden noch unzureichend erforscht sind.

Die vorliegende Arbeit enthält drei Studien, die sich mit SCD im Bereich objektiv normaler kognitiver Leistungsfähigkeit sowie im MCI Bereich beschäftigen. Die Studien orientierten sich dabei an einem derzeit gängigen Arbeitsmodell (Jessen *et al.* 2014a) für den temporären Verlauf subjektiver Gedächtnisbeschwerden im Zuge der Entwicklung der Alzheimer Krankheit. SCD wird dabei als ein frühes Symptom der Krankheit aufgefasst und bildet ein Kernsymptom im Übergangsbereich der präklinischen Phase der Alzheimer Krankheit zur frühen klinischen Phase des MCI. Im Verlaufe der Alzheimer Krankheit können subjektive Gedächtnisbeschwerden wieder abnehmen bzw. die Verlässlichkeit des Urteils sinken, da reduzierte Einsichtsfähigkeit und/oder Leugnung der Beschwerden seitens des Patienten aufgrund fortschreitender Krankheit und damit einhergehender Verschlechterung der kognitiven Leistungsfähigkeit zunehmen. Andererseits ist die Sensitivität objektiver kognitiver Testdiagnostik gerade im eben angesprochenen Übergangsbereich zwischen präklinischer und MCI Phase begrenzt. Gerade hier könnte daher die Erhebung von SCD als zusätzliche Informationsquelle prognostischen Zugewinn bringen. Desweiteren explorieren die hier vorliegenden Studien, quantitative und qualitative Aspekte von SCD (z.B. das „sich Sorgen“ um die erlebte Gedächtnisverschlechterung) hinsichtlich ihrer prognostischen Informationskraft.

Datengrundlage der Studien ist zum einen die deutsche „Study on Ageing Cognition and Dementia in primary care“ (AgeCoDe), eine multizentrische Kohortenstudie von ca. 3200 älteren Hausarztpatienten (nicht dement und mindestens

75 Jahre zu Studienbeginn) mit derzeit bis zu 7.5 Jahren Verlaufsbeobachtung (Studie 1). Als weitere Stichprobe diente eine, ebenfalls multizentrische, Gedächtnisambulanzkohorte von nicht-dementen Patienten des deutschen Kompetenznetzes Demenzen, ein Zusammenschluss von forschenden Uniklinik-Gedächtnisambulanzen in Deutschland. Aus dieser Kohorte konnten Stichproben von ca. 450 MCI Patienten mit Verlaufsdaten von bis zu 36 Monaten (Studie 2), sowie von ca. 250 MCI Patienten mit querschnittlichen Biomarkerdaten (Studie 3) genutzt werden.

Studie 1 untersuchte innerhalb der AgeCoDe Kohorte das Risiko für inzidente Alzheimer Demenz bei Personen mit SCD (genauer: subjektiver *Gedächtnisverschlechterung*) aber noch normaler Testleistung in einem Gedächtnistest. Desweiteren wurde der qualitative Aspekt von Sorgen über den erlebten Gedächtnisabbau im Hinblick auf das Alzheimer Demenz Risiko exploriert. Beide Personengruppen (SCD mit bzw. ohne Sorgen bei normaler Gedächtnistestleistung) wurden mit zwei MCI Gruppen („frühes MCI“ mit leichtem objektivem Gedächtnisdefizit; „spätes MCI“ mit stärkerem objektivem Gedächtnisdefizit) hinsichtlich des Alzheimer Demenz Risikos verglichen. Als Referenzgruppe in diesem Design diente eine Kontrollgruppe von Personen ohne SCD und ohne objektives Defizit. Es zeigte sich hierbei, das *SCD mit Sorgen* mit einem ca. 2.5-fach erhöhten Alzheimer Demenz Risiko verglichen zur Kontrollgruppe einherging. Das Risiko in dieser Gruppe entsprach dem der Gruppe „frühes MCI“. Die Gruppe der Personen, die subjektive Gedächtnisverschlechterung ohne Sorgen berichteten, wies nur ein leicht erhöhtes Risiko für inzidente Alzheimer Demenz auf, welches sich nicht signifikant von der Kontrollgruppe unterschied. Diese Studie unterstreicht die Bedeutsamkeit von subjektiver Gedächtnisverschlechterung, speziell wenn diese als sorgenvoll erlebt wird, als einen frühen prädiktiven Marker für eine spätere Alzheimer Demenz in älteren Allgemeinartzpatienten. Desweiteren weisen die Ergebnisse dieser Studie auch auf die Grenzen neuropsychologischer Schwellenwerte zur Definition von einzelnen Risikostadien der Alzheimer Demenz hin, da sich das Risiko von Personen mit Gedächtnissorgen aber noch „noch normaler Gedächtnisleistung“ nicht von dem derjenigen Personen mit Sorgen und mit minimalem objektivierbaren Defizit unterschied.

Studie 2 untersuchte die prädiktive Vorhersagekraft von sorgenvollen subjektiven Gedächtnisbeschwerden für inzidente Alzheimer Demenz bei

Gedächtnisambulanzpatienten mit einer MCI Diagnose. Dabei wurde zunächst die Hypothese geprüft ob sorgenvolles SCD zusätzlich zur objektiven Gedächtnistestleistung, welche (im Gegensatz zum prä-MCI Stadium) in diesem Risikostadium bereits substantiellen prädiktiven Wert hat, einen Beitrag zur Vorhersagekraft von inzidenter Alzheimer Demenz leisten kann. Desweiteren wurde geprüft ob die Vorhersagekraft von SCD mit Sorgen von der Ausprägung des objektiven Gedächtnisdefizits zum Zeitpunkt der Messung beeinflusst („moderiert“) wird. Der Grund für diese Annahme wurde oben in der Beschreibung des Arbeitsmodells für den temporären Verlauf von SCD im Zuge der Alzheimer Krankheit dargelegt. Die Ergebnisse der Studie lieferten Evidenz für die Gültigkeit beider Hypothesen. Das Vorhandensein von sorgenvollen Gedächtnisbeschwerden bei MCI Patienten ging mit einem mehr als zweifach erhöhten Risiko für inzidente Alzheimer Demenz im Verlaufszeitraum von durchschnittlich ca. 2.5 Jahren einher. Die Größe dieses Haupteffekts war vergleichbar mit dem des APOE4 Genotyps, des wichtigsten genetischen Risikofaktors für die sporadische Alzheimer Demenz, und bestand auch unter statistischer Kontrolle für die objektive Gedächtnisleistung. Desweiteren zeigte sich entsprechend der zweiten Hypothese ein signifikanter Interaktionseffekt zwischen objektiver Gedächtnisleistung und sorgenvollen Gedächtnisbeschwerden im Hinblick auf das Alzheimer Demenz Risiko. Das mit Vorhandensein von sorgenvollem SCD assoziierte Risiko war besonders hoch bei nur leicht objektiv beeinträchtigten Patienten und sank mit abnehmender Gedächtnisleistung, d.h. es war niedriger bei zur Basismessung bereits stärker beeinträchtigten MCI Patienten. Die Ergebnisse dieser Studie validieren bzw. erweitern zum einen die Befunde von Studie 1 zur besonderen Bedeutung von Sorgen über die erlebte Gedächtnisverschlechterung durch eine Replikation des Effektes in einem anderen Setting (Memory Clinic) und anhand von Individuen, die sich in einem näher an der Demenz befindlichen Risikostadium (MCI) befinden. Zum anderen liefern sie empirische Evidenz für die im oben beschriebenen Arbeitsmodell postulierte Dynamik von SCD im Hinblick auf die Nutzbarkeit als prädiktiver Marker. Der Nutzen von SCD ist besonders hoch bei noch früher objektiver Beeinträchtigung während er im bereits fortgeschrittenen MCI Stadium limitiert zu sein scheint.

Als Fortsetzung von Studie 2 untersuchte die dritte Studie dieser Arbeit die Prädiktionskraft von Gedächtnissorgen bei MCI Patienten im Hinblick auf das

Vorhandensein eines Alzheimer Demenz typischen Biomarkerprofils. Es wurden die gleichen Hypothesen formuliert wie auch bei der Vorhersage inzidenter Alzheimer Demenz in Studie 2. Zusätzlich wurde hier auch ein quantitatives Maß für SCD eingesetzt und mit dem Prädiktor der sorgenvollen Gedächtnisbeschwerden verglichen. Es zeigte sich auch hier, dass beide SCD Maße signifikante Prädiktoren für das Vorhandensein eines Alzheimer Demenz typischen Biomarkerprofils waren, dies auch unter Kontrolle der objektiven Gedächtnisleistung. Ein Interaktionseffekt zwischen SCD und objektiver Gedächtnisleistung konnte hingegen nicht gefunden werden, was möglicherweise auch an der geringeren Stichprobengröße verglichen zur longitudinalen Studie 2 gelegen haben mag (nur ca. 33% der MCI Kohorte haben Biomarker Information). Das Hauptergebnis dieser Studie, die Assoziation von SCD mit Biomarkern der Alzheimer Demenz, erweitert bereits aus dem präklinischen Bereich vorliegende Befunde zu einer solchen Assoziation und legt nahe, dass eine bessere Operationalisierung von SCD, welche über den unspezifischen Bericht von kognitivem Abbau gemäß MCI Kriterien hinausgeht, auch noch im MCI Stadium von prädiktivem Nutzen sein könnte.

Zusammenfassend haben die hier vorgestellten Studien eine Reihe von Beiträgen zur Erforschung von SCD im Bereich der Alzheimer Krankheit geleistet. Ergebnisse dieser Arbeit haben z.B. Eingang in die Definition eines Rahmenkonzeptes für die Erforschung von SCD im Bereich der präklinischen Alzheimer Krankheit gefunden (Jessen *et al.* 2014a). Diese Kriterien erwähnen den qualitativen Aspekt der Sorgen um die erlebte Gedächtnisverschlechterung, zusammen mit weiteren Aspekten, als einen Faktor, der die Wahrscheinlichkeit von Alzheimer als Ursache der Beschwerden erhöht.

Grenzen der vorliegenden Studien sind vor allem durch die Form der retrospektiven Analyse und die damit verbundene eingeschränkte Anzahl der SCD Aspekte bzw. Items, die untersucht werden konnten, gegeben. Weitere Forschung ist nötig um zu bestimmen, welche Aspekte von SCD, in welchem Stadium der prodromalen Alzheimer Krankheit besonders prädiktiv für eine spätere Alzheimer Demenz sind, und wie diese Aspekte optimal erfasst werden sollten. Desweiteren ist unklar, ob SCD selbst als ein longitudinales Outcomemaß in klinischen Frühinterventionsstudien verwendet werden könnte. Mit dieser Frage verbinden sich Fragen nach Zeitstabilität, Reliabilität und Änderungssensitivität von SCD Operationalisierungen bzw. Messverfahren, welche weitgehend noch nicht erforscht

sind. Da diese Fragen auch selbst für objektive Testverfahren nicht hinreichend geklärt sind, und daher intensiv beforscht werden, könnten Erkenntnisse diesbezüglich auch für die SCD Forschung nutzbar gemacht werden. Die forschende Neuropsychologie kann hier, aufgrund ihrer Schnittstellenfunktion zwischen psychometrischer Grundlagen- und klinisch angewandter Forschung, wichtige Beiträge leisten.

Important terms and abbreviations

Abbreviation	Definition and Explanation
AD	Alzheimer's disease. AD is a neurodegenerative disease that leads to progressive cognitive and functional decline. AD is commonly divided into an asymptomatic stage (biomarkers abnormal, absence of cognitive impairment), and a symptomatic stage (biomarkers abnormal, presence of cognitive impairment). The symptomatic stage can be divided clinically into the stage of (pre- mild cognitive impairment) Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI) and dementia (Visser <i>et al.</i> 2012). If biomarker information is available, an in-vivo diagnosis of MCI or dementia due to AD is possible according to research criteria of either an International Working Group (IWG2 criteria) or the National Institute on Aging and the Alzheimer's Association (NIA-AA criteria).
APOE	Apolipoprotein E gene, "APOE4" describes the dementia risk allele epsilon 4. "Positive ApoE4 status" comprises individuals with heterozygous and homozygous APOE4 genotype.
CERAD	Consortium to Establish a Registry for Alzheimer's Disease. The CERAD is a research consortium that was founded in the USA in 1986 with the aim to standardize procedures for diagnosis and evaluation of AD. The neuropsychological test battery developed by CERAD has been employed in many US and international studies and is also often used in the routine memory clinic practice. The German version of the CERAD test battery is the core battery of the DCN cohort (see study 2 and study 3 of this thesis) and parts of the CERAD have also been used in the AgeCoDe study (see study 1). The battery consists of various subtests, including the Mini-Mental State Examination (MMSE), and is specifically designed to assess the cognitive domains most commonly affected in AD. The various subtests are described in the methods section of study 2 and 3. The Word List Delayed Recall subtest was used throughout the studies as a measure of objective memory impairment and to define the amnesic MCI groups in study 1.
CSF	Cerebrospinal Fluid (from which biomarkers of AD pathology can be measured). The commonly derived AD biomarkers from CSF are CSF-A β 42, a marker of brain amyloid pathology, and CSF-Tau/CSF-pTau181, markers of Tau-mediated neuronal dysfunction and degeneration.

- FCSRT** Free and Cued Selective Reminding Test. The FCSRT is an episodic memory measure that controls for successful encoding and probes response to cueing. Recall in the FCSRT consists of a free recall phase and a cued recall phase in which semantic cues are given for the non-recalled words of the free recall phase. The initial prodromal AD criteria put forward by an International Working Group of Dubois and colleagues (Dubois *et al.* 2007) specified a memory deficit *not normalized by cueing* as the core clinical phenotype of prodromal AD and favored tests like the FCSRT to measure this specific deficit. The FCSRT was used as an alternative memory measure to the CERAD delayed free recall in study 3 of this thesis.
- HR** Hazard Ratio, a measure of effect size in Cox Proportional Hazard Regression analysis. The HR gives the relative risk factor associated with a categorical or continuous exposure variable in comparison to a reference category or value. A Hazard Ratio greater than one means a greater risk in the exposed group or with increasing values of the continuous measure (e.g. HR = 2 means “two times the risk”). A Hazard Ratio smaller than one means less risk. The range of a HR is from zero to infinity.
- MCI** Mild Cognitive Impairment. MCI is defined as a condition of objective mild deficits in one or more cognitive domain together with evidence of a cognitive decline from worse performance. Importantly, the level of cognitive impairment must not significantly interfere with daily living (i.e. a diagnosis of dementia is not warranted). In the absence of longitudinal objective test information, evidence of a *decline in performance* is usually corroborated, subjectively, by the patient and/or by an informant or a clinician who knows the patient well. The criterion of SCD is therefore not mandatory for the diagnosis of MCI.
- Pre-MCI** Pre-MCI is used as a prefix to Subjective Cognitive Decline (SCD) in this thesis. Used in conjunction with SCD it describes individuals with SCD but *normal* cognitive test performance, i.e. not warranting a diagnosis of MCI. The term “pre-MCI SCD”, thus, describes a specific *patient group*, not the symptom of SCD per se.
- MMSE** Mini-Mental State Examination. The MMSE is a common, short neuropsychological assessment tool to measure global cognitive functioning in MCI and dementia (Folstein *et al.* 1975). The MMSE is included as a subtest in the German version of the CERAD neuropsychological assessment battery.

- MRI** Magnetic resonance imaging. MRI is a medical imaging technique that uses magnetic fields and radio waves instead of radionuclides (see PET) to visualize anatomic structures and processes in the body. In Alzheimer’s disease, brain imaging via MRI is used to measure atrophy of brain structures (“*structural MRI*”) and is considered a marker of Tau-mediated neurodegeneration. In contrast to structural MRI, *functional MRI* is a technique that uses the natural association between cerebral blood flow and neuronal activation to measure the brain’s activity in specific areas, e.g. during performance of a cognitive task.
- OR** Odds Ratio, a measure of effect size in logistic regression analysis. The metric of the odds ratio is similar to the Hazard Ratio (HR, see above).
- PET** Positron emission tomography. PET is a functional imaging technique that uses nuclear positron-emitting radionuclides (tracers) to visualize functional processes in the body. In AD research PET brain imaging is used mostly in two forms: 1.) Brain PET *A β imaging* is used to visualize amyloid β (A β) plaque formation in the brain. The most common tracer compound in this regard is Pittsburgh compound B (“PiB-PET imaging”). 2.) As a measure of neuronal dysfunction, ¹⁸F-fluoro-deoxy-glucose PET (*FDG-PET*) is used to measure reduced brain metabolism (which indicates reduced synaptic activity). Besides these 2 established PET imaging forms, *Tau-imaging* has emerged as an in vivo imaging technique of tau pathology in the brain.
- SCD** Subjective Cognitive Decline. SCD describes the subjective notion of cognitive worsening. This term describes the symptom per se, not a diagnostic patient group (see also *pre-MCI SCD* and section 2.4.1).
- SCD-I** SCD-Initiative. The SCD-I is an international network of research experts on SCD in the field of preclinical (i.e. pre-MCI) AD. The aim of the SCD-I is to improve SCD operationalization and assessment and to develop common SCD criteria for better comparability across international studies (Jessen *et al.* 2014a).
- SMDS** Subjective Memory Decline Scale (Jorm *et al.* 1997). The SMDS is a quantitative SCD scale. It is used as one of two SCD measures in study 3 of this thesis. It contains four questions on self-experienced increasing difficulties in everyday memory (e.g. “Do you have more trouble remembering things that have happened recently?”; “Are you worse at remembering where belongings are kept?”). Responses to each question are rated as follows: 0, “no, not more difficult than in the past”; 1, “Yes, a bit worse than in the past” 2, “yes, much more difficult than in the past”. A summary score of 0-8 points can be derived.

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