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Sex-specific Association of Subjective Cognitive Decline and
Apolipoprotein E ϵ 4 Genotype with Risk of Incident Mild Cognitive
Impairment

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1 INTRODUCTION

With the aging population, demographic change is one of the key challenges our society is facing today. According to estimations from the German Federal Statistical Office, between 24% to 30% of the German population will be over the age of 66 years in 2060 compared with 19% in 2018 (Statistisches Bundesamt, 2019). This change is accompanied by increasing numbers of age associated diseases leading to serious consequences for the social and health care system. A prominent example is dementia by which approximately 1.6 million people are affected in Germany and an estimated 50 million people worldwide (Patterson, 2018). Based on data from the German Federal Statistical Office, it is estimated that the number of dementia patients in Germany will increase up to 3 million until the year 2050. The most common form of dementia is Alzheimer's disease (AD). It already has a strong impact on society and health economics. Not only are the increasing numbers of AD patients problematic but also the still missing causal therapies. Treatment options for AD are limited to a symptomatic approach and to slowing down disease progression. Drug development in the field of AD has shown very high failures with about 146 failed attempts during clinical trials between 1998 and 2017, resulting in a 2.7% success rate (PhARMA, 2018). Current research therefore focuses on early detection, identification of preventative strategies, and a better understanding of the etiology as well as pathogenesis of AD. Looking at earlier stages in the course of the disease, two important concepts have been developed: subjective cognitive decline (SCD) and mild cognitive impairment (MCI). Individuals with SCD are defined as experiencing self-perceived cognitive worsening whilst their cognitive performance is objectively normal. The later stage MCI includes individuals with cognitive performance outside the appropriate age and educational range, who are not (yet) demented and show intact activities of daily living. Both concepts might be promising targets for early intervention and prevention strategies and will be described in detail later. Neurodegenerative processes leading to pathological changes begin up to 20 years before onset of clinical symptoms of AD dementia (Jack et al., 2013). Individuals with SCD and MCI may already be affected by this pathology.

1.1 Neuropathology in Alzheimer's disease (AD)

The neuropathological basis for AD is thought to be the accumulation of amyloid beta (A β) peptide in the brain, which leads to extracellular plaques, and the formation of intracellular

neurofibrillary tangles (NFTs) consisting of tau protein. A β is a peptide cleaved by β - and γ -secretases from the amyloid precursor protein (APP), an integral membrane protein expressed in large quantities in the synapses of neurons (Masters and Selkoe, 2012). Different sizes of A β peptides have been found with A β 40 and A β 42 being the two main variants in humans (Vigo-Pelfrey et al., 1993, Portelius et al., 2011). The A β 42 variant is less frequently found than A β 40 but A β 42 is more prone to form insoluble fibrils. These fibrils can then further assemble into amyloid plaques found in brains of AD patients. A β has several functions in the central nervous system (CNS), for instance regulation of neuronal homeostasis and control of synaptic activity (Kamenetz et al., 2003). The latter is an important A β function because synapses have been considered to be affected by AD pathology early in the disease (Selkoe, 2002). Besides A β , tau is the other key protein in AD. It is a microtubule-associated protein that regulates stability of tubulin assembly (Conde and Caceres, 2009). Under healthy conditions, tau helps to polymerize tubulin dimers into a microtubule. Microtubules are part of the cytoskeleton and have many functions like maintaining the cellular structure, for instance of neurons, and axonal transport. In a phosphorylated state, tau can no longer bind to microtubules, which causes microtubule depolymerization needed to restructure the cytoskeleton. In the AD brain, tau is thought to be abnormally hyperphosphorylated and as a result, it accumulates and self-assembles into oligomers and further on into insoluble paired helical filaments that make up the majority of NFTs in neuronal cells (Alonso et al., 1996). Neuropathological changes in AD have historically been detected by post-mortem brain autopsies. With evolving technologies, *in vivo* biomarkers are now available that can visualize pathological hallmarks of AD.

A dynamic model of AD neuropathological progression has been proposed by Jack et al. (2013) (Figure 1, see next page). The temporal first detectable neuropathological change is cortical amyloid deposition shown by evidence of low levels of A β 42 or a decreased ratio of A β 42 to A β 40 in the cerebrospinal fluid (CSF). Extracellular accumulation of A β in large quantities becomes visible later and it is measured by amyloid positron emission tomography (PET) with, for example, Pittsburgh compound B (PiB) as a cortical amyloid PET ligand. After that, tau becomes abnormal at a detectable level, resulting in the formation of intracellular NFTs, which cause neuronal injury and dysfunction. This is reflected by increased concentrations of phosphorylated tau (p-tau) and total tau (t-tau) in the CSF. Neuronal injury and following progressive loss of neurons and their function is assessed indirectly by 18F-fluorodeoxyglucose (FDG)-PET and directly by magnetic resonance imaging (MRI). FDG-PET is a marker of neurodegeneration and shows the potential decrease in cerebral glucose metabolism. A structural MRI can detect atrophy in

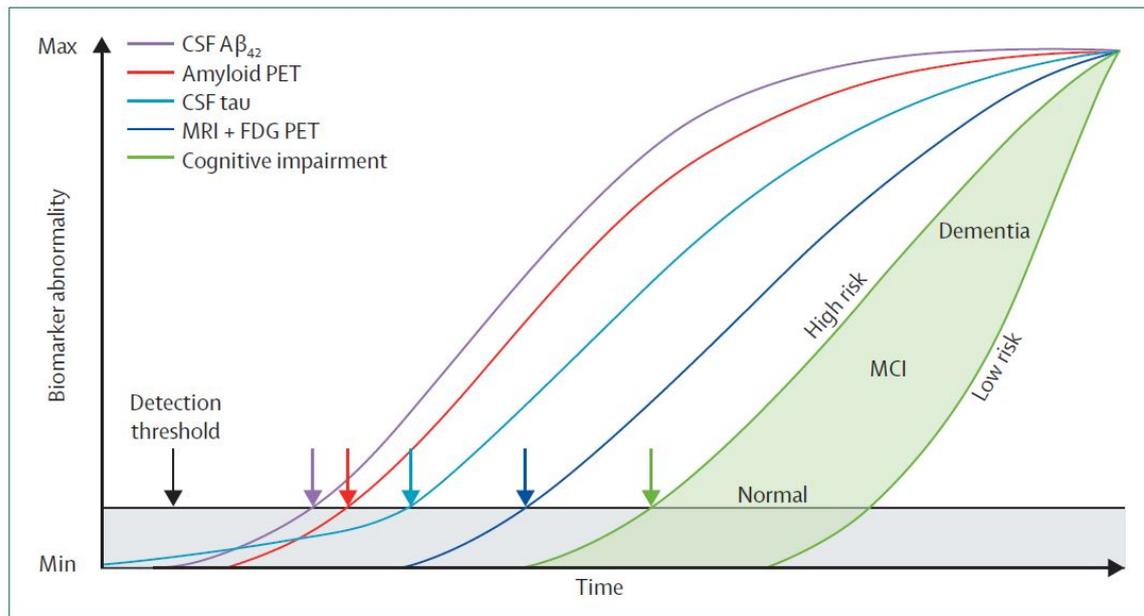


Figure 1: Updated model of dynamic biomarkers of the temporal Alzheimer's disease (AD) pathological cascade across stages and cognitive decline. The first detectable biomarker is amyloid beta 42 ($A\beta_{42}$) in the cerebrospinal fluid (CSF), followed by amyloid positron emission tomography (PET) showing abnormal amyloid pathology. Next, tau becomes abnormal and is detected by increased tau concentrations in the CSF. Magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose (FDG)-PET show abnormal neuronal injury and neurodegeneration. Cognitive impairment including mild cognitive impairment (MCI) is the last abnormality detectable in this model and is depicted as a light green area with high risk and low risk borders to reflect the variation of different cognitive risk profiles. All biomarkers bundle up over time and peak in the right hand corner depicting the maximum risk. Inserted at the bottom of the biomarker abnormality lines is a detection threshold depicted in grey to show that current biomarker need a certain level of pathological load to detect abnormality. *Figure from Jack et al. (2013) reused in this dissertation with permission from Elsevier (RightsLink License Number: 4642410865235).*

the brain and directly display brain areas affected by neuronal injury or neurodegeneration.

Markers for AD mainly focus on tau and $A\beta$. To date, only CSF and PET markers can validly detect neuropathological changes directly caused by tau and $A\beta$ because of AD. Very recently, several tracers for tau PET have been developed that successfully (with high specificity and selectivity, i.e. high diagnostic accuracy) display tau disease pathology in vivo (Chien et al., 2013, Gobbi et al., 2017). Both CSF and PET are either invasive or expensive methods. On that account blood-based biomarkers are currently being developed and promising candidates are under way (Hampel et al., 2018).

A widely accepted hypothesis for the cause of AD is the amyloid hypothesis, which mainly follows the temporal order described above. It is supported by genetics. Individuals with a family history of early-onset AD were found to have mutations in genes that code amyloid: *APP* and the APP processing secretases presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*).

The idea of the underlying pathological cascade caused by amyloid is as follows:

- (1) A β is incorrectly cut from APP by secretases resulting in extracellular A β misfolding. This causes aggregation of monomers to oligomers and on to insoluble fibrils, which ultimately leads to build-up of plaques that are mainly composed of A β 42.
- (2) Activation of microglia and astrocytes leads to inflammatory responses. These cause altered neuronal homeostasis and oxidative injury.
- (3) Tau protein is hyperphosphorylated intracellularly due to altered phosphatase activity, which prevents tau binding to tubulin and causes breakdown of the cell's cytoskeleton. Hyperphosphorylated tau forms paired helical filaments resulting in formation of NFTs. Neurofibrillary tangles are toxic for the cell and ultimately inhibit normal cellular function.
- (4) Later, the accumulation of this pathology causes cellular dysfunction and neurodegeneration.

These steps are hypothesized to cause AD. Over the years, several counter-arguments for the amyloid hypothesis have been introduced. A few of these will be presented hereinafter together with possible explanations:

Brains of many elderly, asymptomatic people or individuals with very subtle cognitive deficits display A β plaques (Price et al., 2009). These individuals may however be in a pre-symptomatic stage with cognitive decline yet to develop. Plaque burden and disease severity only correlate to a small degree (Esparza et al., 2013). Studies have suggested that cognitive deficits correspond to tau tangles more than to A β plaques (Goedert et al., 2017). An important argument specifically raised in the past few years is the failure of numerous clinical trials targeting A β . In return, it has been argued that these trials enrolled patients in later AD stages, which is too late in the disease progression.

Another hypothesis favors tau as the causative protein instead of A β but is not as widely accepted. It states that the formation of NFTs results in oxidative stress. Oxidative stress is an excess of reactive oxygen species in the cell, which can attack any biological molecule. This excess causes damage of neurons and as a result neurodegeneration. Amyloid accumulation and plaque formation is argued to be a protective response because APP expression is increased by energy shortages. Alternative hypotheses (e.g. the inflammation hypothesis and the cholinergic and oxidative stress hypothesis) exist but are not as commonly known and supported.

It has recently been proposed to refer to AD as "Alzheimer's disease with dementia". The idea is that the biomarker profile is evidential for AD, but dementia per se is unspecific and can have multiple causes. It is known that a person has AD because of their biomarker profile and it is known when a person has cognitive deficits as severe as dementia. It is

not known to what extent the cognitive symptoms are attributable to underlying AD pathology, or to other forms of dementia, or to comorbidities. Alzheimer's disease is only one of many possible contributing causes to cognitive impairment. Recently, a new concept for AD classification has been published, the ATN system (A = amyloid beta, T = tau pathology, N = neurodegeneration), which is based on biomarkers (Jack et al., 2018). If biomarkers are available, it is the preferred classification system and allows individuals to be staged as clinically normal, MCI, and dementia with further classification based on biomarkers.

While the neuropathological changes take place, it takes decades until affected individuals develop dementia. Until then, they progress through different pre-dementia stages that partially correlate with AD pathology, often beginning with the experience of SCD. In a longitudinal study, the majority of individuals with SCD that had pathological A β 42 load or an abnormal CSF A β 42/p-tau ratio progressed to MCI or dementia (Sierra-Rio et al., 2016). It has also been shown that SCD is associated with reduced volume in the medial temporal lobe, the first area in the brain to be affected by AD pathology (Jack et al., 1999, Meiberth et al., 2015). Significant associations of A β accumulation with SCD have been found for cortical PiB binding in PET (Amariglio et al., 2012). Regarding MCI, cognitive symptoms may be different for individuals with the same biomarker load depending on various factors (e.g. age, genetic risk factors, comorbidities and cognitive reserve) and the intraindividual neuropathological progression. Some patients with MCI have NFTs and neuritic plaques specifically in the medial temporal lobe (Markesbery et al., 2006). Structural MRI scans of MCI patients characteristically show atrophy in the hippocampus and entorhinal cortex (Dickerson et al., 2001). Many MCI patients show decreased CSF A β 42 and elevated tau (Herukka et al., 2017). Studies with FDG-PET found that MCI patients with glucose hypometabolism in the entorhinal cortex and temporal or parietal lobes are at higher risk of progressing to dementia (Yuan et al., 2009, de Leon et al., 2001). Patients with MCI generally exhibit pathologic patterns similar to those of AD patients. Overall, the course of AD is fluent: pathological changes develop differently for every individual, specifically in the early stages. Particularly newer biomarker assessments do not have clear cut-off values yet and their thresholds are still fluctuant. Moreover, AD stages are a continuum rather than distinct entities.

1.2 Cognition in the course of AD

Cognitive aging is an individual, intrinsic process and evolves differently for everyone. There is an age and education appropriate range in which the cognitive performance is considered normal, even if it declines over time. The human body harbors quality controls and repair mechanisms to cope with biological errors. These protective mechanisms tend to fail as humans age. This causes accumulation of mutations in genes and degenerative proteins, which can ultimately change normal cognitive aging to pathological aging causing dementia.

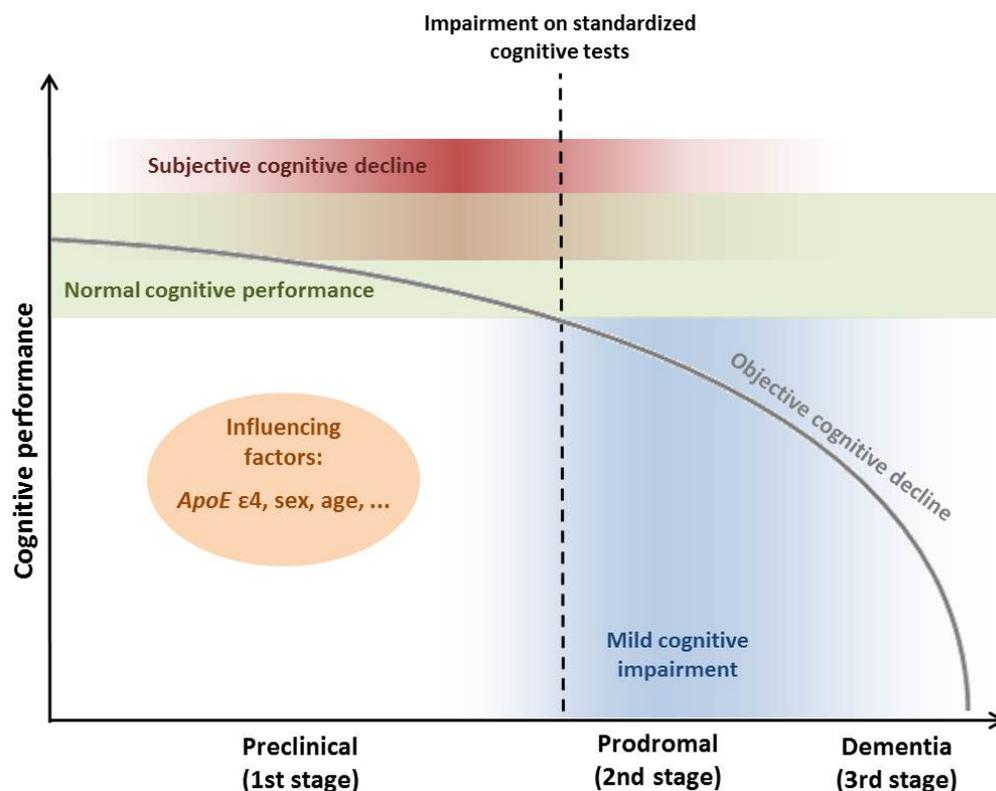


Figure 2: Progression of disease pathology and clinical states of Alzheimer's disease (AD). Three stages of AD are commonly described and they are primarily defined by the objective cognitive performance and decline thereof. The first one is the preclinical stage where individuals are asymptomatic, besides possibly presenting with subjective cognitive decline (SCD, shown as a red bar), and show normal cognitive performance on standardized cognitive tests. The range of normal cognitive performance is indicated by a light green bar. Next is the prodromal stage, where cognitive performance of individuals has declined beyond their appropriate, normal range. With declining cognition, many individuals have mild cognitive impairment (MCI), indicated by a blue area. In the disease progression, cognitive performance may decline further until individuals are in the dementia stage. Abbreviation: *ApoE*, apolipoprotein E.

Alzheimer's disease is often divided into three stages (see Figure 2):

1. The preclinical stage: First pathological processes have started in the brain and abnormal biomarkers can be detected. Regarding their cognitive performance however, individuals are still asymptomatic and objectively perform within their age and education appropriate cognitive range. Subjective cognitive decline describes

a self-perceived cognitive worsening whilst the cognitive performance is in the normal range. It starts in the preclinical phase even though not every individual in the AD continuum experiences SCD.

2. The prodromal stage: When the objective cognitive performance declines beyond the age and education appropriate threshold, individuals reach the prodromal stage characterized by objective cognitive impairment and MCI. It is a transitional state between cognitively normal aging and a manifest dementia with cognitive deficits but normal function of daily activities. Additionally, SCD is part of the MCI criteria by Winblad et al. (2004) described in detail later, but it recedes as the disease progresses.
3. Dementia: In the course of AD, objective cognitive performance then declines further to the point of dementia. The individual disease progression is influenced by many factors, for instance the Apolipoprotein E ϵ 4 genotype (*APOE* ϵ 4) as the main genetic risk factor for AD or biological sex.

The following sections present the concepts of SCD and MCI in the course of AD.

1.3 Subjective cognitive decline (SCD)

Subjective cognitive decline was first described by Reisberg et al. (1982) as “Very Mild Cognitive Impairment”, a phase of clinical AD with early subjective memory deficits but without objective evidence. Terminology in the literature describing this state ranges from subjective memory concerns/complaints (SMC), subjective memory deterioration, subjective cognitive complaints (SCC), subjective memory impairment (SMI) or subjective cognitive impairment (SCI) to subjective cognitive decline (SCD). The terms “cognitive” and “memory” have always been incorporated. Sometimes they are used interchangeably to describe a subjective decline in the general cognition and sometimes “memory” is explicitly used to describe subjective complaints specifically in the memory domain. When individuals are asked about memory they may not describe problems in the actual cognitive domain memory but rather problems relating to other cognitive domains. The words “complaints” and “impairment” are often used interchangeably as well. Complaints imply a reporting by an affected individual whereas impairment rather resembles a cognitive diagnosis or symptom description used clinically. The term “decline” describes a worsening of cognitive capacities. It captures the longitudinal nature of SCD due to AD pathology and should thus be the word of choice. Oftentimes the terminology used in studies was based on the specific research question. Today, use of the term SCD is recommended to define the symptom and identify individuals possibly in the AD

continuum instead of referring to a memory term because the phenomenological nature of SCD has yet to be fully understood (Reisberg and Gauthier, 2008). Thus SCD will be the terminology used in this work.

Subjective cognitive decline in cognition is generally unspecific and can be an indicator for the presence of a range of conditions. It occurs during normal aging, a group often referred to as the “worried well”, but it can also be a sign of psychological factors, affective symptoms, personality traits, and neurologic disorders. Individuals with SCD may ultimately progress to AD dementia but also to other dementia subtypes like vascular dementia. Although the concept of SCD has been studied for a while, a consensus under which circumstances it has a predictive value or is a risk factor for cognitive decline, MCI, and AD is still under progress. Studies focusing on SCD vary tremendously in study population, design, and assessment method. These differences may well be the cause of the contrasting results that have been found in the past. The Subjective Cognitive Decline Initiative (SCI-I) Working Group has proposed a conceptual framework to harmonize SCD research (Jessen et al., 2014a).

SCD core criteria

To begin with, the initiative defined core criteria for SCD preceding MCI to set a common SCD research basis and increase comparability between studies. Individuals must fulfill the following two criteria:

- The individual must experience a persistent decline of cognition in comparison with a previously perceived normal status and the self-experienced decline must be unrelated to an acute event.
- Performance on standardized cognitive tests used to classify MCI or prodromal AD must be in the normal age-, gender-, and education-adjusted range.

Individuals must be excluded or be defined as not having SCD preceding MCI if:

- They are diagnosed with MCI, prodromal AD, or dementia.
- Their SCD can be explained by a medical disorder, medication, substance abuse, or a neurologic or psychiatric disease (symptoms below a clinically diagnostic threshold are accepted).

SCD *plus*

In addition to generally applicable SCD core criteria, the SCD-I working group developed SCD *plus* criteria that contain features supposed to increase the likelihood of preclinical AD (Jessen et al., 2014a):

- concerns (worries)
- SCD in memory rather than in another domain

- age of onset >60 years, onset within the last 5 years
- “Feeling of worse performance than others of the same age group”

The following three SCD *plus* criteria are applicable, if they are available for the study:

- confirmation of cognitive decline by an informant
- presence of the *APOE* ϵ 4 genotype
- biomarker evidence for AD (defines preclinical AD)

A recent study reported consistent SCD and additionally expressed worries as independent predictors of incident MCI in cognitively normal individuals (van Harten et al., 2018). Another study found participants of a population-based cohort with SCD to be older and to show worse cognitive performance than controls (Sanchez-Benavides et al., 2018). This was driven by participants with more than three SCD *plus* features. Comparison of controls and participants with SCD revealed that participants with SCD *plus* features showed a more than threefold higher conversion rate to MCI than participants with complaints in one or more cognitive domains and controls (Fernandez-Blazquez et al., 2016). The study design and research question are therefore important factors that influence the heterogeneous opportunities to assess SCD.

1.3.1 Assessment and classification

There is no gold standard for the assessment of SCD. It has still to be ascertained, which cognitive domains are of greatest interest to identify SCD due to underlying AD. One study found SCD assessment to be highly diverse: 75% of SCD assessments were always unique to one of the investigated studies (Rabin et al., 2015). The major differences will be described in the following subsections.

Single questions vs. questionnaires

Single questions as a tool to assess SCD usually capture broader content. They often inquire about the general presence of cognitive or memory problems as well as change in cognition or memory. Some questions even consider severity of the difficulties. Common types of single questions are for example: “Do you think you have problems with your memory?”, “Do you have complaints about your memory in the last 2 years?”, or “Has your memory changed significantly?”.

Questionnaires as a tool to assess SCD usually capture more specific content, like remembering names, dates, and conversations. Questionnaires can also assess activities of daily living, incorporate a rating system, and ask about the perception by others.

Specific questions are for example “How often is the following a problem for you: Going to the store and forgetting what you wanted to buy”, “Do other people say you ask the same question or repeat the same story?”, or “Do you feel unable to recall the names of good friends?”.

For a recommendation if single vs. multiple questions and general vs. specific ones should be used, the context of SCD use has to be considered. It has been proposed that using single questions as opposed to long questionnaires is sufficient to classify SCD even though single questions might lack specificity because many elderly people experience general SCD (Molinuevo et al., 2016, Slavin et al., 2010). If the evolution of SCD is of interest, questionnaires are preferable. The use of retrospective questions has also been recommended, especially ones including a time referent and possibly onset within the last three years to capture the longitudinal nature of SCD (Gifford et al., 2015b, Jessen et al., 2014a).

Self- and informant report

Subjective cognitive decline is per definition based on a self-report. According to the SCD criteria developed by the SCD-I working group, confirmation of SCD by an informant is not necessary, but it potentially increases the risk of AD dementia. It is not part of the core criteria but of the SCD *plus* criteria described earlier.

Self- and informant reports can independently and additively predict dementia risk (Gifford et al., 2015a). The combination of self- and informant complaint was shown to be related to faster decline on several cognitive tests measuring different domains and global cognition. Informant complaint only was related to faster decline in global cognition and information processing speed compared with participants without any complaint (self and informant). Self-complaint only related to faster decline in episodic memory. Another research group developed a questionnaire called “Subjective Cognitive Decline Questionnaire” (SCD-Q) to quantify SCD (Rami et al., 2014). The same questions were answered by the participant and an informant or caregiver. The part of the questionnaire answered by participants discriminated between individuals with SCD and controls. The informant part discriminated between normal cognition and cognitive impairment. This study also found a significant correlation of informant reports with A β 42 and tau levels. Self-reports and biomarker revealed no correlation. Imaging results of a study from 2015 seemed to show that positive informant confirmation of SCD occurred in a later stage of SCD, closer to the MCI stage (Buckley et al., 2015). Also, high frequency of informant concern was associated with poorer cognitive performance. These participants were presumably later in the progression of AD dementia because poorer performance is measurable.

In summary, the literature suggests that self-reports as well as informant reports (individually and collectively) on cognitive decline in the preclinical stage of AD provide relevant information. Cognitive decline by informant report likely reflects a more progressed stage in preclinical AD than self-report of cognitive decline. Regarding these types of reports, it has generally to be considered that people who have an informant represent a group with intact social relationships and networks, which itself is considered as reducing the risk of decline or loss of functional capacity in dementia.

Study setting

Individuals with SCD are studied in several different research settings like population-based studies, medical help-seeking samples (e.g. patients consulting memory-clinics, AD Centers in the United States, general practitioners, or neurologists), and volunteer samples. The study setting influences the study population, its SCD prevalence, and how SCD is reported. It has been proposed that the prevalence in clinical samples is higher than in population-based samples. The SCD framework by Jessen et al. (2014a) does not recommend any study setting. It suggests that all studies examining SCD provide detailed descriptions of their study design, setting, and population. A recent study from 2018 investigated the risk of progression from SCD to MCI in participants of a population-based study in comparison with participants of a memory-clinic (Snitz et al., 2018). Both groups were at higher risk of progressing to MCI compared with participants without SCD, but participants of the memory-clinic sample had a fourteen times higher hazard ratio than participants of the population-based sample. It has also been shown that individuals with SCD seeking help in a memory-clinic are at higher risk of developing AD dementia than individuals of community-based cohorts (Slot et al., 2019). Individuals visiting a memory-clinic experience possibly more severe SCD as they are actively seeking help. This supports proposals that SCD assessed in a clinical setting is more frequently precipitated by processes of AD pathology.

1.3.2 SCD in the course of AD

In the early stages of AD, self-awareness is functional and SCD may even reflect a heightened awareness of cognitive changes, termed *hypermnesia*, especially in individuals with positive A β burden (Vannini et al., 2017). Individuals affected by AD are often observed losing their ability to adequately judge their cognitive performance, a symptom called *anosognosia*. The predictive value of SCD and its validity in the course of AD are discussed in the following subsections.

SCD and objective cognitive performance

Cross-sectional neuropsychological assessments do not capture the longitudinal nature of SCD. Differences on cognitive tests are per definition unlikely, but dependent on the test used, detection of small differences is possible. Thus, detecting subtle cognitive differences of these groups with currently available neuropsychological assessments is difficult. This is presumably why most studies do not find an association of SCD and one time objective cognitive performance (Buckley et al., 2013, Minett et al., 2008). Cross-sectional assessments can also not differentiate between individuals who had excellent cognitive performance but at the time of assessment have already declined and are now at the same level of cognitive performance as individuals who perform average but have not (yet) declined. Nonetheless, differences between individuals with and without SCD have been found in cross-sectional studies. Participants with SCD performed worse on neuropsychological tests of speed and language (Kielb et al., 2017). SCD was also associated with poorer episodic memory (Rijs et al., 2013). A recently developed neuropsychological approach, the face-name-associative-recognition test, has been shown to measure significant performance differences for participants with SCD and MCI compared with cognitively normal participants (Polcher et al., 2017).

Only few longitudinal studies investigating SCD and objective cognition exist. One study captured cross-sectional in addition to longitudinal results. It showed that the cognitive performance was worse in the SCD group compared with the no SCD group and participants of the SCD group had a steeper decline over time in immediate and delayed recall (Koppara et al., 2015).

SCD and clinical progression

The clinical progression of individuals with SCD has been investigated with MCI and dementia as outcomes in different study settings and under varying conditions. Although nearly all elderly experience at least occasional SCD, in population-based settings it has been found to have a prognostic value for incident MCI and dementia (Reisberg et al., 2010, van Harten et al., 2018). Individuals with SCD presenting at AD Centers have been shown to exhibit higher frequencies of MCI and dementia (Kielb et al., 2017). Also, a higher number of SCD symptoms obtained by a questionnaire in combination with positive A β biomarker predicted MCI and dementia more reliably than fewer SCD symptoms (Buckley et al., 2016). A meta-analysis found that the risk of developing dementia is double in individuals with SCD compared with individuals without SCD, revealing an annual conversion rate to MCI of 6.6% (Mitchell et al., 2014). SCD and early MCI seem to be associated with a similarly increased risk of AD dementia (Jessen et al., 2014b).

Studies investigating additional concerns as a SCD *plus* feature predicting dementia have found positive and negative results (Jessen et al., 2014b, Jessen et al., 2010).

SCD and its interrelationships

SCD has complex interrelationships with various factors. It is complicated to reveal the full impact of these relations because not only are the factors interrelated with SCD, but some of them are themselves connected.

Affective symptoms (anxiety, depression) – Depressive symptoms and SCD have a complex interrelationship, especially regarding cause and effect. Individuals with SCD show higher rates of depressive symptoms than individuals without SCD. On the one hand, depression can cause or worsen the perception of cognitive problems and on the other hand, SCD may contribute to the development of depressive symptoms. SCD has been reported as a result of depression rather than underlying AD pathology (Zlatar et al., 2017). In a study from 2013, SCD severity was mainly influenced by depression and anxiety (Buckley et al., 2013). This implies that depression could lead to an overreporting of SCD. Sometimes, SCD is described as a preclinical stage in the course of dementia with depressive symptoms only being an accompanying expression arising from similar or overlapping neuropathological processes. It has been shown that depressive episodes first appearing in earlier life can lead to increased cognitive decline later. Then again first time depression in late life may be symptomatic of underlying pathological changes related to AD and other dementias (Diniz et al., 2013). Overall, cross-sectional studies consistently identify positive associations of SCD and affective symptoms, whereas longitudinal studies are more ambiguous but still tend to find positive associations (Hill et al., 2016).

Physical health concerns – Physical health problems have been shown to be associated with SCD, including chronic pain, type II diabetes mellitus, and sleep. SCD and chronic pain are potentially associated directly by the experience of pain itself and indirectly by effects pain medication can have on cognition (Malfliet et al., 2017, Higgins et al., 2018). Diabetes and sleep are potentially related to SCD because they temporarily lead to fluctuations in cognitive status (Sunram-Lea and Owen, 2017). Studies have found evidence for a relation of SCD with vascular risk factors like smoking, hypertension, and hypercholesterolemia (Paradise et al., 2011, Sahathevan et al., 2012). This is possibly a result of (beginning) vascular cognitive impairment. Neurological damage itself, caused by stroke or head trauma for instance, can cause temporary SCD (Lamb et al., 2013, Byrne et al., 2017).

Personality – Personality traits are associated with the risk of developing dementia (Low et al., 2013). In line with that, they are interrelated with SCD. Neuroticism has been shown

to be negatively associated with SCD, whereas conscientiousness and openness were positively associated with SCD (Luchetti et al., 2016).

SCD reporting in different cultures – Another factor is reporting of SCD in individuals with different cultural backgrounds. There are differences in perception and acceptance of SCD in different cultures, for instance between Chinese and United States citizens (Wu, 2016). Asked to rate their SCD severity from 1 (none) to 5 (extreme), Chinese adults showed lower severity levels than the Americans. In the Chinese culture, it is generally frowned upon to complain, including complaints about personal health issues like SCD. Thus, collected data about SCD prevalence in China most likely does not reflect real SCD prevalence.

Demographic factors (education, age) – The literature suggests that SCD is more accurate in predicting cognitive decline in highly educated individuals than in individuals with lower levels of education (van Oijen et al., 2007, Chary et al., 2013). As described previously, the SCD *plus* criteria suggest an age of onset for SCD of 60 years or older. SCD reporting of middle-aged individuals is indicative of higher amyloid pathology and a higher hazard of declining to dementia (Wang et al., 2004, Zwan et al., 2016).

1.3.3 Difficulties with the concept and outlook

There have been efforts to harmonize assessment methods, but SCD has still to be operationalized (Jessen et al., 2014a, Molinuevo et al., 2016). No gold standard exists defining the context and assessment of SCD when using it as a predictor for cognitive decline, MCI, and dementia. Thus, direct comparison of study results is difficult. Recently, studies with a focus on SCD have been initiated and more harmonized, comparable approaches on SCD can be expected in the future (Wolfsgruber et al., 2019, Slot et al., 2018, Rodriguez-Gomez et al., 2017).

1.4 Mild cognitive impairment (MCI)

The following section describes the concept of MCI. It is a transitional state between cognitively normal aging and manifest dementia. In the AD continuum, the prodromal stage is characterized by MCI and it is the first stage where cognitive deficits are present and detectable via neuropsychological tests. The cognitive performance of affected individuals ranges outside the appropriate age and educational peer group, but their functional daily life abilities are largely preserved. MCI is associated with increased risk of AD compared with cognitively normal individuals (Manly et al., 2008). However, a

diagnosis does not imply future dementia. Some individuals with MCI transition back to a normal cognitive state and some remain clinically stable while others decline further in their cognitive performance and ultimately develop dementia (Busse et al., 2006).

1.4.1 Concept development

Mild cognitive impairment has initially been used as a descriptive term in 1988 by Reisberg and colleagues with Stage 3 on the Global Deterioration Scale (GDS) (Reisberg et al., 1988). Almost a decade later, the term mild cognitive impairment with its abbreviation MCI was used as an independent diagnostic term (Petersen et al., 1995). The first official detailed definition and description followed a few years later as an early but cognitively abnormal state for individuals with “memory impairment beyond that expected for age and education yet are not demented” (Petersen et al., 1999). General MCI can be caused by a number of conditions besides AD, for instance dementia with Lewy bodies, frontotemporal dementia, vascular cognitive impairment, and also depression. Over the years several terminologies have been used and newly developed to grasp the complete concept of MCI. Besides rating individuals on commonly used scales like the GDS Stage 3 and Clinical Dementia Rating stage 0.5, constructs like *cognitive impairment no dementia*, *mild cognitive disorder* and *mild neurocognitive disorder* have been frequently used. In 2004, MCI subgroups were introduced (Petersen, 2004, Winblad et al., 2004): Amnesic MCI (aMCI) represents a precursor of AD occurring as single-domain type or multiple-domain type; non-amnesic MCI (naMCI) represents a precursor of non-AD dementias like dementia with Lewy bodies, frontotemporal dementia, or vascular dementia. Classification of aMCI single-domain is warranted, if the impairment is isolated to the memory domain. For the classification of aMCI multiple-domain, the memory domain and at least one other cognitive domain, for example language, need to be affected. If the impairment is present in any but the memory domain, naMCI should be classified. The original Mayo Clinic criteria for aMCI have since been revised due to new insights into pathophysiological processes and the clinical spectrum of AD (Albert et al., 2011). At approximately the same time, the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) was published, which incorporates criteria for MCI in the diagnosis of ‘mild neurocognitive disorder’. In 2018, a National Institute on Aging – Alzheimer’s Association (NIA-AA) research framework was published, where the definition of MCI is similar to that of their guideline from 2011 but was further refined (Jack et al., 2018). In this framework, MCI is used as a syndromal cognitive staging instrument to be combined with biomarkers in the AD continuum. For clinical practice, the 2011 criteria

from Albert et al. (2011) are foremost used and the 2018 NIA-AA research framework is only intended for use in research context.

1.4.2 Diagnosis

Core clinical criteria for the diagnosis of MCI as defined by Albert et al. (2011) are:

1. *Concern regarding change in cognition*

The change implies subjectively perceived decline in cognitive performance. It can either be reported by the patient or by a close informant or clinician. This criterion equals SCD, only that as part of the clinical MCI criteria the source of concern is variable.

2. *Objective impairment in one or more cognitive domains*

Objective impairment is defined as a cognitive performance lower than expected considering the patient's age and level of education. This decline should ideally be observed over several assessments. Recommendations to define objective impairment in a domain range from 1 to 1.5 standard deviations (SD) below the mean of the appropriate age and educational peer group. This represents a rather tolerant approach in defining objective impairment for MCI. It is a wide range and individuals with 1 SD in one domain may cognitively be very different from individuals with 1.5 SDs in more than one domain. This liberal approach reflects the variety of MCI approaches found in the scientific literature. The criteria state episodic memory as the most commonly impaired domain in MCI because it resides in a region of the brain that is primarily affected by AD pathology.

3. *Preservation of independence in functional abilities*

Activities of daily living in persons with MCI are at most mildly impaired. Complex tasks they used to perform, including shopping or handling their personal finances, may now be more time consuming, or more error-prone than previously. They may need minimal aids or assistance. This criterion helps differentiate individuals with MCI from those with dementia.

4. *Not demented*

Decline or changes in cognition should only be evident to a mild degree so that performance of social and functional abilities is still preserved and diagnostic criteria for dementia are not fulfilled.

With these four core criteria, MCI can be diagnosed. The diagnosis of MCI is generally dependent upon the operationalization applied. Dependent on the setting (clinical or research), additional factors may be considered and supplementary tools and assessments used, especially in research settings.

Diagnosis in research settings

Research studies often use morphological imaging (MRI or computed tomography (CT) scan), functional imaging (PET, single photon emission computed tomography or magnetic resonance spectroscopy), and also blood tests to acquire further information on the pathology causing MCI and to determine the person's AD biomarker status. This helps to understand the etiology. Brain imaging can for example rule out brain tumors and lesions or reveal evidence for cerebrovascular diseases.

Neuropsychological assessment by a trained neuropsychologist is recommended for MCI diagnosis. It can differentiate if the cognitive decline is related to normal aging or to an underlying pathology. Multiple standard neuropsychological tests and test batteries are available. Typically used scales are the Mini Mental State Examination, Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Test Battery, and GDS (Folstein et al., 1975, Welsh et al., 1994, Reisberg et al., 1982). Dependent on the study setting, performance of an extensive assessment may not be feasible. Time is often a limiting factor in large, population-based studies that therefore mostly use smaller test batteries or neuropsychological screenings.

Clinical diagnosis

In the clinic, a physician usually obtains a detailed clinical history, including biography and social anamnesis, of the patient (Knopman and Petersen, 2014). It is often the only possibility to gain information about individual cognitive changes of a patient when longitudinal cognitive data is not available. Obtaining the clinical history directly from the patient gives the physician also an idea of the nature of possible cognitive deficits. If possible, the history reported by the patient should be compared with that acquired from an informant. Deviations between patient and informant can hint towards anosognosia and are a direct sign of memory deficits. It is also the main tool by which the physician can judge impaired functioning in daily activities. Daily functional performance is assessed as well, as it is a criterion of MCI classification. Alternatively or additionally, assessment of Instrumental Activities of daily living (IADL) via scales is typically used to determine preservation of instrumental abilities instead of a subjective report by the patient or an informant. Medication can be an indicator of other medical conditions presenting with MCI.

Vascular pathology is frequently found to coexist with AD pathology and may contribute to cognitive impairment.

A clinical assessment should also be performed by the physician. It comprises a physical examination that helps to identify concomitant diseases, new ones as well as conditions that have already been revealed by the anamnesis. A neurological examination is recommended to help define the etiology of the cognitive impairment.

The anamnesis might suggest cognitive decline, but impairment and identification of affected domains has to be assessed objectively via scales. The ones usually used in clinical practice are screening tools that can additionally provide clarity about presence of dementia. Sometimes an additional extensive neuropsychological assessment as described above should be performed.

In clinical settings, the MCI diagnosis is mainly of interest because individuals with MCI have a higher risk of progressing to dementia.

Differential diagnosis

In clinical and research settings, determining a differential diagnosis is appropriate. Cognitive impairment consistent with MCI is etiologically heterogeneous. The clinical appearance and symptoms of several diseases are similar to those of MCI (Molano et al., 2010, Schneider et al., 2009). In addition, AD is often accompanied by several comorbidities. All these have to be considered for a differential diagnosis. These diseases can be of physical and of psychiatric origin. Physical illnesses are likely neurologically degenerative or vascular. Depression is the most common psychiatric differential diagnosis but similar to SCD, it is interrelated with MCI (Ismail et al., 2017). Medical treatment of conditions is another factor to consider. Poorly controlled diabetes mellitus for instance negatively influences cognition through effects of hyperglycemia and hypoglycemia (Geijselaers et al., 2017).

1.4.3 Difficulties with the concept

The clinical diagnosis differs from MCI diagnoses for research settings. In research, stages of the AD spectrum are primarily defined based on biomarkers. In contrast, MCI is often just seen as an accompanying cognitive syndrome occurring in some patients. This is in contrast to the clinical setting, where the clinical presentation is more relevant. These definitions are functional for the respective purposes but complicate transfer and application of results obtained in research to the clinic.

Variability of cut-off values in cognitive assessments to define a cognitive performance as impaired for the MCI diagnosis and deviations for cognitive impairment in one or more domains is also problematic. The wide range applied in studies leads to high sensitivity when more liberal criteria are applied and to high specificity in studies using more restrictive criteria. This diversity results in different populations that are defined as having MCI leading to different numbers of MCI patients and heterogeneous results. Age is an important factor to consider, as younger individuals are generally at lower risk of developing incident dementia than older people. MCI diagnosis in younger individuals will possibly have a reduced positive predictive value even though the assessment may have good specificity and sensitivity (Molinuevo et al., 2017).

Studies use longitudinal but also cross-sectional assessments for diagnosing MCI. A diagnosis made with the help of cross-sectional data may entail higher MCI rates caused by other etiologies than AD. Longitudinal assessments might capture the MCI reversion rate. On the one hand, this has been argued to rule out false positive cases (regarding pre-AD MCI), on the other hand, individuals that reverse back to normal cognition are at even higher risk of later decline to dementia (Manly et al., 2008, Roberts et al., 2014). This higher risk has been explained by the cognitive reserve of highly educated individuals coping with early AD effects (Coffey et al., 1999).

Lastly, subjective cognitive complaints have been challenged as a MCI criterion by some investigators. Studies have shown that cognitively normal individuals overestimated their cognitive difficulties, whereas MCI patients underestimated their cognitive deficits (Edmonds et al., 2014, Grambaite et al., 2013). It was argued that SCD contributes to high rates of misdiagnosed MCI cases.

1.5 Epidemiology

According to the World Health Organization, epidemiology “is the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems” (WHO, 2019). This section provides an overview of prevalence and incidence rates of SCD and MCI as the main constructs used in this thesis. It shortly introduces the longitudinal, population-based Heinz Nixdorf Recall (HNR) study, which all analyses in this thesis are based upon.

1.5.1 Prevalence rates of SCD

Prevalence of SCD highly varies depending on study setting, study population, and assessment of SCD. Population-based studies report between 12.3% and 57% prevalence of SCD in participants aged 45 years and older when SCD is assessed with a single question (van Oijen et al., 2007, Jessen et al., 2010, Sanchez-Benavides et al., 2018). Prevalence of SCD in studies using different SCD measures, like consistent SCD or SCD with associated concerns, ranges from 14.4% to 53% (Kielb et al., 2017, Hao et al., 2017, Luck et al., 2018).

1.5.2 Prevalence and incidence rates of MCI

Prevalence and incidence rates of MCI are highly dependent on the diagnostic criteria for MCI. Latest prevalence rates based on 34 studies were published in 2018 (Petersen et al., 2018). MCI commonly begins at age 60 to 64. MCI prevalence was 6.7% for ages 60–64, 8.4% for 65–69, 10.1% for 70–74, 14.8% for 75–79, and 25.2% for 80–84. A recent meta-analysis assessed MCI incidence rates based on seven population-based studies from Europe and the United States: (meta-analysis estimate per 1000 person-years and 95% confidence interval (CI)) 22.5 (5.1–51.4) for 75–79 years, 40.9 (7.7–97.5) for 80–84 years and 60.1 (6.7–159.0) for 85 years and older (Gillis et al., 2019). Prevalence of MCI in the population-based HNR study according to the original Mayo clinic criteria was assessed at first follow-up and was 7.8% (Dlugaj et al., 2010).

1.5.3 The Heinz Nixdorf Recall study

The Heinz Nixdorf Recall (Risk Factors, Evaluation of Coronary Calcification, and Lifestyle) study is a population-based, prospective cohort study in Germany with participants from the cities Bochum, Essen, and Mülheim. The study has a cardiovascular focus and its main goal is to evaluate the predictive value of coronary artery calcifications in comparison with traditional risk factors for the prediction of incidence rates of cardiac events in the general population. Initially, 9484 male and female citizens aged 45 to 75 years were invited to participate in the study (Stang et al., 2005). Of these, 4814 participants were enrolled between 2000 and 2003 (Erbel et al., 2012). Participants were invited to follow-up examinations every 5 years. The second follow-up wave was completed in 2015 with 3087 participants. The HNR study is a well characterized cohort and as a longitudinal, population-based study, best suited to identify risk factors for

cognitive decline with the potential to verify temporal relations and symptoms found in clinical studies with only few patients.

1.6 Risk factors for cognitive decline

There are manifold known and still to be discovered risk factors for cognitive decline or impairment linked to dementia, some of which are potentially modifiable. An extensive article from 2017 has identified nine potentially modifiable risk factors for dementia, showing that 35% of dementia is attributable to these (Livingston et al., 2017). Ranked from early life to midlife to late life, the factors are: less education, midlife hearing loss, hypertension, obesity, smoking, depression, physical inactivity, social isolation, and type II diabetes mellitus. The remaining 65% of dementia is attributable to non-modifiable risk factors among which are sex and the *APOE* ϵ 4 genotype.

1.6.1 Sex

Sex and gender are two distinct entities. They have to be treated as such, especially in medical research, because of their differing influence on diverse mechanisms. Sex refers to male and female differences on a physiological and biological level. The sex chromosomes, XX and XY, and gonadal hormones take effect at the cellular, organ, and system level. Gender, however, refers to differing external influences on biological processes and factors in men and women. A combination of social and cultural experiences, environmental and behavioral factors, may characterize an individual's gender. In this thesis, sex is the risk factor being investigated.

Compared with men, AD prevalence is significantly higher in women, they have a more prominent phenotype and they show more biomarker pathology in the MCI state (in *APOE* ϵ 4 carriers). The Alzheimer's Association Report from 2018 stated an estimated lifetime risk for AD dementia at age 65 of 21.1% for women and 11.6% for men (Alzheimer's Association, 2018). It also revealed that, especially after the age of 80 years, women show higher incidence rates of AD than men. In line with this, a meta-analysis of 56 worldwide population- and community-based studies found a significantly higher (naMCI) MCI prevalence in women (Au et al., 2016). They did not find significant sex-differences for MCI incidence (aMCI, naMCI, all-type MCI). In contrast, a report of the Alzheimer's Association from 2013 found men to have a greater risk of MCI than women (Alzheimer's Association, 2013).

The literature describes that women and men outperform each other on cognitive tasks assessing different cognitive domains (Ngun et al., 2011). Women perform for example better on neuropsychological tasks assessing verbal memory, whereas men outperform women on visuospatial tasks (Proust-Lima et al., 2008, van Exel et al., 2001). Women have also been shown to score better in tasks of cognitive speed than men, although women often have a lower educational level (van Exel et al., 2001).

Sex is an important factor to consider in aging research because it influences differential development of men and women on a biological level. Endocrinologic differences exist between the sexes, for example in gonadal hormones. In this context, estrogen is of special interest due to its neuroprotective effect. Women have higher levels of estrogen than men. When they experience menopause (a process that can last up to 12 years (Avis et al., 2015)), estrogen levels significantly decline, thus attenuating the neuroprotective effect in women. In late-life, men experience estrogen loss to a significantly smaller degree because testosterone can be metabolized to estrogen. Men do not experience consequences of estrogen loss as strongly as women after menopause. Also, male and female brains are morphologically different. Firstly, men generally have a larger cerebral brain volume than women. Secondly, men generally have a higher percentage of white matter than women and women have a higher percentage of grey matter (Cosgrove et al., 2007). In addition, male and female brains show structural differences altering dementia related processes (Skup et al., 2011). Brain volumes in MCI and AD patients decline faster in women than in men, with a later onset but faster disease progression in women than in men.

1.6.2 Apolipoprotein E (*APOE*) ϵ 4 genotype

The 3.6 kb long human apolipoprotein E gene (*APOE*) has three major alleles: ϵ 2, ϵ 3 and ϵ 4 (Das et al., 1985). ϵ 2 (ϵ 2/ ϵ 2 or ϵ 2/ ϵ 3) is the least common of the three alleles and is associated with a decreased risk of developing AD (Farrer et al., 1997). The ϵ 3 allele (ϵ 3/ ϵ 3) is the most common one and deemed risk-neutral. Carrying the ϵ 4 allele (ϵ 4/ ϵ 4 or ϵ 4/ ϵ 3) is the main genetic risk factor for late-onset AD dementia, earlier onset of AD, MCI, accelerated cognitive decline, and also reduced learning efficiency in individuals aged 50 to 60 years (Baxter et al., 2003, Corder et al., 1993, Tervo et al., 2004, Lopez et al., 2003). Research on the ϵ 4/ ϵ 2 allele combination is relatively scarce but indicates that this genotype is most similar to ϵ 4 (Oveisgharan et al., 2018). Worldwide allele frequencies were estimated in a study from 2010 based on over 200 populations as follows: 6.4% ϵ 2, 78.3% ϵ 3 and 14.5% ϵ 4 (Eisenberg et al., 2010). A meta-analysis from 2012 reported

approximate prevalence of the $\epsilon 4$ allele among AD patients in central Europe as 50%, 40% in southern Europe and 60% in northern Europe (Ward et al., 2012).

The *APOE* gene encodes the apolipoprotein E lipid binding protein (ApoE). The 34 kDa protein (299 amino acids) is involved in multiple processes like neurogenesis, A β aggregation and clearance, lipid and cholesterol metabolism, glucose metabolism, synaptic function and tangle formation (Mahley, 1988, Yamazaki et al., 2019). Its main function in the CNS, where it is mainly produced by astrocytes, is cholesterol transport to neurons. The ApoE isoforms arising from *APOE* $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$ only differ in two amino acid residues, which results in differing protein structures altering the proteins' lipid binding properties and ultimately their function. Differences from the alleles result in differing ApoE concentrations, which affects cognition. It is still unclear whether the predominant effect of ApoE4 is a gain of toxic functions, or a loss of protective functions or possibly a combination of both compared with ApoE3 (Liu et al., 2013).

ApoE is involved in AD pathologic processes with A β and tau through a variety of mechanisms, some of which are shown in Figure 3 (see next page). It is proposed to have effects on for instance the blood-brain barrier, the innate immune system, accumulation of A β , and synaptic function (Bell et al., 2012). Due to its altered conformation, ApoE4 is toxic in neurons in contrast to ApoE2 and ApoE3. It is highly susceptible to proteolysis and is then further processed into neurotoxic fragments. Accumulation of these neurotoxic fragments in neurons results in mitochondrial dysfunction and cytoskeleton breakdown (Mahley and Huang, 2012). ApoE4 also affects the innate immune response in the brain and causes a strong inflammatory response by microglia and astrocytes, adding to the already initiated neuroinflammation in AD patients. In AD patients, ApoE is deposited in neuritic plaques and NFTs. This neuropathology is more severe in patients carrying the *APOE* $\epsilon 4$ allele (Huang et al., 2001). A β pathology is increased by ApoE4 relative to the other isoforms in a dose-dependent and isoform-specific manner (Holtzman et al., 2012). ApoE4 leads to a decrease in clearance of A β monomers, whereas ApoE2 results in a higher clearance rate (Castellano et al., 2011). A study in mice and humans (post-mortem) from 2017 showed intriguing evidence that ApoE $\epsilon 4$ is not only involved in amyloid pathology but also in tau pathogenesis, neuroinflammation, and tau-mediated neurodegeneration (Shi et al., 2017). It demonstrated a gain of toxic function through ApoE4 – a key functional characteristic already established in context of A β .

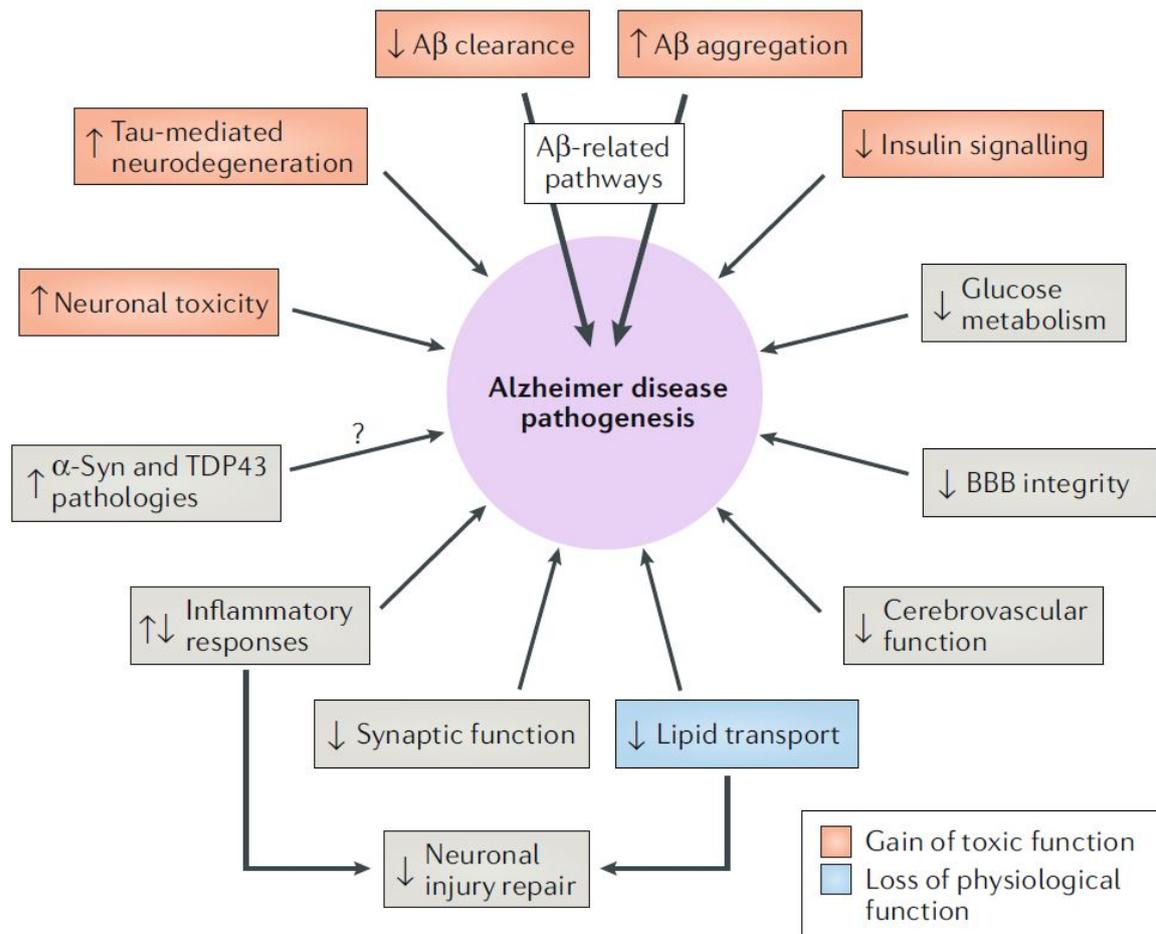


Figure 3: Effects of Apolipoprotein E ε4 (ApoE) on Alzheimer's disease (AD) pathogenic processes. ApoE ε4 is involved in various pathways of AD pathogenesis with some important examples depicted in this figure. Arrows in the boxes illustrate increased and decreased effects of ApoE ε4 on pathogenesis compared with ApoE ε3. Grey boxes indicate processes with insufficient evidence towards either gain of toxic function or loss of physiological function of ApoE ε4. Red boxes indicate processes with evidence suggesting increased AD risk through ApoE ε4. The blue box indicates a process with evidence suggesting loss of physiological function of ApoE ε4. Abbreviations: Aβ, amyloid beta; α-Syn, alpha-synuclein; BBB, blood-brain barrier; TDP, TAR DNA-binding protein. Figure from Yamazaki et al. (2019) reused in this dissertation with permission from Elsevier (RightsLink License Number: 4642411445470).

1.7 Hypotheses

A large meta-analysis revealed that the effects of the *APOE* $\epsilon 4$ genotype are more pronounced in women than in men (Farrer et al., 1997). Research of *APOE* status and SCD is less common and results are mixed. Nonetheless, it seems that carrying the *APOE* $\epsilon 4$ allele affects the relation of SCD with biomarkers, for example leading to elevated $A\beta$ burden or change in hippocampal volume (Zwan et al., 2016, Stewart et al., 2011). Going a step beyond SCD as a risk factor for cognitive decline, *APOE* $\epsilon 4$ carriers have been reported to have higher odds of developing SCD (Krell-Roesch et al., 2015). *APOE* $\epsilon 4$, SCD and sex are important factors regarding cognitive decline and the risk of MCI but their associations and interrelationships are still unclear.

The aim of this thesis is to contribute to the characterization of at risk individuals in the AD continuum by investigating the joint effects of SCD and *APOE* $\epsilon 4$ on cognitive impairment and the risk of incident MCI in the general population with regard to sex. Combining SCD and *APOE* $\epsilon 4$ leads to four different risk profiles in men and women: participants without the risk factors, participants with SCD as the single-risk, participants with *APOE* $\epsilon 4$ as the single-risk, and participants at high-risk displaying both risk factors.

Based on the present literature, my hypotheses are:

- Participants in the four risk profiles differ in their cognitive performance and their risk of incident MCI.
- Participants without SCD and *APOE* $\epsilon 4$ show the best cognitive performance and the lowest risk of incident MCI.
- The male and female high-risk groups show the worst cognitive performance and the highest risk of incident MCI.
- Women show better performance on cognitive tests than men.
- Women have a higher risk of incident MCI than men.

2 MATERIAL AND METHODS

2.1 Study population

In the HNR study, participants were randomly sampled from mandatory registries of residence in the Ruhr Area in Germany. The study outline has previously been described (Schmermund et al., 2002, Stang et al., 2005). Briefly, 4814 participants aged 45 to 75 years were enrolled for baseline (t0) between 2000 and 2003. Participants were invited for follow-up examinations every 5 years (t1, n = 4157, 2005-2008; t2, n = 3087, 2010-2015). A standardized cognitive performance assessment was introduced at the first follow-up examination, t1, and was extended for the second follow-up examination, t2. All data used in the analyses are based on the two follow-up examinations.

The analysis sample was selected as follows: Out of the study population at t1, cognitive data of 71 participants were missing or incomplete. Participants who did not return after t1 were excluded from the analysis (n = 1043). Cognitive data of 177 participants were missing or incomplete at t2. Of the 2866 remaining participants, 9 were excluded due to incomplete data of subjective cognitive assessment at t1 or t2. Missing or incomplete information on depressive symptoms (at t1 and/or t2) led to the exclusion of 361 participants (see '2.4 Assessment of covariates'). A missing *APOE* ε4 status resulted in the exclusion of further 118 participants. Participants with any objective cognitive impairment at t1 were excluded as well (n = 1054). Cognitive impairment at t1 was defined as a performance of one SD below the age- and education-adjusted mean, except for the clock-drawing test where a performance ≥ 3 was rated as impaired (for a detailed description see Winkler et al. (2014)). All participants with a Center for Epidemiologic Studies Depression scale (CES-D, see '2.4 Assessment of covariates') score of 18 and higher at t1 and/or t2 were excluded (n = 123). Three participants were excluded due to a dementia diagnosis. Dementia diagnosis was defined as a previous physician's diagnosis of dementia, meeting the DSM-IV dementia diagnosis criteria or taking cholinesterase inhibitors (anatomic-therapeutic-chemical classification issued by the World Health Organization (WHO), code: N06DA) or other anti-dementia drugs (N06DX) (APA, 1994, WHO, 2004). The final analysis sample consisted of 1198 participants either without MCI or with incident MCI 5 years later at t2.

All participants provided written informed consent. The study was approved by the University of Duisburg-Essen institutional review board and followed established guidelines of good epidemiological practice.

2.2 Neuropsychological assessment

The neuropsychological assessment consisted of the following five cognitive tests at t1:

- (1) Immediate recall measuring immediate verbal memory (Oswald and Fleischmann, 1994). An 8-word list obtained from the Nuremberg Geriatric Inventory (Nürnberger Alters-Inventar, NIA) was used at the beginning of the cognitive assessment. The 8 words were read to the participant who was afterwards asked to recall as many words as possible. The test score ranges from 0 to 8 words with higher scores indicating better performance.
- (2) Labyrinth test measuring speed of processing and executive functioning (Oswald and Fleischmann, 1994). This test was obtained from the NIA. Participants were presented a sheet with a labyrinth printed on it. They were asked to solve the labyrinth in a continuous line from start (in the center) to finish (at the edge) without lifting the pen. After the explanation of this test, the sheet was rotated 90 degrees to prevent the participants from mentally solving the labyrinth already during the test description. Time spent was measured in seconds with higher scores indicating lower performance.
- (3) Animal naming task measuring verbal fluency (Aschenbrenner et al., 2000). Participants were asked to name as many different animals as possible within 1 minute. Measured was the number of animals that occurred to a participant within the given time frame with higher scores indicating better performance.
- (4) Clock-drawing test measuring visuospatial ability (Shulman, 2000). Participants were presented a sheet with a circle representing a clock printed on it. They were asked to draw in all numbers and hands of the clock for the time '10 minutes past 11' as precisely as possible. The score ranges from 0 to 6 points with higher scores indicating lower performance.
- (5) Delayed recall measuring delayed verbal memory (Oswald and Fleischmann, 1994). This test was a repetition of the first test and was thus performed chronologically later in the cognitive assessment. Participants were asked to repeat as many words as they could remember from the same 8-word list they were presented at the beginning of the assessment. The test score ranges from 0 to 8 words with higher scores indicating better performance.

The cognitive assessment was extended at t2 with the following three tests:

- (6) Trail Making Test (TMT) A measuring speed of processing (Tombaugh, 2004). Participants were presented a sheet with consecutively numbered circles printed on it.

They were asked to connect the circles in ascending order without lifting the pen. The test is measured in seconds with higher scores indicating lower performance.

(7) Trail Making Test B measuring speed of processing, visual search and mental flexibility (Tombaugh, 2004). Participants were presented a sheet with circled alternating numbers and letters printed on it. They were asked to connect the circles in ascending order alternating between numbers and letters without lifting the pen. The test is measured in seconds with higher scores indicating lower performance.

(8) Color-word test, a short version of the Stroop task obtained from the NIA (Oswald and Fleischmann, 1994)

- a. Card 1 measuring color word reading. The color words “blue”, “yellow”, “green”, and “red” are printed in black ink on card 1. Participants were asked to read the color words out loud as fast as possible. This test is measured in seconds with higher scores indicating lower performance.
- b. Card 2 measuring color naming. Card 2 has solid bars that are colored in one of the four basic colors printed on it. Participants were asked to name the color of the bars as fast as possible. This test is measured in seconds with higher scores indicating lower performance.
- c. Card 3 has color words printed on it with the ink color being different from the color word. Participants were asked to name the ink color of the color words as fast as possible. This test is measured in seconds with higher scores indicating lower performance. The outcome was defined as “interference performance” by subtracting measured seconds from card 2 from measured seconds from card 3. This measures selective attention and interference performance (Stroop, 1935).

2.2.1 Definition of cognitive impairment at the second follow-up (t2)

Raw data at t2 of tests (1) to (5) (see ‘2.2 Neuropsychological assessment’) were z-transformed using defined norm-data obtained from the HNR study from t1: Z-transformation was based on the mean and SD of the appropriate age- and educational group at t1 with ages 50-59 years, 60-69 years and ≥ 70 years, and education grouped as ≤ 10 years, 11-13 years, and ≥ 14 years. Raw data at t2 of tests (6) to (8) (see ‘2.2 Neuropsychological assessment’) were z-transformed based on the already mentioned educational groups and the age groups 55-64 years, 65-74 years, and ≥ 75 years from t2. These age- and education-adjusted test scores were scaled to have a mean of 10 and a SD of 3 with exception of the clock-drawing test (Ivnik, 1992). All tests were grouped into

one of the following four cognitive domains: (1) attention – TMT A, Color-word test card 1 and card 2; (2) executive function – TMT B, Labyrinth test, Color-word test interference performance, verbal fluency; (3) verbal memory – 8-word list immediate and delayed recall; (4) visuoconstruction – clock-drawing test. For every domain, a domain score was calculated by totaling the newly scaled scores of the corresponding tests. The number of tests in each domain varies. Domain scores were scaled to have a mean of 10 and a SD of 3 to account for these differences.

Participants were then defined to have cognitive impairment at t2 if their performance was more than one SD below the mean (≤ 7) in the domains attention, executive function, verbal memory, or as a score of ≥ 3 in visuoconstruction (Shulman, 2000).

2.2.2 SCD definition

SCD was assessed at t1 with the question “In comparison to two years ago would you rate your memory function as better, same or worse?”. Subjective cognitive decline was defined as present if the participant’s answer was “worse” and is referred to as “SCD” and “SCD+”. Participants who responded “better” or “same” were defined as not having SCD and are referred to as “no SCD” and “SCD-”.

2.2.3 MCI diagnosis

Participants with objective cognitive impairment at t1 were excluded (see 2.1 Study population) and thus, the outcome variable MCI assessed at t2 consist only of incident cases. The MCI diagnosis was based on meeting all of the following published MCI criteria (for a detailed description see section ‘1.4.2 Diagnosis’ (Winblad et al., 2004)): (1) cognitive impairment in at least one of the domains described in section ‘2.2.1 Definition of cognitive impairment at the second follow-up (t2)’; (2) subjective cognitive decline; (3) normal functional abilities and daily activities; (4) no dementia diagnosis.

2.3 APOE genotyping

Cardio-Metabochip BeadArrays were used for genotyping of two single nucleotide polymorphisms (SNPs, rs7412 and rs429358) to discriminate between the *APOE* alleles $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. An *APOE* $\epsilon 4$ -positive genotype was defined as having at least one $\epsilon 4$ allele (2/4, 3/4, 4/4).

2.4 Assessment of covariates

Variables included as covariates in the analyses were chosen based on their effects on SCD and MCI reported in the literature.

Age is still the strongest predictor for cognitive decline. Education is associated with cognition, SCD, and MCI. Both age and educational level served as covariates. Information about participants' socioeconomic status was collected by computer assisted interviews. Besides raw data, education-adjusted data were used by determining four education categories (≤ 10 years, 11–13 years, 14–17 years, and ≥ 18 years). Education was defined after the International Standard Classification of Education based on total years of formal education, combining school and vocational training (UNESCO, 1997).

Depression and SCD are strongly interrelated. The association of depressive symptoms with MCI, especially in women, has previously been shown for the HNR study (Dlugaj et al., 2015). Thus, participants with elevated depressive symptomatology were excluded from the analyses and score on the CES-D was incorporated as a covariate for the analysis sample. We identified depressive symptoms with the 15-item short assessment form of the German version of the CES-D. This scale is a self-report questionnaire with 15 questions that have to be rated on a Likert scale of 0 (rarely or none of the time) to 3 (most or all of the time) by the participant. Thirteen questions had a negative wording and two questions had a positive wording. To match the direction of all questions, the ratings of the two positive questions were reversed for analyses. Participants with any missing item on the CES-D were excluded from the analysis (see '2.1 Study population'). The cut-off score for elevated depressive symptoms was ≥ 18 according to the manual (Radloff, 1977, Hautzinger and Bailer, 1993).

2.5 Statistical analysis

All analyses were performed separately for men and women. Analyses were conducted using IBM SPSS Statistics 25.0, R Statistical Software (version 3.4.2; R Foundation for Statistical Computing, Vienna, Austria), and SAS V.9.4 (SAS Inc., Cary, North Carolina, USA). Level of significance was set a priori as $\alpha = 0.05$.

Participants were divided into four groups:

Group A – reference group, no SCD and *APOE* $\epsilon 4$ -negative genotype

Group B – single-risk group, SCD only

Group C – single-risk group, *APOE* $\epsilon 4$ -positive genotype only

Group D – high-risk group, SCD and *APOE* $\epsilon 4$ -positive genotype

2.5.1 Sociodemographic characteristics

Group comparisons were performed regarding the level of education and number of incident MCI cases at t2 using Pearson's Chi square-test. In case of significant test results, I calculated standardized residuals to reveal group impacts on the level of significance. A residual greater than 2 means that this group contributes more to the level of significance expected. A residual of less than -2 means that this group has a lesser impact on the level of significance than expected. Group comparisons were performed regarding age and CES-D scores at t1 and t2 with analysis of variance (ANOVA). I then performed Tukey Honestly Significant Difference (HSD) post-hoc comparisons to reveal specific group differences in case of significant ANOVA results.

2.5.2 SCD and cognitive performance

Participants of the four SCD and *APOE* ϵ 4 genotype groups were compared regarding their cognitive performance at t1 and t2 with ANOVA. I then performed Tukey HSD post-hoc comparisons where applicable. For the clock-drawing test, I performed Pearson's chi square test, followed by calculating the standardized residuals.

2.5.3 SCD and incident MCI at t2

Binomial logistic regression models were used to estimate odds ratios (ORs) and their 95% CI for all groups and the risk of MCI 5 years later, unadjusted and adjusted for age at t2, level of education and score on the CES-D at t2.

Possible additive effects of SCD and *APOE* ϵ 4 genotype on incident MCI were analyzed by comparing the OR of the high-risk group with the added ORs of both single-risk groups. Measure of interaction on the additive scale "relative excess risk due to interaction" (RERI) was calculated with the following formula (Rothman, 1986):

$$\text{RERI} = \text{OR}_{(\text{group D})} - \text{OR}_{(\text{group C})} - \text{OR}_{(\text{group B})} + 1.$$

With RERI = 0 as reference (no interaction), a RERI > 0 was considered as a positive interaction of SCD and *APOE* ϵ 4 genotype and a RERI < 0 as a negative interaction, with higher and lower scores indicating a stronger interaction effect, respectively.

Attributable proportion due to interaction (AP) was calculated with (Rothman, 1986):

$$AP = RERI / OR_{(\text{group D})}$$

To calculate the Synergy index (S) (Rothman, 1986), I used the following formula:

$$S = [OR_{(\text{group D})} - 1] / [(OR_{(\text{group C})} + (OR_{(\text{group B})})]$$

References for the interaction measures AP and S were 0 and 1, respectively.

Using the delta method, 95% CIs were calculated for RERI, AP and S (Hosmer and Lemeshow, 1992). Measure of interaction on a multiplicative scale was based on the following regression model:

$$\ln[p/(1-p)] = \beta_0 + \beta_1 * SCD + \beta_2 * APOE \epsilon 4 + \beta_3 * SCD * APOE \epsilon 4$$

The odds of the outcome was $p/(1-p)$ and β_3 was the regression coefficient of the modification on a multiplicative scale.

Post-hoc power analyses were performed to identify the minimum sample size per group that was needed to confirm a statistically significant result with a power of $1 - \beta = 0.8$.

3 RESULTS

3.1 Characteristics of the study population

Table 1 shows the sociodemographic characteristics of men. A total of 605 male participants were included in the analyses. Mean follow-up time from t1 to t2 was 5 years for participants in all groups. Group comparisons revealed no significant differences for age and level of education. Results of the ANOVA for men revealed significant differences in CES-D scores at t1 and t2. Post-hoc tests showed that *APOE* ϵ 4-negative men without SCD had significantly lower CES-D scores at t1 than men with SCD only ($p < 0.001$). Men with *APOE* ϵ 4-positive genotype only had significantly lower CES-D scores at t1 than men with SCD only ($p = 0.003$). Men with *APOE* ϵ 4-negative genotype and without SCD had significantly lower CES-D scores at t2 than men with SCD only ($p = 0.004$).

Table 1: Sociodemographic characteristics of men

	<i>APOE</i> ϵ 4- negative, SCD-	<i>APOE</i> ϵ 4- negative, SCD+	<i>APOE</i> ϵ 4- positive, SCD-	<i>APOE</i> ϵ 4- positive, SCD+	ANOVA
	n = 361	n = 93	n = 117	n = 34	$F_{(3, 603)}$, p-value
Age (years), t1	62.81 \pm 6.9	64.09 \pm 7.2	61.99 \pm 6.9	63.38 \pm 6.7	1.65, 0.18
Age (years), t2	68.10 \pm 6.9	69.33 \pm 7.1	67.26 \pm 6.9	68.56 \pm 6.7	1.60, 0.19
Education					
≤ 10 years	12 (3)	5 (6)	2 (2)	3 (9)	0.64, 0.49
11-13 years	146 (40)	39 (42)	49 (42)	9 (27)	
14-17 years	128 (36)	32 (34)	38 (33)	12 (35)	
≥ 18 years	75 (21)	17 (18)	28 (24)	10 (29)	
Score on depression scale (CES-D), t1	4.86 \pm 3.5	6.75 \pm 4.0	5.00 \pm 3.7	6.50 \pm 4.5	8.18, < 0.001
Score on depression scale (CES-D), t2	4.65 \pm 3.8	6.25 \pm 4.5	5.22 \pm 4.1	6.00 \pm 4.6	4.57, 0.002

Note: Owing to rounding, percentages do not always total 100. Abbreviations: ANOVA, analysis of variance; *APOE*, apolipoprotein E; CES-D, Center for Epidemiologic Studies Depression Scale; SCD, subjective cognitive decline; t1, first follow-up examination; t2, second follow-up examination.

Table 2 shows the sociodemographic characteristics of women. A total of 593 female participants were included in the analyses. Mean follow-up time from t1 to t2 was 5 years for participants in all groups. Group comparisons revealed no significant differences for age and level of education. Results of the ANOVA for women revealed significant differences in CES-D scores at t1 and t2. Post-hoc tests were not significant for group comparisons at t1. Women with *APOE* ϵ 4-negative genotype and without SCD had significantly lower CES-D scores than women with SCD only ($p < 0.001$). Women with *APOE* ϵ 4-positive genotype only had significantly lower CES-D scores than women with SCD only ($p = 0.003$).

Table 2: Sociodemographic characteristics of women

	<i>APOE</i> ϵ 4- negative, SCD-	<i>APOE</i> ϵ 4- negative, SCD+	<i>APOE</i> ϵ 4- positive, SCD-	<i>APOE</i> ϵ 4- positive, SCD+	ANOVA
	n = 320	n = 116	n = 108	n = 49	$F_{(3, 589)}$, p-value
Age (years), t1	62.16 \pm 6.6	61.87 \pm 6.7	61.62 \pm 7.4	64.27 \pm 6.7	1.87, 0.13
Age (years), t2	67.43 \pm 6.6	67.18 \pm 6.7	66.89 \pm 7.5	69.45 \pm 6.8	1.71, 0.17
Education					
≤ 10 years	24 (8)	6 (5)	7 (7)	6 (12)	0.64, 0.31
11-13 years	221 (69)	74 (64)	66 (61)	29 (59)	
14-17 years	35 (11)	18 (16)	22 (20)	6 (12)	
≥ 18 years	40 (13)	18 (16)	13 (12)	8 (16)	
Score on depression scale (CES-D), t1	5.82 \pm 4.2	6.97 \pm 4.3	5.56 \pm 4.1	6.92 \pm 4.4	5.78, 0.019
Score on depression scale (CES-D), t2	5.56 \pm 4.1	6.91 \pm 4.3	5.57 \pm 3.9	7.61 \pm 4.8	3.34, 0.001

Note: Owing to rounding, percentages do not always total 100. Abbreviations: ANOVA, analysis of variance; *APOE*, apolipoprotein E; CES-D, Center for Epidemiologic Studies Depression Scale; SCD, subjective cognitive decline; t1, first follow-up examination; t2, second follow-up examination.

The frequency of incident MCI cases at t2 differed significantly between male SCD and *APOE* ϵ 4 genotype groups (Table 3, see next page). Men with SCD only showed significantly higher frequencies of incident MCI compared with the other groups. The significant result of the Chi square-test ($p = 0.003$) originated from this group, shown by a standardized residual of 2.9. The standardized residual for the male high-risk group was also slightly elevated. The frequency of incident MCI cases at t2 differed significantly between female SCD and *APOE* ϵ 4 genotype groups (Table 3, see next page). The high-risk group showed significantly higher frequencies of incident MCI compared with the other groups. The significant result of the Chi square-test ($p = 0.001$) originated from this group, shown by a standardized residual of 3.4.

Table 3: Number of incident MCI cases at t2

	Total	MEN	Standardized residual	WOMEN	Standardized residual
	Incident MCI, n	Incident MCI, n (%)		Incident MCI, n (%)	
<i>APOE</i> ε4-negative, SCD-	261	23 (6)	-1.7	16 of 320 (5)	-1.5
<i>APOE</i> ε4-negative, SCD+	93	17 (18)	2.9	10 of 116 (9)	0.5
<i>APOE</i> ε4-positive, SCD-	117	10 (9)	-0.2	7 of 108 (7)	-0.3
<i>APOE</i> ε4-positive, SCD+	34	5 (15)	1.1	10 of 49 (20)	3.4

Abbreviations: *APOE*, apolipoprotein E; MCI, mild cognitive impairment; SCD, subjective cognitive decline; t2, second follow-up examination.

Table 4 shows the frequency of SCD for men and women at t1. Subjective cognitive decline status at t1 defined the group affiliation of participants in the four SCD and *APOE* ε4 genotype groups. Women in the study sample had more frequently SCD than men. Male and female *APOE* ε4-positive participants had more frequently SCD than male and female *APOE* ε4-negative participants, respectively.

Table 4: SCD frequency in the study sample at t1

	SCD frequency	
	MEN	WOMEN
Total	21%	28%
<i>APOE</i> ε4-negative	26%	36%
<i>APOE</i> ε4-positive	29%	45%

Abbreviations: *APOE*, apolipoprotein E; SCD, subjective cognitive decline; t1, first follow-up examination.

3.2 Cognitive performance

3.2.1 Follow-up t1

At t1, cognitive performance on the five standardized tests differed significantly between male SCD and *APOE* ε4 genotype groups in the semantic category “animals” ($p = 0.016$), shown in Table 5 (see next page). Post-hoc comparisons revealed that *APOE* ε4-negative men without SCD performed better than men with SCD only ($p = 0.005$). Men with *APOE* ε4-positive genotype only performed better than men with SCD only ($p = 0.003$). There were no significant group differences in the other four cognitive tests.

Results

Table 5: Cognitive performance of men at t1

	<i>APOE</i> ε4- negative, SCD-	<i>APOE</i> ε4- negative, SCD+	<i>APOE</i> ε4- positive, SCD-	<i>APOE</i> ε4- positive, SCD+	ANOVA
	n = 361	n = 93	n = 117	n = 34	F _(3, 603) , p-value
8-word list, immediate	5.58 ± 1.0	5.76 ± 1.1	5.85 ± 1.0	5.77 ± 1.1	0.21, 0.89
Labyrinth test	40.07 ± 14.5	42.15 ± 17.3	41.27 ± 16.7	42.06 ± 15.4	0.61, 0.61
Semantic category “Animals”	25.99 ± 5.6	24.11 ± 5.2	26.49 ± 6.2	26.27 ± 7.1	3.46, 0.016
Clock-drawing test					
1 point	298 (83)	75 (81)	90 (77)	31 (91)	1.35, 0.26
2 points	63 (18)	18 (19)	27 (23)	3 (9)	
8-word list, delayed	4.33 ± 1.5	3.97 ± 1.3	4.15 ± 1.3	4.47 ± 1.4	2.05, 0.11

Note: Owing to rounding, percentages do not always total 100. Abbreviations: ANOVA, analysis of variance; *APOE*, apolipoprotein E; SCD, subjective cognitive decline; t1, first follow-up examination.

At t1, cognitive performance on the five standardized tests did not differ significantly between female SCD and *APOE* ε4 genotype groups (Table 6).

Table 6: Cognitive performance of women at t1

	<i>APOE</i> ε4- negative, SCD-	<i>APOE</i> ε4- negative, SCD+	<i>APOE</i> ε4- positive, SCD-	<i>APOE</i> ε4- positive, SCD+	ANOVA
	n = 320	n = 116	n = 108	n = 49	F _(3, 589) , p-value
8-word list, immediate	5.98 ± 1.0	5.99 ± 1.0	6.06 ± 1.0	6.04 ± 1.0	0.16, 0.93
Labyrinth test	42.24 ± 16.6	44.48 ± 17.4	41.89 ± 15.7	43.80 ± 17.5	0.68, 0.57
Semantic category “Animals”	25.38 ± 5.4	25.66 ± 5.5	25.90 ± 6.3	24.92 ± 5.6	0.44, 0.72
Clock-drawing test					
1 point	263 (82)	99 (85)	93 (86)	42 (86)	0.46, 0.71
2 points	57 (18)	17 (15)	15 (14)	7 (14)	
8-word list, delayed	4.32 ± 1.5	4.64 ± 1.4	4.56 ± 1.4	4.65 ± 1.4	2.05, 0.11

Abbreviations: ANOVA, analysis of variance; *APOE*, apolipoprotein E; SCD, subjective cognitive decline; t1, first follow-up examination.

3.2.2 Follow-up t2

At t2, cognitive performance on the eight standardized tests differed significantly between male SCD and *APOE* ϵ 4 genotype groups in the semantic category “animals” ($p = 0.025$), shown in Table 7. Post-hoc comparisons revealed that *APOE* ϵ 4-negative men without SCD performed better than men with SCD only ($p = 0.043$). Men with *APOE* ϵ 4-positive genotype only performed better than men with SCD only ($p = 0.031$). There were no significant group differences in the other seven cognitive tests.

Table 7: Cognitive performance of men at t2

	<i>APOE</i> ϵ 4- negative, SCD-	<i>APOE</i> ϵ 4- negative, SCD+	<i>APOE</i> ϵ 4- positive, SCD-	<i>APOE</i> ϵ 4- positive, SCD+	ANOVA
	n = 361	n = 93	n = 117	n = 34	$F_{(3, 603)}$, p-value
8-word list, immediate	5.58 \pm 1.1	5.60 \pm 1.1	5.60 \pm 1.2	5.35 \pm 1.1	0.47, 0.71
Labyrinth test	44.18 \pm 21.2	46.31 \pm 19.1	45.22 \pm 18.5	47.44 \pm 15.8	0.46, 0.71
Semantic category “Animals”	25.09 \pm 6.3	23.17 \pm 5.2	25.55 \pm 6.4	24.00 \pm 7.1	3.11, 0.025
Clock-drawing test					
1 point	170 (47)	52 (56)	59 (50)	11 (32)	1.15, 0.33
2 points	152 (42)	25 (27)	48 (41)	18 (53)	
\geq 3 points	39 (11)	16 (17)	10 (9)	5 (15)	
8-word list, delayed	3.99 \pm 1.7	3.83 \pm 1.8	3.85 \pm 1.8	3.76 \pm 1.7	0.43, 0.73
Trail Making Test A	40.86 \pm 17.9	41.68 \pm 13.8	38.13 \pm 12.6	38.91 \pm 13.0	1.17, 0.32
Trail Making Test B	107.63 \pm 56.5	114.47 \pm 59.7	104.76 \pm 48.6	117.18 \pm 66.9	0.83, 0.48
Stroop test card 1	14.93 \pm 2.9	15.12 \pm 2.9	14.50 \pm 2.7	15.24 \pm 2.8	1.17, 0.32
Stroop test card 2	22.74 \pm 4.4	23.44 \pm 5.8	22.55 \pm 4.5	23.32 \pm 4.0	0.81, 0.49
Stroop test interference	24.19 \pm 15.6	25.55 \pm 14.7	25.92 \pm 20.9	25.24 \pm 10.7	0.44, 0.73

Abbreviations: ANOVA, analysis of variance; *APOE*, apolipoprotein E; SCD, subjective cognitive decline; t2, second follow-up examination.

At t2, cognitive performance on the eight standardized tests differed significantly between female SCD and *APOE* ϵ 4 genotype groups in TMT B ($p = 0.007$), shown in Table 8 (see next page). Post-hoc comparisons revealed that women with SCD only performed better than women in the high-risk group ($p = 0.007$). There were no significant group differences in the other seven cognitive tests.

Table 8: Cognitive performance of women at t2

	<i>APOE</i> ε4- negative, SCD-	<i>APOE</i> ε4- negative, SCD+	<i>APOE</i> ε4- positive, SCD-	<i>APOE</i> ε4- positive, SCD+	ANOVA
	n = 320	n = 116	n = 108	n = 49	F _(3, 589) , p-value
8-word list, immediate	5.68 ± 1.2	5.92 ± 1.2	5.82 ± 1.2	5.78 ± 1.2	1.34, 0.26
Labyrinth test	50.03 ± 28.7	47.07 ± 24.7	48.66 ± 27.3	45.2 ± 20.5	0.67, 0.57
Semantic category “Animals”	25.26 ± 5.6	24.64 ± 5.5	25.0 ± 5.8	24.65 ± 7.5	0.42, 0.74
Clock-drawing test					
1 point	153 (48)	62 (53)	58 (54)	27 (55)	0.91, 0.43
2 points	112 (35)	38 (33)	38 (35)	12 (25)	
≥ 3 points	55 (17)	16 (14)	12 (11)	10 (20)	
8-word list, delayed	4.2 ± 1.7	4.58 ± 1.7	4.45 ± 2.0	4.2 ± 1.7	1.57, 0.27
Trail Making Test A	40.31 ± 16.7	38.44 ± 12.5	36.82 ± 15.0	39.59 ± 12.4	1.53, 0.21
Trail Making Test B	109.18 ± 56.8	94.53 ± 41.1	102.19 ± 51.3	124.43 ± 70.4	4.12, 0.007
Stroop test card 1	14.65 ± 3.0	14.84 ± 2.5	14.7 ± 2.2	15.59 ± 4.2	1.57, 0.20
Stroop test card 2	21.56 ± 4.1	21.99 ± 4.0	21.78 ± 3.9	21.04 ± 3.1	0.77, 0.51
Stroop test interference	23.39 ± 13.8	22.64 ± 14.3	21.83 ± 10.0	22.49 ± 9.5	1.57, 0.20

Abbreviations: ANOVA, analysis of variance; *APOE*, apolipoprotein E; SCD, subjective cognitive decline; t2, second follow-up examination.

3.3 Risk of incident MCI

Figure 4 (see next page) shows the results from multinomial logistic regression analyses for male SCD and *APOE* ε4 genotype groups. Men with SCD only showed the highest OR for incident MCI at t2. The OR of the high-risk group was elevated, but lower than that of men with SCD only. Men with *APOE* ε4-positive genotype only showed the lowest OR.

Table 9 (see next page) shows the results of the logistic regression analyses for SCD within *APOE* ε4 genotype and measure of effect modification on a multiplicative scale for men. The ORs, adjusted and unadjusted, for incident MCI were increased in men with SCD only. The multiplicative interaction measure showed a trend for negative interaction of SCD and *APOE* ε4 genotype, not reaching statistical significance.

Table 10 (see next page) shows the results of additive interaction measures for men. All measures (RERI, AP, and S) showed a trend for a negative interaction effect of SCD and *APOE* ε4 genotype in men. None of the measures reached statistical significance.

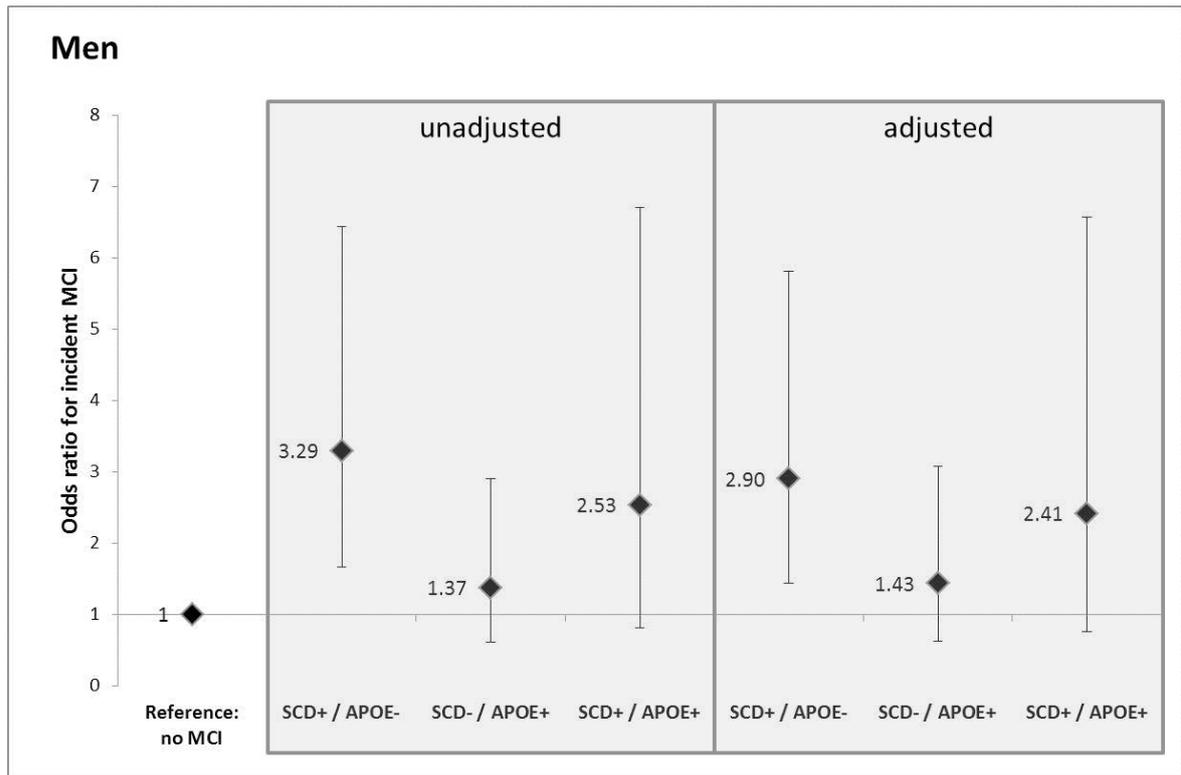


Figure 4: Results from the multinomial logistic regression analyses for men. The figure illustrates risk of incident mild cognitive impairment (MCI) for male single-risk and high-risk subjective cognitive decline (SCD) and apolipoprotein (*APOE*) $\epsilon 4$ genotype groups; unadjusted and adjusted for age, level of education and score on the Center for Epidemiologic Studies Depression Scale. Depicted are odds ratios for incident MCI (black diamonds) with their corresponding 95% confidence intervals (upper and lower bars).

Table 9: Odds ratios of incident MCI for SCD+ within *APOE* $\epsilon 4$ genotype and measure of effect modification on a multiplicative scale for men

	Number of controls/cases	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
<i>APOE</i> $\epsilon 4$ -negative, SCD-	338/23	1 (reference)		1 (reference)	
<i>APOE</i> $\epsilon 4$ -negative, SCD+	76/17	3.29 (1.66 - 6.43)	< 0.001	2.90 (1.43 - 5.81)	0.003
<i>APOE</i> $\epsilon 4$ -positive, SCD-	107/10	1 (reference)		1 (reference)	
<i>APOE</i> $\epsilon 4$ -positive, SCD+	29/5	1.84 (0.54 - 5.63)	0.30	1.69 (0.48 - 5.28)	0.38
Multiplicative scale		0.56 (0.14 - 2.08)	0.40	0.58 (0.14 - 2.22)	0.43

Abbreviations: *APOE*, apolipoprotein E; CI, confidence interval; OR, odds ratio; SCD, subjective cognitive decline.

Table 10: Additive measures of interaction for men

	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Relative excess risk due to interaction	-1.13 (-4.35 - 2.09)	0.49	-0.92 (-4.01 - 2.16)	0.56
Attributable portion due to interaction	-0.45 (-2.03 - 1.14)	0.58	-0.38 (-1.94 - 1.17)	0.63
Synergy index	0.58 (0.10 - 3.25)	0.53	0.60 (0.10 - 3.80)	0.59

Abbreviations: CI, confidence interval; OR, odds ratio.

Figure 5 shows the results from multinomial logistic regression analyses for female SCD and *APOE* $\epsilon 4$ genotype groups. The high-risk group showed the highest OR for incident MCI at t2. Women with SCD only showed the second highest OR and women with *APOE* $\epsilon 4$ -positive genotype only had the lowest OR of incident MCI.

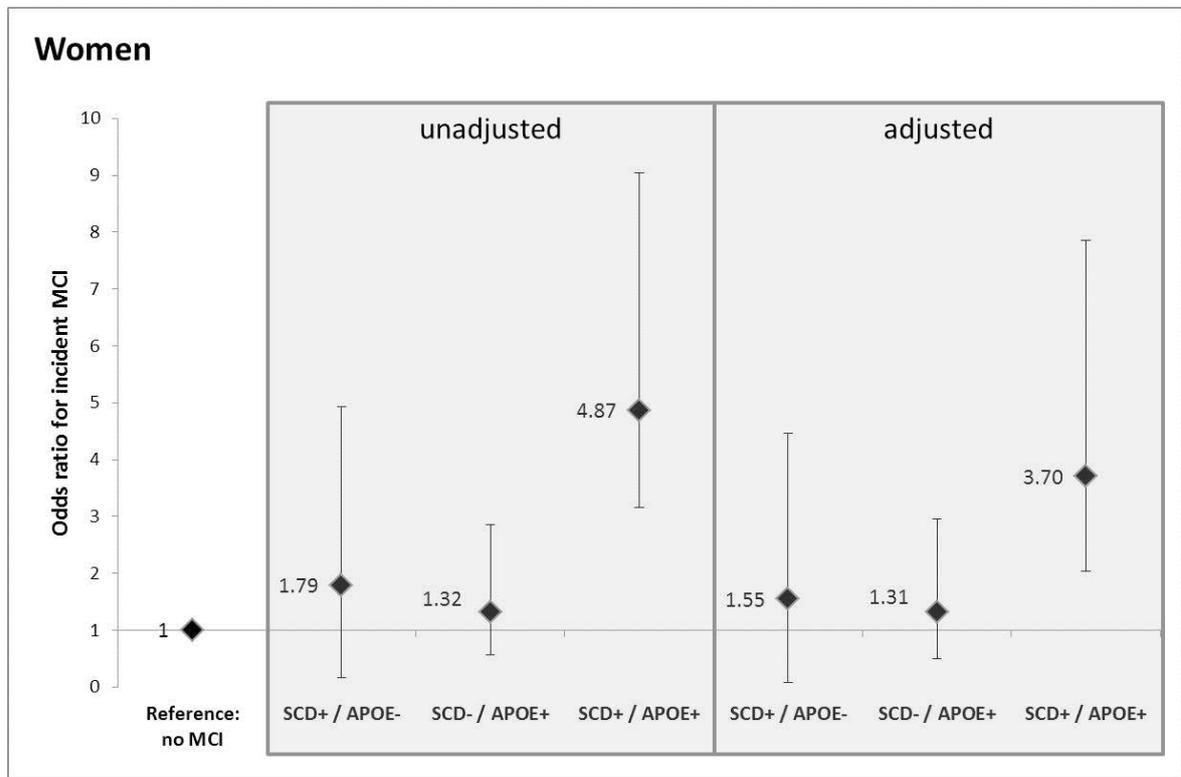


Figure 5: Results from the multinomial logistic regression analyses for women. The figure illustrates risk of incident mild cognitive impairment (MCI) for female single-risk and high-risk subjective cognitive decline (SCD) and apolipoprotein (*APOE*) $\epsilon 4$ genotype groups; unadjusted and adjusted for age, level of education and score on the Center for Epidemiologic Studies Depression Scale. Depicted are odds ratios for incident MCI (black diamonds) with their corresponding 95% confidence intervals (upper and lower bars).

Table 11 (see next page) shows the results of the logistic regression analyses for SCD within *APOE* $\epsilon 4$ genotype and measure of effect modification on a multiplicative scale for women. The OR, unadjusted, for incident MCI was increased for the high-risk group in women. The multiplicative interaction measure showed a trend for positive interaction of SCD and *APOE* $\epsilon 4$ genotype, not reaching statistical significance.

Table 12 (see next page) shows the results of additive interaction measures for women. All measures (RERI, AP, and S) showed a trend for a positive interaction effect of SCD and *APOE* $\epsilon 4$ genotype in women. None of the measures reached statistical significance.

Table 11: Odds ratios of incident MCI for SCD+ within *APOE* ϵ 4 genotype and measure of effect modification on a multiplicative scale for women

	Number of controls /cases	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
<i>APOE</i> ϵ 4-negative, SCD-	304/16	1 (reference)		1 (reference)	
<i>APOE</i> ϵ 4-negative, SCD+	106/10	1.79 (0.76 - 4.02)	0.16	1.55 (0.65 - 3.54)	0.31
<i>APOE</i> ϵ 4-positive, SCD-	101/7	1 (reference)		1 (reference)	
<i>APOE</i> ϵ 4-positive, SCD+	39/10	3.70 (1.33 - 10.85)	0.013	2.82 (0.98 - 8.50)	0.06
Multiplicative scale		2.06 (0.56 - 8.00)	0.28	1.82 (0.48 - 7.25)	0.38

Abbreviations: *APOE*, apolipoprotein E; CI, confidence interval; OR, odds ratio; SCD, subjective cognitive decline.

Table 12: Additive measures of interaction for women

	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Relative excess risk due to interaction	2.76 (-1.06 - 6.59)	0.16	1.84 (-1.23 - 4.92)	0.24
Attributable portion due to interaction	0.57 (0.12 - 1.02)	0.013	0.50 (-0.05 - 1.05)	0.08
Synergy index	3.49 (0.57 - 21.42)	0.18	3.15 (0.35 - 28.05)	0.31

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 13 shows the number of participants necessary for each group to prove that results of logistic regression models are truly significant. Actual numbers of men with SCD only are close to the calculated minimum. Actual numbers of women in the high-risk group are close to the calculated minimum.

Table 13: Post-hoc power analysis for minimum number of cases

	MEN n	WOMEN n
<i>APOE</i> ϵ 4-negative, SCD-	reference	reference
<i>APOE</i> ϵ 4-negative, SCD+	119	759
<i>APOE</i> ϵ 4-positive, SCD-	2288	3870
<i>APOE</i> ϵ 4-positive, SCD+	212	73

Abbreviations: *APOE*, apolipoprotein E; SCD, subjective cognitive decline.

4 DISCUSSION

The aim of this thesis is to investigate the association of SCD and *APOE* ϵ 4 genotype for incident MCI in regard to potential sex-differences in a well characterized population-based cohort. The combined risk factors SCD and positive *APOE* ϵ 4 genotype showed a strong association with incident MCI after 5 years in women, whereas SCD and *APOE* ϵ 4-negativity had the strongest association in men. Accordingly, SCD and *APOE* ϵ 4 genotype revealed a positive interaction effect in women and a negative interaction in men. In the last years, research has focused on prodromal and preclinical stages of AD because pathological changes start decades before the onset of clinical symptoms and there are still no causal therapies. The development of prevention strategies and identification of populations with elevated risk are thus prioritized. This work contributes to this goal by presenting differential risks of SCD and *APOE* ϵ 4 genotype on the development of MCI for women and men in the general elder population. The effects of sex and *APOE* ϵ 4 are understudied in the field of AD research and all factors combined have so far not been investigated.

4.1 SCD, *APOE* ϵ 4, sex, and objective cognitive performance

Cognitive performance at t1 and t2 differed only significantly in single tests. Descriptive comparison of the mean raw data shows some trends: At the first follow-up examination, men without SCD tended to perform better than men with SCD, regardless of *APOE* ϵ 4 genotype. Women with *APOE* ϵ 4-positive genotype performed better than *APOE* ϵ 4-negative women, regardless of SCD status. At the second follow-up examination, the group of *APOE* ϵ 4-positive men without SCD tended to show the best performance (not true for three tests), which is contrary to the expectation that *APOE* ϵ 4-negative men without SCD (used as the control group later on) would perform best. There was no trend for any of the four female groups to generally show better cognitive performance than one of the other groups.

In line with the majority of the literature, cross-sectional associations of SCD and objective cognitive performance at t1 have barely been detected in this work. Only men with SCD seemed to show worse performance in comparison with men without SCD. Such an association of SCD and cognition in men but not in women has been described (Tomita et al., 2014). Longitudinal differences, i.e. SCD assessed at the first follow-up and cognitive performance at the second follow-up, between the four male and female SCD and *APOE*

$\epsilon 4$ genotype groups, respectively, were marginal. Thus, the hypothesis that participants with both risk factors (SCD and *APOE* $\epsilon 4$ -positive genotype) show the worst cognitive performance could not be confirmed. There are several possible explanations for the missing associations of SCD and objective cognition in this work. First, the cognitive tests applied may not be sensitive enough to detect the subtle differences between participants with and without SCD. This is a common problem in large, epidemiologic studies without a neuropsychological focus. These usually assess a multitude of different factors and are consequently limited in time and extent of each assessment. Since the main aim of such studies centers around other factors than for example MCI or dementia, cognitive assessments used are normally brief. That tests are too insensitive for clear differentiation of individuals with and without SCD seems to be the case for the majority of standard cognitive assessments available to date, especially when testing individuals younger than 75 years. The recently developed face-name-associative-recognition test may be a promising approach to differentiate individuals with SCD from normal aging (Polcher et al., 2017). Second, associations of SCD and cognitive performance in population-based studies tended to be weaker than those found in memory-clinic samples (Snitz et al., 2018). This might be explained by the lower SCD prevalence in population-based samples and by the fact that individuals with SCD actively seeking help in a memory-clinic are subjectively more affected. Third, assessing the individual cognitive progression (capturing individual cognitive decline) rather than solely cognitive performance 5 years later may be a more successful approach in identifying longitudinal associations of SCD and objective performance. These factors might also be the reason for undetectable differences and missing tendencies of *APOE* $\epsilon 4$ -positive and *APOE* $\epsilon 4$ -negative participants.

4.2 SCD, *APOE* $\epsilon 4$, sex, and incident MCI

Intriguingly, this thesis showed that results on the association of SCD and *APOE* $\epsilon 4$ genotype with incident MCI were strongly dependent on sex. The most unexpected finding was that having the *APOE* $\epsilon 4$ -negative genotype in combination with SCD led to the highest risk of incident MCI 5 years later – but only in men. In women, the high-risk group exhibiting both factors showed the highest risk for incident MCI, which affirms the initial hypothesis. *APOE* $\epsilon 4$ -negative women with SCD had a slightly increased risk. Interaction analyses of SCD and *APOE* $\epsilon 4$ genotype for risk of incident MCI supported the unexpected result for men and also the result for women consistent with the hypothesis. All measures suggested negative interaction of *APOE* $\epsilon 4$ genotype and SCD in male

participants and positive interaction in female participants. *APOE* ϵ 4 is the most prominent genetic risk factor for conversion to AD dementia. The 3-fold increased risk for *APOE* ϵ 4-negative men with SCD and the only 2.5-fold increased risk for *APOE* ϵ 4-positive men with SCD were therefore surprising. It was likewise unexpected that this was a finding specific to male participants.

The preferred explanation for the results in men arises from an evolutionary theory proposed by Williams in 1957 called “antagonistic pleiotropy” (Williams, 1957). Transferred to *APOE* ϵ 4, the theory describes the following: Carrying the *APOE* ϵ 4 allele is an evolutionary disadvantage later in life as it strongly increases the risk of AD. It can thus be assumed that this genotype must have an earlier beneficial effect otherwise it would not have survived human genetic evolution to the present. The results for men in this work are in line with another study that found evidence for applicability of antagonistic pleiotropy in case of *APOE* ϵ 4, cognition, and male sex (Zokaei et al., 2017). They discovered enhanced memory performance in middle-aged *APOE* ϵ 4-positive men but not in women. This advantage presented itself in a gene dose-dependent manner. No other studies investigated the influence of *APOE* ϵ 4 on cognitive performance or cognitive diagnoses, but the possible mechanism of antagonistic pleiotropy for *APOE* ϵ 4 is supported by imaging studies. These have shown cortical thickening in AD vulnerable areas in *APOE* ϵ 4 carriers in midlife to the beginning of late-life (Espeseth et al., 2012). A functional MRI study also found enhanced functional connectivity from the default mode network to the anterior and posterior cingulate cortex in middle-aged *APOE* ϵ 4 carriers (Goveas et al., 2013). These cortical regions are crucial parts of the salience network, which is involved in a variety of complex brain functions, for example social and affective behavior (Menon, 2015). The default mode network also contributes to a variety of different brain functions, which are thought to include semantic processing as well as episodic and autobiographical memory (Buckner et al., 2008). It has been shown to be altered in AD patients with a reduction in glucose metabolism and accumulation of A β plaques particularly within this network (Jones et al., 2016). Increased connectivity of these networks is associated with better memory. Studies in line with the results showing increased risk of MCI in male *APOE* ϵ 4-negative participants with SCD are generally scarce. In addition, *APOE* ϵ 4 as a risk factor for AD has mainly been studied in old-age where carriers are at higher risk of developing cognitive impairment and AD than non-carriers (Altmann et al., 2014). Strong associations and interaction of *APOE* ϵ 4-positivity and sex on cognitive impairment have been revealed specifically for older women (Beydoun et al., 2012). Studies in children and young adults revealed conversed associations of *APOE* ϵ 4-positivity and cognitive performance (Bloss et al., 2008, Jochemsen et al., 2012). These studies did not incorporate sex differences. Taking these

findings and the above reported results from middle- and older age groups into account, the underlying antagonistic pleiotropy for *APOE* ϵ 4 supports the higher risk of incident MCI in the male non-carriers.

Another possible explanation for the sex-specific difference is a hypothesis based on estrogen levels. Estrogen has been shown to have a neuroprotective effect, which is based on multiple factors like its neuroprotective ability against oxidative stress, its interference with A β plaque formation in the brain, and its impact on the cholinergic system, which is associated with learning and memory (Behl et al., 1997, Francis et al., 1999, Yue et al., 2005). Studies indicate that *APOE* ϵ 4 might neutralize the neuroprotective effect associated with estrogen (Yaffe et al., 2000, Burkhardt et al., 2004). Thus, the high estrogen levels in women do not give a cognitive advantage over men if a woman is an *APOE* ϵ 4 carrier. The missing neuroprotection may lead to higher MCI incidence in female *APOE* ϵ 4 carriers versus non-carriers. Additionally, women suffer from significant estrogen loss after menopause, which might severely affect cognition and increase risk of AD. In comparison with *APOE* ϵ 4-positive men, *APOE* ϵ 4-positive women are at higher risk of developing AD in midlife to early late-life, show higher levels of AD related biomarkers, and have been shown to exhibit reduced connectivity in the precuneus, an area in the brain typically altered in AD patients (Neu et al., 2017, Altmann et al., 2014, Damoiseaux et al., 2012). It has also been shown that sex and *APOE* ϵ 4 interact in individuals with MCI and that female carriers had a steeper decline than male carriers and non-carriers (Wang et al., 2019). Another study found three-way interaction effects of sex, *APOE* ϵ 4 and A β that resulted in *APOE* ϵ 4-positive women with A β load to have a steeper cognitive decline than male *APOE* ϵ 4 carriers (Buckley et al., 2018). All these results support that female but not male *APOE* ϵ 4-positive participants are at higher risk of developing MCI.

Female sex is a prominent risk factor for AD and sex differences have also been found in MCI (Au et al., 2016). Regarding the higher rates of women with AD and possibly MCI, an important factor has to be considered: Women live longer than men and they have lower mortality rates (BiB, 2018a, BiB, 2018b). Men have more severe comorbidities than women and often pass away before reaching an older age. Thus, it is more likely for women to reach older age and therefore to suffer more often from AD.

Animal studies have found sex-specific differences in AD mouse models, particularly decreased presynaptic density present only in female mice (Rijpma et al., 2013). In a healthy state, high presynaptic density ensures efficient synaptic transmission in the CNS. Transferred to humans, this result suggests that women may already be affected differently than men by underlying AD pathology. Thus, another explanation for the differing results of this work in men and women could be that the association of *APOE* ϵ 4

with neurological damage, specifically synaptic dysfunction, may be stronger in women than in men.

Another important factor explaining the differing results is that the meaning of cognitive complaints varies by sex. Women seem to underestimate their memory abilities, whereas men tend to overestimate theirs (Rickenbach et al., 2015). On the one hand, this might be influenced by a higher frequency of affective symptoms in women, which is also reflected by more depressive symptoms in women of the HNR study. On the other hand, men and women differ in personality traits and women may generally be more likely to seek medical care and report cognitive concerns. The present work is in line with these findings, with women having a higher SCD frequency (women: 28%, men: 21%) and reporting additional concerns more often (women: 16% SCD and concerns, 14% SCD and no concerns, 70% no SCD; men: 10% SCD and concerns, 18% SCD and no concerns, 72% no SCD). This could influence the meaning of the relationship between *APOE* ϵ 4 status and MCI risk.

In conclusion, it is generally likely that all these explanations play a role since the relationship of *APOE* ϵ 4, sex, SCD and MCI is highly complex.

4.3 Comparison of cognitive performance and MCI diagnosis

The sex-specific differences of the four SCD and *APOE* ϵ 4 genotype groups in risk of incident MCI were neither seen in the cross-sectional cognitive performance nor in the longitudinal cognitive performance. While cognitive results showed very subtle group differences (even if they were only significant in one test), ORs for incident MCI were quite high. Thus, description and raw values of cognitive performance are valuable to get a general overview of the study population, but investigating individual symptoms in context of SCD seems to be essential. This is supported by a meta-analysis revealing increased conversion rates from SCD to MCI or dementia (Mitchell et al., 2014). It has to be considered that the cognitive performance was assessed at two singular time points and not cognitive decline. A direct comparison with the incident diagnosis is therefore difficult.

4.4 Influence of age, education, and depressive symptomatology

Age, level of education and depressive symptoms were used as covariates in the present work because of their impact on cognition as well as their impact on SCD.

Age is seen as the greatest risk factor for dementia and mortality. Neuropathological changes are present in the majority of individuals aged 80 years and older with normal

cognition. Prevalence of A β pathology ranges from 10% at age 50 in cognitively normal individuals up to 71% at age 90 in individuals with MCI (Jansen et al., 2015). Increasing pathology with advancing age has also been validated in autopsy studies covering an age range of 100 years (Braak et al., 2011). It has even been shown that prevalence for AD biomarkers in all categories (amyloid, tau, neurodegeneration) increases significantly with age beginning in midlife (Jack et al., 2017, Aizenstein et al., 2008). Specifically interesting for the present work is the relationship of age with *APOE* ϵ 4. Carriers are at increased risk of developing AD at a considerably earlier age than non-carriers (Fleisher et al., 2013). Additionally, age is strongly related to cognition and a systematic review has shown an increased conversion risk to MCI or dementia in older individuals with SCD (Mendonca et al., 2016). This shows the need to consider age when investigating cognition.

Education majorly impacts overall cognitive performance of healthy older people (Kaplan et al., 2009). High educational attainment has been recognized as a protective factor for cognitive performance and dementia (Manly et al., 2003, Stern, 2009). It has been found that the risk of AD is lower in highly educated individuals than individuals with low levels of education, whereas prevalence of SCD is higher in this group (Jonker et al., 2000). Regarding SCD and education, the strongest association with low AD risk has been found in cognitively normal individuals with SCD and a high level of education (van Oijen et al., 2007). As a dementia predictor, SCD combined with cognitive tests assessing explicitly memory and executive function has been shown to work best for highly educated individuals. The best predictor for individuals with low educational attainment was instead their score on the Instrumental Activities of Daily Living scale (Chary et al., 2013). Even though there are contrary study results, SCD seems to be more predictive of dementia in highly educated individuals than in individuals with low educational level (Jessen et al., 2014b, Jonker et al., 2000). Several aspects may explain the importance of high education. Subtle cognitive deficits in early AD progression might not be detected by neuropsychological screenings due to ceiling effects in highly educated persons. A difficulty of cross-sectional neuropsychological assessments in individuals with high levels of education is the missing information regarding their previous cognitive performance. Even if they perform within their age and education appropriate range, they may already have deteriorated. These complications could result in false-positive SCD cases that are actually in the MCI stage. Then again, highly educated individuals might be more sensitive to their cognitive changes than individuals with low education. SCD expressed by highly educated individuals might be a more valid symptom of underlying AD pathology. There are different theories explaining the protective effect of education. The most accepted one is the cognitive reserve hypothesis (Figure 6, see next page). It describes that education results in neuronal changes including increased efficacy of processing networks, thereby

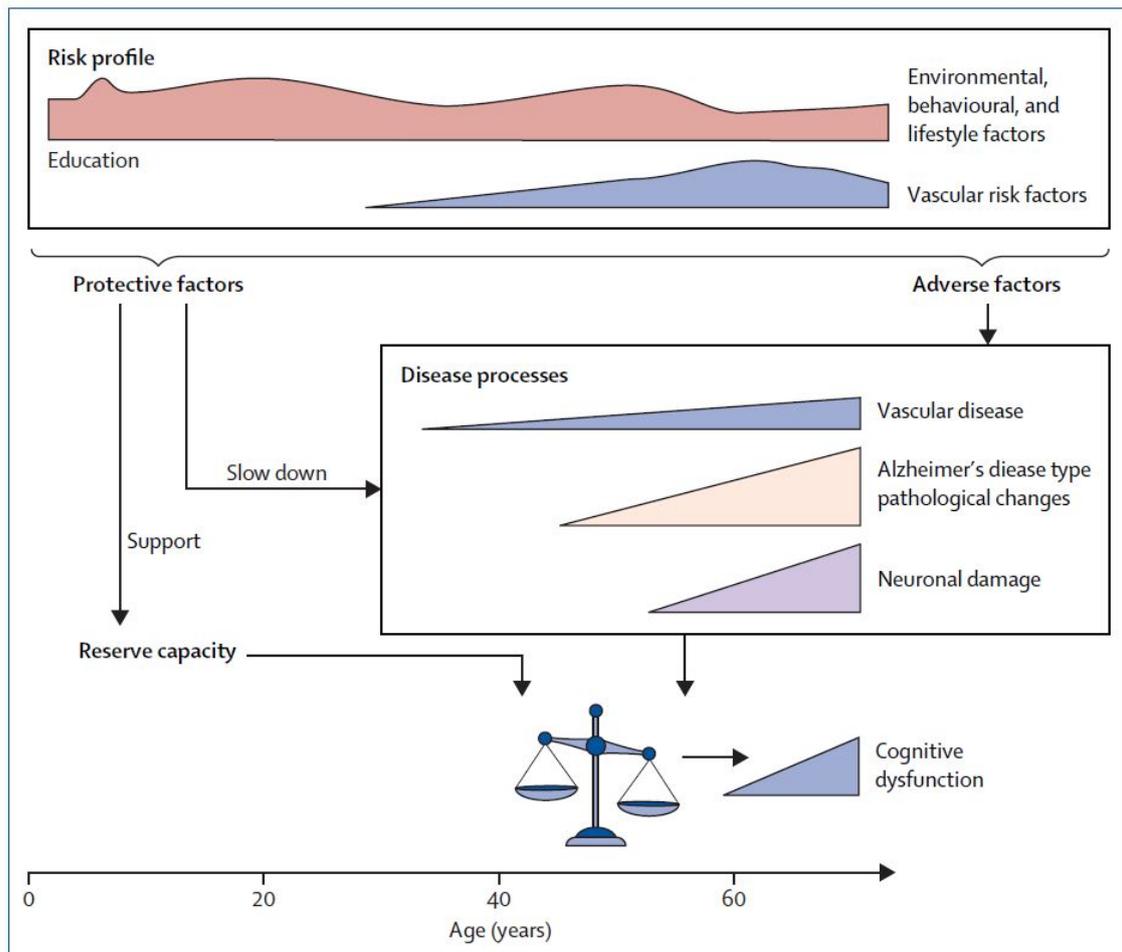


Figure 6: Modifiable risk factors for Alzheimer's disease (AD) across life. The individual risk profile for AD is influenced by protective and adverse factors. Protective factors like education and some environmental, behavioural, and lifestyle factors increase the individual cognitive reserve and may attenuate negative effects of adverse factors. Adverse factors including vascular risk factors increase pathological damage and lead to advancement of the disease progression. Different disease processes cumulate and when pathological AD burden gets too high, cognitive reserve cannot compensate for the neurological damage any more (imbalance of both factors), which results in cognitive dysfunction. *Figure from Biessels (2014) reused in this dissertation with permission from Elsevier (RightsLink License Number: 4642411083682).*

conferring a cognitive reserve compensating pathological brain damage (Stern et al., 2018). Transferred to the progression of cognitive performance, this means that individuals with high cognitive reserve remain cognitively stable for a longer period of time and decline rather late but then rapidly (Silva et al., 2014).

As described previously, SCD has a complex interrelationship with depressive symptoms and it has been shown that the cognitive performance of women in the HNR study is strongly influenced by depressive symptomatology (Dlugaj et al., 2015). Higher rates of depressive symptoms in women might result in higher SCD prevalence. This tendency to express complaints more often may attenuate results found in women. It has thus been suggested to exclude persons with clinically significant depressive symptomatology from SCD research but to include those with subthreshold depressive symptoms because of

the interrelationship of SCD and depressive symptoms (Jessen et al., 2014a). Other researchers argue that this exclusion is not optimal: On the one hand, a history of earlier depression has been shown to increase the risk for pathologic cognitive decline, on the other hand, first-episode late life depression may be a prodromal symptom of AD (Butters et al., 2008). Since SCD and depressive symptoms are interrelated, one is rarely present without the other. A degree of depressive symptoms is thus expected in SCD but SCD in the presence of clinical depression does not correspond to SCD caused by underlying AD pathological processes. The decision to exclude participants with clinically relevant depressive symptoms in this work was based on the recommendation by the SCD framework and studies linking depression to changes in the brain structure and function associated with non-AD dementias rather than AD (Jessen et al., 2014a, Butters et al., 2008, Sexton et al., 2013).

4.5 Sociodemographic characteristics

The HNR study is a well characterized population-based study with a broad age range. Since MCI prevalence increases with age, predicted as 1% at age 60 up to 42% at age 80 (Yesavage et al., 2002), examining a population with an age range of 55 to 85 years is optimal for investigating incident MCI. The four SCD and *APOE* ϵ 4 genotype groups did not differ significantly in their age, and general age effects were included in the analyses (as a covariate). Group differences that were found in regression analyses for incident MCI are likely not a result of age. Men had generally more years of formal education than women. This is an expected distribution considering the investigated age range of the participants. Women have historically been at an educational disadvantage. In these generations men typically spent more years at school and more often received higher education than women (Geißler, 2014). Male and female participants in the four SCD and *APOE* ϵ 4 genotype groups showed significant differences in their CES-D scores at both follow-up examinations. Women had generally more depressive symptoms than men, as was expected. A strong association between depression and female sex has previously been reported for the HNR study (Dlugaj et al., 2015). Women had also a higher frequency of SCD than men. Resulting from their interrelationship, this could partly be influenced by stronger depressive symptomatology in women.

4.6 Methods

In this subsection, some aspects of the chosen methods and approaches are discussed and some alternative explanations are presented.

Control group

The reference group “no MCI” is composed of participants without either subjective or objective cognitive impairment, but also participants with solely subjective or solely objective impairment. It could be argued that only the former should serve as a strict control group. Sensitivity analyses for risk of incident MCI with a strict control group revealed the same tendencies of the four SCD and *APOE* ϵ 4 genotype groups, only with elevated ORs (see appendix section ‘7.5 Sensitivity analysis’). On the other hand, such a control group might be overly conservative as individuals with SCD can already have subtle cognitive deficits. Results using a strict control group might be enhanced and impairment in general (for example having one impaired test score across a cognitive test battery) is normative and not per se clinically relevant (Axelrod and Wall, 2007).

MCI diagnosis

A MCI diagnosis is characterized by different operationalizations of MCI diagnostic criteria, for example cut-off values for definition of cognitive impairment, number and type of cognitive tests used, or assessment of SCD or daily activities. Many studies are not able to perform an extensive neuropsychological assessment and short cognitive screenings are not as sensitive as an extensive neuropsychological examination. To minimize this effect, the short neuropsychological battery used at t1 of the HNR study has been validated against a detailed neuropsychological and neurological examination with a good accuracy to identify participants with MCI (area under the curve = 0.82, 95% CI = 0.78-0.85) (Wege et al., 2011).

Since the test battery was extended for examination at t2, it was necessary to address the question of methodological issues regarding the MCI diagnosis. For longitudinal analyses that include MCI diagnoses at both time points, it would be ideal to build MCI diagnoses based on the exact same criteria using only the exact same tests. For other analyses (i.e. longitudinal analyses with incident MCI as outcome) it would be ideal to use the extended test battery for MCI diagnosis to improve accuracy. Thus, two sets of MCI diagnoses were created for t2 as described. The MCI diagnosis based on the extended assessment was chosen for this work because longitudinal analyses were performed with incident MCI as outcome and the research question did not lead to comparisons of MCI diagnoses at the two follow-ups.

Selection bias

Participants of the HNR study were randomly selected from mandatory registries, which reduced the selection or volunteer bias. A common issue in longitudinal population-based studies is the selection bias that evolves over the course of follow-ups. Every study experiences drop-outs and individuals canceling participation, either voluntarily or involuntarily, are usually in large part the ones with (serious) medical conditions. In this work, two aspects have to be considered. First, there was no assessment of cognitive performance in the HNR study at baseline. Second, cognitive data originated from the first and second follow-up examination, which resulted in a healthier cohort. Potential bias should be minimized as only cognitively normal participants at t1 were included.

SCD assessment

As suggested by the literature, inclusion of informant report, additional SCD *plus* criteria, or non-cognitive measures, such as items related to personality, might have strengthened SCD as a symptom to identify individuals at risk. However, informant report would not have necessarily improved the results because informants recognize cognitive changes later in the disease progression than individuals themselves. In comparison with the SCD core criteria, performance on standardized tests was not gender-adjusted because diagnoses were made according to the core clinical MCI criteria that recommend adjustment for age and education only. Even though SCD was assessed via self-report of a single question at one time point, the question used was retrospective and therefore captured the longitudinal nature of SCD as recommended by the SCD-I working group.

Interaction

A multiplicative scale is frequently used to assess interaction of two exposures, even though it is the most complicated to interpret. It is likely the most commonly used because the standard statistical programs offer models with multiplicative interaction measure directly included. Reporting of interaction on additive scales was additionally chosen in this work as the main interaction measure because it is relevant for assessing implications for public health. The additive scales inform about the direction of the interaction and are thus directly interpretable. The interaction effects of SCD and *APOE* ϵ 4 genotype were not statistically significant but estimates with corresponding 95% CIs of the measures were primarily presented to assess estimate precision.

***APOE* ϵ 4 genotype**

Results of the single-risk groups showed that the *APOE* ϵ 4-positive single-risk groups had the lowest risk of incident MCI, which was the case for men and women. *APOE* ϵ 4-

positive participants were defined as being either hetero- or homozygous. Due to insufficient group sizes, analyses could not be performed separately in homozygous and heterozygous participants. It has been shown that effects of *APOE* ϵ 4 are allele dose-dependent and the *APOE* ϵ 4-positive groups in this work are a mixture of ϵ 3/ ϵ 4 and ϵ 4/ ϵ 4 carriers (Liu et al., 2013). Results of the *APOE* ϵ 4 single-risk groups can, therefore, be assumed to be alleviated and the actual genetic impact of *APOE* ϵ 4 may be stronger.

AD biomarker

The HNR study started 19 years ago with a cardiovascular focus. Since then, AD biomarkers have developed steadily and are now seen as a critical tool in AD research. Since the study was designed before this advancement of biomarkers and their rising importance, additional biomarker information is not available in the HNR study and interpretation of the results was limited.

4.7 Conclusion and outlook

Taken together, this work suggests that SCD is associated with the risk of MCI within at least 5 years. It adds to the field of research by proposing that this association is not sex neutral and it is differentially dependent on the interaction effects of *APOE* $\epsilon 4$ and SCD because the highest associations with MCI were found in female carriers and male non-carriers. This could explain the heterogeneous results which studies have found regarding the predictive value of SCD. Sex is specifically in AD research an understudied topic and these results highlight its importance. The course of AD and its pathology may vary by sex. Incorporating sex in AD research and identifying the sex-specific differences in AD stages may improve prevention strategies and ultimately outcomes. Based on the results of this work, it can be assumed that the concept of SCD for identifying individuals at risk for cognitive decline and MCI can be applied in the general population. SCD may prove a useful tool as it is non-invasive, easily feasible and economical, especially in the absence of objective markers (e.g. biomarkers) that are not as cost-effective or are more invasive. As described by previous research, this work also revealed the highly complex nature of SCD. Further studies will have to focus on a better characterization of SCD by implementing more distinctions like sex and *APOE* $\epsilon 4$ genotype. Defining additional associations of SCD with multiple factors (e.g. depressive symptoms, personality traits, vascular risk factors) will help to differentiate subpopulations at risk. Future research will have to further validate the results found in the present work in an external sample, with an even larger sample size and with additional biomarkers to define the setting in which SCD is a risk factor for cognitive decline to the point of MCI and AD.

5 SUMMARY

The aim of this work was to reveal potential joint effects of the risk factors subjective cognitive decline (SCD) and apolipoprotein E (*APOE*) ϵ 4 genotype on incident mild cognitive impairment (MCI) in men and women separately.

Six hundred and five men and 593 women of the general population were grouped according to their presence or absence of SCD and *APOE* ϵ 4 genotype and examined separately. Groups were compared regarding their sociodemographic characteristics and their objective cognitive performance. Risk of incident MCI was analyzed with logistic regression models. *APOE* ϵ 4-negative men and women without SCD served as the reference group. Potential interaction effects of SCD and *APOE* ϵ 4 genotype on incident MCI were estimated.

Participants in the different SCD and *APOE* ϵ 4 genotype groups showed very subtle differences regarding their cognitive performance. It could be shown for the first time that two risk factors for cognitive decline, SCD in objectively normal individuals and *APOE* ϵ 4, have a differential interaction effect on incident MCI and that this association is dependent on sex. The highest risk for incident MCI after 5 years was observed for *APOE* ϵ 4-negative men with SCD (single-risk group), approximately 2.5-fold increased, and for *APOE* ϵ 4-positive women with SCD (high-risk group), approximately 3.5-fold increased, compared with individuals without the two risk factors. This suggests that SCD in cognitively healthy individuals of the general population may have a different impact as a predictor of incident MCI in men and women as well as *APOE* ϵ 4 carriers and non-carriers. It should thus be examined and interpreted with regard to these differences.

The selected study sample of the longitudinal Heinz Nixdorf Recall study is representative of the older, general population in an optimal age range to investigate preclinical and prodromal Alzheimer's disease (AD) stages. This work highlights the need to further characterize SCD as a complex, interconnected construct or symptom. Its optimal assessment remains to be established.

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7.3 List of abbreviations

AD	Alzheimer's disease
aMCI	Amnesic mild cognitive impairment
ANOVA	Analysis of variance
AP	Attributable portion due to interaction
APOE	Apolipoprotein E
APP	Amyloid precursor protein
A β	Amyloid beta
CES-D	Center for Epidemiologic Studies Depression scale
CI	Confidence interval
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
DSM	Diagnostic and Statistical Manual of Mental Disorders
FDG	¹⁸ F-fluorodeoxyglucose
GDS	Global Deterioration Scale
HNR	Heinz Nixdorf Recall
HSD	Honestly significant difference
IADL	Instrumental activities of daily living
kb	Kilobase
kDa	Kilodalton
MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
naMCI	Non-amnesic mild cognitive impairment
NFTs	Neurofibrillary tangles
NIA	Nürnbergger Alters-Inventar
NIA-AA	National Institute on Aging – Alzheimer's Association
OR	Odds ratio
PET	Positron emission tomography
PiB	Pittsburgh Compound B
PSEN	Presenilin
p-tau	Phosphorylated tau
Recall	Risk Factors, Evaluation of Coronary Calcification, and Lifestyle
RERI	Relative excess risk due to interaction
S	Synergy index

SCC	Subjective cognitive complaints
SCD	Subjective cognitive decline
SCD-Q	Subjective Cognitive Decline Questionnaire
SCI	Subjective cognitive impairment
SCI-I	Subjective Cognitive Decline Initiative
SD	Standard deviation
SMC	Subjective memory concerns/complaints
SMI	Subjective memory impairment
SNP	Single nucleotide polymorphism
t0	Baseline examination
t1	First follow-up examination
t2	Second follow-up examination
TMT	Trail Making Test
t-tau	Total tau

7.4 Raw data logistic regression analyses (risk of incident MCI)

Listed in the following two tables are the raw data used to create Figure 4 and Figure 5.

Table A: Results from the multinomial logistic regression analyses for risk of incident MCI in men

MEN	Number of controls/cases	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
<i>APOE</i> ϵ 4-negative, SCD-	338/23	1 (reference)		1 (reference)	
<i>APOE</i> ϵ 4-negative, SCD+	76/17	3.29 (1.66 - 6.43)	< 0.001	2.90 (1.43 - 5.81)	0.003
<i>APOE</i> ϵ 4-positive, SCD-	107/10	1.37 (0.61 - 2.90)	0.42	1.43 (0.62 - 3.08)	0.38
<i>APOE</i> ϵ 4-positive, SCD+	29/5	2.53 (0.81 - 6.70)	0.08	2.41 (0.75 - 6.57)	0.11

Abbreviations: *APOE*, apolipoprotein E; CI, confidence interval; OR, odds ratio; SCD, subjective cognitive decline.

Table B: Results from the multinomial logistic regression analyses for risk of incident MCI in women

WOMEN	Number of controls/cases	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
<i>APOE</i> ϵ 4-negative, SCD-	304/16	1 (reference)		1 (reference)	
<i>APOE</i> ϵ 4-negative, SCD+	106/10	1.79 (0.76 - 4.02)	0.16	1.55 (0.65 - 3.54)	0.31
<i>APOE</i> ϵ 4-positive, SCD-	101/7	1.32 (0.49 - 3.18)	0.56	1.31 (0.49 - 3.21)	0.57
<i>APOE</i> ϵ 4-positive, SCD+	39/10	4.87 (2.01 - 11.37)	< 0.001	3.70 (1.48 - 8.90)	0.004

Abbreviations: *APOE*, apolipoprotein E; CI, confidence interval; OR, odds ratio; SCD, subjective cognitive decline.

7.5 Sensitivity analysis

Listed in the following two tables are the results of the sensitivity analyses. I performed logistic regressions for risk of incident MCI with strict control groups, i.e. participants with only objective cognitive impairment at t2 and participants with only subjective cognitive impairment at t2 were excluded.

Table C: Results from the multinomial logistic regression sensitivity analyses for risk of incident MCI in women

MEN	Number of controls/cases	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
<i>APOE</i> ϵ 4-negative, SCD-	222/23	1 (reference)		1 (reference)	
<i>APOE</i> ϵ 4-negative, SCD+	22/17	7.46 (3.46 - 16.12)	< 0.001	7.33 (3.20 - 16.92)	< 0.001
<i>APOE</i> ϵ 4-positive, SCD-	63/10	1.53 (0.67 - 3.31)	0.29	1.64 (0.69 - 3.69)	0.24
<i>APOE</i> ϵ 4-positive, SCD+	10/5	4.83 (1.41 - 14.87)	0.008	5.28 (1.43 - 17.74)	0.008

Abbreviations: *APOE*, apolipoprotein E; CI, confidence interval; OR, odds ratio; SCD, subjective cognitive decline.

Table D: Results from the multinomial logistic regression sensitivity analyses for risk of incident MCI in women

WOMEN	Number of controls/cases	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
<i>APOE</i> ϵ 4-negative, SCD-	180/16	1 (reference)		1 (reference)	
<i>APOE</i> ϵ 4-negative, SCD+	48/10	2.34 (0.97 - 5.43)	0.05	1.67 (0.66 - 4.08)	0.27
<i>APOE</i> ϵ 4-positive, SCD-	67/7	1.18 (0.44 - 2.89)	0.73	1.02 (0.36 - 2.62)	0.96
<i>APOE</i> ϵ 4-positive, SCD+	17/10	6.62 (2.56 - 16.84)	< 0.001	5.10 (1.88 - 13.57)	0.001

Abbreviations: *APOE*, apolipoprotein E; CI, confidence interval; OR, odds ratio; SCD, subjective cognitive decline.

7.6 Neuropsychological assessment "Modul Kognition"

Heinz Nixdorf Recall Studie		Dokumentationsbogen	
Modul Kognition			
Probanden - Etikett	UntersucherIn: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		
	Datum: <input type="text"/>		

INSTRUKTION: IN DIESEM MODUL WERDEN ALLGEMEINE FRAGEN ZUM GEDÄCHTNIS GESTELLT. STELLEN SIE SICHER, DASS BEIM AUSFÜLLEN DIESES MODULS KEINE ANDERE PERSON ANWESEND IST. DER TEXT IN GROSSBUCHSTABEN ENTHÄLT ERKLÄRUNGEN UND WIRD NICHT VORGELESEN; **nur der fett gedruckte Text wird vorgelesen.**

BITTE TRAGEN SIE VOR BEGINN DIE PROBANDENNUMMER NICHT NUR IM FRAGEBOGEN, SONDERN AUCH IN DEN BEIDEN AUFGABENBLÄTTERN EIN.

STELLEN SIE SICHER, DASS DER TEST OHNE STÖRUNGEN ABLAUFEN KANN. AM ARBEITSPLATZ MÜSSEN EIN STIFT FÜR DEN PROBANDEN UND EINE STOPPUHR VORLIEGEN.

EINLEITUNG:

„Wie vor fünf Jahren auch, führen wir auch diesmal einige Aufgaben zum Gedächtnis durch. Ich werde Ihnen bei jeder Aufgabe ganz genau erklären, was zu tun ist, sollten Sie etwas nicht ganz genau verstanden haben, fragen Sie bitte nach.“

FALLS DER PROBAND FRAGT: WIESO MAN DAS MACHEN MUSS, KÖNNT IHR SAGEN:

„Es ist bekannt, dass Herz-Kreislauf-Erkrankungen ebenfalls mit dem Gehirn im Zusammenhang stehen, da das Gehirn durch Gefäße mit Blut versorgt wird. Diesen Zusammenhang möchten wir in der Studie ebenfalls untersuchen.“

„Zunächst würde ich Ihnen gerne einige Fragen zu Ihrem Gedächtnis stellen:“

1. „Wie würden Sie selbst Ihr Gedächtnis im Moment einstufen? Würden Sie sagen, es ist...“
ANTWORTEN VORLESEN

Ausgezeichnet..... 1

keine Angabe 9

Sehr gut 2

Gut 3

Mittelmäßig..... 4

Schlecht 5



DIE ANWEISUNG IST GEGEBENFALLS ZU WIEDERHOLEN BZW. DURCH ANZEIGEN DES WEGES MIT DEM FINGER ZU ERWEITERN. HAT DIE TESTPERSON DIE AUFGABE VERSTANDEN, WIRD DAS AUFGABENBLATT UM 90 GRAD GEDREHT, SO DASS DER PFEIL MIT DER NUMMER 2 AUF DIE TESTPERSON ZEIGT.

„Versuchen Sie nun von hier innen (ZUR MITTE DEUTEN) mit dem Stift möglichst schnell zum Ausgang zu gelangen.“

DER TESTLEITER STOPPT DIE ZEIT BIS ZUM ERREICHEN DES ZIELS. NACH 3 MINUTEN WIRD DER TEST ABGEBROCHEN (MAXIMALE TESTZEIT 180 SEKUNDEN).

Testzeit in Sekunden: _____ ANMERKUNGEN: _____

5. „Jetzt möchte ich Sie bitten, so viele verschiedene Tiere zu nennen, wie Ihnen einfallen. Sie haben eine Minute Zeit. Haben Sie alles verstanden? Dann los!“

GEBEN SIE GENAU EINE MINUTE ZEIT. HÖRT DIE TESTPERSON AUF, BEVOR DIE ZEIT ABGELAUFEN IST, ERMUNTERN SIE SIE ZUM WEITERMACHEN. SCHWEIGT DIE TESTPERSON 15 SEKUNDEN LANG, SO WIEDERHOLEN SIE DIE ANWEISUNG ("NENNEN SIE BITTE MÖGLICHST VIELE VERSCHIEDENE TIERE"). DAS ZEITLIMIT WIRD NICHT VERLÄNGERT, WENN DIESE ANWEISUNG WIEDERHOLT WIRD.

DAS ERGEBNIS ERGIBT SICH AUS DER SUMME ALLER AKZEPTABLEN BEZEICHNUNGEN FÜR TIERE. ALS KORREKT GELTEN ALLE VERTRETER DES TIERREICHS:

ES ZÄHLEN:

- REAL EXISTIERENDE UND MYTHOLOGISCHE TIERE
- BEZEICHNUNGEN VON TIERARTEN UND RASSEN INNERHALB EINER ART
- BEZEICHNUNGEN FÜR MÄNNLICHE UND WEIBLICHE TIERE UND DEREN NACHKOMMEN INNERHALB EINER ART

ES ZÄHLEN NICHT: WIEDERHOLUNGEN UND EIGENNAMEN

Anzahl der korrekt genannten Tiere: _____ ANMERKUNGEN: _____

6. UHREN-TEST

BITTE AUFGABENBLATT UZT-1 VORLEGEN. SAGEN SIE DEM PROBANDEN:
„Bitte zeichnen Sie eine Uhr mit allen Zahlen und Zeigern. Die Zeiger sollen die Zeit 11 Uhr und 10 Minuten anzeigen.“

MAXIMALE DAUER DES TESTS = 3 MINUTEN

FALLS DER PROBAND DIE UHRZEIT NICHT EINTRÄGT, BITTE KURZ DARAUFG HINWEISEN:
„Bitte tragen Sie ebenfalls die Uhrzeit ein“

ANMERKUNGEN: _____



7. „Vor kurzem habe ich Ihnen eine Liste von Wörtern vorgelesen. An welche Wörter können Sie sich noch erinnern?“

BITTE ANKREUZEN

Großstadt	<input type="checkbox"/>
Küste	<input type="checkbox"/>
Pfirsich	<input type="checkbox"/>
Mädchen	<input type="checkbox"/>
Sessel	<input type="checkbox"/>
Feier	<input type="checkbox"/>
Bettler	<input type="checkbox"/>
Nagel	<input type="checkbox"/>
	<input type="checkbox"/>
Fehlerhafte Nennungen	<input type="checkbox"/>

DIE LISTE DARF NICHT MEHR VORGELESEN WERDEN!!!!

ALLE WÖRTER, DIE RICHTIG GENANNT WERDEN, ANKREUZEN

DER PROBAND HAT MAXIMAL 1 MINUTE ZEIT!

SYNONYME NENNUNGEN (z.B. „HIRN“ FÜR „GEHIRN“) ZÄHLEN ALS RICHTIGE ANTWORT.

FALLS DER PROBAND SOFORT SAGT: MIR FÄLLT NICHTS MEHR EIN, BITTE EINMAL ERMUTIGEN „Denken Sie in Ruhe nochmal nach, vielleicht fällt Ihnen doch noch was ein.“ WENN DER PROBAND VERNEINT, ODER 1 MINUTE UM IST, MIT DER NÄCHSTEN AUFGABE WEITER MACHEN.

ANMERKUNGEN:

8. TRAIL-MAKING-TEST (TMT)

AUFGABE A:

BITTE AUFGABENBLATT „TMT A, ÜBUNGSBLATT“ VORLEGEN. SAGEN SIE DEM PROBANDEN:

„Auf diesem Blatt sind verschiedene Zahlen. Beginnen Sie bitte bei der Zahl 1 und zeichnen eine Linie zur Zahl 2 (BITTE MIT DEM FINGER ZEIGEN), von 2 zu 3 (BITTE MIT DEM FINGER ZEIGEN) und von 3 zu 4 (BITTE MIT DEM FINGER ZEIGEN) usw. Zeichnen Sie die Linien so schnell wie möglich.“

„Alles verstanden? Dann los!“

WENN DIE TESTPERSON IM ÜBUNGSBEISPIEL EINEN FEHLER MACHT, WIRD SIE SOFORT DARAUF AUFMERKSAM GEMACHT.

WENN DAS ÜBUNGSBLATT VERSTANDEN WURDE, ZUR TESTUNG ÜBERGEHEN MIT DEM AUFGABENBLATT „TMT A“.

„Gut. Jetzt machen wir mit dem nächsten Blatt weiter.“

„Bitte verbinden Sie nun alle Zahlen, so wie gerade auf dem Übungsblatt, von 1 bis 25 in aufsteigender Reihenfolge. Zeichnen Sie die Linien so schnell wie möglich. Hier ist der Anfang. (BITTE AUF DEN ANFANGSKREIS ZEIGEN). Sind sie bereit? Los!“

DER TESTLEITER STOPPT DIE ZEIT BEIM „LOS“ BIS ZUM ERREICHEN DER ZAHL 25. NACH 3 MINUTEN WIRD DER TEST ABGEBROCHEN (MAXIMALE TESTZEIT 180 SEKUNDEN).

Testzeit in Sekunden : ANMERKUNGEN:

**AUFGABE B:**

BITTE AUFGABENBLATT „TMT B, ÜBUNGSBLATT“ VORLEGEN. SAGEN SIE DEM PROBANDEN:

„Auf diesem Blatt sind Zahlen und Buchstaben. Beginnen Sie bitte bei der Zahl 1 und zeichnen eine Linie zum Buchstaben A (BITTE MIT DEM FINGER ZEIGEN), dann vom A zur 2 (BITTE MIT DEM FINGER ZEIGEN), von der 2 zum B (BITTE MIT DEM FINGER ZEIGEN), vom B zur 3 (BITTE MIT DEM FINGER ZEIGEN), von der 3 zum C (BITTE MIT DEM FINGER ZEIGEN) usw. Sie sollen also abwechselnd aufsteigend eine Zahl und einen Buchstaben verbinden. Zeichnen Sie die Linien so schnell wie möglich.“

„Alles verstanden? Dann los!“

WENN DIE TESTPERSON IM ÜBUNGSBEISPIEL EINEN FEHLER MACHT, WIRD SIE SOFORT DARAUF AUFMERKSAM GEMACHT.

BEI FEHLERN: „Erinnern Sie sich daran, dass sie zuerst eine Zahl, und dann den Buchstaben, dann wieder die Zahl und wieder den Buchstaben verbinden sollen.“ BITTE AUCH HIER BEIM ERKLÄREN MIT DEM FINGER FOLGEN!

WENN DAS ÜBUNGSBLATT VERSTANDEN WURDE, ZUR TESTUNG ÜBERGEHEN MIT DEM AUFGABENBLATT „TMT B“.

„Gut. Jetzt machen wir mit dem nächsten Blatt weiter.“

„Ich würde Sie auch hier bitten abwechselnd eine Zahl und einen Buchstaben, so wie gerade auf dem Übungsblatt, miteinander zu verbinden. Zeichnen Sie die Linien so schnell wie möglich. Hier ist der Anfang. (BITTE AUF DEN ANFANGSKREIS ZEIGEN)“.

„Sind Sie bereit? Los!“

DER TESTLEITER STOPPT DIE ZEIT BEIM „LOS“ BIS ZUM ERREICHEN DER ZAHL 13. NACH 5 MINUTEN WIRD DER TEST ABGEBROCHEN (MAXIMALE TESTZEIT 300 SEKUNDEN).

Testzeit in Sekunden : _____ ANMERKUNGEN: _____

9. FARBWÖRTER-TEST

„Kommen wir nun zur letzten Aufgabe:“

„Die folgende Aufgabe heißt Farbwörter-Test. Bei dieser Aufgabe kommt es ebenfalls darauf an, möglichst schnell zu sein.“

TAFEL 1

BITTE LAMINIERTER TAFEL 1 VORLEGEN

„Hier sind die Wörter rot, grün, gelb und blau. Lesen Sie diese Wörter so schnell wie möglich. Beginnen Sie hier (TESTLEITER DEUTET AUF DAS WORT LINKS OBEN) und lassen Sie kein Wort aus (TESTLEITER DEUTET AUF DIE LESERICHTUNG)“.



„Alles soweit verstanden? Dann los!“

GENAUE LESEZEIT FÜR ALLE 36 WÖRTER STOPPEN:
FEHLER WERDEN WÄHREND DER TESTZEIT KORRIGIERT.

Testzeit in Sekunden : _____ ANMERKUNGEN: _____

TAFEL 2
BITTE LAMINIERTER TAFEL 2 VORLEGEN

„Hier sind die Farben rot, grün, gelb und blau abgedruckt. Sie sollen die Farben so schnell wie möglich benennen. Beginnen Sie hier (TESTLEITER DEUTET AUF FARBFELD LINKS OBEN) und lassen Sie kein Farbfeld aus (TESTLEITER DEUTET AUF DIE LESERICHTUNG)“.

„Alles soweit verstanden? Dann los!“

GENAUE BENENNZEIT FÜR ALLE 36 FARBTAFELN STOPPEN:
FEHLER WERDEN WÄHREND DER TESTZEIT KORRIGIERT.

Testzeit in Sekunden : _____ ANMERKUNGEN: _____

TAFEL 3
BITTE LAMINIERTER TAFEL 3 VORLEGEN UND NUR DIE ERSTE ZEILE SICHTBAR MACHEN. DEN REST BITTE MIT EINEM BLATT ABDECKEN:

„Auf diesem Blatt sind Wörter in den Farben rot, grün, gelb und blau abgedruckt. Sie brauchen diese Wörter nicht zu lesen. Sie sollen so schnell wie möglich sagen, in welchen Farben die Wörter gedruckt sind. Dies können Sie hier (BITTE AUF DAS ERSTE WORT UND DANN IN LESERICHTUNG ZEIGEN) versuchen.“

RICHTIGE ANTWORTEN DER ERSTEN ZEILE ZUM MITLESEN:

GRÜN, ROT, BLAU, GELB, GRÜN, BLAU

TRETEN FEHLER AUF, WIRD DIE ANWEISUNG NOCHMALS WIEDERHOLT UND DIE ERSTE ZEILE EIN ZWEITES MAL GEÜBT.

WENN DIE ERSTE ZEILE PROBLEMLOS KLAPPT:

„Fahren Sie jetzt hier so rasch wie möglich fort (TESTLEITER DEUTET AUF DEN ANFANG DER ZWEITEN ZEILE UND DANN IN LESERICHTUNG).“

„Alles soweit verstanden? Dann los!“

RICHTIGE ANTWORTEN ZUM MITLESEN:

ROT, GELB, GRÜN, BLAU, ROT, BLAU
 GELB, GRÜN, BLAU, GRÜN, GELB, ROT
 GELB, BLAU, GELB, BLAU, GRÜN, ROT
 GRÜN, GELB, ROT, GELB, BLAU, GRÜN
 BLAU, ROT, GRÜN, ROT, BLAU, GELB
 ROT, BLAU, ROT, GRÜN, GELB, GRÜN



GENAUE BENENNZEIT FÜR ALLE 36 WÖRTER STOPPEN.
TRETEN FEHLER AUF, WIRD DIE TESTPERSON BEI LAUFENDER ZEIT KORRIGIERT.

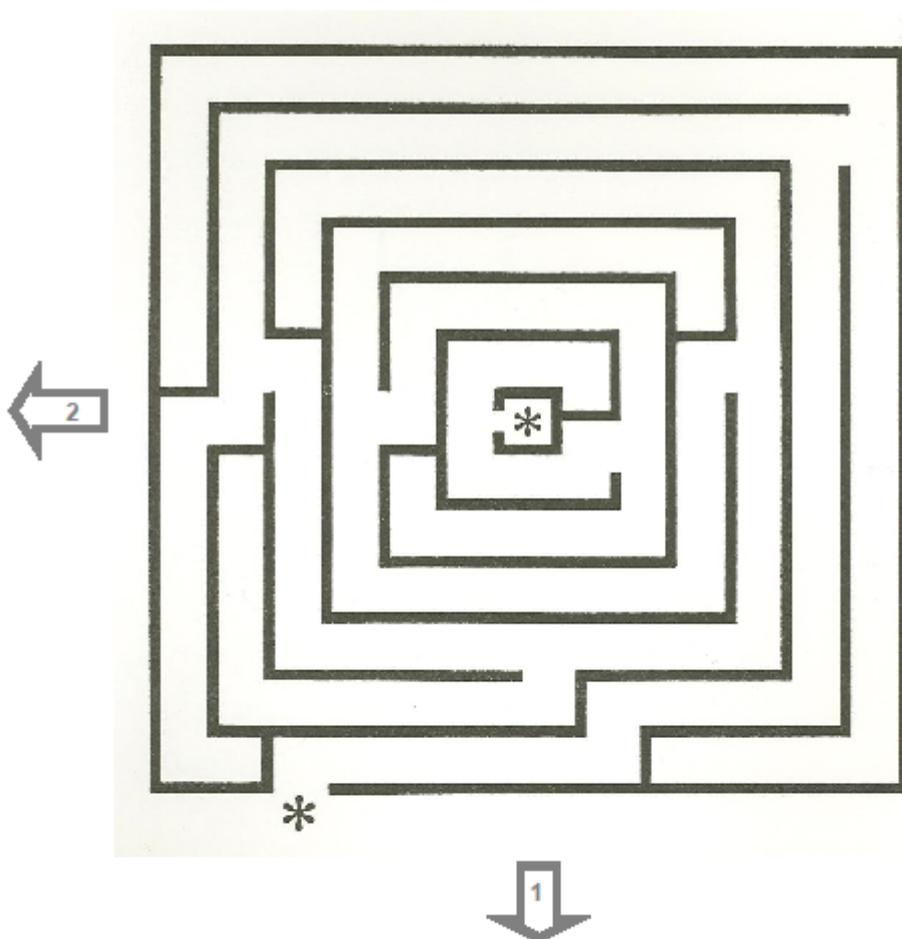
GENAUE LESEZEIT FÜR ALLE 36 WÖRTER STOPPEN:

Testzeit in Sekunden : ANMERKUNGEN: _____



Aufgabenblatt: LT-1

Prob-ID: _____

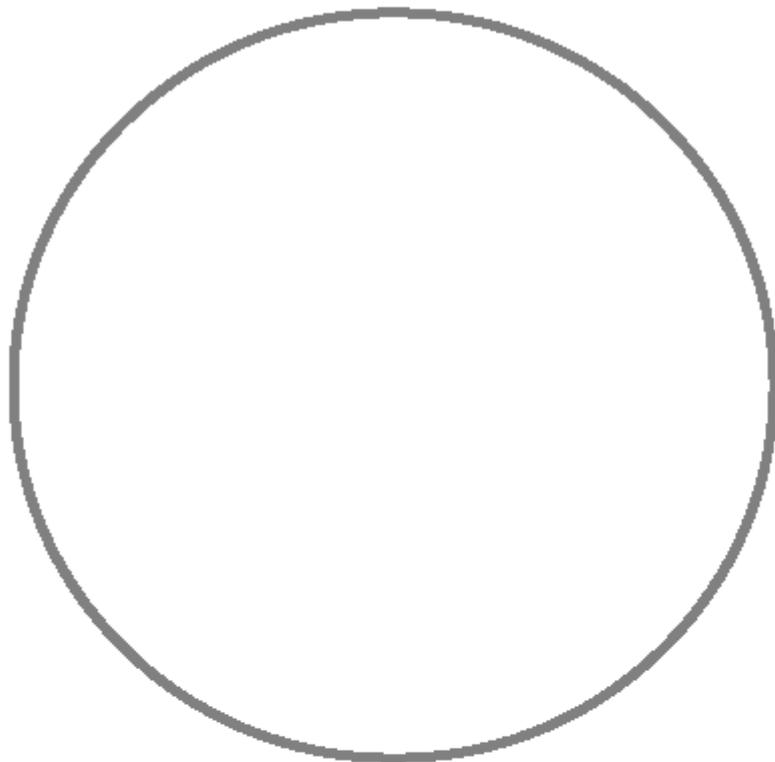




Aufgabenblatt UZT-1

Prob-ID: _____

**BITTE ZEICHEN SIE EINE UHR MIT ALLEN ZAHLEN UND ZEIGERN! DIE ZEIGER
SOLLEN DIE ZEIT 11 UHR UND 10 MINUTEN ANZEIGEN!**

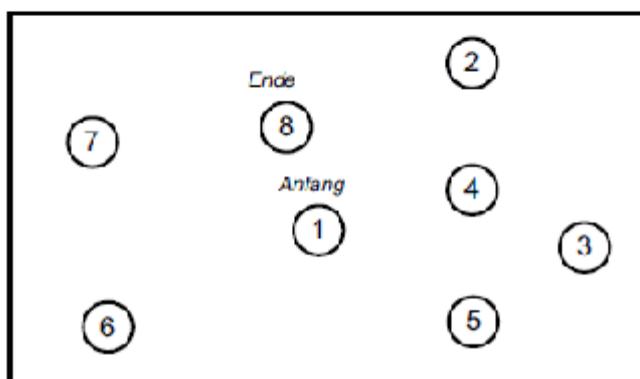




TMT A, Übungsblatt

Prob-ID: _____

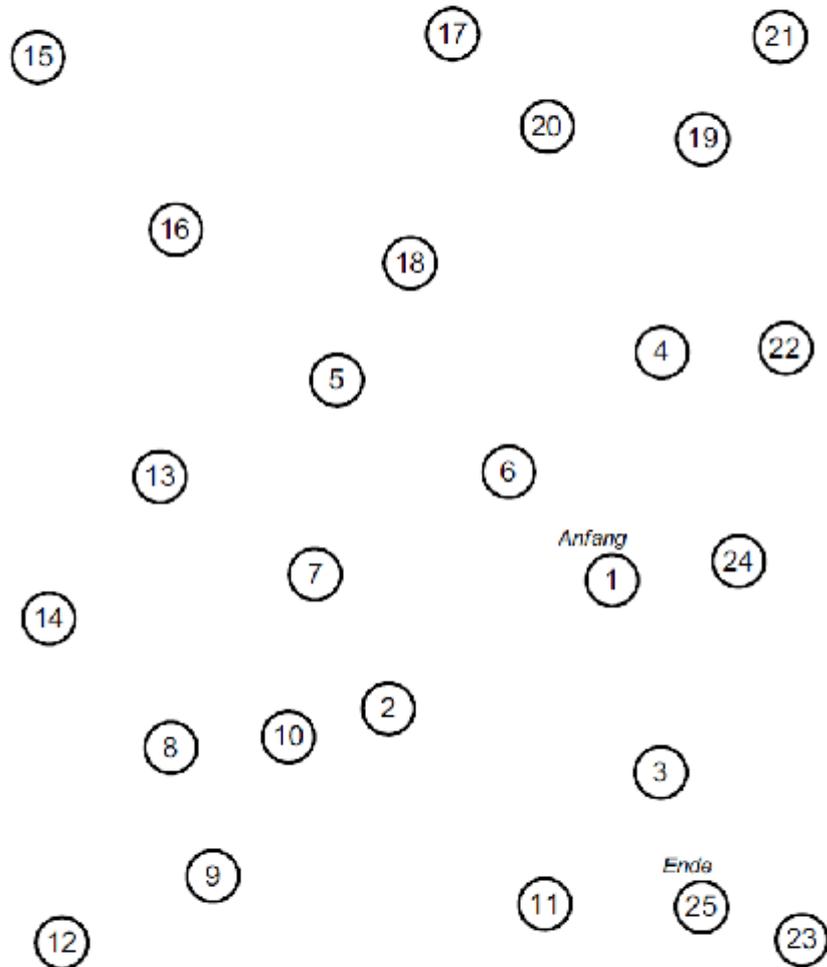
Übungsbeispiel





TMT A

Prob-ID: _____

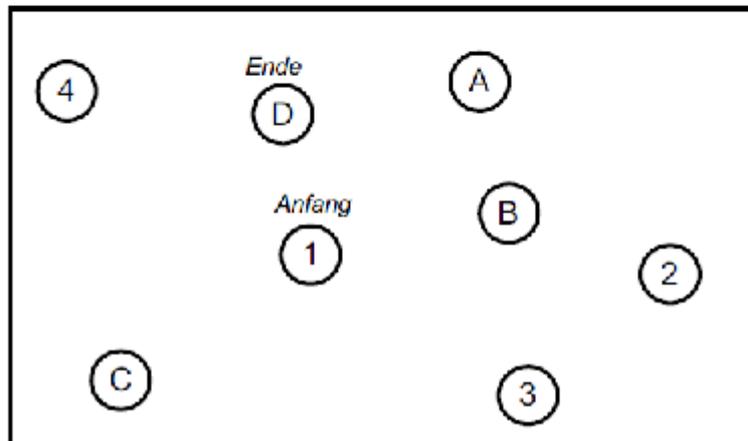




TMT B, Übungsblatt

Prob-ID: _____

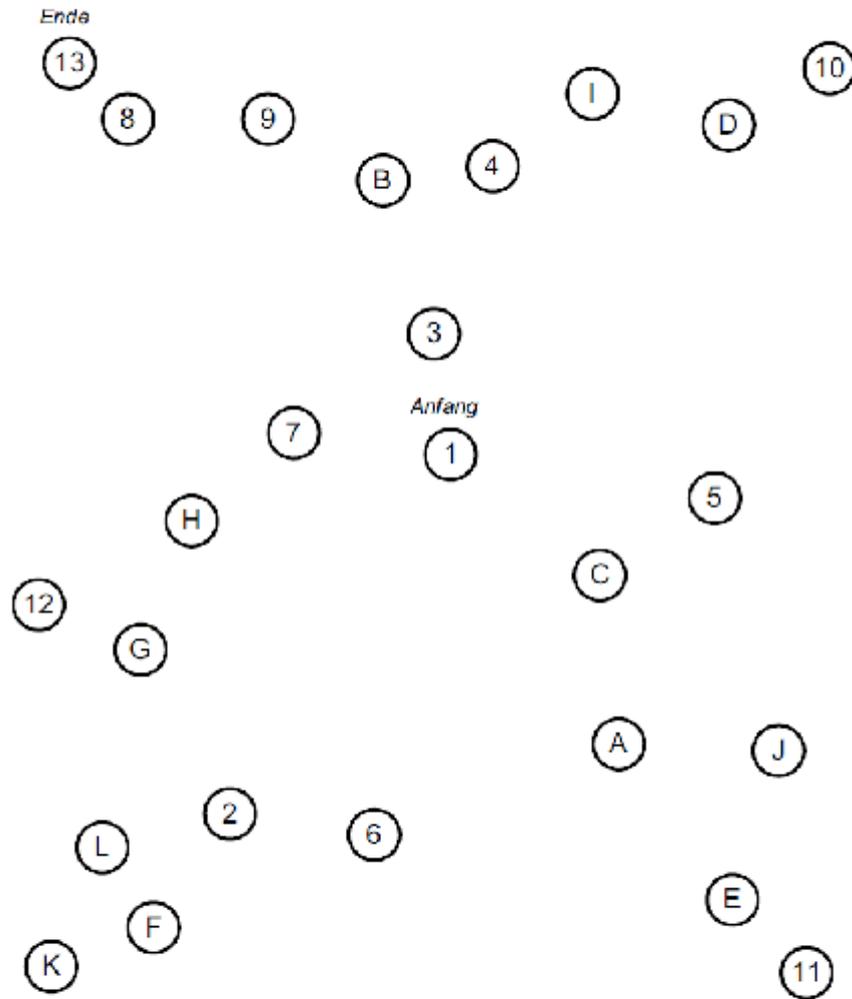
Übungsbeispiel





TMT B

Prob-ID: _____



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I thank **my parents**, **my sister**, and **my friends** for their unlimited support and that I can always count on you, no matter what.

9 CURRICULUM VITAE

Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten.