Mobility and cognition in patients with cognitive impairment and Alzheimer's disease

Doctoral thesis

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Summary

Background: The number of people with cognitive impairment and dementia is increasing worldwide. This development will put considerable strain on health services, and it will be increasingly important to help people with dementia to live safely at home for as long as possible. One of the main threats to independent living is impairments in abilities related to mobility, such as balance, walking, and spatial navigation. These abilities are scarcely studied in clinical practice. Increased knowledge of the character of such mobility impairments in patients with mild cognitive impairment and dementia of various severity may help in the development of interventions aimed at postponing the loss of mobility skills.

Aims: The overall aims of this thesis were (1) to explore how mobility performance differs between groups with different levels of cognitive impairment (papers II and III) and how mobility changes over one year in people with early onset Alzheimer's disease (AD) (paper I), and (2) to explore the relationship between mobility and different domains of cognitive function (papers II and III).

Methods: This thesis includes three papers which all apply a cross-sectional design. We also applied a one-year longitudinal follow-up in paper I. The samples in the three studies mainly consist of patients recruited from memory clinics in Malmø, Sweden (paper I) and in Oslo, Norway (papers II and III). Paper I included 72 patients with early onset dementia in the cross-sectional part, and 25 of the 42 patients with early onset AD also attended a one-year follow-up. Paper II included 170 patients in three groups: 33 with subjective cognitive impairment (SCI) or mild cognitive impairment (MCI), 99 with mild AD, and 38 with moderate AD. In paper III, we used a subsample of 128 patients from the sample included in paper II: 19 with SCI, 20 with MCI, and 89 with mild AD.

Outcomes: In all three papers, we used performance-based measures of mobility. In paper I, we used timed measures of several mobility tasks. In paper II, we used the Balance Evaluation Systems Test (BESTest) to assess the various aspects of balance. In paper III, we used the Floor Maze Test to assess spatial navigation during walking. The cognitive domains were in papers II and III assessed using tests from the test battery in the Norwegian Dementia Register.

Statistical analyses: Between-group differences were analyzed using different versions of analysis of variance (papers I and II), Chi-square tests (papers I and III) and the Mann-Whitney U-test (paper III). The relationship between the mobility measures and the cognitive domains were analyzed using multiple regression analysis (papers II and III). Changes over time were analyzed using the paired samples *t*-test (paper I).

Results: Paper I: Patients with early onset AD had inferior mobility performance compared to patients with other forms of early onset dementia. The performance of the patients with early onset AD deteriorated from baseline to the one-year follow-up. Papers II and III: We found between-group differences (based on severity of cognitive impairment) in all aspects of balance measured by the BESTest and also in spatial navigation measured by the Floor Maze Test. The worst performance was in the group with the most pronounced cognitive impairment. Executive function was the only cognitive domain independently associated with all the mobility outcomes in the multivariate models.

Conclusions: We found differences between each of the groups in all aspects of balance (paper II) and also in spatial navigation (paper III). In our longitudinal study of early onset AD we also saw a small decline in mobility over one year (paper I). Although our findings from these cross-sectional indicate a decline in mobility through the stages from SCI to MCI, mild AD, and moderate AD, these findings need to be confirmed in longitudinal studies. With regard to the second aim, executive function was associated with all aspects of balance, and also with spatial navigation. The explained variances were generally high in the models of the aspects of balance. However, for spatial navigation, the models provided only minor explained variances. Future studies are needed to validate the Floor Maze Test against real-life navigation.

Definitions of central concepts

The concepts are in general also defined the first time they appear in the thesis.

Mobility is defined as the ability to move independently and safely from one place to another.[1] In this thesis we will use this term to also encompass balance and spatial navigation which are abilities that are essential to mobility.

Cognition is the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses.[2]

Balance is used as a generic term describing the dynamics of body posture to prevent falling.[3]

Walking is to move at a regular pace by lifting and setting down each foot in turn, never having both feet off the ground at once.[2] In the thesis we will use walking and gait (i.e., the manner of walking) interchangeably.

Spatial navigation is the ability to determine and maintain a route from one place to another.[4]

List of papers

Paper I

Tangen GG, Londos E, Olsson J, Minthon L, Mengshoel AM. A longitudinal study of physical function in patients with early-onset dementia. Dement Geriatr Cogn Dis Extra 2012;2:622-631

Paper II

Tangen GG, Engedal K, Bergland A, Moger TA, Mengshoel AM. Relationships between balance and cognition in patients with subjective cognitive impairment, mild cognitive impairment, and Alzheimer disease. Phys Ther 2014;94:1123-1134.

Paper III

Tangen GG, Engedal K, Bergland A, Moger TA, Hansson O, Mengshoel AM. Spatial navigation measured by the Floor Maze Test in patients with subjective cognitive impairment, mild cognitive impairment, and mild Alzheimer disease. Revised and resubmitted to International Psychogeriatrics.

The papers are referred to in the thesis by their Roman numerals.

Abbreviations

AD	Alzheimer's disease
APOE	Apolipoprotein E
BESTest	Balance Evaluation Systems Test
CERAD	Consortium to Establish a Registry for Alzheimer's disease
CI	Confidence interval
CT	Computer tomography
GPS	Global Positioning System
ICD-10	International Statistical Classification of Diseases and Related Health Problems, version 10.
IQR	Interquartile range
MCI	Mild cognitive impairment
MMSE	Mini Mental Status Examination
MRI	Magnetic resonance imaging
m/s	meters per second
NDR	Norwegian Dementia Register
SCI	Subjective cognitive impairment
SD	Standard deviation
TMT A	Trail Making Test part A
TMT B	Trail Making Test part B

1 Introduction

The increase in life-expectancy worldwide is a very positive development. However, conditions such as cognitive impairment and dementia become more common with age, and the number of people living with dementia is forecasted to increase dramatically in the years to come.[5] Dementia is a leading cause of disability and institutionalization; it represents a substantial burden on family caretakers, and can be a financial burden on society in the western world. In 2010 the estimated costs of care associated with dementia in the United States were between 157 and 215 billion dollars.[6] Although dementia is a key predictor for admission to nursing homes,[7] most people with dementia live at home for many years before they are admitted to nursing home care.[8] It is mandatory that we are able to provide secure and necessary care at home in order to maintain the quality of life of patients and their caretakers, but it is also important to meet the costs of care for society.

Dementia is primarily characterized by decline of cognitive function that leads to severe impairments in activities of daily living. However, dementia also entails changes in emotional and affective behavior and deterioration of physical function such as mobility (i.e., the ability to move around). Among the dramatic events that frequently occur in relation to mobility in people with dementia are falls,[9;10] and among the major risk factors for falls are gait and balance impairments, use of medication and cardiovascular instability.[10] The consequences of falls for elderly persons with dementia are more severe than for persons without dementia, such as increased risk for hip fractures.[11] Also, after a hip fracture they are less likely to recover function in terms of self-care and mobility,[12] as well as a higher risk of admission to nursing home[13] and of mortality.[14] Still, knowledge on successful fall-preventive interventions for people with dementia have been scarce,[15] however a recent review article concluded that physical exercise has a positive effect on preventing falls in older adults with cognitive impairment.[16] Our study aims to provide a better understanding of balance abilities in relation to type and severity of cognitive impairments that may be useful for designing tailored interventions for persons with cognitive impairment and dementia. However, the relationship between physical exercise and cognition will not be addressed in this thesis.

Getting lost is another dramatic event that occurs in relation to mobility in persons with dementia and causes concern and frequent intervention from caretakers. It is also a major risk for admission to nursing home.[17] Walking outdoors is a valued and important part of

independent mobility, and there are many good reasons for encouraging such activity. Balancing the risk of getting lost with the benefit of physical activity and participation in activities is the dilemma many patients and their caretakers face on a daily basis. Systematic evaluation of patients' navigational abilities in clinical practice is however almost absent, and in this thesis we will present a test that assesses spatial navigation during walking.

My own interest in mobility in persons with dementia started when I worked as a physical therapist at a geriatric outpatient clinic at Bærum Hospital in Norway. When I started my clinical work, I knew very little about dementia, and even less about how dementia affected physical function. However, during the next years I examined hundreds of patients and held almost equally many discussions with my fellow physical therapist and the rest of the interdisciplinary team. Still I strived to assess, describe, and understand the movement patterns that I observed in the clinical assessments, such as the cautious gait and the lack of natural spontaneity in movements. The learning process and the curiosity I had for this field of mobility inspired me to engage in research on this topic. At the time I started my clinical as well as research career I discovered that there were relatively few research reports addressing mobility in patients with dementia. During my time as a Master's student and as a Ph.D. student, the amount of research on mobility in persons with dementia has grown substantially, yet there are still many questions remaining on the interplay between cognition and mobility that requires interdisciplinary efforts.

The main themes in this thesis, cognition and mobility, are complex constructs, as well as balance, navigation, executive function and the other constructs we have studied. While we have strived to shed light on this complexity in the thesis, we have been forced to make pragmatic choices to be able to study these complex themes, such as using single tests to represent each of the complex cognitive domains.

The overall aim of the thesis is to explore the relationship between cognition and aspects of mobility in persons with cognitive impairment and Alzheimer's disease. In particular, the focus will be on the relationships between mobility, particularly balance and spatial navigation and the following: a) severity of cognitive impairment/stages of cognitive decline, and b) different domains of cognitive function. A better understanding of the relationship between mobility and cognition may help clinicians and researchers to identify persons at risk of falling, getting lost, and functional decline, and to develop ideas for future interventions aimed at preventing these negative events persons with dementia.

2 Cognition, cognitive impairment and dementia

Decline in cognitive function is the hallmark of dementia. Therefore, cognition as a construct will be presented as well as the conditions of cognitive impairment involved in this thesis.

2.1 Cognition

Cognition is derived from the Latin word "cognitio" which in turn comes from "cognocere" meaning "to come to know".[2] In modern literature the term cognition is often used to refer to our ability to think. More specifically, cognition may be defined as the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses.[2;18] Cognition is thus not a unitary concept and involves abilities such as perception, memory, reasoning, judgment and use of language. Given the diversity of abilities involved in cognition it is common to refer to cognitive *domains* in relation to assessment of cognitive function. Cognitive impairment refers to a decline in function in either one or several domains of cognitive function.[19] To explore the relationship between mobility and cognition in depth, it is a necessary step to look beyond cognition as a uniform ability and also address the various cognitive domains. The classifications of the different cognitive domains vary between professional disciplines and traditions. In this thesis the focus will be on some of the most well-established cognitive domains that are relevant for mobility in persons with dementia: memory, executive function, attention, and spatial cognition.

Memory is perhaps the most well-known cognitive domain that is declined in most dementia disorders. Memory is not a unitary concept, and several distinctions between subtypes are defined. Short-term memory refers to the ability to remember limited amounts of information for a very brief (i.e., seconds) period of time. Long-term memory on the other hand refers to the ability to remember both a larger amount of information and for longer periods of time.[20] Intact long-term memory function depends on the ability to both acquire, encode, store, and retrieve information.[21] The long-term memory function involves both semantic memory of general facts and knowledge and episodic memory. Episodic memory is related to your own experiences (also called autobiographical memory) and also involves spatial and temporal characteristics of these experiences.[21;22] Patients with Alzheimer's disease (AD) often have

impairments of episodic memory, especially related to encoding and storing of new information.[23] A typical clinical observation is when a patient forgets recent conversations, visits or events. A subdivision of long-term memory function is explicit and implicit memory; explicit memory requires conscious recollection of previous experiences,[21] while implicit memory is a type of memory in which previous experiences aid the performance of a task without conscious awareness of these experiences, such as singing along a well-known song or brushing teeth.[24] In this thesis the learning aspect of the memory function is emphasized given that this is a premise for establishing lasting memories.

Executive function is another complex cognitive function, and can be defined as the ability to plan, initiate, monitor, and carry out goal-directed behavior.[25;26] Executive function is considered as a higher-level cognitive function that implies a control function of other cognitive functions.[27] To achieve effective goal-directed behavior it is not only important to be able to initiate and plan actions, but it is also important to be flexible, to be able to shift plans and to inhibit irrelevant information or responses during action. The prefrontal cortex is connected to more regions than any other region of the cortex, and it is described to have a central role in the integrity of executive functions.[25] The inherent diversity of abilities involved in executive function is naturally difficult to grasp in single assessments, and they also entail a lack of a gold standard measure. In this thesis we have chosen to emphasize set-shifting ability, which is a form of cognitive flexibility.

Attention is another term commonly used in everyday language. In the research literature, attention is often divided into three main categories: selective, sustained, and divided attention.[28] *Selective* attention is the ability to focus on certain objects, or stimuli, at the exclusion of others for brief periods of time. *Sustained* attention, also referred to as vigilance, is the maintenance of abilities to focus attention for a more extended time period. *Divided* attention refers to the ability to attend to two or more competing tasks simultaneously.[19;28] Attention is a cognitive ability often considered as a part of executive function. However, presently attention will be treated as a separate cognitive domain because there has been some focus on the relationship between attention and performance on mobility and balance tasks in healthy elderly.[29]

Spatial cognition is the last cognitive domain to be emphasized in this thesis. It involves the interrelationships among people, objects, and space[30] represented by visuospatial perception, mental imagery, spatial memory, and navigation.[31] Two different aspects of spatial abilities

are emphasized: visuoconstruction and spatial navigation. *Visuoconstruction* is perhaps the aspect of spatial cognition that is most often assessed in cognitive/neuropsychological settings and involves the ability to draw or assemble visual stimuli in accordance with a specific design or mental image.[32]

Spatial navigation is the main topic in paper III and may be defined as the ability to determine and maintain a route from one place to another.[4] To maintain a sense of direction and location while moving around in the environment is a critical cognitive ability of both humans and animals. Successful navigation is traditionally associated with intact function of the medial temporal lobe (including the hippocampal formation), but it is also associated with other areas of the brain such as the parietal cortex, the prefrontal cortex, and the caudate nucleus.[33;34] Tasks related to spatial navigation is often divided into two reference frames for the navigator's perspective: egocentric and exo (or allo-) centric navigation. In the egocentric reference frame the person uses him or herself as the center, while in the exocentric reference frame the person establishes his or her position based on an external (map-like) reference system.[35] The exocentric reference frame has been linked to the hippocampal and parahippocampal regions,[36] and it is therefore of particular interest to study in persons with AD.

2.2 Conditions with cognitive impairment

In this thesis, the focus is primarily on AD, although in paper I patients with other forms of dementia are also included. Since AD is a progressive, degenerative disease it is likely that the disease process begins in advance of the point in time where the patient's symptoms are so pronounced that he or she fills the criteria for dementia. The idea or hypothesis of such a continuum is illustrated by Sperling and colleagues[37] in Figure 1. During the last few decades there has been an increasing focus on the transitional phase between normal ageing and dementia. Persons that experience changes (i.e., decline) in their cognitive functioning without filling the criteria for dementia are of interest for clinicians and researchers that seek to identify persons at risk for developing AD and other dementias. The overall aim of studying persons with MCI is in most studies to be able to point out who will benefit from preventive efforts or potential future treatment for AD. In this thesis, however, we have included persons that have sought medical help for cognitive problems without filling the criteria for dementia in order to gain knowledge on the early changes of mobility related to

AD. Two at-risk-conditions are described in this continuum: subjective cognitive impairment (SCI) and mild cognitive impairment (MCI). These conditions will be presented later in this chapter.

The challenge of doing research on the continuum leading to AD is that the intermediate stages between healthy ageing and dementia are naturally characterized by heterogeneous groups of persons with unequal future development ahead of them. To illustrate this, longitudinal studies of persons with MCI found that about 50% progressed to dementia (most to AD), 18% reverted to normal and the others remained stable.[38] In the text we will refer to SCI and MCI as stages in the continuum leading to AD. However, we will underline that we are aware that both these conditions also cover people with other causes for their memory concern than incipient AD for instance depression or a physical disorder.

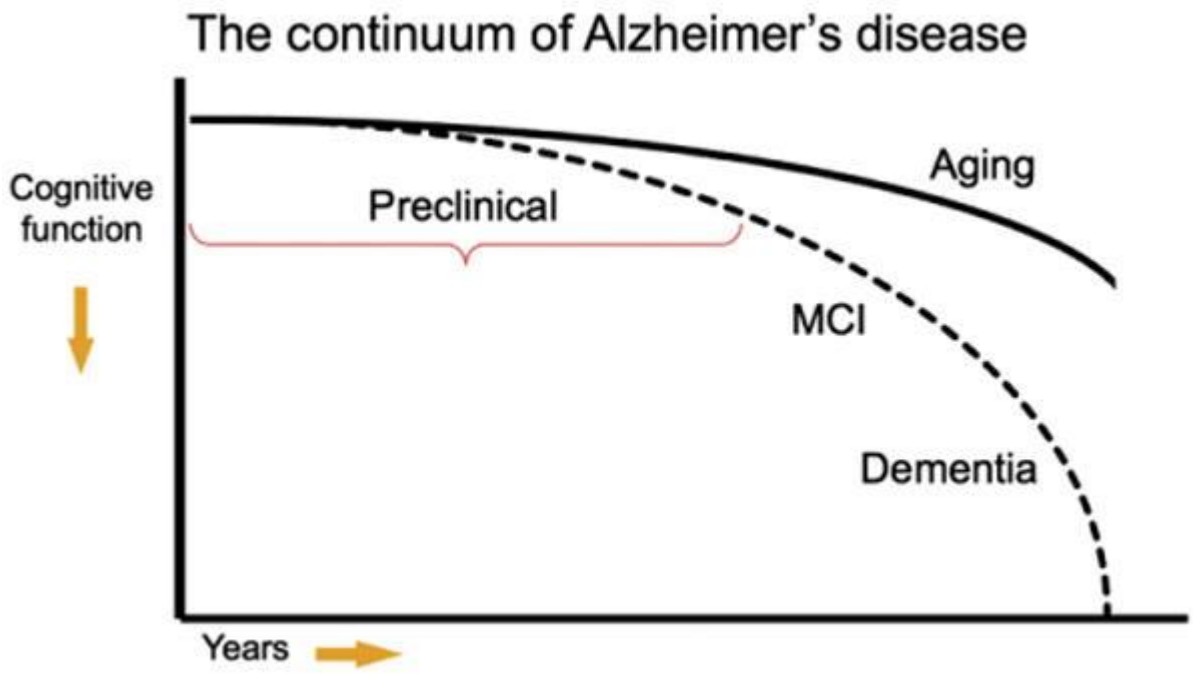

Figure 1. A hypothetical model of the clinical trajectory of AD.[37] Reprinted from Alzheimer's & Dementia, 2011; 7(3), by Sperling and colleagues, with permission from Elsevier. The SCI condition is situated in the "preclinical" phase in this model. Note that this model do not imply that all persons in the preclinical and MCI phase will progress to dementia/AD.

2.2.1 Subjective cognitive impairment

The earliest stage in the continuum from healthy ageing to dementia is often referred to as SCI. Several other terms are also used for this "almost-normal" condition, such as subjective memory complaints, subjective memory deficits, subjective cognitive decline, and as in Figure 1 preclinical dementia.[39;40] Since SCI is not embedded in diagnostic frameworks, definitions may have varied between studies. Common characteristics in clinical studies (and also how we have identified patients with SCI in our study) include the following: subjective decline of memory or other cognitive function, performances within the normal range on cognitive/neuropsychological tests, and absence of dementia and mild cognitive impairment. In population studies, however, the presence of SCI have been established by simply asking "is your memory getting worse?"[40] As a consequence the prevalence of subjective concern for memory in samples of community-based elderly varies widely.[41;42] Many of those who report some sense of worsening of memory will never develop AD, however future cognitive decline is probably more likely if the concern for memory decline is so severe that the persons seeks medical help at a memory clinic.

Longitudinal studies have found that persons with subjective memory complaints are more likely to develop further cognitive decline, MCI, or dementia than those who are not concerned about their memory function.[43-46] Demographic characteristics may also help to identify persons with SCI that are most likely to progress to dementia. Van Oijen and colleagues[47] found that the risk of AD was higher in persons with higher education than in persons with lower education in a sample of persons with SCI. One explanation for this may be that the cognitive screening tests have ceiling effects in persons with a high level of education, so that their changes in cognitive function go undetected. Another explanation could be that persons with a high level of education engage in activities that are cognitively more demanding than others, and this may make these persons more aware of even subtle changes in their cognitive function.

Another way to study SCI as a stage of preclinical AD is to examine the relationship between SCI and brain changes related to AD. Such studies have found that subjective memory complaints are associated with atrophy of structures in the medial temporal lobe[48-50] and AD

pathology at autopsy.[51] These studies underline the potential of the SCI condition as a pre-MCI stage in the development between healthy ageing and AD.

It is important to remember that the pace of cognitive decline may be slow in this initial phase, which is also illustrated in Figure 1. Reisberg et al.[39] suggested that the SCI stage of incipient AD may last up to 15 years before manifesting decline to MCI and dementia. A Swedish study that recruited participants from a memory clinic found that during the 3-year follow-up period, 88% of the patients that were diagnosed with SCI at baseline remained stable (i.e., did not develop MCI or dementia), while 60% of the patients with MCI remained stable.[52] There are also studies that have not confirmed the association between SCI and future cognitive decline;[53] however, in a follow-up study of the same population the authors concluded that memory complaints were an early manifestation of memory impairment.[54]

Besides being associated with increased likelihood for future cognitive decline and dementia, subjective memory concerns are also associated with depression,[55-57] personality traits,[57;58] a number of different medical conditions, substance abuse, and medication. We are well aware of this heterogeneity, but we still believe that it is important to include this group of patients when exploring the relationship between cognition and mobility across the continuum of AD.

2.2.2 Mild cognitive impairment

The next stage on the continuum between healthy ageing and dementia is MCI. This condition has received massive interest in research since the first paper on MCI was published in 1988 by Reisberg and colleagues.[59;60] Several different criteria have been applied for MCI during the years; however there is considerable agreement that a person with MCI has some degree of cognitive impairments that can be confirmed by performances below reference values on various cognitive tests. At the same time a person with MCI has generally preserved abilities of daily living and thus does not fulfill the criteria for dementia.

In 2004, the original Petersen/Mayo criteria[61] which emphasized memory impairment were revised by an international working group to include impairments of other cognitive domains and to allow "minimal impairment" of complex daily functions.[62] The new criteria, known as the Winblad criteria (which we have used in this thesis) are presented in Table 1. A recent study of patients attending Norwegian memory clinics reported impairments in complex activities of daily living in about 66% of the patients with a diagnosis of MCI.[63] This finding

is in line with other studies.[64;65] There is still no consensus for the degree of functional impairment that is acceptable within the MCI criteria, and the evaluation therefore requires the judgment of a clinician.

Table 1. The Winblad criteria for MCI[62]

1. The persons is not normal, nor meet the criteria for dementia
2. Evidence of cognitive deterioration for age:
- Objective measured decline over time in cognitive task performance, and/or
- Subjective report of decline by patient and/or informant and objective cognitive deficits
3. Preserved activities of daily living and minimal to no impairment on complex instrumental functions

Not all patients with MCI are typical representatives for the continuum between healthy ageing and dementia. MCI may also occur after stroke, and these patients may not have had any cognitive deterioration beforehand; they may also remain stable or improve their cognitive function in the recovery phase after the stroke.[66] Clinical subtypes for MCI are also described according to the cognitive domain that is affected. The most common distinction is amnestic-MCI (characterized primarily by memory deficits) and non-amnestic-MCI (deficits in several cognitive domains, with or without memory deficits), and some also add a division for affection of a single domain or multiple domains.[62;67] In this thesis we have not applied this sub-categorization of MCI, although the exclusion criteria we have applied in our studies probably makes the amnestic-MCI subtype most common.

Prevalence studies have been conducted in several countries and in populations generally above 60 years old. The prevalence rates of MCI vary substantially across these studies, from 3.2%[68] to 24.3%,[69] and this discrepancy probably reflects issues such as for example the use of different MCI criteria, use of cognitive tests, differences of age of the studied populations (the prevalence rates increase with age), and differences in design.[70]

Several studies are conducted to assess how many converts from MCI to AD (i.e., conversion rates) and to identify predictors for conversion. A crucial factor for describing the conversion rate is the source of participants. Patients recruited from population-based samples have in general lower conversion rates than patients recruited from clinical settings such as memory clinics.[71] Reviews of annual conversion rates for persons with MCI recruited from clinic

samples (similar to our sample) estimates approximately 10-15%, while for population-based samples this rate is generally less than 10%.[71] A recent long-term population-based prospective study estimated that median dementia (AD) free survival time was 3.5 years from the onset of MCI, with a conversion rate of 7.3%.[72] Established predictive factors for conversion include clinical severity, to be a apolipoprotein e4 carrier or not, and the presence of biomarker findings related to AD.[59] Although many patients with MCI will remain cognitively stable or even revert to normal cognition, they still represent a high risk group for the development of AD and other dementias.[73] The MCI condition is therefore of special importance in order to shed light on mobility across the stages of cognitive impairment in this thesis.

2.3 Dementia

Dementia is a syndrome caused by structural diseases of the brain. This implies that dementia is an umbrella term covering a variety of brain diseases. The characterizing main features are cognitive decline and changes in social and emotional behavior, and these characteristics are included in the International Statistical Classification of Diseases and Related Health Problems, version 10 (ICD-10) criteria for dementia which is presented in Table 2.[18] The routines for evaluation and assessments of these characteristics are presented in the Methods section.

Table 2. Diagnostic research criteria for dementia according to the ICD-10[18]

Decline in: a) memory b) other cognitive abilities involving judgment and thinking, and in general processing of information
Preserved awareness of the environment
Decline in emotional control, motivation, or change in social behavior.
State of cognitive decline must have lasted for more than 6 months. The degree of cognitive decline must be so severe that it affects the individuals' ability to carry out activities of daily living.

Most brain disorders causing dementia are of a progressive nature. It is common to describe the progression of dementia in stages according to a combination of the severity of cognitive impairment and dependence in activities of daily living.[74;75] Descriptions of three stages of dementia are incorporated in the ICD-10 diagnostic criteria for research in accordance to how the decline in memory and other cognitive abilities affects the ability to carry out activities of daily living.[18] Severity of dementia is determined by the cognitive domain (e.g., memory or other cognitive functions) with most severe impairment, implying that a person with moderate decline in memory but only mild impairments of other cognitive abilities, has a moderate degree of dementia.

Mild degree of dementia: The degree of memory loss or decline in other cognitive abilities is sufficient to interfere with everyday activities, but not so severe that it makes the person dependent on others. However, more complicated tasks cannot be undertaken.

Moderate degree of dementia: The degree of memory loss or decline in other cognitive abilities makes the person incapable of living without support from others, and the person needs help in all tasks beside the most basic chores.

Severe degree of dementia: The person no longer has the ability to retain new information, and often fails to recognize close relatives.

2.3.1 Dementia disorders

Dementia may be classified into three main types of disorders; the most common is degenerative brain diseases such as Alzheimer's disease (AD), dementia with Lewy bodies, frontotemporal lobe dementia, and Parkinson's disease with dementia. The second most common type is vascular dementia, which involves both small vessel disease and dementia after infarcts. The third category is secondary dementia which may originate from a variety of conditions such as alcoholism, brain tumors, encephalitis, head trauma, vitamin deficiency, endocrine disease, and several other conditions. Diagnostic precision is complicated by findings from autopsy studies that have shown that persons with dementia often have brain abnormalities related to more than one type of dementia (i.e., so called mixed dementias), which is more common in the oldest old patients with dementia.[76;77]

AD has a well established position as the most common disease leading to dementia; the prevalence of the other dementia disorders however varies from study to study.[77-79] There are several reasons underlying the uncertain prevalence rates, such as which diagnostic criteria are applied and also which population are included in the studies. Overall, though, dementia with Lewy bodies and vascular dementia are considered as the second and third most common forms of dementia.[80;81]

2.3.2 Alzheimer's disease

Alois Alzheimer diagnosed Auguste Deter with AD in 1906, which means it is now over 100 years since the first patient was diagnosed with AD. Dr. Alzheimer described aggregated beta-amyloid in plaques and neurofibrillary tangles in Deter's brain after her death, and these findings are still considered the neuropathologically hallmarks of AD.[82] AD is a degenerative progressive disease that initially affects structures in the medial temporal lobe (such as entorhinal cortex and para-and hippocampal area) and then further affects other parts of the cortex (i.e., temporal, parietal and frontal lobes), while subcortical structures are largely spared.[83]

Clinical presentation

Clinically, persons with AD often experience memory impairments for recent personal events as one of their first symptoms. They may also have difficulties finding words, lose track of thoughts during conversation and get disoriented in familiar environments.[8;84] Impairments in activities of daily living can initially be observed in more complex settings such as paying bills, learning to use new electronic equipment, and shopping, while later on there will be also be problems with more basic activities such as personal hygiene and getting dressed. Most persons with AD also experience behavioral changes such as increased irritability, apathy, anxiety, and depression.[85;86]

According to the ICD-10, the clinical diagnosis of AD is made when the general clinical criteria of dementia are present, and there should be no evidence of any other type or causes of dementia. The diagnosis is further supported by signs of affection of cortical functions such as aphasia, apraxia, reduced motivation and drive, changes in social behavior, and evidence of cerebral atrophy, preferably shown to increase over time.[18] Subtypes of AD are also defined, including AD with early onset, AD with late onset and atypical or mixed AD. The most

common subtype is the late onset AD that is characterized by onset after 65 years and evidence of slow, gradual onset and progression with primarily affection of memory. Given that approximately 95% of all cases have late onset AD, the general description of AD in this thesis is primarily related to this subtype. However, since paper I concerns mobility in patients with early onset AD, this subtype will be presented more explicitly later in this section.

Epidemiology

AD is the most prevalent dementia disorder and accounts for about 60% to 70% of all cases of dementia.[87] The importance of ageing on development of AD has substantial influence on the estimated future prevalence of AD. About one in nine persons aged 65 years and above has AD;[8] however, among persons above 85 years old the number increase to one in three.[88] A recent systematic review and meta-analysis estimated that about 35.6 million people worldwide had dementia in 2010, and the majority of these will probably have AD.[5] Further, the authors of that study expected the numbers to double every 20 years to 65.7 million in 2030 and 115.4 million in 2050. This increase is mostly attributed to the expected increase of people with dementia in low and middle income countries. There are, however, also indications that generational cohort effect exists in prevalence of dementia, suggesting that later-born generations have a lower risk of dementia than previous generations in the past century.[89] This study was carried out in England, and it is uncertain to what extent these findings apply for low and middle income countries. There are no certain numbers on how many have AD in Norway, but approximations based on the Rotterdam-study in conjunction with a small Norwegian study forms estimates that around 70 000 persons may have dementia in Norway today.[90;91]

Risk factors

The underlying cause leading to AD is still not established; however, several risk factors for the development of AD have been identified, including both genetic and non-genetic risk factors and also protective factors. Gene mutations in one of three genes—amyloid precursor protein, presenilin 1 and presenilin 2—are the cause of AD in less than 5% of patients with AD, and these rare forms of familiar AD usually exhibit an early onset.[92] Among several potential risk genes, the ApoE e4 allele entails 3-10 times increased risk of AD.[93;94] The non-genetic risk factors includes both non-modifiable factors such as ageing, which is the overall

most important risk factor, and modifiable factors such as presence of cerebrovascular disease, depression, elevated blood pressure, diabetes, metabolic syndrome, smoking, alcohol, and a history of traumatic brain injury.[92;94;95] The best established protective factors include physical activity, exercise, intellectual activity and education.[94;96] Social participation is also recognized as a protective factor from development of AD.[97]

Early onset Alzheimer's disease

The ICD-10 diagnostic criteria for the early onset subtype of AD includes onset before 65 years, a relatively rapid onset and progression (compared to late onset AD), and in addition to memory impairment there should also be signs of temporal, parietal, and/or frontal lobe involvement such as aphasia, agraphia, and apraxia.[18] The age cut-off is an arbitrary division based on sociological aspects such as retirement age rather than biological age, and it is generally accepted that the early onset and late onset subtypes do overlap.[98] Early onset AD is a rare condition compared to the late onset subtype. Recent prevalence estimates suggest that there are 10.6 to 153 persons with early onset AD per 100 000 of the population.[99] AD is the most common form of early onset dementia; however, AD is relatively less common than in late onset dementia.[100;101] Frontotemporal lobe dementia is relatively more common in early onset than in late onset dementia.[102-104]

Several studies have examined clinical differences between early and late onset AD. Non-memory and atypical presentations such as apraxia and impairments in executive and visuospatial function are more common in patients with early onset AD than in patients with late onset AD.[105-108] This atypical clinical presentation combined with the notion of AD as a disease of old age may explain why the time to get the correct diagnosis is generally longer for persons with early onset AD compared to late onset AD.[109] Although the ICD-10 list "relatively rapid progression" as a criterion for the early onset subtype of AD, inconsistent findings regarding whether early onset AD is characterized by rapid progression exists.[110-112] Compared to persons without dementia at the same age, persons with early onset have elevated risk for mortality.[113;114]

There is no doubt that AD is a devastating condition for all affected regardless of age. However, persons that develop dementia in their 50s and 60s are part of the work force, and often they have responsibilities for children still living at home. The early onset subtype, therefore, raises some particular challenges beyond the diagnostic process. Caretakers (often

spouses and children) have reported frustration, grief, and loneliness because of dementia in the family, and conflicts between children and the affected parent was common. Reduced income and financial problems are also common findings both related to the patient not being able to work longer, but also because many caretakers had reduced their working hours to care for their family member with dementia.[115;116]

Most research is naturally focused on late onset AD since this is the most common form of AD, and there is still few studies involving the early onset subtype of AD. It is therefore a need to gain more knowledge on the condition itself and to study mobility in dementia in patients less disturbed by the normal changes related to ageing.

3 Mobility

In this thesis mobility is defined as the ability to move independently and safely from one place to another.[1] So mobility is an essential part of activities of daily living, of participation in cultural, social, and physical activities and thus of importance for quality of life. Mobility is known to decline with higher age even in healthy elderly,[117;118] and impairments of mobility are closely related to functional decline and disability.[119]

The understanding of mobility in this thesis is based on the systems approach for motor control as described by Shumway-Cook and Woollacott.[1] This approach looks upon motor control and movement as the result of interaction between the individual, the task, and the environment. A person's functional capacity for movement is thus determined by the person's capacity to undertake the demands by the task and the environment.[120] While this theory most often refers to "motor control", the same conceptual model may just as well refer to "mobility", and this is how the model will be referred to further in this thesis. Complex cooperation between several interrelated systems within the individual is necessary for successful mobility. Broadly, these systems concern *perception* (i.e., integration of sensory impressions to meaningful information), *cognition* (i.e., the central processing and modulation to achieve specific goals or intents) and *action* (i.e., the motor output from the central nervous system).[1]

During the last few decades, the systems approach has also been applied to explain and understand balance.[121-123] There is no universal definition of balance, and different terms such as postural control, balance, postural stability, are often used interchangeably.[124] In this thesis, we consider these terms as synonyms, and the term balance will be used throughout the text. Balance may in a wide-sense be defined as "a generic term describing the dynamics of body posture to prevent falling,"[3] or more specifically as the ability to regulate the body's position in space for the dual purposes of stability and orientation.[1] Regardless of definition balance is a prerequisite for our ability to carry out everyday activities in a safe and efficient manner. The human body has a relatively narrow base of support, a high center of gravity and many moveable joints, so the act of maintaining balance while in an upright stance is a demanding task.[124] The complex interaction to achieve balance includes both musculoskeletal and neural systems.[1;121] The musculoskeletal systems involve factors such as biomechanical alignment, joint range of motion, muscle strength, etc. The neural systems include both peripheral and

central processes, such as motor processes (i.e., organization of neuromuscular synergies for coordinated functional movements), sensory processes (i.e., organization and coordinating information from visual, vestibular, and somatosensory systems) and higher level processes (i.e., cognitive influences that also provide adaptive, and anticipatory adjustments).[1]

The functional goals of these systems are to maintain postural alignment (e.g., while sitting or standing) to facilitate voluntary movement such as reaching forward, and to recover from external disturbances such as a slip on icy pavement.[122;124] The strategies to achieve these goals can be either proactive/anticipatory, reactive/compensatory, or a combination of these.[125;126] The natural consequence of not being able to maintain balance is falling, so "balance" is as an important topic for both physical therapists and other health professionals. The systems approach for balance has implications for how physical therapists should address balance impairments by seeking to determine which underlying aspects of balance are impaired in order to tailor interventions.[121;122;127]

Balance is challenged in various degrees during the different mobility tasks, and one of the most demanding tasks is walking. Human walking is typically characterized by a symmetrical alternating gait pattern.[128] During the step cycle, the line of gravity will fall outside the base of support, and we keep repeating this unstable maneuver over and over again.[3] Walking is therefore a demanding mobility task that can be described by three requirements the systems theory relate to all mobility tasks; progression, stability and adaptation. *Progression* is generated during walking by coordinated rhythmic patterns of muscle activation of the legs and the upper body to move the person's body in the desired direction. *Stability* is constantly challenged during walking, and walking has therefore been compared to a series of controlled falls. When the surface changes or we are disturbed, we need to be able to *adapt* to these changes.[1] This understanding underlines the importance for intact balance control for efficient and safe walking, which is also expressed in the frequently used "gait and balance" term.

Walking was for a long time considered as an automatic motor task that did not require cognitive influence. However, during the last few decades a lot of research has focused on the cognitive contributions, in line with the systems approach, to walking performance. Lundin-Olsson and colleagues [129] demonstrated in 1997 that elderly who "stopped walking while talking" were more prone to falling than those who were able to sustain conversation during walking. Since then, this dual task approach has been the most common method for testing whether walking requires attention.[29;130] The underlying rational is that if walking is

independent of attentional resources, then there would be no affection of walking when the persons simultaneously performs other tasks such as manual tasks (e.g., carrying a tray) or cognitive tasks (e.g., counting backwards).[131] However, even healthy young people display decreased cognitive performance while walking as long as the cognitive task is sufficiently difficult.[131;132] Walking is therefore no longer considered as solely an automated motor activity independent of cognitive influence. In the three papers in this thesis, walking has been used in different ways to explore mobility in persons with cognitive impairment. In paper I, walking is represented by tasks such as walking on a flat surface and also stair walking. In paper II, balance is examined during dynamic walking tasks in the last subscale of the BESTest. In paper III, we have examined performances in spatial navigation where the patients must figure out the correct pathway to walk.

Few studies (other than the dual task studies) have focused on the relationship between mobility and impairments in separate cognitive domains in persons with AD. The studies that have looked into this relationship have found associations between executive functioning and various measures of gait stability,[133-135] but not with gait speed.[134] Limitations of these studies involve small samples and limited exploration of other cognitive domains. A study of gait in patients with MCI did however include global cognition, working memory, executive function, and attention as independent variables, and working memory was the only factor that remained significantly associated with slow gait after adjustments.[136]

The systems theory is a useful approach to gain understanding of motor control, movement, balance, and walking. However, in order to make meaningful use of walking skill in the community, it is also necessary to be able to navigate in both familiar and unfamiliar surroundings. Although the systems theory emphasizes that movement emerges from interactions between the individual, the task, and the environment, the individuals' ability to maneuver in the environment is not properly addressed in this approach. Patla and Shumway-Cook[137] provided a thorough description of eight environmental factors related to independent mobility in the community, however, the ability to navigate in the community did not receive much attention. Spatial navigation is not defined as part of the cognitive process described in the systems theory; however, it is in this thesis incorporated in the extended understanding of mobility as a construct.

4 Mobility in persons with SCI, MCI and AD

In the review of the literature regarding mobility in persons with cognitive impairment and/or AD, studies that were published up to 2010 are included, as these formed the literature base on which we designed our study. More recent studies will be included in the discussion section of the thesis.

For a long time persons with mild degrees of AD were thought to show no kind of mobility limitations.[138] This understanding was also incorporated in formal documents such as the National Institute of Neurological and Cognitive Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for AD published in 1984, where disturbances of gait in an early stage of AD would argue against a diagnosis of probable AD.[139] Later, several studies confirmed that mobility impairments are more common in other dementias than AD,[140-143] but studies also demonstrated conflicting results such as no difference in gait speed between persons with AD and dementia with Lewy bodies dementia.[144] The lack of focusing on mobility in the early 80s is also seen in the Global Deterioration Scale for Assessment of Primary Degenerative Dementia, published in 1982, which does not describe decline of walking until severe stages of dementia.[145] The Clinical Dementia Rating scale, also published in 1982, incorporates six domains of cognition and functioning but does not mention physical function at all.[146]

The first paper I have found with focus on gait and balance impairments in patients with AD dates back to 1983 when Henriet Visser compared 11 patients with AD of moderate degree with healthy age- and sex-matched control persons. She reported that the patients with AD had shorter step lengths, lower gait speed, lower stepping frequency, greater step variability, and greater sway path than the control persons without dementia.[147] During the last two decades the interest for physical function and mobility in persons with cognitive impairment and AD has evolved tremendously.

Several approaches are used to understand the development of mobility impairments related to severity of cognitive decline in persons with AD. The gold standard would be longitudinal studies following a large cohort of healthy persons for a long period of time. In that way one would be able to describe the first subtle changes as well as the development throughout the

course of preclinical dementia and further through the stages of AD. However, given a series of practical reasons, as far as I know no such studies exist. The knowledge of development of decline in mobility is therefore gathered from longitudinal studies of shorter time spans as well as cross-sectional studies that have compared groups of persons at different degree of cognitive impairment and stages of dementia.

4.1 Mobility impairments in persons with SCI and MCI

To the author's knowledge, no study of mobility in persons with SCI exists. Probably this is related to the heterogeneous character of the condition. Several studies of mobility in persons with MCI have been published, and most studies have focused on comparisons of walking abilities between persons with MCI and healthy controls. In general the findings of these studies indicate that persons with MCI have worse performances on different aspects of walking (e.g., clinical evaluation of gait, gait speed, stride length and variability, and dual task walking) compared to healthy controls.[148-154] Differences in gait performance are found in both amnestic and non-amnestic groups of MCI compared to a healthy control group.[151] Fewer studies have examined balance in populations with MCI, although studies have found differences in postural sway between persons with MCI and healthy controls using platform systems.[155;156] Mobility impairments have also been associated with disability in persons with MCI.[149] However studies have been published that have not been able to detect differences between persons with MCI and healthy controls, these studies used clinical balance and walking tasks as outcome variables.[157;158] Although several studies have been conducted in this field, this thesis will provide a more comprehensive assessment of the various aspects of balance in persons with MCI than has been previously published.

4.2 Mobility impairments in persons with AD

In this section I will first present estimates of prevalence of mobility impairments in AD, and then I will look at studies that have examined the relationship between severity of cognitive decline and mobility either in cross-sectional studies or in longitudinal studies. Lastly, studies of the relationship between mobility and cognitive domains, in particular spatial navigation, will be reported.

The prevalence of gait disorders or mobility impairments is hard to establish given various outcome measures and the large heterogeneity in the characteristics of the involved sample of participants. Most studies report prevalence rates of gait and/or balance impairments between 30% and 50% in home-dwelling persons with AD.[159-162] The corresponding rates in healthy control persons in these studies are between 7% and 26%.[141;159-162] The lowest prevalence rate of gait impairments was reported in Allan's[141] study, where 25% of the patients with AD had gait impairments (measured by the Tinnetti scale). The highest rate was reported by Thomas and colleagues,[142] who found gait impairments in 52.7% using a clinical evaluation of concern for the safety of independent walking as an outcome measure. Regardless of methodological issues, all these studies reported more gait and/or balance impairments in persons with AD than in healthy controls.[141;159-162] Thus, there is a need for more knowledge on the development and the character of mobility impairments in persons with AD at different stages.

Comparisons of mobility impairments across the continuum of AD

Studies have shown that persons with AD display worse performances on several different aspects of walking compared to cognitively healthy controls such as slower gait, increased gait variability or other deviations of gait pattern,[134;144;147;154;157;158;163-167] more pronounced effects of dual task on gait,[153;168] and also lower scores on composite scores of walking tasks or lower-extremity function.[141;148] Balance impairments are also more pronounced in patients with AD than in healthy control groups, as studies using clinical outcomes such as Bergs balance scale[166] and the Tinnetti balance scale[141] have shown. Various platform systems have also been used to detect more subtle changes in postural sway, and they have identified differences between persons with AD and healthy controls.[147;155;165;169] Deterioration of balance with increasing severity of AD was found in a study where impairments on the Tinnetti balance scale was related to lower Mini Mental Status Examination (MMSE) scores and low ADL scores.[170]

A handful of studies have compared mobility performances between groups of healthy controls and groups with MCI and AD. Such studies are of special importance for the understanding of mobility related to the continuum between healthy ageing and AD (Table 3).

Table 3. Overview of selected studies comparing mobility performances between groups of healthy controls, MCI and AD.

Author, year	Groups, n	Age, mean (SD) or median (range)	Main outcomes	Main findings
Pettersson, 2005[157]	Healthy: 33 MCI: 51 AD: 22	57 (9.2) 60 (7.3) 68 (9.9)	Bergs Balance scale Tinetti Gait Timed Up and Go	Healthy vs MCI: no differences MCI vs AD: no differences
Eggermont, 2010[150]	Healthy: 22 MCI: 22 AD: 22	76.5 (7.4) 76.3 (8.1) 77.1 (9.6)	Gait speed Timed Up and Go Sit to stand	Healthy vs MCI: Gait speed slower in MCI group, other no differences MCI vs AD: no differences
Goldman, 1999[158]	Healthy: 43 MCI: 40 AD: 20	73.2 (7.7) 72.0 (7.5) 73.7 (7.8)	Gait speed	Healthy vs MCI: no difference MCI vs AD: AD slower than MCI
Pettersson, 2007[171]	Healthy: 25 MCI: 6 AD: 6	55 (4.7) 59 (3.4) 58 (1.9)	Gait speed Gait speed dual task	Healthy vs MCI: no differences AD slower than healthy group MCI vs AD: not reported
Nakamura, 1997[165]	Healthy: 15 Mild AD: 15 Moderate AD: 15 Severe AD : 15	77.1 (3.4) 75.9 (3.6) 77.5 (4.0) 78.1 (3.2)	Postural sway Gait speed	Healthy vs mild AD: no differences in gait Postural sway increased with each stage of AD
Leandri, 2009[155]	Healthy: 15 MCI: 15 AD: 15	76.0, 70-86 77.6, 69-84 77.6, 66-84	Postural sway	Healthy vs MCI: sway increased in MCI MCI vs AD: sway increased in AD
Aggarwal, 2006[148]	Healthy: 558 MCI: 198 AD: 60	74.6 (6.7) 78.7 (7.0) 81.9 (3.1)	Lower limb function (gait, balance, sit to stand)	Healthy vs MCI: MCI more impaired MCI vs AD: AD more impaired

SD = standard deviation.

The findings from the cross-sectional studies presented in Table 3 are not entirely consistent to the MCI condition's role as an in-between-group of healthy ageing and AD with regard to mobility level. The study with the largest sample size (n=816) conducted by Aggarwal and colleagues[148] found that mobility performances of persons with MCI were inferior to cognitively healthy persons but were still superior to persons with AD. However, their sample was part of the Religious Order Study and involved only Catholic clergy members; this raises questions about the generalizability of their study to other populations. A general drawback of most of the other studies is the relatively low sample sizes. Pettersson's study from 2007[171] is the only study using well-established outcomes in a population of early onset AD of which I am aware. Unfortunately the group of early onset AD consisted of only six patients, which limits the generalizability of the findings. Mobility in patients with early onset AD is therefore a largely unexplored area of research. Compared to walking there are relatively few studies of balance, and also very few studies that involve comparisons of different stages of AD. It also seems clear that evaluation of mobility performances in the early phases of cognitive impairment and dementia demands sensitive assessment tools without ceiling effects.

Mobility performances observed in longitudinal studies

The few longitudinal studies of mobility in persons with AD confirm the impression from the findings in the cross-sectional studies, that a decline in cognition is associated with a decline in mobility. Hebert and colleagues followed-up with a group of home-dwelling persons with AD for up to 4 years.[172] They concluded that physical performance declined over time, and that a faster decline was seen in those with lower cognitive score at baseline. It should be noted that the mean score of the MMSE at baseline was as low as 13.5 points (SD 8.1); this indicates a moderate to severe degree of dementia. Scarmeas and colleagues studied parkinsonian signs (e.g., rigidity, bradykinesia, posture/gait abnormalities) in persons at early stages of AD for a mean period of 3.6 years, and they found that the prevalence of the posture/gait sign increased as the disease progressed.[173] Another study of parkinsonian signs in persons with AD reported an 8.9% increase of the gait and posture score over a 4-year follow-up.[174] Change over time was also investigated in a study of quantitative measures of walking with a one-year follow-up of patients with mild and moderate degrees of AD.[175] The results showed reduced gait speed and stride length and an increase in double support and stride variability.

Most longitudinal studies have not focused on the development of mobility impairments. Instead they have used mobility measures as predictors for future cognitive decline and thus do not necessary provide information that is fruitful for designing interventions. The presence of gait and posture impairment as well as quantitative gait measures such as gait speed, variability, and stride length have consistently been identified as independent predictors of future cognitive decline[176-180] and dementia[159;180-182] in longitudinal studies of community-dwelling cognitively healthy persons. Other studies have found that the degree of gait and balance dysfunction was related to risk of AD in persons with MCI[148] and that disturbed gait or balance performances predicted higher rates of cognitive decline[159;183-185] and increased risk for institutionalization and mortality[186] in persons with AD. These studies indicate that mobility impairments may occur at a very early phase of dementia and that interventions aimed at preventing this decline therefore should start as early as possible.

4.3 Mobility and spatial navigation in persons with SCI, MCI, and AD

In this thesis, the cognitive ability of spatial navigation is emphasized as an essential skill for independent mobility in society. Failure in spatial navigation may lead to topographical disorientation, i.e., the inability to find one's way in large-scale environments.[187] Large-scale environments refer to buildings, neighborhoods, cities etc., and require walking or other forms for locomotion.[188] The ultimate consequence of impairments of spatial navigation is getting lost, an experience we all can relate to. Getting lost can be an early sign of AD and is also a common reason for the need for institutionalized care.[17] Despite the importance of spatial navigation, there is no established consensus regarding how to conduct such assessments. Brunsdon and colleagues[187] stated that research on topographical disorientation is hindered by factors such as terminological confusion, lack of theoretically driven assessments, and "an ongoing failure to examine topographical skills in real-life settings". The few studies we have found that have assessed spatial navigation during walking in patients with cognitive impairment have used either route learning tasks in hospital settings[189] or virtual reality tasks conducted on a treadmill.[190] Much of the knowledge on navigational impairments is therefore derived from assessments without the dynamic of movement through environmental settings, such as questionnaires or clinical interviews,[191-193] a human analogue of the Morris water

maze test,[194-197] pencil-and-paper tasks, or being taken through a route learning test in a wheelchair.[33;198]

Studies have reported that approximately 50% of community-dwelling people with AD experience navigational impairment,[33;192;199] and navigational impairments have also been reported in patients with mild cognitive impairment (MCI).[33;194;196] A study of subgroups of MCI even found no differences in spatial navigation between persons with amnestic MCI (i.e., primarily memory impairments) and persons with AD.[194] In contrast to studies focusing on walking and balance, groups of persons with SCI are also included in studies of spatial navigation. Although the sample sizes are low, the results from these studies indicate that persons with SCI do not exhibit impaired spatial navigation.[194;195] However, since most of these studies have used outcomes tasks without involvement of walking, the interplay between navigational impairments and movement remains largely unexplored in persons with cognitive impairment.[35;200;201]

This interplay between movement and navigation is reported to be important in studies involving healthy persons without cognitive impairment. Lövdén and colleagues[201] studied the influence of postural demands on spatial navigation by comparing the performances between healthy young and older adults on a VR-based way-finding task while walking on a treadmill. In this study the performances of both groups deteriorated when they walked without support in comparison to walking while holding the handrails, but the performance of the older adults deteriorated the most. These results from Lövdén et al. indicate a dual-task effect on way-finding during motor activity in healthy people. This effect was also present in a study comparing active (i.e., using a joystick to control their movements in the virtual environment) and passive (i.e., watching the virtual environment screen) conditions of a virtual reality based wayfinding task, where a detrimental effect of active learning was observed.[202] So, it is likely that a navigational assessment which involves walking may have both real-life applicability and also the ability to detect subtle changes in spatial navigation in patients with cognitive impairment or dementia.

4.4 The rationale for this thesis

Mobility, defined as the ability to move independently and safely from one place to another, is a fundamental ability for human life. The existing research has through the use of outcomes

mostly suitable for screening purposes established that persons with AD have poorer mobility performances than healthy persons at the same age.

While previous studies generally have treated balance as a unitary construct, we wanted in our study to use an outcome that allowed us to target the various aspects of balance in line with the systems theory approach. By shifting from global to comprehensive outcomes we aimed to expand the knowledge platform on which physical therapists base their interventions. For persons with cognitive impairment and AD, safe and independent mobility is however not only threatened by impaired balance and walking ability, but also by the loss of the ability to determine and maintain a route from one place to another. Spatial navigation is an essential skill to participate in activities in society, and there is a need for assessments tools with real-life applicability that may help to identify persons who may be at risk for getting lost. By assessing spatial navigation during walking, we aimed to be able to explore differences in navigation between patients at the earliest stages of cognitive impairment. Cognition will also be treated as a complex construct, and we will explore the relationship between mobility and cognitive domains.

Although the SCI and the MCI conditions involve persons with heterogeneous backgrounds we believe that it is more fruitful to see AD as a continuum rather than as a disease that is either absent or present. In this thesis we aim to contribute to a more nuanced understanding of the complexity of the mobility construct in persons at possible different stages in the continuum of AD.

5 Aims of the thesis

The overall aims of this thesis were to explore how mobility performance differs between groups with different levels of cognitive impairment, and to explore the relationship between mobility and different domains of cognitive function. The aims of each paper are described below:

Paper I:

- To compare mobility performance between patients with early onset AD and patients with other early onset dementias.
- To explore which variables were associated with the Timed Up and Go test.
- To examine changes in mobility over one year in patients with early-onset AD.

Paper II:

- To explore differences in performance on the BESTest between patients with Subjective or Mild Cognitive Impairment, mild AD and moderate AD.
- To examine which cognitive domains were associated with impaired balance control when controlled for demographic and health-related characteristics.

Paper III:

- To evaluate differences in spatial navigation between patients with Subjective Cognitive Impairment, Mild Cognitive Impairment and mild Alzheimer's disease.
- To examine which cognitive tests that are associated with error-free performance on the Floor Maze Test.

6 Methods

6.1 Design

In all three papers we applied a cross-sectional design; we also applied a one-year longitudinal design in paper I. A cross-sectional design is based on data collected at one point in time. This design is useful for describing populations, exploring associations and generating hypotheses.

6.2 Recruitment of participants

In all three papers we recruited participants using a convenience sampling strategy.

Paper I

In paper I, the sample consisted of patients with early onset dementia recruited from the Memory Clinic in Malmö, Sweden in the period of 2005–2011. Patients were included in two sets; the first 28 patients were included either from their first visit to the Memory Clinic, or they were included in relation to follow-up appointments. The second 44 patients were recruited from a prospective clinical observational study of patients with early onset dementia. Inclusion criteria were the same for both sets: they had to be home-dwelling and have a mild or moderate degree of early onset dementia. Patients that needed physical assistance during the mobility assessment procedure were excluded.

Paper II

Participants in paper II were all part of the author's own data collection at Oslo University Hospital (the Memory Clinic at Ullevål and the Geriatric Day Hospital at Aker) and in collaboration with the local authority dementia team in Nes. All patients attending the Memory Clinic were screened for eligibility by the author who also contacted them (or their relatives according to degree of dementia), gave information and set up an appointment if they were willing to participate. Patients included at their initial visit to the Memory Clinic were also part of the Norwegian Dementia Register (NDR). Others were included while attending their yearly follow-up appointments at the Memory Clinic, having prior appointments before the NDR was initiated.

We also included patients from the NDR at the Geriatric Day Hospital at Aker, but we stopped recruitment at this site after a few months because few patients were eligible. In Nes, the author and the head nurse of the local dementia team collaboratively screened the patients for eligibility. The nurse invited the patients, and the author informed the patients, asked for consent, and conducted the formal inclusion. The sample consisted of 137 (80.6%) patients from the Memory Clinic, 23 (13.5%) patients from the dementia team in Nes, and 10 (5.9%) patients from the Geriatric Day Hospital.

The inclusion criteria for participants in paper II were (a) home-dwelling, (b) able to walk comfortably without walking device, (c) able to communicate in Norwegian, and (d) have a tentative diagnose of SCI, MCI or AD. Exclusion criteria were (a) severe stage of AD, (b) diagnosis of dementia other than AD, (c) severe hearing or vision impairment, (d) other neurological conditions such as stroke with motor symptoms, Parkinson's disease, or multiple sclerosis, or (e) musculoskeletal conditions causing pain that disturbed walking. The inclusion period was from January 2011 to August 2012.

Paper III

In paper III the sample is almost identical to the sample recruited at the Memory Clinic in Oslo in paper II, as we did not carry out the Floor Maze Test at Aker nor in Nes. Since we wanted to emphasis the early phases of AD we excluded patients with moderate degree of AD. To be able to explore differences between the SCI and the MCI group in performances on the Floor Maze Test, we included seven more patients with SCI using purposeful sampling strategy during November 2013. A flow chart of the inclusion and exclusion of participants in paper II and III is illustrated in Figure 2.

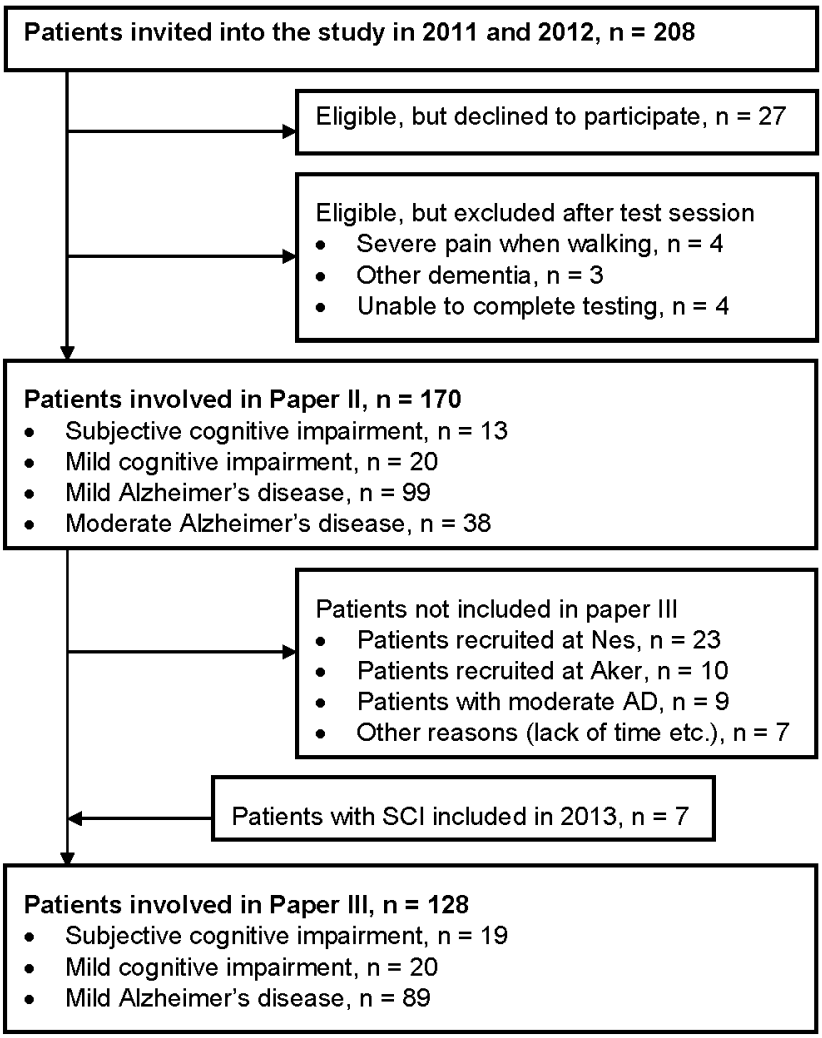

Figure 2. Flowchart of the participants involved in papers II and III.

6.2.1 Diagnostic procedure and categorization of the participants

The diagnostic process for patients attending the Memory Clinic in Oslo is illustrated in Figure 3. This procedure included interviews with both patient and an informant (usually a member of family), cognitive testing, neurological, physical and psychiatric examination, laboratory tests, and brain imaging.[203] Additional examination such as spinal fluid analysis and assessment by a neuropsychologist, were also conducted when appropriate.

Some of the patients recruited from the local authority dementia team in Nes had been diagnosed at the Memory Clinic at Akershus University Hospital. The remaining patients had a structured, but less comprehensive examination by the local dementia team in cooperation

with the family doctor. This team consisted of two specially-trained nurses with extensive experience in working with patients with dementia. The assessments conducted by the dementia team consisted of cognitive testing (MMSE and Clock Drawing Test), evaluation of the patient's ability to perform activities of daily living, and information about burden of care for the family. The family doctor supplemented this information with a physical examination, blood sample analyses, and referrals to computer tomography (CT) or magnetic resonance imaging (MRI) scans when needed.[204] In the most complex cases, such as young patients, patients with atypical presentations, or unclear etiology, the patients were referred to memory clinics.

The diagnostic procedures were reasonably identical in the memory clinics. Differences were related to the cognitive tests used and the criteria applied. In paper I, we used the diagnoses set by the staff at the Memory Clinic in Malmø, where the National Institute of Neurological and Cognitive Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for AD was applied.[139] Consensus criteria such as those outlined by Neary et al. for frontotemporal lobe dementia[205] and the McKeith criteria for dementia with Lewy bodies[206] were applied. For other diagnoses of dementia such as vascular dementia, criteria from the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders were applied.[207]

In papers II and III the participants were invited into the study based on the tentative diagnosis made after their first visit to the Memory Clinic. However, these diagnoses may have been altered later in the diagnostic process after a weekly consensus meeting (see Figure 3). To ensure consistent diagnostic evaluation and categorization of the degree of AD in our study, an experienced (i.e., more than 30 years of experience) geriatric psychiatrist reviewed the diagnoses made at the consensus meeting and categorized the patients as having either mild or moderate degree of AD based on all available information. Of the 50 patients with a tentative diagnosis of "questionable MCI" after their first visit, 13 were classified as having SCI, and 17 were diagnosed with mild degree AD by the psychiatrist. The ICD-10 diagnostic criteria for research were used for the diagnosis of AD (see Table 2) and for categorizing those with AD as having either mild or moderate degree of AD. To diagnose MCI, we used the Winblad criteria (see Table 1).[62] Persons who, despite their own experience of cognitive deterioration, performed within the normal range (less than 1.5 SD below the norm) on the cognitive test battery (therefore not filling the criteria for MCI) was assigned to the SCI

group.[203] To reduce the risk of bias, the psychiatrist was blinded to the results of the mobility assessments during this diagnosis/categorization process.

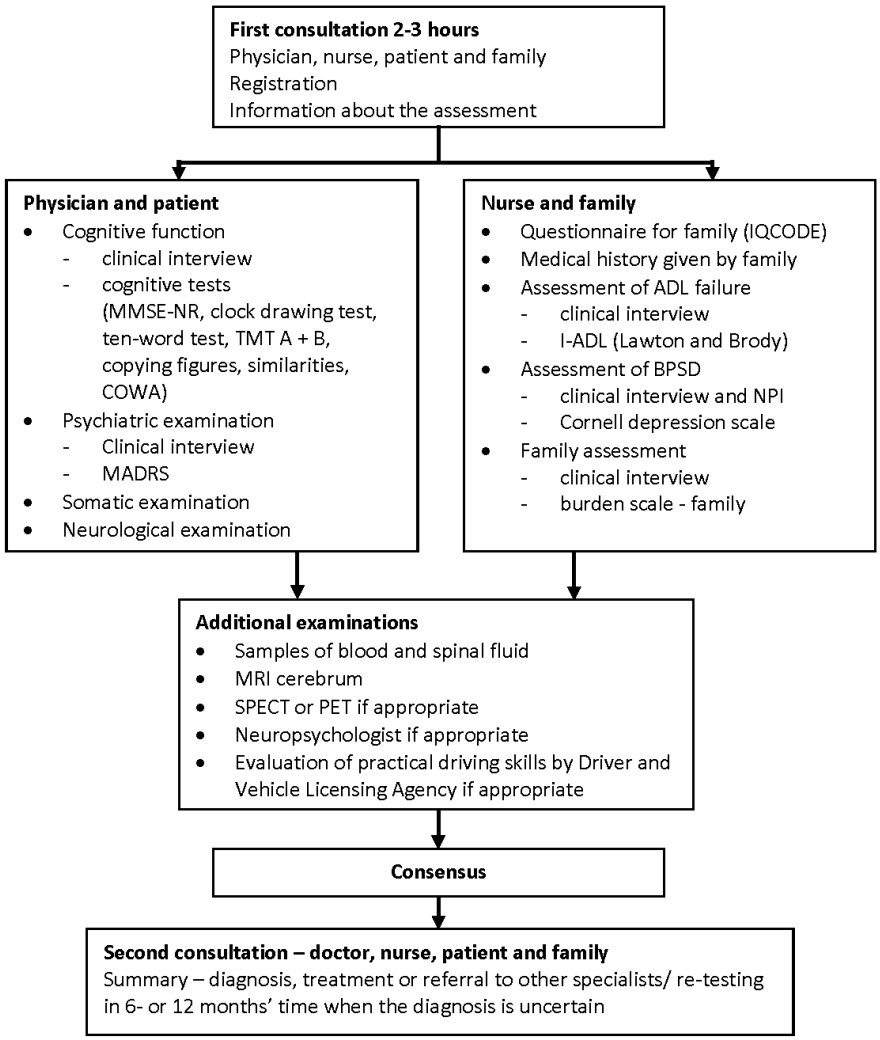

Figure 3. Procedure for assessment at the Memory Clinic.[203] Reprinted with permission from the authors. MMSE-NR: Mini Mental Status Examination – Norwegian revision, TMT: Trail Making Test, COWA: Controlled Oral Word Association, MADRS: Montgomery-Aasberg Depression Rating Scale, IQCODE: Informant Questionnaire for Cognitive Decline, ADL: Activities of Daily Living, I-ADL: Instrumental ADL, NPI: Neuropsychiatric Inventory, MRI: Magnetic Resonance Imaging, SPECT: Single-photon emission computed tomography, PET: Positron emission tomography. BPSD: Behavioral and Psychological Symptoms of Dementia.

6.3 Measurements

6.3.1 Mobility assessments

Paper I

In the Malmø-study all mobility assessments were carried out by the physical therapist who worked at the Memory Clinic, and he was therefore not blinded to diagnostic information. This therapist had extensive experience with examinations of patients with dementia. The assessments were videotaped using a standardized protocol for research purposes. The data used in this paper are derived from the videotapes, and timing and scoring was performed by the author (blinded to information about diagnoses at this point). In the videos there were walking tests that were omitted because of methodological issues.

Timed Up and Go test: Timed Up and Go was used to assess basic mobility.[208] The physical therapist instructed each patient to rise from the chair, walk at their normal pace to a line 3 m away, turn, walk back and sit down again. Timing started when the patient moved their back away from the back of the chair and ended when they sat down in the chair again. If the patient showed hesitation during the test, the physical therapist repeated the instructions (such as "and sit down again"). Both timing and the need for cueing during the test were assessed based on the videotapes. The Timed up and Go showed excellent test-retest values (ICC >0.9) in two studies of older people with dementia,[209;210] and a high test-retest value (ICC= 0.76) in a study of persons with AD.[211]

Timed stair walking. A training staircase with handrails and three steps on one side, a plateau, and a sloped ramp on the other side was used in this test. The physical therapist instructed each patient to walk over the staircase starting with the steps and ending with the slope. Timing started when the patient placed a foot on the first step and ended when both feet were back on the floor on the other side.

Timed rising from the floor. In this test the physical therapist instructed each patient to get up from lying supine on a soft mat on the floor. Timing started when the patient lifted their head from the floor, and ended when they were standing stable in an upright position.

Clinical Outcome Variables Scale. This is a functional mobility scale.[212] In the original version each of 13 items is scored by the physical therapist on an ordinal scale from 1 to 7. We used only 5 of the 13 items: rolling to the side, supine lying to sitting over the bed edge, sitting balance, standing up from lying on the floor, and performance of ambulation. This modified version would give a total score ranging from 5 to 35 points, higher scores indicating higher levels of independence.

I have not found any studies of psychometric properties for the last three tests in persons with dementia.

Paper II and III

In 167 of the 170 patients included in paper II, the author conducted the tests. The remaining three were tested by another physical therapist. All the patients included in paper III were tested by the author. The assessments were conducted in quiet and undisturbed surroundings at all three sites. The author was not blinded to the tentative diagnoses of the participants at the time of conducting the mobility assessments.

Balance Evaluation Systems Test. The Balance Evaluation Systems Test (BESTest) was used to assess balance performance in paper II. This test was developed, tested, and published by Fay Horak and colleagues in 2009[123] and thus, it is a relatively new assessment tool for evaluating balance. It was developed to identify underlying systems used for balance control, consistent with systems theory. Thirty-six items are grouped into six subscales thought to reflect the following systems: I. Biomechanical Constraints, II. Stability Limits/Verticality, III. Anticipatory Postural Adjustments, IV. Postural Responses, V. Sensory Orientation and VI. Stability in Gait. These subscales are described in more detail in Table 4. Each of the items is scored by on a 4-point ordinal scale, where 0 is the worst and 3 is the best performance. The subscale sums and the total score are converted to percentages (0-100%, where 100% is best).

Table 4. Descriptions of the subscales in the BESTest[123]

Subscale	Description
I. Biomechanical Constraints	Strength, flexibility and alignment of posture.
II. Stability Limits / Verticality	Internal understanding /perception on how far the center of mass can be moved beyond the base of support before losing balance and understanding of postural upright.
III. Anticipatory Postural Adjustments	Adjustments made to counteract the forces from voluntary movements.
IV. Postural Responses	Both in-place and stepping reactions to involuntary displacements of balance, such as slips, trips, pushes.
V. Sensory Orientation	Evaluations of body sway during various alterations of sensory information.
VI. Stability in Gait	Stability during walking under various challenging conditions. One of the items is illustrated in Figure 4.

Each patient carried out all tasks barefooted except for the walking tasks in the Stability in Gait subscale. It takes up to 30 minutes to complete the 36 tasks in the BESTest. Because we aimed to score each patient's first attempt at each task, we ensured they understood the tasks by giving both repeated instructions and demonstrations of how to perform them. Pilot testing prior to this study allowed us to anticipate that the three tasks related to compensatory stepping responses in subscale IV (Postural Responses) were the most difficult to comprehend for our participants (many did not lean sufficiently beyond their stability limits for the first attempt). For consistency, we allowed up to three attempts on these three tasks. Other deviations from the standard protocol involved the use of verbal cueing for patients that hesitated during the timed tasks, and for the Timed up and Go Dual Task (in subscale VI), we used the "random numbers" alternative as the cognitive task for all patients.

Figure 4. Nurse Mette Vinke demonstrating item 25 in the BESTest: Step over obstacle. Photo by Anbjørg Kolaas.

The BESTest has been translated into Norwegian by a team of physical therapists and researchers consistent with recommendations for back-to-back translations. The author was part of this team. We used a preliminary version that was almost identical to the final version. The original author, Fay Horak, has approved the final version of this translation, but it is not yet published because it is part of an ongoing project of a master's student at the University of Oslo. Reliability is not established for the BESTest in persons with cognitive impairment, however in samples of older people (without cognitive impairment), high levels of test-retest and inter-rater reliability are reported.[123;213]

Paper III

The Floor Maze Test. The Floor Maze Test is a test of spatial navigation during walking, developed by Sanders and colleagues[214] in the Einstein Group in New York. We derived the size and proportions of the maze from a picture of the Floor Maze Test in the original paper (see Figure 5) and created the maze on a dark blue wax cloth with white tape marking the lines of the maze.

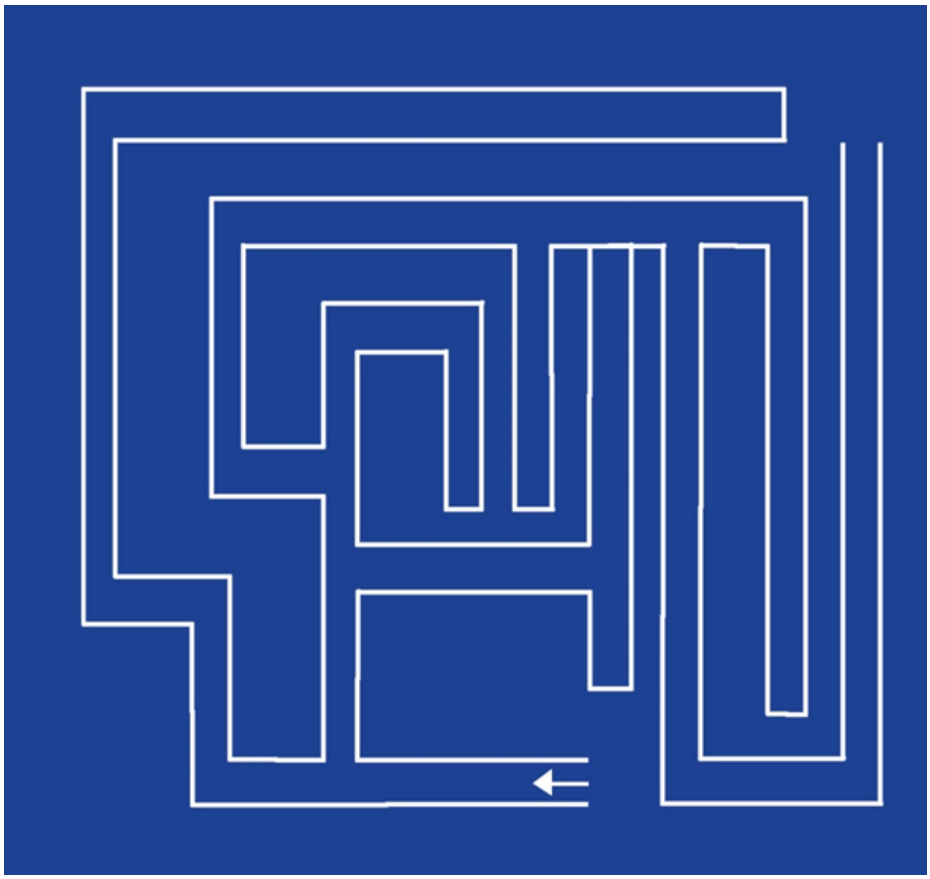

Figure 5. Illustration of the Floor Maze Test.

As each patient was positioned at the entry of the maze, they were instructed with following: "You are now at the entry of the maze. The way out is over here (demonstration of exit). You are now going to plan how you will walk through the maze while you are standing here. Let me know when you have found your way and are ready to start walking". Instructions were repeated when patients asked questions during the test, and they could start over from the maze entry if they asked to. Timing was not stopped until they reached the exit of the maze. We used one dichotomous variable to indicate whether their walk through the maze was error-free or with errors, and made three timed measures: 1. Planning Time (time from instruction completion to the initiation of walking), 2. Immediate Maze Time (time used to walk through the maze, including wrong turns), and 3. Delayed Maze Time (second walk through the maze, ten minutes after the first walk). An example of a walk through the maze with errors is illustrated in Figure 6.

Figure 6. Nurse Mette Vinke demonstrating an error, walking down one of the dead ends in the Floor Maze Test. Photo by Anbjørg Kolaas.

6.3.2 Cognitive assessments

We used cognitive tests that were incorporated in the test battery of the NDR because we aimed to recruit most of our participants from this register. The cognitive tests were therefore conducted by any of a number of physicians at the Memory Clinic, by the staff at the Geriatric Day Hospital, or by the dementia team. The tests we used are presented in Table 5.

Table 5. Overview of cognitive tests used in the three papers

Cognitive assessment	Cognitive domain	I	II	III
Mini Mental Status Examination	Global cognition	X	X	X
Clock Drawing Test	Visuoconstruction		X	X
The Word List Learning Test	Memory, learning		X	X
Trail Making Test A	Attention		X	X
Trail Making Test B	Executive function		X	X
Verbal Fluency Test	Language		X	

The Mini Mental Status Examination. The Mini Mental Status Examination (MMSE)[215] was used to describe the patients' level of cognitive function and also as a measure of global cognition in all three papers. It is one of the most-used cognitive screening instruments and is used worldwide. The test consists of 20 items involving orientation for time and place, registration and recall, attention, language, the ability to follow written and verbal commands and the ability to copy figures. Scores can range from 0 to 30, where a higher score indicates better performance. The MMSE is considered to have adequate test-retest (Pearson $r = 0.89$) and interrater (Pearson $r = 0.83$) reliability in patients with dementia.[215] The Norwegian version has also proved to be a reliable and valid measure of cognition in persons with dementia.[216]

The Trail Making Test. The Trail Making Test (TMT)[217] was used in paper II and III. It consists of parts A and B, both of which consist of 25 circles spread out on a sheet of paper. In part A, the circles enclose numbers that the patient is asked to connect in increasing order (1-25). In part B, the circles enclose both numbers (1-13) and letters (A-L), and the patient is asked to connect the circles in increasing order, but this time also alternating between numbers and letters (1-A-2-B-3, etc.) The tests were stopped after five minutes, however

patients that insisted on continuing were allowed one extra minute. The TMT-A was used to measure attention and processing speed, and the TMT-B was used to measure executive functioning and set-shifting (the ability to go back and forth between multiple tasks). Despite the extensive use of the TMT, I have not been able to find information about reliability for patients with dementia.

In paper II we used ordinal scoring to avoid a floor effect related to patients unable to complete the test. In so doing, we divided the timed scores into four categories based on normative age-adjusted time intervals for both tests[218]: 0, cannot complete; 1, slower than –2 SD of the norms; 2, between –1 and –2 SDs; and 3, better than –1 SD. In paper III we used the timed performance as a continuous measure. To our knowledge, reliability values are not established for persons with dementia.

The Clock Drawing Test. We used the Clock Drawing test in papers II and III to evaluate visuoconstructive abilities.[219] Several variations regarding both procedure and scoring can be found for this test. In our case, we gave each patient a piece of paper with a pre-drawn circle on it and asked them to draw the numbers so that the circle looks like the face of a clock and then to draw the hands of the clock to read 11:10. The 6-point scoring system described by Shulman (0-5, where 5 is best) was used in both papers II and III, however in paper III we dichotomized this score into 0-4 points vs 5 points. The Clock Drawing Test is considered a reliable test in patients with dementia,[219;220] but the exact ICC values vary depending on the version of the test.

The Word List Learning Test. Also known as "Ten word test" or "Word List learning" from the Consortium to Establish a Registry for Alzheimer's disease (CERAD),[221] this test was used to evaluate the learning aspect of memory in papers II and III. The word list consists of ten unrelated nouns, and each word is written on a card. These cards are presented to the patient at two-second intervals, and they read the words out loud to confirm that the word is registered. This is repeated twice more, each in a different order. After each trial, the patient is asked to recall the words. The outcome is the total numbers of correct words across the three trials with a maximum score of 30. Both inter-rater reliability and one-month test-retest reliability are substantial for patients with dementia for this test and for the Verbal Fluency test.[222]

The Verbal Fluency Test from the CERAD, Animal category. This test was used to assess semantic verbal fluency.[221] Each patient is given 60 seconds to name as many animals as possible, and the score is the number of different animals.

6.3.3 Demographic and clinical information

The samples in the three papers are described by: age, sex, education, comorbidity, employment status, use of medication, ApoE e4 (paper I), walking habits (paper II) and body mass index (paper II). In addition to the results of the various cognitive and physical tests, the main covariates in the regression analysis were: age, sex, education and comorbidity. Age was used as a continuous variable in paper III, and in paper II it was categorized into three groups (51-69 years, 70-79 years and 80-92 years). Comorbidity was used as a dichotomous variable (yes or no) in the regression analysis in all three papers. In paper I we based this dichotomization on information derived from the medical records. In papers II and III we used information from the medical records and the NDR, but also asked this direct question to the patient and informant: "Do you have any injury or condition, such as arthritis, hip prosthesis or previous fractures that may affect your balance?"

6.4 Statistical analyses

The statistical analyses in paper I were performed using PASW Statistics 18.0 (SPSS Inc., Chicago, IL., USA), while in papers II and III we used IBM SPSS Statistics version 20 (IBM Corp, Armonk, New York).

In all three papers we presented the results of continuous variables with normal distribution using means and standard deviations, continuous variables with skewed distributions using medians and interquartile ranges (or by 1st and 3rd quartile), and categorical variables using numbers and percentages. Parametric statistics were used when variables were normally distributed, and non-parametric statistics are used for variables with skewed distribution and categorical variables. We used a 5 % level of significance for all analyses, unless otherwise is explicitly stated. All statistical tests were 2-tailed. Descriptive analyses were carried out in all three papers; however we present only the main statistical methods used to analyze the research questions in the section below. We used Cohens[223] proposed guidelines for interpretation of effect sizes.

Multiple regression analyses

In all three papers we conducted multiple regression analyses to explore associations between mobility outcomes as dependent variables and demographic variables and cognitive tests as independent variables. Despite some differences in building the models, there were several elements consistent across these analyses that we would like to mention. The first concerns choice of independent variables, which in all three papers was based mainly on clinical reasoning and where relevant also on results from previous studies. We examined the bivariate correlations between each of the independent variables to check for cases of collinearity (defined in the present analyses as a correlation coefficient greater than 0.7); however, we did not exclude any variable based on such findings. Furthermore, we have carefully inspected the residual plots for outliers and deviations from normal distributions to assure that the model assumptions were not violated.

Several procedures to perform a multiple linear regression analysis exist. Based on the explorative character of our research questions, we decided to use the backward removal approach in the analyses reported in all three papers. Using this approach, we first entered all the independent variables into the model, and then excluded the variable with the smallest contribution (largest *P* value). We continued in this way, until we had only variables that were significantly associated with the dependent variable. The only exception for this procedure was made in paper II, where we wanted to explore the associations between the BESTest scales and the cognitive tests while adjusting for demographic factors. We therefore decided to enter our independent variables in two blocks; the first block contained the demographic factors and the second block contained the cognitive tests. The first block was kept in the model throughout the entire analysis, while we used the backward removal approach on the variables in the second block. Final models are presented with adjusted explained variance, which crudely assess how well the model fits the data. All regression coefficients in these analyses are represented by the unstandardized B, which represents the slope of the regression line (the amount of change in the dependent variable Y resulting from a change of 1 unit of the independent variable X, while statistically controlling for the other independent variables).[224]

Table 6. An overview of the statistical analysis used in the three papers

Statistics	Paper I	Paper II	Paper III
Statistical analysis of differences			
Exploring within-group differences:			
Paired *t* test	X		
McNemar test	X		
Exploring between-group differences:			
Chi-square test	X		X
Mann-Whitney test			X
Univariate analysis of variance	X		
2-way between-groups analysis of variance		X	
Kruskal-Wallis test		X	
Statistical analysis of relationships			
Exploring relationships:			
Correlations (Pearson *r* and Spearman's r_s)	X	X	X
Multiple regression analysis	X	X	X

Table 6 shows the analyses we used to analyze the main research questions in the three papers. In addition, some comments related to these analyses are provided below.

Comments to the analyses in paper I: In the univariate analysis of variance, where we compared performances on the mobility outcomes between the groups of early-onset AD and early-onset other dementia while controlling for sex, we used a 1% level of significance because the assumption of homogeneity of variance was violated.

Comments to the analyses in paper II: To compare performances on the BESTest scales between the three groups, we conducted two-way analysis of variance between groups where we controlled for age. When the main effects were significant, we also performed Bonferroni

post hoc comparisons to identify the pairwise differences, and at the same time adjusting for multiple comparisons.

Comments to the analyses in paper III: In the multiple regressions analyses, we log-transformed the skewed dependent variables and back-transformed the regression coefficients and confidence intervals using the formula [exp(estimate) - 1] x 100 %, thus reporting percentages.

Sample sizes

The data used in the study of patients with early-onset dementia presented in paper I were collected before we became involved in the study. Therefore, we did not make sample size calculations for this study.

When we planned the study presented in papers II and III, we made a sample estimate based on gait speed which we initially thought would be our main outcome. We used the recommendations for meaningful change (0.1 m/s) and estimated SD (0.15-0.16 m/s) from a study including both community-dwelling older people and sub-acute stroke patients (n = 200).[225] The sample size was calculated with a power of 80% and a significance level of 5%, which suggests that we would need 42 persons in each of the three groups. Because of concern of enough power for other outcomes we decided to increase the sample size by 20%, to 50 persons in each group. As a general rule, for the multiple regression analyses, we aimed to have at least 10 persons for each independent variable.[226]

We did not achieve the desired sample size in each of the three groups. Implications of this will be addressed in the discussion section. In paper II we made a post-hoc power analysis for the multiple regression analyses to ensure that we had a sufficient number of patients in relation to the independent variables we wanted to include in the analysis. Based on 11 independent variables, a power level of 0.80, a significance level of 5% and the lowest observed R^2 (0.20), we would need 78 patients in the regression analysis. An R^2 of 0.20 equals moderate to large effect size ($R^2/(1- R^2)$).[227]

For paper III we estimated that to be able to detect a large effect size (>0.35) with 80% power, a significance level of 0.05 and nine independent variables, we would need a sample of at least 54 patients in the regression analysis.

6.5 Ethical considerations

All patients gave their informed written consent to participate in both studies. The study in paper I was approved by the Internal Board of Ethics at Skåne University Hospital. The study in papers II and III was approved by the Regional Committee for Medical and Health Research Ethics in the South East of Norway and also by the Oslo University Hospital's Privacy and Data Protection Officer.

To include patients with cognitive impairment in research is a delicate issue. To be able to consent to participate, it is required that the information about the project is understandable for each individual. The standardized formal information and consent forms provide a level of information that may compromise the availability of any reader regardless of cognitive impairment. Because we included patients with very different degrees of cognitive impairment, we tailored the information toward each patient's level of impairment. To achieve this, we tried to give the patients, and their family member when appropriate, sufficient oral information as well. We focused on three key issues: the purpose of the study and what kind of assessment they were going to participate in, that participation was voluntary and a decline would have no consequences for the patient's continuing health care, and that we would assure that the routines for keeping their information unavailable to persons outside the project was followed. We invited only those patients whom we felt had comprehended these issues.

Most patients were invited by telephone. Those with the lowest MMSE scores were discussed with the nurse who knew the patient to determine if the patient were able to respond to such a call. We contacted a family member when the nurse or the medical record indicated this necessity. When in doubt, we sought to ask the patient in person during their ordinary visits to the Memory Clinic.

To ensure the patients were not injured during the assessment sessions the physical therapists were prepared to provide support if a patient was about to fall. There were no falls or injuries in relation to these assessments.

7 Main results

In this section we present the characteristics of the participants in the three papers (Table 7), and the main findings from each of the studies. More comprehensive presentations of the results are given in papers I, II, and III.

Table 7. Characteristics of the participants included in papers I, II, and III

	Paper I (n = 72)	Paper II (n = 170)	Paper III (n = 128)
Age, mean (SD)	60.9 (4.1)	72.4 (9.1)	69.8 (8.1)
Men, n (%)	34 (47.2%)	85 (50%)	69 (53.9%)
Years of education, mean (SD)	10.7 (2.4)	12.7 (3.6)	13.9 (3.4)
Work-related status, n (%)			
Working	15 (20.8%)	22 (12.9%)	21 (16.4%)
Sick leave/disability benefit	28 (38.9%)	24 (14.1%)	20 (15.6%)
Retired	14 (19.4%)	117 (68.8%)	83 (64.8%)
Other	7 (9.7%)	7 (4.2%)	4 (3.1%)
Missing	8 (11.1%)	0	0
Use of cholinesterase inhibitors, n (%)	42 (58.3%)	51 (31.1%)	28 (22.2%)
Mini Mental Status Examination, median (IQR)	21.5 (6)	25.0 (6)	26.0 (4)

The participants in paper I were significantly younger, had less education, and lower MMSE scores ($p<0.001$ for each) than the participants in paper II. If we exclude the participants with SCI and MCI from the sample in paper II, the differences still remain significant at $p<0.001$.

7.1 Paper I

Differences in mobility between persons with AD and other dementias

The first aim of this study was to compare mobility performances among patients with early onset AD and patients with other types of early onset dementia. The patients with early onset AD performed significantly better than those with other dementias on all measures of mobility: Timed up and Go ($P = 0.003$), timed stair walking, timed rise from floor and modified Clinical Outcome Variables Scale ($P < 0.001$ for each). There was no difference between the groups regarding the need for cueing during the performance of Timed up and Go test ($P = 0.82$).

Associations between Timed Up and Go and independent variables

A second aim of the study was to explore which variables were related to Timed up and Go in a multiple regression analysis. The independent variables in this analysis were diagnostic group, MMSE score, sex, education and comorbidity. After a backward removal procedure, we found that the diagnostic group variable (AD vs other dementia) was the only variable independently associated with time on Timed Up and Go (B = -3.7, 95% CI –5.7 to –1.8, $P < 0.01$). This indicated that having a diagnosis other than AD increased the time on the Timed Up and Go test by 3.7 s. The adjusted explained variance of the final model was 0.23.

Changes in mobility at the one-year follow-up of patients with AD

The last and primary aim of the study was to examine the changes in mobility over a one-year period in the patients with AD, and we re-examined 25 patients with AD one year after baseline assessments. The performances on the Timed up and Go ($P = 0.028$) and the timed stair walking ($P = 0.02$) were significantly worse at the one-year follow-up. The differences on Timed Up and Go are illustrated in Figure 7. The need for cueing during this test was unchanged from baseline to follow-up ($P = 1.0$). The changes in timed rise from floor ($P = 0.56$) and the modified Clinical Outcome Variables Scale ($P = 0.48$) were not statistically significant.

In conclusion we found that the patients with early onset AD had better performances than those with other early onset dementia on all mobility tests. However, mobility performances got slightly worse between baseline and the one-year follow-up in the group of early onset AD patients.

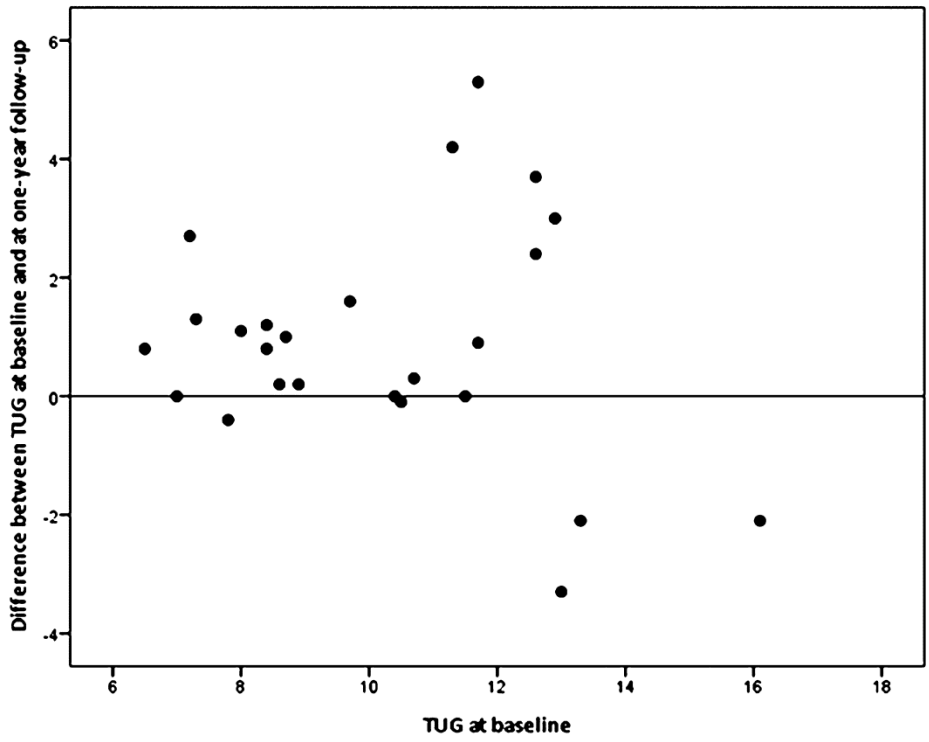

Figure 7. Illustration of the differences in performance on the Timed Up and Go between baseline and the one-year follow-up plotted against the time at baseline for the 25 patients with early onset AD. No difference between baseline and follow-up is indicated by the horizontal line. Copyright © 2012 Karger Publishers, Basel, Switzerland.

7.2 Paper II

Differences in the various aspects of balance between the SCI/MCI, mild AD and moderate AD groups

The first aim of this study was to compare the performances on the BESTest between the three groups with different levels of cognitive impairment: SCI/MCI, mild AD, and moderate AD. Mean scores and confidence intervals for the subscales are illustrated in Figure 8. The performances of the three groups were significantly different from each other, adjusted for age, on all the subscales and also on the total score of the BESTest (P = 0.005 to <0.001). The

mild AD group performed worse than the SCI/MCI group, but better than the group with moderate AD. We found large effect sizes of the group differences on the total score (η_p^2 = 0.24) and subscales Stability in Gait (η_p^2 = 0.27) and Anticipatory Postural Adjustments (η_p^2 = 0.18). The between-group differences on the other subscales had medium effect sizes (η_p^2 = 0.07-0.10).

Associations between the various aspects of balance and cognitive domains

The second aim of this study was to examine which cognitive tests were related to the different aspects of balance, and we performed multiple regression analyses with each of the BESTest subscales as dependent variables. The subset with a complete dataset for the regression analyses consisted of 111 (65.3%) patients. These patients were younger and had better MMSE scores than those excluded from the regression analysis because of missing data.

Independent variables in the regression analysis were demographic variables age, sex, education, comorbidity and walking habits, and cognitive tests MMSE, Word List Learning test, Clock Drawing Test, Verbal Fluency Test, and TMT A and B. The TMT B was significantly associated with each of the BESTest scales (P = 0.017 – <0.001). The only other cognitive test that was significantly associated with any of the BESTest scales was the Verbal Fluency Test which remained in the final model of the Stability in Gait subscale (P = 0.01).

Among the demographic factors age contributed to all the final models, sex was in the final model of Anticipatory Postural Adjustments and Total Score, and comorbidity contributed to the final models of Biomechanical Constraints, Anticipatory Postural Adjustments, Sensory Orientation, Stability in Gait, and Total Score. Education and walking habits were not independently associated with any of the BESTest scales.

The explained variances of the final models ranged from 0.20 for the Sensory Orientation subscale to 0.64 for the Total Score. In effect size terms, this corresponds to medium effect size (f^2 = 0.32) for the Sensory Orientation subscale and large effect sizes (f^2 = 0.54-1.22) for the Total Score and the other subscales.

In conclusion, we found differences in all measured aspects of balance between each of the groups, with the lowest scores in the group with moderate AD. All aspects of balance were associated with executive function.

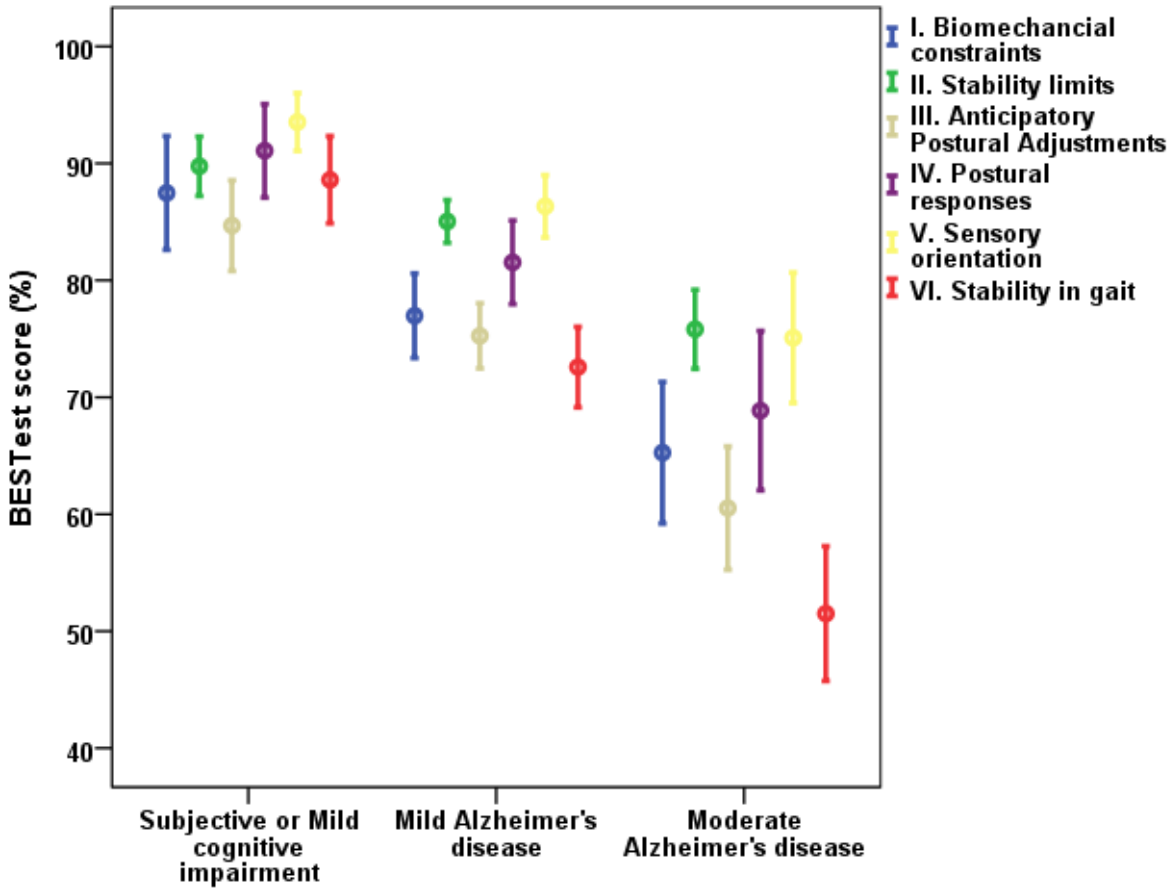

Figure 8. Mean score and 95 % confidence intervals for the six subscales of the Balance Evaluations Systems Test (BESTest) for the groups of subjective or mild cognitive impairment, mild Alzheimer's disease and moderate Alzheimer's disease. Higher score indicates better performance. Reprinted from *Phys Ther*. 2014;94(8):1123-1134, with permission of the American Physical Therapy Association. Copyright© 2014 American Physical Therapy Association.

Additional analyses: Associations between the various aspects of balance and cognitive domains

After publication we discovered that we had a flaw in the regression analyses in paper II. The flaw concerns the independent variables TMT A and B, and the Clock Drawing Test. The data we used from the NDR are ordinal versions of these tests; however, we forgot to create dummy variables before entering them in the regression models. Therefore, to examine if this

flaw had influenced the results, we re-analyzed the regression analyses using TMT A and B as continuous variables, and the Clock Drawing Test as a dichotomous variable (same cut off as in paper III). The final models from these analyses are presented in Table 8.

Table 8. Associations between the Balance Evaluation Systems Test and cognitive assessments, adjusted for demographic factors (*n*= 79)

	I. Biomechanical Constraints				**II. Stability Limits**			
	B[a]	**95% CI**	***P***	**Adj. $R^{2\,b}$**	**B[a]**	**95% CI**	***P***	**Adj. $R^{2\,b}$**
Trail Making Test A					-0.04	-0.07, -0.02	0.003	0.31
Trail Making Test B	-0.05	-0.09, -0.01	0.016	0.37				
	III. Anticipatory Postural Adjustments				**IV. Postural Responses**			
	B[a]	**95% CI**	***P***	**Adj. $R^{2\,b}$**	**B[a]**	**95% CI**	***P***	**Adj. $R^{2\,b}$**
Trail Making Test B	-0.04	-0.07, -0.004	0.028	0.38	-0.05	-0.09, -0.02	0.005	0.33
	V. Sensory Orientation				**VI. Stability in Gait**			
	B[a]	**95% CI**	***P***	**Adj. $R^{2\,b}$**	**B[a]**	**95% CI**	***P***	**Adj. $R^{2\,b}$**
Verbal Fluency Test					0.71	0.099, 1.32	0.023	
Trail Making Test B	-0.05	-0.09, -0.02	0.004	0.23	-0.05	-0.09, -0.01	0.022	0.45
	Total Score							
	B[a]	**95% CI**	***P***	**Adj. $R^{2\,b}$**				
Trail Making Test B	-0.04		<0.001	0.55				

[a]Unstandardized Coefficient, [b]The R^2 value for the entire model including demographic factors

7.3 Paper III

Differences in spatial navigation between the SCI, MCI and the mild AD group

The first aim in paper III was to explore the differences in spatial navigation between patients with SCI, MCI and mild AD. We found that patients with SCI were faster than those with MCI on all the three components of the Floor Maze Test: Planning Time (P = 0.013), Immediate Maze Time (P = 0.021) and Delayed Maze Time (P = 0.031). There were no statistical significant differences in Planning Time (P = 0.57) or Immediate Maze Time (P = 0.12) between patients with MCI and those with mild AD. However, the patients with MCI

were faster than the patients with mild AD on the Delayed Maze Time (P = 0.02), and they had also a higher proportion of error-free performance on the Immediate Maze Time (P = 0.007) than the mild AD patients.

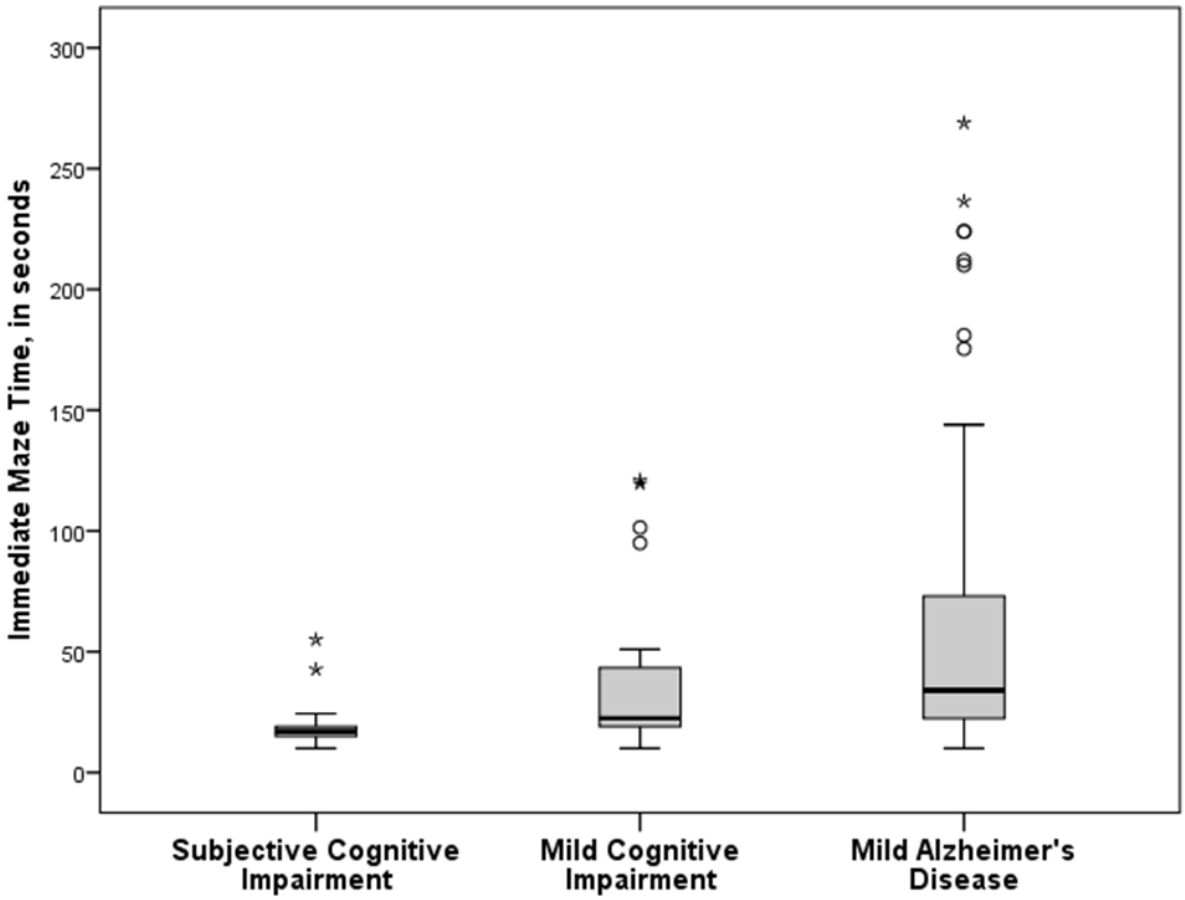

Figure 9. Box plots showing the median, interquartile ranges, and outliers for the Immediate Maze Time component of the Floor Maze Test.

Associations between spatial navigation, demographic factors and cognitive domains

The second aim of this paper was to explore which of the demographic factors and cognitive tests were associated with performance on the three components of the Floor Maze Test. The patients included in the regression analysis had higher levels of education (P = 0.03) and better MMSE scores (P < 0.001) than the patients who were excluded from this analysis because they had missing data or were unable to complete the Floor Maze Test.

In the regression analysis we log-transformed the Floor Maze Test components because of their skewed distributions (see Figure 9). We included these demographic variables: age, sex,

education and gait speed. The cognitive tests included as independent variables were MMSE, Word List Learning Test, Clock Drawing Test and TMT A and B. Planning Time was associated only with the MMSE score (B = -6.4, 95% CI 12.3, -0.1, $P = 0.049$), and the adjusted explained variance was 0.04. Immediate Maze Time was significantly associated with the TMT B (B = 0.4, 95% CI 0.3, 0.6, $P < 0.001$), and the adjusted explained variance was 0.23. The final model of the Delayed Maze Time consisted of the TMT B (B = 0.4, 95% CI 0.2, 0.6, $P < 0.001$) and the Word List Learning test (B = -3.6, 95% CI -6.5, -0.6, $P = 0.018$), and the adjusted explained variance was 0.31. None of the sociodemographic factors were independently associated with any of the three Floor Maze Test components.

The *B*-coefficient of 0.4 % indicates that if the performance on the TMT B increased by 10 seconds, the corresponding change in the Immediate Maze Time would be 4%. The estimated effect size [$f^2 = R^2 / (1 - R^2)$] of the multiple regression model was small for the Planning Time ($f^2 = 0.12$) while for the Immediate Maze Time and Delayed Maze Time they were large[227] ($f^2 = 0.41$ and $f^2 = 0.56$, respectively).

In conclusion, we found differences in the performances between the SCI and MCI groups and between the MCI and the mild AD groups, with worse performances in the group with more severe cognitive impairment. Executive function was associated with the Floor Maze Test, but explained variances were low. None of the demographic factors were associated with the Floor Maze Test.

8 Discussion

In this chapter, methodological issues regarding the internal and external validity of the study will be discussed first and will be followed by a general discussion of the main findings in the light of recent literature across each of the separate papers. Detailed discussion on findings and methodological issues regarding each of the separate research questions from each paper will not be addressed in this part, as this is covered in the individual papers.

8.1 Discussion of methodological issues

8.1.1 Internal validity

Design

In all three papers we have applied a cross-sectional design, which in general is suitable to describe a sample at one point in time and to examine associations between variables. This may serve as a foundation to plan for longitudinal studies or intervention studies.[224;226]

We compared mobility between groups of increasing severity of cognitive impairment, which may be regarded as an attempt to simulate a trajectory of mobility decline in the continuum of AD. To achieve this we should ideally have applied a longitudinal design where we followed the same sample of patients for years. There are however also those who argue that cross-sectional studies may be used to shed light about processes (i.e., mobility decline) evolving over time by measuring this process at different points in its evolution with different stages (i.e., of cognitive impairment).[224] To be able to infer our findings in this perspective there should be no other possible explanations besides the difference in cognitive group responsible for the differences we have observed in mobility. The heterogeneous character of patients categorized as having SCI and MCI, where a large proportion probably never will develop AD, makes it very difficult to infer findings related to these groups into a "change over time" perspective. This is also the case in our study, and we cannot claim that our findings of between-group differences show a decline in mobility.

However, given the enormous effort needed to conduct a longitudinal study, in terms of both numbers of participants and length of follow-up, to investigate the decline in mobility

covering the same range of cognitive impairment, knowledge derived from cross-sectional studies are still valuable. In line with the stated aims of this thesis—to explore between group differences in mobility, and to explore the relationship between cognitive domains and mobility—the cross-sectional design is suitable. However, in order to draw valid conclusions from our cross-sectional studies, special attention needs to be paid to the issues of group assignments and assessor blinding.

The group assignments are based on clinical judgment and it is therefore important to limit the sources of variation in this part of the study. To ensure consistency in the group assignments, this work was performed by an experienced geriatric psychiatrist who was blinded to the results from the mobility assessments. Several patients with a tentative diagnosis of MCI after the initial visit to the Memory Clinic were instead assigned to the mild AD or the SCI groups in our study. None of the patients diagnosed with AD were assigned to another group during this process, which is probably because the clinicians refrain from setting the diagnosis of AD until they are as certain as can be; AD is after all a progressive disease without a cure at the moment. We believe that the thorough work with the group assignments provides trust in valid and consistent categorization of our participants.

The blinding of the psychiatrist in the diagnostic work is particularly important for internal validity given that the physical therapists were not blinded for the patients' tentative diagnoses at inclusion and during the assessments. Information about the tentative diagnoses may have inferred bias by making the physical therapists prone to score the patients' performance accordingly to the degree of cognitive impairment. This risk of bias was reduced by the many patients with tentative MCI being assigned to either the SCI or the mild AD group. For the seven extra patients with SCI we recruited during November 2013 the risk of bias is clearly present, since these patients were recruited with the purpose to have the equal number of participants in the SCI group as in the MCI group. This sampling strategy may have reduced the internal validity; however, the observed differences are also statistically significant without these seven extra patients with SCI.

In paper I, the mobility assessments were part of the daily clinical routine at the Memory Clinic in Malmø, and the physical therapist who instructed the patients was not blinded to the diagnostic information available at the time of these assessments. However, this lack of blinding will have little influence given that the author used the video recordings from these

assessments to time and evaluate the mobility outcomes for the purpose of this study. Also, the author was blinded to diagnostic information during the work with these video recordings.

So, lack of blinding of the physical therapists who conducted the assessments for tentative diagnoses pose a threat to the internal validity; however, the potential influence is not critical given the blinding of the psychiatrist who conducted the group assignments in papers II and III and blinding of the author who rated and timed the performances in paper I.

Outcome measures

In paper I we used several timed performance-based tasks, such as walking over a staircase, rising from the floor, and the Timed Up and Go test. These tasks are characterized by moving from one place to another which is in line with the definition of mobility, and I believe that both the construct validity and the face validity should be satisfactory for these tasks.

The main outcome measures of papers II and III, the BESTest and the Floor Maze Test, are both rather novel tests, and the different aspects of validity of the tests are not yet properly established. Our aim in paper II was to explore balance in line with the understanding of the systems theory, and the BESTest was therefore the obvious choice since it is developed based on the systems theory.[123] There are currently no factor analyses that have confirmed the six subscales of the BESTest as separate constructs/entities, so the content validity is not confirmed with regard to its theoretical foundation. However, it is important to remember that in systems theory the subsystems of balance are regarded as inter-related,[1;123] and I believe that it is likely to expect a substantial amount of overlapping information from the subscales. The moderate to large (r_s between 0.5 -0.7) correlations between the subscales indicate that we have examined separate but related balance abilities. The comprehensiveness of the BESTest was confirmed in a study where the content of several balance scales were compared, and the BESTest showed the greatest breadth of content based on the International Classification of Function.[228] So, despite that the validity of the BESTest has not been properly established in populations with cognitive impairment and dementia, it still appears to be a suitable tool for our purpose to assess a range of different aspects of balance.

The Floor Maze Test has only been used in one published study so far in which a large sample of cognitive healthy persons in the US was included. The test was developed as a clinical test of exocentric navigation for this study.[214] The low correlation (r = 0.299) between the Floor

Maze Test and a paper-and-pencil maze in this original paper suggests that solving a task on paper is conceptually different from solving the approximately same task while walking. However, there has not been any attempt to validate the Floor Maze Test against real-life spatial navigation so far, and there is also a lack of a gold standard measure in this field. Getting lost is of course the ultimate failure of spatial navigation; however, it is desirable to be able to detect and monitor more subtle changes in spatial navigation in order to be able to identify persons at risk before the impairments become so pronounced that the person gets lost. We were able to detect differences between the SCI and the MCI group in our study, so the Floor Maze Test appears to be a sensitive outcome measure. However, validation against real-life navigational performance remains to be established, and our results should be interpreted with this in mind.

We aimed to use tests that were suitable in the clinical settings where we conducted our studies, which imply that the tests should not require expensive or advanced equipment, and they should be accepted by the patients. Besides the four patients we excluded (Figure 2), the remaining patients completed the assessments without any overt lack of motivation or effort to complete the tasks they were given. This may be attributed to acceptable face validity of the tests. The performance-based tests in all three papers turned out to be both feasible and well tolerated in our sample of patients with cognitive impairment.

The validity of our outcome measures is also reliant on satisfactory reliability properties. The reliability of performance-based outcomes depends on the patients' ability and motivation to understand and carry out the tasks they are given. It is not self-evident that patients with dementia are able to meet such requirements, and many studies have excluded persons with cognitive impairment from reliability studies of performance-based tests. The Timed Up and Go test is the only one of the mobility outcome measures, that has been examined for reliability properties in persons with dementia,[229;230] which may be considered as a limitation of our study. However, in the last decade several studies have investigated the reliability of several performance-based measures in patients with dementia, and overall they seem to be as reliable as in other populations.[209;210;231] Also, the patients we examined had a milder degree of cognitive impairment than patients involved in previous reliability studies. Thus, I think it is fair to assume that the reliability of the outcomes used in our studies do not deviate too much from the findings in studies of samples without cognitive impairment.

Statistical analyses

Last but not least, I will comment on the implications of some issues related to the statistical analyses in our studies, including accuracy of results, missing data, and sample size issues.

Accuracy of results

In paper II we had a flaw across all the regression analyses caused by incorrect use of ordinal variables as continuous variables in the analyses. However, in the re-analyses of the regression models (Figure 8) the results remain largely unchanged. An exception was the final model of subscale II Stability Limits, where TMT A was the only variable in the final model instead of TMT B in the published results. The explained variances tended to be around 5% lower compared to the published values in paper II. Overall, the conclusion is still that executive function, measured by the TMT-B, is the most important cognitive domain for balance. The downside is of course that the sample involved in the regression analysis is then smaller (n= 79) as the patients that were unable to complete the TMT-B are omitted from the analyses due to missing data.

Missing data

We have missing data related to the cognitive tests that we use as independent variables in the multiple regression analysis in papers II and III. There are several possible approaches to handling issues with missing data, and they are chosen depending on the extent and patterning of the missing values. In cases where data are missing at random and not to a large extent, there is the possibility to substitute missing values with values that represent the "best guess".[224] However, in our study, we had most missing data in the patients with the most severe cognitive impairment; thus, they were not random. Therefore, we did not consider to substitute the missing data in any way, and instead we chose to exclude the patients with missing data from the regression analyses. Missing data on the TMT-B is not the case only for our study. McGough et al.[232] reported that 10.8% of participants with MCI were unable to complete the TMT-B within the 300 seconds time frame. Ashendorf and colleagues[233] reported that 15.4% of a sample of healthy elderly, MCI, and AD were unable to complete the TMT-B, mostly related to degree of cognitive impairment.

The amount of missing data could perhaps have been less if we conducted additional cognitive tests in relation to inclusion in our study. However, cognitive testing is demanding

and tiring for persons with cognitive impairment. Prior to the study we had therefore decided not to perform additional cognitive testing of the patients in order not to interfere with the clinical practice at the Memory Clinic. We figured that too many cognitive test sessions may lead to reduced willingness to attend the routine control appointments that they were more dependent on and may also lead to reduced willingness to participate in our study. The consequence is that we have to limit the generalization of our results from the multiple regression analysis to populations with a milder degree of cognitive impairment.

Sample size issues

We were not able to include 50 patients in each group as we originally planned for in the study in Oslo. Small samples increase the risk of making type II errors. A type II error refers to the failure to reject a false null hypothesis.[226] However, both in paper II and paper III we were able to reject our null hypothesis that there were no differences between the groups, which relate to the rather large effect sizes of the between-group differences. Also in paper I we have small samples; however, we found consistent differences between the groups of AD and other dementia, and we also detected decline in mobility performances in the one year follow-up of the AD group. I therefore think that the small samples in our studies did not lead to type II errors.

A consequence of the missing data in one or several of the cognitive tests in our study in Oslo was that we had relatively fewer patients in the multiple regression analysis in papers II and III than in the between-group analyses. There are several approaches to determine the necessary sample size in relation to the number of independent variables of interest. Altman[226]suggests two general rules for determining how many independent variables a model may include such as $n/10$ where n is the sample size, or to use the square root of the sample size. We used these rules beforehand to briefly check if we had the sufficient number of patients related to the variables we wanted to include in our model. Then after performing the analyses we made post hoc analyses based on the effect sizes of the regression models. Since our models had in general rather large effect sizes, we were able to conclude that we had a sufficient number of participants in relation to the number of independent variables. However, we would not have been able to detect small effects in these models. Besides the risk of type II errors, small samples also imply that we have to be careful when we interpret the results in relation to a more general population which will be addressed in the discussion of the external validity.

8.1.2 External validity

The external validity of a study relates to whom, in what setting, and at what times the results can be generalized.[234] Threats to the external validity are peculiarities of the research setting, biased selection process of participants, small sample sizes, and unsatisfactory internal validity.

The research setting in all three papers are predominantly memory clinics, although we in paper II included some patients through a local authority dementia team. Given that the memory clinics do not have the capacity to carry out the diagnostic work for all persons with suspected dementia in the community, their prioritizations influence to whom we may generalize our results. The memory clinics prioritize patients that are home-dwelling, young, and with diffuse symptoms. For the study in paper I concerning patients with early onset dementia, this is of course a strength. The Memory Clinic in Malmø has even the regional responsibility, with exception for persons with suspected frontotemporal lobe dementia, for diagnostics assessment of persons younger than 65 years. In the Oslo study we aimed to compensate for the rather young, urban and less cognitively impaired sample at the Memory Clinic by also including patients from the Geriatric Day Hospital at Aker and from the local authority dementia team in a rural community in Nes. At Aker there were fewer eligible patients than expected, so we ended the effort to include patients from this site. In Nes, however, we were able to include about 20 patients to complement our memory clinic sample. Together, our sample in papers II and III had a wide age distribution and also represented patients from both urban and rural communities.

The selection process itself is largely determined by the choice of inclusion and exclusion criteria. In both the Oslo and the Malmø study we included only patients that were home-dwelling and able to walk without noticeable pain or the use of a walking device, which is very much in line with the characteristics of the memory clinic patients in general. In the longitudinal part of the study in paper I, only 25 of the 42 (60%) patients with AD attended the follow-up assessment after one year. Although we have no complete information about the reasons for not attending, it is likely that it was the well-functioning patients that were retested, since the main reason for not attending the follow-up was admission to a nursing home. Based on this information we suggest that our findings from paper I can be generalized to home-dwelling, ambulatory persons with early onset dementia (other than persons with frontotemporal lobe dementia).

In the study described in papers II and III we consecutively screened all patients that attended the Memory Clinic for suitability according to our inclusion and exclusion criteria. Only 27 out of the 208 patients (13%) who were invited to participate declined our invitation (Figure 2). High participation rate is one of the advantages of a cross-sectional design since it is less demanding to participate in a study that only involves one test session than to oblige oneself to longitudinal studies or intervention studies. The high level of participation contributes to confidence in the generalizability of our sample. However, in general our results from papers II and III are most likely to be generalizable to independently ambulatory, home-dwelling persons with a mild degree of cognitive impairment and AD.

In relation to generalizability, special attention has to be paid to the SCI group. As mentioned in the introduction, the SCI condition represents a heterogeneous group of patients that are concerned about their memory related to systemic, neurologic, or psychiatric diseases, to psychological strains such as sorrow or work-related stress, or in several cases they may also be concerned for their own cognitive health because they have close relatives with dementia. But according to previous research, the SCI condition represents a high-risk state for future development, and some of them will be in a preclinical stage of dementia, in most cases AD.[45;47] The characteristics of groups with SCI are likely to vary between studies, given the lack of well-defined criteria. In our study this group is quite small, which also reduced the generalizability. Then, on the other hand it is important to gain more knowledge about this group, as patients classified as SCI are frequently attending the memory clinics.[203] After all, these patients are so concerned that their family doctor has referred them to a memory clinic. In our group, the level of education was high (mean 14.8 years of education) which may also explain why they were still able to perform within the normal range of scores on the standard cognitive test batteries.[47]

To sum up the discussion of the methodological issues, the internal validity seems acceptable in the three papers, and the findings may be generalized to home-dwelling, ambulatory persons attending outpatient specialist health services for dementia assessment.

8.2 Discussion of results

In this thesis we examined how mobility performance in terms of balance and spatial navigation differed between groups with different levels of cognitive impairment, and we also

explored the relationship between mobility and different domains of cognitive function. The overarching goal of the thesis was to provide useful information to design interventions aimed at enabling persons with cognitive impairment and dementia to maintain their ability of independent mobility for as long as possible. The main findings across the three papers will be discussed, and I will address how these findings may help to direct future interventions.

8.2.1 Relationship between mobility and severity of cognitive impairment

In our studies we found differences in mobility regarding both balance and spatial navigation during walking between groups of patients with different degrees of cognitive impairment. In all the comparisons we made, these differences were characterized by worse performance in the group exhibiting the most pronounced cognitive impairment. These cross-sectional findings are supported by the decline in mobility we observed in the one-year follow-up of patients with early onset AD in paper I.

When we planned this study, we did expect to find results that indicated a decline in mobility with increasing severity of cognitive impairment, based on findings from previous studies and clinical experience. However, we anticipated that these differences would be most pronounced between the groups of mild and moderate AD. The consistent results of differences between the groups of mildest cognitive impairment were therefore more surprising to us. Since our longitudinal study is small and the two cross-sectional studies make it hard to conclude that we have observed an ongoing decline, it is important to compare our results with other studies to see if these strengthen or weaken our findings.

The findings from cross-sectional studies of walking published in recent years are not unambiguous. Differences in walking between healthy elderly and persons with MCI was found by Pedersen and colleagues.[235] Muir et al.[153] on the other hand did not find any differences in gait speed or stride time variability between healthy elderly persons, persons with MCI and persons with mild AD; however, they only included persons without a history of falls. The participants in the study by Muir et al. may therefore not be representative to the general population with MCI and AD, as falls are reported in about 50% of home-dwelling elderly with AD.[9]

Longitudinal studies of walking abilities in persons with AD have been published in recent years, and the reported findings all indicate a decline in walking performance over time,[236-238] which is in line with the results from the longitudinal parts of our study of patients with early onset AD (paper I). Two of the papers are from the same small (n = 22 at follow-up) but well-designed study of home-dwelling patients with AD in Sweden. The results of these two studies indicated a deteriorating performance over a two-year period on both clinical gait measures[236] and quantitative gait characteristics.[237] The third longitudinal study involved a 4-year follow-up of 686 home-dwelling persons with AD in France, where the authors according to the results of the study estimated a yearly decline in walking ability of about 13%.[238] The mean age of the participants in Rolland's study[238] was 77.8 years, and older age was an important risk factor for a decline of walking performance. In the Swedish study, the mean age was 71 years.[236;237] So, the participants in both these studies were considerably older than our participants with early onset AD whose mean age at baseline was 59.7 years. Although the changes we observed in our study were of limited importance on an individual level, our results still extend the findings from other studies. Our findings indicate that a decline in mobility is also present in the youngest patients with AD. Age-related changes and comorbidities are likely to be less pronounced in our young persons, and the changes observed during the follow-up are therefore likely to be connected to the progress of AD, not ageing. We therefore suggest that our longitudinal study in paper I contributes to the view that a decline in cognition and mobility are rather parallel processes in patients with an established clinical diagnose of AD.

Relatively few studies have been published on the relation between balance and severity of cognitive function, and the most recent studies generally confirm that there are differences in balance between healthy elderly and persons with AD,[239;240] although studies with contrary findings have also been published.[241] The most relevant study that could be compared to our study is the one by Suttanon and colleagues.[240] In their study, balance was treated as a multidimensional construct in line with the systems approach in an almost similar manner as in our study, and the authors identified differences in all the measured aspects of balance between healthy elderly and persons with mild to moderate AD.

By carrying out a very comprehensive assessment of balance in the continuum of AD, I hoped that we could be able to provide new knowledge on which aspects of balance interventions should target, and at what stage interventions should be initiated. Since both our study and the

study by Suttanon and colleagues[240] found deficits across all the measured aspects of balance, recommendations about interventions targeted towards specific aspects are hard to give. However, it is important to note that the last subscale, "Stability in Gait", had the lowest scores (i.e., worst performance) in all of our three groups. The tasks included in this subscale are all dynamic, and the tasks challenge biomechanical constraints (e.g. alignment, strength), anticipatory and reactive postural responses, sensory information, and also specific cognitive demands in the dual task item. So, this subscale may perhaps not represent a subsystem, but rather a fusion of the other subsystems. Given the lack of longitudinal studies of balance in persons with cognitive impairment and AD, our study has presumably applied the most comprehensive assessment of balance in this population, and our findings in papers I and II indicate that interventions aimed at maintaining balance and mobility in general should be initiated even in the youngest patients and also in patients with MCI.

Differences in mobility between groups of SCI, MCI and mild AD were also demonstrated for spatial navigation in paper III; this is in line with other studies concerning spatial abilities, although the outcome measures are not directly comparable. Given that navigational impairments are well known in patients with AD, I will dwell a bit more on the results related to the MCI group. Despite that we had relatively few patients in the SCI and the MCI group, we found that the MCI group spent longer time on all the three components of the Floor Maze Test than the SCI group. However, they were more successful than the patients with AD in completing the Floor Maze Test without errors. This may reflect how the patients in the MCI group cope in real-life with other tasks as well. Given the Winblad criteria[62] they should have no or minimal impairments of complex activities in daily life. However these criteria do not address issues like increased effort, modifications of the tasks, time spent doing daily activities, or if several attempts are needed. Studies of mobility in elderly without cognitive impairments has described increased tiredness or compensation by changes in method, frequency, or time used to carry out tasks in the preclinical stages of mobility disability.[242;243]

Our findings corroborate results from recent studies of worse performance in patients with MCI compared to healthy controls and in patients with AD compared to patients with MCI on a real-life route learning task.[244] They also agree with previous study results regarding inferior performances on a virtual maze task in patients with MCI compared to healthy controls.[245] However, there is still a lack of studies that investigate spatial navigational ability in relation to mobility in real-life in the early and intermediate stages of cognitive decline.[246] The Floor

Maze Test is described by the original authors as a test of spatial navigation with real-life applicability.[214] Although this test involves walking, it is still a huge leap to claim real-life applicability. In order to be able to identify persons at risk for getting lost, future studies should seek to validate the Floor Maze Test, or other simple feasible tests of spatial navigation towards real-life navigational measures. Paper III is the most explorative in the thesis, both regarding the groups and the outcome we used for assessing spatial navigation during walking. The fact that our findings are in line with findings from other studies contributes to the trustworthiness of our results; however, this study should primarily be considered as hypothesis-generating for future studies.

Although we found rather large between-group differences of mobility it is important to acknowledge the great variability within each group. The variability was most pronounced in the groups with most severe cognitive impairments and also worst performances on the mobility outcomes. In paper II, the SCI/MCI group had narrow confidence intervals indicative of either homogenous performance or ceiling effect on the BESTest (Figure 8). In the two other groups, however, the variability within each group was pronounced. In paper III the same pattern of variability is observed for performance on the Immediate Maze Time component of the Floor Maze Test, as illustrated in Figure 9. So despite the rather large differences at the group level, there is considerable variability on the individual level. Longitudinal studies would be valuable to determine what characterizes the persons with well-preserved mobility despite advanced cognitive impairment, and also those who develop mobility impairments early in the course of cognitive decline.

Longitudinal studies of cognitively healthy elderly people have been published during recent years, and the findings from these studies indicate that slow gait precedes and predict cognitive decline[247] and dementia.[248] The coexistence of slow gait and cognitive complaints in persons without impairments of activities of daily living or dementia has even been suggested as a "motoric cognitive risk" syndrome.[249] In a recent prospective multi-country study, this suggested syndrome was a strong and early risk factor for future cognitive decline and dementia.[250] These studies underline our recommendations that interventions aimed to maintain mobility may benefit from being initiated as soon as these persons make contact with health services.

8.2.2 Relationship between mobility and cognitive domains

In papers II and III we have demonstrated that executive dysfunction was significantly associated with mobility (i.e., balance and spatial navigation). This was done in regression models that included measures of attention, memory, visuoconstruction, global cognition, and demographic factors. The role of executive function for mobility was consistent in our analyses, while global cognition as measured by the MMSE did not contribute to the results of the regression models in any of the three papers. We were uncertain beforehand if we should include the MMSE in the regression models in papers II and III, because we were concerned that this global measure would "overshadow" the separate cognitive domains. On the other hand, by identifying significant associations between our measures of mobility and executive function while controlling for the MMSE, we assume that we have actually strengthened our findings. The MMSE is often used to determine severity of cognitive impairment: however, it has been criticized for the lack of items related to executive function, and also for being less sensitive than other measures in detecting MCI,[251] which may explain why it did not contribute to any of the models in our sample with generally high scores in the MMSE. Our findings indicate that the relationship between cognition and mobility applies not only to the severity of cognitive function, but also to specific cognitive domain of executive function.

The relationship between executive function and mobility in terms of gait and balance in persons with cognitive impairment and dementia is known from previous[133-135] and recent studies.[232;252;253] However, I will argue that our studies contribute to an expanded understanding of this relationship. In the study by McGough et al.[232] the association between executive function and performance-based measures of mobility (Timed Up and Go and gait speed) in sedentary home-dwelling older persons with MCI was established after adjusting for age, sex, comorbidity, depressive symptoms, and body mass index. A common shortcoming of this and several other studies is that executive function has been the only cognitive domain included in the studies. This makes it difficult to evaluate if executive function serves as a marker of general cognitive function, or if it is the specific contribution of executive function to mobility. By assessing executive function, other cognitive domains, and measures of global cognitive function in the same regression analysis, we have made a contribution to strengthen the trust of the importance of executive function to mobility. Our study also expands the

results from the other studies with the consistent associations between all the aspects of balance measured by the BESTest and executive function.

The rationale for exploring the relationship between the Floor Maze Test, demographic factors and cognitive domains was to examine to what degree the independent variables explained the performances on the Floor Maze Test, and also to identify which of the variables were associated with the Floor Maze Test. This is of course different from the rational in paper II, as spatial navigation is a cognitive ability in itself. However, spatial navigation is closely linked to real-life mobility, as noted in the special paper concerning aging, the central nervous system and mobility that emerged from a workshop hosted at the Gerontological Society of America conference in 2012.[254] Executive function was in our study associated with the two components of the Floor Maze Test that involves walking, but not with the stationary component Planning Time. This largely corroborates the results from the original paper where they performed factor analysis of the neuropsychological test battery, and the executive function/attention factor predicted performance on all three Floor Maze Test components in adjusted regression models.[214] The explained variances for the regression models are unfortunately not reported in this study.

In a recent study of route learning performance (i.e., the ability to learn and retrace a route in a hospital setting) in groups of normal ageing, MCI and AD, the authors examined how well assessments of memory (i.e., word list recall) and executive function (i.e., verbal fluency) predicted route learning performance.[244] Both measures were significantly associated with the route learning task, so these findings are in accordance with our results. Similar to our results, no demographical factors were significantly associated with route learning performance. However, in contrast to our findings, the explained variance of the model in the paper by Benke et al.[244] was as high as 58%. The relationship between the Floor Maze Test and real-life route learning tests is not established; however, it is still difficult to explain the large discrepancy in explained variance between Benke's and our studies. Benke and collegaues[244] commented that their findings stand in contrast with other studies of route learning, where route learning performance was not predicted by neuropsychological measures.[33;198] The literature is thus not consistent regarding the relationship between neuropsychological/cognitive test batteries and navigational skills. Our findings contribute to the concern that navigational impairments may go undetected, and that efforts should be made to address this in diagnostic work.

Finally, I would like to once again emphasize that executive function is a complex construct. Executive function may be regarded as a separate cognitive domain, but also as executing control over the other cognitive domains. Royall[25] argues that executive function may explain some variance in most cognitive measures. The outcomes in our studies are performance-based outcomes that are characterized by the ability to conduct the tasks according to a set of quality-criteria and timed spent conducting these tasks. Given that executive function may be characterized as the ability necessary for successful goal-directed behavior,[25] the relationship between executive function and our mobility outcome measures makes sense. It is important to keep in mind that real-life mobility is far more demanding than our assessments conducted in quiet and undisturbed settings. Clinicians are therefore encouraged to pay attention to patients with executive function impairments, as they are likely to have difficulties related to mobility in the community.

9 Conclusions

The main aims of this study were to explore how mobility performance differs between groups with different levels of cognitive impairment, and to explore the relationship between mobility and different domains of cognitive function in home-dwelling and ambulatory persons with cognitive impairment and AD.

We found differences between each of the groups on all aspects of balance (paper II) and also on spatial navigation (paper III). In our longitudinal study of early onset AD we also saw a small decline in mobility over one year (paper I). Although our findings indicate a decline in mobility through the stages from SCI to MCI, mild AD, and moderate AD, these findings need to be confirmed in larger longitudinal studies.

With regard to the second aim, we found consistent associations between executive function and all aspects of balance and also between executive function and spatial navigation. For the models with the aspects of balance as dependent variables the explained variances were generally high, while rather minor explained variances were observed for the models with spatial navigation. Future studies are needed to validate the Floor Maze Test against real-life navigation.

9.1 Implications for clinical practice and future research

My main motivation for doing research in the field of dementia and the major idea behind this thesis was to provide knowledge that may contribute to helping persons with cognitive impairment and dementia to remain independently mobile in the society for as long as possible. The findings of this thesis cannot be extended that far, but they suggest directions for both research and clinical practice.

The main reason for exploring mobility across groups of increasing severity of cognitive impairment was to try to identify at which stage interventions are needed in order to prevent unnecessary decline. Our findings indicate that mobility should be addressed as soon as the patients make contact with health services. All participants in our studies were home-dwelling and were able to walk without a walking device; still, we observed group-differences of impairments in mobility, and also decline over one year in the study of early onset AD. Early

intervention, also in the youngest patients, is probably necessary in order to prevent or postpone the transition from observed impairments to manifest disability.

Since we found deficits across all the aspects of balance that we measured, exact recommendations about which aspects of balance one should target when planning interventions for persons with cognitive impairment and AD are hard to give. The high variability in the groups with mild and moderate AD also underlines the need for individual assessments. However, the generally low scores on the "Stability in Gait" subscale may suggest that it may be beneficial to incorporate tasks that challenge the dynamic balance control in during walking. During the last years, intervention studies have combined physical exercise and cognitive stimulation specially aimed at executive functions.[241;255] Although these studies have been small and non-randomized, their results are still promising with regard to the potential for exploiting the interplay between cognitive and motor function.

The results from paper III suggest that both persons with MCI and mild AD have difficulties with solving spatial navigation tasks. Clinicians should make sure that navigation is properly addressed in the clinical interview when patients are attending memory clinics, as the standard cognitive test battery does not seem to capture these impairments. The MCI group, and perhaps also the mild AD group, may be the ideal target populations for trying modern technology such as Global Positioning Systems (GPS) devices, as they are still able to learn new technology and also to express their views regarding the integrity of autonomy and privacy when considering use of tracking devices. Such GPS equipment may also be useful for future studies to measure a person's out-of-home mobility with far better reliability and precision than retrospective interviews.

Future longitudinal studies with a longer-term follow-up are warranted to confirm the impression of progressive decline of mobility from our studies, and also to establish predictors for future decline in balance and spatial navigation. Further suggestions also involve the use of MRI to compare mobility with location and amount of structural changes in the brain. Lastly, we recommend that studies should address the validity of the Floor Maze Test as a measure of real-life spatial navigation, and also to provide relevant cut-offs for identifying persons at risk for getting lost.

It is important to remember that all the participants in our studies are home-dwelling and able to walk without a walking device. The differences in mobility that we observed are therefore

all related to the mild end of a disability spectrum. For most of these persons, physical function is therefore not an obstacle for participation in exercise or physical and social activities in the community.

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