Gait characteristics in people with cognitive impairment – the relationship between step length and cadence

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Spring 2016

Acknowledgements

My grandmother was diagnosed with dementia when I was in my intern year, finishing my physiotherapy education. During my many visits at her home and eventually nursing home, I observed how this type of disease affected not only her, but also everyone around her. She deteriorated quickly, not only mentally but also physically. I took a particular interest in dementia, as I learned how little we actually know about it. After several talks and encouragement from my friend Dr. Lasse Giil, I decided that I wanted to find out more about the relationship betweem gait function and dementia.

Writing this thesis has been an interesting process with an extreme learning curve and moments of both despair and prosperity. There are several people I have to thank for all the help along the way. First of all, my two supervisors Ingvill Fjell Naterstad and Rolf Moe-Nilsen deserves a huge thank you for all their knowledge and feedback. I would like to thank Arne Nakling, geriatrician at Betanien Hospital for excellent cooperation and patient access. In addition, I would like to thank the librarian Regina Küfner Lein for helping me with research in databases. My good friend Thomas Olsen deserves a thank you for all the multiple feedbacks on assignments and encouraging words in frustrating times.

Last but not least I want to thank my cohabitant Silje Vedvik for putting up with me this year and supporting me no matter what.

Abstract

Background: Approximately 70 000 people in Norway are suffering from some form of dementia. Gait and balance impairment in patients with Alzheimer's disease has been recognized for years. Reduced walking speed has been observed not only in patients with Alzheimer's disease, but also patients with mild cognitive impairment. However, the step length cadence relationship (walk ratio) is yet to be studied in individuals with cognitive impairment. Walk ratio has been suggested as a more specific variable than gait speed, as it says something about the quality of how we walk.

Aim: The first aim of the thesis was to explore the association between the minimal mental state examination (MMSE)-score and walk ratio by reviewing relevant literature. The second aim was to see if walk ratio can predict group membership between participants with subjective cognitive impairment, mild cognitive impairment and healthy controls.

Methods: A literature review of studies where either walk ratio or spatiotemporal gait parameters was reported in populations of cognitive impaired old persons was conducted. In addition, a cross-sectional trial with a 10-meter gait assessment for participants with subjective cognitive impairment, mild cognitive impairment and healthy controls was conducted.

Results: The literature review yielded a strong correlation between walk ratio and MMSE – score ($r = 0.69$). Linear regression showed that age did not contribute significant to the model. The cross-sectional trial showed that walk ratio could not predict group membership to either mild cognitive impairment or subjective cognitive impairment. However, a decrease in velocity was predictive of both subjective cognitive impairment (OR = 0.967 [95% CI 0.938 to 0.997], $P = 0.03$) and mild cognitive impairment (OR = 0.963, [95% CI 0.930 to 0.996], $P = 0.03$).

Conclusion: There was a strong association between the MMSE – score and walk ratio. In addition, a decrease in velocity seems to be predictive of both mild cognitive impairment and subjective cognitive impairment. These findings support the fact that there is an association between degree of cognitive impairment and gait function and that gait impairment can be found in early stages of dementia.

Sammendrag

Bakgrunn: Rundt 70 000 mennesker i Norge har en form for demens. Nedsatt gangfunksjon og balanse har lenge vært kjent hos pasienter med Alzheimers sykdom. Lav ganghastighet har blitt observert hos pasienter med Alzheimers sykdom, men også hos pasienter med mild kognitiv svikt. Forholdet mellom steglengde og kadens (gangratio) har så langt ikke blitt undersøkt hos pasienter med kognitiv svikt. Gangratio blir sett på som en mer spesifikk variabel enn ganghastighet, da den forteller mer om hvordan vi går og ikke bare hastigheten.

Mål: Det førte målet med oppgaven var å undersøke sammenhengen mellom the minimal mental state examination (MMSE) – score og gangratio ved en gjennomgang av relevant litteratur. Det andre målet var å undersøke om gangratio kunne predikere gruppetilhørighet mellom deltakere med subjektiv kognitiv svikt, mild kognitiv svikt og friske kontroller.

Metode: Det ble utført en litteratur gjennomgang av studier der enten gangratio eller spatiotemporale gangparameter var rapportert hos eldre mennesker med kognitiv svikt. I tillegg ble det utført en tverrsnitt studie med en 10-meter lang gangtest for deltakere med subjektiv kognitiv svikt, mild kognitiv svikt og friske kontroller.

Resultat: Litteraturgjennomgangen resulterte i en sterk korrelasjon mellom gangratio og MMSE-score (r = 0.69). Liner regresjon viste at alder ikke bidro signifikant til modellen. Tverrsnittstudien viste at gangratio ikke kunne predikere gruppetilhørighet for hverken mild kognitiv svikt eller subjektiv kognitiv svikt. En nedgang i ganghastighet var derimot prediktivt for både subjektiv kognitiv svikt (OR = 0.967 [95% CI 0.938 to 0.997], P = 0.03) og mild kognitiv svikt (OR = 0.967 [95% CI 0.938 to 0.997], P = 0.03).

Konklusjon: Det var en tydelig sammenheng mellom MMSE-score og gangratio. I tillegg var en nedgang i ganghastighet predikerende for både subjektiv kognitiv svikt og mild kognitiv svikt. Disse resultatene støtter tidligere forskning som rapporterer at det er en sammenheng mellom grad av demens og gangfunksjon, i tillegg til at nedsatt gangfunksjon kan oppstå i svært tidlige stadier av demens.

Index

Index of tables

Index of figures

Definitions

Dementia	A syndrome of acquired persistent intellectual impairment characterized by deterioration in at least three of the following domains; memory, language, visuospatial skills, personality or behaviour, and manipulation of acquired knowledge (Kowall and Budson, 2011).
Alzheimer's disease	A degenerative brain disorder characterized by progressive intellectual and behavioral deterioration (Kowall and Budson, 2011).
Mild cognitive impairment	Impairment (adjusted for age and education) in one or more domains of cognition, with relative sparing of global cognitive functions (McGough et al., 2011).
Subjective cognitive impairment	A clinical stage where subjective memory complaints exist in the absence of detectable objective cognitive deficits (Fonseca et al., 2015).
Walk ratio	The ratio between step length and cadence (Sekiya et al., 1996).
Gait Cycle	A pattern of movement that start with on foot making contact with the floor, and continuing until the next occasion when the same foot makes contact with the floor again (Baker and Hart, 2013).
Step	The movement of one foot in front of the other (Baker and Hart, 2013).
Stride	A step of one foot followed by another step for the other (Baker and Hart, 2013).

Step length	The distance that one part of the foot travels in front of the same part of the other foot during each step (Baker and Hart, 2013).
Stride length	The distance that one part of the foot travels between the same instant in two consecutive gait cycles (Baker and Hart, 2013).
Step/stride width	A measure of the mediolateral separation of the feet (Baker and Hart, 2013).
Double support	The phase where both feet are in contact with the floor (Baker and Hart, 2013).
Velocity	The distance travelled in a given time. It is determined by the cadence and step/stride length (Baker and Hart, 2013).
Stride time	This is the duration of one gait cycle (Baker and Hart, 2013).
Cadence	Number of steps per minute (Baker and Hart, 2013).

Abbreviations

AD	Alzheimer's disease
SCI	Subjective cognitive impairment
MCI	Mild cognitive impairment
MMSE	Minimal mental state examination
SL	Step length
WR	Walk ratio

Introduction

1.1 Background

According to the Norwegian Directorate of Health approximately 70 000 people in Norway are suffering from some form of dementia (Helsedirektoratet, 2011), and it is likely that more and more will develop this condition due to an increasing proportion of elderly (Helsedirektoratet, 2011). Dementia is defined as a syndrome of acquired persistent intellectual impairment characterized by deterioration in at least three of the following domains; memory, language, visuospatial skills, personality or behaviour, and manipulation of acquired knowledge (Kowall and Budson, 2011). Alzheimer's disease (AD) is the most common form of dementia, responsible for more than half of the cases (Gras et al., 2015, Jacobsen and Toverud, 2009, Weller and Dickson, 2012). Subjective cognitive impairment (SCI) and mild cognitive impairment (MCI) are conditions describing early stages of dementia, and can persist for several years (Jessen et al., 2014). Previous studies have shown that patients with MCI and AD have reduced motor function compared with healthy elderly subjects (Aggarwal et al., 2006, Goldman et al., 1999, Kluger et al., 2008). The loss of independence and safe mobility due to balance and gait dysfunction in AD patients has been recognized for years (Gras et al., 2015), and reduced walking speed has been observed among patients with both MCI and AD (Aggarwal et al., 2006, Goldman et al., 1999, Gras et al., 2015). However, few studies have investigated motor function in people with SCI.

Gait speed has long been acknowledged as an important aspect of gait and is often used as an objective measure of functional mobility in both clinical settings and research (Peters et al., 2013). Furthermore, gait speed is a predictor of life length (Hardy et al., 2007), future functional decline, risk of falling (Peters et al., 2013), health costs and health status (Purser et al., 2005). There is sufficient evidence to consider gait speed as a strong predictor of adverse outcomes in community dwelling elderly (Abellan van Kan et al., 2009).

The step length/cadence relationship, also known as the walk ratio (WR) (Sekiya et al., 1996), is yet to be studied in individuals with cognitive impairment. WR is calculated by dividing the length of one step by the cadence (number of steps per minute). As an example, imagine a healthy individual walking in a dark room or on a slippery surface. It would be reasonable to

assume that the walking strategy would include short and fast steps as compensation to increase stability, yielding a low WR. In contrast, normal step length and cadence would be preferred in a well-lit space or on a dry surface. Interestingly, when adjusted for stature, WR is almost independent of walking speed, age and sex and is generally constant in healthy elderly (Egerton et al., 2011, Rota et al., 2011). Rota et al. (2011) reported that the WR tells us something about the quality of how we walk, as opposed to gait speed, which may be affected by factors such as motivation and physical condition. They argued that WR is a more specific variable than gait speed, and suggested that WR can be a parameter for comparing health and disease. A lower value or change in WR could either predict disease or provide an indication of improvement or of functional decline.

WR is seldom reported in gait studies, but spatiotemporal characteristics like step length and cadence are frequently reported and lend themselves to calculate WR. Considering that studies have shown that patients with MCI and AD have impaired gait function (Aggarwal et al., 2006, Goldman et al., 1999, Kluger et al., 2008), examining WR in a population who has subsequently shown to have reduced gait function is intriguing. Hence, it is of interest to do 1) a literature search investigating spatiotemporal characteristics to see if there is an association between the degree of dementia and WR, and 2) a cross-sectional trial in a clinical setting to evaluate the WR in an early, pre-dementia stage (SCI and MCI) population. This is of relevance when we know that the development of AD initiates long before patients become symptomatic (Egerton et al., 2011), and physical function may decrease simultaneously or before the development of cognitive problems (Tangen et al., 2014). WR may possibly be used to predict disease even in an early stage of cognitive impairment. Because the WR is more or less independent of gait speed it could be a more sensitive and specific measure of gait function. It tells us more about how we walk, and not just how fast we walk.

1.2 Aims of the thesis

The first aim of this thesis is to explore the presumed association between the minimal mental state examination-score and walk ratio by reviewing relevant literature where either WR or spatiotemporal gait parameters are reported in populations of cognitively impaired elderly persons. The second aim is to investigate if walk ratio can predict group membership between patients with SCI, MCI and healthy controls in a clinical setting. This may also give an indication of whether or not gait impairment is present in early stages of dementia.

Theory

2.1 Dementia

Dementia is defined as a syndrome of acquired persistent intellectual impairment characterized by deterioration in at least three of the following domains: memory, language, visuospatial skills, personality or behaviour, and manipulation of acquired knowledge (Kowall and Budson, 2011). Brodal (2007) explains dementia as an acquired global reduction of intellectual abilities, reason and personality, without changes in the state of consciousness. At late stages of dementia, the patients are no longer oriented for time, place or situation (Jacobsen and Toverud, 2009). Dementia rarely appears before the age of 60, but the rate increases with age, especially after the age of 75. It is estimated that one third of people over 85 years of age have signs of dementia (Jacobsen and Toverud, 2009) and it is one of the leading causes of disability in the elderly population (Tangen et al., 2014). Dementia can have multiple causes, but a common factor is a widespread degeneration of the cortical synaptic connection (Brodal, 2007). Dementia can occur after repeated infarcts that eventually may destroy brain tissue. These infarcts in the white matter lead to what is known as vascular cognitive impairment. Most cases of dementia, however, are caused by neurodegenerative diseases that gradually leads to loss of neurons (Brodal, 2007).

2.1.1 Alzheimer's disease

The majority of patients with dementia have Alzheimer's disease (AD), which is a progressive neurodegenerative disease without a known cause or treatment (Gras et al., 2015, Jacobsen and Toverud, 2009). It usually starts to evolve before the age of 60 (Brodal, 2007). The symptoms are associated with psychiatric, cognitive and physical impairments, leading to loss of independence, major healthcare costs and a heavy burden on relatives (Tangen et al., 2014). The involvement of entorhinal cortex, the hippocampus and the frontal and parietal associative cortical areas is well established (Suva et al., 1999), whereas the primary motor cortex is generally accepted to be less involved or even spared (Brodal, 2007, Suva et al., 1999). However, a study performed by Suva et al. (1999) found that the primary motor cortex was significantly involved in AD and suggested the presence of motor dysfunction in late or terminal stages of the disease.

2.1.2 Mild cognitive impairment

MCI is a term describing an individual who has some degree of cognitive impairment, but does not meet the criteria for dementia. Although it is regarded a common condition that occurs between normal aging and dementia, there is a lack of consensus about its definition (Aggarwal et al., 2006). The core clinical criteria for MCI are personal concern regarding decline in cognitive function preferably confirmed by an informant, objective impairment in one or more cognitive domains, normal general cognitive function and independence in functional abilities (Albert et al., 2011). The literature indicates that people with MCI score more poorly on neuropsychological and motor tests and are at a higher risk for future dementia development compared with cognitively unimpaired (Kluger et al., 2008). MCI is associated with an increased risk of developing AD, but far from all patients with MCI develop AD (Aggarwal et al., 2006).

2.1.3 Subjective cognitive impairment

SCI may be the earliest point of clinical AD symptomatology (Fonseca et al., 2015). SCI describes the occurrence of a person reporting or admitting to cognitive function that they feel is impaired (Stewart, 2012). The terminology of this stage varies, but SCI is an increasingly accepted term (Fonseca et al., 2015). The criteria for SCI are experienced persistent decline in cognitive function in comparison with previously normal status, in addition to normal age-, gender, and education-adjusted performance on standardized cognitive tests. In addition, the perceived decline cannot be explained by psychiatric or neurologic disease, medial disorder, medication or substance use (Jessen et al., 2014). Fonseca et al. (2015) describe SCI as a disease stage where possible neuropathological damage is offset by compensatory mechanisms. It is a risk factor for further cognitive decline to both MCI and AD (Jessen et al., 2014). SCI has been a controversial entity since it first was considered as a research topic. Clearly, impaired cognitive function can have a heterogeneous origin, like depression or other mental disorders, and many people reporting memory problems have no observable or objectively measured deficits (Stewart, 2012). However, empirically it is likely that people developing dementia at some point notice their cognitive impairments, without seeking help. And even though SCI is a condition that is difficult to define, there are very few other ways in which these patients will be detected (Stewart, 2012).

2.2 Gait

Locomotion is characterized by three essential requirements: progression, postural control and adaption (Shumway-Cook and Woollacott, 2012). Progression is ensured through patterns that produce and coordinate rhythmic patterns of muscle activation that successfully move the body. Postural control is the ability to establish and maintain appropriate posture for locomotion and dynamic stability. The ability to adapt gait is important for meeting the goals of the individual and the demands of the environment. These requirements must be met with strategies that are both energy-efficient and effective in minimizing stress to the body (Shumway-Cook and Woollacott, 2012).

Gait is a complex mode of behaviour involving the entire body. Navigation through complex environments requires the use of sensory inputs to assist in the control and adaption of gait (Shumway-Cook and Woollacott, 2012). Gait includes stance and swing phases. During stance phase, we need to generate forces against the support surface. The goals of the swing phase include advancement of the swing leg and repositioning of the limb in preparation for weight acceptance. In addition, strategies used to accomplish progression and postural control must be flexible to accommodate changes in speed and direction or alteration in the surface The stance phase starts when the foot strikes the ground, and the swing phase starts when the foot leaves the ground. At their usual pace, an adult typically keeps each leg 60 percent of the cycle duration in the stance, and 40 percent in swing. Approximately, the first and last 10 percent of the stance phase are spent in double support (Shumway-Cook and Woollacott, 2012).

Kinematic studies suggest that all normal subjects use the same movement strategy for walking. However, studies describing muscles and forces associated with gait suggest that there are a tremendous variability in the way the strategy is achieved (Shumway-Cook and Woollacott, 2012).

2.3 Walk ratio

Gait speed is the product of step length (SL) and cadence and we can use an infinite combination of these variables when walking (Sekiya et al., 1996). Usually, WR remains constant at a value around 0.65 (± 0.08) cm/(step/min) when normalized for height in an adult healthy population (Sekiya et al., 1996). WR tells us more about the quality of how we walk, while gait speed is a measure of performance. A low ratio tells us that an individual takes small steps and has a high step frequency. A higher ratio tells us that the individual takes longer steps, holds a lower frequency or both. Curiously, Rota et al. (2011) points out that during indoor short distance walking, the ratio between step length and cadence remains constant, once both are normalized for height. Other gait parameters, kinematic or kinetic, change with different gait speed but the WR maintains independent of speed except at extremely slow or fast speed (Sekiya and Nagasaki, 1998). In addition, WR has shown to be independent of age and sex (Egerton et al., 2011, Sekiya et al., 1996) in healthy populations. Sekiya et al. (1996) suggest that the WR can be an index for describing temporal and spatial coordination or gait pattern at any given speed. Since the WR remains constant over a wide range of walking speed, it suggests that human walking is extremely coordinated as to keep the ratio constant. It also seems like the preferential WR is the one that reduces energy cost (Cavagna and Franzetti, 1986, Sekiya et al., 1996). Further, it is suggested that a deviation from the normal WR during free walking may indicate or reveal some form of abnormal walking patterns (Sekiya and Nagasaki, 1998). Studies have also shown that smaller steps and a higher cadence might predict falls in elderly (Barak et al., 2006, Callisaya et al., 2012)

2.4 Gait function with aging and cognitive impairment

With increasing age follows several structural and biochemical alterations in the brain (Brodal, 2007). Both mental and motor processes slow down, especially for task with high demand of speed and when learning new tasks. Highly automated intellectual and also motor skills (such as walking), are less affected by age (Brodal, 2007). However, both gait and balance are often impaired in older adults. They are major contributors to falls among this population and usually have a complex origin (Salzman, 2010). A meta-analysis (Bohannon and Williams Andrews, 2011) found that gait speed varies as a function of age and sex. They also found that the velocity decreases each decade after 60 to 69 years. Changes in gait may have different reasons, where many are related to underlying medical conditions (Salzman, 2010). One study

found that in neurologically healthy elderly people, the velocity of gait and length of stride was reduced between 17-20 percent, compared to young adults (Elble et al., 1992). In addition, studies have shown that elderly who fall have abnormal walking patterns. Both shorter stride length and lower velocity seems to be present in fallers compared with non-fallers in an elderly population (Wolfson et al., 1990). Salzman (2010) writes that characteristics of gait that changes with age is increased stance width, increased time in double support, bent posture, and less vigorous force developed at the moment of push off. This may represent adaptions to alterations in sensory or motor systems to give a more stable gait pattern. Twenty percent of older adults actually maintain normal gait into very old age (Salzman, 2010). Thus, Salzman (2010) argue that these kinds of gait impairments are caused by one or more underlying conditions.

Studies report that dementia in itself is a risk factor for falling in elderly populations (Persad et al., 2008, Shaw, 2002, van Doorn et al., 2003) and that patients with dementia have poorer prognosis when falls occurs (Shaw, 2002). In AD, gait disorders are common, with prevalence increasing with the progression of AD. It has been suggested that AD related gait disorders are not only an accompanying result of the disease, but also a specific sign of AD-related cognitive decline (Annweiler et al., 2012). Annweiler et al. (2012) suggest that studying AD-related gait disorders is attractive in the sense that it can predict adverse outcomes such as falls, loss of independency, institutionalization, hospitalization and death. Gait disorder may also even appear before memory impairments in patients with AD. Thus, gait disorders might be a supplement for early diagnosing AD. AD related gait disorders have been related to the impairment of higher levels of gait control at subcortical and cortical levels. It remains unclear which brain structure and related lesions are specifically involved and could explain the gait impairments. In other types of dementia like Parkinsonism, that links with basal ganglia disorders, gait disorders are well described and understood (Annweiler et al., 2012).

Gait disorders are also reported in MCI, owing to probable changes in higher levels of motor control (Annweiler et al., 2013). It has been reported that MCI patients have slower gait speed (Montero-Odasso et al., 2012, Verghese et al., 2008), but also lower gait stability (Beauchet et al., 2013). It has been suggested that cognitive decline can lead to gait disorders independent of decline in muscle strength, tone or osteoarticular functions that may accompany aging (Annweiler et al., 2013). Annweiler et al. (2013) showed that abnormal metabolite ratios in the primary cortex and lower primary motor cortex volume in patients with MCI, were associated

with poor gait performance while single and dual tasking. They argued that this underscored the possible involvement of decreased neuronal function in the primary motor cortex causing gait disorders observed in MCI (Annweiler et al., 2013). To the best of our knowledge, no studies have examined gait function in populations with SCI.

Method

This is a twofold study consisting of a literature review investigating the association between WR and the degree of cognitive impairment, and a cross- sectional trial in a clinical setting investigating gait impairment in patients with cognitive impairment compared to healthy controls.

3.1 Part 1 – Literature review

3.1.1 Study design

Because no studies have explored WR in a population with cognitive impairment an exploratory literature search for studies examining gait function in this population was conducted. The results were narrowed down to studies containing the variables needed to calculate WR of the participants in the studies.

3.1.2 Search strategy

The literature search for this thesis was performed through PubMed, PEDro, AMED, Cochrane, Embase, MEDLINE and PsycINFO with assistance from an experienced librarian (last search date: 13th of March 2015). The search terms were as follows: (step length OR stride length) AND (cadence OR step frequency OR gait OR walk speed OR velocity OR walk ratio) AND (dement* OR Alzheimer* OR mild cognitive impairment). The search terms were used as mesh terms or text words and were adjusted for the different databases. The full search strategy is available in the appendix. Unpublished studies and abstracts were not included. Languages were restricted to English or Norwegian due to time resources. Article references were screened for potentially relevant studies, resulting in 16 additional articles. The PRISMA 2009 Flow Diagram (Moher et al., 2009) was used to illustrate the selection process of the studies.

3.1.3 Inclusion and exclusion criteria

The study population had to be patients with cognitive impairment for which the diagnostic process was accounted for. The studies had to include the gait variables step length, cadence, WR or the possibility to calculate WR for the different groups of participants. In addition, to compare the degree of cognitive impairment between studies the Minimal Mental state examination (MMSE)-score had to be included, a short examination focusing on the cognitive aspects of mental function (Folstein et al., 1975). To make the different gait assessment

comparable, it had to be stated whether the studies measured «steady state» walking, which is walking without the acceleration or deceleration phase. Only the studies measuring steady state walking were included in the study. The gait assessment had to be done on a level floor and not for example on a treadmill. The participants also had to be free of neurological or orthopaedic diseases that could affect the gait assessment. Study design was not considered as an exclusion criteria, because different designs could be eligible for inclusion.

3.1.4 Variables and data collection

Data was collected from the included studies. Some of the studies had several groups like control groups and interventions groups, resulting in a higher number of groups than the number of included studies. Variables extracted from the studies were baseline MMSE-score, age and WR from each group, thus the mean of each group was used in further analysis. Follow up data from longitudinal cohorts studies without intervention was included. Healthy control groups were included as long as they met the criteria for inclusion.

3.1.5 Analysis

Statistics was performed in Microsoft Excel for Windows 8 and in the Statistics Package for Social Science (SPSS) 22.0 for Windows. The following baseline variables were computed: MMSE-scores, WR and age. We retrieved and calculated WR from cadence and step length in studies that did not explicitly include WR as a variable. To see if the results were affected by sample size, the variables were weighted according to the number of participants, and weighted group means were compared with the original group means. The weighted group means did not differ from the original means, thus the original means were used in further analysis. Using bootstrapping procedures in the correlations and regression analysis confirmed that departures from normality did not affect the results. Therefore, only parametric procedures without bootstrapping are presented for correlation and regression. For correlations and sample characteristics, Pearson's R was used. For explained variance, linear regression was conducted. The independent variables were also checked for multicollinearity. The independent t-test was used to compare means between controls and people with cognitive impairment. The significant threshold was set at .05.

3.2 Part 2 – Cross-sectional study

3.2.1 Study design

A cross-sectional design was used in order to assess WR in populations with SCI and MCI and compare them to healthy controls.

3.2.2 Study population

The study population included patients diagnosed with SCI or MCI in addition to a healthy control group. They were diagnosed and recruited through the dementia-disease initiation project. The participants were diagnosed by a geriatrician according to the recommendation from the National Institute on Aging-Alzheimer's association (Albert et al., 2011). Thus, the patients completed a thorough diagnostic process before entering the study. Eligible subjects were screened for cognitive function with the following test battery; Trail making A & B (Reitan and Wolfson, 1993), FAS (Benton, 1989), The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Fillenbaum et al., 2008), Minimal mental state examination (MMSE) (Folstein et al., 1975), Clock-drawing (Shulman, 2000). To be diagnosed with MCI the participants had to score below the normality cut-off in at least one of the tests. The normality cut-off used for MMSE was ≥28 points and ≥1.5 standard deviations for the remaining tests. The inclusion criteria for the symptomatic groups in the dementia-disease initiation project was recently acquired symptoms of cognitive impairment, between the age 40-85 and having Norwegian, Swedish or Danish as their first language. The control group contained participants without cognitive symptoms. Exclusion criteria were brain injury, including stroke, known dementia, severe psychiatric disease, intellectual disability, severe somatic disease that can affect cognitive function or medical treatment that could affect cognitive function. In addition, exclusion criteria for this cross-sectional study were neurological disease, orthopaedic injuries or operations that could cause gait impairment or inability to walk 10 meters without aid.

3.2.3 Power

There are no studies examining WR in a population with cognitive impairment, thus estimating the sample size needed from previous studies was not possible. In the literature review, the mean numbers of participants per groups were 20. Since these were studies investigating gait variables in populations with cognitive impairment, this sample size was used as an indicator of required power.

3.2.4 Data collection

The 10-meter walk test

The 10-meter walk test is commonly used for the assessment of walking speed and has high test-retest and interrater reliability (Peters et al., 2013). It requires a 20 meter walking path including 5 meters for acceleration and deceleration at either side (Peters et al., 2013), illustrated in Figure 1. This test needs little equipment and is easy to perform. A line was drawn at the start and at the end of the walkway. The participants were told not to stop before reaching the end line. First, they were instructed to walk at their preferred speed («your usual pace»), second, they were asked to walk fast, («as fast as you can without running or losing your balance») and third, slow («waiting for the bus»).

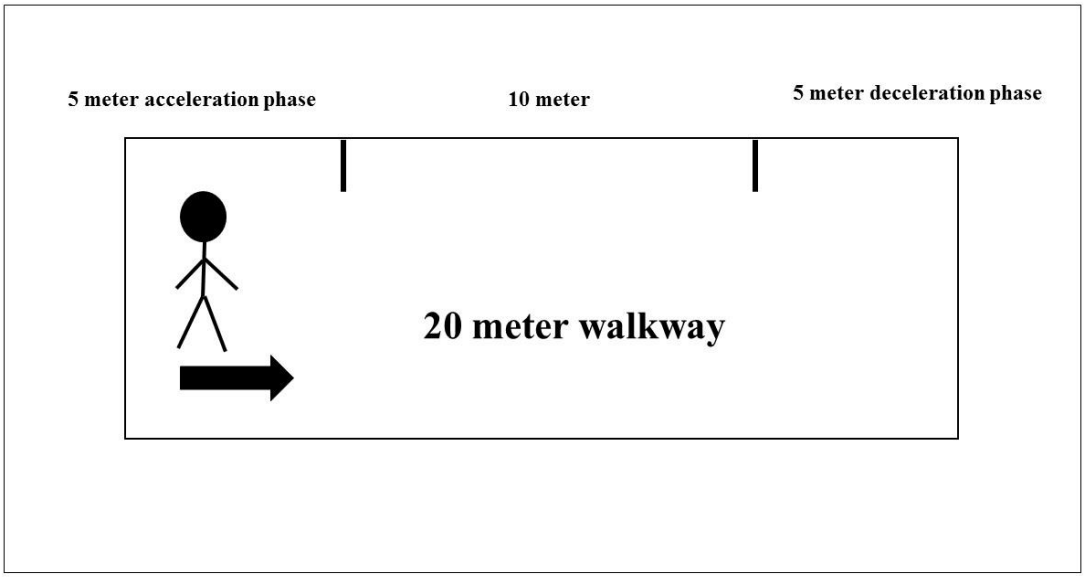

Figure 1. Illustration of a 10-meter walk test

The test measured steady state walking with dynamic start. The observer started the stopwatch as the participant passed a small, discrete, 5-meter mark on the floor, and stopped at a similar 10-meter mark, so that only the mid 10 meters walking was timed, thus excluding the acceleration and decelerations phases. The number of steps used to complete 10 meters was counted by the observer. Data of two consecutive trails were collected and the average was used in further analysis.

Other variables

Other variables collected from the participants were body height without shoes, gender and age.

3.2.5 Analysis

Gait variables

The gait variables needed to calculate WR were step length and cadence. These were calculated from data collected from the 10-meter walk test.

Velocity (m/s) = 10 meters / time (seconds)
Step length (cm) = 1000 cm / number of steps
Meters walked pr. minute = walking speed x 60 seconds
Cadence: steps pr. min = meters walked pr. minute / step length
WR = Step length / cadence

Adjustment for height

Because gait parameters are dependent on stature, they need to be adjusted for size when making comparisons between subjects. It is assumed that step length is proportional to leg length and that cadence follows pendulum laws. The equation for the frequency (f) of a simple pendulum is:

$f = [\sqrt{(g/L)}]/(2*3.14)$ (Store norske leksikon, 2009)

The equation demonstrates that f is proportional to the inverse of the square root of the length (L) of the pendulum since acceleration due to gravity (g) is a constant. If cadence follows pendulum laws, cadence is therefore proportional to the inverse of the square root of leg length. If leg length is assumed proportional to body height, cadence is also proportional to the inverse of the square root of body height. In this study, adjustment for height were done in accordance with the recommendations of Sekiya et al. (1996) who followed the above principles when adjusting gait parameters to average body height. The following formulas were used:

Adjusted step length: SL_n = (step length/height) *(average height)
Adjusted cadence: CAD_n = cadence*(height/average height) ^{½}
Adjusted walking speed: $V_n = SL_n*CAD_n$

Adjusted walk ratio = SL_n/CAD_n

Statistical analysis

Statistics was performed in Microsoft Excel for Windows 8 and the Statistics Package for Social Science (SPSS) 22.0 for Windows. The following variables were computed: Step length, cadence, WR and velocity for the three gait speeds for the three different groups. The data were normally distributed. Pearson's R was used for correlation. One-way Multinomial logistic regression was used to compute odds ratios (OR) for the different groups, making it possible to adjust for other variables. To measure the overall differences between groups, analysis of variance (ANOVA) was used. Further, Dunnet's post hoc test was used to compare the MCI and SCI group to the control group. The significance threshold was set at 0.05.

3.3 Ethical considerations

The participants in this study were recruited from the dementia-disease initiation project. This project protocol was approved by the regional ethic committee (appendix). This thesis is a subproject to the original dementia-disease initiation project, approved by the leader of the project, Dag Aarsland (appendix). The participants volunteered and signed a written consent. They were informed that they could withdraw from the study at any time, without having to explain why. The 10-meter walk test was considered as minimal invasive, and efforts were made to make sure no harm would come to the patient during the assessment. The assessment was supervised by a physiotherapist. Information about the participant's name and identification number was always kept separate. Other information about the participants was always kept on paper and locked in.

3.4 Resources, equipment and expenses

There were few expenses related to this thesis. The dementia-disease project refunded the participants travel expenses. The equipment needed was tape, a stopwatch, measurement band and a well-lit hallway. The author has a 10 percent post at the dementia-disease project to help with the original study. In additions, a scholarship from the physiotherapy fund was received.

Results

4.1 Part 1 - The literature review

Figure 2 shows an overview of the study selection process. The initial database search yielded 483 studies. Removing duplicates, a total of 273 studies were left for screening of title and abstract. Additionally, 16 studies were added through references from studies achieved from the literature search. Last, 117 studies were further screened in full text, yielding a total of 16 studies for inclusion as displayed in Table 2. The ranges of the meters walked between the included studies were 3.7 meters – 10.0 meters. One of the studies measured fast walking speed (Schwenk et al., 2014), but the remaining studies measured preferred gait speed.

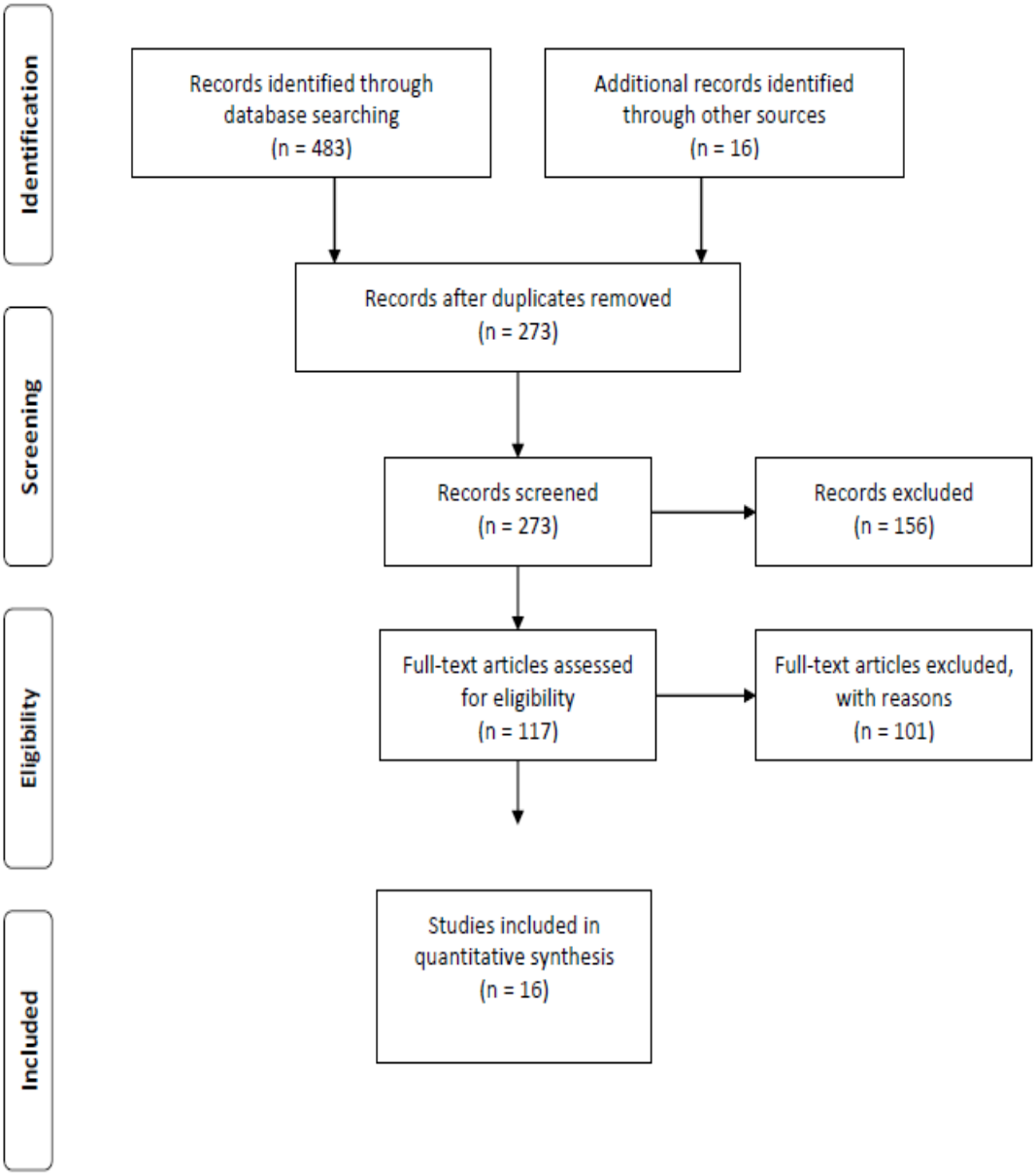

Figure 2. Flow diagram of the study selection process

Table 1. Included studies from the literature review

Article	Author	Year	Journal	Method	N	Population	MMSE	Age	Velocity (m/s)	Cadence steps/min	Step length (cm)	WR
A longitudinal study of gait function and characteristics of gait disturbance in individuals with Alzheimer's disease	Cedervall, Y., Halvorsen, K., & Aberg, A. C.	2014	Gait & Posture 39 (2014) 1022–1027	Longitudinal study	21	Mild Alzheimer's disease	25,0	72	1,14	110,3	62	0,56
					21	Mild Alzheimer's disease a)	22,0	73	1,10	110,0	60	0,55
					21	Mild Alzheimer's disease b)	21,0	74	1,01	106,3	57	0,54
Multimodal exercise intervention improves frontal cognitive functions and gait in Alzheimer's disease: A controlled trial	de Melo Coelho, F. G., Andrade, L. P., Pedroso, R. V., Santos-Galduroz, R. F., Gobbi, S., Costa, J. L. R., & Gobbi, L. T. B.	2013	Gait & Posture, 39(4), 1022-1027	Intervention study	14	Mild and Moderate Alzheimer's disease	19,5	78	0,79	103,0	46	0,45
					13	Mild and Moderate Alzheimer's disease	19,0	77	0,71	99,1	43	0,43
Gait and risk of falls associated with frontal cognitive functions at different stages of Alzheimer's disease	de Melo Coelho, F. G., Stella, F., de Andrade, L. P., Barbieri, F. A., Santos-Galduroz, R. F., Gobbi, S., Costa, J. L. R. & Gobbi, L. T. B.	2012	Aging, Neuropsychology, and Cognition, 19(5), 644-656.	Cross-sectional study	12	Mild Alzheimer's disease	22,0	76	0,78	99,6	47	0,47
					11	Moderate Alzheimer's disease	16,2	80	0,67	98,1	41	0,42
Effects of multicomponent exercise on spatial-temporal gait parameters among the elderly with amnestic mild cognitive impairment (aMCI): Preliminary results from a randomized controlled trial (RTC)	Doi, T., Makizako, H., Shimada, H., Yoshida, D., Tsutsumimoto, K., Sawa, R., Misu, S. & Suzuki, T	2012	Archives of Gerontology and Geriatrics 56 (2013) 104–108	Randomized controlled trial	25	Amnestic mild cognitive impairment	26,8	75	1,10	115,8	57	0,49
					25	Amnestic mild cognitive impairment	26,6	77	1,10	117,9	56	0,48
Balance and Gait of Adults With Very Mild Alzheimer Disease	Gras, L. Z.,Kanaan, S. F., McDowd, J. M., Colgrove, Y. M., Burns, J. & Pohl, P. S.	2015	J Geriatr Phys Ther. 2015 Jan-Mar;38(1):1-7.	Cross-sectional study	13	Normal controls	29,0	73	1,49	116,1	77	0,66
					13	Very mild Alzheimer's disease	24,8	73	1,07	103,6	62	0,60

Article	Author	Year	Journal	Method	N	Population	MMSE	Age	Velocity (m/s)	Cadence steps/min	Step length (cm)	WR
Gait and cognition: The relationship between gait stability and variability with executive function in persons with and without dementia	Ijmker, T., & Lamoth, C. J.	2012	Gait & Posture 35 (2012) 126–130	Cross-sectional study	14	Older controls	28,5	80	1,40	112,1	61	0,54
					12	Younger controls	29,1	64	1,19	112,4	64	0,57
					15	Alzheimer's disease and fronto temporal dementia	19,6	82	0,67	100,8	40	0,40
Quantitative gait analysis under dual-task in older people with mild cognitive impairment	Montero-Odasso, M., Casas, A., Hansen, K. T., Bilski, P., Gutmanis, I., Wells, J. L., & Borrie, M. J.	2009	Journal of NeuroEngineering and Rehabilitation 2009, 6:35	Reliability study	13	Mild cognitive impairment	28,0	77	1,19	108,4	65,88	0,61
Dual-Task complexity Affects Gait in People With Mild Cognitive Impairment: The Interplay Between Gait Variability, Dual Tasking, and Risk of Falls	Montero-Odasso, M., Muir, S. W., & Speechley, M.	2012	Arch Phys Med Rehabil Vol 93	Cross-sectional study	26	Normal controls	29,5	72	1,34	115,6	70	0,61
					43	Mild cognitive impairment	27,8	75	1,11	107,6	62	0,58
Gait assessment in mild cognitive impairment and Alzheimer's disease: The effect of dual-task challenges across the cognitive spectrum	Muir, S. W., Speechley, M., Wells, J., Borrie, M., Gopaul, K., & Montero-Odasso, M.	2012	Gait & Posture 35 (2012) 96–100	Cross-sectional study	22	Normal controls	29,5	71	1,36	114,6	71	0,62
					29	Mild cognitive impairment	27,5	74	1,16	111,4	62	0,56
					23	Alzheimer's disease	24,2	78	1,11	108,7	61	0,56
Spatial and temporal gait parameters in Alzheimer's disease and aging	Nadkarni, N., Mawji, E., McIlroy, W., & Black, S.	2009	Gait & Posture 30 (2009) 452–454	Cross-sectional study	34	Normal controls	29,0	74	1,19	109,0	65	0,60
					40	Alzheimer's disease	25,0	74	0,99	101,0	59	0,58
Gait and Subcortical Hypertensities in Mild Alzheimer's Disease and Aging	Nadkarni, N. K., McIlroy, W. E., Mawji, E., & Black, S. E.	2009	Dement Geriatr Cogn Disord 2009;28:295–301	Cross-sectional study	21	Alzheimer's disease + c)	25,0	77	0,96	102,0	56	0,55
					21	Alzheimer's disease-	24,0	71	1,02	101,0	61,5	0,61
					15	Normal Controls +	28,0	76	1,11	106,0	62	0,58
					18	Normal controls-	29,0	69	1,27	112,0	69	0,62

Article	Author	Year	Journal	Method	N	Population	MMSE	Age	Velocity (m/s)	Cadence steps/min	Step length (cm)	WR
Improvements in gait characteristics after intensive resistance and functional training in people with dementia: a randomized controlled trial	Schwenk, M., Zieschang, T., Englert, S., Grewal, G., Najafi, B., & Hauer, K.	2014	BMC Geriatrics 2014, 14:73	Randomized controlled trial	20	Mild to moderate dementia	21,0	80	1,33	137,1	58,29	0,43
					29	Mild to moderate dementia	21,7	82	1,29	134,5	57,66	0,43
Test-retest reliability of spatial and temporal gait parameters of people with Alzheimer's disease	Wittwer, J., Webster, K., Andrews, P., & Menz, H.	2008	Gait & Posture 28 (2008) 392–396	Reliability study	20	Alzheimer's disease	22,0	81	1,06	106,5	59,7	0,56
Reproducibility of gait variability measures in people with Alzheimer's disease	Wittwer, J. E., Webster, K. E., & Hill, K.	2013	Gait & Posture 2013, 38:3, s. 507-10	Reliability study	16	Alzheimer's disease	21,0	81	1,00	104,7	57,35	0,55
The effects of a concurrent motor task on walking in Alzheimer's disease	Wittwer, J. E., Webster, K. E., & Hill, K.	2014	Gait & Posture, 39(1), 291-296.	Cross-sectional study	30	Alzheimer's disease	20,6	80	1,12	109,6	60,7	0,55
A longitudinal study of measures of walking in people with Alzheimer's disease	Wittwer, J. E., Webster, K. E., & Menz, H. B.	2010	Gait & Posture 32 (2010) 113–117	Longitudinal study	11	Mild Alzheimer's disease	24,5	80	1,12	105,9	64	0,60
					8	Moderate Alzheimer's disease	16,6	78	0,93	101,8	54	0,53
					19	Normal controls	28,9	80	1,18	111,0	64	0,58

a) 1-year follow-up (no intervention between)
b) 2-year follow-up (no intervention between)
c) Severity of MRI findings denoted as + and -.

4.1.2 Association between walk ratio and MMSE

Descriptive statistics of the literature review are displayed in Table 2. Since some studies stratified their participants into different groups of cognitive impairment, or had intervention and control groups, the total number of groups was 34. The total amount of participants in these studies was 688. There was 25 groups with cognitive impairment with a total of 515 participants, leaving 9 groups of healthy controls with a total of 173 participants. Follow-up data was used from one of the studies (Cedervall et al., 2014), meaning data from the same participants (n=21) were used twice.

Table 2. Descriptive statistics of WR, MMSE and age from the literature review

		Mean	SD
Total group (n = 34)	WR	0.54	0.07
	MMSE	24.4	3.9
	Age	75.9	4.1
Cognitive impairment (n = 25)	WR	0.52	0.07
	MMSE	22.9	3.3
	Age	77.0	3.3
Healthy controls (n = 9)	WR	0.60	0.03
	MMSE	28.9	0.5
	Age	73.1	5.0

WR: Walk ratio

MMSE: Minimal mental state examination

SD: Standard deviation

Table 3. Correlation between WR, MMSE and age from the literature review

		WR	MMSE	Age
Total group (n = 34)	WR	1.00	0.69*	- 0.54*
	MMSE	0.69*	1.00	- 0.55*
	Age	- 0.55*	- 0.55*	1.00
Cognitive impairment (n = 25)	WR	1.00	0.58*	- 0.52*
	MMSE	0.58*	1.00	-0.50*
	Age	- 0.52*	- 0.50*	1.00
Healthy controls (n = 9)	WR	1.00	0.42	- 0.32
	MMSE	0.42	1.00	- 0.52
	Age	- 0.32	- 0.52	1.00

Data were analysed using Pearsons's r correlation coefficient
* Correlation is significant at the < 0.05 level

WR: Walk ratio
MMSE: minimal mental state examination

The correlations between the variables are displayed in Table 3. The correlations between WR and MMSE for the total group was high (r = 0.69, $P < 0.001$). The explained variance between WR and MMSE was R^2=0.48. A scatterplot between WR and MMSE is displayed in Figure 3. There was an inverse correlation between WR and age for the total group (r = -0.55, P= 0.001). The explained variance between WR and age was R^2=0.30 as depicted by Figure 4.

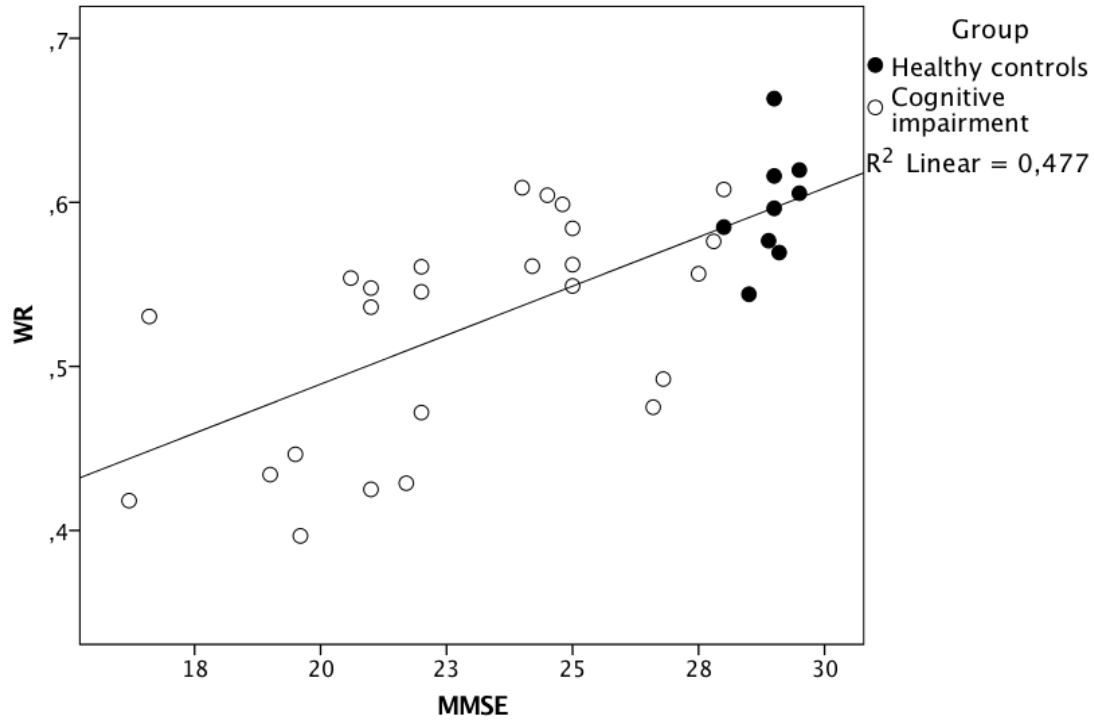

Figure 3. Scatterplot of the relationship between WR and MMSE

WR: Walk ratio (step length / cadence)

MMSE: Minimal mental state examination

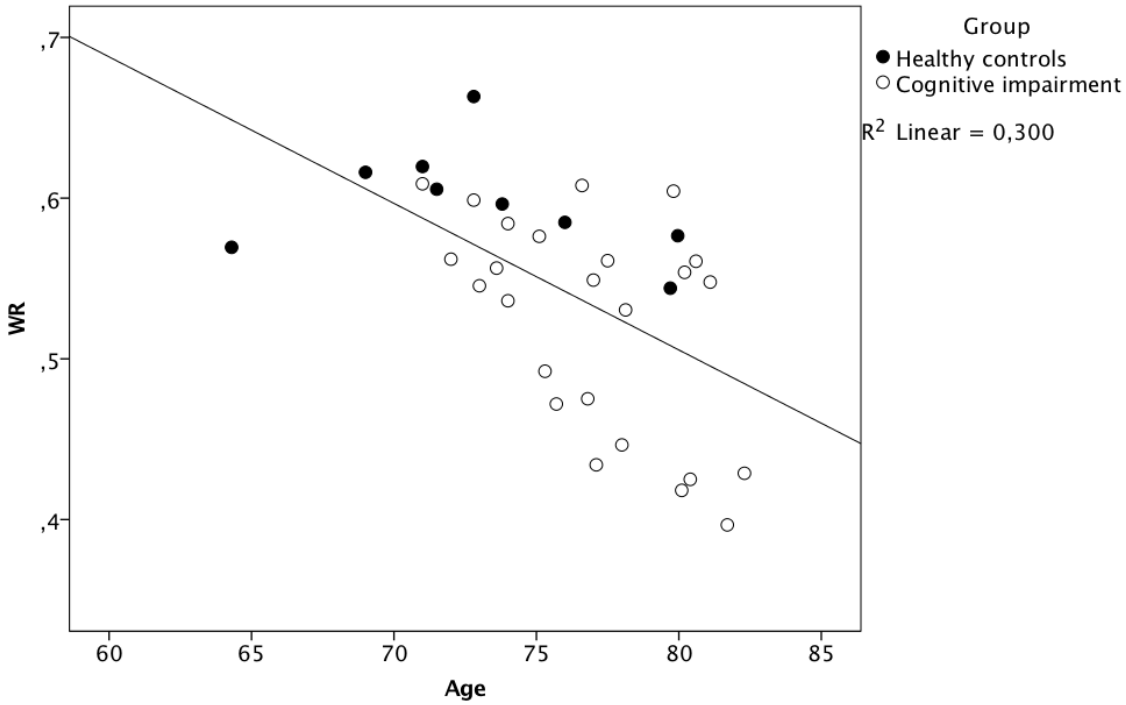

Figure 4. Scatterplot of the relationship between WR and Age

WR: Walk Ratio (step length / cadence)

Using linear regression between WR, MMSE and age, with WR as the dependent variable, resulted in $R^2 = 0.52$. Across the individual independent variables, only MMSE had a significant contribution to this model ($P < 0.001$) as opposed to age ($P = 0.12$). There was no multicollinearity between the independent variables MMSE and age.

Differences between participants with cognitive impairment and healthy controls

Within the cognitive impairment group, the correlation between WR and MMSE was $r = 0.58$ ($P = 0.03$), which was lower than the total group correlation. The explained variance between WR and MMSE was $R^2 = 0.33$. WR was linearly regressed over MMSE and age, with WR as the dependent variable, resulting in $R^2 = 0.4$. The independent t-test showed that the control group had a statistical significantly higher WR ($P < 0.001$) and MMSE-score ($P < 0.001$) compared to the cognitive impairment group. The participants from the control group had significant lower age ($P = 0.01$) than the participants in the cognitive impaired group. However, the linear regression within the cognitive impaired group showed that only MMSE had a significant contribution to the model ($P = 0.04$) as opposed to age ($P = 0.12$). In addition, there was no multicollinearity between the independent variables MMSE and age.

4.2 Part 2 – Cross sectional study

In total, 75 participants were screened for eligibility. Five participants were excluded due to orthopaedic or neurological disorders, resulting in 70 eligible participants. These were classified as controls (n=23), SCI (n=28) and MCI (n=19). The enrolled controls were 8 men and 14 women (mean age 60.0 ± 8.0, mean MMSE 29.7±0.8). The SCI groups consisted of 12 men and 16 women (mean age 63.1 ± 9.1, mean MMSE 29.6±0.6). Finally, the MCI groups were 12 men and 7 women (mean age 68.5 ± 8.6, mean MMSE 27.8±2.0). Descriptive statistics of the different measures of gait performance are presented in Table 4.

Table 4. Descriptive statistic of the different gait variables from the cross-sectional trial

		Slow gait speed		**Normal gait speed**		**Fast gait speed**	
Group		Mean	SD	Mean	SD	Mean	SD
Control (n=23)	WR (step length/cadence)	0.66	0.11	0.59	0.07	0.56	0.09
	Velocity (cm/s)	105.4	22.9	155.2	20.4	205.0	21.4
	Step length (cm)	63.5	5.9	73.6	6.3	82.1	6.5
	Cadence (steps pr. min)	98.8	16.6	126.4	12.5	150.1	16.4
SCI (n=28)	WR (step length/cadence)	0.64	0.11	0.59	0.07	0.55	0.10
	Velocity (cm/s)	96.1	18.7	140.8	20.8	195.4	29.2
	Step length (cm)	60.1	6.0	70.1	6.5	79.5	6.3
	Cadence (steps pr. min)	95.8	15.8	120.2	12.3	147.6	20.1
MCI (n=19)	WR (step length/cadence)	0.63	0.17	0.60	0.07	0.58	0.07
	Velocity (cm/s)	102.2	16.8	135.8	24.8	180.8	27.2
	Step length (cm)	61.3	8.7	69.7	7.7	78.8	6.8
	Cadence (steps pr. min)	100.8	15.8	116.3	13.2	137.3	14.9

SCI: Subjective cognitive impairment
MCI: Mild cognitive impairment
WR: Walk ratio
SD: standard deviation

There were statistical differences between groups in velocity, determined by the one-way ANOVA at preferred gait speed (P = 0.01) and at fast gait speed (P = 0.02). A post hoc Dunnet's test showed that there were statistical significant differences between MCI and controls (P = 0.005) and between SCI and controls (P = 0.02) in velocity at preferred gait speed. In addition, there were statistical significant differences between MCI and controls (P = 0.002) at fast gait speed. None of the other gait variables differed significantly between groups. Error bars comparing mean WR and mean velocity between groups are presented in Figure 5 and 6.

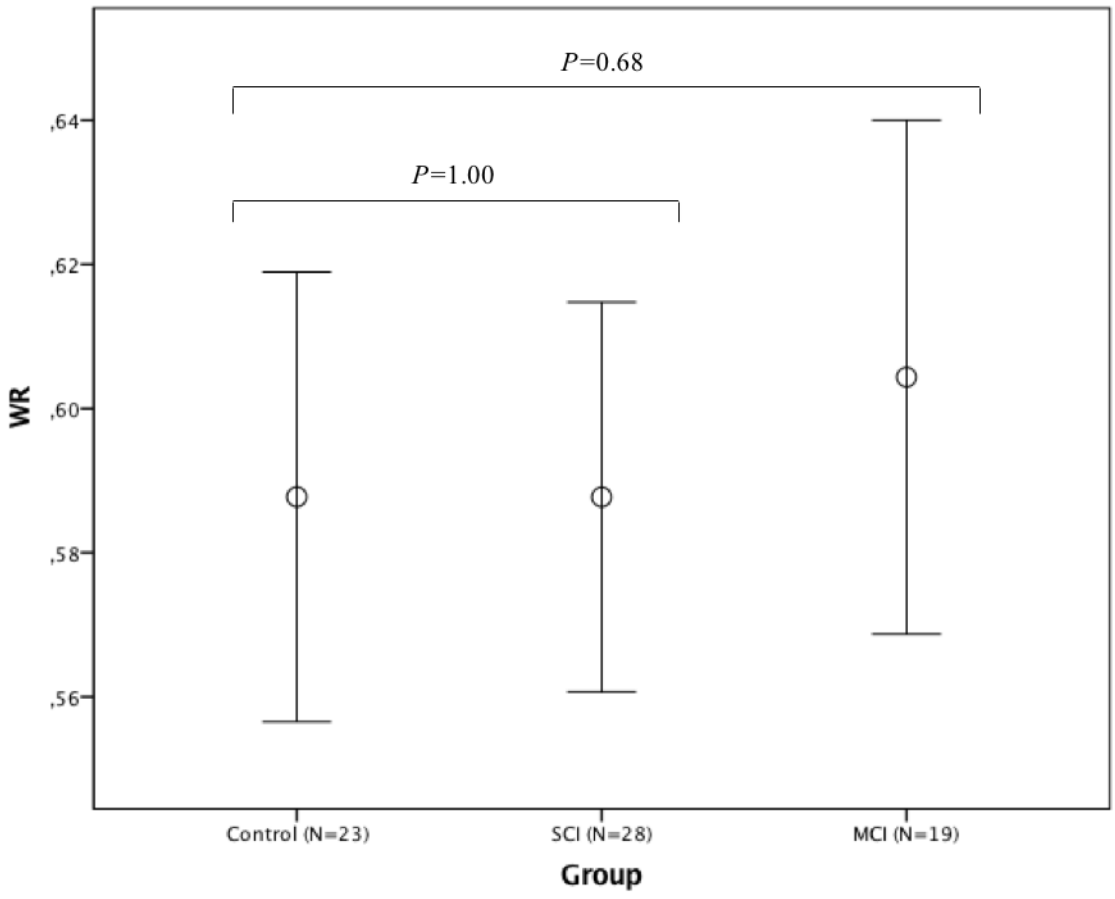

Figure 5. Difference in mean walk ratio at preferred gait speed

Error bars with 95% confidence intervals
WR: Walk ratio
SCI: Subjective cognitive impairment
MCI: Mild cognitive impairment

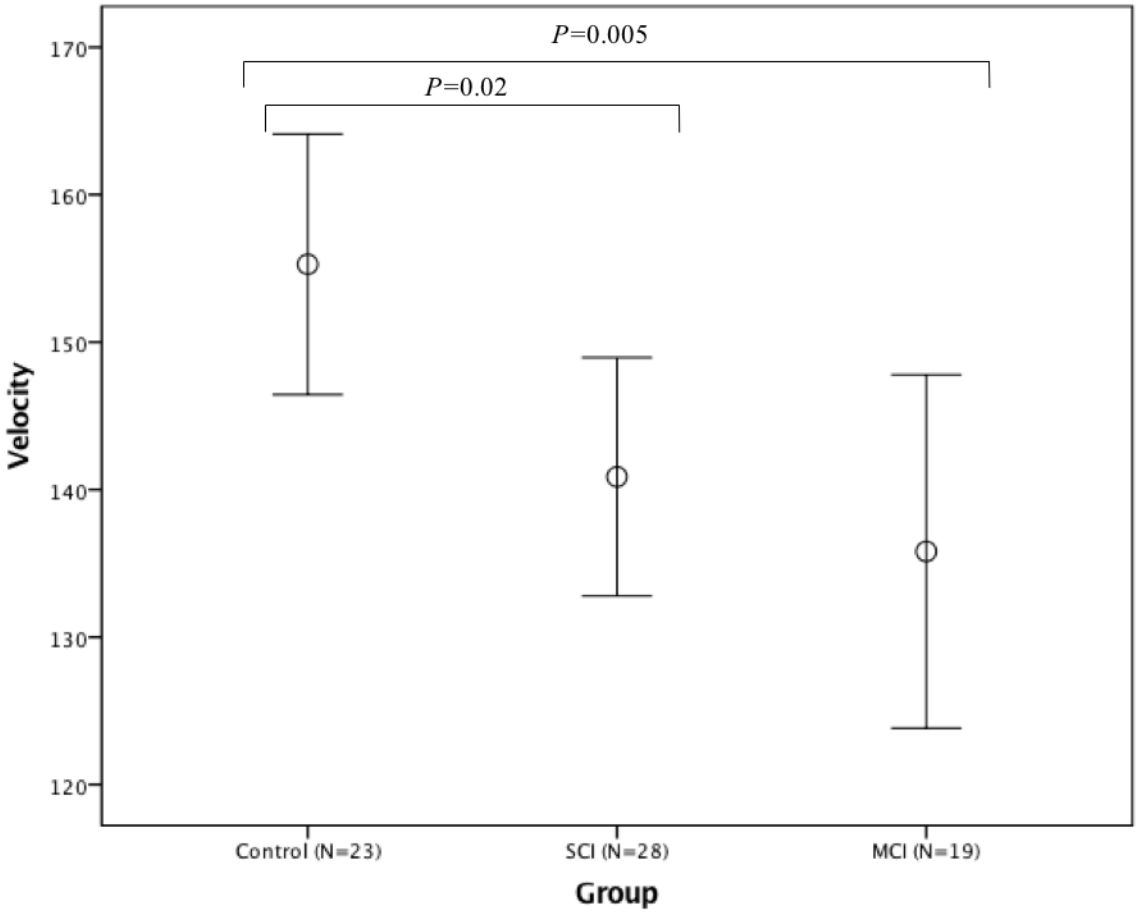

Figure 6. Difference in mean velocity at preferred gait speed

Error bars with 95% confidence intervals
SCI: Subjective cognitive impairment
MCI: Mild cognitive impairment

A multinomial logistic regression analysis was conducted with diagnostic group (0 = control, 1 = SCI, 2 = MCI) as the dependent variable, the different gait variables as the independent variables and age and gender as independent covariates. When adjusted for age and gender the Multinomial logistic regression analysis showed that velocity at preferred speed and had a statistical significance decrease in odds ratio for predicting group membership for both SCI (OR = 0.967 [95% CI 0.938 to 0.997], $P = 0.03$) and MCI (OR = 0.963, [95% CI 0.930 to 0.996], $P = 0.03$). Further, the analysis showed that velocity at fast speed could predict MCI group membership (OR = 0.973, [95% CI 0.944 to 0.998], $P = 0.03$).

WR did not significantly predict group membership for SCI or MCI at any speed, neither did step length nor cadence. Higher age predicted MCI group membership (OR = 1.07 [95% CI 1.01 to 1.21], *P* = 0.02). The results are displayed in table 6. and 7. To look for associations between age and velocity in the MCI group a partial correlation was conducted. There was no significant correlation between age and velocity at preferred speed (r = 0.11, *P* = 0.66), or fast gait speed (r =- 0.04, *P* = 0.87).

Table 5. Odds ratio for velocity at normal gait speed for SCI and MCI, compared with controls

Group	**OR (95% CI)**	***P*-value**
SCI (relative to control group)		
Age	1.03 (0.96 to 1.11)	0.38
Velocity normal gait speed	0.967 (0.938 to 0.997)	0.03
Gender	1.07 (0.31 to 3.71)	0.92
MCI (relative to control group)		
Age	1.07 (1.01 to 1.21)	0.02
Velocity normal gait speed	0.963 (0.930 to 0.996)	0.03
Gender	1.67 (0.40 to 7.01)	0.48

Odds ratio estimated from the multinomial logistic regression model

SCI: subjective cognitive impairment
MCI: Mild cognitive impairment
CI: Confidence interval
OR: Odds ratio

Table 6. Odds ratio for velocity at fast gait speed for SCI and MCI, compared with controls

Group	**OR (95% CI)**	***P*-value**
SCI (relative to control group)		
Age	1.04 (0.97 to 1.19)	0.30
Velocity fast gait speed	0.99 (0.97 to 1.01)	0.24
Gender	1.11 (0.33 to 3.70)	0.87
MCI (relative to control group)		
Age	1.11 (1.02 to 1.22)	0.02
Velocity fast gait speed	0.971 (0.944 to 0.998)	0.03
Gender	1.43 (0.33 to 6.18)	0.63

Odds ratio estimated from the multinomial logistic regression model

SCI: subjective cognitive impairment
MCI: Mild cognitive impairment
CI: Confidence interval
OR: Odds ratio

Discussion

5.1 Method

This thesis was a twofold. The literature review was first conducted to examine if there was an association between WR and cognitive impairment. Previous research has examined gait function in patients with cognitive impairment. So far, there has been paid little attention to the WR in this population. One study (Schwenk et al., 2014) included WR as one of the gait variables, but it was not the primary aim of the study. Therefore, a literature review for studies making it possible to calculate WR in cognitive impaired patients was needed. The second part of this thesis was a cross-sectional trial examining WR in pre-stages of dementia. Current evidence supports the existence of early stages of dementia (Fonseca et al., 2015), and it has been suggested that gait disorders are present even before memory impairment (Annweiler et al., 2012).

5.1.1 Part 1 – literature review

Literature search

The literature search was conducted and structured with assistance of an experienced librarian. Additionally, studies were comprehended from other sources such as references lists to prevent missing relevant studies. However, it is still possible that suitable studies could be overlooked or missed.

Study selection

The literature review's inclusion and exclusion criteria were vital for the study selection. Thus, different study designs were included in the review. The aim of the studies was of less importance because it was the only the baseline data themselves that would be included in the literature review. Follow-up data after interventions were not of interest because the data could be influenced by the intervention. The inclusion of the population had to be accounted for. In addition, the gait assessment had to be reliable and comparable between the studies.

Several measures were implemented to ensure comparability. The included studies had professional physicians using current guidelines to diagnose the participants. Studies including neurological or orthopaedic patients were excluded for the sake of not influencing the results. All of the included studies had quantitative measures of gait assessment and the assessment

was performed on an even floor level. Using data from different assessment might affect the results. The verbal instructions and the clinical setting would vary across studies and was not possible to correct for. However, all the studies used dynamic start and measured steady state walking. This excluded the deceleration and acceleration phases, making the results more comparable between studies. The number of meters walked varied between the studies. However, walking speed seems to be highly reliable in both community-dwelling and mixed setting studies (Rydwik et al., 2012) and Peters et al. (2013) stated that a 10-meter and 4-meter walk test had excellent agreement between the two tests when measuring gait speed.

One of the studies measured fast gait speed (Schwenk et al., 2014) and not preferred gait speed. However, gait speed was not an inclusion criteria because WR is independent of gait speed (Rota et al., 2011, Sekiya et al., 1996). Two of the included studies (Coelho et al., 2013, Coelho et al., 2012) did not specify directly whether they measured steady state walking. They were after consideration included in the study because they both included step length and cadence as variables, indicating that they measured steady state walking, since otherwise information on step length and cadence would not have been unambiguous. Baseline data and follow up data were used in one of the longitudinal studies (Cedervall et al., 2014) and might influence the data as these participants were overrepresented in the analysis. However, this was an observational study without intervention and the participants (n=21) deteriorated both in MMSE score and in WR during the two year follow up.

MMSE as a measure of cognitive impairment

The MMSE-score was used as measure of cognitive impairment in the literature review. Of course, there are several other criteria than the MMSE when evaluating the degree of cognitive impairment and none of the studies used the MMSE-score alone for diagnosis. One problem with the MMSE is the low dynamic performance range for normal individuals. This increases the likelihood that patients in early stages of dementia scores within the normal range (Trzepacz et al., 2015). Franco-Marina et al. (2010) claims that ceiling effects of the test are often found in MCI and occur more frequently in people with high education. This is important to consider when interpreting the results, because the MMSE might not be sensitive enough to detect cognitive impairment in patients with low impairment and high education. It was not possible to correct for cofounders like education in the literature review, as this was not reported in the studies. Studies have found that the MMSE has low sensitivity to discriminate

MCI from healthy controls (Lonie et al., 2009) and there is no firm consensus on the cut-off values used to distinguish disease severity (Gras et al., 2015). In addition, the MMSE-test was not designed to detect MCI patients (Pezzotti et al., 2008). However, the test is found to be valid, reliable and useful in quantitatively estimating the severity of cognitive impairment (Folstein et al., 1975, Petersen et al., 2001). Furthermore, MMSE was the best test for exploring associations with WR across studies as it is the most frequently used cognitive test in both clinical trials and in epidemiological studies (Franco-Marina et al., 2010).

Generalizability of the result from the literature review

Calculating new variables from published studies may provide uncertain and inaccurate results. The data were also taken from group means, and not individuals, leading to uncertain values since the mean of the individual ratios of two variables is not equal to the ratio of their means. Further, height and gender were not possible to adjust for in this part of the study since these data were not available. With higher age, women lose height more rapidly than men (Sorkin et al., 1999), and this loss is mainly in the trunk area and does not affect leg length. Therefore, correcting for body height under the assumption that leg length is proportional to body height would result in a slight overcorrection returning a somewhat larger WR. Older women with reduced WR will therefore demonstrate WR closer to normal reference values. However, an unadjusted WR still gives an indication of association between WR and cognitive impairment for both men and women. Last, the results of this study were calculated from a total of 688 participants across 16 studies. The high number of participants strengthens generalizability of the results.

5.1.2 Part two – cross-sectional study

Study design

A cross-sectional design has limitations compared to a cohort design which would allow exploring changes over time. The results do not say anything about cause-effect. However, it is rather unlikely that locomotor behaviour influence cognitive function, but more likely, that cognitive function influence locomotor behaviour. In this trial, we only included participants in early stages of dementia and healthy controls. It would be preferable to have an AD group in addition to explore gait differences in a group with more severe cognitive impairment. Because this thesis was a part of an ongoing project, we did not include patients with AD. No other

studies have investigated motor function in SCI as one group. Tangen et al. (2014) investigated balance impairment in MCI and SCI but treated both MCI and SCI as one group. This is problematic because that would make a very heterogeneous group. Treating the participants with SCI as one group is a strength in this study. The cross-sectional trial has limitations as no power analysis was conducted, which makes it difficult to assess the generalizability to the MCI and SCI population due to possible type I and type II statistical errors. The MCI and SCI group were not compared to each other because a sharp demarcation between degrees of cognitive impairment is difficult as it relies on high test sensitivity (Jessen et al., 2014) and clinical judgement (Albert et al., 2011). In addition, there is a lack of consensus of cut-off values for distinguishing diagnosis on some of the cognitive tests (e.g. MMSE) which may lead to false-positive identifications (O'Bryant et al., 2008).

Diagnostic process

There are also sources of error related to the diagnostic process, as it not only depends on objective measures but also on clinical judgment (Albert et al., 2011). The outcome relied on the correct diagnosis and categorization of the patients. Albert et al. (2011) emphasize that the distinctions between normal cognition and different degree of dementia are difficult, thus, clinical judgement is important to make these distinctions. Kluger et al. (2008) suggested that the differences in findings between studies might be a result of the different definitions concerning MCI. Furthermore, previous research concerning SCI is limited by the lack of common standards (Jessen et al., 2014). A strength of our study is that the participants were diagnosed by an experienced geriatric physician according to current established guidelines (Albert et al., 2011). The trial had strict exclusion criteria in order to rule out cofounders that could interfere with the diagnostic process and with the gait assessment. However, cofounders might still be present. For instance, if all patients with some form of somatic pain or lack of sleep were excluded it would deeply affect the sample size and power of the study, even if these were conditions that theoretically could influence gait patterns.

Gait assessment

The same observer conducted the gait assessment throughout the trial, avoiding errors due to inter-rater reliability. A stopwatch was used for time measurement and the steps of the participants were counted. One might argue that counting the steps gives a rougher measure compared to an automatic gait analysis, which could provide data that are more exact. However, Peters et al. (2013) found excellent agreement between automatic timer and

stopwatch for a 10-meter walk test when measuring velocity. The reliability and validity of a 10-meter gait assessment is also found to be high (Peters et al., 2013). Studies have also found high test-retest reliability for gait speed in elderly adults (Rydwik et al., 2012, Steffen et al., 2002). In additions, Sekiya & Nagasaki (1998) found that the WR is a reliable measure for evaluating walking patterns in pathological and aging populations. The observer for the gait assessment was not consistently blinded to the diagnosis of the participant, leading to possible bias. However, the main interest was the WR, which could not be obtained directly from the gait assessment but calculated afterword. Thus, it is not likely that the observer greatly affected the results during the gait assessment. The same verbal instructions were used for each of the participants.

5.1.3 Comparability between the literature review and the cross-sectional trial

The two different parts of this thesis investigate different aspects. Whilst the literature review only investigates the association between MMSE and WR, the cross-sectional trial explored how WR and other gait variables could predict cognitive impairment. The MMSE-scores used for cognitive assessment in the cross-sectional trial would not be suitable for analysis because the participant's cognitive function was too high to make comparison between MMSE and WR. Still, the results from the different parts of this thesis could complement each other as they explore WR for different degrees of cognitive impairment. Combining these two approaches made it possible to examine WR both in a possible pre-stage of dementia and in patients with diagnosed dementia.

5.2 Results

5.2.1 Part 1 – results from the literature review

The association between MMSE and walk ratio

Our results showed a strong correlation between MMSE–score and WR in the total test population, also when excluding the healthy controls. The association between WR and the MMSE-score is interesting because WR usually is a constant value in normal healthy populations, independent of age, sex and gait speed (Egerton et al., 2011, Rota et al., 2011, Sekiya and Nagasaki, 1998, Sekiya et al., 1996). Sekiya et al. (1996) reports that a constant WR is followed by optimal stability in temporal and spatial parameters and a minimum of attentional demand during walking. A deviation from this constant might indicate an abnormal walking pattern (Sekiya and Nagasaki, 1998). Our results also showed that the healthy controls had statistically significant higher WR compared with the impaired group. The association between WR and MMSE is of importance as it may provide information on different gait strategies in cognitively impaired patients. As the severity of cognitive impairment increased, the gait pattern seemingly changes towards decreased step length and increased cadence. This may imply that WR is not constant in patients with cognitive impairment, as it supposedly is in healthy elderly. Few prior studies have examined WR in a cognitively impaired population. One study (Schwenk et al., 2014) measured a mean WR of 0.43 in patients with mild to moderate dementia, lower than Sekiya & Nagasaki's (1996) proposed constant of 0.65. It has been reported that gait variables like step length (Gras et al., 2015, Shaw, 2002) and stride length (Nadkarni et al., 2009a, Nadkarni et al., 2009b) is lower in patients with various degree of AD compared to older healthy adults. This would yield a lower WR as long as there was no change in cadence and is consistent with our findings.

Despite the lack of research on WR in a cognitively impaired population, other studies have found associations between gait impairments and the MMSE-score. A high MMSE-score appeared as an independent protective factor for gait impairment and a low MMSE-score was associated with balance and gait impairments in patients with AD (Mazoteras Munoz et al., 2010). In addition, velocity is reported as an independent predictor of MMSE-score decline (Abellan van Kan et al., 2009). These findings support our results that there is an association between MMSE-score and gait impairments. Further, this could indicate that the severity of gait impairment vary with the degree of cognitive impairment. There is also evidence that gait

dysfunction increased the risk of cognitive impairment in elderly without known dementia (Verghese et al., 2002, Verghese et al., 2007). This is in agreement with our findings, as a lower MMSE-score associates with a lower WR.

Gait dysfunction is more frequently reported with age and it have been reported that velocity decreases with age (Bohannon and Williams Andrews, 2011, Elble et al., 1992, Salzman, 2010) and that gait variables such as stance phase and stride with seem to increase with age. Salzman (2010) suggest that this might be an adaptation to changes in sensory or motor systems to increase gait stability. Elble et al. (1992) found that velocity and stride length were reduced between 17 - 20 percent in healthy elderly compared to young adults. Bohannon & Williams (2011) reported that velocity decreases each decade after 60 to 69 years. However, age did not explain the association between WR and MMSE in our study although our participants had a mean age of 75.9.

Cognitive impairment and functional imaging

Our results support the previous reported association between cognitive decline and gait impairment. These results are compelling because it has been generally accepted that the primary motor cortex has been less involved in AD (Brodal, 2007) and that motor dysfunction mostly is present in late or terminal stages of the disease (Suva et al., 1999). It is difficult to know whether the studies in the literature review included late stages of AD due to the different diagnostic processes. There are, however, evidence suggesting that there is a preclinical phase of AD, where pathological and functional imaging changes are present before individuals become symptomatic (Fonseca et al., 2015). The association between MMSE and WR found in our study implies that gait abnormalities vary with the degree of cognitive impairment. However, it remains unclear which brain structure and related lesions are specifically involved and could explain gait impairments (Annweiler et al., 2012).

Gait impairment and falls

The results from our literature review are also interesting because other studies have found that abnormal walking patterns could predict adverse outcomes such as falls. Other gait variables like stride variability and increased time in double support have been reported as predictors of falls in elderly populations (Maki, 1997). Wolfson et al. (1990) found decreased stride length

and velocity among elderly with a history of falls. One study (Barak et al., 2006) found that elderly with a history of falls had higher cadence and shorter strides compared with non-fallers, which would indicate a lower WR. Changes in gait strategies may be a compensation for loss of gait stability, and a lower WR may be an adaption to the loss of stability. In addition, both dementia and cognitive impairment are risk factors for falls (Shaw, 2002, van Doorn et al., 2003) and they also have poorer prognosis for making a good recovery compared with cognitively normal patients (Shaw, 2002). The results from the literature review support other studies reporting that gait function may be impaired in dementia, and that interventions may be needed to avoid adverse outcomes such as falls.

5.2.2 Part 2 – results from the cross-sectional trial

Walk ratio and cognitive impairment

The cross-sectional trial showed that WR was not able to predict SCI or MCI group membership when compared to healthy controls. Normally, WR remains constant at a value around 0.65 when adjusted for height (Sekiya et al., 1996). The mean WR for the three different groups were actually somewhat lower (Table 4). WR is a small entity with small variations and it could be that using an automatic gait analysis would be more accurate for measuring this entity. It is also possible that the power in this study was too small to detect a difference between controls and the two cognitive impairment groups. The results from the literature review indicated a linear relationship between WR and MMSE-score. There was little difference in MMSE-scores among the three groups in the cross-sectional trial. This was partially because MMSE was not the only test used for diagnosing the different groups. The MCI patients could score within normal range on the MMSE but lower on the other tests in the diagnostic process. Participants with SCI had to score within normal range of the MMSE, otherwise they would be diagnosed MCI. The mean MMSE-score in the literature review was much lower for the participants with cognitive impairment (mean 22.9 ± 3.3) compared to the mean MMSE-core of the MCI group (mean 27.8 ± 2.0) and the SCI group (mean 29.6 ± 0.6) in the cross-sectional trial. Considering that both MCI and SCI have high MMSE-scores, findings in our literature review indicate that WR would also be high. The results from the literature review may also imply that a decrease in WR would present itself in later stages of the disease. One study (Wittwer et al., 2010) found that patients with mild to moderate AD had significantly lower velocity at baseline compared to healthy controls but there was no

difference in other gait variables. However, at the 12-month follow up the AD group showed a significant reduction in velocity, but also in stride length and an increase in time spent in double support. These findings may imply that gait variables might deteriorate later with disease progression.

Decreased velocity predicts MCI and SCI group membership

Our results found that there are significant differences in velocity even in the early stages of dementia compared with healthy controls. Decreased velocity at preferred gait speed predicted both MCI and SCI group membership. This is interesting because gait speed is found to be a predictor of adverse outcomes such as falls, cognitive decline and mortality (Abellan van Kan et al., 2009). These results could indicate that gait is impaired in very early stages of dementia. Current evidence still shows some inconsistency regarding various degrees of cognitive impairment and gait impairment. A cross-sectional trial (Pettersson et al., 2005) found impaired motor function in patients with very mild AD in performance-based tests, but not in MCI patients. However, they used clinical performance-based tests and did not measure gait variables directly. Studies have reported that velocity is decreased in patients with established AD compared to healthy controls, but there was no significant difference in velocity between MCI and healthy controls (Beauchet et al., 2013, Goldman et al., 1999). However, Maquet et al. (2010) found significant difference between gait speed in AD and MCI compared to controls in both single task and dual task. They also found an association between gait speed and MMSE-score. The patients with higher MMSE-score walked faster, which is interesting as our results from the literature review showed that a higher MMSE-score was associated with a higher WR.

Some evidence suggests that motor impairment can predict cognitive decline. Aggerwal et al. (2006) found that lower limb impairment, measured by performance-based tests, in MCI patients were more likely to develop AD compared with to those without lower limb impairment. A longitudinal study (Buracchio et al., 2010) followed 204 healthy subjects older than 65 years old during16 years. They found that the participants that converted to MCI had a significant decrease in gait speed compared to the non-converters. More interestingly, among the MCI converters the decrease in gait speed started 12.1 years before the onset of MCI. One cohort (Wang et al., 2006) found an association between gait speed and future cognitive decline in person with and without MCI. A decrease in gait speed increased the risk of AD and

dementia during a 6-year follow up time for both MCI and healthy controls, indicating that gait impairment could be present even before the onset of memory impairment. These studies also support our findings that decreased gait speed might be present in very early stages of cognitive impairment, not only MCI but also SCI. This is of clinical relevance as the SCI patients without objective cognitive impairment seemingly have objective gait impairments. Further, these findings might be of relevance to the diagnostic process of these patients as they may be an early marker of cognitive impairment.

Our study also showed that both decreased velocity at fast gait speed and age was predictive of MCI. Age is found to be a predictor of cognitive decline (Fonseca et al., 2015) and gait speed is known to decrease with age (Bohannon and Williams Andrews, 2011). However, it was no association between velocity and age in the MCI group. Velocity at fast gait speed is a relatively unexplored topic since most studies investigate preferred gait speed in cognitively impaired populations. However, Gras et al. (2015) found that patients with mild AD actually had significantly slower velocity at preferred gait speed, but not at fast gait speed compared with healthy adults. Another study found that higher stride-to-stride variability in stride time was a specific gait disturbance in MCI patients at fast gait speed (Beauchet et al., 2013). The MCI patients in our study were not able to increase their velocity to the same extent as the SCI group and the control group, which could imply a decline in physical capacity.

The MCI group in our study had higher velocity at preferred gait speed compared with MCI patients in previous studies (Maquet et al., 2010, Wang et al., 2006, Muir et al., 2012). The reason for this might be due to differences in diagnostic processes or inaccurate measurement methods. A review (Graham et al., 2008) found that gait speed was higher when measuring steady state walking compared with static start, but the result did not reach statistical significance. However, the mentioned studies actually measured steady state walking, making it unlikely that the difference was due to a static or dynamic test protocol. It is also important to mention that one literature review (Abellan van Kan et al., 2009) found 1.0 meter per second as a cut point for increased risk of adverse outcomes. Thus, all our participants were within normal limits of velocity at preferred gait speed. However, there were still significant differences in gait speed between cognitive impaired and controls. Abellan Van Kan et al. (2009) suggested that an acceleration of decline in velocity might be an early warning for future cognitive decline. It is possible that it is the onset of an accelerated decline in velocity that is important and not the velocity itself.

In addition to cognitive deterioration, a decrease in physical capacity may lead to further loss of independence for patients developing dementia. Walking is an important activity for mobility and participation in society (Rydwik et al., 2012). The loss of activities of daily living (ADL) capacity is a crucial problem for patients with AD (Gauthier et al., 1997) and may consequently be followed by adverse outcomes as institutionalization. Studies have found that AD patients' ability to cope with ADL could be increased by improving their physical capacity regardless of their mental capacity (Rolland et al., 2007, Santana-Sosa et al., 2008). An early detection of gait impairment can contribute to intervention and possible prevention of further impairment.

Subjective cognitive impairment and motor impairment

To the best of knowledge, no previous studies have examined motor function in participants with SCI. The fact that there is a difference in velocity in the SCI group compared to healthy controls is interesting because it is a relatively unexplored population. Our results combined with previous research supports that gait velocity may be impaired in early stages of dementia, even before any memory impairments.

Both SCI (Jessen et al., 2014) and MCI are risk factors for further cognitive decline (Jessen et al., 2014, Kluger et al., 2008). However, most of the people with such heterogeneous conditions will not deteriorate to dementia. Which of the subjects that will ultimately progress to develop dementia is unknown. It might be that differences in gait impairment can be seen between subjects that deteriorate and those who do not, not only in MCI and in SCI, but also healthy subjects.

5.3 Clinical implications

Dementia has a huge impact on function and quality of life, not just for the patients but also for the families affected. Early detection of patients with increased risk for dementia is important because it can provide early aid and interventions, such as physical interventions aimed to maintain physical independence as long as possible. As described, the onset of motor impairment might present itself years before the onset of memory impairments. Detecting decreased gait velocity might contribute to detecting these risk patients, as velocity might be a

non-specific marker of cognitive impairment. In addition, our results implied that WR decreases with cognitive impairment. Detecting gait abnormalities in dementia is important considering the possible increased risk of other adverse outcomes such as falls. A gait assessment, such as the 10-meter walk test, is also easy to perform and implement in a clinical setting.

5.4 Future research

The cross-sectional trial is a part of an ongoing cohort and further research will explore changes over time in both cognitive function and gait variables among the three groups. In addition, longer studies with larger samples are needed to support the findings of reduced velocity in patients with SCI and MCI, as there is limited resreach and some conflicting results on this topic. More research is needed to further investigate the relationship between WR and cognitive impairment not only in early stage dementia but also in established dementia. It would also be interesting to see if WR was affected by simultaneous cognitive tasks in early stages of cognitive impairment, since the dual-task-paradigm offers an approach to detect gait problems when cognition is impaired (Muir et al., 2012).

Conclusion

The results from the literature review showed that there was an association between WR and the MMSE-score in patients with various degree of dementia. This could indicate an association between the degree of cognitive impairment and WR and that movement strategies change with increased cognitive impairment. Our cross-sectional trial found no difference in WR between controls and the cognitive impairment groups, indicating that there was no difference in movement strategy between the groups. However, decreased velocity at preferred gait speed was predictive of both MCI and SCI. In addition, the MCI group walked significantly slower at fast gait speed. It seems like both SCI and MCI use the same strategy while walking as healthy controls, but for some reason, they walk slower.

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APPENDICES

Appendix 1: Approval by the local Science Ethical Committee

Appendix 2: Information letter and written consent form

Appendix 3: Approval of sub-project

Appendix 4: Search strategy

Appendix 1

Approval by the local Science Ethical Committee

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Det medisinske fakultet
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http://www.etikkom.no/REK/

Regional komité for
medisinsk forskningsetikk
Vest-Norge (REK Vest)

Bergen, 15.10.04
Sak nr. 04/9119

Professor Dag Årsland
Psykiatrisk klinikk, SiR
Armauer Hansens vei 20
4000 STAVANGER

Ad prosjekt: Demensprosjektet på Vestlandet – DEMVEST (REK Vest nr. (167.04)

Det vises til din søknad om etisk vurdering datert 10.09.04, inklusiv søknad om opprettelse av forskningsbiobank fra ansvarshavende Ole-Bjørn Tysnes (ikke datert eller underskrevet). REK Vest vurderte studien i møte den 30.09.04.

Generelt synes komiteen at søknaden var uoversiktlig med blant annet mange vedlegg, og det var vanskelig og tidkrevende å finne ut hvor de ulike vedleggene hørte hjemme. Søknaden omfatter også to studier (DEMVEST og Haugesundsstudien) og en mener at en burde ha hatt en søknad for hver av disse studiene. En slik måte å presentere studien på vanskeliggjør vurderingen. Når det gjelder vedleggene mener vi at i tillegg til at de nummereres (og den nummerering som var her var svært forvirrende samtidig som at ikke alle vedlegg var nummerert) , bør det foreligge en vedleggsliste hvor det går frem hva de enkelte vedleggene gjelder. Imidlertid er komiteens hovedinntrykk at dette kan være et nyttig prosjekt. En har ellers følgende kommentarer:

- En antar at det må utarbeides egen biobanksøknad for Haugesundstudien. Done
- Komiteen synes språket i forespørslene til deltakerne ser noe vanskelig tilgjengelig ut, sett i forhold til pasientgruppen. Hva mener prosjektleder om det?
- Hvorfor er det nødvendig med tre samtykkeerklæringer?
- Der er to forespørsler om deltakelse til de eldre, hvorav den ene er generell og den andre kun omfatter avgivelse av hjerne til obduksjon. Hvorfor har en valgt å skille?
- Opplysningene om prosedyrene etter at døden har inntrådt blir etter komiteens mening for detaljerte (vedlegg 29). Dette avsnittet bør utgå.
- Vedlegg 16: Bør være norsk variant.
- Vedlegg 31: Bør ta inn i forespørselen at pårørende blir bedt om å fylle ut et skjema om belastning for pårørende.

- Vedlegg 5B og 2D: Begrepene svekket og sviktende brukes om hverandre. En bør bruke det første begrepet da det er mer dekkende for tilstanden.

En ber om tilbakemelding.

Vennlig hilsen

Grethe Seppola Tell
leder

Arne Salbu
sekretær

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http://www.etikkom.no/REK/

Regional komité for
medisinsk forskningsetikk
Vest-Norge (REK Vest)

Bergen, 18.11.04
Sak nr. 04/9119

Professor Dag Årsland
Psykiatrisk klinikk, SiR
Armauer Hansens vei 20
4000 STAVANGER

Ad prosjekt: Demensprosjektet på Vestlandet – DEMVEST (REK Vest nr. (167.04)

Det vises til ditt svarbrev datert 22.10.04 med vedlagt revidert forespørsel (versjon 22.10.04) og søknad om opprettelse av forskningsbiobank datert 11.09.04 (ansvarshavende: Dr. Ole-Bjørn Tysnes).

REK Vest v/leder har vurdert saken. En har ikke flere merknader og studien, inklusiv søknad om forskningsbiobank er derved klaret fra denne komité sin side.

Vi ønsker dere lykke til med gjennomføringen og minner om at komiteen setter pris på en sluttrapport, eventuelt en kopi av trykt publikasjon når studien er fullført.

Vennlig hilsen

Grethe Seppola Tell
leder

Arne Salbu
sekretær

Appendix 2

Information letter and written consent form

Forespørsel om deltakelse i prosjektet "Når hukommelsen svikter"

Bakgrunn og hensikten
Hensikten med prosjektet er å kartlegge risikofaktorer forbundet med nevrologiske sykdommer og undersøke hvorfor hukommelsesvansker og andre kognitive problemer oppstår. Alzheimers sykdom og Parkinsons sykdom er sykdommer vi ønsker å fokusere spesielt på, særlig i tidlig fase.

Hvor mange med disse og andre hjernesykdommer vil utvikle kognitiv svikt? Kognisjon er summen av ulik hjerneaktivitet, slik som hukommelse, læring, minner, språk og orienteringsevne. Generelt er det økt sannsynlighet for at pasienter med en hjernesykdom vil utvikle kognitiv svikt hvis sykdommen er av kronisk natur. Kognitive vansker kan oppstå tidlig i et sykdomsforløp med få eller ingen samtidige fysiske symptomer, men det finnes også flere andre debutsymptomer utover kognitiv svikt som kan dominere.

Et overordnet mål for prosjektet er derfor å bedre diagnostikk og behandling av pasienter med hjernesykdom som allerede har eller har økt sjanse for å utvikle kognitive problemer.

Studien er et nasjonalt samarbeid der de enkelte institusjonene som deltar er ansvarlige for studien og sin del av biobanken. Deltakende institusjoner i Norge er Akershus universitetssykehus, Oslo universitetssykehus, Stavanger universitetssykehus, Helse Fonna, St. Olavs hospital og Universitetssykehuset i Nord-Norge. I tillegg deltar Gøteborgs universitet i Sverige. Prosjektleder og overordnet ansvarlig er professor Tormod Fladby ved Akershus universitetssykehus.

Hva innebærer studien
Du blir forespurt fordi du opplever å ha vansker med hukommelsen eller har en annen nedsatt kognitiv funksjon, eller har en tilstand som er forbundet med risiko for å utvikle dette. Du kan også bli forespurt om å delta som kontrollperson, dersom du er ektefelle eller samboer med noen som har nedsatt kognitiv funksjon.

For deg som pasient vil deltakelse i prosjektet innebære analyser av blod og ryggmargsvæske, tester av kognitiv funksjon og bilder av hjernen (MR). Utover dette ønsker vi å kartlegge ulike kroppslige symptomer ved en grundig legeundersøkelse samt eventuelle depressive plager, søvnvansker og viktige funksjoner i dagliglivet for øvrig. Samtidig som de diagnostiske prøvene blir tatt, blir det tatt ekstra rør med ryggmargsvæske og blod som blir lagret i en forskningsbiobank. Dersom det blir restmateriale etter diagnostisk analysering, vil dette restmateriale også bli lagret i biobanken. Det vil bli tatt blodprøver for analyse av arvematerialet (DNA og RNA). Disse analysene vil ikke ha noen diagnostisk verdi for deg som deltaker og det vil derfor ikke bli gitt genetisk veiledning.

For noen pasientgrupper vil det være aktuelt å tilby utvidede rutineundersøkelser; Nevropsykologisk undersøkelse som innebærer testing av kognitive funksjoner (f. eks hvordan man husker eller konsentrerer seg ved forskjellige oppgaver) og skanning av hjernen som kartlegger aktivitetsfordelingen i ulike deler av hjernen (PET). Redusert aktivitet forteller noe om nedsatt eller endret hjernefunksjon. PET-skanning tar omtrent 20 minutter, og medfører ikke risiko eller ubehag utover det som er vanlig ved en vanlig hjerne skanningsundersøkelse (CT/MR). Søvnregistrering vil være aktuelt for pasienter med spesifikke søvnforstyrrelser. Dette foregår ved såkalt polysomnografi over natten hvor elektroder vil avlese hjerne- og muskelaktivitet.

For deg som er kontrolldeltaker vil eventuell deltakelse medføre blodtrykksmåling, blodprøvetaking, enkel testing av kognitive funksjoner, ovennevnte hjerneskannings undersøkelse (MR og PET) og eventuelt en ryggmargsvæskeundersøkelse. Denne undersøkelsen kan for noen oppleves som en ulempe, men en kontrolldeltaker kan selv velge å delta i studien, med eller uten ryggmargsvæskeundersøkelse. Det er liten risiko for bivirkninger og ubehagelige følgetilstander som forbigående hodepine mv. i denne aldersgruppen (kun 2.6 % rapporterer mild hodepine etter punksjon, Zetterberg et al., 2010). Muntlig informasjon om gjennomførelsen av ryggmargsvæskeundersøkelse vil bli gitt av studielege. Det vil bli tatt blodprøver for analyse av arvematerialet (DNA og RNA). Disse analysene vil ikke ha noen diagnostisk verdi for deg som deltaker og det vil derfor ikke bli gitt genetisk veiledning.

Fordelen med å inkludere friske kontroller er at deltakelsen kan gi økt forståelse av nevrologiske prosesser i normal aldring. Hittil har det vært mange studier som har inkludert pasienter med kognitiv svikt, men få som kan sammenligne med et representativt kontrollmateriale.

Mellom to til tre år etter at du ble inkludert i forskningsprosjektet, vil vi innkalle deg som deltar, som pasient eller kontrolldeltaker, inn til en oppfølgingsundersøkelse. I denne undersøkelsen vil det bli gjennomført ny hjerne skannings undersøkelse (MR/PET), samt ny kartlegging av kognitive funksjoner og nye blodprøver. Dette vil også bli en klinisk kontrolltime der vi vurderer utviklingen av tilstanden, og om det eventuelt er noe i behandlingen som bør endres.

Mulige fordeler og ulemper
Hvis du velger å bli med i prosjektet, vil du få en grundigere utredning enn det som vanligvis er tilgjengelig, og du vil også bli fulgt opp med kontrollundersøkelser av fagpersoner med spisskompetanse innen dette feltet. Dette medfører at du da må gjennomgå flere undersøkelser enn ellers. Analyser i blod og ryggmargsvæske, tester av kognitiv funksjon og bilder av hjernen (MR/PET), kan i fremtiden bidra til bedre diagnostikk og bedre behandlingsmuligheter. Ved behov vil du få tilbud om behandling eller henvisning til andre spesialister.

Hva skjer med prøvene og informasjonen om deg?
Prøvene tatt av deg og informasjonen som registreres om deg, vil kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres. Etter prosjektets slutt vil materiale og opplysninger bli destruert/slettet etter interne retningslinjer innen prosjektslutt 31.12.2025

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling.
Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte din lokale kontaktperson eller prosjektleder Tormod Fladby ved Nevroklinikken, Akershus universitetssykehus på telefon 67 96 95 27.

Personvern
Opplysninger som registreres om deg er journalopplysninger fra gjeldende utredning og/eller behandling og analyseresultater fra forskningsprosjektet. Alle personopplysninger er

underlagt taushetsplikt og behandles i henhold til datatilsynets retningslinjer. Du har rett til innsyn i hvilke opplysninger som er registrert om deg. Du kan kreve å få slettet opplysningene om deg dersom du ønsker det. Databehandlingsansvarlig er forskningsansvarlig ved den enkelte institusjon.

Biobank
Ryggmargsvæske- og blodprøvene som blir tatt vil bli lagret i en nasjonal forskningsbiobank (DDI - dementia disease initiative). Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet inngår i biobanken og fritt kan sendes mellom institusjonene som deltar i prosjektet. Prosjektleder Tormod Fladby er ansvarshavende for forskningsbiobanken. Biobanken planlegges å vare til 31.12.2025. Etter dette vil materiale bli destruert og opplysninger vil bli anonymisert slik at det ikke lenger vil være mulig å knytte deg til opplysningene, dette etter interne retningslinjer.

Utlevering av materiale og opplysninger til andre
Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at avidentifiserte prøver og avidentifiserte opplysninger er tilgjengelig for alle samarbeidspartnere i denne multisenterstudien. Dersom materiale sendes til utlandet (Gøteborg, Sverige) vil dette alltid skje i tett samarbeid med og under ledelse av den norske prosjektledelsen.

Rett til sletting av prøver
Hvis du sier ja til å avgi biologisk materiale til biobanken, har du rett til å få innsyn i hvilke prøver som er registrert på deg. Dersom du ønsker å trekke tilbake samtykket kan du kreve å få destruert innsamlede prøver, med mindre materialet allerede er inngått i analyser er brukt i vitenskapelige publikasjoner.

Økonomi
Studien er finansiert gjennom forskningsmidler fra Norges Forskningsråd.

Forsikring
Ved deltakelse i studien er deltakelsen dekket av norsk pasientskadeerstatning.

Informasjon om utfallet av studien
Du som deltaker har rett til å få informasjon om utfallet/resultatet av studien. Dersom du ønsker det, kan du få opplyst hvilke publikasjoner som er skrevet på grunnlag av prosjektet.
Det er opprettet en hjemmeside for prosjektet der resultater vil bli presentert etter hvert som de blir publisert:

https://sites.google.com/site/demdisini/

Samtykke til deltakelse i studien

"Når hukommelsen svikter"

Jeg har mottatt skriftlig og muntlig informasjon angående studien
"Når hukommelsen svikter"

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert av lege eller sykepleier)

Appendix 3

Approval of sub-project

Re: DDI og master

Aarsland Dag Legg til i Kontakter 19.02.2015 Dokumenter

Til: mari k.knapstad

1 vedlegg (55,5 kB) Outlook.com Aktiv visning

Hei ja det er helt greit.
Her er godkjenning fra REK
Lykke til

Hilsen fra HOvden ;-)

Dag

2015-02-18 16:54 GMT+01:00 mari k.knapstad <mariknap@hotmail.com>:

> Hei Dag. Har hatt møte med veiledere, og så lenge studier kommer opp og går innen rimelig tid forstetter jeg som først tenkt med å "låne" pasienter fra Arne. De har sett samtykke skjemaet for DDI og mener at min test (en 10m lang gangtest) vil kunne falle innunder dette samtykket (spesielt siden TUG allerede faller innunder dette samtyket).
>
> Det jeg trenger er en skriftlig bekreftelse fra deg (bare på epost) om at mitt prosjekt ligger innefor det som allerede er godkjent.

Appendix 4

Search strategy

Search strategy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
13. March 2015

1 (((step length or stride length) and (cadence or step frequency)) or ((gait or walk) adj1 (speed or velocity)) or walk ratio).tw. (3382)
2 exp Dementia/ (123008)
3 Mild Cognitive Impairment/ (2687)
4 (dement* or alzheimer* or mild cognitive impairment).tw. (143746)
5 2 or 3 or 4 (176151)
6 1 and 5 (142)

7 (walking or gait or walk).tw. (82535)
8 Gait/ or Walking/ (35194)
9 7 or 8 (91539)
10 5 and 9 (2376)

Database: (Ovid) Embase <1974 to 2015 March 12>
13. March 2015

1 (((step length or stride length) and (cadence or step frequency)) or ((gait or walk) adj1 (speed or velocity)) or walk ratio).tw. (4567)
2 exp dementia/ (240302)
3 mild cognitive impairment/ (11231)
4 (dement* or alzheimer* or mild cognitive impairment).tw. (190050)
5 2 or 3 or 4 (272867)
6 1 and 5 (233)

Database: Ovid AMED (Allied and Complementary Medicine) <1985 to March 2015>
13. March 2015

1 (((step length or stride length) and (cadence or step frequency)) or ((gait or walk) adj1 (speed or velocity)) or walk ratio).tw. (887)
2 exp dementia/ (2200)
3 mild cognitive impairment/ (13)
4 (dement* or alzheimer* or mild cognitive impairment).tw. (2920)
5 2 or 3 or 4 (2920)
6 1 and 5 (8)

Database: Ovid PsycINFO <1806 to March Week 2 2015>
13. March 2015

1 (((step length or stride length) and (cadence or step frequency)) or ((gait or walk) adj1 (speed or velocity)) or walk ratio).tw. (694)
2 exp dementia/ (55715)
3 (dement* or alzheimer* or mild cognitive impairment).tw. (74190)
4 2 or 3 (75209)
5 1 and 4 (66)

Comment: Mild cognitive impairment is not a mesh term I PsycINFO. Mesh term «Cognitive impairment» is to wide.

Cochrane library (Wiley)
13. March 2015

#1 (((step length or stride length) and (cadence or step frequency)) or ((gait or walk) near/1 (speed or velocity)) or walk ratio):ti,ab,kw (Word variations have been searched) 1957
#2 (dement* or alzheimer* or mild cognitive impairment):ti,ab,kw (Word variations have been searched) 9394
#3 #1 and #2 34

PEDRO:
13 of March 2015
(((step length or stride length) and (cadence or step frequency)) or ((gait or walk) near/1 (speed or velocity)) or walk ratio)

In PEDro:
step length AND cadence

stride length AND cadence

step length AND step frequency

stride length AND step frequency

gait speed

gait velocity

walk speed

walk velocity

walk ratio

combined with

dement* or alzheimer* or mild cognitive impairment)

Combinations:
"step length" cadence dement*

"step length" cadence alzheimer*

"step length" cadence "mild cognitive impairment"

stride length AND cadence dement

stride length AND cadence alzheimer*

stride length AND cadence "mild cognitive impairment

step length AND step frequency dement*
step length AND step frequency alzheimer*
step length AND step frequency "mild cognitive impairment"

stride length AND step frequency dement*
stride length AND step frequency alzheimer*
stride length AND step frequency "mild cognitive impairment"

gait speed dement* (3)
gait speed alzheimer*
gait speed "mild cognitive impairment" (1)

gait velocity dement*(1)
gait velocity alzheimer*
gait velocity "mild cognitive impairment"

walk speed dement*

walk speed alzheimer*
walk speed "mild cognitive impairment"

walk velocity dement*
walk velocity alzheimer*
walk velocity "mild cognitive impairment"

walk ratio dement* (1)
walk ratio alzheimer*
walk ratio "mild cognitive impairment"

Total 5