UPPSALA UNIVERSITET

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1765

Timed Up-and-Go Dual-Task Tests for Early Detection of Dementia Disorder

HANNA BOZKURT ÅHMAN

ACTA UNIVERSITATIS UPSALIENSIS UPPSALA 2021

ISSN 1651-6206
ISBN 978-91-513-1270-5
URN urn:nbn:se:uu:diva-451233

Dissertation presented at Uppsala University to be publicly examined in Defence via Zoom, Wednesday, 13 October 2021 at 09:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish. Faculty examiner: Professor Jorunn Helbostad (Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway).

Abstract
Åhman, H. B. 2021. Timed Up-and-Go Dual-Task Tests for Early Detection of Dementia Disorder. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1765. 75 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-1270-5.

Dementia constitutes an important and growing public health concern. There is a need for new, simple, and inexpensive methods to detect dementia disorders early in the disease progression. For this purpose, dual-tasking, i.e., simultaneous performance of two tasks, has been proposed.

The overall aim of this thesis was to explore if Timed Up-and-Go (TUG) dual-task (TUGdt) tests can be used for early detection of dementia disorder. Cross-sectional and longitudinal designs were used. Participants were recruited when undergoing memory assessment at memory clinics (patients) and through advertisements (controls). The TUGdt tests involved TUG combined with the cognitive tasks a) naming animals (TUGdt NA) and b) reciting months in reverse order (TUGdt MB). The tests were video recorded. Test outcomes were calculated using time scores and/or verbal performances. Additionally, the data collection comprised clinical tests and medical record reviews.

Paper I included 90 patients who had carried out lumbar puncture as part of the memory assessment. By Spearman's rank correlation, the TUGdt NA test outcomes "number of animals" and "animals/10 s" correlated negatively to the cerebrospinal fluid biomarkers t-tau and p-tau, suggesting that neurodegeneration is associated with dual-task performance. In **Paper II**, 298 patients and 166 controls participated. Logistic regression models showed that "animals/10 s" and "months/10 s" discriminated significantly between dementia, mild cognitive impairment (MCI), subjective cognitive impairment (SCI), and controls. Thus, TUGdt testing could be useful in diagnostic assessments. **Paper III** involved 172 patients, initially diagnosed with MCI or SCI, for whom diagnostic information was available after 2.5 years. Logistic regression showed inverse associations between "animals/10 s" and dementia incidence, particularly for patients <72 years (median age). For these younger patients, the predictive capacity of "animals/10 s" was excellent. Hence, TUGdt NA has potential for predicting dementia from SCI or MCI, particularly among younger patients. **Paper IV** included 166 controls for presenting TUGdt reference values in age- and sex-specific groups, and 43 controls for test-retest reliability. Reference values were calculated with quantile regression and may be useful in clinic and research. Intra-class correlation coefficients showed excellent reliability for time scores, while the other test outcomes were poor to good. "Animals/10 s" showed fair to good reliability despite being a ratio of other variables, which negatively affects reliability.

In summary, TUGdt NA has the potential to be used for early detection of dementia disorder, and the test outcome "animals/10 s" merits further evaluation.

Keywords: Dual-task, dementia, mild cognitive impairment, subjective cognitive impairment

Hanna Bozkurt Åhman, Department of Public Health and Caring Sciences, Geriatrics, Box 609, Uppsala University, SE-75125 Uppsala, Sweden.

ISSN 1651-6206
ISBN 978-91-513-1270-5
URN urn:nbn:se:uu:diva-451233 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-451233)

List of Papers

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

I. Åhman HB, Giedraitis V, Cedervall Y, Lennhed B, Berglund L, McKee KJ, Kilander L, Rosendahl E, Ingelsson M, Åberg AC. (2019) Dual-Task Performance and Neurodegeneration: Correlations Between Timed Up-and-Go Dual-Task Test Outcomes and Alzheimer's Disease Cerebrospinal Fluid Biomarkers. *J Alzheimers Dis*, 71(s1):75–83

II. Åhman HB, Cedervall Y, Kilander L, Giedraitis V, Berglund L, McKee KJ, Rosendahl E, Ingelsson M, Åberg A. C. (2020) Dual-task tests discriminate between dementia, mild cognitive impairment, subjective cognitive impairment, and healthy controls – a cross-sectional cohort study. *BMC Geriatr*, 20(1): 258

III. Åhman HB, Berglund L, Cedervall Y, Kilander L, Giedraitis V, McKee KJ, Ingelsson M, Rosendahl E, Åberg AC. (2020) Dual-Task Tests Predict Conversion to Dementia – A Prospective Memory-Clinic-Based Cohort Study. *Int J Environ Res Public Health*, 17(21):8129

IV. Åhman HB, Berglund L, Cedervall Y, Giedraitis V, McKee KJ, Rosendahl E, Åberg AC. (2021) Timed “Up & Go” Dual-Task Tests: Age- and Sex-Specific Reference Values and Test-Retest Reliability in Cognitively Healthy Controls. *Phys Ther*, Epub ahead of print, https://doi.org/10.1093/ptj/pzab179

Contents

Abbreviations

APOE ε4	Apolipoprotein E ε4
$A\beta_{42}$	Amyloid beta 42
AD	Alzheimer's disease
ADL	Activities of daily living
CI	Confidence interval
CSF	Cerebrospinal fluid
CT	Computerized tomography
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ICC	Intraclass correlation coefficient
ICD-10	International Classification of Diseases, Tenth Revision
MCI	Mild cognitive impairment
MCR	Motoric cognitive risk syndrome
MDC	Minimal detectable change
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
ROC	Receiver operating characteristic
p-tau	Phosphorylated tau
SEM	Standard error of measurement
sOR	Standardized odds ratio
SCI	Subjective cognitive impairment
t-tau	Total tau
TUG	Timed Up-and-Go
TUGdt	Timed Up-and-Go dual-task
TUGdt NA	Timed Up-and-Go dual-task Naming Animals
TUGdt MB	Timed Up-and-Go dual-task Months Backwards
UDDGait™	Uppsala-Dalarna Dementia and Gait

Introduction

New methods to detect dementia disorders at an early stage in the disease progression are sought after [1]. Dual-task testing, i.e., tests involving concurrent performance of two tasks, has been proposed to be useful in this regard [2, 3]. In recent years, several different dual-task test designs have been explored but, at present, no consensus has been reached regarding how such a test should optimally be designed for detection of dementia disorders [4].

This thesis involves evaluation of different aspects of measurement properties and presentation of normative reference for two versions of the Timed Up-and-Go dual-task (TUGdt) test. The results contribute to the knowledge of how dual-task testing could be used for early detection of dementia disorder.

Dementia disorders

Prevalence and incidence

According to the World Health Organization, approximately 50 million people live with dementia worldwide, and this number is expected to increase to 152 million by 2050 [5].

Globally, the prevalence of dementia is 5–8% in those aged ≥ 60 years [6]. The prevalence is generally reported higher among women than men, which is largely explained by women's longer average life expectancy [7]. Every year, almost 9.9 million new cases of dementia are anticipated worldwide [8]. The rapid increase is driven by population aging in low- and middle-income countries [5]. In high-income countries the prevalence and incidence of dementia appear to remain stable or be decreasing, possibly due to amelioration of public health [9, 10]. In Sweden, 130,000–150,000 individuals live with dementia, and every year 20,000–25,000 individuals receive such a diagnosis [11].

Risk factors

The strongest known risk factor for dementia is age, with prevalence doubling every 5 years after the age of 65 [6]. The age of 65 years and above is often used to define "older adults" [12], so also in this thesis. Although age is a strong risk factor, dementia is not necessarily a consequence of aging and does not only affect older people [8]. Other recognized risk factors for dementia are

lifestyle-related factors such as mid-life hypertension, low educational level, diabetes mellitus, and tobacco use [7-9]. Further potential risk factors include physical inactivity, obesity, unbalanced diets, alcohol misuse, mid-life depression, social isolation, cognitive inactivity [8], and non-modifiable genetic risk factors, e.g., apolipoprotein E ε4 (*APOE* ε4) [7].

Diagnostic criteria and classification of diagnoses

In this thesis, dementia is defined according to the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) [13], since these criteria were used by the memory clinics involved. The more recent edition of the manual (DSM-V), in which dementia is denoted as a "major neurocognitive disorder," was thus not used. To classify specific diagnoses, the International Classification of Diseases, Tenth Revision (ICD-10) was used [14].

Definition of dementia according to the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) [13]

A1. Memory impairment

A2. At least one of the following:

- Aphasia
- Apraxia
- Agnosia
- Disturbance in executive functioning

B. The cognitive deficits in A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning

C. The cognitive deficits do not occur exclusively during the course of delirium

Types of dementia disorders – symptoms and treatment

Dementia is an umbrella term for several disorders caused by different pathophysiological processes, describing a stage at which the disease has caused symptoms that affect activities of daily living (ADL). The most common dementia disorders are: Alzheimer's disease (AD) (50–75% of cases), vascular dementia (20%), dementia with Lewy bodies (5%) and frontotemporal dementia (5%) [15]. Alzheimer's disease is generally a slowly developing neuro-

degenerative disease characterized by a progressive loss of synapses and neurons, with accumulated amyloid-beta (Aβ) plaques and neurofibrillary tangles containing tau proteins [16]. In the early stages forgetfulness, reduced ability to form new memories for recent events and to find right words, along with impairments in problem-solving and decision-making are common symptoms [15]. Vascular dementia can be caused by both large- and small-vessel disease. The symptoms and time course differ due to the variability of lesions and locations [17]. Dementia with Lewy bodies is neuropathologically characterized by deposition of alpha-synuclein in the form of Lewy bodies and Lewy neurites. The cognitive deficits develop gradually and are most noticeable in attention, visuospatial, and executive functioning [18]. Frontotemporal dementia is characterized by atrophy of the frontal and temporal lobes, with a variable protein pathology. The clinical subtypes of frontotemporal dementia correspond to the specific areas of brain atrophy [19]. The pathophysiological processes of the described dementia disorders may overlap significantly [15]. When the underlying pathology causing dementia is not known, the term "unspecified dementia" is used [14].

There are ongoing intense research efforts to find treatments that could prevent, delay onset, or slow the progression of AD by targeting different mechanisms [20]. Recently, a disease-modifying drug aiming at reducing Aβ plaques was approved for AD treatment in the United States. Although it has been shown that the drug successfully reduces the plaque burden, the clinical benefits are not yet established [21]. The only available pharmacological treatment for dementia in Sweden today aims for symptomatic relief [7]. To improve cognitive function – primarily for patients with AD – acetylcholinesterase inhibitors and memantine are the registered medications [15]. Supportive treatments for physical and psychosocial health are usually considered essential [7, 9].

Cognitive impairment preceding dementia

Possible stages preceding dementia, especially AD, have been identified [22, 23]. Subjective cognitive impairment (SCI) and mild cognitive impairment (MCI) are the cognitive disorder diagnoses that may be forerunners of dementia disorders. Figure 1 illustrates changes in cognitive function over time, in which SCI and MCI precede dementia. These cognitive disorders are not distinctly separated from each other from a clinical viewpoint, neither in time nor in symptoms. Each diagnosis may last up to decades. Although SCI and MCI are associated with future dementia incidence, the cognitive function may – at any point of time during these stages – cease to decline and remain stable (B and D in Fig. 1) or ameliorate to normal levels (A and C in Fig. 1). It should be noted that the trajectory of cognitive function in normal aging does not

necessarily decline as depicted in the figure, since there are considerable individual differences [24].

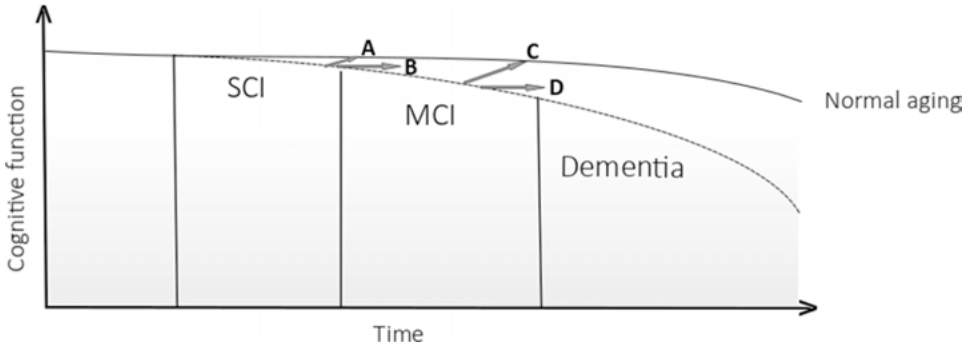

Figure 1. Diagram illustrating possible changes in cognitive function over time in normal aging and in stages of subjective cognitive impairment (SCI), developing into mild cognitive impairment (MCI), and further to dementia. The arrows represent possible trajectories: A) reversion from SCI to normal cognition, B) remaining stable in the SCI stage, C) reversion from MCI to normal cognition, and D) remaining stable in the MCI stage. The figure was inspired by Sperling 2011 [25].

Subjective cognitive impairment

The earliest stage in a potential dementia development, SCI, denotes a subjective experience of cognitive decline, without the presence of cognitive impairment as indicated by established tests [23]. The prevalence of SCI is reported to be between 17% and 50% among older adults [26, 27]. The large variation in prevalence is most likely explained by different interpretations of the diagnostic criteria, such as controlling for the presence of an objective cognitive impairment [23, 27]. At memory clinics, approximately one fourth of new assessments result in SCI [28]. Subjective cognitive impairment as a foregoing stage before MCI and dementia is considered to constitute subtle changes in cognition that the individual perceives before the impairment is detectable objectively [29]. However, a subjective cognitive decline is in many cases caused by other underlying conditions, such as depression or psychosocial stress, and may not be related to a progressive cognitive impairment leading to dementia [30-32]. Overall, in 5 years, around 11% of cases with SCI develop dementia [33]. The progression to dementia may occur without any intermediate diagnosis; however, the deterioration is usually slow, with MCI being the transitional phase between SCI and manifest dementia. The annual conversion rate from SCI to MCI is approximately 7% [33].

Mild cognitive impairment

As opposed to SCI, the diagnosis of MCI entails an objective, measurable cognitive impairment. The impairment is greater than what could be expected in relation to age and education, but without affecting the ability to perform

ADL [22]. The objective measurement of the cognitive impairment is generally based on cognitive test scores of 1.0–1.5 standard deviation below adjusted norm scores on at least one test of memory, executive functioning, language, attention, or visuospatial skills [34]. Subtypes of MCI have been identified, which depend on which cognitive domain is affected: amnestic MCI single-domain, amnestic MCI multiple-domain, non-amnestic MCI single-domain, and non-amnestic MCI multiple-domain [35].

The overall prevalence of MCI is approximately 16% in individuals between 70 and 89 years [36], and the prevalence increases with age [37, 38]. No sex differences have been shown in the prevalence of MCI [37, 39]. The annual conversion rate from MCI to dementia is between 10% and 15% in clinical samples [40], and it is estimated that eventually half of all patients with MCI will convert to dementia [41]. Thus, there are a considerable number of patients with MCI who do not progress to dementia but remain stable over time or revert to normal cognition [42]. The reasons for disease progression or reversion have been explored in different studies and may be explained by demographic and clinical factors, such as age, gender, educational level, *APOE ε4*, hypertension, and depressive symptoms [43, 44].

At present, there are no specific pharmacological treatments for cognitive disorders at the stages preceding dementia [45]. Since these disorders may be related to a range of neurologic and psychiatric conditions, the treatment of underlying causes, e.g., depression, may influence the cognitive symptoms. Additionally, multi-domain interventions addressing lifestyle-related risk factors may benefit cognition in individuals with an elevated risk of dementia [46].

Memory assessment

Base and extended memory assessment

Due to the complexity of the diagnostic criteria, no isolated finding or test result is sufficient for a diagnosis of dementia, MCI, or SCI. A multifaceted memory assessment is thus required, from which the findings result in a diagnosis [13, 18, 19, 22, 47, 48].

When an individual's cognitive decline is suspected to be caused by a dementia disorder, the Swedish National Board of Health and Welfare recommends that a base memory assessment be carried out [11]. The aim of a base memory assessment is to determine the cause of the cognitive symptoms, leading to – or ruling out – a diagnosis. The base memory assessment is also intended to determine how to minimize or compensate for the patient's loss of functions [11].

A base memory assessment implies a careful evaluation of the patient's history including interviews with the patient and – whenever possible – a close

relative, physical and psychological examinations, cognitive testing, structural brain imaging with either computerized tomography (CT) or magnetic resonance imaging (MRI), and structured assessment of ADL [11]. The cognitive testing consists primarily of the Mini Mental State Examination (MMSE) and the Clock Drawing test. The MMSE is used for detection of impairment by evaluating cognitive abilities such as orientation, attention, recall, and language [49]. Even though it is well established and frequently used in many countries, the diagnostic and predictive value of MMSE has been questioned [50]. For example, MMSE does not involve assessment of executive functions [50], and its validity is low for detecting mild degrees of impairment [51]. As a stand-alone test, MMSE is not sensitive in identifying future dementia incidence among MCI patients [52]. The Clock Drawing test is recommended to be carried out as a complement to MMSE in a base memory assessment [11]. The Clock Drawing test involves cognitive abilities such as visuospatial skills, on-demand motor execution, visual memory and reconstruction, and executive function [53]. It is a sensitive tool to detect severe cognitive impairment, but it lacks sensitivity when the impairment is mild [54]. Brain imaging is used to detect structural changes, e.g., infarcts, white matter lesions, and atrophies, and can thus be an aid to a base memory assessment when differentiating between dementia diagnoses [7].

The ADL is primarily assessed by interviews with the patient and his/her close relative, and should include consideration of previous abilities and current comorbidities [11]. Determining whether or not a decline in ADL is related to the cognitive disorder is an essential part of the base memory assessment, since it is one of the criteria that separate dementia from MCI.

If the base memory assessment is insufficient to make a diagnosis, or if there is a need for more detailed information of the symptoms and underlying biochemical abnormalities, the Swedish National Board of Health and Welfare recommends an extended memory assessment [11]. The extended memory assessment comprises methods such as neuropsychological testing covering various cognitive domains, lumbar puncture for cerebrospinal fluid (CSF) analysis, positron emission tomography (PET) to measure glucose metabolism, and – more rarely – single-photon emission computed tomography (SPECT) to measure dopamine transport and blood flow to the brain [11]. These methods are generally only available at specialized memory clinics and are all invasive, expensive, and/or time-consuming [1].

There are numerous neuropsychological tests available for an extended memory assessment, and the choice depends on which specific cognitive domain needs further evaluation. For example, tests of verbal fluency, particularly semantic fluency, in which the patient names as many different animals as possible in 60 seconds, has shown a high discriminative and predictive capacity for AD [55].

A CSF analysis may be performed in order to differentiate AD from other disorders. A low concentration of amyloid beta 42 ($A\beta_{42}$) combined with high

total tau (t-tau) and phosphorylated tau (p-tau) is characteristic for AD [56] and has a sensitivity and specificity of around 90% in the prediction of future conversion to AD dementia among patients with MCI [57]. Analysis of CSF biomarkers, as well as PET and SPECT scans may reveal AD pathology several years before the onset of symptoms [57, 58]. Recently, a new blood-based test involving the measurement of tau phosphorylated at threonine 181 (tau181) in plasma has shown results with a diagnostic accuracy for AD that is comparable to CSF analysis and PET scan [59]. However, this method is still being evaluated and is not yet available for clinical use.

In summary, memory assessments involve complex processes. Characteristic traits in cognitive function, brain imaging and biomarkers, are used by the geriatrician as pieces of a puzzle to identify a specific disorder. Additionally, since it is common that patients with mild symptoms seek health care for memory assessment, the prediction of how the impairment will develop is at least as important as determining a current diagnosis. Presently, the most effective way of predicting dementia in MCI patients appears to be reached by combining results from clinical cognitive tests, CSF biomarker analysis, and/or brain imaging [60, 61]. Regular re-evaluations are recommended to track disease progression [11].

Mobility and cognition

The term *mobility* has different meanings depending on the context [62]. The International Classification of Functioning, Disability, and Health, defines mobility as "moving and changing body position or location or by transferring from one place to another**,** by carrying, moving or manipulating objects, by walking, running or climbing, and by using various forms of transportation" [63]. In this thesis, mobility refers to movements – i.e., motor tasks – executed by the individual's own body. *Cognition* involves processes and components such as "perception, attention, reasoning, learning, language, memory and decision-making that gather, organize and convert information into knowledge and integrate it in existing experience" [64]. Different aspects of mobility (e.g., walking and chair stands) and of cognition (e.g., memory and executive function) have been shown to be interrelated [65].

Mobility and cognition in aging

Human aging generally involves mobility impairment due to anatomic and functional changes in neuromuscular, sensory, and cognitive systems [66]. However, there are considerable differences between individuals, and functional ability may remain unaffected by age [66]. Similarly, the effect of aging on cognitive function is largely individual [24]. Converging evidence has shown that mobility and cognition are interrelated, and more so with higher

age [65, 67, 68]. This interrelation is explained by shared brain circuits that are vulnerable to multiple age-related changes [67, 69]. Both mobility and cognition are compound concepts, and the relationships between their subdomains are not yet fully understood [65]. Gait (or walking) is the most thoroughly studied motor task in this context. In contrast with the general perception 20 years ago, walking should not be regarded as an automated task. Walking requires higher cortical involvement such as executive function and attention [70]. Habitual gait speed – the most common measure of walking ability – has been shown to decrease with age from as early as the fourth decade [71]. Other gait disturbances, such as shorter step length and wider step width, are also associated with aging [68, 72].

The mobility test Timed Up-and-Go

The relationship between mobility and cognition has been studied through various functional tests [73]. One of the best-established tests to assess functional mobility among older adults is the Timed Up-and-Go (TUG) [74]. The TUG involves timing a consecutive sequence of motor tasks, in which the test person starts from sitting in a chair, stands up when given a signal, walks three meters, turns around, walks back to the chair and sits down again. The TUG can be regarded as one compound motor task that comprises separate subtasks, all of them motorically demanding [75-77]. Because the TUG involves several subtasks, processing of instructions, and planning of the performance, the test implicates higher demands on cognitive functions than only walking [78]. In cross-sectional studies, a slower performance of TUG has shown to be associated with the following cognitive domains: global cognition [79], executive function [76, 78], memory [78, 80], attention [78], and visual-motor performance [81]. When analyzed separately, the durations of transitions and turning during TUG are associated with executive functions [82]. Turning additionally depends on processing speed [82] and visual-spatial processing [77]. The time to perform the entire TUG test is in general affected by age in cognitively healthy adults from the age of 60 years [83, 84].

Mobility and cognitive disorders

Mobility impairments and cognitive disorders often co-exist in older adults [85, 86]. There have been few studies investigating whether there are differences in mobility in individuals with SCI compared with cognitively healthy individuals. One cross-sectional study has shown that mobility, as measured by TUG time score, differed significantly in comparisons between female carriers of *APOE* ε4 with SCI and healthy controls [87]. However, no differences in time scores were seen between the entire SCI group and healthy controls [87]. Similarly, gait parameters such as stride velocity, stride length [88], and gait variability [89] have not been shown to differ between individuals with SCI and healthy controls. The diagnostic entity SCI is generally considered to

be heterogeneous [90], which is why differentiating groups of individuals with SCI from cognitively healthy individuals is challenging.

In line with the comparisons between SCI and healthy controls, studies have shown that TUG time scores do not differ between individuals with MCI and healthy controls [77, 91, 92]. However, impairments in performance of TUG subtasks have been detected in MCI by the use of an inertial sensor that measured angular velocity and acceleration [77]. Moreover, other elements that may affect mobility such as deficits in balance [93] and coordination [94], and reduced velocity and stride length [93, 95] are more common among individuals with MCI than among cognitively healthy individuals. In community-dwelling individuals with MCI aged 70 and older, gait slowing or gait disturbances have been shown to be present in 46%, which is almost three times more than among cognitively healthy controls [95]. These gait abnormalities are generally subtle and may require sensitive measurements such as quantification of gait parameters by instrumental devices to be detected [96]. Studies comparing individuals with MCI and dementia disorders have suggested that both TUG time scores and gait disturbances during straight-line walking (e.g., decreased gait speed and step length), depend on the level of cognitive function [91, 97, 98].

The presence of mobility impairments is well established in manifest dementia [99]. This is perhaps most notable through the increased fall risk; the incidence of falls is nearly 10 times higher among community-dwelling people with vs. without dementia [100]. Moderate to severe gait and balance disorders are present in approximately 50% of cases with dementia [101]. Moreover, the patterns of motor function, gait, and balance differ across subtypes of dementia, which may be useful for differential diagnosis [101-103]. According to a clinic-based study, 79% of patients with vascular dementia, 75% with dementia with Lewy bodies, and 25% with AD demonstrate gait and balance disorders [101]. Consequently, other measures of motor impairments have been shown to be more prominent in non-AD dementia disorders than in AD [102]. Even so, in comparisons with healthy controls, individuals with AD generally have shorter step length and reduced speed during walking [99], as well as slower TUG performance [91, 98].

Since SCI and MCI are heterogeneous diagnostic entities that do not necessarily lead to dementia disorders, longitudinal rather than cross-sectional results may be considered more clinically relevant when investigating relationships between cognition and mobility. It has been suggested that a concurrent decline of cognition and mobility is common in normal aging [68]. Pathological cortical changes, on the other hand, appear to cause mobility dysfunctions to be detectable before cognitive symptoms [68]. Slower performance of the TUG test has been shown to be associated with cognitive decline after three years among cognitively healthy adults aged 80 and older [104], as well as with dementia incidence after four years among cognitively healthy adults aged 66 years [105]. However, conflicting results have been reported in a large

study in which TUG time score did not predict cognitive decline after 6 years among high-functioning community-dwelling older adults [106]. Straight-line walking speed has been studied more thoroughly than the TUG test concerning prediction of cognitive decline; in an increasing number of studies, slow gait speed predicts cognitive decline and dementia incidence among cognitively healthy adults in different age groups above 60 years [107-109]. As early as 12 years before cognitive symptoms appear, slowing of gait has been shown to occur [110]. The combination of walking slowly and experiencing subjective cognitive symptoms has been proposed to compose a sensitive measure of dementia prediction [111]. Verghese et al. introduced this concept, denoted "motoric cognitive risk syndrome" (MCR), in which slow gait speed (one standard deviation or more below age- and sex-appropriate mean values) in the presence of cognitive complaints (without fulfilling the criteria of dementia) has been shown to predict cognitive decline and dementia incidence, especially vascular dementia, in community-dwelling adults from the age of 60 years [111-113].

Continuing the line of reasoning presented above concerning the shared brain circuits of cognitive and motor control, it is plausible that cognitively challenging conditions influence mobility. It has been shown that subtle gait disturbances are more likely to manifest when an attention-demanding task is performed during gait, compared with only walking [93, 114] – i.e., under a dual-task condition.

Dual-task testing

Definition

In this thesis, the definition of dual-tasking used is the one proposed by McIsaac et al. (p. 2) [115]: "Dual-tasking is the concurrent performance of two tasks that can be performed independently, measured separately and have distinct goals." These goals are further specified: they should be separate and functionally independent [115]. To narrow the definition even more, the focus of the current thesis is on "cognitive-motor dual-tasking," which means that one of the included tasks is cognitive in character and the other one is motor in character (as opposed to e.g., motor-motor or cognitive-cognitive dual-tasking) [115]. Dual-task interference occurs when one or both task performances are altered compared with their being performed separately, i.e., single-task performances [116]. Plummer et al. have presented a framework for categorizing motor-cognitive interference which includes nine patterns based on combinations of a) no change, b) improved, or c) impaired performance in the motor and in the cognitive task, respectively [117]. Thus, in order to investigate the dual-task interference according to this classification, both tasks must be performed both separately and simultaneously [118].

Three main dual-task theories

There are three main theories explaining the mechanisms underlying dual-task interference. The bottleneck theory suggests that only one task can be processed at a time due to a serial processing of the two tasks, when they require the same neural networks or when networks overlap [119]. In contrast, the capacity-sharing theory argues that the processing of different tasks can proceed in parallel, but that the capacity to do so is limited if they require common limited resources [120]. How the capacity is allocated may be voluntary or not [120]. The non-voluntary selection of strategy may be explained by the model of task prioritization [121], in which it is suggested that prioritization of tasks is determined by factors that minimize danger and maximize pleasure, which is why factors such as an individual's physical capacity to avoid falling when walking has an impact on how the capacity is allocated. As opposed to the two first theories, the cross-talk theory suggests there is a sort of facilitation when performing two tasks that use the same neural pathways and do not disturb each other [122]. An example of this phenomenon has been seen in young and cognitively healthy adults, where a rhythmic cognitive task increased gait speed during dual-task performance compared to single-task performance [123]. It has been argued that each theory can explain different combinations of tasks and that no single theory is applicable to all dual-task situations [124].

Montero-Odasso et al. coined the expression "brain stress test" as an explanation for dual-task interference [125]. "Brain stress test" summarizes well the notion of dual-task testing, namely that the simultaneous performance of two tasks controlled by shared cortical networks challenges the brain to a higher extent than when tasks are performed separately.

Factors that may affect dual-task ability

Advanced age has been shown to be associated with increasing difficulties with dual-tasking [126-128]. This association is explained by well-known age-related processes such as deterioration of prefrontal cortical circuitry, loss of brain mass, and executive dysfunction [123, 129, 130]. Nevertheless, because of the known individual variability in both mobility and cognition due to aging [24, 66], there is reason to expect that the dual-task ability does not necessarily decline with age.

The possible effect of depression on dual-task ability has been studied among cognitively healthy older adults, and the results are inconsistent [131-135]. However, in individuals with AD, the presence of depression appears to influence dual-task ability negatively [136]. Gender, as a separate factor, does not seem to influence dual-task ability among cognitively healthy young adults [137]. But from the age of 67 years, there are conflicting results regarding differences between cognitively healthy women and men in spatiotemporal gait parameters during dual-tasking [138, 139]. Education appears to be

another possible influencing factor, possibly depending on the choice of cognitive task. For a dual-task test involving reciting days of the week in reverse order and TUG, the level of education among cognitively healthy individuals over the age of 80 years has been shown to affect dual-task ability, but to a lesser extent than its influence on MMSE results [131]. Similarly, dual-task ability has been shown to be associated with educational level among older adults without dementia when using continuous subtractions by ones, and TUG [140]. However, the association with educational level was not present when the cognitive task involved naming animals [140]. Executive function among cognitively individuals, as well as among individuals with cognitive disorders, has been shown to be associated with dual-task ability [70, 141-143].

Cognitive disorders such as MCI and AD [144], vascular dementia [145], frontotemporal dementia [146], and dementia with Lewy bodies [102] are associated with dual-task difficulties. Additionally, several other neurological disorders, such as Parkinson's disease [147], traumatic brain injury [148] and multiple sclerosis [149], may cause impaired dual-task ability.

Dual-task testing in cognitive disorders

The interest in investigating dual-task testing in individuals with cognitive disorders has been extensive since the end of the 1990's, most likely following two ground-breaking papers: In 1997, Lundin-Olsson et al. demonstrated that nursing home residents who "stop walking when talking" were more likely to fall than those who could maintain a conversation while walking [150]. This finding attracted much attention to dual-tasking and its possible clinical utility. The same year, Camicioli et al. showed that "walking while talking" resulted in a slower gait speed among AD patients than among cognitively healthy older adults [151]. Following these studies, numerous investigations have been carried out to explore the use of dual-task testing to reveal diagnostic status among patients at different stages of cognitive impairment [144, 151-156], as well as to identify those who, in the course of time, will decline cognitively [125, 157, 158]. In these studies – also when using the narrowed definition of "cognitive-motor dual-tasking" given above – a variety of test components, instructions, and test outcomes have been used.

Test components, instructions, and test outcomes

Many previous dual-task studies focus on the motor task and in what way the motor task is affected by dual-task interference [126]. Therefore, the two tasks included are often referred to as the primary task (motor) and the secondary task (cognitive) [126]. This implies that the motor task is studied under a dual-task condition – alone or in comparison with a single-task condition – and the cognitive task is merely seen as disturbance [159].

The motor task generally involves either a certain distance of straight-line walking at comfortable or fast speed, with or without the acceleration and deceleration phases, the TUG test [154, 155, 160], or an obstructed pathway or treadmill [118]. The motor task used in a certain study depends on the intended test outcomes (e.g., studying gait variability requires a certain number of consecutive steps), as well as whether or not an additional load on executive functions is desired (e.g., TUG or obstructed pathway) [161]. The cognitive component used in dual-task testing is most often verbal and challenges executive functions and/or working memory [118]. The character of the cognitive task is often arithmetic (continuous subtractions by ones, threes, or sevens), involves verbal fluency (animals, names, phonemic fluency), or reciting the alphabet (in order or alternate letters) [115, 161]. Some of these cognitive tasks are discrete, whereas others are continuous, which should be considered, since this affects the consistency of the attentional load [118]. For the level of difficulty of the cognitive task, it has been recommended that it should be neither too easy nor too difficult, but close to the threshold of the individual's capacity [144]. Thus, the cognitive tasks are not interchangeable [3], and since the attentional load of the tasks affects the test performance, it is essential to consider the choice of tasks in relation to the target population.

Moreover, intentional or unintentional attentional priority to one of the test components may have a considerable effect on dual-task performance [162, 163]. Thus, the instructions given to the test person regarding prioritizing between tasks may indeed affect the test results. Such instructions vary across studies [118] – usually neither of the tasks are asked to be prioritized [154], or both tasks equally [153]. One reason for these instructions is that the testing should resemble real life [154, 163]. However, when interpreting the results from such studies, different strategies of prioritization should be considered. There is an unintentional strategy called *posture first*, which stipulates that cognitively healthy adults normally prioritize the motor task over the cognitive performance [164], a preference that is explained from an evolutionary perspective [165]. This strategy has been shown to diminish with age [166], and even to invert (posture-second strategy) in people with Parkinson's disease [167]. It is of particular interest to reflect upon intentional or unintentional priorities when studying the outcome measures, since singling out results from only one of the tasks could be misrepresentative of the complete dual-task performance.

In dual-task studies in which the focus is on the motor task, gait parameters and/or results related to gait speed are most commonly studied. Dual-task gait parameters are measured by an electronic walkway, inertial sensors, or by a motion-capture system, and the outcome measures vary [168], e.g., step length, step width, and step variability. When the motor task is straight-line walking, gait speed is commonly used as the outcome measure, whereas time scores are presented when the motor task is TUG. Since the TUG time score, i.e., the completion time of TUG, is correlated to gait speed [74], dual-task

gait speed when using straight-line walking and dual-task time score when using TUG are related. The outcome measure dual-task gait cost is the relative difference in gait speed or time score between single- and dual-task performances and thereby adjusts for an individual's baseline gait characteristics [4]. Dual-task gait speed and dual-task gait cost are the most established dual-task test outcomes [4, 115, 169].

Test outcomes related to the cognitive task are less frequently reported than motor-related ones, as the cognitive task is often seen as a disturbance of the motor task [159]. However, because of the possible effect of prioritization between tasks, it has been recommended that the cognitive task outcomes should be studied alongside with those of the motor task [4, 116]. When reported, cognitive/verbal outcomes are described by the number of words, the number of errors, or the dual-task cognitive cost (the relative difference in cognitive performance between single- and dual-task performances) [170]. In this thesis, when "dual-task cost" is mentioned without specification of which task (gait or cognitive) it refers to, it signifies that of the gait. This abbreviation is frequently used in the literature and could be explained by the fact that the cost measure relating to gait is far better established than the cognitive one.

Combining motor and cognitive results by calculating the number of words recited per time unit during a test is a rarely used dual-task test outcome [171, 172]. This combined outcome decreases the effect of prioritization between tasks by capturing both the motor and cognitive aspect of the dual-task performance. One version of this outcome – "number of figures counted down by one second" (test components: TUG and subtractions from 50 by ones) – has been shown to differ between patients with AD and a control group [172]. Additionally, "number of correct calculations per second" and "number of animal names per second" (test components: 6-meter straight-line walking and a. counting down from 50 by twos and b. naming animals, respectively), have shown to differ between older adults with higher and lower cognitive function as measured by an MMSE score under vs. over 25 [171].

Another type of dual-task outcome has recently been studied, where categories were used to classify the performances [155]. The assessment was based on alterations in either one of the tasks included, which resulted in classification of performances (normal, moderate deviation, and severe deviation) that could differentiate between groups of individuals without cognitive impairment, with MCI, and with AD [155].

There is growing evidence that results from dual-task testing are more informative than those of single-task testing concerning cognitive function [144]. However, determining what tasks to include and deciding how to instruct prioritization have been identified as the key limitations of the clinical use of dual-task testing [4]. Moreover, although dual-task gait speed has been suggested to be the most relevant parameter in dual-task testing for older adults [4], there is no broad consensus regarding what test outcome is optimal.

Measurement properties

The quality of tests is primarily assessed by evaluation of their measurement properties [173]. The main measurement properties of a test are *validity* – the ability to measure the construct it purports to measure, and *reliability* – the extent to which the measurement is free from measurement error [174]. Validity and reliability are interconnected; a measure with an unacceptable level of reliability implies low validity, whereas a measure with high reliability does not necessarily imply high validity [173].

Different aspects of validity have been in focus in several dual-task studies that involve straight-line walking. One aspect is concurrent criterion validity, which signifies whether or not a test outcome is systematically related to a measurement standard assessed at the same point in time [173]. Criteria such as clinical cognitive test results have been used, leading to suggestions that among individuals with MCI, dual-task gait cost is associated with memory [175] and with global cognition [176].

Additionally, the discriminative validity of various dual-task test outcomes to differentiate between groups of different cognitive status has been evaluated. For the differentiation between groups of individuals with cognitive disorders and cognitively healthy controls, in particular dual-task gait speed [153, 170], TUG dual-task time scores [154, 155], dual-task gait cost [153, 176], and gait variability [144, 156] have shown evidence of discriminative validity.

In the literature, there are a limited number of dual-task studies that have encompassed evaluation of the test outcomes' validity concerning prediction of incident dementia. Mainly, the outcomes dual-task gait speed, gait variability [157], and dual-task gait cost [125] have shown potential for predictive validity among individuals with MCI.

There are different aspects of reliability that may be relevant in dual-task testing. In this thesis, the focus will be on the most frequently studied aspect of reliability, namely the test-retest reliability. Test-retest reliability represents the extent to which scores for individuals who have not changed are the same for repeated measurements over time [174]. The test-retest reliability of various dual-task test outcomes has been described among individuals without cognitive disorders in different age groups above 60 years using intraclass correlation coefficients (ICCs) [177-181]. Regardless of which test components were used, the reliability of dual-task gait speed or time scores is reported to be excellent [177-179, 182, 183] (levels of ICC estimates defined according to Rosner [184]). The reliability of dual-task gait cost and cognitive task outcomes has been reported as poor to good [179, 183], while the reliability of gait variability has been shown to be poor [178, 185], most likely due to an insufficient number of steps during testing [185].

In dual-task testing of individuals with cognitive disorders, it appears that the test outcomes' reliability is comparable to that of cognitively healthy people. For individuals with dementia, test-retest reliability has been shown to be

excellent for dual-task time scores [181, 186]. For gait parameters such as step length and step width, the reliability is also reported to be excellent among individuals with MCI [187] and with AD [188]. The reliability of dual-task gait cost has been shown to be poor to good [180, 186], and that of cognitive task outcomes was fair to excellent among individuals with dementia [186].

Minimal detectable change (MDC) is calculated by linear transformation of the standard error of measurement (SEM) and is recommended to be reported in studies of test-retest reliability [189]. In a few dual-task test studies, MDCs for test outcomes have been described, namely for dual-task gait speed (among healthy adults over the age of 60 years) [182], for dual-task gait cost (among older adults with and without cognitive decline) [180], and for certain gait parameters (among patients with AD) [188]. The MDC of a test outcome is useful in both clinical and research settings to determine whether a change in performance is real, rather than due to measurement error [190].

In summary, several previous dual-task studies involving cognitively healthy older adults as well as individuals with cognitive impairment have reported aspects of satisfactory measurement properties. However, because these studies have used different test designs, test outcomes, and/or definitions of populations, the results of validity and reliability cannot be directly applied to other dual-task tests. Thus, measurement properties should be evaluated for all newly developed tests in order to determine their potential usefulness for research and clinical purposes [191, 192].

Rationale

The World Health Organization has labeled dementia a public health priority [193]. As the aging population increases globally, the number of individuals with dementia disorders is expected to double every 20 years [194]. In order to initiate future disease-modifying therapies before the pathological damage has become extensive, a correct diagnosis and prognosis as early as possible in the disease progression are sought after [90, 108]. Also, a correct diagnosis is necessary to initiate drug treatments for symptomatic relief [7], and to provide the individual an opportunity to make life choices for the future [195]. Today, base memory assessments comprise many elements where no separate test is sufficiently sensitive to identify early-stage dementia disorders [51, 54], and dementia is underdiagnosed in primary care [196]. More advanced and accurate diagnostic methods are available in extended memory assessments, but as these methods are invasive, expensive, and/or time-consuming, their accessibility is limited [1]. Thus, simple tools that could be used to detect and predict dementia disorders are lacking [1, 197, 198].

The growing awareness of the relationship between mobility and cognitive processes has led to an interest in using motor-related characteristics, such as

gait, in predicting dementia disorders [197]. Even more informative test results have been seen when gait is combined with simultaneous performance of a cognitive task [93, 114, 144, 175], which is why motor-cognitive dual-task testing has been proposed as a useful tool for detection of cognitive disorders [1, 2, 93]. However, the limited knowledge of what task components and test outcomes are optimal and lack of clarity in how to frame the test instructions have been identified as key impediments to clinical use [4].

A dual-task test that is easy to administer, with well-defined test components and a standardized protocol, which could detect cognitive disorders and indicate individuals who – at earliest possible stage in the disease progression – will develop a dementia disorder, would fill an important gap in research and clinical practice.

Aims

The overall aims of the current thesis were to explore if TUGdt tests could be useful in early detection of dementia disorder, as well as to present normative reference values for the TUGdt test outcomes, and to evaluate the reliability for these test outcomes among cognitively healthy controls.

Specific aims were to:

I. investigate correlations between TUGdt test outcomes and the AD CSF biomarkers $A\beta_{42}$, t-tau, and p-tau,
II. compare the results of TUG and TUGdt testing among individuals with a) dementia disorders, b) MCI, c) SCI, and d) healthy controls and thereby establish whether the test outcomes can discriminate the groups from each other,
III. investigate if TUGdt test outcomes can predict conversion to dementia among individuals with SCI or MCI over a 2.5-year period, and
IV. present normative reference values for TUGdt test outcomes in age- and sex-specific groups from the age of 50 years, as well as to establish the TUGdt test outcomes' test-retest reliability among individuals without cognitive impairment.

Methods

This thesis forms part of the ongoing project Uppsala-Dalarna Dementia and Gait (UDDGait™) [199]. A brief overview of the study foci and participants in the studies included in this thesis is given in Table 1.

Setting and participants

The data collection was carried out at three locations: The memory clinics in Uppsala University Hospital (Papers I–IV) and in Falu Hospital (Papers I–III) and at Åland University (Paper IV). A power calculation was carried out to determine the baseline sample size, based on the assumed predictive capacity of TUGdt cost and statistical power of 90%, presumptions of clinically relevant predictive capacity, dementia incidence within three years, and dementia prevalence among patients undergoing memory assessment [199].

Patients were recruited when appointed for memory assessment at the memory clinics (April 2015 – February 2017). They carried out the baseline data collection (referred to as the UDDGait™ assessment) before any diagnosis was set. The exclusion criteria were: Need of an interpreter to communicate in Swedish, inability to rise from a sitting position or to walk three meters back and forth, and indoor use of a walker. Individuals without cognitive impairment were recruited as healthy controls through advertisement and flyers. For controls, the inclusion criteria were: No experienced memory problems, ability to rise from a sitting position and to walk three meters back and forth without the use of a walker, aged 50 years or older, and an MMSE score of 27 or above. The inclusion of the healthy controls was purposeful in order to complete age- and gender-specified groups. The inclusion of patients and healthy controls is shown in Figure 2.

Table 1. Overview of study foci and participants in Papers I–IV

	Paper I	**Paper II**	**Paper III**	**Paper IV**
Study focus	Concurrent criterion validity: Correlations between TUGdt test performance and AD CSF biomarkers $A\beta_{42}$, t-tau, and p-tau	Discriminative validity: Discrimination between dementia, MCI, SCI, and healthy controls by the use of TUGdt test outcomes	Predictive validity: Prediction to dementia among individuals with MCI or SCI	Normative reference values and test-retest reliability
Participants	Patients undergoing memory assessment who as part of the memory assessment underwent lumbar puncture	Patients undergoing memory assessment (n = 298) and controls without cognitive impairment (n = 166)	Patients undergoing memory assessment for whom diagnostic information was available after 2.5 years	Healthy controls without cognitive impairment
Sample, N (women)	90 (38)	464 (218)	172 (77)	Reference sample 166 (85) Reliability sample 43 (22)
Mean age, years (age range)	71 (49–84)	71 (39–94)	71 (39–91)	Reference sample 70 (50-91) Reliability sample 69 (50-89)

Diagnosis (n)	AD: 21 Non-AD dementia: 9 MCI: 52 SCI: 8	AD: 50 Non-AD dementia: 36 MCI: 135 SCI: 77 No cognitive disorder diagnosis: 166	<u>Baseline</u> MCI: 111 SCI: 61 <u>Follow-up</u> Dementia: 51 Non-dementia: 121	No cognitive disorder diagnosis: 188*

*Twenty-one individuals from the reference sample also took part in the reliability testing, and apart from these participants, an additional 22 individuals were included for reliability testing.

TUGdt = Timed Up-and-Go dual-task; AD = Alzheimer's disease; CSF = cerebrospinal fluid; MCI = mild cognitive impairment; SCI = subjective cognitive impairment

.

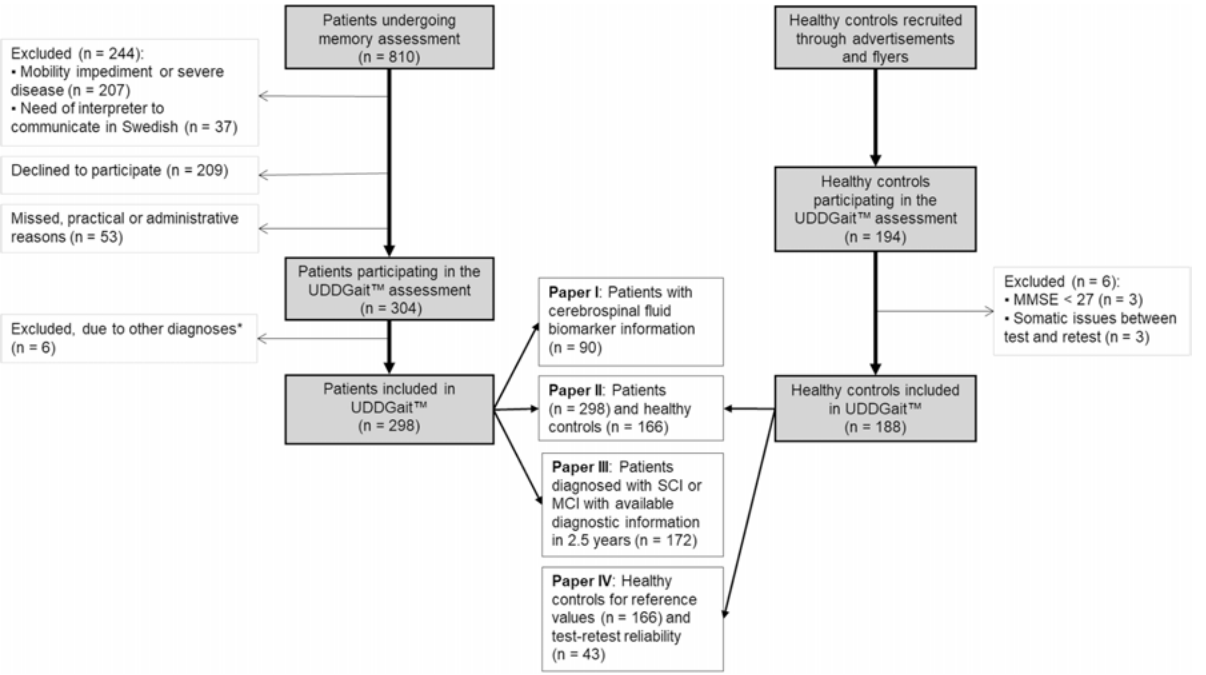

Figure 2. Flow chart showing inclusion and exclusion of participants in Papers I–IV.

*Other diagnoses: malignant neoplasm of frontal lobe (n = 1); unspecified personality and behavioral disorder due to known physiological condition (n = 1); disorientation, unspecified (n = 1); major depressive disorder, single episode, unspecified (n = 1); idiopathic normal pressure hydrocephalus (n = 1); multiple sclerosis (n = 1)

MCI = mild cognitive impairment; MMSE = Mini Mental State Examination; SCI = subjective cognitive impairment; UDDGait™ = Uppsala-Dalarna Dementia and Gait

Specific descriptions of the participants in Papers I–IV are presented below and in Table 1.

Paper I. Patients who underwent lumbar puncture as part of the memory assessment were included (N = 90, mean age 71 years, age range 49–84 years), i.e., a sub-sample of the patients who carried out the UDDGait™ assessment. Among these, 21 individuals were diagnosed with AD, 9 with other dementias, 52 with MCI, and 8 with SCI.

Paper II. The total sample (N = 464, mean age 71 years, age range 39–94 years) involved the patients included in UDDGait™ (n = 298) and cognitively healthy controls (n = 166). The sample included 50 individuals with AD, 36 with non-AD dementia, 135 with MCI, and 77 with SCI.

Paper III. Patients who were diagnosed with MCI or SCI in connection with the memory assessment for whom diagnostic information was obtainable after 2.5 years were included (N = 172, mean age 71 years, age range 39–91 years). Of these, 111 individuals were diagnosed with MCI, and 61 with SCI at baseline. At follow-up, 51 individuals had converted to dementia, and 121 individuals had not.

Paper IV. In the reference sample, the healthy controls participating in Paper II (n = 166, mean age 70 years, age range 50–91 years) were included. Twenty-one of these participants carried out a retest and were thereby also part of the reliability sample. An additional 22 individuals were included at Åland University via purposive sampling to achieve a similar representation of women and men across ages above 50 years. In the reliability sample, a total of 43 individuals were included (mean age 69 years, age range 50–89 years).

Ethical considerations

There are ethical issues in research involving patients with cognitive impairment. The patients included in the studies of this thesis are a vulnerable group. First of all, they have some degree of cognitive impairment, which may entail difficulties concerning informed consent. Additionally, these individuals are in a distressing situation; undergoing memory assessment often causes worry not only for the patient but also for his or her relatives. However, for research that aims to enable early identification of dementia disorders, it is necessary to involve this group in studies.

The informed consent must be particularly considered when involving participants with cognitive disorders in research. In the studies included in this thesis, careful ethical considerations were continuously made to ensure that

participation was based on informed consent. Patients received adapted information about the study and what participating would entail, first by letter, then by telephone, then at the occasion of the memory assessment, when written and verbal information was given again. If a relative was present at the occasion of the memory assessment, they could take part of the information and be involved in deciding on participation, if the patient so wished. Patients who agreed to participate signed a study agreement. At all times, the patients' self-determination was supported and any signs of unwillingness to participate in the research were considered.

Since the TUGdt tests were video recorded, all participants were asked specifically if the recordings could be used for educational purposes or for scientific presentations. The face would then be blurred so that the person would not be recognizable. If the participant agreed, a box in the study agreement could be ticked, otherwise the box was left unticked. The participant was informed that all recordings – as well as all other collected data – were stored safely and locked up.

Moreover, the data collection involved assessments that could reveal symptoms previously unknown to the participant, e.g., signs of depression or cognitive impairment. The test leader followed a protocol for these situations: If the depression screening indicated depressive symptoms, the test leader communicated this to the participant. For patients, a contact with the memory clinic's counsellor was offered, and for healthy controls, a contact with the primary care was recommended. Since the healthy controls were recruited as being "cognitively healthy," they were presumably unaware of any cognitive difficulties. If aberrant cognitive test results (MMSE score < 27 or an incorrect Clock Drawing test) were found in healthy controls, the test leader communicated this to the participant. Then, if the participant so wished, the test leader offered him/her a telephone appointment with one of the memory clinic geriatricians to discuss the results, or – for participants in Åland – a contact with primary care was recommended. Among patients, aberrant cognitive test results were not acted upon by the test leader, since the patients were currently undergoing memory assessment. With these precautions made, participation was judged to entail minimal risks for the individual's health and integrity.

The Regional Ethical Review Board in Uppsala approved the studies included in this thesis (2010/097/1;2, 2014/068/1;2).

Data collection and data preparation

The data collection procedures for all studies included in this thesis followed the structure detailed in the study protocol [199]. The UDDGait™ assessment involved: TUG and TUGdt testing; demographic data reported by the participants, including age, marital status, and educational level (university education or not); four cognitive tests (MMSE [200], Clock Drawing test [201],

Trail Making Test A and B [202], and Verbal Fluency test [203]); depression screening (the Geriatric Depression Scale 4-item [204]); and three functional physical tests (a short version of the General Motor Function Assessment Scale [205], static balance in accordance with Bohannon [206], and hand grip strength using a dynamometer [207]) (Table 2). If the cognitive tests had been performed in conjunction with the memory assessment, or within the last 3 months, the tests were not carried out again, but results were collected from medical records.

Table 2. Data collection according to the UDDGait™ assessment.

The UDDGait™ assessment	**Papers I–III**	**Paper IV**	
		Reference values	Reliability test/retest
Demographic data*	x	x	x/-
Mini Mental State Examination	x	x	x/x
Clock Drawing test	x	x	x/-
Trail Making Test A & B	x	x	x/-
Verbal Fluency test Naming Animals	x	x	x/-
Geriatric Depression Scale 4-item	x	x	x/-
Timed Up-and-Go	x	x	x/x
Timed Up-and-Go dual-task Naming Animals	x	x	x/x
Timed Up-and-Go dual-task Months Backwards	x	x	x/x
General Motor Function Assessment Scale, short version	x	x	x/x
Static balance	x	x	x/x
Grip strength	x	x	x/x

*Age, gender, marital status, educational level
UDDGait™ = Uppsala-Dalarna Dementia and Gait
x = performed
- = not performed

The TUGdt testing was led by physical therapists, and carried out in the following order: single-task TUG, TUGdt Naming Animals (TUGdt NA), and TUGdt Months Backwards (TUGdt MB). Standardized instructions were given to the participants before each test. Single-task TUG was performed according to the original test procedures [74]: The test person started from a sitting position in a chair, stood up at the test leader's signal, walked three meters and passed a marking on the floor, turned around, walked back to the chair, and sat down again. The test leader timed the performance with a stopwatch, from when the test person's back left the backrest until his/her posterior touched the seat of the chair. For TUGdt NA, the participants were instructed to name different animals while completing the movement sequence. For TUGdt MB, they were asked to recite months in reverse order, starting from the last month of the year. The participants were instructed to complete all tests at their own speed, both in regard to the motor and the cognitive task,

and if they did not know what to say, they were asked to finish the mobility sequence. To ensure that spontaneous instructions were not used, the test leader was not allowed to give additional instructions for encouragement or cueing during the test. Exceptions were made in certain specified situations, such as answering direct questions from the participant (for details, see the study protocol [199]).

The TUG and TUGdt tests were timed with a stopwatch to an accuracy of 0.01 second and video recorded with two cameras (Fig. 3).

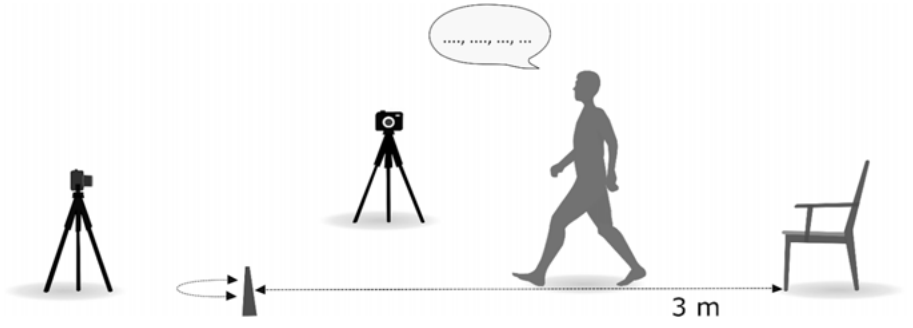

Figure 3. Overview of the Timed Up-and-Go dual-task test setup.

Subsequently, the video recordings were analyzed to obtain the verbal performances related to the cognitive tasks. The verbal performances, i.e., the number of different animals named during TUGdt NA and the number of months recited in correct reverse order during TUGdt MB, were collected. These numbers were additionally validated by another member of the research team. Dual-task cost was calculated as 100*(TUGdt time score –TUG time score)/TUGst time score [115]. To capture both mobility performance in terms of time score and verbal performance of the dual-task tests, the previously rarely used measure "words per time unit" [171, 172] was calculated. To calculate "words/10 s," a participant's number of words was divided by the time needed to perform the test, multiplied by ten. That is, for "animals/10 s": 10*(number of animals named during TUGdt NA/TUGdt NA time score). Thus, all TUG and TUGdt test outcomes used in the analyses were based on stopwatch measures and/or number of words: TUG single-task time score, TUGdt NA time score, TUGdt MB time score, TUGdt NA number of animals, TUGdt MB number of months, TUGdt NA cost, TUGdt MB cost, TUGdt NA animals/10 s, and TUGdt MB months/10 s.

The physical therapist who performed the UDDGait™ assessment did not know the participants' diagnoses, nor were the results from this assessment known to the diagnosing geriatrician.

The above-described data collection and data preparation were used in Papers I–IV. Additional descriptions of data collection and data preparation are presented separately for Papers I–IV below.

Paper I. The lumbar puncture procedures followed the same routine in both specialist clinics and the samples were sent to the same laboratory. Laboratory technicians analyzed the CSF $A\beta_{42}$, t-tau, and p-tau by Sandwich ELISAs (INNOTEST, Fujirebio, Ghent, Belgium). The technicians were blinded to all information from the memory assessment or UDDGait™ assessment. Subsequently, baseline diagnoses and information on biomarker concentrations were collected from the participants' medical records.

Paper II. Baseline diagnoses that were made in connection with the memory assessment were acquired from the participants' medical records subsequently to the UDDGait™ assessment.

Paper III. Baseline diagnoses were acquired from the participants' medical records. To collect diagnostic status at 2.5 years after baseline, the participants' medical records were reviewed again. For patients who had been re-evaluated at a memory clinic, the medical records were reviewed to classify participants as "converted to dementia," whereas in cases when non-dementia had been confirmed at least 1.5 years after baseline, the participant was classified as "not converted to dementia." For participants who had not been re-evaluated at a memory clinic, their primary care medical records were reviewed by a geriatrician. Evidence for conversion or non-conversion to dementia was found by using established criteria. In the cases where information from the medical records was insufficient, MMSE scores from an UDDGait™ follow-up assessment at two years after baseline were used to support that the participant had not deteriorated cognitively. Higher, unchanged, or a maximum of one point lower MMSE score compared with the baseline results was judged to signify non-conversion to dementia [208] .

Paper IV. The test and retest session of the reliability testing were led by the same physical therapist. For the retest session, the UDDGait™ assessment was carried out again after 10+/-4 days, except for demographic data, Geriatric Depression Scale 4-item, Clock Drawing test, and Trail Making Test A and B, which were not repeated (Table 2).

Data analyses

Measurement properties

The evaluation of the TUGdt test outcomes involved different aspects of the measurement property validity (Papers I, II, and III). Aspects of validity are defined and used in various ways in the literature. In this thesis, the validity terms are based on the general use in rehabilitation medicine [173]. Through cross-sectional analyses of correlations between TUGdt performance and the

AD CSF biomarkers, the concurrent criterion validity of the TUGdt test outcomes was evaluated (Paper I). The AD CSF biomarkers were considered measurement standard as they are established indicators of a concept [209]. Discriminative validity was studied by investigating the TUGdt test outcomes' capacity to discriminate between diagnostic groups and healthy controls (Paper II). Comparing groups of individuals who are expected to perform differently ("known-group comparisons") is an established method to determine discriminative validity [173].

The investigation of the TUGdt test outcomes' predictive capacity involved diagnostic data: dementia vs. non-dementia (Paper III). Because of the prospective approach, this aspect of validity is labeled predictive validity [173, 209].

The other main measurement property, reliability, was studied using a test-retest design (Paper IV). The test-retest design was chosen to study the extent to which the TUGdt test outcomes were the same over time for individuals who, in all probability, had not changed [174].

Statistical analyses

The SPSS version 25 (IBM Corp., Armonk, NY, USA), SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA), and R version 3.6.3 (R Core Team 2020) were used for analyses. Participants' characteristics were summarized by means and standard deviations, or frequencies and percentages, when appropriate. The test outcomes were presented as medians with interquartile ranges, because they were not normally distributed. Statistical tests were two-tailed, and the significance level was set at $p < 0.05$. The statistical analyses used in each paper are presented below.

Paper I. Spearman's rank correlation was used for analyses between TUGdt test outcomes (i.e., time score, dual-task cost, number of words, and "words/10 s" for TUGdt NA and MB) and AD CSF biomarkers, adjusted for age, gender, and educational level. Additionally, correlations between cognitive tests (MMSE and Verbal Fluency test scores) and CSF biomarkers, were analyzed. Subsequently, a sensitivity analysis that included only participants diagnosed with AD and MCI was carried out in order to substantiate that not only specific diagnoses explained the correlations.

Paper II. Associations were examined between the TUGdt test outcomes (i.e., time score, dual-task cost, number of words, and "words/10 s" for TUGdt NA and MB) pairwise between groups using logistic regression models. Analyses were adjusted for age (as a continuous variable), gender, and educational level. The results were expressed as standardized odds ratios (sORs) with 95% confidence intervals. For "number of animals" and "number of months," as well as "animals/10 s" and "months/10 s," the sORs expressed the risk increase per

one standard deviation *decrease* of the variable. For all other variables, the sORs expressed the risk increase per one standard deviation *increase* of the variable. Bonferroni correction was applied to account for multiple comparisons between the groups of main interest (adjacent groups regarding cognitive function): dementia vs. MCI, MCI vs. SCI, and SCI vs. healthy controls. Thus, the critical *p*-value was set to 0.05/3 = 0.0167. Receiver Operating Characteristics (ROC) curves were constructed and the areas under the curves (c-statistics) were analyzed to determine the discriminative capacity of the TUGdt test outcomes by the adjusted logistic regression models.

Paper III. Logistic regression models were used to predict dementia incidence (Model 1: unadjusted; Model 2: adjusted for age (continuous variable), gender, and educational level; Model 3: adjusted for age (continuous variable), gender, educational level, MMSE score, and Clock Drawing test score (dichotomized: 1–6 points or 7 points, signifying inadequate or adequate performance). Results were expressed as sORs with 95% confidence intervals. As in Paper III, for **"**number of animals" and "number of months," as well as "animals/10 s" and "months/10 s," the sORs expressed the risk increase per one standard deviation *decrease* of the variable. For all other variables, the sORs expressed the risk increase per one standard deviation *increase* of the variable. In the adjusted models, tests of effect modification by age, as a continuous variable, and gender were performed on associations between TUGdt test outcomes and dementia incidence. When effect modification was statistically significant, analyses were carried out stratified by age (under the median age/median age and above) and/or by gender. To determine predictive capacity, ROC curves were constructed for univariate and adjusted models, and c-statistics were calculated. Incremental ROC curves were completed to show improvements of predictive capacity when TUGdt test outcomes were added to a model with demographic characteristics and standard tests alone. The c-statistics were defined according to Hosmer et al: 0.5–0.7 signifies poor predictive capacity, 0.7–0.8 acceptable, 0.8–0.9 excellent, and 0.9–1.0 outstanding [210].

Paper IV. Quantile regression was used to calculate normative reference values for the TUGdt test outcomes for men and women respectively, in the age groups 50–59, 60–69, 70–79, and 80 years and older. A sensitivity analysis was carried out where participants with and without university education were analyzed separately for comparison, since a relatively high proportion of the participants (73%) had a university education.

For evaluations of test-retest reliability, the repeated assessments of the TUGdt tests were analyzed by single measurement absolute agreement ICCs estimated from a two-way mixed effects (with participant as random factor and time as fixed factor) linear model. The TUGdt time scores and cost

measures were non-normally distributed and therefore log-transformed. Bootstrap estimation was used for the 95% confidence intervals.

In this thesis, the following limits were used to label levels of reliability: ICC < 0.4 denotes poor reliability, 0.4 ≤ ICC < 0.75 fair to good reliability, and ICC ≥ 0.75 excellent reliability [184]. For additional information of reliability, SEM and MDC were calculated. Bland-Altman plots with median differences and limits of agreement (2.5th and 97.5th percentiles) were used to quantify possible systematic error. A 95% confidence interval for a median difference that did not cover zero was defined as a statistically significant difference. Moreover, a sensitivity analysis was performed where only participants who carried out the retest within 10+/-4 days were included.

Results

Paper I

Significant correlations were found between certain TUGdt NA test outcomes and concentrations of CSF t-tau and p-tau: The number of animals named correlated negatively to t-tau (r = -0.281, p = 0.008) and p-tau (r = -0.267, p = 0.012), and "animals/10 s" correlated negatively to t-tau (r = -0.267, p = 0.012) and p-tau (r = -0.249, p = 0.020) (Fig. 4). No correlations were found between $A\beta_{42}$ and any of the TUGdt NA or TUGdt MB outcomes. Significant negative correlations were additionally found between MMSE score and t-tau (r = -0.303, p = 0.004), MMSE score and p-tau (r = -0.302, p = 0.004), and Verbal Fluency test score and t-tau (r = -0.244, p = 0.025).

A sensitivity analysis showed that the associations between TUGdt outcomes and CSF biomarker levels were similar in a subgroup of patients with AD and MCI, to those in the entire sample.

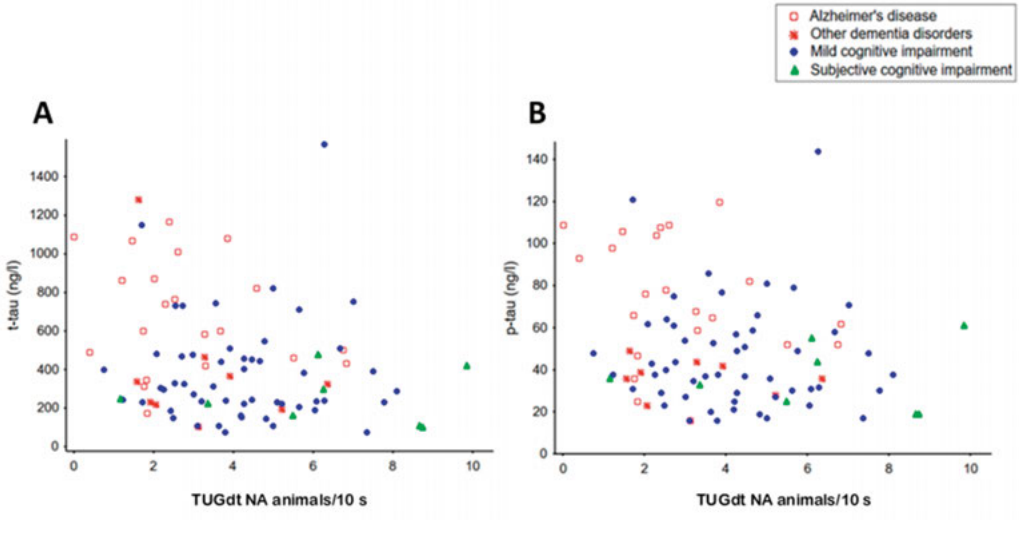

Figure 4. Associations between A) t-tau concentration and "animals/10 s," and B) p-tau concentration and "animals/10 s," including the distribution of diagnoses.

t-tau = total tau; p-tau = phosphorylated tau; TUGdt NA = Timed Up-and-Go dual-task Naming Animals

Paper II

The ranges of the TUGdt test outcome "animals/10 s" is presented across groups of individuals with dementia, MCI, SCI, and healthy controls in Fig 5.

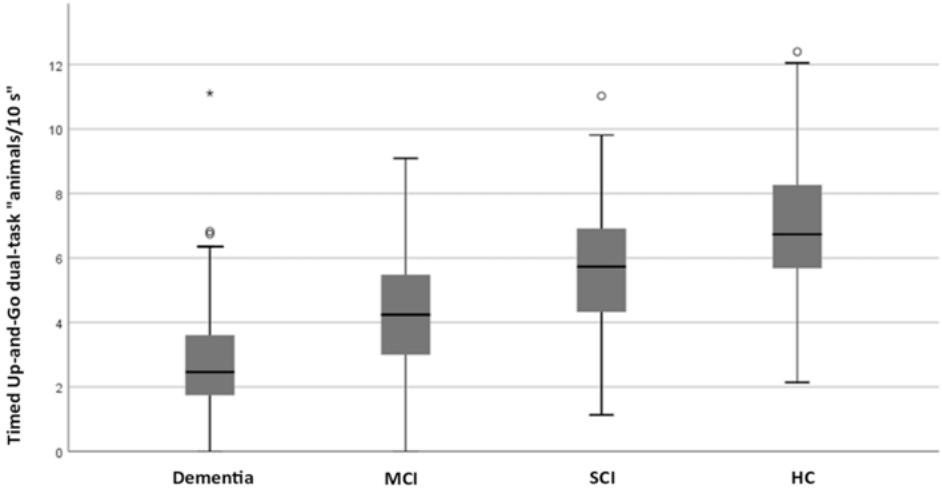

Figure 5. Boxplot showing the distribution of results for "animals/10 s" during Timed Up-and-Go dual-task Naming Animals across groups.

MCI = mild cognitive impairment; SCI = subjective cognitive impairment; HC = healthy controls

The analyses were focused on comparisons between adjacent groups regarding cognitive function, i.e., dementia vs. MCI, MCI vs. SCI, and SCI vs. controls. Several of the investigated TUGdt test outcomes showed discriminative capacity between the investigated groups. "Animals/10 s" and "months/10 s" resulted in the overall highest standardized odds ratios (sOR) among the TUGdt test outcomes. For these test outcomes, the sORs were of similar strength in all comparisons, which is exemplified by "animals/10 s" in Table 3. Moreover, "number of animals" as well as "number of months" discriminated between all groups. Neither of the dual-task cost outcomes discriminated between groups.

Table 3. Standardized odds ratios of Timed Up-and-Go dual-task test outcome "animals/10 s": dementia vs. mild cognitive impairment, mild cognitive impairment vs. subjective cognitive impairment, and subjective cognitive impairment vs. healthy controls.

		sOR	95% CI	*p*-value
TUGdt NA, animals/10 s	Dementia vs. MCI	3.29	2.01–5.40	<.001
	MCI vs. SCI	2.15	1.40–3.31	<.001
	SCI vs. HC	2.85	1.79–4.52	<.001

All results are adjusted for participant age, gender and educational level.
Statistically significant if $p < 0.05$, with Bonferroni correction if $p < 0.0167$.
sOR = standardized odds ratio; CI = confidence interval; TUGdt NA = Timed Up-and-Go dual-task Naming Animals; MCI = mild cognitive impairment; SCI = subjective cognitive impairment; HC = healthy controls

Paper III

Of all TUGdt test outcomes, "animals/10 s" resulted in the highest sORs for dementia incidence in unadjusted and adjusted models in the total sample. An effect modification was found on "animals/10 s" by age as a continuous variable in the adjusted models. The total sample was then stratified by the median age (72 years), and analyses were performed in these age groups. The associations between "animals/10 s" and dementia incidence in the total sample and among the younger participants are presented in Table 4.

Table 4**.** Standardized odds ratios for conversion to dementia in the total sample and among participants younger than 72 years in unadjusted and adjusted models.

		Total Sample	Participants < 72 years
TUGdt NA, animals/10 s	**Model 1**		
	sOR (95% CI)	4.1 (2.3–7.2)	19.4 (3.5–106.2)
	p-value	<.001	<.001
	Model 2		
	sOR (95% CI)	3.1 (1.7–5.8)	20.9 (3.3–133.1)
	p-value	<.001	.001
	Model 3		
	sOR (95% CI)	1.9 (1.0–3.7)	11.1 (1.9–71.3)
	p-value	.067	.009

Model 1: unadjusted. Model 2: adjusted for age, gender, and educational level. Model 3: adjusted for age, gender, educational level, Mini Mental State Examination, and Clock Drawing test. Statistically significant if $p < 0.05$.
TUGdt NA = Timed Up-and-Go dual-task Naming Animals; sOR = standardized odds ratio; CI = confidence interval

The area under the ROC curve (c-statistics) was 0.76 for "animals/10 s" in the total sample, and incremental ROC-curve analyses showed a marginal added

value for this variable over the predictive capacity of age, gender, educational level, and MMSE score (Fig. 6B). The c-statistics for "animals/10 s" among patients younger than 72 years was 0.89. Adding "animals/10 s" to age, gender, educational level, and MMSE score increased the c-statistics from 0.83 to 0.91 (Fig. 6). Additionally, TUGdt NA showed to have a greater capacity compared to the two original single-task tests that it is based on, i.e., TUGst time score and Verbal Fluency score for predicting dementia conversion among the participants younger than 72, with c-statistics increasing from 0.86 to 0.89.

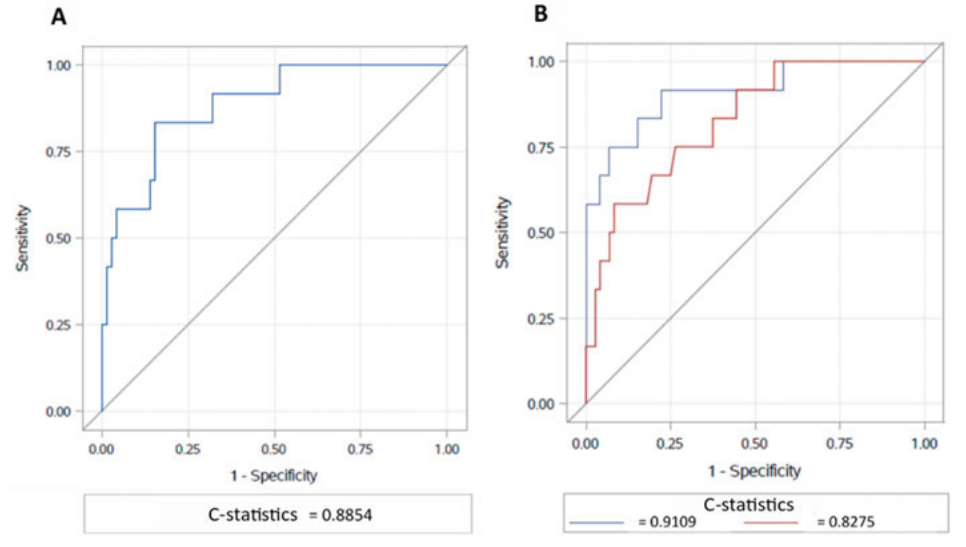

Figure 6. Receiver Operating Characteristic curves presenting prediction of progression to dementia from mild and subjective cognitive impairment among participants aged 72 years and younger. A) Predictive capacity of "animals/10 s," B) Red curve: Predictive capacity of age, gender, educational level, Mini Mental State Examination score; Blue curve: "Animals/10 s" added to age, gender, educational level, and Mini Mental State Examination score.

Paper IV

Reference values for the TUGdt test outcomes were presented by the 2.5th and 97.5th percentile for women and men in the age groups 50–59, 60–69, 70–79, and ≥ 80 years. The reference values represent the upper and lower limits of 95% of the healthy controls in each age and gender group. Table 5 presents the test outcome "animals/10 s" among women and among men in age groups.

Table 5. Reference values for Timed Up-and-Go dual-task test outcome "animals/10 s" for women and men in age groups, presented by the 2.5th and 97.5th percentile including 95% confidence intervals.

		50-59 years	60-69 years	70-79 years	≥ 80 years
TUGdt NA animals/10 s	Women 2.5th perc 97.5th perc (95% CI)	**5.4** (4.6–6.3) 12.5 (10.4–14.5)	**4.6** (4.1–5.2) 11.7 (10.4–13.0)	**4.0** (3.4–4.5) 11.1 (9.7–12.4)	**3.3** (2.4–4.1) 10.4 (8.4–12.4)
	Men 2.5th perc 97.5th perc (95% CI)	**5.3** (4.4–6.1) 11.5 (9.4–13.6)	**4.0** (3.5–4.6) 10.3 (9.0–11.7)	**2.9** (2.4–3.5) 9.4 (8.0–10.7)	**1.7** (0.9–2.5) 8.3 (6.2–10.3)

Bold text indicates the value that is clinically useful for comparisons, in this case the 2.5th percentile.
TUGdt NA = Timed Up-and-Go dual-task Naming Animals; perc = percentile; CI = confidence interval

The reliability of TUGdt NA and MB time scores was excellent (ICC = 0.85; 0.86) [184]. "Number of animals," "animals/10 s," as well as "months/10 s" showed fair to good levels of reliability (ICCs between 0.45 and 0.58), whereas the reliability for both cost measures and "number of months" was poor (ICCs between 0.34 and 0.39) (Table 6). Overall, the reliability of the TUGdt NA test outcomes appeared to be slightly higher than that of the TUGdt MB test outcomes. For TUGdt NA time score, the SEM was 0.95 and MDC 2.63, and for "animals/10 s," the SEM was 1.33, and MDC 3.69.

Table 6. Intra-class correlation coefficient estimates for Timed Up-and-Go dual-task test outcomes with 95% bootstrap confidence intervals.

Dual-Task Test Result	ICC Estimate (Bootstrap CI 95%)
TUGdt NA	
Time score (s)	0.86 (0.77–0.91)
NA cost (%)	0.34 (0.10–0.54)
Number of animals	0.57 (0.39–0.69)
Animals/10 s	0.58 (0.37–0.74)
TUGdt MB	
Time score (s)	0.85 (0.74–0.92)
MB cost (%)	0.39 (0.21–0.56)
Number of months	0.38 (0.10–0.60)
Months/10 s	0.45 (0.20–0.67)

ICC = intra-class correlation coefficients; CI = confidence interval; TUGdt NA = Timed Up-and-Go dual-task Naming Animals; TUGdt MB = Timed Up-and-Go dual-task Months Backwards

The Bland-Altman plots revealed significant median differences for TUGdt MB time score (0.23, 95% CI 0.12 to 0.75), and for TUGdt NA animals/10 s (-0.79, 95% CI -1.06 to -0.18) (Fig. 7). These differences signified a slower TUGdt MB performance the second test session compared with the first, and fewer animals named per 10 s. the second test session compared with the first.

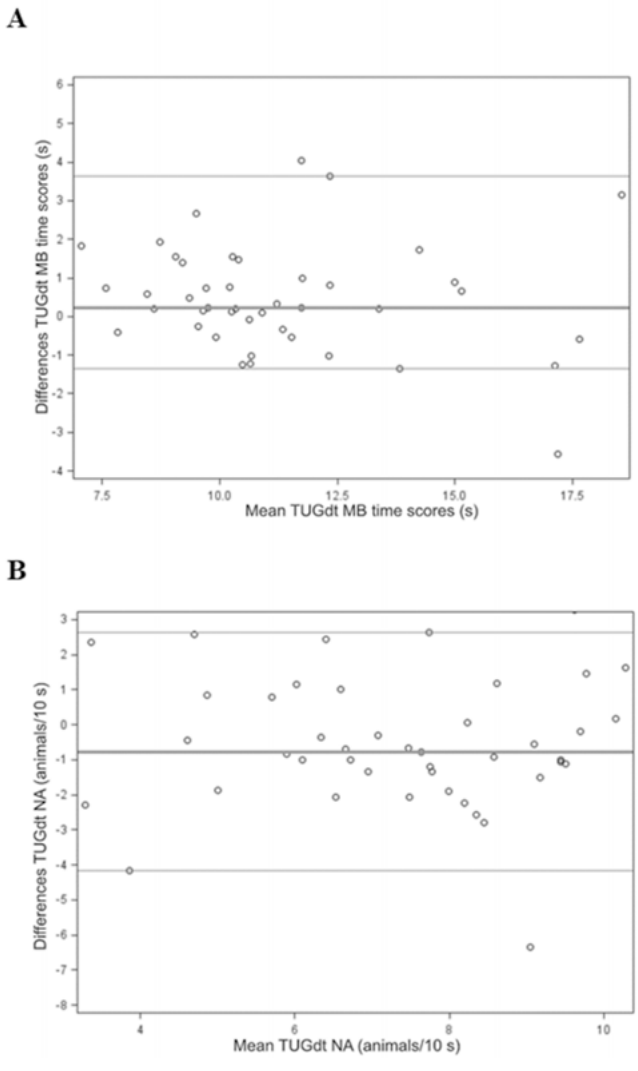

Figure 7. Bland-Altman plots for A) Timed Up-and-Go dual-task Months Backward time score (original values, i.e., prior to log transformation), and B) Timed Up-and-Go dual-task Naming Animals "animals/10 s". Reference lines for median difference and limits of agreement.

Discussion

To the author's knowledge, the TUGdt tests used in the studies in this thesis, i.e., the specific test components, instructions, and outcomes, have not previously been studied. In particular, the use of "words/10 s" as presented in this thesis, appears to be the very first based on TUG and the cognitive tasks NA or MB. Because of the novelty of the test outcome "animals/10 s," and the findings regarding its I) association to neurodegeneration as determined by the CSF biomarkers t-tau and p-tau, II) discriminative validity between dementia, MCI, SCI, and controls, III) predictive validity in predicting dementia, and IV) fair to good reliability among controls, this test outcome will be of particular focus in the following sub-sections, in which the results of Papers I–IV are discussed.

Validity

Cross-sectional validity

The concurrent criterion validity of TUGdt test outcomes in relation to AD CSF biomarkers was explored in Paper I. The associations found between certain TUGdt NA test outcomes and CSF t-tau and p-tau indicated that these outcomes are valid measures for neurodegeneration in the investigated sample. That is, since t-tau and p-tau are established indicators of neurodegeneration, the significant correlations suggest that the test outcomes "number of animals" and "animals/10 s" partly measure the same construct. On the one hand, t-tau and p-tau are relevant criteria for the construct as they are biological markers without any component of subjective evaluation. On the other hand, t-tau and p-tau are not specific to dementia-related neurodegeneration but may reflect other types of neurodegenerative processes [211, 212]. The AD pathology is supported by a certain profile of elevated levels of t-tau and p-tau in combination with low levels of $A\beta_{42}$ in CSF, which has high sensitivity and specificity for the detection of AD [57]. Since the associations in Paper I were not found between TUGdt test outcomes and the AD CSF profile in its entirety, these test outcomes should not be seen as valid measures specifically for AD. Moreover, the validity of the measures is conditional upon the sample. The sample comprised first visit memory assessment patients for whom it was

considered relevant to analyze AD CSF biomarkers, most likely due to assumed AD. Presently, it is not possible to draw conclusions on the validity of the TUGdt test outcomes beyond this current sample.

It has previously been shown that individuals with SCI are more likely than controls to present an AD-typical pattern of CSF biomarkers [90] and that the pattern, on the group level, becomes increasingly abnormal in the stages from SCI to MCI, and further to AD [213]. A subgroup analysis of the validity of TUGdt test outcomes in the SCI group in the current sample was not possible to carry out due to the limited subgroup size.

The lack of associations between TUGdt performance and CSF $A\beta_{42}$ may be explained by the notion that $A\beta_{42}$ concentrations become abnormal very early in the AD disease progression and then stabilize at abnormal levels [214]. Similarly, a more recent study has concluded that dual-task impairments are associated with tau pathology, rather than with $A\beta_{42}$ among patients with MCI [215]. However, associations between dual-task cost and $A\beta_{42}$ have been found in a sample of healthy controls, MCI, and mild AD [155]. The divergent results found in that study, compared to Paper I, may be explained by dissimilar samples and the use of different cognitive tasks and instructions.

In Paper II, the TUGdt test outcomes "animals/10 s" and "months/10 s" discriminated between group of individuals with dementia vs. MCI, MCI vs. SCI, and SCI vs. controls. The discriminative validity was determined by "known-group" comparisons [173], where clinical diagnoses – and absence of diagnosis – were used to define the groups. Cognitive disorder diagnoses are well-defined constructs according to established standards; however, the distinctions between dementia, MCI, and SCI are not unequivocal. Especially, the exact time for diagnosis depends on many factors. For example, one central distinction between MCI and dementia is that in the latter, ADL is affected. Depending on an individual's previous choice of activities and what could be considered an affected performance, this distinction may be complex. For an individual whose spouse handles all of the more complex ADLs (not because the individual is not capable, but out of habit or tradition), a decline in ADL that would be evident in other individuals may go far before being noted. In summary, clinical diagnoses of cognitive disorders are not completely clear-cut, but they are the most relevant groups to use for evaluating the TUGdt test outcomes' discriminative validity.

Comparing different test outcomes' discriminative validity between studies is not uncomplicated, since the designs of the dual-task test vary widely. In two previous studies, TUG combined with cognitive tasks (NA, and continuous subtraction by ones starting from 100, respectively) were used to investigate discrimination between cognitive disorder diagnoses and healthy controls. In those studies, dual-task time scores could differentiate between AD, MCI, and healthy controls [154, 155]. Similarly, in Paper II, both TUGdt NA and MB time scores could differentiate between dementia, MCI, and healthy controls. It is to be noted that individuals with SCI rarely have been included

in previous discriminative dual-task studies [153]. When included, neither dual-task gait speed nor dual-task gait cost (test components involving six meter straight-line walking while naming animals, or continuous subtractions by ones or by sevens) has shown capacity of discriminating between SCI and MCI [153]. Similarly, in Paper II, TUGdt time scores – which are not equivalent to dual-task gait speed, however related – and dual-task cost did not discriminate between SCI vs. MCI. Interestingly, when combining the motor and verbal results by using "animals/10 s," the distinction between SCI and MCI could be made.

In Paper IV, age- and sex-specific normative reference values were presented. The validity of these reference values to correctly discriminate individuals with and without dementia has not yet been analyzed. An important point when considering the reference values in relation to classification and clinical utility is that the reference values should not be viewed as cut-off measures. The reference values merely give cross-sectional information, not predictive, and should be regarded as an indication of the range of a cognitively healthy performance.

Predictive capacity

In Paper III, the results suggested that there is potential for "animals/10 s" to predict dementia incidence in the total sample. An effect modification was found by age as a continuous variable in adjusted models, and therefore analyses were performed stratified by age.

The finding that the predictive validity of TUGdt testing was weaker in higher age corresponds with previous studies involving different methods that are used to detect pathological processes. Several diagnostic methods are insensitive in higher ages, either because of lack of expected pathology, or a presence of pathological findings that will not develop into clinical symptoms within the individual's lifetime [216, 217]. A mixed neuropathology – including normal age-related changes – is often seen with advancing age [197, 218]. In contrast, younger memory clinic patients are more likely to have non-degenerative reasons for their cognitive complaints, e.g., depression or stress [90]. Possibly, these underlying causes for cognitive decline have little effect on dual-task ability, which would explain the strong predictive validity of TUGdt "animals/10 s" among younger patients.

The predictive validity of TUGdt NA among the younger half of the sample was further substantiated by showing that "animals/10 s" added predictive capacity to a model of age, gender, educational level, MMSE, and Clock Drawing test. Thus, "animals/10 s" entailed additional information about who would convert among younger patients with SCI or MCI, apart from what was revealed by demographic characteristics and the cognitive tests that are included in a base memory assessment.

To the author's knowledge, previous longitudinal studies of dual-task tests and dementia incidence have not analyzed the predictive validity of test outcomes in different age groups. However, several test outcomes have previously shown predictive capacity in different populations: In studies involving straight-line walking, measures of gait variability have shown potential to predict dementia among individuals with MCI (cognitive task: continuous subtractions) [157] as well as among healthy adults above the age of 70 (cognitive task: reciting alternate letters of the alphabet) [158]. Dual-task gait speed [157] and dual-task gait cost [125] have shown to predict conversion from MCI to dementia (cognitive task: continuous subtractions). On the other hand, among cognitively healthy older adults, it was found that dual-task gait speed (cognitive tasks: reciting alternate letters of the alphabet, or naming animals with a specific first letter) was not associated with future cognitive decline as measured by clinical cognitive tests [106, 219]. The only previous dual-task study that involved TUG and prediction of dementia did not show any associations between dual-task time score or dual-task gait cost and progression to AD among individuals with MCI (cognitive task: continuous subtractions) [155]. Based on these previous studies, it appears that the results are highly dependent on the choice of test components, test outcomes, and population.

Reliability

The reliability of the test outcomes among cognitively healthy individuals varied from poor to excellent, which is comparable with previous study results involving similar dual-task test outcomes [179, 183]. The excellent levels of reliability for the TUGdt time scores further confirms that the speed of performance is a reliable measure, possibly explained by the participants consciously following the instructions to keep walking if they did not know what to say, and/or unconsciously by the posture-first strategy [183, 220]. The verbal outcomes, represented by the number of words (number of different animals, and number of months recited in correct reverse order) produced during TUGdt NA and MB, showed a lower level of reliability than the time scores. Similar results have been found in previous dual-task studies [220] and are explained by cognitive measures being variable by nature [179]. Additionally, the motor task, even though it requires higher cortical involvement, should be seen as a more automatized task than the cognitive tasks that were used. This implies that a verbal mistake or hesitation during testing impacts the verbal test outcomes and does not primarily affect the speed of the mobility performance. Moreover, since the duration of the TUGdt tests is limited, a random verbal mistake may have a large impact on the verbal test outcomes. Verbal mistakes may affect the verbal performance negatively. However, there is no

possibility of such random variability that would *positively* influence the performance. Thus, for the clinical use of the test, it is possible that this could weaken the specificity of the test, but not its sensitivity.

A known concern with cognitive tests is the risk of a learning effect [221], and it would be conceivable that TUGdt NA and MB would imply such an effect. The Bland-Altman plots of TUGdt MB time score and TUGdt NA "animals/10 s" suggested systematic error, but in the opposite direction of what could be explained by learning. That is, the performances appeared not to be improved, but impaired at the second test occasion compared with the first one. Since the differences were numerically small and no other TUGdt variables showed significant differences between the test occasions, the error may be seen as due to random error.

The TUGdt test outcomes "animals/10 s" and "months/10 s" showed fair to good reliability. The reliability of these measures is naturally affected by cognition being variable, as mentioned above. Moreover, they are ratios of two measures, which can influence the reliability negatively by inflated systematic error [183]. Interestingly, despite these built-in challenges, these measures showed a level of reliability that permits potential clinical usefulness. Dual-task test outcomes that represent "number of words per time unit" are rarely used in previous research, and previous investigations of their reliability seem to be lacking.

The TUGdt cost measures were based on time scores and could therefore be assumed to entail reliable results. However, these outcomes were also calculated by the ratio of two other measures and have consistently – by the use of different dual-task designs – been shown low levels of reliability [179, 183, 186]. These findings have led to calls for awareness when using dual-task cost as a test outcome [179, 186].

Results from all reliability testing should be interpreted with consideration of how the test is meant to be used [222]. The MDC of "animals/10 s" suggested that a change of at least four animals/10 s would signify a true change. This high number indicates that TUGdt NA most likely cannot be used to evaluate change over time. However, the aim of TUGdt NA is mainly to identify or predict dementia at one test occasion, and for this purpose, the level of reliability appears to be sufficient. The primary reason for this argument is the notion that validity depends on reliability [173], and the predictive validity of "animals/10 s" as shown in Paper III, was strong. That is, if a measure is not sufficiently reliable, it cannot be valid, since it would not provide a relevant estimate of the ability it intends to measure.

Methodological strengths and limitations

Setting and participants

A central strength of the methods used is the clinical setting. The TUGdt tests were carried out without the use of laboratory equipment, which reinforced the ecological validity [223], i.e., similarity to real-world activities, although this aspect of validity was not explicitly studied. On the other hand, since patients followed the clinical routine, the memory assessment methods differed between individuals which entailed that not all data (e.g., AD CSF biomarker concentrations) were available for all participants. Moreover, for Paper III, the patients were not invited for a follow-up memory assessment specifically for the purpose of the study, but visits were scheduled according to the routines. The use of supplemental information to determine presence or absence of dementia at follow-up, instead of using diagnoses based on complete re-evaluations at the memory clinic, may be considered a limitation. The complementary reviews were however performed by an experienced geriatrician and based on established criteria, which was judged to be trustworthy. For cases where the diagnostic information was lacking, MMSE scores were used to rule out the presence of dementia, which should be seen as a less precise method. However, for determining non-conversion to dementia, a higher, unchanged or maximum one point less MMSE score was required. Previous research has shown that changes in MMSE scores of 2–4 points indicate a reliable change [208]. Although MMSE has shown bluntness as a stand-alone diagnostic tool, it has shown effectiveness in ruling out dementia [224].

Classification of MCI subtypes was not part of the clinical routine at the memory clinics; therefore such information was not available in the patients' medical records. Previous dual-task research has shown that amnestic and non-amnestic MCI can be differentiated by dual-task gait speed and dual-task gait cost [175]. The classification of MCI subtypes could indeed have contributed with further knowledge in the prediction of specific dementia disorders, as the MCI subtypes may give information on the presumed etiology [35].

The inclusion of patients with SCI in Papers I–III was considered a strength. It is important to include individuals in research that are in early stages of the disease progression leading to dementia, both for the opportunities of timely pharmacological treatment, and for the possibilities of ruling out a dementia diagnosis among individuals who are struggling with worry and withdrawal because of their concerns of a progressive cognitive decline [225].

Although SCI has been suggested to be the most relevant stage to target dementia prediction [198], individuals diagnosed with SCI are lacking in previous predictive dual-task studies. In Paper III, only two individuals had converted to dementia from SCI after 2.5 years, which ruled out an analysis of the SCI subgroup in that material. A longer time to follow-up in the same sample would imply that more individuals have converted to dementia, which would

enable analyses of the predictive validity of the TUGdt test outcomes among patients with SCI.

For cognitively healthy controls (Papers II and IV), the normal cognitive function was confirmed by the inclusion criterion of an MMSE score > 27. Nevertheless, the sample may well have included individuals with preclinical dementia. In order to ensure that the sample consisted only of truly healthy controls, a process of prospective exclusion of diagnosed individuals would have had to be carried out after a certain time, which was not considered feasible. Moreover, the healthy controls in the reference sample were recruited in university cities and the proportion of participants with university level education was high, which may have affected their test performances. However, a sensitivity analysis was carried out in this sample, which resulted in negligible differences related to educational level. Furthermore, the reference sample was recruited in age groups from the age of 50 years and above, since patients younger than that are rarely afflicted by cognitive disorders. However, as seen in Paper II, younger individuals – as young as 39 years old – were included, which is why additional age groups in the reference sample could have been clinically useful.

All study participants were Swedish-speaking, and the need of an interpreter was an exclusion criterion. Since the TUGdt testing involved verbal performance, generalizing the findings to other languages should be made with caution. The cognitive tasks NA and MB in their original, single-task form are used in different languages [226, 227], and in previous dual-task studies, languages such as English or Portuguese have been used for the cognitive task NA [154, 156]. However, direct comparisons between languages remain to be investigated.

The Timed Up-and-Go dual-task tests

The TUGdt testing procedures were previously tested and developed in a pilot study [199], and all TUGdt tests were led by trained physical therapists. The TUGdt testing were carried out before diagnoses were made, which minimized the risk of observer bias. In the following subsections, strengths and limitations concerning the TUGdt test components, test instructions, and test outcomes, are discussed.

Test components

The test components were carefully chosen based on clinical experience and previous research [144, 160, 199, 228]. The choice of using TUG as the motor task, instead of the more frequently used straight-line walking, was based on the advantages of using a more complex mobility task. The complexity of the TUG subtasks [118] challenges executive functions more than gait alone [78] and could thereby be more sensitive to such dysfunction. Executive dysfunction may be indicated by a prolonged TUG time score because TUG involves

fluid transitions between the subtasks [77], something that is not embodied in straight-line gait speed. Apart from executive function, TUG is related to spatial orientation, which is an early symptom of AD [229]. The TUG has also shown associations with ADL [74, 98], which is relevant based on the diagnostic criterion for dementia involving ADL decline.

Both of the cognitive tasks used in the TUGdt testing were based on well-established tests of cognitive function [227, 230]. The choice of using NA as the cognitive task in the TUGdt NA, was based on recommendations and previous experience [144, 160]. On the other hand, MB was previously unknown as a dual-task test component. The choice of the cognitive tasks was based on the notion that the original, single-task tests NA and MB challenge cognition somewhat differently. Both NA and MB test semantic memory and executive function, but MB targets the working memory to a larger extent [227, 230, 231]. When structuring the UDDGait™ assessment, the MB was thought to be more challenging than NA, which is why the tests TUG, TUGdt NA, and TUGdt MB were consistently carried out in this order, and not randomized. The assumption of differences in difficulty between the TUGdt tests appeared to be accurate; in the total sample in Paper II, only one participant discontinued the TUGdt NA, and six participants discontinued the TUGdt MB.

An often-recommended cognitive task in dual-task testing is continuous subtractions by sevens from 100 or 50 [126, 170]. However, even though it is central for the cognitive task to be attention-demanding, it should not cause undue stress [70]. Mathematical skills may differ largely among individuals, and the performances of individuals who are not comfortable with mathematical tasks are severely affected [70]. Moreover, using subtractions as a cognitive task has implied results that are associated with educational level, while using verbal fluency did not [140]. On the other hand, if the cognitive task is too automatized, such as counting by ones, or reciting the alphabet, the rhythmic feature of the cognitive task may facilitate the motor task [123]. The use of an easy task could therefore, as put forward by the cross-talk theory, eliminate the effect of "brain stress test." This notion of appropriate level of difficulty is of course dependent on the cognitive function of the target population. Based on the findings in Papers I–IV, the level of difficulty of the cognitive tasks NA and MB in combination with TUG, appeared to be appropriate in order to produce useful outcome measures.

Test instructions

The instructions given by the test leader were standardized, since it is known that the instructions given in performance-based tests and in dual-task testing may affect the performance [118, 159] and that standardization controls for that source of variability [173]. Because the motor task was instructed to be performed at a self-selected, comfortable pace, and the cognitive task meanwhile, neither of the tasks was to be performed as fast as possible. Also, the motor task should be finalized if the participant did not know what to say,

which would give them an opportunity to complete the test without an apparent feeling of failure. The purposes of these instructions were to avoid other strategies of prioritization and to decrease the possible perceived discomfort that may characterize conventional tests of cognitive function, in which the individual commonly is forced to expose his/her incapacity.

The importance of instructions may also be related to dual-task theories. According to the bottleneck theory, tasks cannot be processed simultaneously, and resource allocation favors one task [115], which gives more importance to the instructions of priority. The bottleneck theory has been criticized in cognitive-motor dual-tasking since two tasks can evidently be performed in several everyday activities (e.g., playing instruments or doing sports) [232]. However, this critique does not consider the precondition of dual-task testing as defined by McIsaac et al. [115], namely that the two tasks should have different goals. Moreover, it is possible that bottleneck processes occur at such high speed that alterations in dual-task performance are imperceptible when the tasks are more automatized [232]. The importance of instructions is also supported by the capacity sharing theory, since performances of separate tasks are thought to compete for the joint capacity, and intentional priority of one task naturally favors this task.

Thus, the instructions used for the TUGdt testing were chosen with care based on several considerations. However, unintentional strategies such as the posture-first or posture-second strategies [164-166] cannot be controlled for by standardized instructions. Therefore, regardless of instructions, it should be essential to use test outcomes that include the performance of both tasks.

Test outcomes

Several TUGdt test outcomes were explored in Papers I–IV: time scores, number of words, dual-task costs, and "words/10 s." Overall, "words/10 s" during TUGdt NA, i.e., "animals/10 s" excelled among the test outcomes. This could be understood by the effect of combining the results of both included tasks in one measure. The use for this combined measure decreased the possible influence of prioritization between tasks, which most likely was the case in test outcomes that focused on one of the tasks. The risk of floor effects is judged to be small in the target population, even though among patients with advanced cognitive impairment, the measure may result in zero animals named per 10 seconds. There is no risk of a ceiling effect.

The use of verbal performances as test outcomes places high demands on the accuracy of these results. The participants' verbal performances (the number of different animals, and the number of months recited in correct reverse order) were collected by listening to the video recordings subsequent to the testing. All verbal performances were additionally validated by another member of the research team, which resulted in more trustworthy numbers than if these had been counted during testing.

Dual-task cost is one of the best-established dual-task test outcomes [3]. However, in Papers I–IV the TUGdt cost measures did not show any signs of usefulness. This could be explained by methodological differences between the current TUGdt tests and other test designs, both by the use of the TUG as the motor task, being more demanding than straight-line walking and thereby causing the relative differences between single- and dual-task performances to be less useful, and also by the instructions of prioritizing the motor task over the verbal one. Moreover, the use of presenting dual-task cost related only to gait – without including the cost of the cognitive task – has been disputed, since important information may be missed [233, 234].

Dual-task cognitive cost was not used as a test outcome in Papers I–IV, because the data collection did not include single-task verbal testing for this purpose. In order to calculate the dual-task cognitive cost, the participant's time duration of each dual-task test would be used to establish the time for their single-task verbal tests. Single-task verbal tests would then be performed during this time duration, and the relative difference in number of words between single- and dual-task performances would be the outcome [235]. Such results, along with dual-task gait cost, could have brought about further understanding of prioritization between tasks.

Additional data collection

Apart from the TUGdt testing, the UDDGait™ assessment included clinical cognitive and functional tests. The cognitive tests were chosen based on the clinical routine. For example, MMSE was used since it is a standard test in base memory assessments as recommended by the Swedish National Board of Health and Welfare [11], while the Montreal Cognitive Assessment (MoCA) was not, although it has been suggested to be more informative than MMSE for patients with MCI [236]. The functional physical tests were carried out for descriptive purposes. However, the standing balance test and the short version of General Motor Function Assessment Scale showed ceiling effects; therefore more challenging tests could have provided further descriptive information.

Data analyses

Power

The power calculation that was carried out prior to the inclusion of patients to the UDDGait™ assessment was partly based on presumptions of the predictive capacity of TUGdt cost. However, as demonstrated in this thesis, the TUGdt cost measures did not show any capacity to predict dementia. On the other hand, the samples were sufficiently large to show statistically significant

results for the predictive capacity of e.g. “animals/10 s”. All analyses of subsamples of interest, however, were not possible to carry out due to the limited sample sizes. The sample sizes in Papers I and III did not allow for criterion validity or predictive validity to be evaluated in the SCI subgroup. Similarly, in Paper III, the number of individuals with specific dementia disorders at follow-up was too low for separate analyses of predictive validity. Given that gait velocity and balance generally are more affected in non-AD dementias than in AD [103, 237], subgrouping the dementia group could entail findings that certain TUGdt test outcomes are more associated with certain dementia diseases. Moreover, a larger sample in Paper III could have enabled exploration of the optimal threshold for the age limit, instead of using the median value.

For the reliability testing, the study sample was on the lower side according to certain recommendations, in which a minimum of 50 participants is considered adequate [238]. However, the sample was well over 30 participants, which is recommended elsewhere [239].

Measurement properties

To provide different perspectives of validity, concurrent criterion validity, discriminative validity, and predictive validity were chosen. Several other aspects of concurrent criterion validity could have been analyzed, e.g., by using brain images. However, due to the clinical focus of UDDGait™, and lack of resources for such analyses, the clinical diagnoses were mainly used.

As concerns the reliability testing, the test and retest sessions were carried out according to established recommendations for such studies, i.e., similar test conditions, control for stability between sessions, and the use of an appropriate time interval [189]. There were deviations from the set time interval of 10+/-4 days, which could be seen as a limitation. However, results from a sensitivity analysis in which only participants who carried out the retest within 10+/-4 days were substantially similar to those of the entire sample. Furthermore, for practical reasons, the test and retest sessions were not performed at the same time of day, which could have been done to minimize the risk of variability. Additional aspects of reliability, such as inter-rater reliability was not investigated, but standardized instructions were used, which decreased the risk of the test leader acting differently on different occasion and thereby influencing motivation and test performance [173].

Reliability testing should be carried out in the target population [240]. However, the current thesis presents results from reliability testing among cognitively healthy individuals as a first step, and data collection among individuals with cognitive disorders is ongoing. Previous studies have indicated that several dual-task test outcomes’ reliability is on comparable levels to that of cognitively healthy individuals [181]. However, because of the nature of cognitive disorders, these individuals may have difficulties in comprehending instructions, executing appropriate motor actions, as well as remembering

them during the testing [241], meaning that a higher variability could be expected.

Statistical analyses

In Paper I, non-parametric correlation coefficients by Spearman's rank test were used to assess relationships, and adjustments were made for potentially confounding variables (age, gender, educational level). The inclusion of multiple test outcomes in the analyses may be considered a limitation, as it implies a risk of inflated Type 1 errors. However, the explorative outset implied a number of analyses. The results should be confirmed in other studies.

In Papers II and III, results from the logistic regression analyses were expressed as sORs, i.e., odds ratios per increase or decrease of one standard deviation of the variables, in order to compare the capacity of the test outcomes regardless of their measurement units. Potentially confounding variables were considered by adjustments for age as a continuous variable, gender, and educational level. Moreover, in Paper II, Bonferroni correction was applied to reduce the risk of an inflated type I error due to multiple testing between groups. The comparisons were made between the groups that are clinically challenging to differentiate between, i.e., dementia vs. MCI, MCI vs. SCI, and SCI vs. healthy controls. Thus, those three comparisons resulted in the critical *p*-value 0.05/3 = 0.0167. Potentially, Bonferroni correction may increase the probability of type II errors, and therefore the statistical significance with and without correction was clarified for all *p*-values in Paper II.

In Paper III, logistic regression models were used. Instead, Cox regression analyses, which allow taking into account the time to diagnosis, could have been carried out. However, due to the uncertainties of the exact time of a diagnosis and the relatively short follow-up time, the Cox method was judged to be less relevant in this material. The stratification by median age (72 years) that was carried out after finding a strong effect modification of age as a continuous variable on TUGdt NA could be questioned. The split is justified mathematically by being the median age in the sample and was not set as a threshold based on previously established age limits (e.g., 65 years). In the younger age group in the sample, there were relatively few participants who converted to dementia. This resulted in wide confidence intervals, implying that the associations could be anything from moderate to very strong.

In Paper IV, reference values were calculated by quantile regression by age and sex. This method takes into account that reference values vary by covariates and is preferable to direct calculation of percentiles within subgroups due to the difficulty of calculating confidence intervals for extreme percentiles in small samples. The statistical analyses used for test-retest reliability – ICC, SEM, MDC, and Bland-Altman plots – are recommended methods for this purpose [189].

Conclusions and future perspectives

Conclusions

The main conclusion is that the TUGdt tests, in particular TUGdt NA, can provide useful information in memory assessment of patients with cognitive disorders. Specifically, the TUGdt NA test outcome "animals/10 s" has shown potential for early detection of dementia disorder.

- The TUGdt NA "number of animals" and "animals/10 s" were associated with neurodegeneration, as determined by concentrations of the AD CSF biomarkers t-tau and p-tau.
- The TUGdt NA "animals/10 s" and TUGdt MB "months/10 s" demonstrated high discriminative capacity between groups of individuals with dementia, MCI, SCI, and healthy controls.
- The TUGdt NA "animals/10 s" predicted dementia incidence and improved models with demographic characteristics and standard cognitive tests regarding the prediction of conversion from SCI or MCI to dementia, particularly among patients younger than 72 years. Furthermore, among the younger patients, dual-task testing showed evidence of added value compared to the original single-task tests.
- Age- and sex-specific normative reference values for TUGdt NA and MB test outcomes, potentially useful for research and clinical purposes, were presented. The test-retest reliability analyses indicated excellent reliability for TUGdt NA and MB time scores, and poor to good reliability for the other TUGdt test outcomes. The reliability of TUGdt NA "animals/10 s" was fair to good, which was judged as sufficient for the purpose of one-assessment testing.

Clinical implications and future perspectives

From a clinical point of view, the TUGdt NA is a feasible test: it is quick and does not require extensive test leader training or advanced technical equipment, and the test results are easy to analyze. From a patient's perspective, this test can be argued to be less stressful than many other tests involved in memory assessment. Used as a tool ahead of any memory assessment, the

TUGdt NA could become an aid in determining if specialist assessment is needed. Or, as a part of a base or extended memory assessment, the test could be useful as an alternative or a supplement to other assessments. Either ahead of, or as a part of a memory assessment, the TUGdt NA could improve the care path for people with cognitive disorders, and lead to earlier initiated pharmaceutical and non-pharmaceutical interventions that may improve their cognitive function and quality of life.

This thesis involves evaluation of validity, initial investigations of reliability, and presentation of normative reference values. However, further research should be carried out before TUGdt testing could be used clinically for diagnostic or prognostic purposes. Such studies should involve diagnostic accuracy including determining cut-off values with appropriate levels of sensitivity and specificity, studies of reliability among individuals with cognitive disorders, and specific investigations of applicability, feasibility, and implementation. Additionally, an elaborate manual including the standardized test procedure, use of the scoring, and handling of the results would be a requirement for clinical use. Apart from these studies, there are numerous possible future perspectives to explore based on the findings presented, only a few of which will be addressed here.

The simplicity of the TUGdt tests is highlighted as a strength. The testing procedure could be made even simpler by omitting the cameras and only using a device for audio uptake. In that case, the only equipment needed for the test would be a chair and means to record sound and measure time, both of which are available in any mobile phone. On the other hand, since gait patterns differ across dementia subtypes [242], incorporating measures of gait parameters could add diagnostic value to the TUGdt tests. Portable devices such as inertial sensors that register gait parameters could therefore be explored in future investigations. Given the rapid technological advances of user-friendly devices [243, 244], the TUGdt test could be developed technologically without losing the advantage of clinical simplicity.

The composition of the TUGdt tests could enable further clinical applications. For physical therapists, observation of a dual-task test performance – particularly when involving one of the best-established tests of functional mobility, i.e., TUG – could imply findings of different character. Detection of physical impairments, fall risk, or risk of physical inactivity are possible areas of future studies. As such, the TUGdt tests would not be limited to revealing cognitive function but could be used as clinical tools with multiple areas of applications. Specific focus on the TUGdt subtasks, e.g., gait initiation or turning, have previously been suggested to entail information of dual-task interference [118] and could reveal information that is useful regarding both cognitive and functional status. Also, such investigations could raise awareness about the cognitive aspect of functional tests. That is, tests that are proposed to measure physical function in which simultaneous attention to mobility and

cognition is required, such as real-world walking [245], may not result in measures that solely reflect physical ability.

In summary, this thesis may be seen as a contribution to the knowledge of how dual-task testing could potentially be used for early detection of dementia disorder, as well as a stepping-stone for further studies.

Acknowledgments

This work was carried out at the Department of Public Health and Caring Sciences, Geriatrics at Uppsala University, and supported by grants from the Swedish Research Council, the Promobilia Foundation, the Geriatric Foundation, the Alzheimer Foundation Sweden, the Uppsala-Örebro Regional Research Council, the Swedish Society of Medicine, the Thureus Fund for Geriatric Research, and the Commemorative Foundation of Ragnhild and Einar Lundström.

I would like to extend my gratitude and appreciation to all of you that have been a part of making my doctoral studies possible.

To my principal supervisor Anna Cristina Åberg, through your enormous dedication to UDDGait™, you enabled my doctoral studies. Thank you for leading the way with your never-ending enthusiasm for what you do, your eye for details in academic writing, and the immense amounts of time and energy you have spent to educate me in the jungle of scientific research. And to my co-supervisors Martin Ingelsson and Erik Rosendahl, thank you for your generous sharing of knowledge, and always having time for spot-on feedback spiced with encouragement and reassurance.

To the remaining members of the UDDGait™ research group: Lars Berglund, Ylva Cedervall, Vilmantas Giedraitis, Lena Kilander, and Kevin McKee, thank you for your patience and guidance. By being the talented yet humble persons you are, all blessed with a sense of humor, you created a fine seedbed for my learning.

To my fellow doctoral students, and all researchers at Geriatrics and Clinical Nutrition and Metabolism, thank you for forming an amiable workplace atmosphere, for the exchange of ideas and advice, and for friendship.

To other friends near and far, thank you for being only a phone call away and providing support in all things that matter.

To my beloved parents Bertil and Birgitta, and my siblings Josef, Samuel, Kristina, and Rebecka, with your respective families, thank you for your help in linguistic and intellectual matters, as well as for your enormous mental support.

To my daughters Elsa and Ylva, my dear sources of joy and energy, thank you for being who you are. Without your cuddles to recharge me, no doctoral thesis would have been written.

And, to my late husband Ali, who left this world in the middle of life and in the middle of my doctoral studies. Thank you for being my greatest supporter, never doubting my capability in academics or any other regard. I know you would be proud of me.

References

1. Laske, C., et al., Innovative diagnostic tools for early detection of Alzheimer's disease. Alzheimers Dement, 2015. **11**(5): p. 561-78.
2. Montero-Odasso, M., *Gait as a biomarker of cognitive impairment and dementia syndromes. Quo vadis?* Eur J Neurol, 2016. **23**(3): p. 437-8.
3. Montero-Odasso, M., et al., *CCCDTD5 recommendations on early non cognitive markers of dementia: A Canadian consensus.* Alzheimers Dement (N Y), 2020. **6**(1): p. e12068.
4. Montero-Odasso, M., et al., *Consensus on Shared Measures of Mobility and Cognition: From the Canadian Consortium on Neurodegeneration in Aging (CCNA).* J Gerontol A Biol Sci Med Sci, 2018.
5. WHO, *Towards a dementia plan: a WHO guide*. 2018.
6. Prince, M., et al., *The global prevalence of dementia: a systematic review and metaanalysis.* Alzheimers Dement, 2013. **9**(1): p. 63-75.e2.
7. Hugo, J. and M. Ganguli, *Dementia and cognitive impairment: epidemiology, diagnosis, and treatment.* Clin Geriatr Med, 2014. **30**(3): p. 421-42.
8. WHO, Global action plan on the public health response to dementia 2017 - 2025. 2017.
9. Livingston, G., et al., Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet, 2020. **396**(10248): p. 413-446.
10. Matthews, F.E., et al., A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. Lancet, 2013. **382**(9902): p. 1405-12.
11. Socialstyrelsen, Vård och omsorg vid demenssjukdom (National guidelines for care and treatment of people with dementia diseases). 2017.
12. Lundebjerg, N.E., et al., When It Comes to Older Adults, Language Matters: Journal of the American Geriatrics Society Adopts Modified American Medical Association Style. J Am Geriatr Soc, 2017. **65**(7): p. 1386-1388.
13. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. 1994, Alexandria: American Psychiatric Association.
14. WHO. International Classification of Diseases and Related Health Problems (ICD). [cited 2021 1 May]; Available from: https://www.who.int/standards/classifications/classification-of-diseases.
15. Cunningham, E.L., et al., Dementia. Ulster Med J, 2015. **84**(2): p. 79-87.
16. Vickers, J.C., et al., Defining the earliest pathological changes of Alzheimer's disease. Curr Alzheimer Res, 2016. **13**(3): p. 281-7.
17. Jellinger, K.A., Morphologic diagnosis of "vascular dementia" - a critical update. J Neurol Sci, 2008. **270**(1-2): p. 1-12.
18. McKeith, I.G., Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. J Alzheimers Dis, 2006. **9**(3 Suppl): p. 417-23.

19. McKhann, G.M., et al., Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol, 2001. **58**(11): p. 1803-9.
20. Cummings, J., et al., Alzheimer's disease drug development pipeline: 2020. Alzheimers Dement (N Y), 2020. **6**(1): p. e12050.
21. Kuller, L.H. and O.L. Lopez, ENGAGE and EMERGE: Truth and consequences? Alzheimers Dement, 2021. **17**(4): p. 692-695.
22. Winblad, B., et al., Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med, 2004. **256**(3): p. 240-6.
23. Reisberg, B. and S. Gauthier, Current evidence for subjective cognitive impairment (SCI) as the pre-mild cognitive impairment (MCI) stage of subsequently manifest Alzheimer's disease. Int Psychogeriatr, 2008. **20**(1): p. 1-16.
24. Nyberg, L. and S. Pudas, Successful Memory Aging. Annu Rev Psychol, 2019. **70**: p. 219-243.
25. Sperling, R.A., et al., Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement, 2011. **7**(3): p. 280-92.
26. Mitchell, A.J., The clinical significance of subjective memory complaints in the diagnosis of mild cognitive impairment and dementia: a meta-analysis. Int J Geriatr Psychiatry, 2008. **23**(11): p. 1191-202.
27. Jonker, C., M.I. Geerlings, and B. Schmand, Are memory complaints predictive for dementia? A review of clinical and population-based studies. Int J Geriatr Psychiatry, 2000. **15**(11): p. 983-91.
28. Wahlund, L.O., E. Pihlstrand, and M.E. Jönhagen, Mild cognitive impairment: experience from a memory clinic. Acta Neurol Scand Suppl, 2003. **179**: p. 21-4.
29. Jessen, F., et al., A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement, 2014. **10**(6): p. 844-52.
30. Buckley, R., et al., Factors affecting subjective memory complaints in the AIBL aging study: biomarkers, memory, affect, and age. Int Psychogeriatr, 2013. **25**(8): p. 1307-15.
31. Yates, J.A., L. Clare, and R.T. Woods, Subjective memory complaints, mood and MCI: a follow-up study. Aging Ment Health, 2017. **21**(3): p. 313-321.
32. Eckerström, M., et al., High Prevalence of Stress and Low Prevalence of Alzheimer Disease CSF Biomarkers in a Clinical Sample with Subjective Cognitive Impairment. Dement Geriatr Cogn Disord, 2016. **42**(1-2): p. 93-105.
33. Mitchell, A.J., et al., Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. Acta Psychiatr Scand, 2014. **130**(6): p. 439-51.
34. Petersen, R.C., et al., Mild cognitive impairment: a concept in evolution. J Intern Med, 2014. **275**(3): p. 214-28.
35. Petersen, R.C., Mild cognitive impairment as a diagnostic entity. J Intern Med, 2004. **256**(3): p. 183-94.
36. Petersen, R.C., et al., Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging. Neurology, 2010. **75**(10): p. 889-97.
37. Overton, M., M. Pihlsgård, and S. Elmståhl, Prevalence and Incidence of Mild Cognitive Impairment across Subtypes, Age, and Sex. Dement Geriatr Cogn Disord, 2019. **47**(4-6): p. 219-232.

38. Luck, T., et al., Mild cognitive impairment: incidence and risk factors: results of the leipzig longitudinal study of the aged. J Am Geriatr Soc, 2010. **58**(10): p. 1903-10.
39. Au, B., S. Dale-McGrath, and M.C. Tierney, Sex differences in the prevalence and incidence of mild cognitive impairment: A meta-analysis. Ageing Res Rev, 2017. **35**: p. 176-199.
40. Mitchell, A.J. and M. Shiri-Feshki, Temporal trends in the long term risk of progression of mild cognitive impairment: a pooled analysis. J Neurol Neurosurg Psychiatry, 2008. **79**(12): p. 1386-91.
41. Mitchell, A.J. and M. Shiri-Feshki, Rate of progression of mild cognitive impairment to dementia--meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand, 2009. **119**(4): p. 252-65.
42. Gao, Q., et al., Mild Cognitive Impairment Reversion and Progression: Rates and Predictors in Community-Living Older Persons in the Singapore Longitudinal Ageing Studies Cohort. Dement Geriatr Cogn Dis Extra, 2018. **8**(2): p. 226-237.
43. Scuteri, A., et al., Depression, hypertension, and comorbidity: disentangling their specific effect on disability and cognitive impairment in older subjects. Arch Gerontol Geriatr, 2011. **52**(3): p. 253-7.
44. Xue, H., et al., Factors for predicting reversion from mild cognitive impairment to normal cognition: A meta-analysis. Int J Geriatr Psychiatry, 2019. **34**(10): p. 1361-1368.
45. Petersen, R.C., Mild Cognitive Impairment. Continuum (Minneap Minn), 2016. **22**(2 Dementia): p. 404-18.
46. Ngandu, T., et al., A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet, 2015. **385**(9984): p. 2255-63.
47. McKhann, G., et al., Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology, 1984. **34**(7): p. 939-44.
48. Chui, H.C., et al., Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology, 1992. **42**(3 Pt 1): p. 473-80.
49. Crum, R.M., et al., Population-based norms for the Mini-Mental State Examination by age and educational level. Jama, 1993. **269**(18): p. 2386-91.
50. Nieuwenhuis-Mark, R.E., The death knoll for the MMSE: has it outlived its purpose? J Geriatr Psychiatry Neurol, 2010. **23**(3): p. 151-7.
51. Tombaugh, T.N. and N.J. McIntyre, The mini-mental state examination: a comprehensive review. J Am Geriatr Soc, 1992. **40**(9): p. 922-35.
52. Arevalo-Rodriguez, I., et al., Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev, 2015(3): p. Cd010783.
53. Mendez, M.F., T. Ala, and K.L. Underwood, Development of scoring criteria for the clock drawing task in Alzheimer's disease. J Am Geriatr Soc, 1992. **40**(11): p. 1095-9.
54. Nishiwaki, Y., et al., Validity of the Clock-Drawing Test as a screening tool for cognitive impairment in the elderly. Am J Epidemiol, 2004. **160**(8): p. 797-807.
55. McDonnell, M., et al., Verbal fluency as a screening tool for mild cognitive impairment. Int Psychogeriatr, 2020. **32**(9): p. 1055-1062.

56. Hampel, H., et al., Core candidate neurochemical and imaging biomarkers of Alzheimer's disease. Alzheimers Dement, 2008. **4**(1): p. 38-48.
57. Hansson, O., et al., Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet Neurol, 2006. **5**(3): p. 228-34.
58. Valotassiou, V., et al., SPECT and PET imaging in Alzheimer's disease. Ann Nucl Med, 2018. **32**(9): p. 583-593.
59. Janelidze, S., et al., Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. Nat Med, 2020. **26**(3): p. 379-386.
60. Mazzeo, S., et al., Combining Cerebrospinal Fluid Biomarkers and Neuropsychological Assessment: A Simple and Cost-Effective Algorithm to Predict the Progression from Mild Cognitive Impairment to Alzheimer's Disease Dementia. J Alzheimers Dis, 2016. **54**(4): p. 1495-1508.
61. Eckerstrom, C., et al., A combination of neuropsychological, neuroimaging, and cerebrospinal fluid markers predicts conversion from mild cognitive impairment to dementia. J Alzheimers Dis, 2013. **36**(3): p. 421-31.
62. Soubra, R., A. Chkeir, and J.-L. Novella, A Systematic Review of Thirty-One Assessment Tests to Evaluate Mobility in Older Adults. BioMed research international, 2019. **2019**: p. 1354362-1354362.
63. International classification of functioning, disability, and health : ICF. 2001, Version 1.0. Geneva : World Health Organization, [2001] ©2001.
64. Bercht, A.L. and N. Wijermans, Mind the mind: How to effectively communicate about cognition in social-ecological systems research. Ambio, 2019. **48**(6): p. 590-604.
65. Demnitz, N., et al., Cognition and mobility show a global association in middle- and late-adulthood: Analyses from the Canadian Longitudinal Study on Aging. Gait & posture, 2018. **64**: p. 238-243.
66. Lord, S.R., K. Delbaere, and D.L. Sturnieks, Chapter 10 - Aging, in Handbook of Clinical Neurology, B.L. Day and S.R. Lord, Editors. 2018, Elsevier. p. 157-171.
67. Clouston, S.A.P., et al., The Dynamic Relationship Between Physical Function and Cognition in Longitudinal Aging Cohorts. Epidemiologic Reviews, 2013. **35**(1): p. 33-50.
68. Morris, R., et al., Gait and cognition: Mapping the global and discrete relationships in ageing and neurodegenerative disease. Neurosci Biobehav Rev, 2016. **64**: p. 326-45.
69. Pugh, K.G. and L.A. Lipsitz, The microvascular frontal-subcortical syndrome of aging. Neurobiol Aging, 2002. **23**(3): p. 421-31.
70. Yogev-Seligmann, G., J.M. Hausdorff, and N. Giladi, The role of executive function and attention in gait. Mov Disord, 2008. **23**(3): p. 329-42; quiz 472.
71. Bohannon, R.W. and A. Williams Andrews, Normal walking speed: a descriptive meta-analysis. Physiotherapy, 2011. **97**(3): p. 182-9.
72. Aboutorabi, A., et al., The effect of aging on gait parameters in able-bodied older subjects: a literature review. Aging Clin Exp Res, 2016. **28**(3): p. 393-405.
73. Demnitz, N., et al., A systematic review and meta-analysis of cross-sectional studies examining the relationship between mobility and cognition in healthy older adults. Gait & Posture, 2016. **50**: p. 164-174.
74. Podsiadlo, D. and S. Richardson, The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc, 1991. **39**(2): p. 142-8.

75. Janssen, W.G., H.B. Bussmann, and H.J. Stam, Determinants of the sit-to-stand movement: a review. Phys Ther, 2002. **82**(9): p. 866-79.
76. Herman, T., N. Giladi, and J.M. Hausdorff, Properties of the 'timed up and go' test: more than meets the eye. Gerontology, 2011. **57**(3): p. 203-10.
77. Mirelman, A., et al., Association between performance on Timed Up and Go subtasks and mild cognitive impairment: further insights into the links between cognitive and motor function. J Am Geriatr Soc, 2014. **62**(4): p. 673-8.
78. Donoghue, O.A., et al., Association between timed up-and-go and memory, executive function, and processing speed. J Am Geriatr Soc, 2012. **60**(9): p. 1681-6.
79. Van Patten, R., et al., The Utility of the Timed Up-and-Go Test in Predicting Cognitive Performance: A Cross-Sectional Study of Independent Living Adults in a Retirement Community. J Appl Gerontol, 2020. **39**(10): p. 1163-1168.
80. Kimura, N., et al., Memory and physical mobility in physically and cognitively-independent elderly people. 2007. **7**(3): p. 258-265.
81. Cohen, R.G., et al., Mobility and Upright Posture Are Associated with Different Aspects of Cognition in Older Adults. Front Aging Neurosci, 2016. **8**: p. 257.
82. Sunderaraman, P., et al., Differential Associations Between Distinct Components of Cognitive Function and Mobility: Implications for Understanding Aging, Turning and Dual-Task Walking. Front Aging Neurosci, 2019. **11**: p. 166.
83. Bohannon, R.W., Reference values for the timed up and go test: a descriptive meta-analysis. J Geriatr Phys Ther, 2006. **29**(2): p. 64-8.
84. Steffen, T.M., T.A. Hacker, and L. Mollinger, Age- and gender-related test performance in community-dwelling elderly people: Six-Minute Walk Test, Berg Balance Scale, Timed Up & Go Test, and gait speeds. Phys Ther, 2002. **82**(2): p. 128-37.
85. Montero-Odasso, M. and V. Hachinski, Preludes to brain failure: executive dysfunction and gait disturbances. Neurol Sci, 2014. **35**(4): p. 601-4.
86. Scherder, E., et al., Gait in ageing and associated dementias; its relationship with cognition. Neurosci Biobehav Rev, 2007. **31**(4): p. 485-97.
87. Yoon, B., et al., Balance and Mobility Performance Along the Alzheimer's Disease Spectrum. J Alzheimers Dis, 2020. **73**(2): p. 633-644.
88. Teo, W.P., et al., Altered prefrontal cortex responses in older adults with subjective memory complaints and dementia during dual-task gait: An fNIRS study. Eur J Neurosci, 2020.
89. Pieruccini-Faria, F., et al., Gait variability across neurodegenerative and cognitive disorders: Results from the Canadian Consortium of Neurodegeneration in Aging (CCNA) and the Gait and Brain Study. Alzheimers Dement, 2021.
90. Garcia-Ptacek, S., et al., Subjective cognitive impairment: Towards early identification of Alzheimer disease. Neurologia, 2016. **31**(8): p. 562-71.
91. Eggermont, L.H., et al., Lower-extremity function in cognitively healthy aging, mild cognitive impairment, and Alzheimer's disease. Arch Phys Med Rehabil, 2010. **91**(4): p. 584-8.
92. Ibrahim, A., D.K.A. Singh, and S. Shahar, 'Timed Up and Go' test: Age, gender and cognitive impairment stratified normative values of older adults. PLoS One, 2017. **12**(10): p. e0185641.
93. Bahureksa, L., et al., The Impact of Mild Cognitive Impairment on Gait and Balance: A Systematic Review and Meta-Analysis of Studies Using Instrumented Assessment. Gerontology, 2017. **63**(1): p. 67-83.

94. Franssen, E.H., et al., Equilibrium and limb coordination in mild cognitive impairment and mild Alzheimer's disease. J Am Geriatr Soc, 1999. **47**(4): p. 463-9.
95. Verghese, J., et al., Gait Dysfunction in Mild Cognitive Impairment Syndromes. Journal of the American Geriatrics Society, 2008. **56**(7): p. 1244-1251.
96. Allali, G. and J. Verghese, Management of Gait Changes and Fall Risk in MCI and Dementia. Curr Treat Options Neurol, 2017. **19**(9): p. 29.
97. Allali, G., et al., Gait phenotype from mild cognitive impairment to moderate dementia: results from the GOOD initiative. Eur J Neurol, 2016. **23**(3): p. 527-41.
98. de Oliveira Silva, F., et al., Stages of mild cognitive impairment and Alzheimer's disease can be differentiated by declines in timed up and go test: A systematic review and meta-analysis. Arch Gerontol Geriatr, 2019. **85**: p. 103941.
99. van Iersel, M.B., et al., Systematic review of quantitative clinical gait analysis in patients with dementia. Z Gerontol Geriatr, 2004. **37**(1): p. 27-32.
100. Allan, L.M., et al., Incidence and prediction of falls in dementia: a prospective study in older people. PLoS One, 2009. **4**(5): p. e5521.
101. Allan, L.M., et al., Prevalence and severity of gait disorders in Alzheimer's and non-Alzheimer's dementias. J Am Geriatr Soc, 2005. **53**(10): p. 1681-7.
102. Fritz, N.E., et al., Motor performance differentiates individuals with Lewy body dementia, Parkinson's and Alzheimer's disease. Gait Posture, 2016. **50**: p. 1-7.
103. Mc Ardle, R., et al., What Can Quantitative Gait Analysis Tell Us about Dementia and Its Subtypes? A Structured Review. J Alzheimers Dis, 2017. **60**(4): p. 1295-1312.
104. Katsumata, Y., et al., Timed up and go test predicts cognitive decline in healthy adults aged 80 and older in Okinawa: Keys to Optimal Cognitive Aging (KOCOA) Project. J Am Geriatr Soc, 2011. **59**(11): p. 2188-9.
105. Lee, J.E., et al., Association Between Timed Up and Go Test and Future Dementia Onset. J Gerontol A Biol Sci Med Sci, 2018. **73**(9): p. 1238-1243.
106. Donoghue, O., et al., Baseline Mobility is Not Associated with Decline in Cognitive Function in Healthy Community-Dwelling Older Adults: Findings From The Irish Longitudinal Study on Ageing (TILDA). The American Journal of Geriatric Psychiatry, 2018. **26**(4): p. 438-448.
107. Beauchet, O., et al., Poor Gait Performance and Prediction of Dementia: Results From a Meta-Analysis. J Am Med Dir Assoc, 2016. **17**(6): p. 482-90.
108. Kikkert, L.H.J., et al., Walking ability to predict future cognitive decline in old adults: A scoping review. Ageing Res Rev, 2016. **27**: p. 1-14.
109. Hackett, R.A., et al., Walking Speed, Cognitive Function, and Dementia Risk in the English Longitudinal Study of Ageing. J Am Geriatr Soc, 2018. **66**(9): p. 1670-1675.
110. Buracchio, T., et al., The trajectory of gait speed preceding mild cognitive impairment. Arch Neurol, 2010. **67**(8): p. 980-6.
111. Verghese, J., et al., Motoric cognitive risk syndrome and the risk of dementia. J Gerontol A Biol Sci Med Sci, 2013. **68**(4): p. 412-8.
112. Verghese, J., et al., Motoric cognitive risk syndrome: multicountry prevalence and dementia risk. Neurology, 2014. **83**(8): p. 718-26.
113. Sekhon, H., et al., Motoric cognitive risk syndrome, incident cognitive impairment and morphological brain abnormalities: Systematic review and meta-analysis. Maturitas, 2019. **123**: p. 45-54.

114. Rosano, C., A.L. Rosso, and S.A. Studenski, Aging, brain, and mobility: progresses and opportunities. J Gerontol A Biol Sci Med Sci, 2014. **69**(11): p. 1373-4.
115. McIsaac, T.L., E.M. Lamberg, and L.M. Muratori, Building a Framework for a Dual Task Taxonomy. BioMed Research International, 2015. **2015**: p. 591475.
116. Klotzbier, T.J. and N. Schott, Cognitive-Motor Interference during Walking in Older Adults with Probable Mild Cognitive Impairment. Front Aging Neurosci, 2017. **9**: p. 350.
117. Plummer, P., et al., Cognitive-motor interference during functional mobility after stroke: state of the science and implications for future research. Arch Phys Med Rehabil, 2013. **94**(12): p. 2565-2574.e6.
118. Bayot, M., et al., The interaction between cognition and motor control: A theoretical framework for dual-task interference effects on posture, gait initiation, gait and turning. Neurophysiol Clin, 2018. **48**(6): p. 361-375.
119. Pashler, H., Dual-task interference in simple tasks: data and theory. Psychol Bull, 1994. **116**(2): p. 220-44.
120. Tombu, M. and P. Jolicoeur, A central capacity sharing model of dual-task performance. J Exp Psychol Hum Percept Perform, 2003. **29**(1): p. 3-18.
121. Yogev-Seligmann, G., J.M. Hausdorff, and N. Giladi, Do we always prioritize balance when walking? Towards an integrated model of task prioritization. Mov Disord, 2012. **27**(6): p. 765-70.
122. Navon, D. and J. Miller, Role of outcome conflict in dual-task interference. J Exp Psychol Hum Percept Perform, 1987. **13**(3): p. 435-48.
123. Beurskens, R., et al., Age-related changes in prefrontal activity during walking in dual-task situations: A fNIRS study. International Journal of Psychophysiology, 2014. **92**(3): p. 122-128.
124. Wollesen, B., et al., Influence of a visual-verbal Stroop test on standing and walking performance of older adults. Neuroscience, 2016. **318**: p. 166-77.
125. Montero-Odasso, M.M., et al., Association of Dual-Task Gait With Incident Dementia in Mild Cognitive Impairment: Results From the Gait and Brain Study. JAMA Neurol, 2017. **74**(7): p. 857-865.
126. Al-Yahya, E., et al., Cognitive motor interference while walking: a systematic review and meta-analysis. Neurosci Biobehav Rev, 2011. **35**(3): p. 715-28.
127. Brustio, P.R., et al., Age-related decrements in dual-task performance: Comparison of different mobility and cognitive tasks. A cross sectional study. PLoS One, 2017. **12**(7): p. e0181698.
128. Li, K.Z.H., et al., Cognitive Involvement in Balance, Gait and Dual-Tasking in Aging: A Focused Review From a Neuroscience of Aging Perspective. Front Neurol, 2018. **9**: p. 913.
129. Raz, N., et al., Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb Cortex, 2005. **15**(11): p. 1676-89.
130. Grady, C.L. and F.I. Craik, Changes in memory processing with age. Curr Opin Neurobiol, 2000. **10**(2): p. 224-31.
131. Ansai, J.H., T.R. Aurichio, and J.R. Rebelatto, Relationship between dual task walking, cognition, and depression in oldest old people. Int Psychogeriatr, 2016. **28**(1): p. 31-8.
132. Nebes, R.D., et al., Dual-task performance in depressed geriatric patients. Psychiatry Res, 2001. **102**(2): p. 139-51.
133. Hausdorff, J.M., et al., Dual-task decrements in gait: contributing factors among healthy older adults. J Gerontol A Biol Sci Med Sci, 2008. **63**(12): p. 1335-43.

134. Kaschel, R., et al., Alzheimer's disease, but not ageing or depression, affects dual-tasking. J Neurol, 2009. **256**(11): p. 1860-8.
135. Ferreira, J., et al., Dual task in healthy elderly, depressive and Alzheimer's disease patients. Jornal Brasileiro de Psiquiatria, 2019. **68**: p. 200-207.
136. Nakaaki, S., et al., Greater impairment of ability in the divided attention task is seen in Alzheimer's disease patients with depression than in those without depression. Dement Geriatr Cogn Disord, 2007. **23**(4): p. 231-40.
137. Almajid, R. and E. Keshner, Role of Gender in Dual-Tasking Timed Up and Go Tests: A Cross-Sectional Study. J Mot Behav, 2019. **51**(6): p. 681-689.
138. Hollman, J.H., J.W. Youdas, and D.J. Lanzino, Gender differences in dual task gait performance in older adults. Am J Mens Health, 2011. **5**(1): p. 11-7.
139. Johansson, J., A. Nordstrom, and P. Nordstrom, Greater Fall Risk in Elderly Women Than in Men Is Associated With Increased Gait Variability During Multitasking. J Am Med Dir Assoc, 2016. **17**(6): p. 535-40.
140. Tomas-Carus, P., et al., Differences between two types of dual tasks according to the educational level in older adults. Arch Gerontol Geriatr, 2020. **91**: p. 104216.
141. Sheridan, P.L., et al., Influence of executive function on locomotor function: divided attention increases gait variability in Alzheimer's disease. J Am Geriatr Soc, 2003. **51**(11): p. 1633-7.
142. Coppin, A.K., et al., Association of executive function and performance of dual-task physical tests among older adults: analyses from the InChianti study. Age Ageing, 2006. **35**(6): p. 619-24.
143. Srygley, J.M., et al., When does walking alter thinking? Age and task associated findings. Brain Res, 2009. **1253**: p. 92-9.
144. Muir, S.W., et al., Gait assessment in mild cognitive impairment and Alzheimer's disease: the effect of dual-task challenges across the cognitive spectrum. Gait Posture, 2012. **35**(1): p. 96-100.
145. Inasaridze, K., et al., Dual task impairments in vascular dementia. Behav Neurol, 2010. **22**(1-2): p. 45-52.
146. Rucco, R., et al., Spatio-temporal and kinematic gait analysis in patients with Frontotemporal dementia and Alzheimer's disease through 3D motion capture. Gait Posture, 2017. **52**: p. 312-317.
147. McIsaac, T.L., et al., Cognitive-Motor Interference in Neurodegenerative Disease: A Narrative Review and Implications for Clinical Management. Frontiers in psychology, 2018. **9**: p. 2061-2061.
148. Leclercq, M., et al., Dual task performance after severe diffuse traumatic brain injury or vascular prefrontal damage. J Clin Exp Neuropsychol, 2000. **22**(3): p. 339-50.
149. Cameron, M.H. and Y. Nilsagard, Balance, gait, and falls in multiple sclerosis. Handb Clin Neurol, 2018. **159**: p. 237-250.
150. Lundin-Olsson, L., L. Nyberg, and Y. Gustafson, "Stops walking when talking" as a predictor of falls in elderly people. Lancet, 1997. **349**(9052): p. 617.
151. Camicioli, R., et al., Talking while walking: the effect of a dual task in aging and Alzheimer's disease. Neurology, 1997. **48**(4): p. 955-8.
152. MacAulay, R.K., et al., Improving Sensitivity to Detect Mild Cognitive Impairment: Cognitive Load Dual-Task Gait Speed Assessment. J Int Neuropsychol Soc, 2017. **23**(6): p. 493-501.
153. Cullen, S., et al., Are Cognitive Subtypes Associated with Dual-Task Gait Performance in a Clinical Setting? J Alzheimers Dis, 2019.

154. Borges Sde, M., M. Radanovic, and O.V. Forlenza, Functional mobility in a divided attention task in older adults with cognitive impairment. J Mot Behav, 2015. **47**(5): p. 378-85.
155. Nielsen, M.S., et al., The Diagnostic and Prognostic Value of a Dual-Tasking Paradigm in a Memory Clinic. J Alzheimers Dis, 2018. **61**(3): p. 1189-1199.
156. Montero-Odasso, M., S.W. Muir, and M. Speechley, Dual-task complexity affects gait in people with mild cognitive impairment: the interplay between gait variability, dual tasking, and risk of falls. Arch Phys Med Rehabil, 2012. **93**(2): p. 293-9.
157. Gillain, S., et al., Gait speed or gait variability, which one to use as a marker of risk to develop Alzheimer disease? A pilot study. Aging Clin Exp Res, 2016. **28**(2): p. 249-55.
158. Ceide, M.E., et al., Walking While Talking and Risk of Incident Dementia. Am J Geriatr Psychiatry, 2018. **26**(5): p. 580-588.
159. Holtzer, R., C. Wang, and J. Verghese, The relationship between attention and gait in aging: facts and fallacies. Motor control, 2012. **16**(1): p. 64-80.
160. Cedervall, Y., K. Halvorsen, and A.C. Aberg, A longitudinal study of gait function and characteristics of gait disturbance in individuals with Alzheimer's disease. Gait Posture, 2014. **39**(4): p. 1022-7.
161. Beauchet, O., et al., Dual-task-related gait changes in the elderly: does the type of cognitive task matter? J Mot Behav, 2005. **37**(4): p. 259-64.
162. Yogev-Seligmann, G., et al., How does explicit prioritization alter walking during dual-task performance? Effects of age and sex on gait speed and variability. Phys Ther, 2010. **90**(2): p. 177-86.
163. Verghese, J., et al., Walking while talking: effect of task prioritization in the elderly. Arch Phys Med Rehabil, 2007. **88**(1): p. 50-3.
164. Montero-Odasso, M. and M. Speechley, Falls in Cognitively Impaired Older Adults: Implications for Risk Assessment And Prevention. J Am Geriatr Soc, 2018. **66**(2): p. 367-375.
165. Holtzer, R., et al., Neurological Gait Abnormalities Moderate the Functional Brain Signature of the Posture First Hypothesis. Brain topography, 2016. **29**(2): p. 334-343.
166. Bloem, B.R., et al., The Multiple Tasks Test: development and normal strategies. Gait Posture, 2001. **14**(3): p. 191-202.
167. Bloem, B.R., et al., The "posture second" strategy: a review of wrong priorities in Parkinson's disease. J Neurol Sci, 2006. **248**(1-2): p. 196-204.
168. Mancioppi, G., et al., The use of Motor and Cognitive Dual-Task quantitative assessment on subjects with mild cognitive impairment: A systematic review. Mech Ageing Dev, 2021. **193**: p. 111393.
169. Belghali, M., et al., Loss of gait control assessed by cognitive-motor dual-tasks: pros and cons in detecting people at risk of developing Alzheimer's and Parkinson's diseases. Geroscience, 2017. **39**(3): p. 305-329.
170. Hunter, S.W., et al., A framework for secondary cognitive and motor tasks in dual-task gait testing in people with mild cognitive impairment. BMC Geriatr, 2018. **18**(1): p. 202.
171. Theill, N., et al., Simultaneously measuring gait and cognitive performance in cognitively healthy and cognitively impaired older adults: the Basel motor-cognition dual-task paradigm. J Am Geriatr Soc, 2011. **59**(6): p. 1012-8.
172. Gillain, S., et al., The value of instrumental gait analysis in elderly healthy, MCI or Alzheimer's disease subjects and a comparison with other clinical tests used in single and dual-task conditions. Ann Phys Rehabil Med, 2009. **52**(6): p. 453-74.

173. Carter, R.E. and J. Lubinsky, Rehabilitation research: principles and applications. 2016, St. Louis, Missouri: Elsevier.
174. Mokkink, L.B., et al., The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. J Clin Epidemiol, 2010. **63**(7): p. 737-45.
175. Montero-Odasso, M., et al., The Motor Signature of Mild Cognitive Impairment: Results From the Gait and Brain Study. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 2014. **69**(11): p. 1415-1421.
176. Yang, Q., et al., Gait Change in Dual Task as a Behavioral Marker to Detect Mild Cognitive Impairment in Elderly Persons: A Systematic Review and Meta-analysis. Arch Phys Med Rehabil, 2020. **101**(10): p. 1813-1821.
177. Hofheinz, M. and C. Schusterschitz, Dual task interference in estimating the risk of falls and measuring change: a comparative, psychometric study of four measurements. Clin Rehabil, 2010. **24**(9): p. 831-42.
178. Smith, E., et al., The reliability of the quantitative timed up and go test (QTUG) measured over five consecutive days under single and dual-task conditions in community dwelling older adults. Gait Posture, 2016. **43**: p. 239-44.
179. Yang, L., et al., Psychometric properties of dual-task balance assessments for older adults: A systematic review. Maturitas, 2015. **80**(4): p. 359-369.
180. Venema, D.M., et al., Minimal Detectable Change in Dual-Task Cost for Older Adults With and Without Cognitive Impairment. J Geriatr Phys Ther, 2018.
181. Pettersson, A.F., E. Olsson, and L.O. Wahlund, Effect of divided attention on gait in subjects with and without cognitive impairment. J Geriatr Psychiatry Neurol, 2007. **20**(1): p. 58-62.
182. Hars, M., F.R. Herrmann, and A. Trombetti, Reliability and minimal detectable change of gait variables in community-dwelling and hospitalized older fallers. Gait & Posture, 2013. **38**(4): p. 1010-1014.
183. Muhaidat, J., et al., The test-retest reliability of gait-related dual task performance in community-dwelling fallers and non-fallers. Gait Posture, 2013. **38**(1): p. 43-50.
184. Rosner, B.A., Fundamentals of Biostatistics. 2006: Thomson-Brooks/Cole.
185. Hollman, J.H., et al., Number of strides required for reliable measurements of pace, rhythm and variability parameters of gait during normal and dual task walking in older individuals. Gait & Posture, 2010. **32**(1): p. 23-28.
186. Lemke, N.C., et al., Validity, test-retest reliability, sensitivity to change and feasibility of motor-cognitive dual task assessments in patients with dementia. Arch Gerontol Geriatr, 2017. **70**: p. 169-179.
187. Montero-Odasso, M., et al., Quantitative gait analysis under dual-task in older people with mild cognitive impairment: a reliability study. J Neuroeng Rehabil, 2009. **6**: p. 35.
188. Wittwer, J.E., et al., Test-retest reliability of spatial and temporal gait parameters of people with Alzheimer's disease. Gait Posture, 2008. **28**(3): p. 392-6.
189. Mokkink, L.B., et al., The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation, 2010. **19**(4): p. 539-549.
190. Haley, S.M. and M.A. Fragala-Pinkham, Interpreting change scores of tests and measures used in physical therapy. Phys Ther, 2006. **86**(5): p. 735-43.
191. de Vet, H.C.W., et al., Measurement in Medicine: A Practical Guide. 2011: Cambridge University Press.

192. Scholtes, V.A., C.B. Terwee, and R.W. Poolman, What makes a measurement instrument valid and reliable? Injury, 2011. **42**(3): p. 236-40.
193. World Health Organization. Dementia: A Public Health Priority. 2012 [cited 2018 18 june]; Available from: http://www.who.int/mental_health/publications/dementia_report_2012/en/.
194. Alzheimer's Disease International. World Alzheimer Report 2015: the Global Impact of Dementia. 2015 [cited 2019 26/8]; Available from: https://www.alz.co.uk/research/world-report-2015.
195. Petersen, R.C., et al., Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology, 2018. **90**(3): p. 126-135.
196. Connolly, A., et al., Underdiagnosis of dementia in primary care: Variations in the observed prevalence and comparisons to the expected prevalence. Aging & Mental Health, 2011. **15**(8): p. 978-984.
197. Grande, G., et al., Measuring gait speed to better identify prodromal dementia. Exp Gerontol, 2019. **124**: p. 110625.
198. Hessen, E., et al., Subjective Cognitive Impairment Is a Predominantly Benign Condition in Memory Clinic Patients Followed for 6 Years: The Gothenburg-Oslo MCI Study. Dementia and geriatric cognitive disorders extra, 2017. **7**(1): p. 1-14.
199. Cedervall, Y., et al., Timed Up-and-Go Dual-Task Testing in the Assessment of Cognitive Function: A Mixed Methods Observational Study for Development of the UDDGait Protocol. Int J Environ Res Public Health, 2020. **17**(5).
200. Folstein, M.F., S.E. Folstein, and P.R. McHugh, "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res, 1975. **12**(3): p. 189-98.
201. Park, J., E. Jeong, and G. Seomun, The clock drawing test: A systematic review and meta-analysis of diagnostic accuracy. J Adv Nurs, 2018. **74**(12): p. 2742-2754.
202. Tombaugh, T.N., Trail Making Test A and B: normative data stratified by age and education. Arch Clin Neuropsychol, 2004. **19**(2): p. 203-14.
203. Tallberg, I.M., et al., Swedish norms for word fluency tests: FAS, animals and verbs. Scand J Psychol, 2008. **49**(5): p. 479-85.
204. Almeida, O.P. and S.A. Almeida, Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. Int J Geriatr Psychiatry, 1999. **14**(10): p. 858-65.
205. Aberg, A.C., B. Lindmark, and H. Lithell, Development and reliability of the General Motor Function Assessment Scale (GMF)--a performance-based measure of function-related dependence, pain and insecurity. Disabil Rehabil, 2003. **25**(9): p. 462-72.
206. Bohannon, R.W., et al., Decrease in timed balance test scores with aging. Phys Ther, 1984. **64**(7): p. 1067-70.
207. Bohannon, R.W., Test-Retest Reliability of Measurements of Hand-Grip Strength Obtained by Dynamometry from Older Adults: A Systematic Review of Research in the PubMed Database. J Frailty Aging, 2017. **6**(2): p. 83-87.
208. Hensel, A., M.C. Angermeyer, and S.G. Riedel-Heller, Measuring cognitive change in older adults: reliable change indices for the Mini-Mental State Examination. Journal of neurology, neurosurgery, and psychiatry, 2007. **78**(12): p. 1298-1303.

209. Sim, J. and P. Arnell, Measurement validity in physical therapy research. Phys Ther, 1993. **73**(2): p. 102-10; discussion 110-5.
210. Hosmer JDW, L.S., Sturdivant RX., Applied Logistic Regression, 3rd edition. 2013, New York.
211. Körtvelyessy, P., et al., Biomarkers of Neurodegeneration in Autoimmune-Mediated Encephalitis. Frontiers in neurology, 2018. **9**: p. 668-668.
212. Naserkhaki, R., et al., cis pT231-Tau Drives Neurodegeneration in Bipolar Disorder. ACS Chem Neurosci, 2019. **10**(3): p. 1214-1221.
213. Colijn, M.A. and G.T. Grossberg, Amyloid and Tau Biomarkers in Subjective Cognitive Impairment. J Alzheimers Dis, 2015. **47**(1): p. 1-8.
214. Jack, C.R., Jr., et al., Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol, 2010. **9**(1): p. 119-28.
215. Nilsson, M.H., et al., The effects of tau, amyloid and white matter lesions on mobility, dual tasking and balance in older people. J Gerontol A Biol Sci Med Sci, 2020.
216. Velickaite, V., et al., Cognitive function in very old men does not correlate to biomarkers of Alzheimer's disease. BMC Geriatr, 2017. **17**(1): p. 208.
217. Mielke, M.M., et al., Indicators of amyloid burden in a population-based study of cognitively normal elderly. Neurology, 2012. **79**(15): p. 1570-1577.
218. Kikkert, L.H.J., et al., Gait characteristics and their discriminative power in geriatric patients with and without cognitive impairment. J Neuroeng Rehabil, 2017. **14**(1): p. 84.
219. Deshpande, N., et al., Gait speed under varied challenges and cognitive decline in older persons: a prospective study. Age and Ageing, 2009. **38**(5): p. 509-514.
220. Yang, L., C. He, and M.Y. Pang, Reliability and Validity of Dual-Task Mobility Assessments in People with Chronic Stroke. PLoS One, 2016. **11**(1): p. e0147833.
221. Calamia, M., K. Markon, and D. Tranel, Scoring higher the second time around: meta-analyses of practice effects in neuropsychological assessment. Clin Neuropsychol, 2012. **26**(4): p. 543-70.
222. Gadotti, I., E. Vieira, and D. Magee, Importance and clarification of measurement properties in rehabilitation %J Brazilian Journal of Physical Therapy. 2006. **10**: p. 137-146.
223. Schaefer, S., The ecological approach to cognitive-motor dual-tasking: findings on the effects of expertise and age. Frontiers in psychology, 2014. **5**: p. 1167-1167.
224. Mitchell, A.J., A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. J Psychiatr Res, 2009. **43**(4): p. 411-31.
225. Hill, N.L., et al., Subjective Cognitive Impairment and Affective Symptoms: A Systematic Review. Gerontologist, 2016. **56**(6): p. e109-e127.
226. Ardila, A., A cross-linguistic comparison of category verbal fluency test (ANIMALS): a systematic review. Archives of Clinical Neuropsychology, 2019. **35**(2): p. 213-225.
227. Meagher, J., et al., Months backward test: A review of its use in clinical studies. World J Psychiatry, 2015. **5**(3): p. 305-14.
228. Cedervall, Y., L. Kilander, and A.C. Aberg, Declining physical capacity but maintained aerobic activity in early Alzheimer's disease. Am J Alzheimers Dis Other Demen, 2012. **27**(3): p. 180-7.

229. Costa, R., et al., Spatial orientation tasks show moderate to high accuracy for the diagnosis of mild cognitive impairment: a systematic literature review. Arq Neuropsiquiatr, 2020. **78**(11): p. 713-723.
230. Henry, J.D., J.R. Crawford, and L.H. Phillips, Verbal fluency performance in dementia of the Alzheimer's type: a meta-analysis. Neuropsychologia, 2004. **42**(9): p. 1212-1222.
231. Vaughan, R.M., et al., Semantic and Phonemic Verbal Fluency Discrepancy in Mild Cognitive Impairment: Potential Predictor of Progression to Alzheimer's Disease. J Am Geriatr Soc, 2018.
232. Hommel, B., Dual-Task Performance: Theoretical Analysis and an Event-Coding Account. J Cogn, 2020. **3**(1): p. 29.
233. Plummer, P. and G. Eskes, Measuring treatment effects on dual-task performance: a framework for research and clinical practice. Front Hum Neurosci, 2015. **9**: p. 225.
234. Agmon, M., et al., The role of gender in the association between personality and task priority in older adults' dual-tasking while walking. BMC Geriatr, 2018. **18**(1): p. 1.
235. Cullen, S., et al., Guidelines for Gait Assessments in the Canadian Consortium on Neurodegeneration in Aging (CCNA). Can Geriatr J, 2018. **21**(2): p. 157-165.
236. Nasreddine, Z.S., et al., The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc, 2005. **53**(4): p. 695-9.
237. Allan, L.M., et al., Prevalence and Severity of Gait Disorders in Alzheimer's and Non-Alzheimer's Dementias. Journal of the American Geriatrics Society, 2005. **53**(10): p. 1681-1687.
238. Mokkink, L.B. COSMIN Study design checklist for patient-reported outcome measurement instruments. 2019 [cited 2020; Available from: https://www.cosmin.nl/wp-content/uploads/COSMIN-study-designing-checklist_final.pdf.
239. Terwee, C.B., et al., Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol, 2007. **60**(1): p. 34-42.
240. Bruton, A., J.H. Conway, and S.T. Holgate, Reliability: What is it, and how is it measured? Physiotherapy, 2000. **86**(2): p. 94-99.
241. Hauer, K. and P. Oster, MEASURING FUNCTIONAL PERFORMANCE IN PERSONS WITH DEMENTIA. 2008. **56**(5): p. 949-950.
242. De Cock, A.M., et al., Comprehensive Quantitative Spatiotemporal Gait Analysis Identifies Gait Characteristics for Early Dementia Subtyping in Community Dwelling Older Adults. Front Neurol, 2019. **10**: p. 313.
243. Buckley, C., et al., The Role of Movement Analysis in Diagnosing and Monitoring Neurodegenerative Conditions: Insights from Gait and Postural Control. Brain Sci, 2019. **9**(2).
244. Blumenthal, J., et al., Cognitive capacity and smartphone dual-task gait measurement. Procedia Computer Science, 2017. **111**: p. 87-94.
245. Poole, V.N., et al., Motor-Cognitive Neural Network Communication Underlies Walking Speed in Community-Dwelling Older Adults. Front Aging Neurosci, 2019. **11**: p. 159.

Acta Universitatis Upsaliensis

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1765

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title "Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine".)

Distribution: publications.uu.se
urn:nbn:se:uu:diva-451233

ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2021