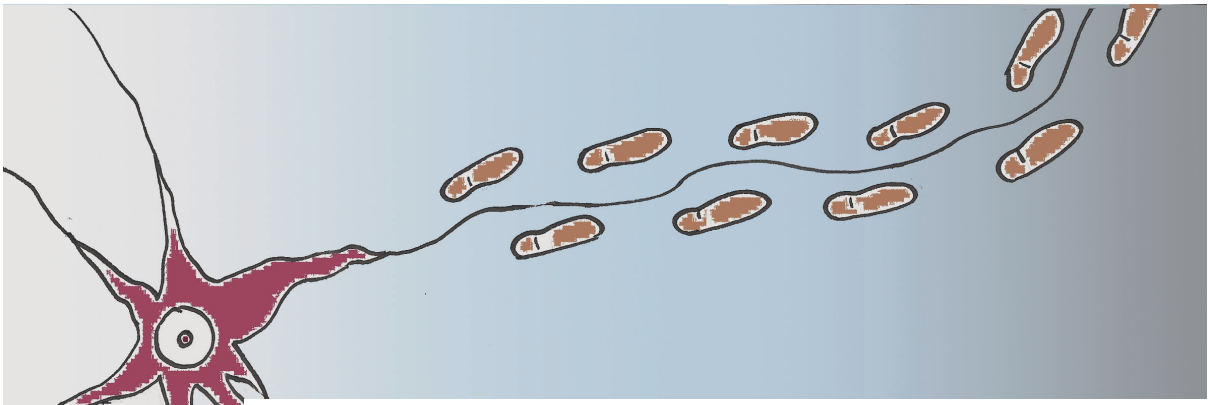
Objective and subjective aspects related to walking in people with neurodegenerative disorders

Lindh-Rengifo, Magnus

2022

Document Version:
Publisher's PDF, also known as Version of record



Objective and subjective aspects related to walking in people with neurodegenerative disorders

MAGNUS LINDH-RENGIFO
DEPARTMENT OF HEALTH SCIENCES | FACULTY OF MEDICINE | LUND UNIVERSITY

Printed by Media-Tryck, Lund 2022 NORDIC SWAN ECOLABEL 3041 0903

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Health Sciences

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2022:173
ISBN 978-91-8021-335-6
ISSN 1652-8220

Objective and subjective aspects related to walking in people with neurodegenerative disorders

Magnus Lindh-Rengifo

LUNDS
UNIVERSITET

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Health Science Centre, Lund. December 16th, 2022 at 09.00.

Faculty opponent
Associate professor David Moulaee Conradsson, Karolinska Institute

Organization LUND UNIVERSITY Department of Health Sciences	**Document name:** Doctoral dissertation **Date of issue:** 16th of December 2022
Author: Magnus Lindh-Rengifo	Sponsoring organization

Title and subtitle Objective and subjective aspects related to walking in people with neurodegenerative disorders

Abstract

INTRODUCTION: The two most common neurodegenerative disorders are Alzheimer's disease (AD) and Parkinson's disease (PD). They affect millions of people worldwide and will increase in the upcoming decades. Mild cognitive impairment (MCI) is considered an intermediate stage between unimpaired cognition and major neurocognitive disorder (i.e., "dementia"). Decreased gait speed seems to precede cognitive decline, but little is known about how objective gait is structured as well as how it is associated with common AD-related brain pathologies in patients with MCI. Such knowledge can be of value for future longitudinal follow-ups, which could determine whether specific gait components or parameters are of diagnostic or prognostic value. Although gait impairments are common in people with PD and considerable research have been published on objective gait measures in people with PD, less is known about subjective aspects related to walking in people with PD. A better understanding of perceived walking difficulties and concerns about falling in people with PD could lead to a better targeted rehabilitative and physiotherapeutic care.

AIM: The overarching aim was to explore objective gait characteristics in people with MCI (Studies I-II) and without MCI (Study I) in terms of structure and relation to brain pathology. Moreover, the aim was to explore how perceived walking difficulties and concerns about falling evolve over time in people with PD and to identify predictive factors.

METHODS: This thesis comprises four studies. Studies I-II had a cross-sectional design and focused on objective gait (comfortable speed) as a single task. Study I included 333 individuals (MCI, n = 114; cognitively unimpaired, n = 219) and two principal component analyses of common gait parameters were performed. Study II (n = 96 patients with MCI) investigated the effect of AD-related brain pathologies (i.e., tau, amyloid-β and white matter hyperintensities) on distinct gait parameters using multivariable linear regression analysis (MLR). Studies III-IV included people with PD and used longitudinal (baseline and a 3-year follow-up) data. Using paired samples t-test, Study III (n = 148) investigated the evolution of perceived walking difficulties (assessed with the generic Walk-12) as well as identified important factors for predicting perceived walking difficulties after a 3-year period (analysis: MLR). Study IV (n = 151) focused on how concerns about falling (assessed with the Falls Efficacy Scale-International) evolved over time and also identified predictors of concerns about falling (analysis: MLR).

RESULTS: Four independent components of gait were identified when analyzing objective gait measures in people with and without MCI; Variability, Pace/Stability, Rhythm and Asymmetry. In patients with MCI, increased tau-PET pathology in AD-related regions of interest was associated ($p \leq 0.024$) with increased step velocity variability and step length. In people with PD, perceived walking difficulties and concerns about falling had increased after 3 years ($p < 0.001$). Motor (e.g., perceived balance problems while dual tasking and concerns about falling) and non-motor related factors (i.e., pain) predicted perceived walking difficulties. Personal (i.e., age) and motor related factors (e.g., perceived balance problems while dual tasking) predicted concerns about falling. Perceived balance problems while dual tasking predicted both a change in perceived walking difficulties (other predictors: global cognitive function) and concerns about falling (other predictors: age and sex) ($p \leq 0.043$).

CONCLUSIONS: Relationships between common gait parameters seem similar in people with and without MCI. The identified components of gait provide a basis for how common gait parameters are related during single task gait. A better understanding of the effect of tau-PET pathology on distinct aspects of gait (i.e., increased step length and step velocity variability) is of interest for physical therapists that assess these patients. Future longitudinal studies (as well as studies including other samples and settings) need to corroborate or refute these findings. Importantly, future longitudinal studies should also address the diagnostic and prognostic value of different gait parameters. In addition, rehabilitation efforts for people with PD could target significant predictors related to perceived walking difficulties and concerns about falling, such as motor (e.g., perceived balance problems while dual tasking) as well as non-motor factors (e.g., pain). That is, future intervention studies could target modifiable factors when aiming at improving subjective aspects related to walking in people with PD.

Key words: Neurodegenerative disorders, Parkinsons disease, Mild cognitive impairment, Gait, Walking, Perceived walking difficulties, Concerns about falling

Classification system and/or index terms (if any)

ISSN and key title**:** 1652-8220		**Language:** English
Recipient's notes	**Number of pages:** 120	**ISBN:** 978-91-8021-335-6

Signature Date 2022-11-10

Objective and subjective aspects related to walking in people with neurodegenerative disorders

Magnus Lindh-Rengifo

LUNDS
UNIVERSITET

Cover illustration by Max da Rocha

Faculty of Medicine
Department of Health Sciences
Lund University

ISBN 978-91-8021-335-6
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2022

Till det som får mig att leva, inte enbart existera

Table of contents

Svensk populärvetenskaplig sammanfattning

De två vanligaste neurodegenerativa sjukdomarna är Alzheimers sjukdom och Parkinsons sjukdom. Vid dessa sjukdomar sker en ansamling av proteiner i hjärnan som tros bidra till nedbrytning av nervceller; denna nedbrytning kan pågå under flera decennier innan diagnos kan ställas. Dessa sjukdomar har en stor påverkan på de drabbades livskvalité och självständighet i vardagen. Gångförmåga är en viktig faktor som är kopplad till självständighet. Att utvärdera och åtgärda gångsvårigheter utgör centrala uppgifter för en fysioterapeut.

Gånghastighet har ofta använts som en tillförlitlig markör för hälsostatus. Låg gånghastighet har även kopplats samman med en ökad risk för att utveckla kognitiv nedsättning och kognitiv sjukdom (”demens”). Kanske kan även andra gångaspekter, till exempel variation i steglängd, vara relevanta att undersöka när det gäller kognitiv nedsättning. Lindrig kognitiv funktionsnedsättning (MCI) kan ses som ett mellanliggande stadium mellan kognitivt frisk och demenssjuk. I detta skede finns en objektiv försämring i kognitiv förmåga men den påverkar inte självständigheten i vardagen. I dagsläget finns det lite forskning som gäller hur objektiv gång kan klassificeras hos personer med MCI. Det vill säga, hur olika gångmått, så som steglängd och gånghastighet, kan struktureras och hur de relaterar till varandra. Dessutom finns det bristfällig kunskap huruvida Alzheimertypiska sjukdomsmarkörer i hjärnan relaterar till olika gångaspekter hos personer med MCI.

När det gäller Parkinsons sjukdom finns det mycket forskning som visar hur objektiva gångaspekter påverkas av sjukdomen. Däremot finns det mindre kunskap om hur subjektiva aspekter (upplevda gångsvårigheter och en bekymran för att falla) påverkas över tid, inklusive en bristfällig kunskap kring vilka faktorer som kan förklara en framtida försämring av dessa aspekter.

Det övergripande syftet med denna avhandling var att få en bättre förståelse av både objektiva och subjektiva aspekter relaterade till gång i olika neurodegenerativa sjukdomar. Avhandlingen inkluderar personer med MCI (studier I-II) och personer med Parkinsons sjukdom (studier III-IV).

Tre av fyra studier (studier I-III) berör objektiva eller subjektiva gångaspekter, medan den fjärde studien berör bekymran för att falla i samband med olika vardagsaktiviteter. Avhandlingens två första studier använder sig av tvärsnittsdata

(det vill säga data inhämtad under ett tillfälle). Studie I undersöker hur objektiv gång kan klassificeras och studerar relationen mellan olika objektiva gångparametrar hos personer med MCI respektive hos kognitivt opåverkade individer. Studie II undersöker effekten av olika Alzheimerrelaterade sjukdomsförändringar (exempelvis sjukliga proteinansamlingar) i hjärnan på objektiva gångparametrar hos personer med MCI.

Studie III och IV använder sig av data insamlad vid två olika tidpunkter: en baslinje-mätning och en uppföljning 3 år senare. Studierna undersöker hur upplevda gångsvårigheter och bekymran för att falla förändras över tid hos personer med Parkinsons sjukdom. Utöver detta undersöks vilka faktorer som kan förutsäga dessa två subjektiva gångrelaterade aspekter.

Avhandlingens resultat

Hos både kognitivt opåverkade individer samt personer med MCI identifierades fyra komponenter av gång: *variabilitet* (variationen i ett gångmått), *tempo*/*stabilitet*, *rytm* samt *asymmetri* (skillnaden mellan höger och vänster sida). Hos patienter med MCI sågs ökad tau-inlagring (ett protein nära kopplat till Alzheimers sjukdom) i Alzheimerrelaterade områden i hjärnan vara associerat med ökad steglängd, samt med ökad variation i gånghastigheten. Sistnämnda indikerar att variationsmått av gånghastighet kan vara av värde för personer med en ökad risk att utveckla Alzheimers sjukdom. Det krävs dock studier med upprepade uppföljningar under flera år för att kunna fastställa huruvida gångparametrar kan vara av diagnostiskt/prognostiskt värde för personer som har en ökad risk att utveckla demens.

Hos personer med Parkinsons sjukdom ökade både upplevda gångsvårigheter samt bekymran för att falla efter 3 år. Att både upplevda gångsvårigheter och bekymran för att falla ökar efter en 3-årsperiod antyder att det är viktigt att följa upp dessa aspekter kontinuerligt. Detta eftersom de kan bidra till sänkt fysisk aktivitetsnivå, upplevd delaktighet och livskvalité. Flera faktorer visade sig kunna förutspå upplevda gångsvårigheter och bekymran för att falla hos personer med Parkinsons sjukdom. Upplevda balanssvårigheter när två saker görs samtidigt förutsåg både ökade upplevda gångsvårigheter och mer uttalad bekymran för att falla 3 år senare. Även smärta förutsåg upplevda gångsvårigheter hos personer med Parkinsons sjukdom. Dessa potentiellt förändringsbara faktorer skulle kunna adresseras i framtida insatser som syftar till att förbättra subjektiva aspekter kopplat till gång hos personer med Parkinsons sjukdom.

List of scientific articles

This thesis is based on the following papers:

I. Lindh-Rengifo M, Jonasson SB, Ullén S, Stomrud E, Palmqvist S, Mattsson-Carlgren N, Hansson O, Nilsson MH. Components of gait in people with and without mild cognitive impairment. *Gait & Posture*, 2022, 93, pages 83-89.

II. Lindh-Rengifo M, Jonasson SB, Ullén S, Van Westen D, Stomrud E, Palmqvist S, Mattsson-Carlgren N, Nilsson MH, Hansson O. Effects of brain pathologies on objective gait parameters in patients with mild cognitive impairment. *Manuscript.*

III. Lindh-Rengifo M, Jonasson SB, Ullén S, Mattsson-Carlgren N, Nilsson MH. Perceived walking difficulties in Parkinson's disease- predictors and changes over time. *BMC Geriatrics*, 2021, Vol. 21, issue 1, pages 221.

IV. Lindh-Rengifo M, Jonasson SB, Mattsson N, Ullén S, Nilsson MH. Predictive Factors of Concerns about Falling in People with Parkinson's Disease: A 3-year longitudinal study. *Parkinson's Disease*, 2019, 4747320.

Abstract

INTRODUCTION: The two most common neurodegenerative disorders are Alzheimer's disease (AD) and Parkinson's disease (PD). They affect millions of people worldwide and will increase in the upcoming decades. Mild cognitive impairment (MCI) is considered an intermediate stage between unimpaired cognition and major neurocognitive disorder (i.e., "dementia"). Decreased gait speed seems to precede cognitive decline, but little is known about how objective gait is structured as well as how it is associated with common AD-related brain pathologies in patients with MCI. Such knowledge can be of value for future longitudinal follow-ups, which could determine whether specific gait components or parameters are of diagnostic or prognostic value. Although gait impairments are common in people with PD and considerable research have been published on objective gait measures in people with PD, less is known about subjective aspects related to walking in people with PD. A better understanding of perceived walking difficulties and concerns about falling in people with PD could lead to a better targeted rehabilitative and physiotherapeutic care.

AIM: The overarching aim was to explore objective gait characteristics in people with MCI (Studies I-II) and without MCI (Study I) in terms of structure and relation to brain pathology. Moreover, the aim was to explore how perceived walking difficulties and concerns about falling evolve over time in people with PD and to identify predictive factors.

METHODS: This thesis comprises four studies. Studies I-II had a cross-sectional design and focused on objective gait (comfortable speed) as a single task. Study I included 333 individuals (MCI, n = 114; cognitively unimpaired, n = 219) and two principal component analyses of common gait parameters were performed. Study II (n = 96 patients with MCI) investigated the effect of AD-related brain pathologies (i.e., tau, amyloid-β and white matter hyperintensities) on distinct gait parameters using multivariable linear regression analysis (MLR). Studies III-IV included people with PD and used longitudinal (baseline and a 3-year follow-up) data. Using paired samples t-test, Study III (n = 148) investigated the evolution of perceived walking difficulties (assessed with the generic Walk-12) as well as identified important factors for predicting perceived walking difficulties after a 3-year period (analysis: MLR). Study IV (n = 151) focused on how concerns about falling (assessed with the Falls Efficacy Scale-International) evolved over time and also identified predictors of concerns about falling (analysis: MLR).

RESULTS: Four independent components of gait were identified when analyzing objective gait measures in people with and without MCI; Variability, Pace/Stability, Rhythm and Asymmetry. In patients with MCI, increased tau-PET pathology in AD-related regions of interest was associated ($p \leq 0.024$) with increased step velocity variability and step length. In people with PD, perceived walking difficulties and concerns about falling had increased after 3 years ($p < 0.001$). Motor (e.g., perceived balance problems while dual tasking and concerns about falling) and non-motor related factors (i.e., pain) predicted perceived walking difficulties. Personal (i.e., age) and motor related factors (e.g., perceived balance problems while dual tasking) predicted concerns about falling. Perceived balance problems while dual tasking predicted both a change in perceived walking difficulties (other predictors: global cognitive function) and concerns about falling (other predictors: age and sex) ($p \leq 0.043$).

CONCLUSIONS: Relationships between common gait parameters seem similar in people with and without MCI. The identified components of gait provide a basis for how common gait parameters are related during single task gait. A better understanding of the effect of tau-PET pathology on distinct aspects of gait (i.e., increased step length and step velocity variability) is of interest for physical therapists that assess these patients. Future longitudinal studies (as well as studies including other samples and settings) need to corroborate or refute these findings. Importantly, future longitudinal studies should also address the diagnostic and prognostic value of different gait parameters. In addition, rehabilitation efforts for people with PD could target significant predictors related to perceived walking difficulties and concerns about falling, such as motor (e.g., perceived balance problems while dual tasking) as well as non-motor factors (e.g., pain). That is, future intervention studies could target modifiable factors when aiming at improving subjective aspects related to walking in people with PD.

Abbreviations

Aβ	Amyloid-β
AD	Alzheimer's disease
ADAS (cog)	Alzheimer's Disease Assessment Scale, cognitive subscale
ADD	Alzheimer's disease dementia
ADL	Activities of daily living
aMCI	Amnestic mild cognitive impairment
naMCI	Non-amnestic mild cognitive impairment
BioFINDER	Biomarkers for identifying neurodegenerative disorders early and reliably
CSF	Cerebrospinal fluid
CU	Cognitively unimpaired
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FES-I	Falls Efficacy Scale-International
FOF	Fear of falling
HHPD	Home and health in people ageing with Parkinson's disease
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination
Motor-ACT	Motor aspects and activities in relation to cognitive decline
MRI	Magnetic resonance imaging
PADLS	Parkinson's Disease Activities of Daily Living Scale
PCA	Principal component analysis
PD	Parkinson's disease
PET	Positron emission tomography
PROM	Patient-reported outcome measure

SCD	Subjective cognitive decline
SUVR	Standardized uptake value ratio
TIA	Transient ischemic attack
UPDRS III	Unified Parkinson's disease rating scale, part III
VaD	Vascular dementia
Walk-12G	Generic Walk-12
WMH	White matter hyperintensities

Thesis at a glance

Study I. Components of gait in people with and without mild cognitive impairment, n = 333.	
Aim	To define components of single task gait by exploring objective gait characteristics in people with MCI (with signs of an incipient neurocognitive disorder) and cognitiviely unimpaired (CU) people.
Methods	Cross-sectional data included 114 persons with MCI and 219 CU. Gait at comfortable speed was assessed by using an electronic walkway (GAITRite®). Principal component analyses (PCAs, varimax rotation) included 17 (MCI) and 15 (CU) gait parameters, respectively.
Results	Four components of gait were identified in both the MCI and the CU group: Variability, Pace/Stability, Rhythm and Asymmetry. Three components had the same highest loading gait parameter (step velocity variability, step length and step time) in both groups. For Asymmetry, the highest loading parameter was stance time asymmetry (MCI) and swing time asymmetry (CU).
Conclusions	Gait components are similar in people with and without MCI, however some differences exists. Highly loading gait parameters in the various components might be suitable core variables in future studies, as they represent distinct components of gait.
Study II. Effects of brain pathologies on objective gait parameters in patients with MCI, n = 96.	
Aim	To explore independent effects of tau and amyloid-β (Aβ) pathology as well as white matter hyperintensities (WMH), on objective gait parameters (i.e., step velocity variability, step length, step time and stance time asymmetry) from various components of gait in patients with MCI.
Methods	Multivariable linear regression analyses using cross-sectional data. Independent variables: Positron emission tomography (PET) tau, PET Aβ and WMH. Dependent variables: four gait parameters (see aim).
Results	Tau pathology was associated with increased step velocity variability as well as with increased step length. The effects remained when investigating specific Braak regions (I-II, III-IV and V-VI). Aβ-PET load and WMH showed no significant associations with the studied gait parameters
Conclusions	Gait variability might be a sensitive gait component in relation to tau pathology in people with MCI with an incipient neurocognitive disorder. Physical therapists should pay specific attention to step velocity variability when assessing gait in patients with MCI
Study III. Evolution of perceived walking difficulties in people with Parkinson's disease (PD), n = 148.	
Aim	To investigate how perceived walking difficulties evolve over a 3-year period in people with PD. A specific aim was to identify predictive factors of perceived walking difficulties.
Methods	Perceived walking difficulties was assessed with the generic Walk-12 (Walk-12G) questionnaire. Paired samples t-test examined the change after 3 years. Walk-12G scores at the 3-year follow-up were the dependent variable in multivariable linear regression analyses. Model 1 investigated predictors of perceived walking difficulties (controlled for age). Model 2 also controlled for baseline Walk-12G, targeting predictors of *a change* in perceived walking difficulties.
Results	Perceived walking difficulties increased after 3 years; the increase exceeded the standard error of measurement. Model 1 identified concerns about falling, perceived balance problems while dual tasking (DT) and pain as statistically significant predictors. Model 2 identified perceived balance problems while DT and global cognitive functioning as predictors of a change in perceived walking difficulties.
Conclusions	Perceived walking difficulties increased after 3 years in people with PD. Motor and non-motor aspects were predictive factors. Targeting modifiable aspects (e.g., perceived balance problems while DT) might have an effect on perceived walking difficulties in future intervention studies.
Study IV. Predictive factors of concerns about falling in people with Parkinson's disease, n = 151.	
Aim	To identify predictive factors of concerns about falling after 3 years in people with PD, with and without adjusting for concerns about falling at baseline.
Methods	Concerns about falling was assessed with the Falls Efficacy Scale – International (FES-I) at baseline and after 3 years. The latter was dependent variable in multivariable linear regression analyses that identified predictive factors of concerns about falling (model 1) after 3 years and predictors of a change in concerns about falling (model 2, controlling for baseline FES-I).
Results	In Model 1, perceived walking difficulties was the strongest predictive factor, followed by age, perceived balance problems while DT and difficulties/dependence in activities of daily living. Model 2 identified perceived balance problems while DT, increased age and female sex as significant predictors of a change in concerns about falling.
Conclusions	Perceived balance problems in DT and age predicted both concerns about falling and a change in concerns about falling. Several modifiable factors were identified as predictors. Targeting these factors could help address concerns about falling in rehabilitation of people with PD.

Rationale

Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common forms of neurodegenerative disorders. To date, there is no curative treatment for the underlying pathology. Physiotherapists often assess and treat aspects related to walking in their clinical practice. A comprehensive understanding of both objective and subjective aspects related to walking in people with AD and PD could nurture interventions that result in that individuals remain physically active, independent and maintain their quality of life for as long as possible. A better understanding of these aspects of walking may also be important from a diagnostic and prognostic perspective.

The number of people living with a major neurocognitive disorder ("dementia") is expected to greatly increase until 2050. AD is the most common form of dementia, i.e., about 70% of all dementia cases. Gait disturbances can be seen as a prodromal sign of future cognitive decline. In the AD continuum, mild cognitive impairment (MCI) can be seen as an intermediate stage between cognitively healthy and dementia. People with MCI perform worse than cognitively healthy on objective gait measures. However, they walk better than people with dementia. Little is known about how common gait parameters in people with MCI relate to each other as well as how their structure differs in comparison to the structure of gait parameters in people without MCI. Moreover, there are knowledge gaps regarding the independent effects of common dementia related pathology on objective gait performance in people with MCI. A better understanding of the effect of specific Alzheimer-related pathology on various aspects of gait might help in directing focus on more specific gait parameters in people with MCI.

As PD is clearly affecting motor functions, objective aspects of gait in people with PD have been researched in depth. However, subjective aspects relating to walking reflect how the person perceives their difficulties or concerns. A better understanding of which variables that affect perceived walking difficulties and concerns about falling, as well as how they evolve over time is warranted. This information might help target modifiable factors in future intervention studies and help direct the rehabilitative care that is provided.

Introduction

This thesis has a specific focus on gait (studies I-III) and concerns about falling (study IV). In this first part of the introduction, I focus on these constructs in general terms and in relation to cognitively healthy older people.

Gait

Gait is a person's manner of walking [1]. In this thesis the terms gait and walking are often seen and used interchangeably. Although, in relation to the International Classification of Function, Disability and Health (ICF), *gait* is considered a neuromusculoskeletal and movement-related body function [2]. The term gait focuses on movement patterns, often involving descriptions of these patterns. Gait can for example be described in terms of having an asymmetrical or hemiplegic gait pattern. Gait parameters that objectively describe measures of gait, such as step length, step time or variability are commonly used when discussing different patterns of gait. *Walking* in relation to ICF is more specifically seen as an activity of mobility [2]. Walking (i.e., the process of coordinated locomotion, step by step, with one foot in contact with the ground at all times) is often intended to keep us moving in a goal-directed course. Walking might seem automated, demanding little interaction across different abilities. However, far from such a simplistic view, walking involves a highly complex set of movements and interactions between different systems and functions to keep us erect and moving. The abilities needed to walk safely involve e.g., muscular, visual, vestibular, proprioceptive, neurological and cognitive functioning [3, 4]. In everyday situations, walking is often performed concurrently while performing another task (e.g., talking), often referred to as dual task walk [5]. This thesis focuses on gait as a single task.

Gait and cognition

Gait has previously been considered an automated process with little involvement from the more cognitively complex domains (e.g., executive or attentional functioning). However, gait should rather be considered a task requiring several

cognitive functions, such as executive and attentional ability [4-6]. Gait not only demands the direct execution of movements, but also adjustments of gait patterns due to anticipatory movements and predictive gait programs [7]. No single part of the brain is exclusively in control of all motor tasks involved in gait. When performing single task gait, several different brain areas such as the basal ganglia, cerebellum and cerebral cortex are involved in initiating, executing and regulating gait movement [8, 9]. These areas are affected by the visual and somatosensory input that also affect gait [8].

Different situations and surroundings demand different abilities to manage incoming information [5]. To walk safely in everyday life, gait needs to be both repetitive and flexible in altering for example gait speed, step length and step width [5]. Altering gait requires variability in gait. Variability has been proposed as one aspect of gait enabling and considering gait control [5, 10, 11].

Objective and subjective gait measures

Walking performance can be measured both objectively and subjectively. Objective measures include for example using a stopwatch, wearable sensors or an instrumented walkway. The person can then be asked to walk for example at a comfortable self-selected pace, fast pace or while performing an additional concurrent task (i.e., dual task walking). Body-worn sensors and instrumented walkways provide more detailed objective data, such as spatiotemporal parameters. These additional measures are not obtained when only using a stopwatch. The same gait variables measured with different electronic gait instruments, such as body-worn sensors and instrumented walkways, are often well correlated when assessed in clinical settings [12]. While instrumented walkways are more often used in a research setting, body-worn sensors can more easily be used in a home-based context [13].

Subjective walking ability can be measured from different perspectives, such as the perspective of the clinician or the patient's own perspective. Examples of clinician-based outcome measures include item 29 of the unified Parkinson's disease rating scale part III (UPDRS III) [14], the Functional Gait Assessment [15] and the gait oriented sub assessment of the Tinetti performance oriented mobility assessment [16]. Measuring walking performance from the patient's point of view requires use of a patient-reported outcome measure (PROM) [17, 18]. PROMs are commonly used to evaluate the effectiveness of clinical studies from the patients perspective and can provide an additional perspective on a trial or health status [18]. In relation to gait, PROMs often relate to how the individual perceives their walking ability. One such subjective walking assessment is the generic Walk-12 (Walk-12G) [19]. The Walk-12G includes 12 items regarding the patient's perception of their walking

difficulties during the last two weeks. In people with Parkinson's disease (PD), Walk-12G has been moderately correlated with the objective gait parameter step velocity, which indicates that the Walk-12G might represent another perspective of gait than objective gait performance [20].

Gait cycle

During habitual straightforward walking, a gait cycle starts with the initiation of a foot's contact with the ground (e.g., right foot) and ends when the same foot is in contact with the ground again [1, 21]. The gait cycle consists of the combined step length of each foot. The *step* length is the distance between the contact of one foot and the initial step contact of the opposite foot. The distance starting from the heel center of one foot to the consecutive footprint of the same foot is named *stride* length [1, 21, 22]. During continuous walking in a straightforward direction, this gait cycle is repeated. Gait cycle time periods can be divided into stance phases and swing phases of the limbs [1, 21]. A stance period is the period when a foot or limb is in contact with the ground and supports the body weight. It can involve periods of both single and double support. When the body weight is supported by a single foot, the opposite foot can swing forward (i.e., the swing phase) and ends the swing phase by touching the ground again. When both feet are on the ground, the body weight is shifted from one foot to the other and the cycle repeats [1, 21]. Figure 1 illustrates a schematic view of commonly used temporal gait measures.

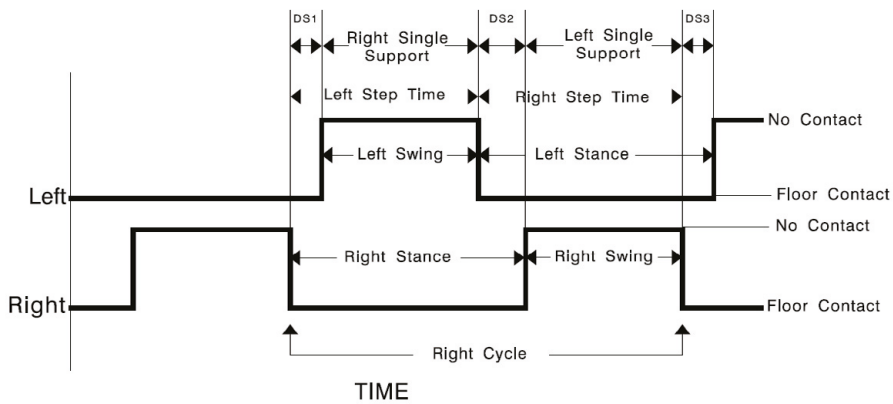


Figure 1. Schematic view of temporal gait parameters. Figure reprinted with permission from the GAITRite Electronic Walkway Technical Reference (WI-02-15), Revision L.

Gait parameters

Gait can be assessed objectively and quantitatively in different dimensions. It is most commonly measured in dimensions using temporal parameters (e.g., step or stride time), spatial parameters (e.g., step or stride length) or through the combination of the two dimensions, i.e., spatiotemporal parameters (e.g., gait velocity).

Gait velocity or gait speed is a commonly investigated gait parameter. It is regarded as a reliable and valid measure of overall physical health [23-25], linked to both future survival [25, 26] and cognitive function [25, 27]. Gait speed is easily measured using a marked path and a stopwatch [23, 28]. However, other gait parameters might provide more precise associations with pathology [10, 29], gait control [10, 11, 30] and falling [10, 30] in older adults. These other parameters (e.g., variability and asymmetry measures) retaining to spatiotemporal gait require more sensitive technology. Objective data collections of gait often produce an abundance of gait parameters [13, 31]. Variables generated through more advanced technologies frequently include mean measures and standard deviances of step or stride time, length and width, stance time, swing time and double support time [13, 31]. Several gait parameters are closely related, and it can be difficult to differentiate the relationship between the different parameters.

Components of gait

Gait parameters can be categorized using different dimension reduction techniques, such as exploratory factor analysis or principal component analysis (PCA). Using these dimension reduction techniques have led to the identification of several gait components in older adults, explaining approximately 80-85% of the variance of the included gait parameters [32-37]. Components named pace, rhythm and variability have been identified in several PCAs that included older adults [32-37]. While some gait parameters consistently tend to load to similar components of gait, the gait parameters identified in the components of previous PCAs are not always identical.

Studies in older adults without dementia showed that the pace component includes gait speed and step or stride length [32-37]. As gait speed is closely related to the pace component, multiple studies have investigated gait parameters relating to pace. In older adults without dementia, a reduced gait speed has been associated with several factors, such as reduced balance self-efficacy, decreased attentional ability, reduced muscle strength and older age [34]. Using a standardized composite score of the pace component, decreased pace has been associated with a decline in executive functioning [32].

A rhythm component of gait in older adults without dementia is often comprised of temporal gait parameters such as step time, swing time or cadence, and generally have to do with the repetitive nature of walking as well as timing of gait [1, 34].

Variability measures are measures of the intra-individual inconsistencies of a specific gait parameter [38] and can be linked to the control of gait [10, 11, 30], underlying pathology [29, 32] and future falls [10, 39]. Such measures are based on the within-person standard deviation of a spatial, temporal or spatiotemporal gait parameter [10]. It can be computed using standard deviation (SD) or coefficient of variation (CoV). Using within-person SD is regarded as an absolute measure of variability whereas CoV is regarded as a relative measure of variability [39, 40]. Step-based gait parameters have shown to be more reliable than stride-based gait parameters for measuring gait variability [41].

Other components of gait include asymmetry [34, 36], base of support [33, 35, 37], postural control [34] and phases [33, 35, 37]. Including other types of walking tasks, such as turning or tandem walking generate additional components [35, 37].

Asymmetry gait parameters concern the bilateral coordination of the limbs and relate to the differences between the two sides of the body (i.e., left and right steps) during walking [42, 43]. All people have some form of asymmetry in their gait, but these asymmetries are often clinically insignificant [1]. Gait asymmetry is more pronounced in older people with underlying pathology (such as a chronic neurological disease, e.g., PD [44] or stroke [42]), indicating that a more pronounced asymmetry measure could signal disturbances of functions relating to safe gait [44]. Asymmetry measures are generated by using step-based gait parameters. [34, 41]. In PCAs only including stride-based measures, no gait asymmetry parameter can be included, and an asymmetry component is thus not generated in such PCAs.

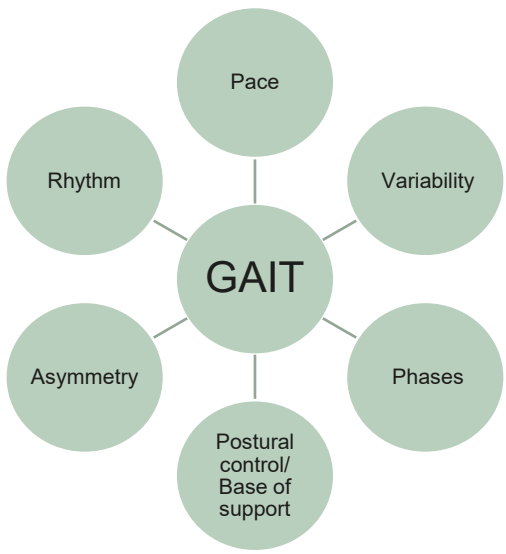


Figure 2. Overview of commonly reported components of gait, based on prior studies of older adults without dementia.

A postural component, including step or stride width together with an additional gait parameter, has been identified in several PCAs on older adults [33-35]. The additional gait parameter differs in the various PCAs. One study included step length asymmetry [34], whereas other included step or stride width variability [33, 35]. Including phases of the gait cycle (i.e., percentages of the gait cycle) identified a phase component as well [33, 35, 37]. As components of gait, derived from the PCAs, are distinct from one another they can be said to represent various aspects of gait; aspects that might be differently affected, depending on cognitive status or type of brain pathology. Figure 2 depicts an overview of commonly reported components of gait.

The performance on certain objective gait parameters, representing different components of gait have been associated with the presence of fear of falling (FOF) [45-49]. The following section discusses these concepts and their relationship.

Fear of falling – concerns about falling

Concerns about falling is a construct relating to FOF and the terms are often discussed interchangeably [50]. Other aspects of FOF include balance confidence [51], fall-related activity avoidance [52] and fall-related self-efficacy [53]. Several of these constructs of FOF are conceptualized relating to Bandura's model of self-efficacy [54]. The model suggests that the level of belief in one's own capabilities to manage an event is an important factor to consider in regard to individual performance in a particular situation [54]. Importantly, FOF can be a realistic appraisal of one's situation, due to near falls or previous falls leading to pain, injury or embarrassment [50]. This can be considered a well adaptive response to a significant risk (i.e., falling). The response can also be maladaptive, leading to avoidance behavior and subsequently leading to negative effects on several aspects of life [55]. These types of appraisals and responses can be seen in people both with [56] and without known neurological pathology [55]. In older adults, FOF is related to an increased risk of falling [57] and a decreased level of physical activity [58]. It can have a profound negative effect on quality of life [55].

The prevalence of FOF in community dwelling older adults range between 20-85% [55, 59, 60]. Depending on the measure used for assessing FOF, prevalence numbers vary, but generally FOF increases with age and is more pronounced in women [55, 61]. A large proportion of older adults with FOF have not experienced a fall event [61]. FOF is associated with objective gait parameters related to more cautious gait, such as slower gait speed [45-48], shorter stride length [45-48] as well as increased stride width [46, 48] and double support time [45-48] independent of previous falls, in older adults [45]. The presence of FOF is also associated with increased gait variability in older adults [47, 49].

This thesis focuses on concerns about falling. The Falls Efficacy Scale-International (FES-I) assesses the level of concerns about falling in 16 specific activities, including social events. The total score ranges 16-64, with a higher score indicating more concerns about falling. Several of the items incorporate walking, such as "*walking in the neighborhood*", "*going to the shop*" and "*walking in a crowded place*" [62].

Few longitudinal studies have identified predictors of FOF; even fewer so relating to concerns about falling. Using a dichotomized question regarding FOF in Mexican American older adults identified both personal and environmental predictors of FOF (i.e., female sex, depression, limitations in instrumental activities of daily living (ADL), global cognitive functioning, comorbidities, multiple prior falls and frequent familial interactions) [63]. Prior experiences of falls have shown conflicting results in predicting a change in concerns about falling over time [64, 65]. Concerns about falling increased in short term (one month) but did not increase over a longer period (12 months) [64]. Another study reported no difference in change of concerns about falling in older adult fallers and non-fallers over a 3-month period [65]. Reasons for the discrepancies in findings could be that the short-term effect did not last for a 3-month period as well as differences in samples, and prior falls during the previous year was an exclusion criterion in one of the studies [64].

A longitudinal perspective is a prerequisite for identifying predictive factors. Such a perspective can help clarify the impact of predictors of an outcome and the outcome variable as well as identify similarities and differences in relation to cross-sectional associations. A better understanding of which specific variables that independently predict concerns about falling could assist in deciding which variables that primarily should be addressed in future intervention studies.

Neurodegenerative disorders

This thesis has a specific focus on people with mild cognitive impairment (MCI) (studies I-II) and PD (studies III-IV). MCI can be seen as an intermediate stage of cognitive function between normal cognitive function and major neurocognitive disorder (dementia). Those with MCI who also have markers of a neurodegenerative disorder have a higher risk of progression to dementia. Persons who have subjective cognitively decline (SCD) but no objective deterioration in cognitive performance (study I) are according to guidelines considered cognitively unimpaired (CU) [66].

Neurodegenerative disorders consist of a heterogenous group of diseases where different areas of the brain degenerate. The two most common forms are Alzheimer's disease (AD) and PD, which affect millions of people worldwide [67]. Neurodegenerative diseases are not a consequence of ageing, although they are strongly age-related [67, 68]. Symptoms from neurodegenerative disorders generally manifest later in life [68, 69] and are uncommon in people under the age of 60 (with noticeable exceptions such as familial AD [70] and Huntington's disease [71]).

Neurodegenerative diseases are generally characterized by the accumulation of aggregates of specific proteins in the brain and the subsequent degeneration of the cerebral cortex [72]. The neurodegeneration initially occurs in specific areas of the brain; as the disease progresses, the degeneration is generalized to more widespread areas of the cortex [72].

Alzheimer's disease and dementia

AD accounts for between 60-70% of all cases of major neurocognitive disorder (commonly known as dementia and described as dementia in this text) [67, 69, 73]. Dementia is a global health challenge as the prevalence is estimated to treble by the year 2050 [74]. It is a syndrome that can originate from different causes and leads to a significant decline or impairment in several cognitive functions. These impairments have a profound impact on the independence of executing everyday activities, such as paying bills [75].

The two most common types of dementia are AD dementia (ADD), followed by vascular dementia (VaD) [69]. AD is linked to symptoms relating to memory storage, decision making and planning familiar tasks [76], whereas symptoms relating to VaD are much more variable, depending on severity and affected location. VaD is however often linked to slower processing speed and attentional deficits [77]. These dementias originate from different pathologies, although the presence of a mixed pathology is not uncommon [69, 78]. AD pathology includes

aggregation of amyloid-β (Aβ) plaques and tau tangles. The aggregations can be measured directly by using a positron emission tomography (PET) or indirectly in cerebrospinal fluid (CSF) or blood plasma. From a conceptual perspective, PET measures have often been related to a disease *stage*, closely related to atrophy of the brain and severity of clinical cognitive severity [79, 80]. CSF measures might instead be considered markers of disease *state*, indicating the intensity of the disease process [79-81]. Although, certain CSF tau measures (e.g., phosphorylated tau, [p-tau] 217) seem to change dynamically throughout the disease process and could therefore provide some disease stage information [82]. In studies looking over the entire cognitive spectrum (i.e., CU, MCI and people with ADD), CSF tau measures will likely correspond to structural imaging and atrophy degree [83]. However, in earlier cognitive clinical stages, pathological CSF tau measures more closely correlate with Aβ PET deposition [84] than with tau PET deposition thresholds in the brain [73]. Aβ and tau CSF measures are likely indicating an AD pathological process [84]. Compared to CSF measures, using a PET measure for measuring the different brain pathologies can more precisely provide an in depth look at the specific effect of pathology deposition in specific subgroups of people, such as people with MCI, on objective gait parameters.

VaD commonly originates from hemorrhages or a loss of blood to smaller blood vessels of the brain [85]. The blood loss leads to lesions in white matter of the brain [85]. These lesions can be identified with the help of magnetic resonance imaging (MRI), where hyperintensities in the white matter (WMH) of the brain are detected [86]. The WMHs can lead to an array of different symptoms and have been linked to several gait impairments in older adults with MCI [87-89] and older adults without dementia [90-92]. These prior studies did not consider amyloid or tau pathology in their analyses. While not a neurodegenerative disorder, older people with WMH have an increased risk of developing cognitive impairment and dementia [86, 93].

Subjective cognitive decline and mild cognitive impairment

Subjective cognitive decline (SCD)

Two main features characterize SCD. First, a persistent decline in cognitive functioning perceived by the person in question. This decline should not be related to a recent event. The second feature is that the cognitive decline is not shown on standardized cognitive tests [94]. Many individuals experience some form of cognitive decline with increasing age [94]. Although people with SCD have an increased risk of progression to dementia compared to people without cognitive symptoms [95], most of them will not progress into further cognitive decline [94]. As people with SCD are classified partly based on their lack of decline in cognitive tests, this group can in certain regards be considered pertaining to a CU subset [66, 94].

Mild cognitive impairment (MCI)

The clinical criteria for classifying people with MCI are: i) a cognitive impairment reported by the individual or a close informant (e.g., spouse), ii) evidence of modest cognitive impairment as per objective standardized measures, in one or more cognitive areas, iii) preserved independence in performing everyday activities, and iv) not fulfilling the criteria for dementia [96]. The diagnostic and statistical manual of mental disorders (DSM-5) has similar criteria although mild and major neurocognitive disorder are differentiated by the severity of the cognitive impairment and the effect of the cognitive deficit on the ability to function independently [75].

People with MCI can be further subclassified by differentiating which cognitive domain that is primarily affected (e.g., impairment in memory or executive functioning). Furthermore, individuals with MCI are often subclassified by an impairment in amnestic ability, i.e., the ability to retain and recall information from the past: amnestic MCI (aMCI) versus non-amnestic impairment (naMCI) [97]. People can also be classified as having multidomain cognitive impairment with or without a memory component impairment (multidomain aMCI and multidomain naMCI, respectively) [97].

Parkinson's disease

PD is characterized by a decreased production of dopamine in the substantia nigra pars compacta in the brain [71, 98, 99]. The loss of dopamine producing cells leads to the deterioration of motor functions [71, 100]. Later in the disease process, Lewy bodies (aggregations of the protein alpha-synuclein) are identified throughout the cortex [71, 98, 101].

PD is initially characterized (i.e., cardinal signs of the disease) by bradykinesia (slowness of movement), rest tremor, rigidity and postural instability [71, 102]; the symptoms often begin unilaterally. Diagnosing PD is mainly based on clinical evaluation that requires the presence of bradykinesia and at least one of the cardinal signs; tremor or rigidity [102]. Other common motor impairments in PD include reduced arm swing, a stooped posture and reduced gait speed [103]. As the disease progresses, the severity of motor symptoms are enhanced and festinations (i.e., a quickening and shortening of the step length) [103, 104] and freezing of gait [105] will affect a great number of people with PD [103].

Although PD is often considered a disease primarily affecting motor aspects of life, several non-motor symptoms are also common, including fatigue, pain, anxiety, autonomic dysfunction, orthostatic hypotension and cognitive impairment [106].

No curative treatment for PD exists as of today [71]. Medication including levodopa often has a symptomatic effect on motor symptoms, although the treatment

effectiveness on motor symptoms is not uncommon to waiver off after some years [103]. The diminishing responsiveness to the levodopa treatment leads to fluctuations in motor functions with so called "on and off periods" when the motor symptoms are well managed ("on") or less well managed ("off") [103].

The next part of the introduction will focus on objective gait in people with MCI (studies I-II) as well as perceived walking difficulties and concerns about falling in people with PD (studies III-IV).

Neurodegenerative disorder and gait

Gait in people with MCI

People with MCI walk slower than cognitively healthy during single task (i.e., walking as a single activity) [107-111]. Objective gait parameters (e.g., gait speed, stride length, stride time and stride time variability) generally seem to worsen in parallel with cognitive decline [107-111]. In turn, people with MCI exhibit better gait capacity than people with dementia [107]. Comparing different subcategories of MCI, Allali et al., showed consistently worse capacity across all included spatiotemporal gait parameters in people with naMCI compared to those with aMCI [107]. This difference in gait capacity between those who had an amnestic deficit and those who had a non-amnestic deficit was seen across all included cognitive stages (i.e., in people with MCI, mild dementia and moderate dementia) [107]. Differences in spatiotemporal gait parameters between different cognitive stages (i.e., CU, MCI, mild dementia and moderate dementia) and subtypes of MCI are often exacerbated when the gait task is either performed at a faster speed [110, 112] or during a dual task setting [108, 109, 113].

While certain aspects of objective gait have been thoroughly investigated in older adults without dementia and in people with MCI (e.g., gait speed), other aspects are much less studied (e.g., asymmetry measures and step-based variability measures). In contrast to older adults without dementia, the relationships between the large number of gait parameters have not been thoroughly explored in people with MCI. The only published PCA study that focused on people with MCI considered seven stride-based gait parameters relating to gait and falling. That study identified three components of gait: pace, rhythm and variability [114]. Other aspects relating to habitual single task gait might provide a more comprehensive perspective on the relationships between gait parameters in people with MCI than specifically fall-focused gait parameters. A more informed picture of how and which gait parameters are grouped together could help prioritize certain characteristic gait parameters in future studies. It could also help better explain the relationship between common gait parameters.

Alzheimer related pathology and gait

The hallmark pathologies related to AD are Aβ plaques and tau tangles [73]. An increase of Aβ pathology, assessed both via PET imaging [115-117] and CSF [118], has been related to slower gait speed in older people without dementia. Deposition of Aβ has also been associated with decreased cadence, increased double support time and increased variability in stance time [117]. Another study found associations between Aβ and increased variability in three gait measures: gait speed, cycle time and cadence. No associations with mean gait measures were found [119]. Together, these studies indicate that gait variability measures might be sensitive markers of Aβ deposition in cognitively healthy older adults. These studies did not take tau pathology into account. They also only included older people without dementia [115, 116] or cognitively healthy older people [117, 119], i.e., excluding people with MCI and dementia. Two other studies reported that tau pathology (total tau, CSF) in older adults (including CU, people with MCI and people with dementia) was associated with decreased gait speed [120] and a gait rhythm component [121]. One of these studies did not take Aβ pathology into account during analyses of tau [121] whereas the other study differentiated the study sample based on Aβ pathology status in a sensitivity analysis [120]. None of these studies accounted for WMH [120, 121].

White matter hyperintensities and gait

In people with MCI, WMH have been associated with slower gait speed [87] as well as increased stride length variability [89]. Regionally, sublobar lesions have been associated with shorter stride length and increased walking angle [88].

To the best of my knowledge, no studies have investigated the effect of different brain pathologies (Aβ, tau and WMH) on different aspects of gait, also considering the other two pathologies. Few studies have investigated objective gait parameters exclusively in people with MCI, i.e., in relation to AD pathology. A better understanding of the effect of AD-related pathology on unique aspects of gait in people with MCI might improve future care by providing more detailed advice on which gait parameters to focus on.

Walking difficulties in people with PD, including assessments

Already in the early stages of the disease, people with PD tend to have a reduced gait speed [122] and shorter step length [122] than age-matched healthy adults [103, 122, 123]. PD is characterized by a unilateral onset of motor dysfunction, leading to an initial asymmetry of motor symptoms to one side of the body (such as reduced arm swing) [103, 123]. Moreover, a decreased range of motion and altered posture leads to diminishing movements relating to gait. Gait variability seem enhanced in people with PD as compared to age-matched controls [124, 125].

In mild to moderate stages of PD, gait features are more bilaterally affected, and bradykinesia is more pronounced. This leads to longer periods of time in double support of the limbs. Less automation of movements leads to gait initiating problems and turning is also affected (the body turns in blocks). Together with freezing of gait and festinations, these motor deficits lead to even more reduced balance/postural control and an increased risk of falls [103].

During the advanced stages of the disease, gait impairments worsen and arrests in gait and movements are more expressed, such as freezing of gait [103]. As gait capacity is diminished, fall risk and fall events are increased [126]. The diminished capacity often leads to the need and use of mobility devices.

Assessments of subjective walking ability can for example be done by using certain items from the UPDRS [14]. The UPDRS is based on the clinician's subjective rating and is often used in a clinical setting. Assessing everyday walking ability from the perspective of the patient provides a unique perspective and can be done by using the questionnaire Walk-12G [19]. The Walk-12G is considered a valid and reliable PROM in people with PD [19], which focuses on the patient's subjective perspective of their walking difficulties in everyday life, during the last two weeks. Perceived walking difficulties have been moderately correlated with the objective gait parameter gait velocity [20, 127] and poorly correlated with other gait parameters representing different components of gait (e.g., rhythm. variability, asymmetry) in people with PD [20]. This indicates that perceived walking difficulties may be a construct retaining to belief in one's ability in everyday walking, rather than objective performance in a laboratory setting. Another cross-sectional study reported several factors that were associated with perceived walking difficulties in people with PD, including personal factors (e.g., general self-efficacy), motor (e.g., freezing of gait, lower extremity function) and non-motor factors (e.g., orthostatic hypotension) [128]. Quantitative and longitudinal studies focusing on perceived walking difficulties are scarce within the field of PD.

Taking a longitudinal perspective on perceived walking difficulties could lead to a better understanding of potential predictive factors. A longitudinal perspective could also assist in directing focus at important predictors when providing long-term care and rehabilitation: what are important factors that lead to a change in perceived walking difficulties? Knowledge of modifiable factors that can be addressed in care and rehabilitation could improve how the person perceives their walking difficulties. This might lead to an improved quality of life. To date, this has not been studied in people with PD.

Fear of falling in people with Parkinson's disease

Fear of falling (FOF) is more pronounced as well as more common in people with PD compared to age-matched controls [129, 130]. Prevalence of FOF in people with PD ranges between 35 and 59% [131-134]. FOF can be regarded as a very stressful symptom [135] and is associated with limiting ADL and reduced physical activity in people with PD [136, 137]. It occurs in people both with and without prior falls [131, 138].

Several cross-sectional PD studies have identified associated factors with FOF by using multivariable analyses [132, 134, 139-143]. These studies identified PD severity [139], PD duration [139], level of independence in ADL [140], motor variables (e.g., problems maintaining balance while dual tasking, knee muscle strength) [132, 134, 139, 141, 142] and non-motor variables (e.g., fatigue, cognitive functioning, anxiety and depressive symptoms) [132, 134, 139-141] as associated factors to FOF. Three cross-sectional studies reported that perceived walking difficulties were associated with FOF [132, 134, 141].

Two cross-sectional studies specifically targeted associated factors with concerns about falling by using the FES-I [141, 143], which is considered a valid and reliable questionnaire in people with PD [144]. One study identified the following independent factors: perceived walking difficulties, orthostatism, age, motor symptoms and fatigue [141]. The other study identified depressive symptoms, use of mobility devices and balance performance as associated factors to concerns about falling [143]. The two studies found conflicting results in relation to the use of mobility devices, depressive symptoms, motor symptoms and age [141, 143].

Knowledge of which factors that contribute to longitudinal changes in FOF is valuable for providing good long-term care of people with PD and FOF. One longitudinal PD study reported that over a 2-year follow-up period, the number of falls during the first year predicted a change in fall-related self-efficacy [145]. Another longitudinal study targeted instead fall-related activity avoidance in people with PD and identified the following independent predictors: perceived walking difficulties, concerns about falling, unsteadiness while turning and pain [146]. As these studies included different FOF related aspects, studies regarding other aspects of FOF could enhance the understanding of the predictive factors and how they are related.

Pinpointing predictive factors of concerns about falling as well as predictors of a change in concerns about falling could assist when prioritizing important factors in future interventions, aiming at reducing FOF. Increased understanding of factors that predict concerns about falling might aid the long-term rehabilitative care.

Aims and Objectives

Overall aim

The overarching aim of this thesis was to explore objective gait characteristic in people with (studies I and II) and without MCI (study I) in terms of structure and relation to brain pathology. Moreover, the aim was to explore how perceived walking difficulties and concerns about falling evolve over time in people with PD and to identify predictive factors (studies III-IV).

Specific aims

The specific aims in relation to the respective study:

I. To define different components of gait as a single task by exploring 18 objective gait characteristics at comfortable gait speed in people with MCI (with signs of an incipient neurocognitive disorder, i.e., with an increased risk of developing dementia) and cognitively unimpaired (CU) people.

II. To investigate how different brain pathologies (i.e., WMH, Aβ and tau pathology) independently relate to objective gait parameters from various gait components in patients with MCI (with signs of an incipient neurocognitive disorder). More specifically, we investigated the gait parameters step velocity variability, step length, step time, and stance time asymmetry.

III. To investigate how perceived walking difficulties evolve over a 3-year period in people with PD. A specific aim was to identify predictive factors of perceived walking difficulties.

IV. To identify predictive factors of FOF (conceptualized as concerns about falling) after three years, with and without adjusting for concerns about falling at baseline, in people with PD.

Materials and Methods

Studies I-II were cross-sectional and utilized baseline data from the larger and longitudinal project *"Motor aspects and activities in relation to cognitive decline"* (Motor-ACT).

Studies III-IV had a longitudinal design and utilized data collected in the longitudinal project "*Home and Health in people ageing with Parkinson's disease*" (HHPD) [147]. Consequently, the method section is divided into two parts. A brief overview of studies I-IV is presented in Table 1.

Table 1. Overview of the studies included in the thesis

	Study I	Study II	Study III	Study IV
Study aim	Defining components of gait	Investigate the effect of AD and VaD pathology on gait parameters.	Predicting perceived walking difficulties	Predicting concerns about falling
Study sample	People with mild cognitive impairment; Cognitively unimpaired	Patients with mild cognitive impairment	People with Parkinson's disease	People with Parkinson's disease
Sample size	MCI (n = 114) CU (n = 219)	n = 96	n = 148	n = 151
Dependent variable	Not applicable	Step velocity variability, step length, step time and stance time asymmetry	Generic Walk-12	Falls Efficacy Scale-International
Main analysis	Principal component analysis	Explorative multivariable linear regression	Multivariable linear regression, for prediction	Multivariable linear regression, for prediction

AD = Alzheimer's disease; VaD = Vascular dementia; MCI = Mild cognitive impairment; CU = cognitively unimpaired; PD = Parkinson's disease.

Motor aspects and activities in relation to cognitive decline: Motor-ACT

Motor-ACT is a longitudinal project targeting motor aspects in people at risk of developing dementia. It is part of the larger project Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably (BioFINDER 2, national clinical trial identification number: NCT03174938). Motor-ACT originally included two of the cohorts that were included into BioFINDER 2; i) cognitively healthy older individuals ii) people with MCI or SCD with an incipient neurocognitive disorder. The data used in this thesis was collected during 2017-2020.

Participants

All participants in studies I-II were recruited from the BioFINDER 2 study.

Cognitively healthy older individuals

Participants in the cognitively healthy cohort were recruited from the regions of Lund and Malmö, Sweden. Individuals were primarily recruited from the study sample previously included in the Malmö Diet and Cancer study [148]. Inclusion criteria: speaking and understanding Swedish so proficiently that an interpreter was not needed, 66-100 years old, and a physician with special interest in cognitive disorders assessed the individuals as not having any cognitive symptoms. In addition, the individual should score 26 or higher on the Mini Mental State Examination (MMSE) [149] and not fulfill the criteria of MCI or dementia, as described in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [75].

Mild cognitive impairment or subjective cognitive decline

In Motor-ACT, participants with MCI or SCD were recruited from the Skåne University Hospital. These participants were believed to have an incipient neurocognitive disorder as assessed by an experienced physician specialized in cognitive disorders of any kind. This was based on clinical assessments, cognitive testing, CSF analyses and brain imaging. Individuals were for example included in this cohort if there was evidence of having either an abnormal (i.e., decreased) Aβ 42/40 ratio (signaling cerebral amyloid pathology [73, 150]), or any MCI cases fulfilling diagnostic criteria of specific types of minor neurocognitive disorders, such as vascular, frontotemporal or Lewy body disease [75].

Individuals were included in the cohort if any of these indicators of incipient neurocognitive disorder were identified along with the fulfillment of the following inclusion criteria: aged 40-100 years, proficiency in Swedish making the use of an interpreter unnecessary, scoring 24 or higher on the MMSE [149] and referred to a

specialized memory clinic due to cognitive symptoms. The symptoms could be experienced by the participants or an informant. Participants should not fulfill the criteria for any type of dementia as per the DSM-5 [75].

Exclusion criteria

Cognitively healthy older individuals as well as those with MCI or SCD were excluded if they: i) refused lumbar puncture, MRI or PET, ii) had a significant unstable systemic illness making participation in the study difficult, iii) had an existing significant alcohol or substance misuse, iv) had obtained a neurodegenerative disorder or had progressed to symptomatic vascular dementia prior to gait assessment, v) used mobility devices during gait assessment, or vi) less than 30 steps were registered on the instrumented walkway during gait assessment. One participant from the cognitively healthy cohort was excluded due to hemiparetic gait. An additional exclusion criterion applied for the cognitively healthy older individuals, i.e., significant neurological or psychiatric illness.

Classification of MCI and SCD

The subclassification of people into MCI or SCD was done based on the cognitive performance on several cognitive tests pertaining to different cognitive domains. The cognitive domains included *memory* (assessed with the delayed recall test of Alzheimer's Disease Assessment Scale [ADAS-cog]) [151], *attention/executive* function (assessed using the Trail Making Test part A and B [152], and the Symbol Digit Modalities Test [153]), *visuospatial ability* (incomplete letters and cube analysis from the Visual Objects and Space Perception battery [154]) and *verbal ability* (short version, 15 line drawings) of the Boston Naming test [155] and animal fluency test [156].

The raw test scores were transformed into standardized scores (z-scores) based upon the performance of a healthy control sample without any signs of brain pathology related to AD (i.e., CSF Aβ and P-tau) [157], The z-scores in each domain were summed and subsequently averaged by the number of tests in that domain. People who had been referred to a memory clinic due to direct or indirect cognitive complaints but performed -1.5 z-scores or better were classified as having SCD [94]. If the performance was worse than -1.5 z-score (adjusted for age and education where appropriate [158]) in at least one cognitive domain, the subject was classified as having MCI. This in agreement with the Petersen MCI criteria [159]. The Petersen criteria [159] refers to the cognitive performance on a group level in people with MCI, but was in this project operationalized as the performance of the individual.

Cognitively unimpaired (CU)

The two groups (i.e., people with SCD and cognitively healthy people) were a uniform group of objectively CU people, based on cognitive testing [94]. As per the National Institute on Aging—Alzheimer's Association (NIA-AA), people with SCD without any objective evidence of MCI should be grouped together with cognitively healthy and classified as CU [66]. Thus, in study I, participants with SCD were pooled with the cognitively healthy older individuals, and this group is referred to as CU.

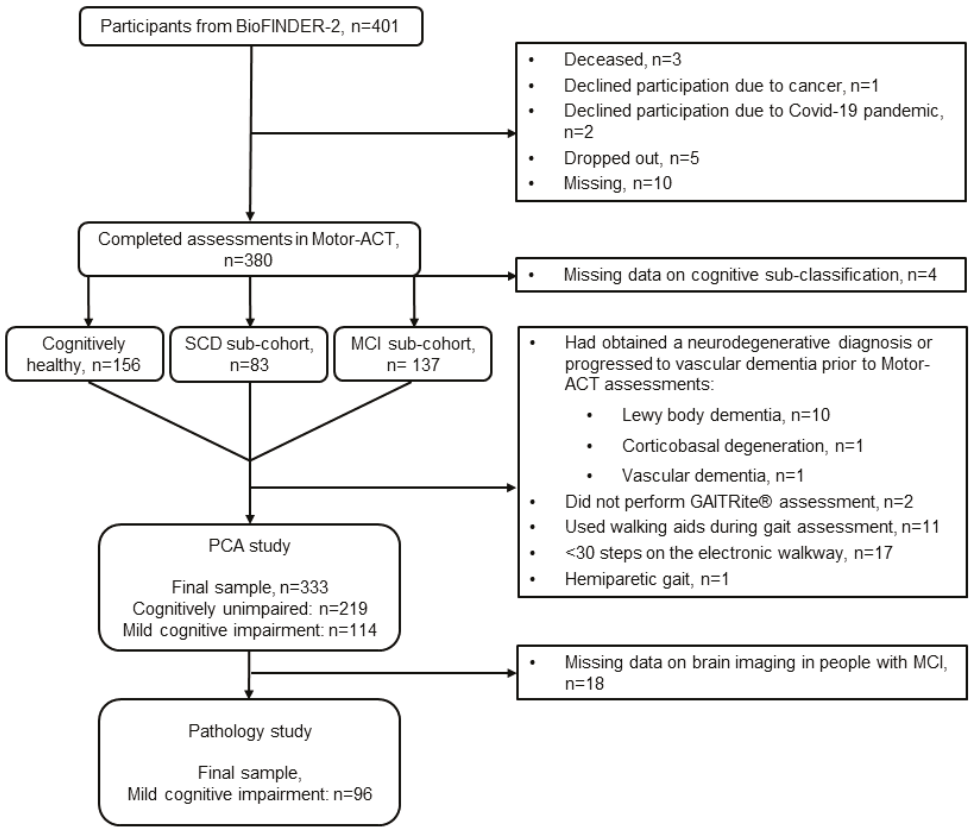


Figure 3. Flowchart of particpant inclusion process into the PCA (study I) and pathology studies (study II).

Procedure

As previously mentioned, all participants in studies I-II were recruited from the BioFINDER 2 study. Extensive cognitive testing (used for classification of participants) was performed directly after inclusion into the BioFINDER 2 study. Participants were then scanned for neurological pathology, using CSF, MRI and

PET imaging. For participants included into the cognitively healthy cohort, motor assessment was conducted on the same day as the cognitive testing. For participants with MCI or SCD, motor assessment was conducted approximately 1 year post inclusion into BioFINDER 2. A flowchart for participation into the two studies are displayed in figure 3.

Gait analysis

Before Motor-ACT was initiated, the test protocol was pilot tested. Motor-ACT included gait assessments in three different settings: single task walking at a comfortable speed, dual task walking (i.e., walking while serial subtracting), and single task walking at a fast speed. This thesis includes data regarding single task walking at a comfortable speed.

Three registered physiotherapists performed the gait assessments, and they were all specifically trained. Participants were instructed to walk for 6 bouts around an elliptically shaped circuit (see figure 4) with an instrumented walkway placed along one side. The participants were instructed to start approximately 1.5 meters before the walkway, walk in their self-selected comfortable gait speed and continue walking past the end of the walkway. The distance before and after the walkway was to ensure measurement of steady state gait and to stabilize gait speed related variables associated to starting and stopping during walking [31, 160]. Passing the end of the instrumented walkway, participants were instructed to turn around a cone positioned to the side of the walkway. Participants were asked to stop after stepping off the walkway for the sixth time.

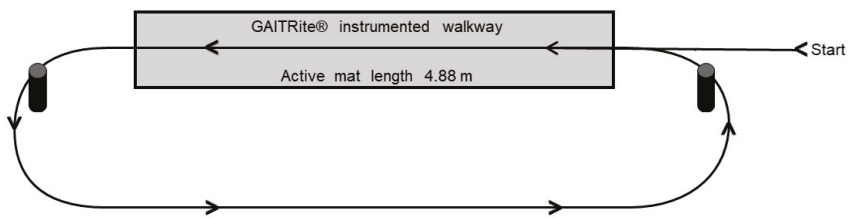


Figure 4. Clinical set up for obtaining spatiotemporal gait data.

Instrumented walkway

The gait measures were collected via an instrumented walkway software (GAITRITE ® platinum, CIR Systems Inc). The instrumented walkway has an active mat length of 4.88 m and width 0.69 m (total mat length: 5.79 m; width: 0.89 m). It includes more than 18,000 sensors; a sampling rate of 120 Hz was used. The measurements of the spatiotemporal parameters from the instrumented walkway are reliable and valid [31, 161].

Objective gait measures

Gait parameters can be sorted into individual steps and step sequence measures (i.e., strides) [31, 38]. Step measures have been considered more reliable regarding gait variability outcomes [38, 41]. The use of step measures also enables calculation of asymmetry measures (i.e., differences between left and right side) as well as separating asymmetry measures from variability measures [38, 41]. Mean step measures were calculated adding the average of each side into a sum and then dividing the result by 2 (see Equation 1). Step variability measures were calculated taking the square root of the combined mean variance of each side (Equation 2). Step asymmetry measures were calculated using the absolute value subtracting the average value of the left side from the right side (Equation 3).

Equation 1 for computing mean gait parameters:

$$\text{Mean} = \frac{Average_{Left} + Average_{Right}}{2}$$

Equation 2 for computing variability gait parameters:

$$Variability = \sqrt{\frac{(Variance_{Left} + Variance_{Right})}{2}}$$

Equation 3 for computing asymmetry gait parameters:

$$Asymmetry = Average_{Left} - Average_{Right}$$

The selection of gait parameters included into the PCA study (study I) were based on prior PCAs of older adults without dementia [32-36], specifically Lord et al., who included 16 gait parameters [34]. In addition, mean double support time and double support time variability were included, as measures of double support time have been associated with cognitive decline [162, 163]. In total, 18 gait parameters were explored in the PCAs. Detailed descriptions of the gait parameters can be found in Appendix 1. The 18 gait parameters are listed in table 2. Gait parameters included in study II are marked with an asterisk.

Table 2. Gait parameters explored in study I

Type of gait parameter		
Mean measures	• Step velocity	• Swing time
	• Step length*	• Stance time
	• Step width	• Double support time
	• Step time*	
Variability measures	• Step velocity variability*	• Swing time variability
	• Step length variability	• Stance time variability
	• Step width variability	• Double support time variability
	• Step time variability	
Asymmetry measures	• Step length asymmetry	• Swing time asymmetry
	• Step time asymmetry	• Stance time asymmetry*

*Included as dependent variables in study II.

PET imaging

Positron emission tomography (PET) is an imaging technique using the fast decay of positron emitting isotopes. It is commonly used for diagnostics of measuring the metabolic activity in different organs. Two PET scans (Aβ and tau PET respectively) were performed on the same PET scan (machine) to minimize inter-variability between scans. The Aβ and tau PET scans were performed at separate days.

An Aβ specific radiopharmaceutical diagnostic agent was used, commonly known as [^{18}F] flutemetamol. It was administrated intravenously; 90 to 110 minutes after the injection, a scan was performed for 20 minutes. The chosen regions of interest (ROI) were prefrontal, lateral temporal, parietal, anterior cingulate, and posterior cingulate/precuneus. Regions of interest in the brain were based on the conventional spread of AD associated Aβ [164-166]. A composite meta-ROI was composed, partially based on software for quantification of brain regions (FreeSurfer software v.6.0, freely available via http://surfer.nmr.mgh.harvard.edu). A standardized uptake value ratio (SUVR) is the ratio of the uptake in one specified region compared to another specific reference region. Pons acted as the reference region when calculating the SUVR. The threshold for pathology levels of Aβ deposition was set at 0.53 where a score of >0.53 is considered pathological [167].

18F-RO6958948, RO948, a PET ligand was used together with a diagnostic radioactive agent to measure the binding of tau aggregates in the cerebral cortex. The meta-ROI included the entorhinal cortex, inferior and middle temporal cortices, fusiform gyrus, parahippocampal cortex and amygdala. This is consistent

with conventional AD tau spread in Braak stages I-IV [168]. The reference region was the inferior cerebellar cortex [169]. The threshold of SUVR was 1.36 and values >1.36 were considered to indicate pathological tau aggregation [170].

Magnetic resonance imaging

Magnetic resonance imaging is an imaging technique that uses the spin or magnetic moment of protons in hydrogen atoms [171]. As hydrogen is an atom that can be found in water and fat tissues it is a useful atom to study in relation to human tissue [171]. With the use of powerful magnets and radiofrequency, protons are stimulated and based on the change in movement of the protons, images of the directed structure can be computed.

White matter lesions can be identified using a fluid attenuated inversion recovery technique (FLAIR) that brightens the signal (i.e., hyperintensities) from affected areas and increases the contrast signal intensity of adjoining areas, such as periventricular tissue, more clearly categorizing lesions close to CSF [86]. From the FLAIR imaging, using the lesion segmentation toolbox implemented in SPM8, an automated segmentation of WMH was performed [172]. This automated segmentation produces an individual total lesion volume, measured in milliliters (mL).

Descriptive data in Studies I-II

Descriptive data concerning participant characteristics (e.g., comorbidities) were collected through a self-administered questionnaire in association with the baseline visit of inclusion into the BioFINDER 2 study. Participants were asked to list their medical conditions and medications. Comorbidities were validated through examination of the medical records in cases of ambiguity (e.g., having listed a medication linked to a specific medical condition but not having listed the medical condition).

Data concerning objective gait measures and anthropometric measures (e.g., body mass index and leg length) were collected during the motor assessment at the physiotherapist. At the same visit, FOF was assessed by using a dichotomized question ("*Are you afraid of falling"*: Yes/No) in the PCA study (study I) and by using the self-reported rating scale FES-I [62] in the pathology study (study II).

Statistical analysis

PCA study (Study I)

Eighteen gait parameters were considered for inclusion into a dimension reduction analysis (i.e., PCA), to identify distinct components of gait, in two different

samples: people with MCI and CU (i.e., people with SCD grouped together with cognitively healthy older adults). Histograms of all gait parameters were inspected visually to assess normality. Four temporal variability measures were log-transformed, and four asymmetry measures were square root transformed to improve normality of distribution. A correlation of ±0.3 between at least two gait parameters was set as the lower limit for including a gait parameter into the forthcoming PCA analysis [173]. Varimax rotation method was used to identify components that were independent or uncorrelated with each other.

Inspection of scree plots were performed for deciding the number of components to keep. To identify the cleanest solution, analyses were rerun twice: one analysis was performed with one less component and another analysis with one additional component than suggested by the scree plot. The cleanest solution was chosen based upon three predefined criteria: i) all gait components should contain at least three gait parameters (a loading of ±0.5 was deemed as a relevant contributing parameter to a component), ii) every gait parameter was included into one of the identified components, and iii) few cross-loadings of a gait parameter with more than one component [174]. Also, the chosen solution should explain a substantial part of the total variance of the model.

As a sensitivity analysis, a separate PCA explored gait parameters of cognitively healthy people (i.e., excluding those with SCD from the CU group) in order to highlight components of gait in cognitively healthy older people.

To allow for comparisons of the 18 gait parameters (non-transformed data) between the different groups, independent-samples t-test or Mann-Whitney U-test were applied where appropriate. A Bonferroni correction threshold to adjust for multiple comparisons and to minimize the possible effect of type 1 error, was set to $p = 0.0028$ (0.05/18, i.e., the alpha level divided by the number of comparisons).

Pathology study (Study II)

The pathology study explored the effect of various ADD (i.e., tau and Aβ) and VaD-related (i.e., WMH) brain pathologies on the highest loading gait parameters from each of the four gait components that were identified in study I. As gait speed is a general indicator of health as well as a common outcome measure in gait research, step velocity was also explored in the following analyses.

These five gait parameters constituted the dependent variables in separate linear regression analyses. Specifically, the investigated gait parameters were: i) step length (cm; the highest loading parameter in the Pace/Stability component), ii) step velocity variability (cm/s; Variability component), iii) step time (s; Rhythm component), iv) stance time asymmetry (s; Asymmetry component) and the additional gait parameter, v) step velocity (cm/s). Stance time asymmetry showed skewed distribution of values and was therefore square root transformed to improve normality of distribution.

Uptake of tau (PET variable, examining a meta-ROI consistent with Braak stages I-IV, measured using SUVR), Aβ (PET variable, examining a neocortical meta-ROI, measured using SUVR) both consistent with conventional AD spread, as well as WMH (continuous variable, total volume measured in mL) were used as independent variables.

Data on age (years) and intracranial volume (ICV, mL) were included as continuous variables. Data concerning sex (male/female), diabetes (no/yes) or history of stroke/TIA (no/yes) were included as dichotomous variables.

The analysis contained several steps; firstly, crude linear associations between the independent variable and each separate outcome variable were inspected. Secondly, basic linear regression was performed to clarify the relationship between the independent variable and the outcome variable. These basic analyses were adjusted for age, sex and in the cases of WMH: also for ICV. The basic associations that showed statistical significance, were inspected in a more complex model, including age, sex, comorbidities (i.e., history of stroke/TIA and presence of diabetes) and also for WMH: ICV.

To account for the possible effect of the time difference between the imaging scans and the motor assessment, the basic linear regression analyses were repeated, also including a time variable (the number of days between the specific imaging scan and the motor assessment). If the unstandardized regression coefficient changed more than 20% after adding the time variable, that time variable was also added into the complex multivariable linear regression analysis.

To better understand the potential effects of tau in conventional AD-related ROIs, regions according to Braak stages (I-II, III-IV and V-VI) [168] were also used as the dependent outcome in the complex multivariable linear regression models. To account for the possible effect of cerebrovascular burden, additional sensitivity analyses were also adjusted for WMH and ICV.

Pearson's correlation coefficient (*r*) was used when assessing potential multicollinearity between independent or controlling variables. A threshold of ±0.7 indicating multicollinearity was decided prior to assessment; no correlation surpassed this limit. The data were inspected visually for fulfillment of assumptions for linear regression (i.e., linearity, normality of residuals, and homoscedasticity) [173].

Home and health in people ageing with Parkinson's disease: HHPD

Participants

Participants were recruited from three hospitals in an outpatient clinic setting, in the southern part of Sweden. Recruitment of participants started by PD specialized nurses from all three included hospitals evaluating inclusion and exclusion criteria. Also, if needed, screening of medical records was performed. Individuals were considered for participation into the longitudinal HHPD project if they met the inclusion criterion of having a PD diagnosis (ICD-10: G 20.9) since at least one year [147]. People were excluded if i) they could not comprehend or speak Swedish sufficiently, ii) had cognitive difficulties or other reasons rendering informed consent unable to provide, or iii) other reasons making participation in most of the data collection impossible.

Data collection procedure

Data collection included both a postal survey and a subsequent home visit. The postal survey was administered approximately 10 days prior to the home visit. The postal survey included several self-administered questionnaires, such as the Walk-12G and FES-I. During the home visit a part of the visit was allocated to a structured interview as well as clinical assessments, such as the chair stand test [175, 176]. The baseline data was collected in 2013, by two project administrators (two occupational therapists); the 3-year follow-up data collection (conducted in 2016) was performed by two other occupational therapists with the help of a PhD student in physiotherapy. The follow-up data collection included also a self-administered postal survey followed by a home visit. All data collectors underwent project specific training, prior to data collection.

Participant recruitment

Out of the people fulfilling the inclusion criteria (n = 653), 216 either had difficulties understanding or speaking Swedish, had severe cognitive difficulties, were living outside of Skåne County or had other reasons making the individual unable to provide informed consent or making it troublesome participating in the majority of data collection. Thus, 437 individuals were deemed as potential participants and invited to participate. Twenty-two individuals were unreachable, two had received a revised diagnosis and 157 persons declined participation. One additional person was excluded due to extensive missing data. As such, at baseline, the final sample constituted of 255 people with PD (data collected from November 2012 until November 2013).

Having completed the baseline assessments and having agreed to be contacted again 255 people were eligible for inclusion into 3-year follow-up data collection wave. Of these people 22 had since deceased, three had moved and one individual answered outside of the follow-up window. Hence, 229 individuals were invited to participate at the 3-year follow-up. Of the invited individuals eight people were unreachable, four people had a revised diagnosis, 51 declined further participation and one individual had extensive missing data and was therefore excluded from the follow-up data sample. In total 165 individuals were included in the sample for the 3-year follow-up [177]. A flowchart of the participants included into the PD-related studies can be seen in figure 5. A specific inclusion criterium existed for the study investigating predictors of perceived walking difficulties as well as the study investigating predictors of concerns about falling in people with PD; individuals with a total score on the outcome measure for both baseline and the 3-year follow-up were included.

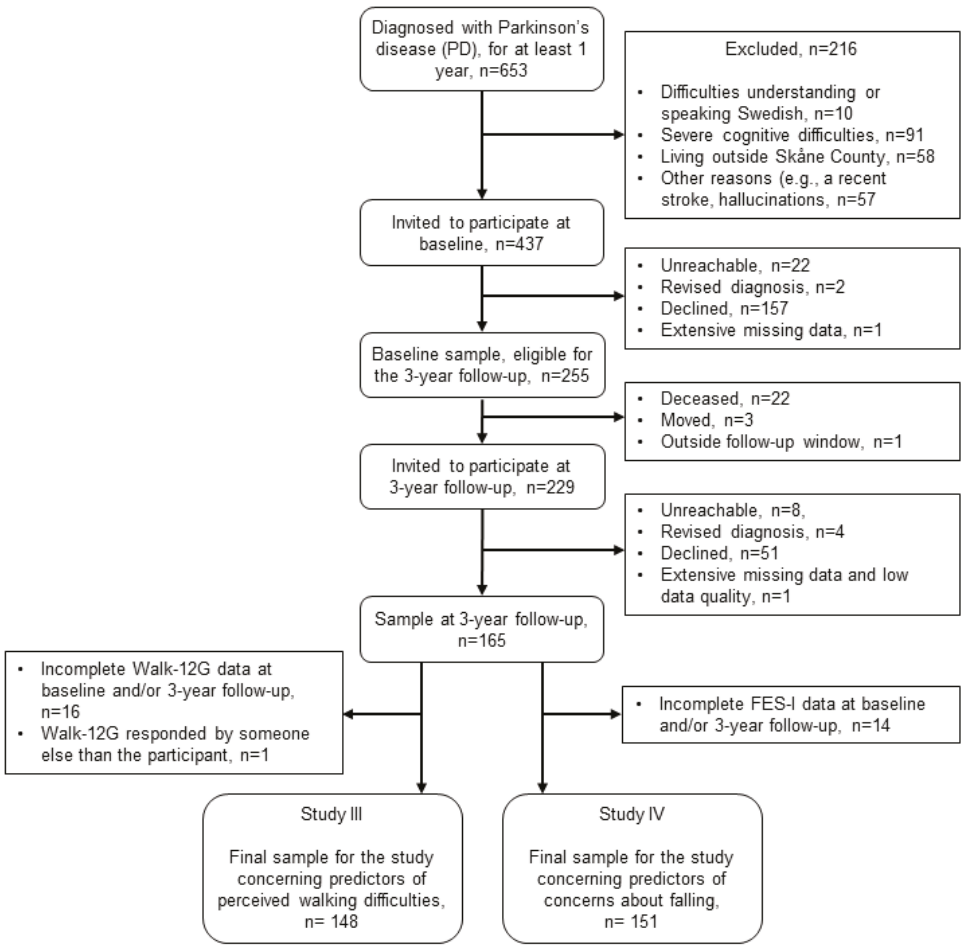


Figure 5. Flowchart of the recruitment process of participants for studies III and IV.

Main outcome measures

Perceived walking difficulties

The Walk-12G was used as a PROM for assessing perceived walking difficulties in everyday life, during the last two weeks [19]. It consists of 12 items that address several aspects of perceived limitations in walking ability, e.g., the distance the individual can walk, balance problems while walking or standing or having to concentrate while walking. The first three items have three response categories ranging from “not at all” (scored as 0) to "a lot or always” (scored as 2). The following nine items have five response categories ranging from “not at all” (scored 0) to “extremely*”* (scored as 4). The score of each item is summed up into a total score ranging 0-42 with higher scores indicating more perceived walking difficulties.

Concerns about falling

The FES-I addresses concerns about falling in daily activities and is comprised of 16 items/activities [62]. Items include activities such as “going to the shop”, “reaching for something above your head or on the ground” and “walking on an uneven surface”. The items were scored from 1 (not at all concerned) to 4 (very concerned), and the item scores were summed up into a total score indicating the level of concerns about falling (range 16-64, higher = worse). It has been suggested a relevant questionnaire for assessing FOF in people with PD [178].

Additional measures

The selection of independent variables was based on factors identified in prior cross-sectional studies as well as theoretical and clinical reasoning concerning the potential relationship of the independent variables, with perceived walking difficulties and concerns about falling, respectively. The independent variables were in general comprised of personal, motor related, non-motor related and environmental factors.

Personal factors

Three variables relating to personal factors were included into both study III and IV: age (years), sex (women = 1) and general self-efficacy, assessed using the General Self-Efficacy scale (scoring range 10-40) where higher scores indicate greater belief in one’s ability to succeed on a task [179].

Motor factors

Perceived balance problems while dual tasking, freezing of gait and UPDRS III were additional measures in both studies. Perceived balance problems while dual tasking was assessed with a dichotomous question (yes = 1): *“Do you experience*

balance problems while standing or walking when doing more than one thing at a time, e.g. carrying a tray while walking?".

Freezing of gait was assessed using the third item from the Freezing of Gait Questionnaire (scoring range 0-4, higher = worse) [180]. If an individual scored > 0 on the original scale, they were categorized as a freezer [134].

In the study investigating predictors of perceived walking difficulties, two items of the UPDRS III were used as separate measures: Postural instability (item 30) and bradykinesia (item 31). These items were dichotomized as having no symptoms of postural instability or bradykinesia (scored as 0 and rated 0 on the original scale of 0-4, higher = worse) or displaying symptoms (scored as 1 and including the scores 1-4 of the original scale). The dichotomization was based on earlier studies or clinical relevance [128, 181]. In study IV, the total score of UPDRS III was used as a continuous measure (scoring range 0-108, higher = worse) [14].

Motor fluctuations and lower extremity function were included in the study investigating predictors of perceived walking difficulties. Motor fluctuations were assessed using a dichotomous question (yes = 1): "Do you feel that the medical effect fluctuates during the day, with periodically increasing parkinsonian symptoms, e.g., when it is time for a new medical dose?"

Lower extremity function was assessed by using the Five Times Chair Stands Test, which was performed as fast as possible (1 trial) [176]. The sample was dichotomized and scoring ≥ 16 seconds was considered having worse lower extremity functioning (= 1) [182]. Twelve participants did not manage this test. They were categorized as having worse lower extremity function. Perceived walking difficulties were assessed using the total score of the Walk-12G.

Difficulties and dependence in ADL was assessed using the questionnaire the Parkinson's Disease Activities of Daily Living Scale (PADLS, scoring range 1-5) [183]. It assesses the impact of PD on ADL. The total score was dichotomized and a score of ≥ 3 was classified as having difficulties and dependence from others in ADL [178]. Although not only a motor related factor, difficulties and dependence in ADL may include difficulties with mobility and the need for assistance in transitions and walking safely.

Non-motor factors

Global cognitive functioning, pain, depressive symptoms, fatigue and orthostatism were considered in both studies. The Montreal Cognitive Assessment (MoCA) was used to assess global cognitive functioning where a higher score indicates better cognitive functioning (scoring range 0-30) [184].

Questions concerning pain ("are you bothered by pain?", yes = 1), fall history during the past 6 months (yes = 1) and depressive symptoms were administered during the home visit. Depressive symptoms were assessed using the Geriatric Depression

Scale (GDS-15, scored 0-15, higher = worse) [185]. Fatigue was assessed using the energy subscale of the Nottingham Health Profile [186] where participants were classified as having fatigue if one of the three questions was affirmative [187]. Orthostatism was assessed dichotomized with item 20 of the self-completed nonmotor symptoms questionnaire [188].

Concerns about falling was assessed with the FES-I using the total score.

Environmental factors

Two questions were dichotomized: a question regarding the living situation (living alone/not living alone) and information about the use of a mobility device outdoors (yes/no). They were included as additional measures in relation to concerns about falling.

Statistical analysis

Comparisons between scores at baseline and at the 3-year follow-up

Paired samples t-test was used for analyzing changes between baseline assessment and the 3-year follow-up, i.e., mean total scores of Walk-12G and FES-I were compared for baseline and the follow-up. The standard error of measurement (SEM; Equation 4) was calculated to determine if the change exceeded the measurement error.

Equation 4 for calculating standard error of measurement:

$$SEM = SD_{pooled}\ x\ \sqrt{1 - \text{Cronbach's alpha}}$$

Equation 5 for calculating pooled standard deviation:

$$SD_{pooled} = \sqrt{\left(\frac{SD^2_{baseline} + SD^2_{3-year}}{2}\right)}$$

Procedure for determining which predictors to maintain in the final model

Pearson's correlation coefficient (r) was used for assessing the relationship between the independent variables, in order to detect any multicollinearity, which was defined as $r > \pm 0.7$. The potential predictors (i.e., independent variables) were entered into univariable linear regression analyses used for studying the associations with the outcome measure (i.e., the Walk-12G and the FES-I, respectively). Inclusion of the potential predictors into a multivariable analysis was based on the

association in the univariable analysis. An independent variable was included if it had a p-value below 0.3. The threshold was set at stated level to minimize the risk of leaving out a confounding variable.

Two different procedures were used for identifying the final models of predictors and the final models of predictors of a change in perceived walking difficulties as well as concerns about falling.

Firstly, following fulfilment of inclusion into the multivariable analyses, all chosen variables were included into an initial model, simultaneously. The variable with the highest p-value was omitted manually from the multivariable linear model. This procedure was repeated until all included variables had a p-value < 0.1. This procedure was used for determining which predictors to maintain in the final model.

For predicting a change in outcome scores, the baseline data of the investigated dependent outcome measure was included as a controlling variable into the multivariable analysis procedure described in the paragraph above. This variable was included in all steps of the process regardless of p-value. In both models, an adjusted *R* square was presented to provide an assessment of the predictive capacity of the model. The final models were inspected for fulfillment of the assumptions for linear regression (i.e., linearity, normality of residuals, and homoscedasticity) [173].

Predicting perceived walking difficulties

Two multivariable linear regression analyses were used; one for predicting perceived walking difficulties and one was used for predicting *a change* in perceived walking difficulties. Walk-12G total score at the 3-year follow-up was used as the dependent variable. The following variables collected at baseline were included as independent variables in both prediction models: sex; concerns about falling; perceived balance problems while dual tasking; postural instability; bradykinesia; freezing of gait; lower extremity function; orthostatism; pain; cognitive functioning; fatigue; general self-efficacy and depressive symptoms.

The first multivariable model identified predictors of perceived walking difficulties in people with PD. As age is so closely associated with gait performance [189, 190] the two multivariable models pertaining to perceived walking difficulties were controlled for age. The second model, considering predictors of a change in perceived walking difficulties, was also controlled for the baseline score of the Walk-12G.

Predictors of concerns about falling

Multivariable linear regression analyses were used for predictive purposes of concerns about falling as well as a change in concerns about falling. The dependent variable was FES-I total score at the 3-year follow-up. Investigating a change in concerns about falling, the multivariable linear model was controlled for the baseline score, throughout the multivariable analysis.

In both prediction models (i.e., predictors of concerns about falling as well as predictors of a change in concerns about falling) the following independent variables, collected at baseline, were included: age; sex; motor symptoms (UPDRS III, total score); motor fluctuations; difficulties and dependence in ADL; use of mobility devices outdoors; perceived walking difficulties; a history of falls the last 6 months, freezing of gait; perceived balance problems while dual tasking; orthostatism; living situation, cognitive functioning; general self-efficacy; pain; depressive symptoms and fatigue.

Ethical considerations

Ethical approval was obtained for the research conducted within the projects HHPD by the Regional Ethical Review Board in Lund, Sweden (Dnr 2012/558 and 2015/611) and Motor-ACT by the Regional Ethical Review Board in Lund (2016-1053) and the Swedish Ethical Review Authority (2019–02681). The studies were conducted in accordance with the Helsinki Declaration for research involving human subjects [191]. All projects had ethical permits before data collections were initiated. All participants provided written informed consent.

Relating to BioFINDER 2, possible participants in the cohort of cognitively healthy individuals were sent information about the project, then contacted via telephone by a research nurse and asked if interested in participating. Those who agreed were scheduled for a baseline visit and were again informed about the project in written form as well as verbally by a project associated medical doctor. At this time point they were asked to sign an informed consent form. The possible participants of the other included cohort (MCI/SCD) were patients at the memory clinic. Prior to a diagnostic visit they were sent information about the project. At the diagnostic visit they were again informed about the project in written and verbal form. They were then asked if they would like to participate, and an informed consent form was signed by those who agreed.

Following inclusion into BioFINDER 2, participants were informed about the Motor-ACT project and invited to participate.

It is imperative that the potential participants understand what their participation implies in relation to several aspects, such as time invested, potential risks and benefits. People with MCI are affected in their cognitive abilities but remain capable and independent in everyday activities. The participants I met were all informed about the project and understood what was going to happen during testing. Some groups can be considered particularly vulnerable. According to the Helsinki declaration, research on vulnerable groups is only justified if the focus of research is responsive to the health needs and priorities of the group. Another criterion is that such research cannot be performed in a non-vulnerable group. This research cannot provide the same information in a non-vulnerable group and as this group of people (i.e., people with cognitive impairment) could likely benefit from the knowledge of this research, the potential benefits outweigh the potential risks [191]. A potential risk could be that in certain tasks, the individual is made aware of their cognitive

and/or physical limitations. This is likely something that that the vast majority of the participants are aware of and should not lead to any long term additional negative feelings. In relation to possible physical limitations, based on the results of the motor assessments, advice and suggestions of specific exercises can be given to the individual.

Pathology data related to Motor-ACT in this thesis were collected through PET and MRI. Performing a PET scan involves injecting a small amount of radioactive tracer and following standard procedure in relation to PET testing. This was approved by the local radiation committee. The use of PET imaging was also approved by Swedish Medical Products Agency. The radioactive isotope has a short half-life, and the risk of long-term harm is considered very small. With that said, injecting a radioactive isotope should be performed only when necessary. The possibility of detecting amounts of pathology in vivo compared to post-mortem provides the research community with an opportunity of better understanding the more direct effect of pathology. The participant always had the possibility of declining further participation during the project.

In Motor-ACT, all patients were assessed as outpatients at the Memory Clinic, Skåne University hospital. The visit was initiated by repeating information about the study and the participant was given the possibility to ask further questions. The testing procedure took about 70 minutes and time for breaks were included throughout the assessment. Objective gait data were collected at the end of the motor assessment. No participant fell during testing or had any other adverse events related to the testing during motor data collection. Possible adverse events could have been the aforementioned or that the participant was fatigued after the physical and cognitive tasks that were performed. This could have affected the remainder of the day as the person needed time to recover. Some participant mentioned being tired during the testing. All participants were given time to recover between different assessments.

Inclusion into research demands a high level of consideration from both the researcher and the participant. One study aspiration should be to affect and involve as few participants as needed to be able to answer the research questions. Thus, power calculations were performed to calculate the number of participants needed in the Motor-ACT/BioFINDER 2-projects as well as in the HHPD project [147].

Information about the HHPD study was sent to all potential participants. These individuals were then contacted via telephone by a project administrator and informed about the project, the voluntary participation, and asked to participate. Those who agreed to participate were scheduled for a home visit. An informed consent form was signed during the home visit. They were informed about the possibility of opting out and that they could do so whenever, without providing a reason. At the baseline visit, the participants were asked if they could be contacted again for the follow-up data collection.

In order to minimize the length of the home visit and thereby the patient burden, a battery of self-administered questionnaires was sent to participants ahead of the home visit. They were instructed to complete the questionnaires prior to the home visit, to enable the project administrator to inspect the questionnaire for any missing data during the home visit. This is in line with the aspiration of involving as few people as possible when conducting research. During the home visit, clinical assessments could be perceived as exhausting for the participant. In such cases, participants were given the opportunity of finishing the data collection at a second home visit. This is in line with the desire to minimize harm. At baseline, eight individuals chose to finish data collection at a second date. A the 3-year data collection, three individuals chose this alternative. This could indicate that the testing was not as arduous for most participants.

Results

Objective gait in people with and without MCI (studies I-II)

Participants in studies I-II

Study I included 114 patients with MCI (mean age 72.7, SD 7.2 years; 49.1% women) as well as people who were CU (n = 219, mean age 73.8, SD 8.1 years; 55.7% women). Study II included 96 patients with MCI (mean age 72.4, SD 7.5 years; 52.1% women), who had also participated in study I. Participant characteristics and descriptive data is presented in Table 3.

Comparisons of gait variables: CU versus MCI (study I)

The MCI group walked significantly slower than the CU group: mean 1.11 m/s (SD 2.09) vs. 1.20 m/s (±1.55), $p < 0.001$. The MCI group also had significantly longer step time, stance time and double support time ($p \leq 0.001$). The asymmetry measures as well as step width variability did not differ significantly ($p \geq 0.028$) between the two groups (please note that the significance level was set to 0.0028 due to Bonferroni correction for multiple comparisons). All other variability measures were significantly higher in the MCI group ($p \leq 0.001$). Detailed comparisons of the gait parameters between the two groups can be seen in Appendix 2.

Components of gait (study I)

In both the MCI and the CU group, step width variability was omitted from the PCA due to weak correlation with the other gait parameters. For the same reason, mean step width and step length asymmetry were excluded from the PCA in the CU group.

In people with MCI, the PCA included 17 gait parameters and identified four components of gait, labeled: *Variability, Pace/Stability, Rhythm* and *Asymmetry*. These components explained 81% of the total variance. The Variability component explained the most variance (23.7%) followed by Pace/Stability (21.4%), Rhythm (21.1%) and Asymmetry (14.8%). See Table 4 for detailed information.

In CU individuals, 15 gait parameters fulfilled the predefined correlation threshold and were consequently included in the PCA. The PCA identified four components of gait which explained 80.3% of the total variance. The components were labeled *Variability* (24.9% of variance explained), *Rhythm* (21.3%), *Pace/Stability* (20.0%) and *Asymmetry* (14.1%). The full PCA solution is presented in Table 5.

Figures illustrating the identified components of gait and included gait parameters are presented in Appendix 3.

In a subsequent sensitivity analysis, those with SCD (n = 76) were excluded from the CU group; this resulted in 143 cognitively healthy individuals. Two gait parameters (i.e., step width and step width variability) were excluded from the PCA due to weak correlations with the other gait parameters; the PCA thus included 16 gait parameters. Four components of gait were identified, explaining 75.7% of the total variance. The components were labeled the same way as in the PCA of the CU group. The main difference was that swing time variability now loaded higher into the Pace/Stability component instead of to the Variability component. Also, step length asymmetry did not load sufficiently (i.e., stronger than ±0.5) into any of the components of gait and was therefore not considered a significant contributor to any component.

Table 3. Participants' characteristics and descriptive data, studies I and II

Characteristic	Study I			Study II	
	Mild cognitive impairment (MCI), n = 114	Cognitiviely unimpaired (CU), n = 219	Missing n MCI/CU	Mild cognitive impairment (MCI), n = 96	Missing n
Age (years), mean (SD)	72.7 (7.2)	73.8 (8.1)	-/-	72.4 (7.5)	-
Sex (woman), n (%)	56 (49.1%)	122 (55.7%)	-/-	50 (52.1%)	-
Education (years), median (q1-q3)	12.0 (9.0-14.3)	11.5 (9.0-14.0)	1/-	12.0 (9.0-14.0)	1
Body mass index (kg/m^2), mean (SD)	25.6 (3.5)	26.7 (3.8)	-/-	25.6 (3.6)	-
Global cognitive functioning (MMSE), mean (SD)	26.8 (2.0)	28.7 (1.3)	-/-	26.8 (2.0)	-
Amnestic MCI (yes), n (%)	75 (68.8)	-	5/-	66 (70.2%)	2
Concerns about falling (FES-I), mean (SD)	20.0 (6.1)	19.2 (4.2)	2/3	20.0 (6.1)	1
Perceived walking difficulties (Walk-12G), mean (SD)	5.8 (7.8)	5.3 (6.8)	1/1	5.7 (7.5)	1
Leg length (cm), mean (SD)*	88.2 (5.8)	88.2 (5.4)	0/1	87.8 (5.7)	-
Intracranial volume (mL), mean (SD)	1495 (144.7)	1524.7 (181.1)	7/10	1503.3 (144.9)	-
History of stroke/TIA (yes), n (%)	7 (6.1%)	7 (3.2%)	-/-	6 (6.3%)	-
History of ischemic heart disease (yes), n (%)	11 (9.6%)	23 (10.5%)	-/-	10 (10.4%)	-
Hypertension (yes), n (%)	36 (31.6%)	78 (35.6%)	-/-	29 (30.2%)	
Diabetes (yes), n (%)	17 (14.9%)	25 (11.4%)	-/-	13 (13.5%)	-
Gait parameters					
Step velocity (m/s), mean (SD)	1.1 (0.2)	1.2 (0.15)	-/-	1.1 (0.2)	-
Step velocity variability (cm/s), mean (SD)	6.2 (2.0)	5.5 (1.8)	-/-	6.3 (2.0)	-
Step length (cm), mean (SD)	61.5 (9.0)	64.4 (7.1)	-/-	61.5 (9.0)	-
Step time (s), mean (SD)	0.5 (0.05)	0.5 (0.04)	-/-	0.6 (0.05)	-
Stance time asymmetry (s), mean (SD)	0.01 (0.01)	0.01 (0.01)	-/-	0.01 (0.01)	-
Pathology, continous data, mean (SD)					
Amyloid-β pathology (SUVR)	0.69 (0.19)	0.55 (0.14)	10/15	0.69 (0.19)	-
Tau pathology (SUVR, Braak I-IV)	1.42 (0.39)	1.20 (0.16)	14/23	1.41 (0.39)	-
Braak stage I-II (SUVR)	1.50 (0.43)	1.23 (0.25)	14/23	1.49 (0.42)	-
Braak stage III-IV (SUVR)	1.41 (0.39)	1.20 (0.16)	14/23	1.41 (0.39)	-
Braak stage V-VI (SUVR)	1.13 (0.18)	1.06 (0.10)	14/23	1.13 (0.18)	-
WMH (mL), median (q1-q3)	7.2 (2.6-16.8)	5.1 (1.5-14.7)	10/14	6.8 (2.4-16.9)	-
Pathology, dichotomous data					
Amyloid-β pathology (abnormal), n (%)	74 (71.2%)	73 (35.8%)	10/15	67 (69.8%)	-
Tau pathology (Braak I-IV, abnormal), n (%)	39 (39%)	13 (6.6%)	14/23	37 (38.5%)	-
Braak stage I-II (abnormal), n (%)	46 (46%)	21 (10.7%)	14/23	44 (45.8%)	-
Braak stage III-IV (abnormal), n (%)	36 (36%)	12 (6.1%)	14/23	34 (35.4%)	-
Braak stage V-VI (abnormal), n (%)	10 (10%)	3 (1.5%)	14/23	10 (10.4%)	-

BMI = Body mass index; FES-I = Falls Efficacy Scale-International (16–64, higher = worse); MMSE = Mini Mental State Examination (0-30, higher = better); SUVR = standardized uptake value ratio. WMH = White matter hyperintensities. Amyloid-β and Tau were assessed with positron emission tomography (PET). PET values are reported as SUVR. Amyloid-β > 0.53 SUVR = pathological, Tau Braak I-IV >1.36 SUVR = pathological. Braak I-II > 1.48 = pathological; III-IV > 1.36 = pathological; V-VI > 1.35 = pathological. White matter hyperintensities were assessed with magnetic resonance imaging.
*Sum of right and left leg length, divided by 2.

Table 4. Principal component analysis of 17 gait parameters in people with mild cognitive impairment: Item loadings of a 4-component solution, n = 114

Gait parameter	Variability	Pace/Stability	Rhythm	Asymmetry
Step velocity variability (cm/s)	**0.899**	-0.225	-0.198	-0.064
Step length variability (cm)	**0.832**	0.217	0.037	-0.082
Step stance time variability (s)[a]	**0.813**	0.233	*0.370*	0.167
Step time variability (s)[a]	**0.747**	0.315	*0.416*	0.209
Double support time variability (s)[a]	**0.734**	0.294	*0.356*	0.156
Step swing time variability (s)[a]	**0.555**	*0.509*	*0.423*	0.250
Mean step length (cm)	-0.293	**-0.813**	-0.103	-0.266
Mean step width (cm)	0.093	**0.719**	-0.024	0.025
Mean step velocity (cm/s)	-0.286	**-0.696**	*-0.494*	-0.289
Step length asymmetry (cm)[b]	-0.022	**0.667**	0.069	0.300
Mean double support time (s)	*0.352*	**0.653**	*0.579*	0.124
Mean step time (s)	0.198	0.186	**0.928**	0.218
Mean step stance time (s)	0.275	*0.409*	**0.828**	0.191
Mean step swing time (s)	-0.072	*-0.449*	**0.801**	0.203
Step stance time asymmetry (s)[b]	0.038	0.152	0.147	**0.915**
Step swing time asymmetry (s)[b]	-0.011	0.194	0.136	**0.908**
Step time asymmetry (s)[b]	0.187	0.217	*0.336*	**0.549**
Variance explained (%)[c]	23.7	21.4	21.1	14.8

Varimax rotation. Bold numbers indicate the highest loading of each gait parameter, which was used to determine the component to which each gait parameter belongs. Italic numbers indicate cross-loadings. MCI = Mild Cognitive Impairment. Table reprinted from published article of study I [192].

[a] Log transformed.

[b] Square root transformed.

[c] Total variance explained: 81.0%.

Table 5. Principal component analysis of 15 gait parameters in cognitively unimpaired people: Item loadings of a 4-component solution, n = 219

Gait parameter	Variability	Pace/Stability	Rhythm	Asymmetry
Step velocity variability (cm/s)	**0.895**	-0.192	-0.228	-0.034
Step length variability (cm)	**0.820**	0.036	0.017	-0.023
Step stance time variability (s)[a]	**0.817**	*0.335*	0.165	0.131
Step time variability (s)[a]	**0.773**	*0.418*	0.139	0.080
Double support time variability (s)[a]	**0.751**	*0.343*	0.162	0.106
Step swing time variability (s)[a]	**0.531**	*0.518*	0.290	0.125
Mean step length (cm)	-0.209	**-0.908**	0.192	-0.061
Mean step velocity (cm/s)	-0.190	**-0.870**	*-0.345*	-0.081
Mean double support time (s)	0.141	**0.624**	*0.615*	0.139
Mean step time (s)	0.076	0.198	**0.972**	0.067
Mean step stance time (s)	0.104	*0.392*	**0.885**	0.105
Mean step swing time (s)	-0.019	*-0.324*	**0.847**	-0.033
Step swing time asymmetry (s)[b]	0.090	0.086	0.020	**0.891**
Step stance time asymmetry (s)[b]	0.128	0.072	0.031	**0.878**
Step time asymmetry (s)[b]	-0.051	0.030	0.067	**0.674**
Variance explained (%)[c]	24.9	20.0	21.3	14.1

Varimax rotation. Bold numbers indicate the highest loading of each gait parameter, which was used to determine the component to which each gait parameter belongs. Italic numbers indicate cross-loadings. Table reprinted from published article of study I [192].

[a] Log transformed.

[b] Square root transformed.

[c] Total variance explained: 80.3%.

Effects of tau, Aβ and WMH on gait parameters in patients with MCI (study II)

Based on the findings in study I, the following four gait parameters constituted dependent variables in separate linear regression analyses in study II: mean step velocity variability (cm/s), mean step length (cm), mean step time (s) and stance time asymmetry (s). That is, the gait parameters with the highest loading in each of the four components in the MCI group were selected. In this framework, an additional fifth gait parameter (mean step velocity; cm/s) was selected as dependent variable in a new regression analysis.

Basic univariable linear regression analyses (adjusted for age and sex) identified tau pathology as significantly associated with increased step velocity variability ($\beta = 0.378$, $p < 0.001$), increased step length ($\beta = 0.337$, $p < 0.001$) and increased step velocity ($\beta = 0.319$, $p < 0.001$). Tau did not show any significant association with the other two gait parameters ($p \geq 0.222$). The other independent variables, i.e., Aβ deposition, ($p \geq 0.090$) and WMH ($p \geq 0.135$, also adjusted for ICV) did not show any significant association with any of five the investigated gait variables. For more detailed information, see Appendix 4.

Adding a time variable as a controlling factor to the otherwise crude, unadjusted models showed that three of the associations were affected by the time difference between the imaging scans and the motor assessment. That is, the unstandardized regression coefficient changed more than 20% when the time variable was added to the model. This applied for the associations between Aβ and stance time, step length, and step velocity, respectively. However, the associations remained statistically non-significant and Aβ were hence not included in the complex modelling.

In the complex multivariable linear regression analyses (see Table 6), tau pathology was significantly associated with increased step velocity variability ($\beta = 0.383$, $p = 0.001$), increased step length ($\beta = 0.336$, $p < 0001$) and increased step velocity ($\beta = 0.317$, $p = 0.001$). These associations remained statistically significant when accounting for cerebrovascular burden (i.e., adding WMH and ICV into the model).

In the main analyses, a meta-ROI was used to study the spread of tau, whereas Table 6 also presents the associations between tau in specific Braak regions and the separate gait parameters (dependent variables). To briefly summarize these results, all significant associations remained significant when studying tau in more specific regions of conventional AD spread. When adding WMH and ICV to these models, the association between tau pathology in Braak stage I-II and step velocity variability was close to the predefined alpha level ($p = 0.049$).

Table 6. Twelve separate multivariable linear regression analyses with step velocity variability, step length or step velocity as dependent variable and various tau measures as the independent variable (each model was controlled for sex, age, history of stroke/transient ischemic attack and diabetes), n = 96

	Dependent variable								
	Step velocity variability (cm/s)			Step length (cm)			Step velocity (cm/s)*		
	B (95% CI)	β	p-value	B (95% CI)	β	p-value	B (95% CI)	β	p-value
Independent variable									
Tau SUVR (Braak I-IV)	2.013 (1.01, 3.02)	0.383	**< 0.001**	7.790 (3.79, 11.79)	0.336	**< 0.001**	17.293 (7.73, 26.85)	0.317	**0.001**
Tau SUVR (Braak I-II)	1.113 (0.14, 2.08)	0.229	**0.024**	6.303 (2.57, 10.04)	0.294	**< 0.001**	12.850 (3.88, 21.82)	0.255	**0.005**
Tau SUVR (Braak III-IV)	2.017 (1.02, 3.01)	0.386	**< 0.001**	7.697 (3.71, 11.68)	0.334	**< 0.001**	17.147 (7.64, 26.65)	0.317	**0.001**
Tau SUVR (Braak V-VI)	4.519 (2.44, 6.60)	0.407	**< 0.001**	13.079 (4.41, 21.75)	0.267	**0.004**	34.023 (13.73, 54.31)	0.296	**0.001**

B = unstandardized regression coefficient; CI = confidence interval; β = standardized regression coefficient; SUVR = standardized uptake value ratio. Tau was assessed with Positron Emission Tomography. The regression models included tau SUVR, according to Braak staging I-IV (entorhinal cortex, inferior/middle temporal, fusiform gyrus, parahippocampal cortex, and amygdala), I-II (entorhinal cortex); III-IV (inferior/middle temporal, fusiform gyrus, parahippocampal cortex, and amygdala); and V-VI (widespread neocortical), respectively, controlling for factors: sex; age; history of stroke/transient ischemic attack; diabetes. Significant p-values (< 0.05) are bolded.

* New analyses included in this framework.

Additional analyses were carried out, where cerebrovascular burden (i.e., white matter hyperintensities and intracranial volume) were added as controlling factors. All associations remained statistically significant with little effect on the results, except between step velocity variability and tau SUVR (Braak I-II): B = 1.012 (0.003, 2.03); β = 0.209, p 0.049

Predictors of subjective aspects related to walking in people with PD

The second part of the thesis included prediction models of perceived walking difficulties and concerns about falling in people with PD.

Participants in studies III-IV

The 3-year follow-up data collection for studies III-IV included 165 individuals with PD. Of these, 148 participants (mean age 67.9, SD 8.92 years; 33.1% women) were included in study III and 151 participants (mean age 68, SD 9.0 years, 35.1% women) were included in study IV. Table 7 presents participants' characteristics and descriptive data related to studies III and IV.

Table 7. Participants' characteristics and descriptive data of people with Parkinson's disease at baseline (studies III-IV)

	Study III, n = 148	Study IV, n = 151	Missing, n study III / IV
Data at baseline			
Age (years), mean (SD)	67.9 (8.9)	68 (9.0)	-/-
Sex (women), n (%)	49 (33.1%)	53 (35.1%)	-/-
PD duration (years), median (q1-q3)	8 (5-11)	8 (5-12)	-/-
PD severity (H&Y during "on" state), median (q1-q3)	2 (2-3)	2 (2-3)	-/-
Perceived walking difficulites (Walk-12G), mean (SD)	14.8 (10.8)	14.8 (10.6)	-/2
Concerns about falling (FES-I), mean (SD)	27.7 (11.8)	28.1 (11.9)	2/-
Balance problems while dual tasking (yes), n (%)	89 (60.1%)	93 (61.6%)	-/-
Difficulties and dependence in ADL (PADLS, yes), n (%)	33 (22.3%)	33 (21.9%)	-/-
Fatigue (NHP-EN, yes), n (%)	76 (51.4%)	79 (52.3%)	-/-
Bothered by pain (yes), n (%)	93 (62.8%)	97 (64.2%)	-/-
Global cognitve functioning (MoCA), mean (SD)	25.7 (3.1)	25.7 (3.1)	2/2
Worse lower extremity function (Five times chair stands test ≥16.0 s = yes), n (%)*	76 (51.4%)	77 (51.0%)	-/-
Postural instability (UPDRS III, item 30, scores ≥ 1 = yes), n (%)	112 (75.7%)	113 (74.8%)	-/-
Depressive symptoms (GDS-15), median (q1-q3)	2 (1-4)	2 (1-4)	5/4
Data at the 3-year follow-up			
Perceived walking difficulites (Walk-12G), mean (SD)	18.7 (12.1)	18.5 (12.1)	-/9
Concerns about falling (FES-I), mean (SD)	32.5 (13.7)	33.1 (14.0)	5/-

H&Y = Hoehn & Yahr staging, possible scoring range 1–5 (higher = worse); Walk-12G = generic Walk-12 (0–42, higher = worse); FES-I = Falls Efficacy Scale-International (16–64, higher = worse); PADLS = Parkinson's disease ADL scale (those who scored > 2 were classified as having difficluties or being dependent on others in daily activities); NHP-EN = energy subscale of the Nottingham health profile (those who affirmed at least one out of three dichotomous questions were classified as having fatigue); MoCA = Montreal Cognitive Assessment (0–30, higher = better); UPDRS III = Unified Parkinson's Disease Rating Scale, motor examination (item scores 0–4, higher = worse); GDS-15 = Geriatric Depression Scale (0–15, higher = worse).

* 12 participants that did not manage the test were classified as having worse lower extremity function. (i.e., ≥ 16.0 s) [182].

Changes over time in perceived walking difficulties (study III) and concerns about falling (study IV) in people with PD

In study III, perceived walking difficulties (i.e., Walk-12G scores) increased significantly after 3 years. The mean (SD) Walk-12G score was 14.8 (10.8) at baseline, versus 18.7 (12.1) at the 3-year follow-up ($p < 0.001$). This implies a worsening of perceived walking difficulties with 3.9 points, which exceeds the SEM in the current sample (2.59 at baseline and 2.32 at the 3-year follow-up).

In study IV, concerns about falling (i.e., FES-I score) increased significantly over a 3-year period. At baseline, the mean (SD) score was 28.1 (11.9), compared to 33.1 (14.0) at the 3-year follow-up ($p < 0.001$). The change exceeds the SEM, which was 2.36 at baseline and 2.25 at the 3-year follow-up.

Predictors of perceived walking difficulties (study III) and concerns about falling (study IV) in people with PD

No signs of multicollinearity were identified between the independent variables in studies III-IV. All potential predictors (13 variables relating to perceived walking difficulties and 17 variables relating to concerns about falling) were sufficiently associated with the dependent variable in question. That is, the p-values were below the inclusion threshold of 0.3, and the variables were hence included into initial multivariable models.

Dependent variable: Perceived walking difficulties (study III)

The following variables predicted perceived walking difficulties at the 3-year follow-up (i.e., Walk-12G scores): concerns about falling (unstandardized regression coefficient, B = 0.461; 95% confidence interval, 95% CI = 0.325, 0.597; $p < 0.001$), perceived balance problems while dual tasking (B = 6.55; 95% CI = 3.61, 9.49; $p < 0.001$) and being bothered by pain (B = 3.79; 95% CI = 1.08, 6.50; $p = 0.006$). Postural instability, global cognitive functioning and age were also included in the final predictive model (due to $p < 0.1$) but the first two were non-significant. Age was included into the model as a controlling variable. The model explained 61.4% of the total variance in the Walk-12G scores at the 3-year follow-up.

Dependent variable: Concerns about falling (study IV)

Perceived walking difficulties were identified as the strongest, independent predictor of concerns about falling at the 3-year follow-up (B = 0.506; 95% CI = 0.284, 0.728; $p < 0.001$), followed by age (B = 0.355; 95% CI = 0.175, 0.534; $p < 0.001$), perceived balance problems while dual tasking (B = 4.96; 95% CI = 0.967, 8.95; $p = 0.015$) and difficulties and dependence in ADL (B = 5.86; 95% CI = 0.137,

10.4; p = 0.011). Depressive symptoms and sex were also included into the final predictive model for predicting concerns about falling but they were non-significant.

The final predictive models of perceived walking difficulties and concerns about falling, including the standardized regression coefficients (β) and p-values of the predictors, are presented in Figure 6.

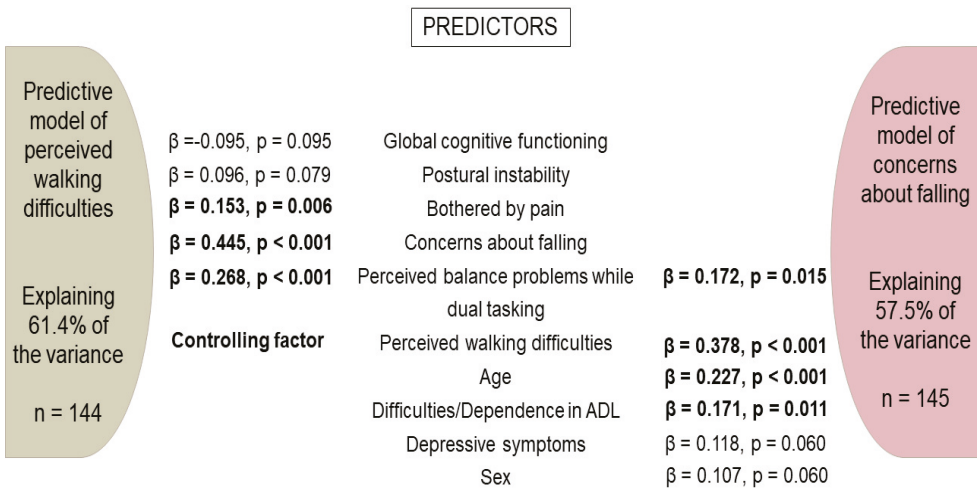


Figure 6. Predictors of perceived walking difficulites (generic Walk-12; left side) and concerns about falling (Falls Efficacy Scale-Internatonal; right side) after a 3-year period in people with PD.
These final models included variables with p-values < 0.1. The numbers next to a variable indicate standardized regression coefficient (β) and p-value. Significant p-values (< 0.05) are bolded.

Predictors of *a change* in perceived walking difficulties (study III) and concerns about falling (study IV) in people with PD

To identify predictors of a change in perceived walking difficulties and concerns about falling at the 3-year follow-up, the regression analyses above were also controlled for baseline values of the dependent variable. However, in study III multicollinearity was identified between the baseline values of the Walk-12G (controlling variable) and the FES-I (r = 0.869). Multicollinearity was also identified between the same variables in study IV, i.e., baseline values of the FES-I (controlling variable) and Walk-12G (r = 0.865). The variables were entered into the respective analysis, but the independent variable was omitted early in the predictor elimination process, respectively. Figure 7 presents the β and p-value of the variables included in the final predictive models of *changes* in perceived walking difficulties and concerns about falling on opposite sides of the figure.

Two statistically significant predictors of *a change* in perceived walking difficulties were identified: perceived balance problems while dual tasking (B = 4.42; 95% CI = 1.55, 7.29; p = 0.003) and global cognitive functioning (B = -0.424; 95% CI =

-0.830, -0.017; p = 0.041). Age and baseline Walk-12G were included into the model as controlling variables. The final model included four additional variables (due to p-values < 0.1). These were: being bothered by pain, postural instability, fatigue and lower extremity function, but none of them were significant predictors of a change in perceived walking difficulties. The final predictive model explained 67.2% of the total variance in Walk-12G total scores at the 3-year follow-up.

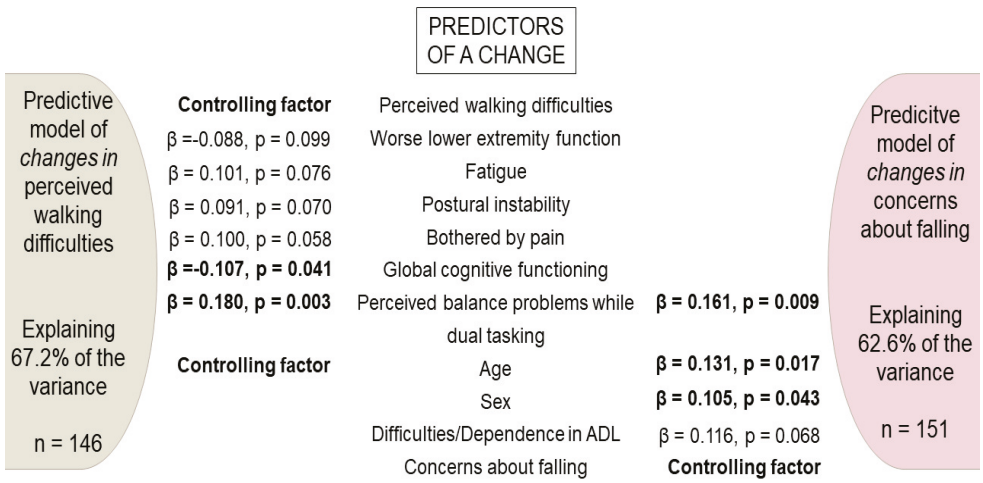


Figure 7. Predictors of a change in perceived walking difficulites (generic Walk-12; left side) and concerns about falling (Falls Efficacy Scale-International; right side) after a three-year period.
These final models included variables with p-values < 0.1. The numbers next to a variable indicate standardized regression coefficient (β) and p-value. Significant p-values (< 0.05) are bolded.

Perceived balance problems while dual tasking (B = 4.62; 95% CI = 1.19, 8.05; p = 0.009), older age (B = 0.204; 95% CI = 0.038, 0.371; p = 0.017) and female sex (B = 3.07; 95% CI = 0.098, 6.05; p = 0.043) were significant predictors of a change in concerns about falling (i.e., controlling for the baseline FES-I score). The final model also included the variable difficulties/dependence in ADL, but this was non-significant. The final predictive model explained 62.6% of the total variance.

Discussion

The overall aim of this thesis was to provide an increased knowledge concerning objective and subjective aspects relating to walking in people with neurodegenerative disorders.

This thesis adds a comprehensive basis for a better understanding of objective gait parameters and components in patients with MCI as well as in CU individuals. A specific focus concerns how brain pathologies are associated with gait parameters that represent different components of gait in patients with MCI. These findings suggest that increased tau deposition is associated with increased step velocity, step length as well as increased step velocity variability.

This thesis also targets subjective aspects related to walking (i.e., perceived walking difficulties and concerns about falling) in people with PD. By investigating these aspects longitudinally, the aim was to gain an increased understanding of how these aspects progress over time. Moreover, determining predictive factors of perceived walking difficulties and concerns about falling, may provide a greater understanding of how to intervene. That is, the identified predictive factors that are modifiable (e.g., perceived balance problems while dual tasking and pain) could be addressed in future intervention studies.

For physical therapists, gait is a key component when assessing and treating patients [123]. Several studies have shown that decreased gait speed precedes cognitive decline [27, 193, 194], and gait assessments have therefore gained an increased interest when targeting those at risk of developing dementia. To the best of my knowledge, little has previously been researched concerning the relationship between different gait parameters in people with MCI with markers of an incipient neurodegenerative disorder. Moreover, few longitudinal studies within the field of PD have addressed perceived walking difficulties or concerns about falling. Such studies are imperative to determine predictive factors. An enhanced understanding of objective and subjective aspects related to walking is anticipated to improve care and rehabilitation of people with MCI and PD. The following sections will discuss the findings of this thesis in more detail.

Components of gait in people with and without mild cognitive impairment

Four components of gait (Variability, Pace/Stability, Rhythm and Asymmetry) were identified both in people with MCI and in CU people. The amount of total variance explained (approximately 80%) was in line with previous PCAs that included older adults without dementia [32-34, 36], as well as with the single previous PCA study that exclusively included people with MCI [114].

Variability

The variability component explained the largest amount of variance (close to 25%) in both groups, i.e., MCI and CU. This value is in line with several prior PCA studies in older adults without dementia [33, 35, 37] as well as in people with PD [195]. That the variability component explained the largest amount of variance contrasted with previously performed PCAs [32-35, 37]. This could be due to that several variability variables were included, which all had their highest loading in the variability component. A component that includes several variables often explains more of the variance than components including less variables. The current study as well as previous PCA studies (e.g., [32-35, 37]) identified a variability component of gait, which signals that variability measures are of relevance.

In this thesis, step velocity variability was the highest loading gait parameter within the variability component in both groups; step length variability was the second highest loading parameter. These findings are in line with several PCA studies of gait in older adults without dementia, which reported that step (or stride) length variability or step velocity variability was the highest loading gait parameter in the variability component [32, 34-37]. In the study by Hollman et al., stride speed variability was considered a part of the variability component, but it loaded lower in relation to many of the other gait parameters linked to the component [33]. Hollman et al., used a stride-based speed variability parameter, they used a relative variability measure and moreover, their participants completed only two walks on an instrumented walkway (mat length 5.6 meters), compared to six laps in this thesis (mat length 5.79 meters). The distance in the study by Hollman et al. would likely amount to approximately 7-10 strides. Generally, a minimum of 30 steps (which translates to 15 strides) should be collected in order for obtaining reliable *step*-based variability measures [41]. Whereas, when using *stride*-based variability measures, as much as 60 strides has been estimated to be required for obtaining reliable stride variability measures during normal walking as a single task [196]. These differences could be reasons for the contrasting results.

Many prior PCA studies used stride-based variability measures. Step-based gait parameters are however considered more reliable than stride-based, and step-based

measures allow for the inclusion of gait asymmetry variables [38, 41]. That is, some of the variance attributed to the variability component in previous PCAs might have been related to asymmetry rather than variability.

Step width variability was omitted from both PCAs in this thesis as it did not reach the predefined inclusion criterium of having a correlation of at least ±0.30 with at least one other gait parameter [173]. While assuming a linear association between increased variability (e.g., stride time variability) and poor gait in older individuals [197, 198], step width variability has portrayed a non-linear association with increased fall risk. That is, in gait speeds > 1.0 m/s, both very high and very low step width variability has been associated with an increased fall risk [198]. This may explain why step width variability did not reach a correlation of ±0.30 and why it was more closely related to other components than Variability in PCAs that did not use such an inclusion threshold [33-35].

As previously mentioned, increased gait variability is associated with increased fall risk [5, 197, 198], but might also be of importance in relation to the control of habitual gait [10, 30, 34, 199]. For example, low stride time variability has been linked to efficient and safe gait patterns and both variability in stride time and length are said to be related to the control of rhythmic stepping mechanism [199]. Increased gait variability is also associated with poorer cognitive functioning, such as executive functioning and attention [107, 162, 199, 200]. In people with aMCI, variability (specifically gait speed variability) is increased as compared to cognitively healthy controls [111, 201], and dual tasking further increases gait variability in people with MCI [109, 111].

Pace/Stability

Step length, step velocity and double support time were identified within the pace/stability component in both groups, and step length was the highest loading gait parameter. Step length (and/or stride length) and gait speed (represented by step velocity in these PCAs) have previously been identified in pace-labelled components in older adults without dementia [32-36] as well as in people with MCI [114]. In older people without dementia, step length and gait speed are decreased (as a result of the shorter steps) while double support time is increased, i.e., as compared to healthy younger adults [202]. The finding that double support time belongs to the pace/stability component is in line with prior studies that included both people with and without MCI as well as in people with PD [32, 114, 195]. In the studies that included temporophasic gait parameters (i.e., temporal parameters constructed by percentages of the gait cycle), double support time was identified in a phase component [33, 35, 37]. However, only one of the prior studies exclusively included people with MCI [114].

In the MCI group of the thesis, step width and step length asymmetry were also identified within the pace/stability component. This was not the case in the CU group. To the best of my knowledge these two gait parameters have not previously been included in PCA studies of gait in people with MCI [114]. However, this finding is in line with a study in cognitively healthy older people [34]. It should be noted that an increased step width can signal balance impairments [1].

Gait speed is often seen as a global outcome measure for predicting future health [26] and has been extensively investigated in relation to cognitive functioning [109, 111]. Both gait speed and step or stride length are decreased in people with MCI as compared to cognitively healthy controls [109, 111]. Being able to ambulate independently in the community is an important feature in everyday life. For example, crossing pedestrian crossings safely is important in everyday activities. A gait speed of 1.2 m/s is often used as a standard speed in many traffic applications and traffic signaling times [203, 204]. The included MCI group had a mean step velocity of 1.1 m/s, as compared to 1.2 m/s for the CU group. While assessed in a different setting, this could indicate that those with MCI would need to increase their gait speed for crossing pedestrian crossings within the predetermined time limit. This stressor of increasing gait speed can lead to increased gait variability [112] and could also require increased cognitive resources [110].

Rhythm

The rhythm component included three temporal gait parameters (i.e., mean step time, swing time and stance time) in both groups. This finding is similar to previous PCAs studies in older adults without dementia [32-36]. In this study, step time was the highest loading gait parameter in the rhythm component. However, several other studies considered cadence instead, i.e., the number of steps divided by the ambulation time [1]. Step time and cadence are closely but inversely correlated where cadence increases when step time decreases (generally considered better gait performance) [1]. The rhythmicity of gait is often related to the action in the brainstem and spinal cord rather than frontal regions of the brain [5, 8, 34, 205].

Asymmetry

Which gait asymmetry parameter that loaded the highest differed between the two groups; stance time asymmetry loaded the highest in the MCI group whereas swing time asymmetry was the strongest loading parameter in the CU group. However, these two gait parameters loaded very similarly in the asymmetry component of both groups. Asymmetry variables have previously been associated with chronic neurological disorders that affect gait performance unilaterally (e.g., PD or stroke) [42, 44]. Gait asymmetry can also be the result of limb dominance and/or differences in strength as well as length between limbs [206, 207]. It should be noted that small

differences between gait parameters of the right and left side are seen in practically all individuals, but such small differences are not clinically significant [1, 207]. Although no normative asymmetry measures have been identified, the asymmetry numbers of the CU group were in line with prior studies using the same asymmetry measures in older adults without dementia [34, 36]. The asymmetry measures in this thesis did not differ significantly between MCI and CU, indicating that the MCI group had similar gait asymmetry as older adults without dementia during single task gait. A better understanding of the effect on gait in more cognitively challenging gait activities, such as dual task or ambulating in the society, might produce more marked differences in asymmetry measures in people with MCI, compared to cognitively healthy individuals.

Summarizing remarks regarding the components of gait in people with and without MCI

The PCAs of people with MCI and CU showed several similarities as well as some differences. In both groups, four components of gait were identified and the highest loading gait parameters in each component were the same in three out of four components. In the asymmetry component, the highest loading parameter was stance time asymmetry in the MCI group, whereas swing time asymmetry loaded highest in the CU group.

Three out of four components consisted of the same variables in both groups. The pace/stability component in the MCI group included two additional variables (step width and step length asymmetry) as compared to the same component in the CU group. These two gait parameters were omitted from the PCA of the CU group as they did not reach the predefined inclusion criteria of being sufficiently correlated with at least one other gait parameter. These results indicate that gait components are similar in people with MCI and CU. The variables step width and step length asymmetry seem more closely related to the pace and stability of gait in people with MCI than among CU.

The identified components of gait showed several similarities with prior studies, which identified gait variability measures within a variability component, gait speed and step or stride length within a pace-labelled component and mean temporal gait parameters within a rhythm component [32-37, 114]. These components appear to be relevant aspects to account for when describing gait in people with or without MCI as well as in older adults without dementia [32-36, 114]. In the studies that also included asymmetry measures, an asymmetry component was identified [34, 36, 38, 195]. Asymmetry measures address potential unilateral differences that might be more manifest in certain neurological conditions, such as PD or stroke, or in more cognitively challenging contexts [44]. As such, asymmetry measures might be more relevant to address in those contexts.

Independent effects of common brain pathologies on gait parameters in patients with MCI

To the best of my knowledge, this is the first study that targets the effect of tau-PET deposition in typical AD-related areas on different aspects of gait in patients with MCI. This study also considers cerebrovascular burden as it is a potential and common confounder of gait capacity and performance. Step time and stride length have previously been included in studies that investigated the effects of Aβ on gait in cognitively healthy older people [117, 119]. However, to the best of my knowledge, no previous study included step velocity variability (although gait speed variability has been used in one study concerning Aβ and gait [119]) or stance time asymmetry as dependent gait variables in such studies. Moreover, none of the four included gait parameters have been investigated in relation to tau-PET pathology. The knowledge gained could help to better understand the effects of different brain pathologies on specific aspects of gait in patients with MCI.

In the framework, a new analysis that included step velocity as the dependent variable was added. The reasoning for this was to facilitate comparisons of these results with prior studies in the research area. Step velocity was used to represent gait speed, as gait speed has often been used as the dependent variable in previous studies of older people without dementia and is considered a global marker of future health status [23, 26] as well as of cognitive decline [27, 193, 194, 208].

Increased tau pathology was statistically significantly associated with increased step velocity variability, step length and step velocity. No associations were statistically significant for Aβ pathology or WMH in relation to any of the included gait parameters (see Appendix 4 for tables on all crude and basic univariable regression analyses). In relation to AD, Aβ plaques can be present even approximately 20 years ahead of dementia onset, whereas accumulated tau-PET pathology is often more closely related to clinical symptoms and disease progression [73]. I will now discuss these findings in more detail.

White matter hyperintensities

In this MCI sample, WMH showed no statistically significant effect on any of the included gait parameters (i.e., step velocity variability, step length, step time, stance time asymmetry and step velocity). Prior studies of people with MCI have reported that a high burden of WMH is significantly associated with reduced gait speed [87] and increased step length variability [89]. Ogama and colleagues identified an association of WMH in sublobar regions with decreased stride length and increased walking angle in people with MCI [88]. In this thesis, WMH was investigated globally and not regionally. Using a regional measure concerning e.g., near the basal ganglia, the corpus callosum or periventricular areas might have influenced the

results. Deposition of specific AD pathology (i.e., tau and Aβ) was not considered in the prior studies [87-89]. In people with PD, gait disturbances seem exacerbated by the presence of WMHs [209, 210]. Using specific ROIs in future studies might provide more detailed information about the effect of WMHs on different aspects of gait.

Amyloid-β pathology

No significant associations were found between Aβ pathology and any of the included gait parameters. Prior studies of older adults without dementia as well as studies of cognitively healthy older adults have found associations between Aβ PET pathology and several gait variables, both mean and variability variables [115-117, 119]. In older adults without dementia, prior studies primarily addressed the gait parameter gait speed [115-117]. One of the studies controlled for cerebrovascular burden [116] but none considered tau pathology. Two of the prior studies included only cognitively healthy people (without MCI or dementia). This thesis only includes individuals with MCI, which was believed to be caused by an incipient neurocognitive disorder (i.e., having an increased risk of progression to dementia). This might be the reason for the discrepancies in results.

While individuals with MCI generally exhibit worse gait than cognitively healthy people, it should be noted that those with naMCI have generally more affected gait than those with aMCI [107]. This was corroborated by these results, where those with aMCI walked statistically significantly faster and had longer step length than those with naMCI (data found in Appendix 5). In this MCI sample, approximately 70% had aMCI, which is more closely related to the progression of AD [211, 212]. The distribution between aMCI and naMCI might explain the non-significant effect of Aβ on the gait parameters in this thesis.

The investigated ROI was a neocortical composite region consisting of the prefrontal, lateral temporal, parietal, anterior cingulate, and posterior cingulate/precuneus areas, in line with conventional Aβ dispersion in AD [73, 165, 166]. As the motor areas of the brain are often affected late in the AD process, this could be an additional reason for why no significant associations were identified between Aβ and the included gait parameters.

Tau pathology

Increased tau pathology in conventional AD areas (Braak stages I-IV) exhibited statistically significant ($p \leq 0.001$) associations with increased values in step velocity variability, step length and step velocity in all model stages. These associations remained statistically significant when investigating the potential effect of tau in different AD-related regions (i.e., Braak stages I-II, III-IV and V-VI,

respectively) [168]. The effect of AD pathology on clinical symptoms can sometimes be confounded by cerebrovascular burden and it is not uncommon having both AD-related pathology and cerebrovascular burden [69, 78]. In this sample, the associations remained statistically significant when also accounting for cerebrovascular burden (WMH and ICV). This could indicate that the effect of tau pathology on step velocity variability, step length and step velocity is not highly influenced by cerebrovascular burden. However, while still statistically significant, the p-value ($p = 0.049$) of the association between increasing tau pathology in Braak stages I-II and step velocity variability while accounting for cerebrovascular burden was close to the predefined alpha level. This indicates that the results should be interpreted cautiously.

The entorhinal cortex (in line with Braak I-II regions) functions include conveying information between the neocortex and the hippocampus [213]. The volume of the hippocampus (included in Braak III-IV) has shown contradictory associations with gait variability, where both spatial and temporal gait variability measures have been investigated [40]. While this thesis investigates the effect of tau pathology, both hippocampal volume and tau pathology can relate to clinical symptoms [214]. Investigating the effect of different areas of gray matter volume, such as the hippocampal volume, might aid in increasing the understanding of brain pathologies on gait. Step velocity variability, i.e., a combination of both temporal and spatial dimensions, has to the best of my knowledge, not previously been investigated in relation to tau pathology. A variability of gait can be desirable for example when managing safe ambulation in everyday life, such as going to the store or avoiding a collision with other people in a store or when crossing a street. These kinds of situations demand the ability to adapt in accordance with the environment. On the other hand, increased gait variability has been associated with increased fall risk and greater decline in cognitive functioning [10, 199, 200]. In the standardized setting that was used for collecting gait data in this thesis, it is reasonable to assume that increased gait variability is an indicator of worse gait per se.

Neocortical regions were investigated in relation to Braak V-VI. In these areas, step velocity variability also increased as tau pathology increased. The neocortical areas are involved in executive and attentional cognitive ability [215]. These capabilities likely influence gait control [5, 215]. The effect of tau load (i.e., looking at the standardized beta coefficient) on step velocity variability was largest in Braak V-VI. This might further indicate the involvement of the neocortex in gait variability.

Gait variability could potentially be influenced by gait speed in people with MCI [112]. Gait speed was therefore included in a sensitivity analysis (data not shown), but it did not influence the statistical significance of the association between tau pathology and step velocity variability.

The associations between increased tau pathology and increased step length and velocity were surprising findings. It seems unlikely that increased tau pathology is

associated with “better” gait. The findings are more likely results of the investigated study sample as well as the investigated brain regions. As discussed earlier, the included MCI sample consists of patients with cognitive impairments believed to be caused by an incipient neurocognitive disorder. That is, in addition to people with markers of AD or VaD, the study sample also includes people whose cognitive complaints are believed to be caused by other neurocognitive disorders, such as Lewy body dementia or frontotemporal dementia. These forms of dementia might initially be more closely related to gait disturbances than AD-related dementia [216, 217]. Also, AD-related tau pathology often targets the direct motor producing areas of the brain (e.g., the primary motor cortex or the supplemental motor area) later in the disease process [73]. This could help explain the surprising associations between tau pathology and step length and step velocity, respectively. If a motor specific ROI had been investigated, the results might have been different.

Comparing step length and step velocity in people with MCI with cognitively healthy older adults within a similar age interval and sex distribution (n = 65 with MCI and n = 77 cognitively healthy, aged 70-80 years, data found in Appendix 5) showed statistically significant differences in step length and step velocity between the groups. Cognitively healthy older adults took longer steps and walked faster. Compared to individuals with naMCI, individuals with aMCI walked statistically significantly faster, had longer step length but did not differ in step velocity variability. So, while increasing tau pathology was statistically significantly associated with increasing step length and step velocity in the sample of MCI, individuals with aMCI (more closely related to AD) performed better in reference to these gait parameters than naMCI, possibly adding to the understanding of the somewhat surprising results.

Subjective aspects related to walking in people with PD

This thesis shows that both perceived walking difficulties and concerns about falling increased over a 3-year follow-up period in people with PD. Moreover, to the best of my knowledge, these are the first studies to identify predictors of perceived walking difficulties and concerns about falling in people with PD. An increased understanding of the evolution of these aspects might aid in the long-term management of people with PD. As PD progresses, objective signs of walking difficulties become more common and increased [103]. However, objective and subjective aspects of walking performance may not always align, and they seem to address different aspects and perspectives of gait [20]. Subjective aspects related to walking, such as perceived walking difficulties and concerns about falling, are aspects that target perceptions of difficulties as well as concerns, i.e., negatively valued aspects. Compared to positively valued aspects, negatively valued aspects may have a stronger effect on perception as well as behavior, as they may address

disabilities that can lead to negative outcomes related to walking, rather than positive outcomes [218].

Predicting perceived walking difficulties

Concerns about falling at baseline was the strongest independent predictor of perceived walking difficulties at the 3-year follow-up. Prior cross-sectional studies have shown that FOF was associated with several objective gait parameters (e.g., reduced stride length and gait speed as well as increased spatial variability) in people with PD [219, 220]. However, a previous cross-sectional study by Kader et al. (based on the same cohort as this study) did not consider FOF and instead identified freezing of gait and general self-efficacy as the two factors that were strongest associated with perceived walking difficulties [128]. In study III, both freezing of gait and general self-efficacy showed significant associations ($p<0.001$) with perceived walking difficulties in univariable linear regression analyses. They were although not independently associated when also including concerns about falling in multivariable analyses. This highlights that factors that are statistically significant in univariable analyses might not be significant when using multivariable analyses, more closely representing a real-life setting. All considered, concerns about falling seems to be an important factor to address and monitor when targeting perceived walking difficulties in people with PD.

Having perceived balance problems while dual tasking predicted perceived walking difficulties at the 3-year follow-up. This variable was not included in the prior cross-sectional study based on the same cohort [128], which instead included postural instability by using item 30 of the UPDRS. The current study included both perceived balance problems while dual tasking and postural instability (item 30, UPDRS). Compared to the prior cross-sectional study where postural instability contributed to increased perceived walking difficulties, it was not a statistically significant predictor in study III. It was however included (as a non-significant factor) in both final models concerning perceived walking difficulties (i.e., the final models of predictors and predictors of a change in perceived walking difficulties, respectively). Approximately 75% of the samples in both studies were categorized as having postural instability. Perceived balance problems while dual tasking were self-rated by the participants of the study whereas postural instability was assessed by the data collector. This could indicate that certain self-perceived perspectives might have a stronger predictive and more long-lasting relation to other self-perceived concepts as compared to assessments made by others. In study III, postural instability was statistically significant in the univariate analysis, signaling a potential relevance to perceived walking difficulties three year later in a less complex model. Also, part of the predictive effect of postural instability might be included in the effect of other factors, such as perceived balance problems while dual tasking. A dual task situation can include an additional motor or cognitive task.

Both situations generally demand a larger cognitive involvement, as attention is divided between several tasks, and demands of executive function, such as decision making, increase [103, 215, 221, 222]. Regardless of the second task, dual tasking affects walking adversely in people with PD [221]. Gait speed is lowered, irrespective of single task gait speed and regardless of type of dual task [221]. On the other hand, a systematic review by De Freitas et al., indicated that exercise and balance focused training that incorporates the dual task paradigm seems to positively influence gait and balance performance in people with PD [223]. All considered, this highlights the importance of addressing dual task ability when assessing and treating people with PD.

Being bothered by pain significantly predicted perceived walking difficulties, which corroborates the findings of the previous cross-sectional study based on the same cohort [128]. Pain is common in people with PD [106, 224] and can vary in accordance with motor state, often being worse during "off-periods" [106]. Providing adequate, timely treatment of pain can include pharmacological treatment, but exercise can also be used for pain management [224, 225]. Exercise therapy such as aerobic, active balance or strength training [224, 225] could be administrated depending on the pain genesis. The current study used a coarse indicator of pain and future studies should address pain in more depth in relation to perceived walking difficulties in people with PD. That is, the current findings do not provide detailed information on which type of pain to address or where the pain is located.

Predicting concerns about falling

This longitudinal study shows that perceived walking difficulties in everyday life is an important factor to consider when targeting concerns about falling in people with PD. It was the strongest independent predictor of concerns about falling, which corroborates previous cross-sectional findings based on the same project [141]. Another cross-sectional PD-study included instead gait speed, which was not independently associated with concerns about falling [143]. It should be noted that cross-sectional studies have shown that perceived walking difficulties are associated also with fall-related self-efficacy [132, 134]. Moreover, a study based on data from the HHPD project has shown that concerns about falling as well as perceived walking difficulties predict fall-related activity avoidance [146]. Both fall-related self-efficacy and fall-related activity avoidance are concepts that relate to FOF [178]. As such, perceived walking difficulties seems closely related to several concepts that relate to FOF, i.e., concerns about falling, fall-related self-efficacy and fall-related activity avoidance. To summarize, perceived walking difficulties seem to be an important factor to address when targeting FOF in people with PD.

This thesis also identified the following additional predictors of concerns about falling in people with PD: age, perceived balance problems while dual tasking and

difficulties/dependence in ADL. That age was a significant predictor of concerns about falling is in line with another longitudinal study using data from the same project, but that study targeted predictors of fall-related activity avoidance [146]. Age has shown contrasting associations to FOF in prior cross-sectional PD-studies [132, 134, 141-143]. Two studies specifically investigated concerns about falling [141, 143]. One of these studies [141] (using data from the same project as this thesis) showed a significant association between age and concerns about falling, whereas the other study [143] did not find such association. As few longitudinal studies have investigated the effect of age on FOF in PD, future studies are needed to confirm or refute the significant association in this thesis. Old age has generally been associated with faster motor progression in PD [226, 227]. The effect of age on clinical features, such as motor progression might explain the predictive ability of age on concerns about falling in people with PD.

Perceived balance problems while dual tasking was independently associated with concerns about falling at the 3-year follow-up. This finding is in line with the study by Franzén et al., which showed a cross-sectional association between balance performance and concerns about falling in people with PD [143]. The latter study evaluated balance by using the Mini-BESTest, which includes 14 items; one of the items assesses mobility (Timed Up & Go) without and with a subtraction task. However, the current finding contrasts with cross-sectional findings from the HHPD project, which showed that perceived balance problems while dual tasking were not independently associated with concerns about falling [141]. This highlights that cross-sectional findings need to be replicated in longitudinal studies, which are a prerequisite for identifying predictive factors. Determining predictive and modifiable factors, increases knowledge about factors that need to be addressed in future interventions. As yet, the quality of evidence for reducing FOF in people with PD has been regarded as 'low to moderate' and further research with high evidence quality is needed [228].

Perceived balance problems while dual tasking showed predictive capacity of both concerns about falling and perceived walking difficulties. Asking about issues regarding balance performance while dual tasking seems to be an important aspect to consider when one strives to address concerns about falling. Also, providing gait and balance training with a dual task component may reduce or prevent a worsening of perceived walking difficulties or concerns about falling in people with PD. In a systematic review and meta-analysis by Abou et al., they studied the effectiveness of physical therapy interventions on FOF in people with PD. This review included studies that used the FES-I or ABC-scale as the primary or secondary outcome measure [228]. They found that interventions which combined gait and balance exercises were effective in reducing FOF in people with PD. Based on these included studies, the review recommended that exercises be performed for at least 30 minutes per session, 5 times a week over a 12-week period. They also recommended that exercises are complemented with advice concerning fall

prevention. Importantly, this review graded the evidence as 'low to moderate' [228]. As of today, few randomized and controlled studies have used perceived walking difficulties or concerns about falling as their primary outcome within the field of PD [228]. There are randomized and controlled studies that evaluated the effect of gait and balance training on concerns about falling in PD, although concerns about falling was not defined as the primary outcome (e.g., [229, 230]). For example, a highly challenging balance training program showed no differences between the exercise group and the control group after a 10-week period (60 minutes per session; 3 times a week) [229]. Another exercise study that lasted for 6 months (40-60 minutes per session; 3 times/week) reported an effect on concerns about falling [230]. Beliefs about the potential negative consequences of one's own capacity to perform everyday activities, such as concerns about falling, might be a factor that can be hard to affect in a positive direction. Individuals tend to value potentially negative outcomes as more impactful than potentially positive ones. Combined with the progressive nature of PD, a lasting concern about falling might be a factor hard to modify or to see the effects on after an intervention that lasted a short time. Thus, an intervention that aims at reducing concerns about falling probably needs to be longer than 10-12 weeks, but this remains to be shown. Fear of falling can result in activity avoidance, which can be considered an appropriate or inappropriate approach, depending on the actual fall risk [56, 231]. This is also important to take into consideration when targeting concerns about falling. Interventions focusing on multicomponent cognitive behavior group sessions aimed at reducing FOF might also prove fruitful for people with PD as it seems for older adults [232, 233].

Difficulties and dependence in ADL was a significant predictor of concerns about falling, which contrasts the cross-sectional findings of the same project [141]. However, several other cross-sectional studies have shown that difficulties and dependence in ADL is associated with FOF in people with PD [132, 134, 140]. This again highlights the need for investigating associations both cross-sectionally and longitudinally. Difficulties and dependence in ADL may include difficulties with mobility and need of assistance in transitions and walking for safe ambulation [183]. Self-assessed ADL ability likely worsens over time in people with PD as the disease progresses [234]. Balance training seem to have some effect on the ability to perform ADL independently [229] and might be a factor to prioritize when aiming at reducing concerns about falling in people with PD.

Predictors of change in perceived walking difficulties and concerns about falling

In the models predicting a change, perceived balance problems while dual tasking was found to predict a change in both perceived walking difficulties and concerns about falling (studies III-IV). A previous study that investigated a change in FOF over a 2-year period, identified an increasing numbers of falls during the first year

as an independent predictor of a change (i.e., decrease) in fall-related self-efficacy [145]. These findings combined underscore that aspects of balance problems while dual tasking and limitation of fall risks seem important to address in rehabilitation. Gait and balance training is often combined with dual task training, which increases the level of difficulty [221, 223]. The reasoning for the latter is that walking while performing a concurrent task demands more cognitive involvement than single task walking [103, 215, 221]. Compared to single task walking, dual task walking is suggested to resemble everyday life more closely [222]. In a study regarding the effects of dual task training on gait speed in people with PD, those with good cognitive functioning at baseline seemed to benefit more from dual task training [235]. The current thesis shows that global cognitive functioning was independently associated with a change of perceived walking difficulties (Study III), which was not the case for a change in concerns about falling (Study IV). That is, when adjusting for baseline walking difficulties, better global cognitive functioning at baseline was associated with reporting less perceived walking difficulties three years later. Prior cross-sectional studies that addressed global cognitive functioning in relation to FOF in people with PD have shown contrasting findings [132, 139, 141]. Two studies found no association with FOF [132, 141] while one study identified that higher MMSE score was associated with lower FOF [139]. In this thesis, the statistically significant association between global cognitive functioning and a change in perceived walking difficulties was close to the predefined alpha level (0.041), which should lead to cautious interpretations of this result. To the best of my knowledge, no other longitudinal study has investigated predictors of a change in perceived walking difficulties.

In this thesis, age and sex were also identified as predictors of a change in concerns about falling. Prior longitudinal studies that investigated a change in other FOF measures found that age significantly predicted a change in fall-related activity avoidance [146], but age did not predict a change in fall-related self-efficacy [145]. The first of these two studies used data from the same longitudinal project as this thesis. It included (as in study IV) in comparison an older group of people with PD (mean 68, SD 9 years [146], vs. median 60, interquartile range 11 years [145]). The PD duration also differed: mean PD duration of 9 years [146] vs. median 4 years [145]. Age seems to be a relevant predictor of a change in concerns about falling and fall-related activity avoidance. These two constructs are closely correlated in people with PD [178]. Fall-related self-efficacy is conceptually more closely related to balance confidence than many other measures of FOF [50]. As such, age might have a different effect on the different constructs related to FOF.

Cross-sectionally, age was not identified as a contributor of perceived walking difficulties [128]. Older age has been associated with slower gait speed and older age at onset has been associated with faster general motor symptom progression in people with PD [226, 236]. While being different perspectives related to walking, it is not unreasonable to assume that age also predicts a change in perceived walking

difficulties ($p = 0.002$ in the final model). Age was however included as a controlling variable throughout the analysis process and was therefore maintained in the model regardless of its p-value. Had the variable been included as an independent variable and not a controlling variable, it would have been part of the final model.

Sex was a significant predictor of a change in concerns about falling. The statistical significance level of the variable sex ($p = 0.043$) in study IV was close to the predefined alpha level, warranting additional caution in interpretation of the results. Concerns about falling was assessed with a PROM. Women in general perceive their health and ability as worse compared to men in people with PD and also seem more prone to falling than men [237]. Sex was included as an independent variable in the study of predictors of a change in fall-related activity avoidance [146]. In that study, it was not significant.

Moreover, it is also likely that both baseline values of the opposite outcome measure in the models investigating predictors of change (i.e., baseline values of concerns about falling on a change in perceived walking difficulties at follow-up, and vice versa) play an important role in the respective outcome measures. This effect was however not seen in the models due to multicollinearity between the two baseline values. Multicollinearity implies that there was a high correlation between the two variables, which denotes that the two concepts (i.e., concerns about falling and perceived walking difficulties) are highly related.

Subjective aspects, such as concerns about falling, perceived walking difficulties, or perceived balance problems while dual tasking, were significant factors for both predicting the outcome measures as well as predicting a change in them. These aspects regard subjective ability that does not always correspond to the objective performance of an individual [20]. This could indicate that the perceptions of walking difficulties target other aspects of gait than objective gait performance does. It might be that a belief in one's own capacity as low is based on previous perceptions on ability, even though objective measures indicate a safe level of gait. Importantly, objective measures and patient reported outcomes reflect different perspectives. Perceived limitations in walking capacity or fear of consequences of falling may result in negative effects on physical activity, decreased participation in social activities and decreased quality of life in people with PD [56, 238, 239]. Thus, interventions aimed at targeting and improving both perceived and objective limitations related to walking capacity, using one of these concepts as the primary outcome measure, might prove more effective than only targeting objective capacity as they address different perspectives. This is however merely a hypothesis and needs to be tested in future studies.

Similarities and differences between the concepts perceived walking difficulties and concerns about falling

Perceived walking difficulties and concerns about falling are concepts that target adjacent, yet different aspects; there is a high, but not perfect correlation between the two scales (r = 0.865; Study IV). The Walk-12G questionnaire targets the perception of walking difficulties in everyday life [19]. Meanwhile, the FES-I questionnaire addresses the level of concerns about falling while performing specific activities both inside and outside of the home [62]. For example, although both scales include an item relating to stair climbing, the Walk-12G asks about limitations in the ability to climb stairs while the FES-I asks whether the respondent is concerned about falling while doing so [19, 62]. It should be noted that many items in both scales relate to walking. Eight out of the 12 Walk-12G items explicitly target different aspects relating to difficulties in walking. Two additional items address the need for support when walking indoors and outdoors (Swedish translated version from the study by Bladh et al. [19]). The two remaining items (i.e., limitations in ability to run and difficulties standing while doing things) address aspects that indirectly can be related to difficulties in walking. The idea that all these items relate to one unitary concept is strengthened by the production of a PCA that included all items of the Walk-12G [19]. This PCA identified one single component surpassing an eigenvalue of 1 (eigenvalue of 8.2).

In the FES-I questionnaire, six out of the 16 items (Swedish translated version by Eva Nordell [240]) explicitly mention walking (i.e., they include the Swedish word "gå" or "promenera"). However, the remaining ten items of FES-I include activities that do not necessarily require walking ability (e.g., "preparing simple meals" and "getting in or out of a chair") [62]. The FES-I addresses concerns about falling in more (principally related to activities outside of the home) and less demanding activities (closely related to activities inside the home) [62, 240]. Importantly, although each item in FES-I relates to concern about falling, none of the items or response options in Walk-12 G explicitly address fear of falling. As such, the two scales address different but adjacent and in certain perspectives, similar aspects, relating to walking.

Walking is often considered an important and highly valued aspect in everyday life [239]. In people with PD with progressively deteriorating ability, aspects of independence and control in walking also relate to being able to participate in social activities [239]. This could indicate that impairments in walking ability affect the sense of confidence, independence and identity of people with PD. These are aspects that relate also to concerns about falling [62]. Perceived limitations in walking ability and concerns about falling might hamper the degree and type of activities an individual participates in. Taken together, both objective and subjective aspects related to walking impairments could have a profound effect on everyday life.

Methodological considerations

The goal of an exploratory factor analysis (FA) or PCA is to summarize and reduce a large number of observable variables into a smaller number of factors or components [173]. Although sometimes treated as the same, a difference between a FA and a PCA is that during the extraction of underlying or explanatory variables, the PCA assumes that all variance is common while in a FA, an assumption is made that the total amount of variance can be partitioned into shared and unique variance. A FA only analyzes what is believed to be the shared variance [173, 174]. A robust model of explanatory components should ideally include variables (i.e., gait parameters) that correlate highly with one component and present low correlations with the other identified components [173, 174]. In relation to study I, while initially using the maximum likelihood method of dimension reduction for analyzing the data, the analysis did not suit the data and the method of principal components was used instead. Some analysis methods are more suitable for certain types of data.

To my knowledge, all previous studies that investigated components of gait used PCA as the dimension reduction method [32-36, 114]. Furthermore, they all used orthogonal varimax rotation as the rotation method, which was used also in this thesis. This was in order to identify independent components while maximizing the variance maintained [173]. Some variables in this thesis needed different forms of transformation to improve normality of distribution before including them in the analysis (e.g., square root transformation since log-transformation did not suit the data). The used method of the thesis seems robust and appropriate relating to the aim of identifying independent components of gait in people with and without MCI. Gait variability measures in studies I-II were based on standard deviation instead of coefficient of variation. This was chosen because it provides clarity for interpretation. That is, variability measures based on standard deviations are expressed in absolute measures instead of in relative measures, as is the case of variability measures based on coefficient of variation.

In the study that investigated the effect of brain pathologies on gait parameters (study II), there was a time difference between the imaging occasions and the motor assessment (the imaging occasions were performed approximately one year prior to the motor assessment). This time difference was in line with the study protocol for the larger project. As the brain pathologies in the MCI sample are assumed to be degenerative and progressive by nature, there is a risk that the individuals have accumulated more pathology in between the imaging sessions and the motor assessment, which might affect their gait performance. However, accounting for the time difference did not seem to affect the relationship between brain pathology and gait performance. Other studies that also had a time difference between imaging session and gait assessment (assessing gait speed) also accounted for this difference [115, 116]. The time difference (median 71 days [115] and mean 16 months respectively [116]) did not significantly affect their study results either.

In relation to the predictor studies in people with PD (studies III-IV), some of the independent variables were transformed into dichotomized variables. This can sometimes be an advantage as it enables the inclusion of certain variables that otherwise might have been omitted from the analyses due to a skewed distribution or a limited sample size for the various response options. The use of a dichotomous variable instead of, e.g., an ordinal scale might simplify the interpretation or possibly add directed clinical relevance to a variable. Dichotomization does however lead to the loss of nuance and detail in a variable. Dichotomization in the present thesis was based on clinical relevance, dichotomizations used in prior studies as well as what was believed to provide insight of the effect of the variable on the outcome measure. For example, postural stability was assessed using item 30 of the UPDRS III [14]. Although originally scored 0-4, in this thesis the item was dichotomized into having no problems with postural stability (original score = 0) or having some form of postural instability (scores 1-4). This dichotomization was based on a previous study using the same scoring division of item 30 of the UPDRS III [181]. The dichotomization of this item might facilitate the investigation of this potential effect on perceived walking difficulties. This dichotomization was also used in a prior cross-sectional study where postural instability was identified as a significant contributor to perceived walking difficulties [128].

The independent variables were chosen based on significant contributors in prior studies that used cross-sectional data as well as clinical and theoretical reasoning regarding potential predictive capacity of perceived walking difficulties and concerns about falling, respectively.

When investigating predictors of a change in perceived walking difficulties and concerns about falling, the baseline value of the outcome measure (i.e., the dependent variable) was accounted for in the regression models. This implies investigating the change over the follow-up period in relation to their baseline value. An alternative method would be to use a delta score of the dependent value (i.e., the difference between the baseline and follow-up score of the investigated variable), without accounting for the baseline score. Understanding what predicts a change while taking the baseline value into consideration might be considered more clinically relevant. Using the following example: Using a delta score and not adjusting for the baseline score tells us which factors predict a worsened FES-I score at follow-up, regardless of baseline score. If it does not matter where on the FES-I spectra an individual was at baseline, such a model would be sufficient. The baseline score however probably influences the future score. From a clinical perspective, a worsening score of 4 points on the FES-I for those who already have a high score at baseline might be considered more worrying than the same change in those who had a low score at baseline. Adjusting for the baseline value in regression models might however hide the effect of other potential predictors that are closely associated with the baseline score of the outcome measure (i.e., exhibiting multicollinearity). For example, due to a stronger association between the adjusting baseline score and

follow-up score of perceived walking difficulties (the outcome measure) compared to the association with the FES-I score, the effect of FES-I did not result in any significance in the model identifying predictors of a change in perceived walking difficulties. This effect likely influenced both predictor models of a change that are included in this thesis, which needs to be considered when interpreting the results.

Strengths and limitations

This thesis provides knowledge of objective gait and its relation to common AD-related brain pathologies in people with MCI as well as perceived aspects relating to walking in people with PD. A strength of this thesis is the inclusion of both objective and subjective measures of gait, although in different cohorts. This thesis provides a more comprehensive understanding of how different gait parameters relate to each other in people with and without MCI. It also provides insights into the effects of common brain pathologies on gait in patients with MCI. Objective gait in people with PD has been extensively researched. However, studying subjective walking related aspects can provide additional perspectives. The longitudinal design of studies III-IV is a strength of this thesis, as it provides knowledge on how these subjective gait aspects evolve over time and enables the identification of predictive factors. The knowledge gained may nurture future intervention studies that address modifiable factors.

In the study samples included in studies I-II, the mean age was approximately 73 years in both groups (i.e., MCI and CU), and the age range was also similar in both groups including people from 48 years old aged up to 91 years. The sex distribution was also similarly and evenly distributed between males and females. Having a sample that includes a wide variety of ages, may enhance the generalizability to a larger population than more specific age cohorts normally included in a study do. Research regarding dementia is often performed on older adults. However, one can develop neurocognitive disorders while still being in a traditional working age. The inclusion of such individuals helps generalize these results to a wider age range. The MCI group included only people whose cognitive symptoms were believed to be caused by an incipient neurocognitive disorder, and who had been referred to a memory clinic. It should be noted that people with MCI who are linked to specialist memory clinics have higher progression rates to dementia than population-based MCI samples [241]. The latter also includes people who have more benign genesis to their MCI. As such, the included MCI group can be considered a more specific sample of individuals with an increased risk of progression to dementia. The results may be more valid for those that have a higher risk of developing dementia.

The sex distribution in the PD sample was in line with general prevalence numbers associated with PD [242]. In contrast to prior studies, who often exclude older

people with PD [243], there was no such exclusion criteria in the studies in this thesis and the age range in the PD sample ranged 46 years (min 45 – max 91 years). This increases the generalizability of the results into the general PD population and can thus be considered a strength of this thesis. The PD sample included people with various disease severity, ranging from mild to very severe PD (Hoehn & Yahr staging min 1-max 5), indicating that aspects from the full range of the disease severity spectrum were represented in the studies. Moreover, MoCA scores of the PD sample indicated that both people with high and low global cognitive functioning were included. This further increases the generalizability of the findings.

The dropout rate in the HHPD project was in line with the a-priori assumptions in the study protocol and was accounted for through power calculations. The choice of collecting data in the homes of the participants as well as through self-administered questionnaires might have made it possible for some individuals to participate, that might have opted out due to poor health if the data collection would have taken place at an outpatient clinic. The method for data collection in studies III-IV can thus be seen as another strength of these studies.

The objective gait data in studies I-II were collected using an instrumented walkway and specific software. Using this instrument enables the collection of several discrete gait parameters that are hard to collect using more commonly featured gait measurement techniques such as a stopwatch and a clearly defined walking distance. This might limit the usability to settings where more complex instruments exist. A strength of this thesis relation to these complex gait parameters was the inclusion and investigation of multiple step-based gait parameters. Several prior studies have used stride-based gait parameters, which makes it impossible to study gait asymmetry. Investigating a more comprehensive set of gait parameters in people with MCI than previous studies provide a broader understanding of the relationship of common gait parameters. The only identified prior PCA study that exclusively included people with MCI focused on gait parameters related to falling [114].

Using PET for imaging tau (study II) is a relatively recent imaging possibility, and this study is one of the first studies investigating tau deposition in typical AD ROIs and its effect on specific gait parameters. PET imaging is an expensive measurement technique, but it provides a more direct measure of the pathology deposition in the targeted areas than CSF measures. As such, the use of PET data can be considered both a strength (i.e., since it provides a direct measure of the pathology) and a limitation of this study (i.e., since the use of PET data is not common clinical practice, which hampers the transferability of the findings). A strength of the study is that it also considered cerebrovascular burden (i.e., WMH), which could influence the effect of AD specific pathologies in studies targeting gait and cognition. Both tau and Aβ deposition in specific motor regions of the brain occur late in conventional AD staging. Exclusively targeting deposition in such motor areas might have altered these results. The MCI sample included patients (i.e., people

referred to a memory clinic) with MCI, which was believed to be caused by an incipient neurocognitive disorder. Population-based MCI samples often also include people that have more benign genesis to their MCI. Neurocognitive disorders such as Lewy body dementia are generally more closely related to gait impairments than AD. As such, targeting other brain pathologies closely related to other neurodegenerative disorders could have affected the results. This was however outside the scope of this thesis. These considerations might help explain some of the results of study II, including what may limit the generalizability of the findings.

Factors that contribute to cross-sectional associations might not be the same factors that predict associations at a later stage, and longitudinal data is a prerequisite for determining predictive factors. Although the Motor-ACT project has a longitudinal design, currently there is only access to baseline data. Consequently, the results of the current cross-sectional studies (I-II) should be interpreted while keeping these aspects in mind.

Several self-administered questions and questionnaires were used in the studies included in this thesis. The Walk-12G and FES-I questionnaires that were used in studies III-IV were part of the postal survey that was sent to the participants. To ensure that the postal survey was responded by the intended participant, there was a finishing question that asked who had responded to the questions: the participant (with or without the help of others), or someone else than the participant. Only questionnaires that were responded by the participant was included in this thesis. There is always a risk that self-administered questionnaire are completed by someone else than the intended participant, and this risk is likely higher for those with a severe PD, i.e., due to fatigue and physical disabilities. Participants however had the opportunity of having someone else read the question out loud or physically fill in the questionnaires for them. In total four individuals (two at baseline and two at the 3-year follow-up) had not responded on the postal survey by themselves. This indicated that it was not a major issue for these studies. People from all levels of Hoehn & Yahr participated in the studies, indicating that also people with severe disease progression participated. Still, when interpreting these results, one should consider that those who were lost for follow-up had more severe PD at baseline [146].

Major conclusions

Objective gait seems comprised of similar components of gait in people with and without MCI. Four components, labeled Variability, Pace/Stability, Rhythm and Asymmetry were identified in both groups. Each component consists of several gait parameters. The highest loading gait parameter in each component might be considered relevant representatives if one wishes to select variables from different components of gait. In both groups, these gait parameters were step velocity variability from the Variability component; step length from the Pace/Stability component and step time from the Rhythm component. In the Asymmetry component, stance time asymmetry was the highest loading parameter in the MCI group whereas swing time asymmetry was the highest loading parameter in the CU group. The identified components of gait provide a basis and understanding for how common gait parameters are related when gait is assessed as a single task, including key gait parameters within each component.

Increased tau-PET load was independently associated with increased step velocity variability in patients with MCI, which indicates that step velocity variability might be a gait parameter to consider when targeting comfortably paced single task gait in future studies of patients with MCI. Findings less intuitive were that increased tau load was independently associated with increased step length and step velocity. Moreover, Aβ as well as general WMH burden were not significantly associated with any of the chosen objective gait parameters. Potential explanations might be that the included MCI sample had markers of a neurodegenerative disorder and the results were likely affected by the included sample and the investigated brain regions, i.e., we did not study brain regions directly associated with gait.

Subjective aspects related to walking (i.e., perceived walking difficulties and concerns about falling) worsened after 3 years in people with PD. Both personal, motor and non-motor related factors seem to be of importance for subjective aspects related to walking. Perceived balance problems while dual tasking was however the only variable that predicted both perceived walking difficulties and concerns about falling as well as a change in these outcome measures.

Clinical implications and future perspectives

Gait assessments are a key task for physical therapists. Our findings in studies I-II are probably of most relevance for physical therapists who work at a specialized Memory Clinic and for researchers, whereas the findings from studies III-IV can be of relevance for physical therapists that assess and treat persons with PD in the chain of care.

- The association between increased tau-PET and increased step velocity variability indicates that physical therapists should pay specific attention to assess step velocity variability when targeting single task gait in patients with MCI. This finding needs to be corroborated or refuted in future longitudinal studies. Such studies could preferably also include dual task gait that includes a cognitive task, which reflects cognitive-motor interference.
- Future studies could compare whether the effect of tau pathology on step velocity variability also applies to other gait variability parameters. Such studies may identify additional variables of interest for gait assessments when targeting people at risk of developing AD. It would then also be of interest to target tau in ROIs more closely related to gait.
- Future longitudinal studies should focus on determining the diagnostic and prognostic value of spatiotemporal gait parameters in relation to different major neurocognitive disorders, e.g., AD, VaD, Lewy body disease.
- Perceived walking difficulties as well as concerns about falling increased over a 3-year period in people with PD. This indicates that these aspects should be assessed at follow-ups by the multidisciplinary PD team. Our findings also suggest that it might be important to specifically ask about perceived balance problems while dual tasking.
- Both personal, motor and non-motor related factors seem to be of importance for subjective aspects related to walking in people with PD. This suggests that future intervention studies might benefit from using an interdisciplinary approach.
- Perceived balance problems while dual tasking seems to be of particular importance for predicting perceived walking difficulties and concerns about falling in people with PD as well as predicting a change in both outcome measures. Targeting modifiable factors, such as balance problems while dual tasking in a clinical setting might reduce perceived walking difficulties and concerns about falling or assist in maintaining them at a stable level. Future intervention studies that use perceived walking difficulties or concerns about falling as their primary outcome are needed to support or refute this suggestion.

Acknowledgements

This thesis was accomplished at the Department of Health Sciences, Lund University, at the Memory Clinic, Skåne University Hospital as well as at home during the Covid-19 pandemic. The thesis was written within the contexts of the Centre for Ageing and Supporting Environments (CASE) and the strategic research area MultiPark, both at Lund University. These contexts have provided me with collegial input and discussions, financial support in publishing scientific papers and attending scientific conferences but also by enabling my own academic journey.

As such, I would like to express my sincere appreciation and gratitude to all those who were involved in my doctoral journey:

Maria "Mia" H. Nilsson, main supervisor and co-author. For believing in me and giving me the opportunity of pursuing and pushing the limits of my own capabilities further than I ever would have pushed myself. For always being available, answering and discussing the endless mails you have received from me. Thank you for guidance both in developing my writing ability but also in understanding how the academic world works. You have my utmost respect, both as a professional and as a person.

Stina B. Jonasson, co-supervisor and co-author. Thank you for all insightful and knowledgeable comments as well as thorough feedback on all my scientific texts. Also, for showing me a way of surviving in academia while having small children.

Niklas Mattsson-Carlgren, co-supervisor and co-author. For swift, precise and expert advice in your scientific feedback.

Susann Ullén, statistician and co-author. For being a kind and supportive co-author while simultaneously providing me with in-depth statistical feedback however, always taking time to explain statistical procedures in a manner that is easy to understand.

Susanne Iwarsson, director of CASE and my closest superior at the research group. Thank you for providing me with a context consisting of multiple fellow doctoral students and academic colleagues to discuss with. Also, thank you for your enthusiasm and candid remarks in relation to the research group.

Oskar Hansson, Sebastian Palmqvist, Erik Stomrud and Danielle van Westen, co-authors. For providing excellent feedback and thus contributing to the improvement of the manuscripts.

Stina Elfverson, Dan Lindholm and Ingrid Hilborn, administrators connected to CASE and/or the research group. For offering me warm and helpful assistance on all things connected to my position.

Frida Niles, administrator connected to the study project Motor-ACT as well as BioFINDER 2. For being a helpful colleague and kind person, always in full control of the administrative endeavors relating to this project.

Participants in the projects, “Home and health in people ageing with Parkinson’s disease” as well as “Motor aspects and activities in relation to cognitive decline: Motor-ACT”. For without the participation of these individuals the studies comprising this thesis would not have been possible. Hopefully the results of these studies will lead to a better rehabilitative care and management in people with mild cognitive impairment as well as people with Parkinson’s disease.

All financial funders for making my doctoral time possible. It has been a privilege being able to study and follow my research topics wholeheartedly.

Elisabet Londos and Eling de Bruin, reviewers at the halfway review. For a fruitful discussion concerning my academic progress at that moment and interesting suggestions for my future studies. Also, Michael Miller for providing me with interesting discussions both at the kappa seminar as well as at my pre-dissertation.

Fellow academic colleagues and doctoral students at the research group Active and Healthy Ageing, for giving me a context where I can discuss and relate my work. Specifically, Nilla Andersson. Nilla, we have been on this journey together and I am glad I had the luck of getting to pursue this PhD alongside you. It has been most interesting to discuss our papers with you; to try out an idea about my manuscripts and then discussing it with you. I believe I have found a warm-hearted colleague and a dear friend. Hopefully we will become colleagues again in the future.

Fellow colleagues at the Memory Clinic in Malmö. For making me feel included into your group. Specifically, Jenny Cappelin. Jenny, thank you for supporting me, encouraging me and providing me with perspective when I felt it was difficult seeing the end of my PhD.

My neighbors for playing with my children and having fruitful discussions about all things in life.

My dear friends, especially Max, Calle and Sirak. For reminding me there are other aspects in life that, at times, should be prioritized. Max, thank you for creating a visual illustration of my thoughts connected to my PhD.

My family in Skåne; Lovisa, Julia, Johan, Tilde, Milton and Ted for giving me, Sanna, Adrian and Maja wonderful and fun times, almost every week.

Lena and Anders, for being kind and caring parents-in-law. Thank you for, often, assisting me and Sanna with the care of Adrian and Maja. And also, for giving me time in your homes to work on my thesis.

My family in Stockholm; Hasse, Yumi, Sen and Lukas. For always meeting and greeting me and my close family with energy, compassion and smiles. Every occasion is packed with fun and activities.

Dilia and Hans-Ove, my mother and father. I am thankful for the compassion and love that you always show me. Thank you both for always trying to guide me towards a positive sentiment.

Sanna, Adrian and Maja, my close family and constant sources of joy. I love you three to the moon and back.

Maja you always greet me with a smile and love being outdoors interacting with everyone, making for many positive interactions with our neighbors and friends.

Adrian, thank you for your understanding during the writing of my thesis. Also, thank you for keeping me active and always wanting to spend time with me. I will always try to play football with you from now on.

Sanna, you have been an amazing support, taking the majority of care of our children during the writing of my thesis. You have provided perspective, had patience with me, encouraged me as well as enabled me to finalize this PhD journey. I would have never finished this work without you. I am forever grateful for all the love and attention you give me and our children. I love you.

References

1. Whittle, M., *Gait Analysis (Fourth Edition) [Elektronisk resurs]*. 2007: Butterworth-Heinemann.
2. World Health Organization, *International classification of functioning, disability and health : ICF*. 2001, World Health Organization: Geneva.
3. Srikanth, V., Sanders, L., Callisaya, M., et al., *Brain aging and gait.* Aging Health, 2010. **6**(1): p. 123-131.
4. Cohen, J.A., Verghese, J., and Zwerling, J.L., *Cognition and gait in older people.* Maturitas, 2016. **93**: p. 73-77.
5. Mirelman, A., Shema, S., Maidan, I., et al., *Gait.* Handb Clin Neurol, 2018. **159**: p. 119-134.
6. Scherder, E., Eggermont, L., Swaab, D., et al., *Gait in ageing and associated dementias; its relationship with cognition.* Neuroscience & Biobehavioral Reviews, 2007. **31**(4): p. 485-497.
7. Takakusaki, K., *Neurophysiology of gait: From the spinal cord to the frontal lobe.* Movement Disorders, 2013. **28**(11): p. 1483-1491.
8. Callisaya, M.L., Beare, R., Phan, T.G., et al., *Global and Regional Associations of Smaller Cerebral Gray and White Matter Volumes with Gait in Older People.* PLOS ONE, 2014. **9**(1): p. e84909.
9. Takakusaki, K., *Functional Neuroanatomy for Posture and Gait Control.* JMD, 2017. **10**(1): p. 1-17.
10. Hausdorff, J.M., *Gait variability: methods, modeling and meaning.* Journal of neuroengineering and rehabilitation, 2005. **2**: p. 19-19.
11. Hausdorff, J.M., *Gait dynamics, fractals and falls: finding meaning in the stride-to-stride fluctuations of human walking.* Hum Mov Sci, 2007. **26**(4): p. 555-89.
12. Greene, B.R., Foran, T.G., McGrath, D., et al., *A comparison of algorithms for body-worn sensor-based spatiotemporal gait parameters to the GAITRite electronic walkway.* J Appl Biomech, 2012. **28**(3): p. 349-55.
13. Cicirelli, G., Impedovo, D., Dentamaro, V., et al., *Human Gait Analysis in Neurodegenerative Diseases: A Review.* IEEE J Biomed Health Inform, 2022. **26**(1): p. 229-242.
14. Fahn S, E.R., Members of the UPDRS Development Committee *Unified Parkinson's Disease Rating Scale, in Recent Developments in Parkinson's Disease. Fahn S,et al., Editors.* . Vol. 2. 1987, Florham Park, NJ: MacMillan Healthcare Information.pp. 153-163, 293-304.

15. Wrisley, D.M., Marchetti, G.F., Kuharsky, D.K., et al., *Reliability, Internal Consistency, and Validity of Data Obtained With the Functional Gait Assessment.* Physical Therapy, 2004. **84**(10): p. 906-918.
16. Tinetti, M.E., *Performance-oriented assessment of mobility problems in elderly patients.* J Am Geriatr Soc, 1986. **34**(2): p. 119-26.
17. Damman, O.C., Verbiest, M.E.A., Vonk, S.I., et al., *Using PROMs during routine medical consultations: The perspectives of people with Parkinson's disease and their health professionals.* Health expectations : an international journal of public participation in health care and health policy, 2019. **22**(5): p. 939-951.
18. Fayers, P.M. and Machin, D., *Quality of life. the assessment, analysis, and reporting of patient-reported outcomes*. Third edition. ed. 2016: John Wiley & Sons Inc.
19. Bladh, S., Nilsson, M.H., Hariz, G.M., et al., *Psychometric performance of a generic walking scale (Walk-12G) in multiple sclerosis and Parkinson's disease.* J Neurol, 2012. **259**(4): p. 729-738.
20. Leavy, B., Löfgren, N., Nilsson, M., et al., *Patient-reported and performance-based measures of walking in mild–moderate Parkinson's disease.* Brain and Behavior, 2018. **8**(9).
21. Perry, J., *Gait analysis*. Normal and pathological function. 2010: SLACK. 19-47.
22. GAITRite systems, *GAITRite Electronic Walkway Technical Reference, Document Number: WI-02-15. Revision L.* 2013, CIR Systems Inc. p. 1-50.
23. Fritz, S. and Lusardi, M., *White Paper: "Walking Speed: the Sixth Vital Sign".* Journal of Geriatric Physical Therapy, 2009. **32**(2): p. 2-5.
24. Middleton, A., Fritz, S.L., and Lusardi, M., *Walking speed: the functional vital sign.* Journal of aging and physical activity, 2015. **23**(2): p. 314-322.
25. Abellan Van Kan, G., Rolland, Y., Andrieu, S., et al., *Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force.* The journal of nutrition, health & aging, 2009. **13**(10): p. 881-889.
26. Studenski, S., Perera, S., Patel, K., et al., *Gait speed and survival in older adults.* Jama, 2011. **305**(1): p. 50-8.
27. Grande, G., Triolo, F., Nuara, A., et al., *Measuring gait speed to better identify prodromal dementia.* Exp Gerontol, 2019. **124**: p. 110625.
28. Peel, N.M., Kuys, S.S., and Klein, K., *Gait Speed as a Measure in Geriatric Assessment in Clinical Settings: A Systematic Review.* The Journals of Gerontology: Series A, 2012. **68**(1): p. 39-46.
29. Byun, S., Han, J.W., Kim, T.H., et al., *Gait Variability Can Predict the Risk of Cognitive Decline in Cognitively Normal Older People.* Dementia and Geriatric Cognitive Disorders, 2018: p. 251-261.
30. Callisaya, M.L., Blizzard, L., Schmidt, M.D., et al., *Ageing and gait variability—a population-based study of older people.* Age and Ageing, 2010. **39**(2): p. 191-197.
31. Bilney, B., Morris, M., and Webster, K., *Concurrent related validity of the GAITRite walkway system for quantification of the spatial and temporal parameters of gait.* Gait Posture, 2003. **17**(1): p. 68-74.

32. Verghese, J., Wang, C., Lipton, R.B., et al., *Quantitative gait dysfunction and risk of cognitive decline and dementia.* J Neurol Neurosurg Psychiatry, 2007. **78**(9): p. 929-35.
33. Hollman, J.H., McDade, E.M., and Petersen, R.C., *Normative spatiotemporal gait parameters in older adults.* Gait & posture, 2011. **34**(1): p. 111-118.
34. Lord, S., Galna, B., Verghese, J., et al., *Independent Domains of Gait in Older Adults and Associated Motor and Nonmotor Attributes: Validation of a Factor Analysis Approach.* The Journals of Gerontology: Series A, 2012. **68**(7): p. 820-827.
35. Verlinden, V.J.A., van der Geest, J.N., Hoogendam, Y.Y., et al., *Gait patterns in a community-dwelling population aged 50 years and older.* Gait & Posture, 2013. **37**(4): p. 500-505.
36. Bernstein, J.P.K., De Vito, A., Weitzner, D.S., et al., *Examining Relationships between Multiple Self-Reported Sleep Measures and Gait Domains in Cognitively Healthy Older Adults.* Gerontology, 2020. **66**(1): p. 47-54.
37. Darweesh, S.K.L., Licher, S., Wolters, F.J., et al., *Quantitative gait, cognitive decline, and incident dementia: The Rotterdam Study.* Alzheimer's & Dementia, 2019. **15**(10): p. 1264-1273.
38. Lord, S., Galna, B., and Rochester, L., *Moving forward on gait measurement: toward a more refined approach.* Mov Disord, 2013. **28**(11): p. 1534-43.
39. Lord, S., Howe, T., Greenland, J., et al., *Gait variability in older adults: a structured review of testing protocol and clinimetric properties.* Gait Posture, 2011. **34**(4): p. 443-50.
40. Tian, Q., Chastan, N., Bair, W.-N., et al., *The brain map of gait variability in aging, cognitive impairment and dementia—A systematic review.* Neuroscience & Biobehavioral Reviews, 2017. **74**: p. 149-162.
41. Galna, B., Lord, S., and Rochester, L., *Is gait variability reliable in older adults and Parkinson's disease? Towards an optimal testing protocol.* Gait & Posture, 2013. **37**(4): p. 580-5.
42. Patterson, K.K., Parafianowicz, I., Danells, C.J., et al., *Gait asymmetry in community-ambulating stroke survivors.* Arch Phys Med Rehabil, 2008. **89**(2): p. 304-10.
43. Cabral, S., *Gait Symmetry Measures and Their Relevance to Gait Retraining*, in *Handbook of Human Motion*. 2018, Springer International Publishing: Cham. p. 429-447.
44. Yogev, G., Plotnik, M., Peretz, C., et al., *Gait asymmetry in patients with Parkinson's disease and elderly fallers: when does the bilateral coordination of gait require attention?* Exp Brain Res, 2007. **177**(3): p. 336-46.
45. Makino, K., Makizako, H., Doi, T., et al., *Fear of falling and gait parameters in older adults with and without fall history.* Geriatr Gerontol Int, 2017. **17**(12): p. 2455-2459.
46. Chamberlin, M.E., Fulwider, B.D., Sanders, S.L., et al., *Does fear of falling influence spatial and temporal gait parameters in elderly persons beyond changes associated with normal aging?* J Gerontol A Biol Sci Med Sci, 2005. **60**(9): p. 1163-7.

47. Reelick, M.F., van Iersel, M.B., Kessels, R.P.C., et al., *The influence of fear of falling on gait and balance in older people.* Age and Ageing, 2009. **38**(4): p. 435-440.
48. Maki, B.E., *Gait Changes in Older Adults: Predictors of Falls or Indicators of Fear?* Journal of the American Geriatrics Society, 1997. **45**(3): p. 313-320.
49. Ayoubi, F., Launay, C.P., Kabeshova, A., et al., *The influence of fear of falling on gait variability: results from a large elderly population-based cross-sectional study.* Journal of neuroengineering and rehabilitation, 2014. **11**: p. 128-128.
50. Hadjistavropoulos, T., Delbaere, K., and Fitzgerald, T.D., *Reconceptualizing the role of fear of falling and balance confidence in fall risk.* J Aging Health, 2011. **23**(1): p. 3-23.
51. Powell, L.E. and Myers, A.M., *The Activities-specific Balance Confidence (ABC) Scale.* J Gerontol A Biol Sci Med Sci, 1995. **50a**(1): p. M28-M34.
52. Yardley, L. and Smith, H., *A prospective study of the relationship between feared consequences of falling and avoidance of activity in community-living older people.* Gerontologist, 2002. **42**(1): p. 17-23.
53. Tinetti, M.E., Richman, D., and Powell, L., *Falls efficacy as a measure of fear of falling.* J Gerontol, 1990. **45**(6): p. P239-243.
54. Bandura, A., *Social foundations of thought and action: a social cognitive theory.* Prentice-Hall series in social learning theory. Englewood Cliffs, N.J.: Prentice- Hall., 1986. **xiii,**: p. 617 p.
55. Schoene, D., Heller, C., Aung, Y.N., et al., *A systematic review on the influence of fear of falling on quality of life in older people: is there a role for falls?* Clinical interventions in aging, 2019. **14**: p. 701-719.
56. Landers, M.R. and Nilsson, M.H., *A theoretical framework for addressing fear of falling avoidance behavior in Parkinson's disease.* Physiotherapy Theory and Practice, 2022: p. 1-17.
57. Young, W.R. and Mark Williams, A., *How fear of falling can increase fall-risk in older adults: Applying psychological theory to practical observations.* Gait & Posture, 2015. **41**(1): p. 7-12.
58. Sawa, R., Asai, T., Doi, T., et al., *The Association Between Physical Activity, Including Physical Activity Intensity, and Fear of Falling Differs by Fear Severity in Older Adults Living in the Community.* J Gerontol B Psychol Sci Soc Sci, 2020. **75**(5): p. 953-960.
59. Zijlstra, G.A., van Haastregt, J.C., van Eijk, J.T., et al., *Prevalence and correlates of fear of falling, and associated avoidance of activity in the general population of community-living older people.* Age Ageing, 2007. **36**(3): p. 304-9.
60. Birhanie, G., Melese, H., Solomon, G., et al., *Fear of falling and associated factors among older people living in Bahir Dar City, Amhara, Ethiopia- a cross-sectional study.* BMC geriatrics, 2021. **21**(1): p. 586-586.
61. Scheffer, A.C., Schuurmans, M.J., van Dijk, N., et al., *Fear of falling: measurement strategy, prevalence, risk factors and consequences among older persons.* Age and Ageing, 2008. **37**(1): p. 19-24.

62. Yardley, L., Beyer, N., Hauer, K., et al., *Development and initial validation of the Falls Efficacy Scale-International (FES-I).* Age Ageing, 2005. **34**(6): p. 614-619.
63. Dierking, L., Markides, K., Al Snih, S., et al., *Fear of Falling in Older Mexican Americans: A Longitudinal Study of Incidence and Predictive Factors.* J Am Geriatr Soc, 2016. **64**(12): p. 2560-2565.
64. Weijer, R.H.A., Hoozemans, M.J.M., Meijer, O.G., et al., *The short- and long-term temporal relation between falls and concern about falling in older adults without a recent history of falling.* PloS one, 2021. **16**(7): p. e0253374-e0253374.
65. Delbaere, K., Close, J.C., Mikolaizak, A.S., et al., *The Falls Efficacy Scale International (FES-I). A comprehensive longitudinal validation study.* Age Ageing, 2010. **39**(2): p. 210-6.
66. Jack, C.R., Bennett, D.A., Blennow, K., et al., *NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease.* Alzheimer's & Dementia, 2018. **14**(4): p. 535-562.
67. Erkkinen, M.G., Kim, M.-O., and Geschwind, M.D., *Clinical Neurology and Epidemiology of the Major Neurodegenerative Diseases.* Cold Spring Harbor perspectives in biology, 2018. **10**(4): p. a033118.
68. Cummings, J.L. and Pillai, J.A., *Neurodegenerative Diseases: Unifying Principles*. 2016: Oxford University Press.
69. Rizzi, L., Rosset, I., and Roriz-Cruz, M., *Global epidemiology of dementia: Alzheimer's and vascular types.* BioMed research international, 2014. **2014**: p. 908915-908915.
70. Wu, L., Rosa-Neto, P., Hsiung, G.Y., et al., *Early-onset familial Alzheimer's disease (EOFAD).* Can J Neurol Sci, 2012. **39**(4): p. 436-45.
71. Hardiman, O. and Doherty, C.P., *Neurodegenerative Disorders. A Clinical Guide*. 1st 2011. ed. 2011: Springer London.
72. Foguem, C. and Kamsu-Foguem, B., *Neurodegeneration in tauopathies and synucleinopathies.* Rev Neurol (Paris), 2016. **172**(11): p. 709-714.
73. Hansson, O., *Biomarkers for neurodegenerative diseases.* Nature Medicine, 2021. **27**(6): p. 954-963.
74. Nichols, E., Steinmetz, J.D., Vollset, S.E., et al., *Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019.* The Lancet Public Health, 2022. **7**(2): p. e105-e125.
75. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* 2013, Arlington, VA, American Psyciatric Association.
76. Zvěřová, M., *Clinical aspects of Alzheimer's disease.* Clinical Biochemistry, 2019. **72**: p. 3-6.
77. O'Brien, J.T. and Thomas, A., *Vascular dementia.* The Lancet, 2015. **386**(10004): p. 1698-1706.
78. Cao, Q., Tan, C.C., Xu, W., et al., *The Prevalence of Dementia: A Systematic Review and Meta-Analysis.* J Alzheimers Dis, 2020. **73**(3): p. 1157-1166.
79. Blennow, K. and Hampel, H., *CSF markers for incipient Alzheimer's disease.* The Lancet Neurology, 2003. **2**(10): p. 605-613.

80. Leuzy, A., Ashton, N.J., Mattsson-Carlgren, N., et al., *2020 update on the clinical validity of cerebrospinal fluid amyloid, tau, and phospho-tau as biomarkers for Alzheimer's disease in the context of a structured 5-phase development framework.* Eur J Nucl Med Mol Imaging, 2021. **48**(7): p. 2121-2139.
81. Blennow, K. and Zetterberg, H., *Biomarkers for Alzheimer's disease: current status and prospects for the future.* J Intern Med, 2018. **284**(6): p. 643-663.
82. Leuzy, A., Janelidze, S., Mattsson-Carlgren, N., et al., *Comparing the Clinical Utility and Diagnostic Performance of CSF P-Tau181, P-Tau217, and P-Tau231 Assays.* Neurology, 2021. **97**(17): p. e1681-e1694.
83. Jack, C.R., Jr., Knopman, D.S., Jagust, W.J., et al., *Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade.* The Lancet. Neurology, 2010. **9**(1): p. 119-128.
84. Mattsson, N., Schöll, M., Strandberg, O., et al., *(18)F-AV-1451 and CSF T-tau and P-tau as biomarkers in Alzheimer's disease.* EMBO Mol Med, 2017. **9**(9): p. 1212-1223.
85. Venkat, P., Chopp, M., and Chen, J., *Models and mechanisms of vascular dementia.* Experimental neurology, 2015. **272**: p. 97-108.
86. Wardlaw, J.M., Valdés Hernández, M.C., and Muñoz-Maniega, S., *What are white matter hyperintensities made of? Relevance to vascular cognitive impairment.* J Am Heart Assoc, 2015. **4**(6): p. 001140.
87. Annweiler, C., Beauchet, O., Bartha, R., et al., *Slow gait in MCI is associated with ventricular enlargement: results from the Gait and Brain Study.* Journal of Neural Transmission, 2013. **120**(7): p. 1083-1092.
88. Ogama, N., Endo, H., Satake, S., et al., *Impact of regional white matter hyperintensities on specific gait function in Alzheimer's disease and mild cognitive impairment.* Journal of Cachexia, Sarcopenia and Muscle, 2021. **n/a**(n/a).
89. Sakurai, R., Inagaki, H., Tokumaru, A.M., et al., *Differences in the association between white matter hyperintensities and gait performance among older adults with and without cognitive impairment.* Geriatr Gerontol Int, 2021. **21**(3): p. 313-320.
90. Soumaré, A., Elbaz, A., Zhu, Y., et al., *White matter lesions volume and motor performances in the elderly.* Ann Neurol, 2009. **65**(6): p. 706-15.
91. Laat, K.F.d., Norden, A.G.W.v., Gons, R.A.R., et al., *Gait in Elderly With Cerebral Small Vessel Disease.* Stroke, 2010. **41**(8): p. 1652-1658.
92. Rosano, C., Brach, J., Longstreth, W.T., Jr., et al., *Quantitative measures of gait characteristics indicate prevalence of underlying subclinical structural brain abnormalities in high-functioning older adults.* Neuroepidemiology, 2006. **26**(1): p. 52-60.
93. Debette, S. and Markus, H.S., *The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis.* Bmj, 2010. **341**: p. c3666.
94. Jessen, F., Amariglio, R.E., Buckley, R.F., et al., *The characterisation of subjective cognitive decline.* The Lancet. Neurology, 2020. **19**(3): p. 271-278.

95. Mitchell, A.J., Beaumont, H., Ferguson, D., 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.
96. Petersen, R.C., Caracciolo, B., Brayne, C., et al., *Mild cognitive impairment: a concept in evolution.* Journal of internal medicine, 2014. **275**(3): p. 214-228.
97. Petersen, R.C., Lopez, O., Armstrong, M.J., 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.
98. Lotharius, J. and Brundin, P., *Pathogenesis of parkinson's disease: dopamine, vesicles and α-synuclein.* Nature Reviews Neuroscience, 2002. **3**(12): p. 932-942.
99. Dickson, D.W., *Parkinson's disease and parkinsonism: neuropathology.* Cold Spring Harbor perspectives in medicine, 2012. **2**(8): p. a009258.
100. Esposito, E., Di Matteo, V., and Di Giovanni, G., *Death in the substantia nigra: a motor tragedy.* Expert Rev Neurother, 2007. **7**(6): p. 677-97.
101. Cheng, H.-C., Ulane, C.M., and Burke, R.E., *Clinical progression in Parkinson disease and the neurobiology of axons.* Annals of neurology, 2010. **67**(6): p. 715-725.
102. Postuma, R.B., Berg, D., Stern, M., et al., *MDS clinical diagnostic criteria for Parkinson's disease.* Mov Disord, 2015. **30**(12): p. 1591-601.
103. Mirelman, A., Bonato, P., Camicioli, R., et al., *Gait impairments in Parkinson's disease.* Lancet Neurol, 2019. **18**(7): p. 697-708.
104. Nonnekes, J., Giladi, N., Guha, A., et al., *Gait festination in parkinsonism: introduction of two phenotypes.* Journal of neurology, 2019. **266**(2): p. 426-430.
105. Giladi, N. and Nieuwboer, A., *Understanding and treating freezing of gait in parkinsonism, proposed working definition, and setting the stage.* Mov Disord, 2008. **23 Suppl 2**: p. S423-5.
106. Schapira, A.H.V., Chaudhuri, K.R., and Jenner, P., *Non-motor features of Parkinson disease.* Nat Rev Neurosci, 2017. **18**(7): p. 435-450.
107. Allali, G., Annweiler, C., Blumen, H.M., et al., *Gait phenotype from mild cognitive impairment to moderate dementia: results from the GOOD initiative.* European journal of neurology, 2016. **23**(3): p. 527-541.
108. Fuentes-Abolafio, I.J., Stubbs, B., Pérez-Belmonte, L.M., et al., *Functional parameters indicative of mild cognitive impairment: a systematic review using instrumented kinematic assessment.* BMC Geriatr, 2020. **20**(1): p. 282.
109. Bahureksa, L., Najafi, B., Saleh, A., 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.
110. Callisaya, M.L., Launay, C.P., Srikanth, V.K., et al., *Cognitive status, fast walking speed and walking speed reserve-the Gait and Alzheimer Interactions Tracking (GAIT) study.* GeroScience, 2017. **39**(2): p. 231-239.
111. Fuentes-Abolafio, I.J., Stubbs, B., Pérez-Belmonte, L.M., et al., *Functional objective parameters which may discriminate patients with mild cognitive impairment from*

cognitively healthy individuals: a systematic review and meta-analysis using an instrumented kinematic assessment. Age Ageing, 2021. **50**(2): p. 380-393.

112. Beauchet, O., Allali, G., Launay, C., et al., *Gait variability at fast-pace walking speed: A biomarker of mild cognitive impairment?* The journal of nutrition, health & aging, 2013. **17**(3): p. 235-239.
113. Doi, T., Shimada, H., Makizako, H., et al., *Cognitive function and gait speed under normal and dual-task walking among older adults with mild cognitive impairment.* BMC Neurology, 2014. **14**(1): p. 67.
114. Pieruccini-Faria, F., Sarquis-Adamson, Y., Anton-Rodrigo, I., et al., *Mapping Associations Between Gait Decline and Fall Risk in Mild Cognitive Impairment.* Journal of the American Geriatrics Society, 2020. **68**(3): p. 576-584.
115. Del Campo, N., Payoux, P., Djilali, A., et al., *Relationship of regional brain β-amyloid to gait speed.* Neurology, 2016. **86**(1): p. 36-43.
116. Nadkarni, N.K., Perera, S., Snitz, B.E., et al., *Association of Brain Amyloid-β With Slow Gait in Elderly Individuals Without Dementia: Influence of Cognition and Apolipoprotein E ε4 Genotype.* JAMA Neurol, 2017. **74**(1): p. 82-90.
117. Wennberg, A.M.V., Savica, R., Hagen, C.E., et al., *Cerebral Amyloid Deposition Is Associated with Gait Parameters in the Mayo Clinic Study of Aging.* Journal of the American Geriatrics Society, 2017. **65**(4): p. 792-799.
118. Skillbäck, T., Blennow, K., Zetterberg, H., et al., *Slowing gait speed precedes cognitive decline by several years.* Alzheimer's & Dementia. **n/a**(n/a).
119. Tian, Q., Bair, W.N., Resnick, S.M., et al., *β-amyloid deposition is associated with gait variability in usual aging.* Gait Posture, 2018. **61**: p. 346-352.
120. Mielke, M.M., Syrjanen, J.A., Blennow, K., et al., *Comparison of variables associated with cerebrospinal fluid neurofilament, total-tau, and neurogranin.* Alzheimers Dement, 2019. **15**(11): p. 1437-1447.
121. Muurling, M., Rhodius-Meester, H.F.M., Pärkkä, J., et al., *Gait Disturbances are Associated with Increased Cognitive Impairment and Cerebrospinal Fluid Tau Levels in a Memory Clinic Cohort.* Journal of Alzheimer's Disease, 2020. **76**: p. 1061-1070.
122. Pistacchi, M., Gioulis, M., Sanson, F., et al., *Gait analysis and clinical correlations in early Parkinson's disease.* Funct Neurol, 2017. **32**(1): p. 28-34.
123. Keus SHJ, M.M., Graziano M. , *European Physiotherapy Guideline for Parkinson's disease.* KNGF/ParkinsonNet, the Netherlands., 2014.
124. Galna, B., Lord, S., Burn, D.J., et al., *Progression of gait dysfunction in incident Parkinson's disease: impact of medication and phenotype.* Mov Disord, 2015. **30**(3): p. 359-67.
125. Djurić-Jovičić, M., Belić, M., Stanković, I., et al., *Selection of gait parameters for differential diagnostics of patients with de novo Parkinson's disease.* Neurol Res, 2017. **39**(10): p. 853-861.
126. Allen, N.E., Schwarzel, A.K., and Canning, C.G., *Recurrent falls in Parkinson's disease: a systematic review.* Parkinsons Dis, 2013. **2013**: p. 906274.

127. Hass, C.J., Buckley, T., and Juncos, J.L., *Subjective versus Objective Measures of Gait Function: Accuracy in Parkinson Disease: 596: May 28 2:30 PM - 2:45 PM.* Medicine & Science in Sports & Exercise, 2008. **40**(5).
128. Kader, M., Ullen, S., Iwarsson, S., et al., *Factors Contributing to Perceived Walking Difficulties in People with Parkinson's Disease.* J Parkinsons Dis, 2017. **7**(2): p. 397-407.
129. Adkin, A.L., Frank, J.S., and Jog, M.S., *Fear of falling and postural control in Parkinson's disease.* Mov Disord, 2003. **18**(5): p. 496-502.
130. Mak, M.K. and Pang, M.Y., *Balance self-efficacy determines walking capacity in people with Parkinson's disease.* Mov Disord, 2008. **23**(13): p. 1936-9.
131. Matinolli, M., Korpelainen, J.T., Korpelainen, R., et al., *Mobility and balance in Parkinson's disease: a population-based study.* Eur J Neurol, 2009. **16**(1): p. 105-111.
132. Lindholm, B., Hagell, P., Hansson, O., et al., *Factors associated with fear of falling in people with Parkinson's disease.* BMC Neurol, 2014. **14**: p. 19.
133. Combs, S.A., Diehl, M.D., Filip, J., et al., *Short-distance walking speed tests in people with Parkinson disease: reliability, responsiveness, and validity.* Gait Posture, 2014. **39**(2): p. 784-8.
134. Nilsson, M.H., Hariz, G.M., Iwarsson, S., et al., *Walking ability is a major contributor to fear of falling in people with Parkinson's disease: implications for rehabilitation.* Parkinsons Dis, 2012: p. Article ID 713236.
135. Frazier, L.D., *Coping with disease-related stressors in Parkinson's disease.* Gerontologist, 2000. **40**(1): p. 53-63.
136. Bryant, M.S., Rintala, D.H., Hou, J.G., et al., *Relationship of falls and fear of falling to activity limitations and physical inactivity in Parkinson's disease.* J Aging Phys Act, 2015. **23**(2): p. 187-193.
137. Ellis, T., Boudreau, J.K., DeAngelis, T.R., et al., *Barriers to exercise in people with Parkinson disease.* Physical Therapy, 2013. **93**(5): p. 628-636.
138. Kader, M., Iwarsson, S., Odin, P., et al., *Fall-related activity avoidance in relation to a history of falls or near falls, fear of falling and disease severity in people with Parkinson's disease.* BMC Neurol, 2016. **16**: p. 84.
139. Gazibara, T., Stankovic, I., Tomic, A., et al., *Validation and cross-cultural adaptation of the Falls Efficacy Scale in patients with Parkinson's disease in Serbia.* Geriatr Gerontol Int, 2013. **13**(4): p. 936-941.
140. Rahman, S., Griffin, H.J., Quinn, N.P., et al., *On the nature of fear of falling in Parkinson's disease.* Behav Neurol, 2011. **24**(3): p. 219-228.
141. Jonasson, S.B., Ullen, S., Iwarsson, S., et al., *Concerns About Falling in Parkinson's Disease: Associations with Disabilities and Personal and Environmental Factors.* J Parkinsons Dis, 2015. **5**(2): p. 341-349.
142. Mak, M.K., Pang, M.Y., and Mok, V., *Gait difficulty, postural instability, and muscle weakness are associated with fear of falling in people with Parkinson's disease.* Parkinsons Dis, 2012. **Article ID 901721**.

143. Franzen, E., Conradsson, D., Hagstromer, M., et al., *Depressive symptoms associated with concerns about falling in Parkinson's disease.* Brain Behav, 2016. **6**(10): p. e00524.
144. Jonasson, S.B., Nilsson, M.H., and Lexell, J., *Psychometric properties of the original and short versions of the Falls Efficacy Scale-International (FES-I) in people with Parkinson's disease.* Health Qual Life Outcomes, 2017. **15**(1): p. 116.
145. Gazibara, T., Tepavcevic, D.K., Svetel, M., et al., *Change in fear of falling in Parkinson's disease: a two-year prospective cohort study.* Int Psychogeriatr, 2017: p. 1-8.
146. Nilsson, M.H., Jonasson, S.B., and Zijlstra, G.A.R., *Predictive Factors of Fall-Related Activity Avoidance in People With Parkinson Disease—A Longitudinal Study With a 3-Year Follow-up.* Journal of Neurologic Physical Therapy, 2020. **44**(3).
147. Nilsson, M.H. and Iwarsson, S., *Home and health in people ageing with Parkinson's disease: study protocol for a prospective longitudinal cohort survey study.* BMC Neurology, 2013. **13**: p. 142.
148. Berglund, G., Elmstähl, S., Janzon, L., et al., *The Malmo Diet and Cancer Study. Design and feasibility.* J Intern Med, 1993. **233**(1): p. 45-51.
149. Folstein, M.F., Folstein, S.E., and McHugh, P.R., *"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.
150. Hansson, O., Lehmann, S., Otto, M., et al., *Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease.* Alzheimer's Research & Therapy, 2019. **11**(1): p. 34.
151. Rosen, W.G., Mohs, R.C., and Davis, K.L., *A new rating scale for Alzheimer's disease.* Am J Psychiatry, 1984. **141**(11): p. 1356-64.
152. Reitan, R.M., *The relation of the trail making test to organic brain damage.* J Consult Psychol, 1955. **19**(5): p. 393-4.
153. Smith, A., *Symbol Digit Modalities Test: Manual*. 2007, Los Angeles: Western Psychological Services.
154. Warrington, E.K. and James, M., *The Visual Object and Space Battery Perception.* . 1991, Bury St Edmunds.: Thames Valley Company.
155. Mack, W.J., Freed, D.M., Williams, B.W., et al., *Boston Naming Test: shortened versions for use in Alzheimer's disease.* J Gerontol, 1992. **47**(3): p. P154-8.
156. Rosen, W.G., *Verbal fluency in aging and dementia.* Journal of Clinical Neuropsychology, 1980. **2**(2): p. 135-146.
157. Borland, E., Stomrud, E., van Westen, D., et al., *The age-related effect on cognitive performance in cognitively healthy elderly is mainly caused by underlying AD pathology or cerebrovascular lesions: implications for cutoffs regarding cognitive impairment.* Alzheimers Res Ther, 2020. **12**(1): p. 30.
158. Borland, E., Nägga, K., Nilsson, P.M., et al., *The Montreal Cognitive Assessment: Normative Data from a Large Swedish Population-Based Cohort.* J Alzheimers Dis, 2017. **59**(3): p. 893-901.

159. Petersen, R.C., *Mild cognitive impairment as a diagnostic entity.* J Intern Med, 2004. **256**(3): p. 183-94.
160. Beauchet, O., Allali, G., Sekhon, H., et al., *Guidelines for Assessment of Gait and Reference Values for Spatiotemporal Gait Parameters in Older Adults: The Biomathics and Canadian Gait Consortiums Initiative.* Front Hum Neurosci, 2017. **11**: p. 353.
161. Webster, K.E., Wittwer, J.E., and Feller, J.A., *Validity of the GAITRite® walkway system for the measurement of averaged and individual step parameters of gait.* Gait & Posture, 2005. **22**(4): p. 317-321.
162. Martin, K.L., Blizzard, L., Wood, A.G., et al., *Cognitive Function, Gait, and Gait Variability in Older People: A Population-Based Study.* The Journals of Gerontology: Series A, 2012. **68**(6): p. 726-732.
163. Savica, R., Wennberg, A.M.V., Hagen, C., et al., *Comparison of Gait Parameters for Predicting Cognitive Decline: The Mayo Clinic Study of Aging.* Journal of Alzheimer's Disease, 2017. **55**: p. 559-567.
164. Thal, D.R., Rüb, U., Orantes, M., et al., *Phases of A beta-deposition in the human brain and its relevance for the development of AD.* Neurology, 2002. **58**(12): p. 1791-800.
165. Palmqvist, S., Zetterberg, H., Mattsson, N., et al., *Detailed comparison of amyloid PET and CSF biomarkers for identifying early Alzheimer disease.* Neurology, 2015. **85**(14): p. 1240-9.
166. Thal, D.R., Attems, J., and Ewers, M., *Spreading of amyloid, tau, and microvascular pathology in Alzheimer's disease: findings from neuropathological and neuroimaging studies.* J Alzheimers Dis, 2014. **42 Suppl 4**: p. S421-9.
167. Palmqvist, S., Janelidze, S., Quiroz, Y.T., et al., *Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders.* Jama, 2020. **324**(8): p. 772-781.
168. Braak, H. and Braak, E., *Neuropathological stageing of Alzheimer-related changes.* Acta Neuropathol, 1991. **82**(4): p. 239-59.
169. Baker, S.L., Maass, A., and Jagust, W.J., *Considerations and code for partial volume correcting [(18)F]-AV-1451 tau PET data.* Data Brief, 2017. **15**: p. 648-657.
170. Leuzy, A., Smith, R., Ossenkoppele, R., et al., *Diagnostic Performance of RO948 F 18 Tau Positron Emission Tomography in the Differentiation of Alzheimer Disease From Other Neurodegenerative Disorders.* JAMA Neurology, 2020. **77**(8): p. 955-965.
171. Reimer, P., Parizel, P., and Stichnoth, F.-A., *Clinical MR Imaging: A Practical Approach*. Vol. 200. 2006: Springer Science & Business Media.
172. Schmidt, P., Gaser, C., Arsic, M., et al., *An automated tool for detection of FLAIR-hyperintense white-matter lesions in Multiple Sclerosis.* NeuroImage, 2012. **59**(4): p. 3774-3783.
173. Tabachnick, B.G. and Fidell, L.S., *Using multivariate statistics*. 6th ed. ed. 2013: Pearson Education.

174. Costello, A.B. and Osborne, J., *Best practices in exploratory factor analysis: four recommendations for getting the most from your analysis.* Practical Assessment, Research, and Evaluation, 2005. **Vol. 10**(Article 7).

175. Guralnik, J.M., Simonsick, E.M., Ferrucci, L., et al., *A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission.* J Gerontol, 1994. **49**(2): p. M85-94.

176. Suteerawattananon, M. and Protas, E.J., *Reliability of outcome measures in individuals with Parkinson's Disease.* Physiotherapy Theory and Practice, 2000. **16**(4): p. 211-218.

177. Kader, M., Jonasson, S.B., Iwarsson, S., et al., *Mobility device use in people with Parkinson's disease: A 3-year follow-up study.* Acta Neurologica Scandinavica, 2018. **138**(1): p. 70-77.

178. Jonasson, S.B., Nilsson, M.H., and Lexell, J., *Psychometric properties of four fear of falling rating scales in people with Parkinson's disease.* BMC Geriatr, 2014. **14**: p. 66.

179. Schwarzer R, J.M., *Generalized Self-Efficacy scale. In Measures in health psychology: A user's portfolio. Causal and control beliefs. J. Weinman, S. Wright, & M. Johnston, eds.* Windsor K: NFER-NELSON,, 1995: p. 35–37.

180. Nilsson, M.H., Hariz, G.M., Wictorin, K., et al., *Development and testing of a self administered version of the Freezing of Gait Questionnaire.* BMC Neurology, 2010. **10**: p. 85.

181. Visser, M., Marinus, J., Bloem, B.R., et al., *Clinical tests for the evaluation of postural instability in patients with parkinson's disease.* Arch Phys Med Rehabil, 2003. **84**(11): p. 1669-74.

182. Duncan, R.P., Leddy, A.L., and Earhart, G.M., *Five times sit-to-stand test performance in Parkinson's disease.* Arch Phys Med Rehabil, 2011. **92**(9): p. 1431-6.

183. Hobson, J.P., Edwards, N.I., and Meara, R.J., *The Parkinson's Disease Activities of Daily Living Scale: a new simple and brief subjective measure of disability in Parkinson's disease.* Clin Rehabil, 2001. **15**(3): p. 241-246.

184. Nasreddine, Z.S., Phillips, N.A., Bédirian, V., et al., *The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment.* Journal of the American Geriatrics Society, 2005. **53**(4): p. 695-699.

185. Sheikh, J.I. and Yesavage, J.A., *Geriatric Depression Scale (GDS): Recent Evidence and Development of a Shorter Version.*, in *Clinical Gerontology: A Guide to Assessment and Intervention.* 1986. p. 165-173.

186. Hunt, S.M., McKenna, S.P., McEwen, J., et al., *A quantitative approach to perceived health status: a validation study.* Journal of epidemiology and community health, 1980. **34**(4): p. 281-286.

187. Hagell, P., Hoglund, A., Reimer, J., et al., *Measuring fatigue in Parkinson's disease: a psychometric study of two brief generic fatigue questionnaires.* J Pain Symptom Manage, 2006. **32**(5): p. 420-432.

188. Chaudhuri, K.R., Martinez-Martin, P., Schapira, A.H., et al., *International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms*

questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord, 2006. **21**(7): p. 916-23.

189. Osoba, M.Y., Rao, A.K., Agrawal, S.K., et al., *Balance and gait in the elderly: A contemporary review.* Laryngoscope investigative otolaryngology, 2019. **4**(1): p. 143-153.
190. Prince, F., Corriveau, H., Hébert, R., et al., *Gait in the elderly.* Gait & Posture, 1997. **5**(2): p. 128-135.
191. World Health Organization. *Declaration of Helsinki: ethical principles for medical research involving human subjects.* Jama, 2013. **310**(20): p. 2191-4.
192. Lindh-Rengifo, M., Jonasson, S.B., Ullén, S., et al., *Components of gait in people with and without mild cognitive impairment.* Gait & Posture, 2022.
193. Montero-Odasso, M., Speechley, M., Muir-Hunter, S.W., et al., *Motor and Cognitive Trajectories Before Dementia: Results from Gait and Brain Study.* Journal of the American Geriatrics Society, 2018. **66**(9): p. 1676-1683.
194. Buracchio, T., Dodge, H.H., Howieson, D., et al., *The Trajectory of Gait Speed Preceding Mild Cognitive Impairment.* Archives of Neurology, 2010. **67**(8): p. 980-986.
195. Arcolin, I., Corna, S., Giardini, M., et al., *Proposal of a new conceptual gait model for patients with Parkinson's disease based on factor analysis.* Biomed Eng Online, 2019. **18**(1): p. 70.
196. Hollman, J.H., Childs, K.B., McNeil, M.L., 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. 23-8.
197. Hausdorff, J.M., Rios, D.A., and Edelberg, H.K., *Gait variability and fall risk in community-living older adults: A 1-year prospective study.* Archives of Physical Medicine and Rehabilitation, 2001. **82**(8): p. 1050-1056.
198. Brach, J.S., Berlin, J.E., VanSwearingen, J.M., et al., *Too much or too little step width variability is associated with a fall history in older persons who walk at or near normal gait speed.* J Neuroeng Rehabil, 2005. **2**: p. 21.
199. Montero-Odasso, M., Verghese, J., Beauchet, O., et al., *Gait and cognition: a complementary approach to understanding brain function and the risk of falling.* J Am Geriatr Soc, 2012. **60**(11): p. 2127-36.
200. Jayakody, O., Breslin, M., Srikanth, V.K., et al., *Gait Characteristics and Cognitive Decline: A Longitudinal Population-Based Study.* Journal of Alzheimer's Disease, 2019. **71**: p. S5-S14.
201. Beauchet, O., Allali, G., Thiery, S., et al., *Association between high variability of gait speed and mild cognitive impairment: a cross-sectional pilot study.* J Am Geriatr Soc, 2011. **59**(10): p. 1973-4.
202. Winter, D.A., Patla, A.E., Frank, J.S., et al., *Biomechanical walking pattern changes in the fit and healthy elderly.* Phys Ther, 1990. **70**(6): p. 340-7.
203. Montufar, J., Arango, J., Porter, M., et al., *Pedestrians' Normal Walking Speed and Speed When Crossing a Street.* Transportation Research Record, 2007. **2002**(1): p. 90-97.

204. Asher, L., Aresu, M., Falaschetti, E., et al., *Most older pedestrians are unable to cross the road in time: a cross-sectional study.* Age Ageing, 2012. **41**(5): p. 690-4.
205. Al-Yahya, E., Dawes, H., Smith, L., et al., *Cognitive motor interference while walking: a systematic review and meta-analysis.* Neurosci Biobehav Rev, 2011. **35**(3): p. 715-28.
206. Laroche, D.P., Cook, S.B., and Mackala, K., *Strength asymmetry increases gait asymmetry and variability in older women.* Med Sci Sports Exerc, 2012. **44**(11): p. 2172-81.
207. Sadeghi, H., Allard, P., Prince, F., et al., *Symmetry and limb dominance in able-bodied gait: a review.* Gait Posture, 2000. **12**(1): p. 34-45.
208. Gale, C.R., Allerhand, M., Sayer, A.A., et al., *The dynamic relationship between cognitive function and walking speed: the English Longitudinal Study of Ageing.* AGE, 2014. **36**(4): p. 9682.
209. Bohnen, N.I. and Albin, R.L., *White matter lesions in Parkinson disease.* Nat Rev Neurol, 2011. **7**(4): p. 229-36.
210. Sohn, Y.H. and Kim, J.S., *The influence of white matter hyperintensities on the clinical features of Parkinson's disease.* Yonsei Med J, 1998. **39**(1): p. 50-5.
211. Tabert, M.H., Manly, J.J., Liu, X., et al., *Neuropsychological Prediction of Conversion to Alzheimer Disease in Patients With Mild Cognitive Impairment.* Archives of General Psychiatry, 2006. **63**(8): p. 916-924.
212. Ward, A., Tardiff, S., Dye, C., et al., *Rate of conversion from prodromal Alzheimer's disease to Alzheimer's dementia: a systematic review of the literature.* Dement Geriatr Cogn Dis Extra, 2013. **3**(1): p. 320-32.
213. Witter, M.P., *Entorhinal Area (Cortex)*, in *Encyclopedia of Neuroscience*, M.D. Binder, N. Hirokawa, and U. Windhorst, Editors. 2009, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 1126-1129.
214. Halliday, G., *Pathology and hippocampal atrophy in Alzheimer's disease.* Lancet Neurol, 2017. **16**(11): p. 862-864.
215. Yogev-Seligmann, G., Hausdorff, J.M., and Giladi, N., *The role of executive function and attention in gait.* Mov Disord, 2008. **23**(3): p. 329-42; quiz 472.
216. Allali, G., Dubois, B., Assal, F., et al., *Frontotemporal dementia: pathology of gait?* Mov Disord, 2010. **25**(6): p. 731-7.
217. Mc Ardle, R., Galna, B., Donaghy, P., et al., *Do Alzheimer's and Lewy body disease have discrete pathological signatures of gait?* Alzheimer's & Dementia, 2019. **15**(10): p. 1367-1377.
218. Norris, C.J., *The negativity bias, revisited: Evidence from neuroscience measures and an individual differences approach.* Soc Neurosci, 2021. **16**(1): p. 68-82.
219. Prell, T., Uhlig, M., Derlien, S., et al., *Fear of Falling Does Not Influence Dual-Task Gait Costs in People with Parkinson's Disease: A Cross-Sectional Study.* Sensors (Basel), 2022. **22**(5).
220. Bryant, M.S., Rintala, D.H., Hou, J.G., et al., *Influence of fear of falling on gait and balance in Parkinson's disease.* Disabil Rehabil, 2014. **36**(9): p. 744-8.

221. Raffegeau, T.E., Krehbiel, L.M., Kang, N., et al., *A meta-analysis: Parkinson's disease and dual-task walking.* Parkinsonism Relat Disord, 2019. **62**: p. 28-35.
222. Kelly, V.E., Eusterbrock, A.J., and Shumway-Cook, A., *A Review of Dual-Task Walking Deficits in People with Parkinson's Disease: Motor and Cognitive Contributions, Mechanisms, and Clinical Implications.* Parkinson's Disease, 2012: p. 918719.
223. De Freitas, T., Leite, P., Doná, F., et al., *The effects of dual task gait and balance training in Parkinson's disease: a systematic review.* Physiother Theory Pract, 2020. **36**(10): p. 1088-1096.
224. Sophie, M. and Ford, B., *Management of Pain in Parkinson's Disease.* CNS Drugs, 2012. **26**(11): p. 937-948.
225. Allen, N.E., Moloney, N., van Vliet, V., et al., *The Rationale for Exercise in the Management of Pain in Parkinson's Disease.* J Parkinsons Dis, 2015. **5**(2): p. 229-39.
226. Raket, L.L., Oudin Åström, D., Norlin, J.M., et al., *Impact of age at onset on symptom profiles, treatment characteristics and health-related quality of life in Parkinson's disease.* Scientific Reports, 2022. **12**(1): p. 526.
227. Levy, G., *The Relationship of Parkinson Disease With Aging.* Archives of Neurology, 2007. **64**(9): p. 1242-1246.
228. Abou, L., Alluri, A., Fliflet, A., et al., *Effectiveness of Physical Therapy Interventions in Reducing Fear of Falling Among Individuals With Neurologic Diseases: A Systematic Review and Meta-analysis.* Arch Phys Med Rehabil, 2021. **102**(1): p. 132-154.
229. Conradsson, D., Lofgren, N., Nero, H., et al., *The Effects of Highly Challenging Balance Training in Elderly With Parkinson's Disease: A Randomized Controlled Trial.* Neurorehabil Neural Repair, 2015. **29**(9): p. 827-836.
230. Canning, C.G., Sherrington, C., Lord, S.R., et al., *Exercise for falls prevention in Parkinson disease: a randomized controlled trial.* Neurology, 2015. **84**(3): p. 304-12.
231. Rider, J.V., Longhurst, J.K., Lekhak, N., et al., *Psychological Factors Associated With Fear of Falling Avoidance Behavior in Parkinson's Disease: The Role of Depression, Anxiety, and Catastrophizing.* J Geriatr Psychiatry Neurol, 2022: p. 10.
232. Zijlstra, G.A., van Haastregt, J.C., Ambergen, T., et al., *Effects of a multicomponent cognitive behavioral group intervention on fear of falling and activity avoidance in community-dwelling older adults: results of a randomized controlled trial.* J Am Geriatr Soc, 2009. **57**(11): p. 2020-8.
233. Rider JV, Longhurst JK, Lekhak N, et al., *Fear of Falling Avoidance Behavior Assessment and Intervention in Parkinson's Disease: A Scoping Review. .* Research and Reviews in Parkinsonism. , 2022. **12:1-17**.
234. Sperens, M., Georgiev, D., Eriksson Domellöf, M., et al., *Activities of daily living in Parkinson's disease: Time/gender perspective.* Acta Neurologica Scandinavica, 2020. **141**(2): p. 168-176.
235. Strouwen, C., Molenaar, E., Munks, L., et al., *Determinants of Dual-Task Training Effect Size in Parkinson Disease: Who Will Benefit Most?* J Neurol Phys Ther, 2019. **43**(1): p. 3-11.

236. Paker, N., Bugdayci, D., Goksenoglu, G., et al., *Gait speed and related factors in Parkinson's disease.* Journal of physical therapy science, 2015. **27**(12): p. 3675-3679.
237. Kovács, M., Makkos, A., Aschermann, Z., et al., *Impact of Sex on the Nonmotor Symptoms and the Health-Related Quality of Life in Parkinson's Disease.* Parkinsons Dis, 2016. **2016**: p. 7951840.
238. Jones, D., Rochester, L., Birleson, A., et al., *Everyday walking with Parkinson's disease: understanding personal challenges and strategies.* Disabil Rehabil, 2008. **30**(16): p. 1213-21.
239. Hammarlund, C.S., Andersson, K., Andersson, M., et al., *The significance of walking from the perspective of people with Parkinson's disease.* J Parkinsons Dis, 2014. **4**(4): p. 657-63.
240. Nordell, E., Andreasson, M., Gall, K., et al., *Evaluating the Swedish version of the Falls Efficacy Scale-International (FES-I).* Advances in Physiotherapy, 2009. **11**(2): p. 81-87.
241. Mitchell, A.J. and Shiri-Feshki, M., *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.
242. Cerri, S., Mus, L., and Blandini, F., *Parkinson's Disease in Women and Men: What's the Difference?* Journal of Parkinson's Disease, 2019. **9**: p. 501-515.
243. Fitzsimmons, P.R., Blayney, S., Mina-Corkill, S., et al., *Older participants are frequently excluded from Parkinson's disease research.* Parkinsonism Relat Disord, 2012. **18**(5): p. 585-9.

Appendix 1-5

Appendix 1. Gait descriptions.

Table A1. Descriptions of gait parameters

Gait parameter	Definition
Step velocity (cm/sec)	Step length divided by step time.
Step length (cm)	Measured along the length of the walkway, from heel center of the current footprint to the heel center of the previous footprint on the opposite foot.
Step width (cm)	Distance from heel center of one footprint to the line of progression formed by two footprints of the opposite foot.
Step time (sec)	Time elapsed from first contact of one foot to first contact of the opposite foot.
Step swing time (sec)	Time elapsed between the last contact of the current footfall to the first contact of the next footfall on the same foot.
Step stance time (sec)	Time elapsed between the initial contact (heel contact) and the last contact (toe off) of the same foot.
Double support time (sec)	The period when both feet are on the floor simultaneously.

Appendix 2. Descriptive gait data.

Table A2. Descriptive data of the 18 gait parameters

	Mild cognitive impairment, n = 114		Cognitively unimpaired, n = 219		P-values
Gait parameter	Mean (SD)	Min-max	Mean (SD)	Min-max	
Mean measures					
Step velocity (cm/s)	111 (20.9)	57.8 - 163	120 (15.5)	73.4 - 159	**< 0.001a**
Step length (cm)	61.5 (9.0)	36.4 - 78.8	64.4 (7.1)	41.6 - 80.7	0.003a
Step width (cm)	9.2 (3.2)	3.2 - 21.2	8.6 (2.5)	2.6 - 16.8	0.118a
Step time (s)	0.56 (0.05)	0.47 - 0.73	0.54 (0.04)	0.45 - 0.67	**0.001a**
Step swing time (s)	0.40 (0.03)	0.32 - 0.51	0.39 (0.03)	0.33 - 0.46	0.131a
Step stance time (s)	0.72 (0.08)	0.57 - 1.04	0.69 (0.06)	0.52 - 0.89	**< 0.001a**
Double support time (s)	0.32 (0.07)	0.20 - 0.65	0.30 (0.05)	0.16 - 0.48	**0.001a**
Variability measures					
Step velocity (cm/s)	6.21 (1.96)	3.10 - 15.1	5.53 (1.75)	2.61 - 15.0	**0.001a**
Step length (cm)	2.65 (0.86)	1.15 - 5.27	2.25 (0.72)	1.05 - 7.97	**< 0.001a**
Step width (cm)	2.17 (0.56)	1.24 - 4.52	2.27 (0.58)	1.22 - 4.69	0.129a
Step time (s)	0.020 (0.009)	0.008 - 0.074	0.016 (0.005)	0.007 - 0.037	**< 0.001b**
Step swing time (s)	0.017 (0.008)	0.007 - 0.065	0.014 (0.004)	0.007 - 0.036	**< 0.001b**
Step stance time (s)	0.024 (0.011)	0.010 - 0.070	0.018 (0.007)	0.008 - 0.056	**< 0.001b**
Double support time (s)	0.022 (0.008)	0.010 - 0.057	0.018 (0.006)	0.007 - 0.058	**< 0.001b**
Asymmetry measures					
Step length (cm)	2.52 (2.39)	0.025 - 15.4	2.16 (2.13)	0.014 - 14.2	0.135 b
Step time (s)	0.017 (0.015)	0.000 - 0.092	0.012 (0.009)	0.000 - 0.042	0.028 b
Step swing time (s)	0.012 (0.012)	0.000 - 0.079	0.009 (0.008)	0.000 - 0.043	0.139 b
Step stance time (s)	0.012 (0.012)	0.000 - 0.073	0.009 (0.008)	0.000 - 0.042	0.074 b

Gait values are non-transformed. Presented p-values are uncorrected; bolded values are significant when using Bonferroni correction (p = 0.0028).
[a] Comparison by using independent-samples t-test. [b] Comparison by using Mann-Whitney U-test. Table reprinted from published article of study I [192].

.

Appendix 3. Components of gait.

Components of gait in people with MCI

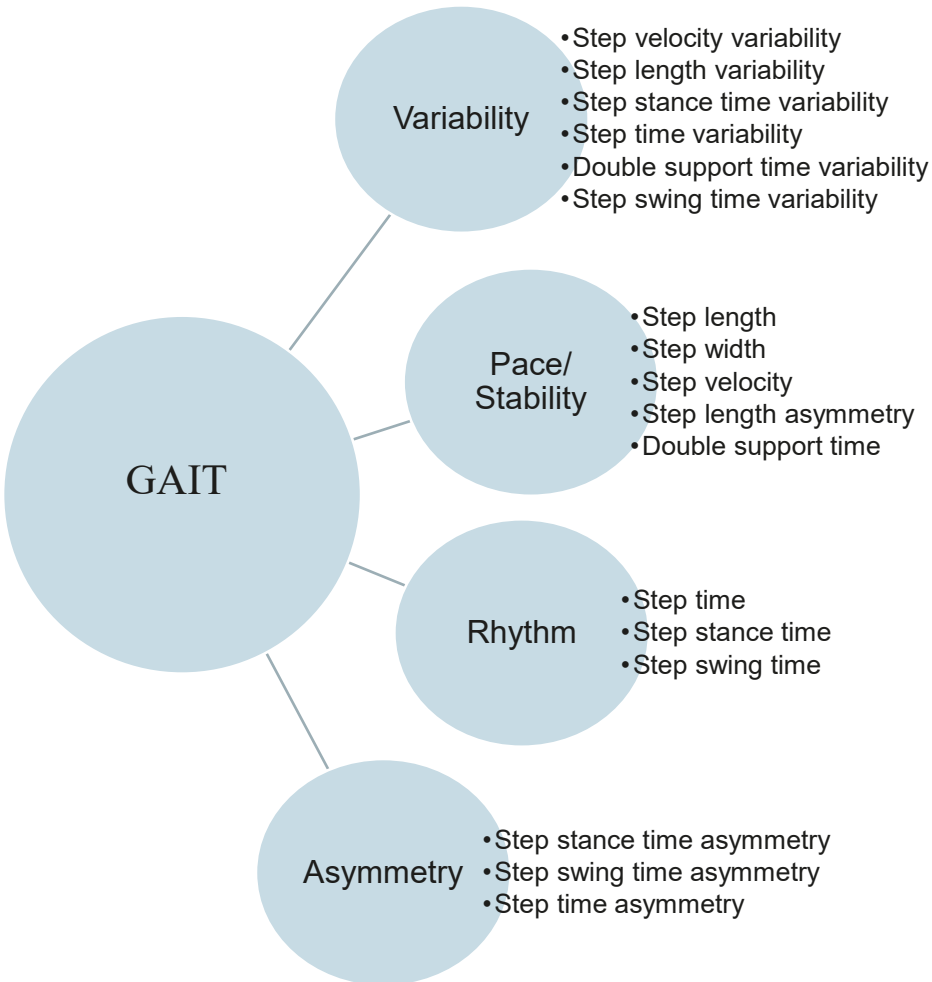


Figure 8. Components of gait in people with MCI, with specific gait parameters listed next to the component to which the gait parameters loaded the highest.

Components of gait in cognitively unimpaired

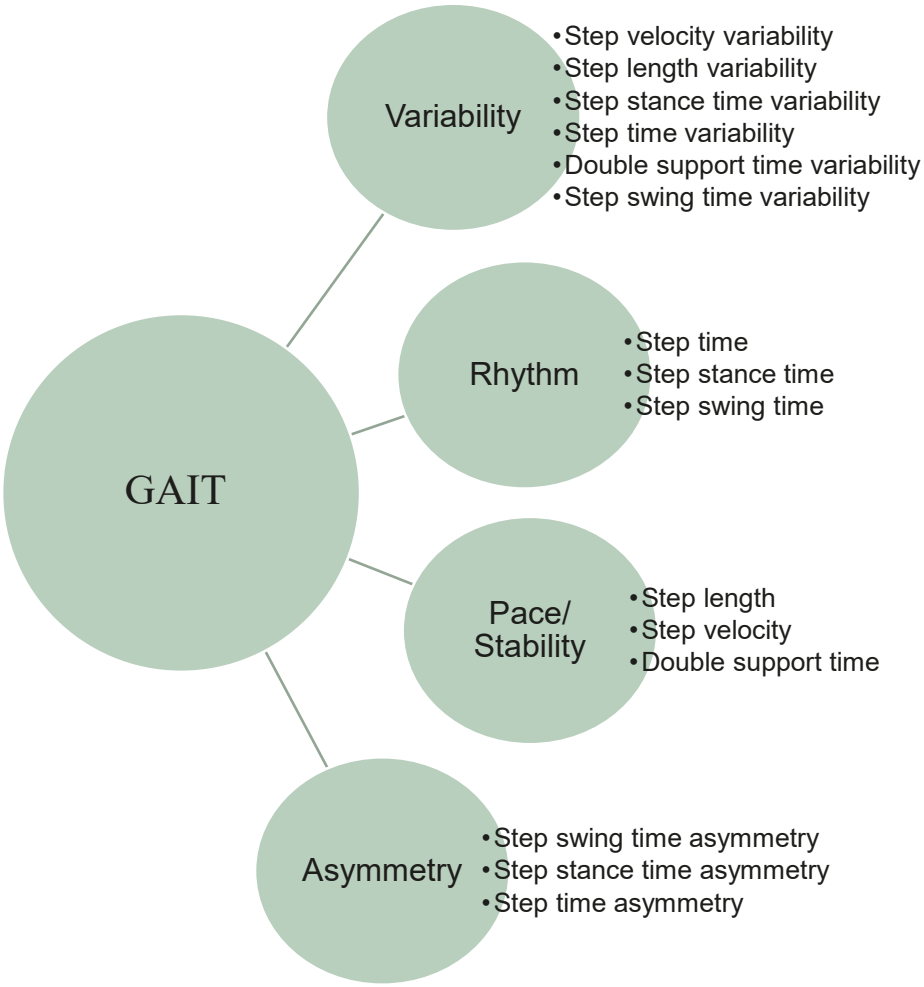


Figure 9. Components of gait in CU individuals, with specific gait parameters listed next to the component to which the gait parameters loaded the highest.

Appendix 4. Crude and basic regression linear regression analyses between brain pathologies and gait parameters.

Table A4:1. Crude and basic linear regression analyses with step VELOCITY (cm/s) as the dependent variable; separate models for each pathology variable (tau, amyloid-β and white matter hyperintensities, respectively), n = 96

Crude (unadjusted)			
Independent variable	B (95% CI)	β	p-value
Tau load (SUVR), Braak stage I-IV	15.358 (4.64, 26.08)	0.282	**0.005**
Amyloid-β (SUVR)	-1.201 (-24.52, 22.11)	-0.011	0.919*
White matter hyperintensities (mL)	-0.145 (-0.40, 0.11)	-0.116	0.261
Basic (adjusted for age and sex + intracranial volume for white matter hyperintensities)			
	B (95% CI)	β	p-value
Tau load (SUVR), Braak stage I-IV	17.373 (7.94, 26.81)	0.319	**< 0.001**
Amyloid-β (SUVR)	10.105 (-11.07, 31.28)	0.089	0.346
White matter hyperintensities (mL)	-0.067 (-0.31, 0.17)	-0.053	0.578

B = unstandardized regression coefficient; CI = confidence interval; β = standardized regression coefficient; SUVR = standardized uptake value ratio. Tau and amyloid-β were assessed using positron emission tomography. White matter hyperintensities were assessed using magnetic resonance imaging. Significant p-values (< 0.05) are bolded.

* The unstandardized coefficient of regression changed > 20% when a time difference variable was added (p-value was then 0.999).

Table A4:2. Crude and basic linear regression analyses with step velocity VARIABILITY (cm/s) as the dependent variable; separate models for each pathology variable (tau, amyloid-β and white matter hyperintensities, respectively), n = 96

	Crude (unadjusted)		
Independent variable	B (95% CI)	β	p-value
Tau load (SUVR), Braak stage I-IV	2.085 (1.09, 3,08)	0.396	**< 0.001**
Amyloid-β (SUVR)	-0.219 (-2,47, 2.04)	-0.020	0.847
White matter hyperintensities (mL)	-0.014 (-0.04, 0.02)	-0.116	0.261
	Basic (adjusted for age and sex + intracranial volume for white matter hyperintensities)		
	B (95% CI)	β	p-value
Tau load (SUVR), Braak stage I-IV	1.988 (0.98, 3,00)	0.378	**< 0.001**
Amyloid-β (SUVR)	-0.383 (-2.67, 1.91)	-0.035	0.740
White matter hyperintensities (mL)	-0,019 (-0.05, 0.01)	-0.160	0.135

B = unstandardized regression coefficient; CI = confidence interval; β = standardized regression coefficient; SUVR = standardized uptake value ratio. Tau and amyloid-β were assessed using positron emission tomography. White matter hyperintensities were assessed using magnetic resonance imaging. Significant p-values (< 0.05) are bolded.

Table A4:3. Crude and basic linear regression analyses with step LENGTH (cm) as the dependent variable; separate models for each pathology variable (tau, amyloid-β and white matter hyperintensities, respectively), n = 96

	Crude (unadjusted)		
Independent variable	B (95% CI)	β	p-value
Tau load (SUVR), Braak stage I-IV	6.496 (1.93, 11.06)	0.280	**0.006**
Amyloid-β (SUVR)	3.020 (-6.88, 12.92)	0.062	0.546*
White matter hyperintensities (mL)	-0.097 (-0.21, 0.01)	-0.182	0.076
	Basic (adjusted for age and sex + intracranial volume for white matter hyperintensities)		
	B (95% CI)	β	p-value
Tau load (SUVR), Braak stage I-IV	7.827 (3.88, 11.78)	0.337	**< 0.001**
Amyloid-β (SUVR)	7.646 (-1.21, 16.50)	0.158	0.090
White matter hyperintensities (mL)	-0.059 (-0.16, 0.04)	-0.111	0.239

B = unstandardized regression coefficient; CI = confidence interval; β = standardized regression coefficient;
SUVR = standardized uptake value ratio.
Tau and amyloid-β were assessed using positron emission tomography. White matter hyperintensities were assessed using magnetic resonance imaging. Significant p-values (< 0.05) are bolded.
* The unstandardized coefficient of regression changed > 20% when a time difference variable was added (p-value was then 0.447).

Table A4:4. Crude and basic linear regression analyses with step TIME (s) as the dependent variable; separate models for each pathology variable (tau, amyloid-β and white matter hyperintensities, respectively), n = 96

	Crude (unadjusted)		
Independent variable	B (95% CI)	β	p-value
Tau load (SUVR), Braak stage I-IV	-0.017 (-0.05, 0.01)	-0.130	0.208
Amyloid-β (SUVR)	0.032 (-0.03, 0.09)	0.119	0.248
White matter hyperintensities (mL)	-0.000 (-0.01, 0.01)	-0.023	0.827
	Basic (adjusted for age and sex + intracranial volume for white matter hyperintensities)		
	B (95% CI)	β	p-value
Tau load (SUVR), Braak stage I-IV	-0.015 (-0.04, 0.01)	-0.119	0.222
Amyloid-β (SUVR)	0.015 (-0.04, 0.07)	0.054	0.583
White matter hyperintensities (mL)	0.000 (-0.01, 0.000)	-0.046	0.654

B = unstandardized regression coefficient; CI = confidence interval; β = standardized regression coefficient;
SUVR = standardized uptake value ratio.
Tau and amyloid-β were assessed using positron emission tomography. White matter hyperintensities were assessed using magnetic resonance imaging. Significant p-values (< 0.05) are bolded.

Table A4:5. Crude and basic linear regression analyses with stance time ASYMMETRY* (s) as the dependent variable; separate models for each pathology variable (tau, amyloid-β and white matter hyperintensities, respectively), n = 96

	Crude (unadjusted)		
Independent variable	B (95% CI)	β	p-value
Tau load (SUVR), Braak stage I-IV	-0.012 (-0.04, 0.02)	-0.091	0.377
Amyloid-β (SUVR)	0.011 (-0.05, 0.07)	0.039	0.704**
White matter hyperintensities (mL)	0.000 (-0.01, 0.000)	-0.065	0.527
	Basic (adjusted for age and sex + intracranial volume for white matter hyperintensities)		
	B (95% CI)	β	p-value
Tau load (SUVR), Braak stage I-IV	-0.013 (-0.04, 0.02)	-0.101	0.308
Amyloid-β (SUVR)	-0.009 (-0.07, 0.05)	-0.033	0.743***
White matter hyperintensities (mL)	0.000 (-0.01, 0.000)	-0.126	0.219

B = unstandardized regression coefficient; CI = confidence interval; β = standardized regression coefficient; SUVR = standardized uptake value ratio.
Tau and amyloid-β were assessed using positron emission tomography. White matter hyperintensities were assessed using magnetic resonance imaging. Significant p-values (< 0.05) are bolded.
* Square root transformed.
** The unstandardized coefficient of regression changed > 20% when a time difference variable was added (p-value was then 0.833).
*** The unstandardized coefficient of regression changed > 20% when a time difference variable was added (p-value was then 0.681).

Appendix 5. Comparisons of gait parameter performance between cognitively healthy and MCI.

Table A5:1. Comparisons between individuals with MCI and cognitively healthy as well as comparisons between aMCI and naMCI

	Cognitively healthy N = 143 Mean (SD)	MCI N = 114 Mean (SD)	Amnestic MCI* N = 75 Mean (SD)	Non-amnestic MCI N = 34 Mean (SD)
Gait parameter				
Step velocity (cm/s)	118.7 (15.3)**	111.3 (20.9)	114.5 (19.9)***	104.1 (21.3)
Step length (cm)	63.6 (6.9)**	61.5 (9.0)	63.1 (8.2)***	57.8 (9.2)
Step velocity variability (cm/s)	5.5 (1.8)**	6.2 (2.0)	6.2 (2.2)	6.3 (1.6)
Step time (s)	0.54 (0.04)**	0.56 (0.05)	0.56 (0.05)	0.56 (0.05)
Stance time asymmetry (s)****	0.1 (0.04)**	0.1 (0.05)	0.1 (0.05)	0.1 (0.06)

* Five individuals had not been sub-classified as amnestic or non-amnestic MCI when data for thesis was extracted.
** Statistically difference cognitively healthy vs, MCI ($p < 0.05$). *** Statistically difference aMCI vs. naMCI ($p < 0.05$).
***** Square root transformed.

Table A5:2. Comparisons between individuals, aged 70-80, with MCI and cognitively healthy as well as comparisons between aMCI and naMCI

	Cognitively healthy N = 77 Mean (SD)	MCI N = 65 Mean (SD)	Amnestic MCI N = 44 Mean (SD)	Non-amnestic MCI N = 18 Mean (SD)
Gait parameter				
Step velocity (cm/s)	119.3 (13.9)**	111.1 (20.2)	115.4 (18.8)***	102.1 (19.4)
Step length (cm)	64.0 (6.2)**	61.4 (8.5)	63.6 (7.3)***	56.6 (8.2)
Step velocity variability (cm/s)	5.1 (1.5)**	6.2 (1.9)	6.0 (2.0)	6.9 (1.6)
Step time (s)	0.54 (0.04)**	0.56 (0.05)	0.56 (0.05)	0.56 (0.05)
Stance time asymmetry (s)*	0.1 (0.04)**	0.1 (0.05)	0.1 (0.05)	0.1 (0.06)

* Square root transformed. ** Statistically difference cognitively healthy vs. MCI ($p < 0.05$). *** Statistically difference aMCI vs. naMCI ($p < 0.05$).