

Understanding the relationship between gait and cognition in mild cognitive impairment subtypes and
probable REM sleep behavior disorder

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Introduction: Mild cognitive impairment (MCI) represents a transition state between normal cognition and dementia. Individuals with amnesic MCI (aMCI) are more likely to develop Alzheimer's disease (AD), whereas individuals with non-amnesic MCI (naMCI) are more likely to progress to non-AD dementias. Individuals with multi-domain (MD-) MCI are more likely to develop dementia than individuals with single-domain (SD-) MCI. Previous research has demonstrated that individuals with MCI have slower gait compared to cognitively unimpaired (CU) older adults, but limited research has characterized gait differences across MCI subtypes over time in these groups. There is also growing evidence that specific gait characteristics are selectively associated with specific cognitive domains, but few studies have investigated these associations longitudinally in MCI. REM sleep behavior disorder (RBD) is a prodromal biomarker of α -synucleinopathies, particularly Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Individuals with RBD are more likely to develop MCI than healthy controls, and the presence of MCI in RBD is associated with greater risk for early phenotypic conversion. Recently, research has highlighted that individuals with isolated RBD exhibit subtle changes in gait. Despite this, no studies to date have explored how the presence of RBD influences gait characteristics in people with MCI. Therefore, this study aimed to a) characterize baseline and longitudinal gait characteristics across MCI subtypes, b) explore how the presence of RBD impacts gait characteristics in MCI, and c) assess whether baseline gait characteristics can predict future decline in specific cognitive domains in MCI.

Methods: This study involved secondary data analysis of data from the Mayo Clinic Study of Aging. 382 individuals with MCI (180 SD-aMCI, 48 SD-naMCI, 134 MD-aMCI, 20 MD-naMCI), and 382 age-, sex- and education-matched CU individuals were included. Mean follow-up duration for the entire sample was 16.8 months. Participants completed gait assessment using an instrumented gait walkway. Informants completed the Mayo Sleep Questionnaire, which was used to determine probable RBD (pRBD) status. Cognition was measured using domain-specific z-scores for attention, memory, language, visuospatial function, as well as global cognition. Linear mixed effects models were used to compare gait outcomes over time between groups and by pRBD status. Principal component analysis and linear mixed effects models were used to derive gait components and assess if they predict change in cognitive domains from baseline to follow-up visits.

Results: All individuals with MCI walked slower, with shorter steps, longer step time, and increased double support (%) compared to CU individuals. Variability of step length, stride velocity and swing time were increased in MD-aMCI compared to CU individuals. Over time, stride velocity and step length decreased, and step time increased in MD-aMCI. The presence of pRBD was associated with decreased stride velocity and step length, and increased stride width and double support (%), particularly in MD-naMCI. Swing time increased over time in people with MD-naMCI and pRBD. Principal component analysis identified three gait factors: pace and stability, timing and rhythm, and variability. The pace and stability factor was negatively associated with global cognition and attention. Surprisingly, the rhythm and timing factor was positively associated with memory. Variability was negatively associated with global cognition and visuospatial function, but this association weakened at follow-up.

Conclusions: Gait analysis may be a helpful tool to distinguish MCI from normal aging. Gait variability and slowing of gait may be specific markers of multi-domain impairment. Gait is impacted by comorbid pRBD in MCI, particularly in MD-naMCI. These findings provide further support for the notion of selective associations between specific gait and cognitive domains in people with MCI. Importantly, further investigation with longer follow-up duration, larger sample sizes, and integration of neuroimaging and fluid biomarkers is needed to better understand the role of gait in predicting future progression to dementia in individuals at risk.

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Dedication

To my parents, whose love and sacrifices have been the foundation of everything I have achieved. Together, you left behind the life you knew to begin again in a new country, and through your courage, you opened a world of opportunities for me.

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List of Abbreviations

AD	Alzheimer's Disease
AP	Anteroposterior
aMCI	Amnesic Mild Cognitive Impairment
ANOVA	Analysis of Variance
CDR	Clinical Dementia Rating Scale
CI	Confidence Interval
CU	Cognitively Unimpaired
DLB	Dementia with Lewy Bodies
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV
EMM	Estimated Marginal Mean
fNIRS	Functional Near Infrared Spectroscopy
iRBD	Isolated Rapid Eye Movement Sleep Behavior Disorder
LBD	Lewy body dementia
MCI	Mild Cognitive Impairment
MD-aMCI	Multi-Domain Amnesic Mild Cognitive Impairment
MD-naMCI	Multi-Domain Non-Amnesic Mild Cognitive Impairment
ML	Mediolateral
MMSE	Mini-Mental State Examination
MSA	Multiple System Atrophy
MSQ	Mayo Sleep Questionnaire
naMCI	Non-Amnesic Mild Cognitive Impairment
PET	Positron Emission Tomography
PD	Parkinson's Disease

pRBD	Probable Rapid Eye Movement Sleep Behavior Disorder
PSG	Polysomnography
RBD	Rapid Eye Movement Sleep Behavior Disorder
SD-aMCI	Single-Domain Amnestic Mild Cognitive Impairment
SD-naMCI	Single-Domain Non-Amnestic Mild Cognitive Impairment
SPECT	Single Photon Emission Computed Tomography
TUG	Timed Up and Go
UPDRS-III	Unified Parkinson's Disease Rating Scale-Part III
VaD	Vascular Dementia
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WMS-R	Wechsler Memory Scale-Revised

Chapter 1: Introduction

As the aging population grows globally, the burden of age-related diseases and neurodegenerative conditions, such as dementia, is projected to increase (Li et al., 2022). Dementia refers to several progressive diseases characterized by neurodegeneration and progressive loss of cognitive abilities and independence (World Health Organization, 2017). In 2019, it was estimated that 55.2 million people were affected by dementia (World Health Organization, 2021). This number is projected to rise to 139 million affected individuals by 2050 (World Health Organization, 2021). There are several subtypes of dementia, but the most common are Alzheimer's disease (AD), followed by vascular dementia (VaD), and dementia with Lewy bodies (DLB) (Brunnström et al., 2009; Goodman et al., 2017; C. Mueller et al., 2017; World Health Organization, 2017).

Mild cognitive impairment (MCI) has been defined as a transition state between normal cognition and dementia (Winblad et al., 2004). Individuals with MCI have increased risk for developing dementia compared to older adults with normal cognition (Roberts et al., 2014). MCI is estimated to affect 12% to 18% of individuals over 60 years old (Petersen, 2016). The rate of progression to dementia in MCI ranges from 4% to 17% across studies (Manly et al., 2008). Therefore, while most individuals with MCI will have cognitive impairment that remains stable or fluctuates, some will go on to decline and develop dementia (Roberts et al., 2014; Xue et al., 2019). Furthermore, studies estimating rates of progression from normal cognition to MCI have reported that annually, 5% to 6% of older adults over 70 years old develop MCI, and this risk increases with age (Roberts et al., 2012). Overall, this highlights that MCI is highly prevalent among older adults and frequently encountered by clinicians (Petersen, 2016). Therefore, early identification and intervention in MCI is important to reduce the risk of progression to dementia.

Gait analysis has been suggested as a potentially useful tool that can help identify individuals at risk of cognitive decline and dementia in a relatively accessible way (Beauchet et al., 2016; Kikkert et al., 2016). Consistently, gait has been reported to predict dementia in older adults up to nine years before clinical dementia symptoms are present (Beauchet et al., 2016).

Several studies have used data reduction techniques to derive gait components from specific gait characteristics. These gait components have also been linked to specific cognitive domains, which suggests the presence of shared neural substrates between gait and cognition (Morris et al.,

2016; Rosano et al., 2012; Wilson et al., 2019). For example, there is evidence that increases in the “rhythm” aspects of gait, which indicated increased step time and swing time and decreased cadence, predict future decline in memory function in healthy older adults (Verghese et al., 2007). On the other hand, decreases in the “pace” aspects of gait, which indicates decreased gait velocity and step length, predict future decline in executive function (Verghese et al., 2007).

Similarly, researchers have previously shown that gait differs between different subtypes of dementia, for example, individuals with Dementia with Lewy Bodies (DLB), which is characterized by decline in executive function and attention, have slower, more variable gait compared to individuals with AD, which is characterized by decline in memory (Elasfar et al., 2025; Mc Ardle et al., 2017, 2019, 2020). As MCI can be subtyped into amnesic MCI, characterized by memory impairment, or non-amnesic MCI, characterized by a non-memory impairment, gait characteristics may differ across MCI subtypes (Petersen et al., 2001; Winblad et al., 2004).

There is strong evidence that individuals with MCI have slower gait speed, decreased step length, increased step time and double support time compared to CU individuals (Choi et al., 2011; Cullen et al., 2019; Du et al., 2023; Goyal et al., 2019; Nascimbeni et al., 2015; Verghese et al., 2007; Yamagami et al., 2023). However, this research often excludes participants with non-amnesic MCI. Additionally, studies that have compared gait between MCI subtypes have been limited and inconsistent, likely due to differences in sample sizes, gait analysis methods, and heterogeneity in MCI samples (Allali et al., 2016; Beauchet et al., 2011; Montero-Odasso et al., 2014; Verghese et al., 2008). There is also lack of research exploring how gait characteristics change over time in MCI subtypes. Moreover, while many studies have explored the association between gait and cognition in healthy older adults and in Parkinson’s disease, less research has aimed to do this in MCI and its subtypes (Morris et al., 2016).

Another prodromal marker of neurodegenerative disease is REM sleep behavior disorder (RBD), which is a parasomnia characterized by dream enactment behavior during REM sleep (Boeve, 2010; Postuma et al., 2019). People with RBD are at high risk of developing α -synucleinopathies, particularly Parkinson’s disease (PD) and DLB (Boeve, 2010; Postuma et al., 2019). It is estimated that by 14 years from diagnosis, approximately 97% of individuals with RBD develop a neurodegenerative disorder, most commonly PD or DLB (Postuma et al., 2019). There is growing evidence that subtle motor changes, including changes in gait, are present in RBD prior to the onset of

parkinsonism and are predictive of future phenoconversion (Del Din et al., 2020; Ehgoetz Martens et al., 2019; Fereshtehnejad et al., 2019; McDade et al., 2013; Postuma et al., 2006, 2009, 2019). The risk of developing MCI is elevated in people with RBD, and the risk of early phenoconversion to PD or DLB is increased in people with co-occurring RBD and MCI (Arnaldi et al., 2021; Gagnon et al., 2009, 2010). However, despite this clinical significance, and evidence that both conditions impact gait independently, no studies to date have investigated how gait is impacted in people who have comorbid MCI and RBD.

Therefore, the aims of this thesis are a) to investigate how gait differs between MCI subtypes, b) to characterize how gait changes over time in MCI subtypes, c) to explore how the presence of pRBD impacts gait characteristics in people with MCI, and d) to evaluate whether baseline gait features can predict longitudinal change in cognitive performance in people with MCI. This research will therefore help improve understanding of gait as a marker of cognitive function and further explore its role as a potential marker for early neurodegenerative disease risk.

Chapter 2: Literature Review

2.1 Gait

Gait describes the movement pattern exhibited during walking (Whittle, 2007). Human gait is very complex, and involves interplay between various organ systems, including musculoskeletal, nervous, sensory, and cardiorespiratory systems (Sarkodie-Gyan & Yu, 2023). Gait is also affected by several factors including age, mood, and cognition (Pirker & Katzenschlager, 2017).

Gait analysis refers to a systematic assessment of a person's walking pattern (Whittle, 2007). Clinically, gait is often analyzed through visual observation of walking by a clinician, or by timing gait trials with a stopwatch (Wade, 1992). As gait speed is relatively easy to measure, it is commonly used as a global representation of gait in clinical and research settings (Wilson et al., 2019). On the other hand, gait speed may not capture subtle changes in gait that occur in aging and disease, particularly in early disease stages (Kikkert et al., 2016; Morris et al., 2001; Wilson et al., 2019). For this reason, it is important to characterize gait more comprehensively, considering spatiotemporal gait characteristics that may reflect subtle and selective changes in gait with aging and disease, particularly neurodegeneration (Morris et al., 2016; Wilson et al., 2019).

A gait cycle, or stride, starts with one foot making contact with the ground and ends when that same foot again comes in contact with the ground (Perry, 2010; Whittle, 2007). A step starts when one foot makes contact with the ground and ends when the opposite foot comes in contact with the ground (Perry, 2010; Whittle, 2007). There are several ways to divide the gait cycle. One method is dividing it into stance and swing phases. Stance refers to the period in which the foot is in contact with the ground, while swing refers to the period in which the foot is in the air (Perry, 2010; Whittle, 2007). The gait cycle can also be divided into double and single support phases (Perry, 2010; Whittle, 2007). In double support, both feet are in contact with the ground (Perry, 2010; Whittle, 2007). In single support, only one foot is on the ground. This typically consists most of the gait cycle (Perry, 2010; Whittle, 2007). Measuring the timing of these phases in a gait cycle is important as it can reveal information about stability and postural control. For example, with age and in degenerative disease, individuals tend to increase time spent in double support, reflecting a compensation for postural instability and impaired balance control due to changes in sensory systems, muscle function, and the nervous system (Aboutorabi et al., 2016).

Spatiotemporal measures of gait can vary and fluctuate over time, and even from one step to the next (Hausdorff, 2005). Research has demonstrated that in healthy populations, variability of gait outcomes between strides is relatively small (Gabell & Nayak, 1984; Hausdorff, 2005; Hausdorff et al., 1997). However, in some neurodegenerative conditions, including PD and DLB, gait variability is increased (Peterson & Horak, 2016). Previous research has also demonstrated that gait variability is closely linked to risk of falls in older adults (Hausdorff et al., 1997, 2003, 2004; Herman et al., 2005; Pieruccini-Faria et al., 2020a; Schaafsma et al., 2003). In PD, increased gait variability has been suggested to indicate a decrease in automatic control of gait, leading to more volitional control of gait, which results in more variability (Peterson & Horak, 2016).

Therefore, while measuring gait speed can provide an overall indicator of gait performance, it may not sufficiently capture the complexity of gait or adequately reflect subtle gait changes that occur in aging and early neurodegenerative conditions (Lord et al., 2013; Mc Ardle et al., 2017; Morris et al., 2016; Wilson et al., 2019). For this reason, a comprehensive approach to quantifying gait is needed when characterizing gait in different neurodegenerative conditions (Lord et al., 2013; Mc Ardle et al., 2017; Morris et al., 2016; Wilson et al., 2019).

2.2 Gait Changes in Normal Aging

Research has demonstrated that as people grow older, they walk slower, with decreased cadence, shorter and wider steps, and increased double support (%) (Aboutorabi et al., 2016). This may be partly explained by muscle weakening due to aging which reduces the force generated to propel the body forward (Aboutorabi et al., 2016; Fukagawa et al., 1995; Herssens et al., 2018; Uematsu et al., 2014).

These changes may also reflect compensatory strategies for postural instability that is associated with aging (Aboutorabi et al., 2016; Herssens et al., 2018; Osoba et al., 2019). Many sensory systems contribute to balance control and postural stability, including proprioceptors in muscles and joints, particularly in the ankle, cutaneous receptors in the feet, visual receptors in the retina, and vestibular receptors in the ear that provide information about body orientation (Osoba et al., 2019). The function of these sensory systems often declines with age (Osoba et al., 2019). For example, research has demonstrated that older adults have decreased awareness of foot position, impaired vestibular function, and slower sensory integration compared to young adults (Hsieh et al.,

2014; Osoba et al., 2019; Robbins et al., 1995). Therefore, slower gait may also be a way of compensating for declines in sensory function that occur with age.

2.3 Cognitive Involvement in Gait

Previously, gait was regarded as an automatic motor task, controlled solely by spinal and subcortical motor circuits (Mirelman et al., 2018; Morris et al., 2016; Wilson et al., 2019; Woollacott & Shumway-Cook, 2002). More recently, research has demonstrated that the control of balance and gait involves cognitive processes, governed by complex neural networks, spanning cortical, subcortical and spinal neural areas (Maki & McIlroy, 2007; Mirelman et al., 2018; Takakusaki, 2017, 2023). Safe and effective gait requires coordinating limb movements and maintaining balance, while visually navigating the environment and making adjustments in response to the environment (Mirelman et al., 2018). Furthermore, cognitive functions, particularly executive function, attention, and visuospatial function, are important in the planning and execution of gait (Mirelman et al., 2018).

Fukuyama et al used single photon emission computed tomography (SPECT) to measure brain activity during real and imagined walking in healthy adults (Fukuyama et al., 1997). They demonstrated that cortical brain regions are active during walking, namely, primary sensorimotor and visual cortices, as well as the supplementary motor area (Fukuyama et al., 1997). The striatum, and cerebellar vermis were also activated by walking (Fukuyama et al., 1997). This study provides evidence that motor control spans cortical and subcortical areas and is not purely controlled by the brainstem and spinal cord. However, this study did not find activation of cognitive association areas, particularly prefrontal regions, during walking, suggesting that in healthy adults, simple walking may be relatively automatic (Fukuyama et al., 1997).

In contrast, more complex walking tasks do elicit activation in these higher-order cognitive association brain regions. For example, Malouin et al used positron emission tomography (PET) to demonstrate that dorsolateral prefrontal, precuneus, inferior parietal, and posterior cingulate brain regions were activated during imagined walking with obstacle navigation in healthy adults (Malouin et al., 2003). More recently, functional near-infrared spectroscopy (fNIRS) has allowed for imaging of activity in prefrontal brain regions while walking (Doi et al., 2013; Holtzer et al., 2011; Mirelman et al., 2014; Springer et al., 2006). These studies have demonstrated increased activity in the prefrontal cortex during dual-task walking in healthy young and older adults (Doi et al., 2013; Holtzer et al., 2011; Mirelman et al., 2014; Springer et al., 2006). Importantly, performing a cognitive task

alone while standing did not elicit the same response (Mirelman et al., 2014). Furthermore, this activation increases in response to the difficulty of the secondary task, with a serial subtraction by seven task resulting in higher prefrontal cortex activation than a simple counting task (Mirelman et al., 2014).

Other studies have used the dual-task paradigm to further demonstrate that gait involves cognitive functions, particularly attention. In older adults and in populations with neurological diseases, for example, PD or stroke patients, the addition of a dual task while walking results in gait becoming slower and more variable (Springer et al., 2006; Yogev-Seligmann et al., 2008). On the other hand, in healthy young adults, dual-tasking results in slower walking, but other aspects of gait remain unaffected (Springer et al., 2006; Srygley et al., 2009). This suggests that aspects of gait require attentional resources, even in healthy young adults. However, in aging and neurological disease, automaticity of motor control may be impacted, resulting in greater need for attentional resources during gait, and therefore, additional changes in gait during dual-tasking, such as increased gait variability (Mirelman et al., 2018; Peterson & Horak, 2016).

Taken together, these studies highlight how gait is not a purely automatic task, but rather also relies on cognitive resources, especially under challenging conditions, such as obstacle navigation or dual-tasking. Furthermore, the attentional resources required for gait seem to increase in aging and in neurological disease. This has important clinical relevance, as it suggests gait can be a helpful marker for predicting cognitive impairment and risk for neurodegenerative conditions, including dementia.

2.4 Gait in Dementia and its Subtypes

Consistent with the understanding that gait involves cognitive input, research has shown that dementia is often accompanied by observable changes in gait, which often present prior to the onset of dementia (Beauchet et al., 2016; Mc Ardle et al., 2017). Gait speed is most often measured in existing literature investigating gait in dementia compared to normal aging, and is consistently found to be slower in people with dementia compared to CU older adults (Mc Ardle et al., 2017). Furthermore, gait is slower and more variable in individuals with more severe dementia compared to individuals in earlier stages of disease, particularly in AD (Allali et al., 2016; Mc Ardle et al., 2017; Nakamura et al., 2009; Ries et al., 2009).

This association between gait and dementia is impacted by dementia subtypes (Mc Ardle et al., 2017). Specifically, gait differs across different dementia subtypes. Changes in gait from healthy

aging are more pronounced in non-AD dementias than AD (Allali et al., 2016; Mc Ardle et al., 2017). Research comparing gait characteristics between individuals with DLB and AD has reported that individuals with DLB walk slower with increased double support (%) (Elasfar, Hameed, Boeve, et al., 2025; Fritz et al., 2016; Mc Ardle et al., 2019, 2020). Individuals with DLB, not AD, also have more variable gait compared to CU older adults (Elasfar, Hameed, Boeve, et al., 2025). This research has also demonstrated that these gait characteristics can distinguish these dementia subtypes with moderate accuracy, which has important clinical implications for the differential diagnosis of these dementia subtypes, as they are commonly misdiagnosed by clinicians (Elasfar, Hameed, Boeve, et al., 2025; Mc Ardle et al., 2019; Tiraboschi et al., 2006). Increased variability in DLB may reflect reductions in automatic control of gait and increased reliance on attention for gait control, which may be explained by accumulation of neuropathology in the brainstem and basal ganglia characteristic of Lewy body diseases (Adler et al., 2019; Beach et al., 2009; Botzung et al., 2019; Peterson & Horak, 2016; Seidel et al., 2015).

Prior research has also characterized gait in VaD compared to AD, reporting that individuals with VaD walk slower, and are more likely to present with neurological gait impairment than AD (Beauchet et al., 2016; Mc Ardle et al., 2017; Tanaka et al., 1995; Verghese et al., 2002). Similarly, neurological gait impairment predicts future VaD in older adults (Verghese et al., 2002, 2007). Individuals with FTD also walk slower with decreased stride length and increased step time and double support compared to AD, as well as increased gait variability when dual-tasking compared to healthy controls, which is not seen in AD (Allali et al., 2010; Rucco et al., 2017). As individuals with non-amnesic MCI can develop any of these non-AD dementias, it may be possible that these gait differences can help distinguish them from individuals with amnesic MCI.

2.5 Gait Predicts Future Cognitive Decline and Dementia

Research has also linked specific cognitive domains with different aspects of gait, which is consistent with findings of gait differences between dementia subtypes (Morris et al., 2016). These unique gait patterns in dementia subtypes may therefore reflect disease-specific cognitive impairments.

Additional evidence of a close relationship between gait and cognition comes from cross-sectional studies investigating these associations in healthy older adults, and individuals with neurodegenerative conditions, particularly PD (Morris et al., 2016). Much like the literature on gait changes in dementia, gait speed is the most frequently studied gait in relation to cognitive functions

(Morris et al., 2016). The findings from this research point to a global association between gait speed and multiple domains of cognition, including, memory, executive function, attention, language and visuospatial function (Morris et al., 2016). This consistent relationship has led researchers to propose that gait speed is a sensitive, but non-specific marker of cognitive health (Morris et al., 2016). In other words, reduced gait speed may reflect global cognitive impairment and neuropathology but lacks the specificity to reveal information about specific cognitive deficits and their underlying cause.

Several studies have used data reduction techniques to derive gait components from discrete gait characteristics and hypothesized they may be independently associated with specific cognitive domains (Hollman et al., 2011; Lord et al., 2013; Verghese et al., 2007; Verlinden et al., 2013). For example, measures of gait variability have shown more selective relationships with particular cognitive domains (Morris et al., 2016). Stride time variability is the most frequently measured variability outcome, and it has been linked to attention and executive function in several studies in cognitively unimpaired older adults (Morris et al., 2016). Other measures of variability, such as step length variability have also been linked to visuospatial function in people with PD (Amboni et al., 2012; Morris et al., 2016). Stride width and double support (%), referred to as “postural control” measures, have similarly been associated with attention and visuospatial function (Morris et al., 2016). Memory, on the other hand, has been previously linked to timing-related aspects of gait, such as step time and swing time (Morris et al., 2016; Verghese et al., 2007). Together, these findings support a more nuanced view of the relationship between gait and cognition, suggesting that while gait speed may potentially serve as a proxy of cognitive impairment globally, specific gait characteristics may offer further insight into specific cognitive functions.

However, it is worth noting that despite some evidence for selective associations between gait and cognition, findings across studies have been inconsistent (Morris et al., 2016). Many reported associations have not been replicated in subsequent studies, for example, the association between gait variability and visuospatial function was not found in another study in PD (Amboni et al., 2012; Lord et al., 2014). These inconsistencies are likely partly due to methodological differences across studies, such as differences in gait assessment and in cognitive test batteries (Morris et al., 2016). This limits generalizability of findings and the ability to conclusively map domain-specific associations between gait and cognition.

Furthermore, longitudinal studies are needed to better characterize the temporal relationship between gait and cognition, particularly to understand if gait can be a helpful tool for predicting future cognitive decline. In a five-year longitudinal study, specific gait factors were shown to predict decline in specific cognitive domains (Verghese et al., 2007). This study used a factor analysis approach, reducing eight gait outcomes into three gait factors reflecting pace, rhythm, and variability (Verghese et al., 2007). Their findings demonstrated that at baseline, an increase in the rhythm factor, which reflected decreased cadence, and increased step time and stance time, predicted further memory decline (Verghese et al., 2007). In contrast, a reduction in pace, which reflected decreased velocity and step length, and increased double support time, predicted declines in executive function (Verghese et al., 2007). Subjects were cognitively unimpaired at baseline, but dementia incidence was measured over the follow-up period. They reported that at baseline, increases in the rhythm and variability factors were associated with increased risk of dementia (Verghese et al., 2007).

Similarly, in a large meta-analysis by Beauchet et al, poor gait performance predicted dementia occurrence and was present three to nine years before onset of clinical dementia symptoms (Beauchet et al., 2016). Previous research has also demonstrated that gait patterns are similar in prodromal stages, for example, Allali et al demonstrated that gait differences between naMCI and aMCI is similar to gait differences between AD and non-AD dementias at mild and moderate stages (Allali et al., 2016). Mc Ardle et al demonstrated that gait was comparable between individuals with LBD and MCI due to LBD (Mc Ardle et al., 2019). Therefore, these findings highlight the potential for gait analysis as an important clinical tool for early prediction and disease monitoring in individuals at risk for dementia.

2.6 Mild Cognitive Impairment (MCI)

MCI refers to a transitional state between normal cognition and dementia (Flicker et al., 1991; Morris et al., 2001; Petersen et al., 1999, 2001). Generally, the criteria for an MCI diagnosis includes subjective complaints of cognitive impairment from the affected individual or their caregiver and objective impairment in one or more cognitive domain, while the ability to participate in activities of daily living remains preserved (Petersen, 2004). While cognitive decline may be a part of normal aging, objective cognitive impairment in MCI is beyond what is expected for an individual's age and level of education (Petersen, 2004).

Various studies have reported the prevalence of MCI in older adults to range between 12% and 18% in people over the age of 60 (Petersen, 2004). Annually, between 4% and 15% of community-dwelling individuals with MCI progress to dementia (Manly et al., 2008). The course of MCI is highly variable, with some individuals advancing to dementia, some individuals remaining stable with MCI, and some even reverting to normal cognition (Petersen, 2004; R. O. Roberts et al., 2014). However, even in individuals who revert to normal cognition, the risk of developing dementia remains elevated compared to individuals who are cognitively normal and were never diagnosed with MCI (Roberts et al., 2014). Therefore, a diagnosis of MCI at any time point is associated with increased risk for developing dementia (Roberts et al., 2014).

MCI can be subdivided into several subtypes, namely aMCI and naMCI, which can each be divided into single-domain or multi-domain subtypes, as shown in Figure 1 (Winblad et al., 2004). Single-domain amnesic MCI (SD-aMCI) is characterized by impairment in memory, while other cognitive functions remain intact (Winblad et al., 2004). Single domain non-amnesic MCI (SD-naMCI) is characterized by impairment in a non-memory cognitive domain, which may be executive function, attention, language or visuospatial function, while memory function remains intact (Winblad et al., 2004). Multi-domain MCI is characterized by impairment in more than one cognitive domain. In multi-domain amnesic MCI (MD-aMCI), memory and other non-memory domains are impaired, whereas in multi-domain non-amnesic MCI (MD-naMCI), multiple non-memory domains are impaired, while memory function is preserved (Winblad et al., 2004).

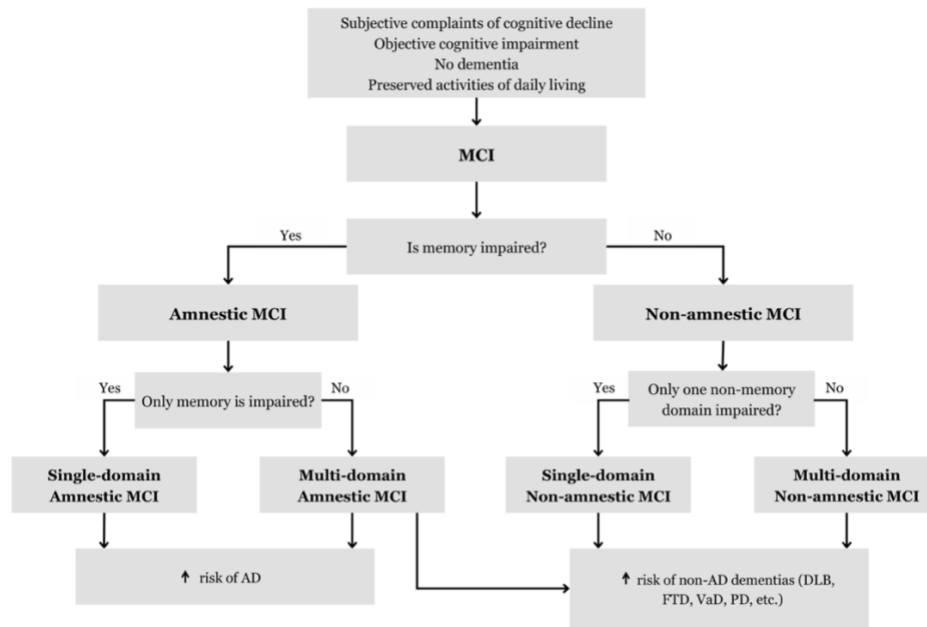


Figure 1: Flowchart of classification of MCI subtypes and risk of dementia according to subtypes. Modified from Winblad et al, 2004.

MCI subtypes also differ in terms of their risk for different dementia subtypes. Individuals with multi-domain impairment are at greater risk of developing dementia compared to those with single-domain impairment (Michaud et al., 2017). Furthermore, individuals with aMCI are more likely to progress to AD than those with naMCI (Serrano et al., 2013). Individuals with naMCI most often progress to non-AD dementias, including DLB, FTD, and VaD (Ferman et al., 2013; Yaffe et al., 2006). DLB is predominantly characterized by deficits in attention and executive functions, as well as visuospatial function (Aarsland, 2016; Mueller et al., 2017). The behavior variant of FTD involves impairment in attention and executive function, however, FTD can also present with impairments in language, known as primary progressive aphasia (Olney et al., 2017). Cognitive impairment in VaD can vary as it depends on location and extent of vascular events that cause this dementia, but individuals with VaD predominantly have impairments in executive function and attention, and less commonly present with memory impairment (Stephan et al., 2009).

2.7 Gait in MCI

Several studies have reported gait differences between individuals with MCI and healthy older adults. Some of the changes that have been reported in MCI included decreased walking speed, step length

and swing time, as well as increased step time and double support (%) compared to healthy controls (Choi et al., 2011; Cullen et al., 2019; Du et al., 2023; Goyal et al., 2019; Nascimbeni et al., 2015; Verghese et al., 2007; Yamagami et al., 2023). This research often either excludes participants with the non-amnesic subtype of MCI. Other times, the type of cognitive impairment in the MCI group is not described, which means multiple subtypes of MCI may be included in these studies and may contribute to heterogeneity in their sample.

Only few studies have directly compared gait between aMCI and naMCI subtypes (Allali et al., 2016; Beauchet et al., 2011; Montero-Odasso et al., 2014; Verghese et al., 2008). The earliest study reported that individuals with aMCI had decreased swing time, and increased stride length variability compared to individuals with naMCI (Verghese et al., 2008). They also reported decreased cadence in naMCI compared to aMCI (Verghese et al., 2008).

Another study by Beauchet et al did not find any differences between aMCI and naMCI groups. Researchers in this study only measured gait velocity and gait velocity variability, and had a smaller sample size than the first study by Verghese and colleagues, which may explain why there was a lack of differences in gait between groups (Beauchet et al., 2011; Verghese et al., 2008). Importantly, there was limited information provided about how individuals were classified into aMCI and naMCI groups in this study.

Montero-Odasso et al reported that participants with aMCI exhibited increased variability in stride time than naMCI (Montero-Odasso et al., 2014). On the other hand, Allali et al reported that participants with naMCI exhibited more reduced stride length and increased stride length variability and stride width variability than participants with aMCI (Allali et al., 2016). This contradicts findings from the first study by Verghese et al, as they found increased step length variability in aMCI relative to naMCI (Verghese et al., 2008).

It is worth noting that in the studies by Montero-Odasso and colleagues and Verghese and colleagues, participants were classified as aMCI if they had impairment in memory, regardless of whether they also had impairment in nonmemory domains, which suggests some participants had MD-aMCI in the aMCI groups (Montero-Odasso et al., 2014). The aMCI group in the study by Montero-Odasso and colleagues actually exhibited greater impairment in executive function than the naMCI group on average (Montero-Odasso et al., 2014). On the other hand, Allali et al classified individuals with concurrent memory and nonmemory domain impairments as naMCI, meaning

individuals who had MD-aMCI were grouped in the naMCI group. This may explain why the results for gait variability outcomes are conflicting between these studies (Allali et al., 2016; Montero-Odasso et al., 2014; Verghese et al., 2008).

Previous studies have also shown that gait speed slows over time in MCI (Masse et al., 2021). One study also reported increases in step length variability and step time over time in MCI subjects who also carried the apolipoprotein E polymorphism $\epsilon 4$ allele, which is a genetic risk factor for Alzheimer's disease (Masse et al., 2021; Sakurai & Montero-Odasso, 2017). However, to date, no longitudinal research has investigated how gait changes over time in different MCI subtypes.

One study by Dodge et al recruited healthy participants and used a motion capture system to measure in-home walking speed and walking speed variability for approximately two years (Dodge et al., 2012). At the end of the study, eight participants had developed aMCI and 31 developed naMCI. They found the participants that developed naMCI were more likely to have had slower walking speed at baseline (Dodge et al., 2012). Individuals who progressed to naMCI also either had the highest or lowest walking speed variability at baseline (Dodge et al., 2012). Therefore, this study provides evidence that gait has the potential to predict future progression to MCI among older adults with normal cognition. However, this study does not directly characterize longitudinal trajectories of change in gait over time in MCI subtypes, nor does it investigate if gait at baseline can predict change in cognition in MCI, which will be important steps in predicting progression to dementia from MCI.

Therefore, to date, only a few studies have aimed to identify how gait differs across MCI subtypes. There is some inconsistency between results which can be explained by differences in sample size, gait variables measured, and heterogeneity in MCI samples. Inconsistent results between these studies highlight the need for more research to better characterize differences in gait between MCI subtypes. Additionally, research with longitudinal follow-up is important to characterize change in gait characteristics over time in different MCI subtypes.

2.8 REM Sleep Behavior Disorder (RBD)

REM sleep behavior disorder (RBD) is a parasomnia, characterized by lack of muscle atonia during REM sleep, leading to dream enactment behavior (Boeve, 2010). Isolated RBD (iRBD) refers to RBD occurring in the absence of any other neurological disorder (Boeve, 2010). iRBD prevalence has been estimated to range between 0.5% to 2.01% of the general population (Kang et al., 2013; Pujol et al., 2017; Rodriguez et al., 2017). Patients with iRBD have a high risk of developing α -synucleinopathies,

namely PD, DLB, and multiple system atrophy (MSA) (Galbiati et al., 2019; Postuma et al., 2019). After 5 years from diagnosis, the estimated risk of phenoconversion to an overt α -synucleinopathy is 33.5% (Postuma et al., 2019). This risk increases to 82.4% after 10 years, and 96.6% after 14 years (Postuma et al., 2019). Majority of individuals with iRBD will phenoconvert to PD or DLB, with a small percentage developing MSA (Postuma et al., 2019; Zhang et al., 2022). In a study by Postuma and colleagues, after an average of 4.6 years of follow-up, 28% of their participants with iRBD had phenoconverted, with 52% developing PD, 43.5% developing DLB, and 4.5% developing MSA (Postuma et al., 2019).

The gold standard for diagnosis of iRBD is a history of dream re-enactment behavior, as well as confirmation with a polysomnography (PSG) that demonstrates REM sleep without atonia, or increased muscle tone during REM sleep, measured using electromyography (Boeve, 2010). However, as access to PSG can be limited by cost or availability of sleep clinics in a given region, several scales have been developed to screen for clinically probable RBD (pRBD), such as the Mayo Sleep Questionnaire (MSQ). This questionnaire is created to be completed by an individual's bed partner. The first question asks if the bed partner has witnessed dream enactment behavior from the patient (Boeve et al., 2013). This specific question has been validated for the diagnosis of pRBD, as it is adequately sensitive (100%) and specific (95%) (Boeve et al., 2013).

2.9 Impact of RBD on Gait

With the potential development of neuroprotective treatments, identifying clinical features that can allow for tracking subtle changes in prodromal disease and thereby monitoring risk of phenoconversion in iRBD is important (Postuma, 2022). Recently, research has demonstrated that individuals with iRBD exhibit declines in motor performance compared to healthy controls, prior to the onset of parkinsonian symptoms (Barber et al., 2017; Del Din et al., 2020; Elasar, Hameed, & Ehgoetz Martens, 2025; Fereshtehnejad et al., 2019; McDade et al., 2013; Postuma et al., 2006, 2009, 2019). For example, studies have demonstrated that individuals with iRBD score higher on the Unified Parkinson's Disease Rating Scale-III (UPDRS-III), take longer to complete the Timed Up-and-Go (TUG), and perform worse on the Alternate Tap test and Purdue Pegboard test, than healthy controls without RBD (Barber et al., 2017; Elasar, Hameed, & Ehgoetz Martens, 2025; Fereshtehnejad et al., 2019; Postuma et al., 2006, 2009, 2019). These motor deficits were useful in

predicting future phenoconversion up to nine years before diagnosis with PD or DLB (Fereshtehnejad et al., 2019).

While the TUG is reported to be less sensitive and accurate at predicting phenoconversion compared to other methods of motor assessment, particularly the Alternate Tap Test, this may be due to limitations of assessing gait performance through timed walks over a short distance (Fereshtehnejad et al., 2019). Zatti et al demonstrated that assessing turning performance during the TUG using inertial sensors revealed subtle changes that are not captured by simply measuring the time it takes to complete the TUG (Zatti et al., 2024). This highlights the importance of considering more quantitative methods of measuring gait in RBD, as they may better predict subclinical changes in motor function prior to onset of parkinsonian symptoms, compared to traditional clinical assessments, such as the TUG (Elasfar, Hameed, & Ehgoetz Martens, 2025).

Consistently, research has also highlighted subtle changes in gait in people with iRBD compared to healthy controls (Del Din et al., 2020; Ehgoetz Martens et al., 2019; McDade et al., 2013). For example, Del Din et al used tri-axial accelerometers worn by participants on the fifth lumbar vertebrae over seven days to quantify free-living gait outcomes in individuals with iRBD compared to healthy controls (Del Din et al., 2020). Their findings showed that participants with iRBD walked slower with decreased gait velocity and cadence, or increased step time, swing time, and stance time, compared to the control group (Del Din et al., 2020). Swing time was also found to be the strongest discriminator of iRBD from HCs (Del Din et al., 2020).

In another study, McDade et al measured gait using an instrumented walkway, and demonstrated that the presence of pRBD in CU individuals was associated with reduced cadence, velocity, stride length, and increased variability of stride time, swing time and double support time (McDade et al., 2013). It is worth noting that participants with pRBD in this study had significantly worse performance on language and visuospatial function assessments than participants without pRBD, however it was within normal values, meaning not impaired enough to be considered MCI, and MMSE scores were normal (McDade et al., 2013).

Ehgoetz Martens et al investigated gait changes in individuals with iRBD compared to healthy controls under single-task, dual-task and fast walking conditions. While they did not report significant differences between individuals with iRBD from healthy controls under normal task conditions, they found that when dual-tasking, healthy controls widened their steps, but individuals

with iRBD did not. This is consistent with parkinsonian gait, as it is typically characterized by narrower steps, possibly due to rigidity and reduced trunk motion, or because anticipatory postural adjustments are diminished in PD, so a narrow-based gait may make gait initiation easier in people with PD (Nonnekes et al., 2018; Pistacchi et al., 2017).

To date, research quantifying the impact of RBD on motor outcomes, including gait has only been conducted in cognitively unimpaired individuals. No research has characterized how the presence of RBD impacts motor function in individuals with cognitive impairment, particularly MCI. This is important given its estimated that individuals with RBD are at increased risk of developing MCI (Boot et al., 2012; Gagnon et al., 2010). In one study, 50% of individuals with iRBD also had concurrent MCI, compared to 8% of healthy controls (Gagnon et al., 2009). Additionally, individuals with iRBD and MCI are at risk of rapid phenoconversion to PD and DLB (Arnaldi et al., 2021). Despite this clinical significance, to date, no studies have investigated how gait is impacted in individuals with comorbid RBD and MCI.

Chapter 3: Objectives and Hypotheses

3.1 Gaps and Rationale

Despite growing evidence that gait analysis may be a helpful early marker for cognitive decline and dementia risk, several key gaps remain in the existing literature.

Firstly, no studies to date have comprehensively compared gait profiles across the four MCI subtypes of SD-aMCI, MD-aMCI, SD-naMCI, and MD-naMCI. Prior research looking at gait in MCI has mostly focused on aMCI, excluding naMCI subtypes, or providing no characterization of MCI subtypes. Existing studies that have compared gait between MCI subtypes characterized MCI as aMCI and naMCI, without considering how the presence of single- or multi-domain impairment may differently impact gait outcomes (Allali et al., 2016; Beauchet et al., 2011; Montero-Odasso et al., 2014; Verghese et al., 2008). Instead, groups are typically collapsed into aMCI and naMCI.

As described before, in prior studies comparing gait between aMCI and naMCI, classification of individuals with multi-domain impairment is different across studies. In two studies they were considered part of the aMCI group, and in one study they were grouped in the naMCI group (Allali et al., 2016; Montero-Odasso et al., 2014; Verghese et al., 2008). One study did not describe whether individuals with multi-domain impairment were included, and if so, whether they were subtyped into aMCI or naMCI (Beauchet et al., 2011). This may explain why results of these studies are contradictory and inconsistent. Multi-domain impairment may impact gait more than single-domain impairment due to more widespread cognitive impairment and greater dementia risk, highlighting the importance of including these subtypes separately (Michaud et al., 2017). Therefore, a comprehensive comparison of gait across all four MCI subtypes is needed to better describe how gait is impacted in each of these subtypes.

Furthermore, while these studies compared gait changes between aMCI and naMCI, there is a lack of longitudinal research examining how gait changes over time within these subtypes. Existing longitudinal research has previously shown that gait slows over time in MCI, regardless of subtype, however, prior research has not characterized how gait changes over time across subtypes in MCI (Masse et al., 2021).

In addition, the influence of comorbid RBD on gait in MCI has yet to be investigated. As discussed previously, the risk of developing MCI is increased in individuals with pRBD, highlighting

that comorbidity of these conditions is common, and associated with a higher risk of early phenoconversion (Arnaldi et al., 2021; Gagnon et al., 2009). As it has been shown that the presence of RBD in cognitively normal populations is associated with subtle changes in gait, prior to phenoconversion, it would be important to characterize how RBD presence affects gait in MCI and its subtypes (Del Din et al., 2020; Elasfar, Hameed, Boeve, et al., 2025; McDade et al., 2013).

Moreover, while existing studies have reported associations between specific gait characteristics and cognitive domains, for example, variability with executive function and attention, most of this evidence is from cross-sectional studies (Morris et al., 2016). Therefore, there is limited longitudinal research exploring domain-specific associations between gait and cognition. Research by Verghese et al has demonstrated that baseline gait factors can predict future change in specific cognitive domains and incidence of dementia in healthy older adults, but these associations have not been explored in people with MCI (Verghese et al., 2007). Understanding whether baseline gait can predict future cognitive function over time in a domain-specific manner has important implications for predicting and monitoring dementia risk in individuals with MCI.

To summarize, the literature gaps that will be addressed by this current study include:

- i. Research comparing gait across MCI subtypes has yielded inconsistent results, highlighting the need for further investigation, particularly by comprehensively subtyping MCI into four domains, namely: SD-aMCI, MD-aMCI, SD-naMCI, and MD-naMCI.
- ii. There is a lack of longitudinal designs to characterize changes in gait in different MCI subtypes over time.
- iii. There is a lack of studies exploring how gait is impacted in people who have comorbid RBD and MCI, despite the risk of early phenoconversion.
- iv. There is limited longitudinal research investigating selective associations between gait outcomes and cognitive function over time, particularly investigating whether gait can predict change in cognitive performance over time in people with MCI.

By addressing these limitations, this work will help advance the current understanding of the relationship between gait and cognition, as well as help enhance early prediction and risk monitoring strategies for dementia using gait analysis in people with MCI.

3.2 Objectives and Hypotheses

Therefore, the current study aims to a) compare gait characteristics across different MCI subtypes, b) characterize change in gait over time in MCI subtypes, c) understand how gait is influenced by the presence of RBD in people with MCI, and d) evaluate if baseline gait can predict future cognitive decline in MCI. Therefore, the main objectives and hypotheses are as follows:

Objective 1: Compare spatiotemporal gait characteristics measured using a pressure sensor walkway during single-task walking in five groups: CU, SD-aMCI, MD-aMCI, SD-naMCI, and MD-naMCI.

Hypothesis 1: It is hypothesized that, compared to CU individuals, individuals with MCI will exhibit decreased stride velocity, decreased step length, greater step and swing time, and greater double support (%). Furthermore, individuals with non-amnesic impairment (SD-naMCI, MD-aMCI, MD-naMCI) will also have greater gait variability than CU individuals, and individuals without non-amnesic impairment (SD-aMCI). Within MCI subtypes, participants with multi-domain cognitive impairment will show slower gait speed, shorter steps, longer step and swing time, greater double support (%), and greater gait variability than people with single-domain impairment. The rationale for this hypothesis is based on findings from studies comparing gait outcomes in people with AD and non-AD dementias, particularly DLB and LBD. Research has shown that people with dementia have slower gait, decreased step length, greater step time, and greater double support (%) than CU individuals, but that greater variability is only found in people with DLB (Elasfar, Hameed, Boeve, et al., 2025; Mc Ardle et al., 2019, 2020). Furthermore, participants with DLB exhibit more pronounced differences in these gait characteristics from CU individuals than participants with AD (Elasfar, Hameed, Boeve, et al., 2025; Mc Ardle et al., 2019, 2020). Given that individuals with aMCI typically progress to AD, while individuals with naMCI typically progress to non-AD dementias, particularly DLB, it is hypothesized similar gait changes will be seen in these MCI subtypes (Petersen, 2004; Winblad et al., 2004). Furthermore, individuals with multi-domain impairment in cognition have greater risk of progression to dementia, so it is hypothesized gait changes will be more pronounced in these subtypes compared to people with single-domain MCI subtypes (Michaud et al., 2017).

Objective 2: Characterize change in gait outcomes over an average follow-up of 16.8 months between five groups: CU, SD-aMCI, MD-aMCI, SD-naMCI and MD-naMCI.

Hypothesis 2: As previous research has reported that gait slows over time in people with MCI, it is hypothesized that all MCI groups will exhibit slower gait from baseline to follow-up, as well as reductions in step length, increases in step time, swing time, and double support (%). Additionally, these changes in gait will be more pronounced in individuals with multi-domain cognitive impairment compared to single-domain impairment (Masse et al., 2021; Michaud et al., 2017). Gait variability is predicted to increase over time in individuals with non-amnestic impairment. This is based on findings evidence of greater gait variability being reported in non-AD dementias (Elasfar, Hameed, Boeve, et al., 2025; Mc Ardle et al., 2019, 2020).

Objective 3: Examine how the presence of pRBD in individuals with MCI impacts gait outcomes.

Hypothesis 3: It is predicted that individuals with MCI and pRBD, particularly groups with non-amnestic impairment, will exhibit early signs of parkinsonian gait, specifically, slower gait, decreased step length and stride width, greater step time, swing time, and double support (%), as well as greater gait variability than people with MCI without pRBD (Galna et al., 2015; Peterson & Horak, 2016). As discussed, individuals with pRBD are likely to develop α -synucleinopathies, particularly PD or DLB, but subtle changes in motor function have been reported to appear in RBD prior to phenoconversion (Del Din et al., 2020; Ehgoetz Martens et al., 2019; Fereshtehnejad et al., 2019; McDade et al., 2013; Postuma et al., 2006, 2009, 2019). The co-occurrence of MCI in these participants indicates they are at risk of early phenoconversion. As cognitive impairment in DLB and PD is commonly in non-amnestic domains, people with non-amnestic impairment, particularly in multiple domains, may be closer to phenoconversion, so their motor function may be more impacted (Aarsland, 2016; Arnaldi et al., 2021).

Objective 4: Assess if gait characteristics at baseline can predict future decline in attention, memory, language, visuospatial function, and global cognition in MCI.

Hypothesis 4: Given the exploratory nature of this objective and the use of a principal component analysis approach (described in Section 4.6.2.) to derive gait domains, a priori hypotheses about specific gait factors were limited. However, based on previous literature mapping associations between specific gait features and cognitive functions, it was anticipated that a) slower “pace”, or reduced stride velocity and increased step length, would

predict decline in global cognition, b) increased gait variability would predict decline in attention and visuospatial function, c) timing-related gait features (e.g., step time) would predict memory decline, and d) postural stability-related gait features (e.g. stride width and double support (%)) would predict decline in executive function and visuospatial function (Morris et al., 2016; Verghese et al., 2007).

Chapter 4: Methods

This project used data collected in the Mayo Clinic Study of Aging and Alzheimer's Disease Research Center in Olmstead County, MN, USA (Roberts et al., 2008). Briefly, subjects were randomly recruited from residents of the Olmstead County using an age- and sex- stratified random sampling strategy. The MCSA study protocols have been approved by the Institutional Review Board of the Mayo Clinic and Olmstead County in Rochester, MN. All participants have provided written informed consent. All participants have provided written informed consent. The University of Waterloo Human Research Ethics Committee approval permitted secondary data analysis of data collected in the Mayo Clinic Study of Aging.

4.1 Participant Recruitment

The Mayo Clinic Study of Aging identified participants from the Rochester Epidemiology Project, which is a medical records-linkage system that covers all medical providers in the Olmstead County (Mayo Clinic and Olmstead Medical Center, predominantly) (Roberts et al., 2008). Using this system, researchers were able to identify all Olmstead County Residents aged 70 to 89 years old on October 1st, 2004, who had been in contact with a medical provider in the past three years. After removal of duplicates and individuals with home addresses outside of Olmstead County, a total of 9,953 individuals were identified for random sampling (Roberts et al., 2008).

Participants were selected using a random stratified-sampling method across four strata: women aged 70 to 79, men aged 70 to 79, women aged 80 to 89, and men aged 80 to 89. In 2012, participant recruitment was extended to include participants aged 50 years and older, and participants over 90 years old (Roberts et al., 2008).

Participants were first contacted using a letter of invitation by mail, which described the purpose of the study. Participants that did not refuse to participate following the letter were contacted by telephone. Participants who expressed interest in participation were invited to complete an in-clinic evaluation. Each participant also had to identify an informant that could join them in order to provide information about their cognitive function, and complete informant-based assessments, including the CDR, MSQ, and Functional Assessments Questionnaire (Boeve et al., 2013; Pfeffer et al., 1982; Roberts et al., 2008).

Several strategies were used to promote study participation, including advertisements in the local newspaper, on the radio, and in posters placed in the community, and presentations on radio stations and at several community events (Roberts et al., 2008).

4.2 Participants

This research included participants diagnosed with MCI and a CU control group. Participants with MCI were included if they met the following inclusion criteria:

- i. Diagnosis of MCI and an MCI subtype classification
- ii. Must have at least one follow-up visit with a diagnosis of MCI

Participants were excluded if they have no gait data available at baseline or any follow-up visits, or if their diagnosis of MCI changes at their second follow-up visit (i.e., they revert to normal cognition status or advance to dementia or any neurodegenerative condition).

CU individuals were matched to participants with MCI by sex, age (± 5 years), education (± 2 years). Sex was prioritized first, followed by age, and education. CU individuals were included if they met the following criteria:

- i. CDR score equal to 0, in order to exclude subjective cognitive impairment
- ii. No objective impairment in any cognitive domain, which is defined by a score above -1.5 SD of the age-appropriate mean for a given cognitive domain (i.e. cognitive function is still intact for that domain.)
- iii. Must have at least one follow-up visit

Participants in the CU group were excluded if they developed MCI, dementia, or any other neurodegenerative condition within follow-up visits.

4.3 Clinical Evaluation

Diagnostic classification was based on data collected from three coordinated evaluations, one by a nurse or coordinator, a neurologist/physician, and neuropsychologist/psychometrist (Roberts et al., 2008).

The nurse/coordinator assessment involved a detailed review of medical and family history. Demographic characteristics were also collected, including date of birth, marital status, education, ethnicity, residence, and a list of their current medications. Current or previous symptoms of anxiety

and depression were assessed using the Patient Health Questionnaire, the Beck Depression Inventory and the Beck Anxiety Inventory (Beck et al., 1961, 1988; Kroenke et al., 1999). Diagnoses of these psychiatric conditions were confirmed by a physician. Review of their medical history involved reporting all prior medical diagnoses, including diabetes, hypertension, heart disease, stroke, and/or cancer. Self-reported medical history was corroborated using information from the records-linkage system. Blood pressure was measured twice using a sphygmomanometer. Height was measured using a stadiometer. Informants of study participants completed the CDR, MSQ, and Functional Activities Questionnaire (Boeve et al., 2013; Morris, 1997; Pfeffer et al., 1982). To review family medical history, participants were asked to list all of their first-degree relatives, and if these relatives had been diagnosed with MCI, dementia, AD, PD, FTD, and amyotrophic lateral sclerosis (Roberts et al., 2008).

The neurological evaluation was performed by a physician (neurologist, psychiatrist, or geriatrician). The physician administered the Short Test of Mental Status to identify any signs of cognitive impairment (Voss & Das, 2025). They diagnosed dementia, depression, anxiety, and/or alcoholism using the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (American Psychiatric Association, 1994). They also administered a modified Unified Parkinson's Disease Rating Scale to identify subjects with PD (Roberts et al., 2008).

Finally, a neuropsychological evaluation was conducted by a psychometrist. This evaluation included subsets of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the Wechsler Memory Scale-Revised (WMS-R), as well as tests to assess four cognitive domains, namely: executive function (Trail Making Test B and Digit Symbol Substitution Test), language (Boston Naming Test and Category Fluency), memory [Logical Memory-II (delayed recall), Visual Reproduction-II (delayed recall), Auditory Verbal Learning Test (delayed recall)] and visuospatial function (Picture Completion and Block Design) (Ivnik, Malec, & Smith, 1992; Ivnik, Malec, Smith, et al., 1992b, 1992a; Kaplan et al., 1982; Lucas et al., 1998; Reitan, 1958; Roberts et al., 2008; Wechsler, 1987a, 1987b). Raw scores on each of these tests were transformed into age- and education-adjusted scores using Mayo's Older American Normative Studies (Roberts et al., 2008). Domain scores were obtained by adding the adjusted and scaled scores of the tests for each domain to allow for comparison across domains. A score for global cognition was created with the z-transformation of the average of the four domains. This process is described in detail in Appendix A:

Section A1. Final decisions about impairment in any cognitive domain were made by consensus agreement between the study evaluators (Roberts et al., 2008).

Following all evaluations, a panel consisting of the study physicians, nurses and neuropsychologists reviewed and discussed all the data for each subject to reach a diagnosis of CU, MCI, or dementia. The committee examined scores on the CDR, neuropsychological battery results, clinical examination reports, and the Short Test of Mental Status results, in order to determine diagnosis. If persons had no subjective or objective cognitive impairment (based on Petersen et al criteria for identifying MCI from normal aging), they were diagnosed as CU (Petersen, 2004). Subjects who met the DSM-IV criteria for dementia were enrolled as participants with dementia (American Psychiatric Association, 1994; Roberts et al., 2008).

Subjects who did not have dementia and were not cognitively normal were classified as having MCI if they met previously published criteria for MCI (Petersen, 2004). Namely, they had

- a. Subjective cognitive decline, expressed by a physician, informant, participant or nurse
- b. Cognitive impairment in at least one of the following domains: attention, memory, language, visuospatial function
- c. No functional impairment, based on the Functional Activities Questionnaire
- d. No dementia, based on the DSM-IV criteria for dementia

They were further classified as having aMCI or naMCI, as having single- or multi-domain MCI based on previously published criteria for MCI subtypes (Petersen, 2004). Subjects classified as having aMCI had cognitive impairment in memory domain. They were classified as SD-aMCI if only memory was impaired, and MD-aMCI if memory and at least one other cognitive domain was impaired. Subjects that had no memory impairment but had MCI were classified as having naMCI. They were classified as SD-naMCI if only one non-memory was impaired, and MD-naMCI if more than one nonmemory domain was impaired (Petersen, 2004; R. O. Roberts et al., 2008).

4.4 Cognitive Outcomes

Cognitive outcomes in the study included domain-level z-scores for attention, language, memory and visuospatial function, as well as an average score of global cognition (Roberts et al., 2008). The detailed process of how these scores were derived is described in the previous section, Section 4.3. Appendix A: Section A1 details how z-scores for each domain were derived (Roberts et al., 2008).

4.5 Gait Outcomes

Gait parameters were assessed using a GAITRite® pressure sensor carpet (CIR Systems Inc., Havertown, PA) that was 5.6 m in length and 0.9 m in width. Subjects were instructed to walk at their normal pace, without walking aids, initiating and terminating their walk 1m before the carpet. Subjects completed a total of two passes on the carpet, walking down the carpet, completing a turn off of the carpet, and walking back down the carpet, returning to starting position. Partial footfalls were removed from the analyzed steps (Roberts et al., 2008).

Protokinetics Movement Analysis Software (PKMAS) used to export gait data from the GAITRite carpet (ProtoKinetics, 2012). Table 1 summarizes all gait outcomes of interest in this study and how they are extracted through PKMAS. All gait outcomes were averaged from both legs. Gait variability outcomes were computed using standard deviation, which is calculated with the following equation:

$$\text{Standard deviation} = \sqrt{\frac{1}{N-1} \sum_{i=1}^N (X_i - \bar{X})^2}$$

Where, N = number of data samples, $\bar{X}$ = mean of data samples, and X_i = a given data sample.

Table 1: Gait outcomes of interest, as defined by PKMAS

Gait Outcome	Definition in PKMAS Software
Step time (s)	Period of time taken for one step measured from first contact of one foot to the first contact of the other foot, measured in seconds.
Step length (cm)	The distance between corresponding successive heel points of opposite feet, measured parallel to the direction of progression for the ipsilateral stride, measured in cm.
Stride velocity (cm/s)	The ratio of stride length to stride time, measured in cm/sec.
Stride width (cm)	The perpendicular distance between the line connecting the two ipsilateral foot heel contacts, measured in cm.
Swing time (s)	The period of time the foot is not in contact with the ground, measured in seconds.
Total double support (%)	The sum of all periods when both feet are in contact with the ground during stance phase, measured as a percentage of the gait cycle time*.
Step time variability (s)	Standard deviation** of step time (s).
Step length variability (cm)	Standard deviation** of step length (cm).
Stride velocity variability (cm/s)	Standard deviation** of stride velocity (cm/s).
Stride width variability (cm)	Standard deviation** of stride width (cm).
Swing time variability (s)	Standard deviation** of swing time (s).

All definitions were obtained from the PKMAS Manual (ProtoKinetics, 2012).

* Gait cycle time, also known as stride time, is the period of time from first contact of one foot, to the following first contact of the same foot (s).

** Standard deviation refers to the amount of dispersion in the samples for the selected measure and is calculated using the equation described above.

Asymmetry of step time, step length, stride width, stride velocity and swing time were calculated using the asymmetry index formula (Robinson et al., 1987). Asymmetry outcomes were not directly compared between groups, however models comparing gait variability were adjusted for asymmetry measures.

4.6 pRBD Status

pRBD status was determined from the MSQ, which was performed by a bedpartner of each participant. Specifically, the first question of the MSQ was used. This question states “Have you ever seen the patient appear to “act out his/her dreams” while sleeping? (punched or flailed arms in the air, shouted or screamed).” If their bed partner answered “yes” to this question, a participant was determined to have pRBD (Boeve et al., 2013).

4.7 Data Analysis

Statistical analyses for each objective in this study are outlined below. All analysis was performed in R Studio (Version 2025.05.1) (R Core Team, 2024).

4.7.1 Clinical and Demographic Characteristics

Clinical and demographic characteristics (sex, age, height, education, MMSE, and CDR) were compared between MCI groups and between individuals with and without pRBD. Sex was compared between groups and pRBD status with a chi-square test. CDR scores were compared between groups, and pRBD status with Kruskal-Wallis tests and Wilcoxon rank-sum tests, respectively. Two-way ANOVAs were used to compare age, education, height, follow-up durations and MMSE data across groups and pRBD status. Residuals were screened for normality using Shapiro-Wilk tests, as well as visual inspection of histograms and QQ-plots. Homogeneity of variances was assessed using Levene’s test. Aligned rank transform ANOVAs were used if assumptions were violated (Wobbrock et al., 2011). Significant main and interaction effects were investigated using pairwise comparisons of estimated marginal means (EMMs) using the ‘emmeans’ package (Lenth et al., 2025).

4.7.2 Objectives 1, 2, 3

The goal of objectives 1 and 2 was to explore how spatiotemporal gait outcomes differ between CU individuals and MCI subtypes and characterize change in gait over time in these groups. It was hypothesized that individuals with MCI will walk slower than CU individuals, and therefore exhibit decreased stride velocity, and step length, and greater step time, swing time, and double support (%). Within the MCI group, the MD-aMCI and MD-naMCI group will walk slower with more variability than the SD-aMCI and SD-naMCI group. Gait variability will also be greater in groups with non-amnesic impairment compared to CU individuals, and SD-aMCI. Over time, both MCI and CU groups will exhibit slowing of gait, however, this will be more apparent in MCI, particularly in the

multi-domain MCI groups. Gait variability will increase over time in groups with non-amnestic impairment relative to CU individuals and individuals with amnestic impairment.

Objective 3 investigates if presence of pRBD also impacts spatiotemporal gait outcomes in MCI. It was hypothesized that the presence of pRBD will be associated with presence of early parkinsonian gait features, particularly in individuals with non-amnestic impairment, such that these participants will exhibit slower gait, decreased step length and stride width, greater step time, swing time, and double support (%), as well as greater gait variability than people with MCI without pRBD.

To test these hypothesis, linear mixed models were used to investigate the effect of MCI subtype, pRBD status and time on the gait outcomes of interest using the lme4 package (Bates et al., 2015; Kuznetsova et al., 2017). MCI subtype classification (group), pRBD status and time (or visit), and their interaction (group * pRBD status * visit) were entered as fixed effects in each model. Given that MCI subtype classification can change over time as cognitive function fluctuates, MCI subtype was treated as a time-varying variable in the models to account for within-subject changes over time. Models were adjusted for covariates including age, sex, height, years of education, and follow-up duration. To isolate gait variability, models for each of the variability measures were further adjusted for stride velocity, and corresponding mean and gait asymmetry index scores (i.e. for step time variability, models were adjusted for all covariates, as well as stride velocity, mean step time and step time asymmetry, calculated using the asymmetry index equation (Robinson et al., 1987)). A random intercept was included for each participant to account for repeated measures.

Prior to interpretation, assumptions of normality and homoscedasticity were confirmed by visual examination of histograms, Q-Q plots, and scatterplots of the model residuals. Outliers were only removed if they were due to an error in data collection (e.g. negative gait measures, double support (%) values $\geq 100\%$). Otherwise, they were kept in the data. If assumptions were violated, e.g. non-normal residuals or highly influential points, robust linear mixed models were used, as they down-weight extreme outliers and provide effect estimates that are robust to assumption violations (Koller, 2016). This was done using the robustlmm package in R (Koller, 2025). Statistical significance and direction of effects did not change between standard and robust linear mixed models, so estimates from the standard models were retained, as this suggests results are robust to assumption violations.

Type III ANOVA tables were computed for each model using the lmerTest package, which utilizes Satterthwaite approximation to calculate degrees of freedom for the fixed effects. Significant main and interaction effects were explored further using post-hoc pairwise comparisons of EMMs with Bonferroni correction using the emmeans package (Lenth et al., 2025).

As the linear mixed models included interaction terms, fixed effect coefficients in the model represented conditional effects, meaning the effect of each variable (diagnosis, time, or pRBD status), within the reference group of the other interacting variables (e.g., for pRBD, the fixed effect coefficient describes the effect of pRBD within the CU group at baseline, which may not capture the overall effect across groups and timepoints). Therefore, to assess the marginal main effects, results of the Type III ANOVAs were used, in conjunction with post-hoc pairwise comparisons of EMMs to confirm group differences.

4.7.3 Objective 4

The goal of objective 3 was to assess if deficits in specific gait characteristics at baseline can predict change in cognition over time in MCI. It was hypothesized that baseline gait components will selectively predict change in performance in different cognitive domains over time in individuals with MCI. Only the participants with MCI were included in this analysis. Cognitive assessment results were only available for Mayo Clinic participants, not participants from the Alzheimer's Disease Research Center, leading to a smaller sample of participants in this analysis.

To test these associations, a principal component analysis was first conducted to derive gait factors, followed by linear mixed models to evaluate associations between baseline gait outcomes and longitudinal changes in cognitive domains.

The principal component analysis was conducted to reduce and address multicollinearity of gait outcomes. The number of components retained was determined using parallel analysis, which compares observed eigenvalues to those obtained from random data. An orthogonal (varimax) was applied to reduce multicollinearity and minimize cross-loadings in order to improve interpretability. Each participant received a component score for each of the retained gait components, which were used as the predictors in the linear mixed models. This was done using the psych and paran packages in R (Dinno, 2025; Revelle, 2025).

Linear mixed models were used to evaluate whether the gait factors at baseline predicted change in cognitive performance, for each domain of memory, attention, language and visuospatial function, as well as global cognition using the lme4 and lmerTest packages (Bates et al., 2015; Kuznetsova et al., 2017). In each model, the dependent variable was the cognitive domain z-score, evaluated at baseline and follow-up. Each model included the following fixed effects: time (baseline vs. follow-up), gait components, and their interaction (e.g., time * (component 1 + component 2 + component 3)). Covariates included in the model were age, sex, height, follow-up duration, MCI subtype classification and pRBD status. It is important to note that the domain-specific cognitive z-scores are already adjusted for age and education based on normative data, as described previously in Section 4.3. Based on this, education was not included in the model as a covariate, as its effects on cognition were already adjusted for in the process of cognitive domain score calculation. However, age was still retained as a covariate to account for its potential confounding effects on the gait factors, as gait is affected by age.

Prior to interpretation of results, assumptions of normality, linearity and homoscedasticity were assessed by visual examination of histograms, Q-Q plots, and scatterplots of the model residuals. Gait factors were not collinear as assessed using variance inflation factors (VIF), where $VIF > 10$ was considered problematic. Cook's distance was calculated and plotted to identify any highly influential points (Cook's distance > 0.5) (Cook, 2025). These points were only removed if they were due to an error in data collection (e.g. negative gait measures, double support (%) values $\geq 100\%$). To determine if any potentially highly influential points (that were not from data collection errors) influenced model results, sensitivity analyses were conducted by repeating the models with these points excluded (Mowbray et al., 2022). Statistical significance and direction of main and interaction effects did not change, suggesting models were robust to the influence of potential outliers (Mowbray et al., 2022).

Significant main and interaction effects were explored further using EMMs (Lenth et al., 2025). The parameters package was also used to obtain standardized coefficients for each model (Lüdtke et al., 2025).

Chapter 5: Results

5.1 Results

A total of 764 participants were included in this study (382 MCI, 382 CU). In total, 450 participants with MCI had gait data available and at least one follow-up visit in the dataset. 55 participants were excluded because they reverted to normal cognition, or had a diagnosis of CU, after follow-up. Twelve more participants were excluded because they received a diagnosis of PD or dementia (AD, DLB, VaD, FTD, or other) after follow-up. One more participant was excluded due to invalid gait data (negative swing time, double support (%) greater than 100%), which resulted in 382 participants with MCI included for this study, as well as 382 age-, sex- and education-matched CU participants.

The number of participants in each group is in Table 1. As mentioned previously, MCI subtype classification was treated as a time-varying variable in the linear mixed models to account for the fact that participants transitioned between subtypes over time.

Table 2: Number of participants in each group at baseline and follow-up.

	CU	SD-aMCI	SD-naMCI	MD-aMCI	MD-naMCI
Participants at Baseline (n)	382	180	48	134	20
Participants at Follow-up (n)	382	151	45	160	26

Abbreviations: CU = cognitively unimpaired; SD-aMCI = single-domain amnesic mild cognitive impairment; SD-naMCI = single-domain non-amnesic mild cognitive impairment; MD-aMCI = multi-domain amnesic mild cognitive impairment; MD-naMCI = multi-domain non-amnesic mild cognitive impairment.

Participant demographic and clinical characteristics for the full sample of MCI and CU participants are presented in Table 2. The table also summarizes the number of participants with pRBD in each of the groups. Main effects of group were found for CDR ($H_{(4)} = 467.45$, $p < 0.001$), and MMSE ($F_{(1,754)} = 60.886$, $p < 0.001$), as well as education ($F_{(1,754)} = 16.326$, $p < 0.001$). MMSE scores were decreased in all MCI groups compared to CU ($p < 0.001$ for all). CDR scores were decreased in CU compared to all MCI groups ($p < 0.001$ for all). The SD-aMCI group had greater years of education than the MD-aMCI group ($p = 0.03$). No other differences in clinical and demographic information were found between group.

Table 3: Demographic and clinical information for all participants by group at baseline.

	CU (n = 382)	SD-aMCI (n = 180)	SD-naMCI (n = 48)	MD-aMCI (n = 134)	MD-naMCI (n = 20)
Age	76.30±8.23	77.36±8.03	75.44±7.61	76.03±8.88	73.02±7.31
Sex (%F)	40.05%	48.34%	43.75%	38.06%	40.00%
Education (years)	14.39±2.71	14.72±2.70	13.62±3.17	13.80±3.12 ^A	14.25±3.71
CDR	0 (0, 0)	0.5 (0, 1) ^C	0.5 (0, 0.5) ^C	0.5 (0, 1) ^C	0.5 (0, 0.5) ^C
MMSE	28.60±1.17	26.55±1.83 ^C	25.91±1.95 ^C	25.19±1.94 ^C	25.80±2.26 ^C
Average follow-up (years)	1.38±0.34	1.44±0.44	1.32±0.37	1.38±0.40	1.49±0.31
Height (cm)	169.78±13.84	166.61±23.73	165.09±26.45	165.24±26.80	170.49±8.66
Participants with pRBD (n) (%)	36 (9.42%)	20 (11.11%)	8 (16.67%)	38 (28.36%)	7 (35.0%)

Data reported as mean ± standard deviation, except sex reported as %F, and CDR reported as median (range). ^C = different from CU, ^A = different from SD-aMCI.

Abbreviations: CU = cognitively unimpaired; SD-aMCI = single-domain amnesic mild cognitive impairment; SD-naMCI = single-domain non-amnesic mild cognitive impairment; MD-aMCI = multi-domain amnesic mild cognitive impairment; MD-naMCI = multi-domain non-amnesic mild cognitive impairment; F = female; CDR = Clinical Dementia Rating scale; MMSE = Mini-Mental State Examination; pRBD = probable REM Sleep Behavior Disorder

Table 3 summarizes participant demographic and clinical characteristics for participants subdivided by pRBD status. Significant main effects of pRBD were observed for age ($F_{(1,754)} = 14.59$, $p < 0.001$), education ($F_{(1,754)} = 16.33$, $p < 0.001$), and height ($F_{(1,754)} = 10.552$, $p = 0.001$), indicating that individuals with pRBD were younger, had taller stature, and completed more years of education overall. Additionally, there was a greater distribution of males in participants with pRBD compared to participants without pRBD ($X^2 = 18.108$, $p < 0.001$). There were no interaction effects of group and pRBD status on any covariates. Table B1 in Appendix B, Section B1 provides a summary of participant demographics and clinical characteristics, subdivided by group and by pRBD status.

Table 4: Demographic and clinical information for all participants by pRBD status.

	pRBD–	pRBD+
Age (years)	78.24 ± 8.04	74.81 ± 8.76*
Sex (F)	43.20%	21.10%*
Education (years)	14.16 ± 2.77	15.19 ± 3.19*
CDR	0 (0, 1)	0.5 (0, 1)
MMSE	26.98 ± 3.05	26.89 ± 2.41
Follow-up duration (years)	1.39 ± 0.37	1.43 ± 0.52
Height (cm)	167.32 ± 19.12	172.95 ± 8.52*

Data reported as mean ± standard deviation, except sex reported as %F, and CDR reported as median (range). * = different from pRBD-. Abbreviations: pRBD- = without probable REM sleep behavior disorder; pRBD+ = with probable REM sleep behavior disorder. F = female; CDR = Clinical Dementia Rating scale; MMSE = Mini-Mental State Examination; pRBD = probable REM Sleep Behavior Disorder

Table 4 summarizes participant demographics and clinical characteristics for the subset of participants with MCI included in the analysis for objective 4. As described in the methods section, full cognitive domain z-scores were not available for participants from the Alzheimer's Disease Research Center, so only 322 participants from the Mayo Clinic were included. Of these participants, 155 had SD-aMCI, 40 had SD-naMCI, 110 had MD-aMCI, and 17 MD-naMCI.

Table 5: Demographic and clinical information for subset of MCI participants at baseline.

	n = 322
Age (years)	77.23 ± 7.87
Sex (F)	42.5%
Education (years)	13.88 ± 2.84
CDR	0.5 (0, 1)
MMSE	25.68 ± 2.41
Follow-up duration (years)	1.44 ± 0.46
Height (cm)	165.01 ± 26.37
Participants with pRBD (n)	35

Data reported as mean ± standard deviation, except sex reported as %F, and CDR reported as median (range). Abbreviations: F = female; CDR = Clinical Dementia Rating scale; MMSE = Mini-Mental State Examination; pRBD = probable REM Sleep Behavior Disorder

5.2 Objectives 1, 2, 3

5.2.1 Main Effects of Group/Diagnosis

Across the 11 gait outcomes of interest, significant main effects of group were found on stride velocity ($F_{(4, 1131.63)} = 11.784, p < 0.001$), step length ($F_{(4, 1068.10)} = 13.831, p < 0.001$), step time ($F_{(4, 1258.56)} = 4.761, p < 0.001$), and double support (%) ($F_{(4, 1197.50)} = 7.018, p < 0.001$). No significant main effects of group were found on swing time ($F_{(4, 1286.31)} = 0.304, p = 0.8$) and stride width ($F_{(4, 1075.12)} = 1.714, p = 0.1$).

Stride velocity was decreased in SD-aMCI ($b = -9.76, SE = 1.79, p < 0.001$), SD-naMCI ($b = -10.19, SE = 2.56, p < 0.001$), and MD-aMCI ($b = -9.01, SE = 1.93, p < 0.001$) than CU. Post hoc comparisons of EMMs revealed that MD-naMCI also had decreased stride velocity than CU ($p < 0.001$). Similarly, step length was also decreased in SD-aMCI ($b = -4.20, SE = 0.73, p < 0.001$), SD-naMCI ($b = -3.94, SE = 1.00, p < 0.001$), and MD-aMCI ($b = -4.23, SE = 1.93, p < 0.001$) than CU. Post hoc comparisons of EMMs revealed that MD-naMCI also had decreased step length than CU ($p < 0.001$). SD-aMCI was associated with greater step time ($b = 0.020, SE = 0.0057, p < 0.001$) compared to the CU group. Post hoc comparisons further revealed significantly greater step time in SD-naMCI ($p = 0.006$), MD-aMCI ($p = 0.006$), and MD-naMCI ($p = 0.003$) than CU participants. Finally, double support (%) was decreased in SD-aMCI ($b = 0.98, SE = 0.45, p = 0.03$) and MD-aMCI ($b = 1.13, SE = 0.68, p = 0.01$), however, post-hoc comparisons revealed it was decreased in all MCI groups compared to CU ($p < 0.001$ for all).

Only the MD-aMCI subtype was associated with greater stride velocity variability ($b = 0.697, SE = 0.180, p < 0.001$), step length variability ($b = 0.324, SE = 0.118, p < 0.001$), and swing time variability ($b = 0.0028, SE = 0.0011, p = 0.01$) relative to CU individuals. There were no main effects of group on step time variability ($F_{(4, 1171.65)} = 1.6471, p = 0.16$), or stride width variability ($F_{(4, 1217.94)} = 0.6028, p = 0.6$). Post hoc differences in EMMs by group are displayed in Figure 2 and Table 5. See Appendix B2: Table B2 for mean and standard deviation values of the gait outcomes of interest for each group, collapsed across time and pRBD status, and Appendix C1: Figure C1 for boxplots depicting raw values of gait outcomes stratified by group.

Table 6: EMMs (95% CI) of Gait Outcomes by Group.

Gait Outcome	CU	SD-aMCI	SD-naMCI	MD-aMCI	MD-naMCI
Stride velocity (cm/s)	110.125 [106.702, 113.547]	98.501 [95.079, 101.923] ^C	94.688 [90.227, 99.149] ^C	95.556 [92.517, 98.594] ^C	92.970 [87.480, 98.460] ^C
Stride velocity var (cm/s)	3.922 [3.709, 4.135]	4.014 [3.743, 4.285]	4.179 [3.754, 4.604]	4.450 [4.216, 4.684] ^C	3.996 [3.484, 4.508]
Step length (cm)	61.385 [59.953, 62.817]	55.808 [54.429, 57.187] ^C	54.702 [52.953, 56.451] ^C	55.115 [53.876, 56.354] ^C	52.963 [50.821, 55.106] ^C
Step length var (cm)	2.250 [2.111, 2.388]	2.203 [2.027, 2.379]	2.193 [1.916, 2.470]	2.412 [2.260, 2.564] ^C	2.156 [1.822, 2.490]
Step time (s)	0.565 [0.555, 0.576]	0.584 [0.573, 0.595] ^C	0.597 [0.582, 0.613] ^C	0.590 [0.580, 0.599] ^C	0.605 [0.586, 0.624] ^C
Step time var (s)	0.021 [0.020, 0.022]	0.023 [0.021, 0.025]	0.022 [0.020, 0.025]	0.022 [0.021, 0.024]	0.022 [0.018, 0.025]
Swing time (s)	0.390 [0.384, 0.396]	0.390 [0.384, 0.397]	0.395 [0.385, 0.404]	0.393 [0.387, 0.399]	0.390 [0.379, 0.402]
Swing time var (s)	0.018 [0.016, 0.019]	0.020 [0.018, 0.021]	0.020 [0.017, 0.022]	0.021 [0.020, 0.022] ^C	0.019 [0.016, 0.022]
Stride width (cm)	12.932 [12.344, 13.519]	13.635 [13.067, 14.203]	13.551 [12.829, 14.273]	13.660 [13.150, 14.169]	14.279 [13.394, 15.165]
Stride width var (cm)	2.298 [2.166, 2.429]	2.418 [2.254, 2.581]	2.413 [2.161, 2.665]	2.353 [2.212, 2.494]	2.205 [1.900, 2.511]
Double Support (%)	30.767 [29.928, 31.606]	32.771 [31.898, 33.644] ^C	33.150 [31.980, 34.320] ^C	32.921 [32.154, 33.687] ^C	35.015 [33.572, 36.458] ^C

Data is displayed as model-adjusted EMM [lower 95% CI, upper 95% CI]. ^C indicates the gait outcome is significantly different from the CU group.

Abbreviations: CU = cognitively unimpaired, SD = single-domain, MD = multi-domain, aMCI = amnesic mild cognitive impairment, naMCI = non-amnesic mild cognitive impairment, var = variability.

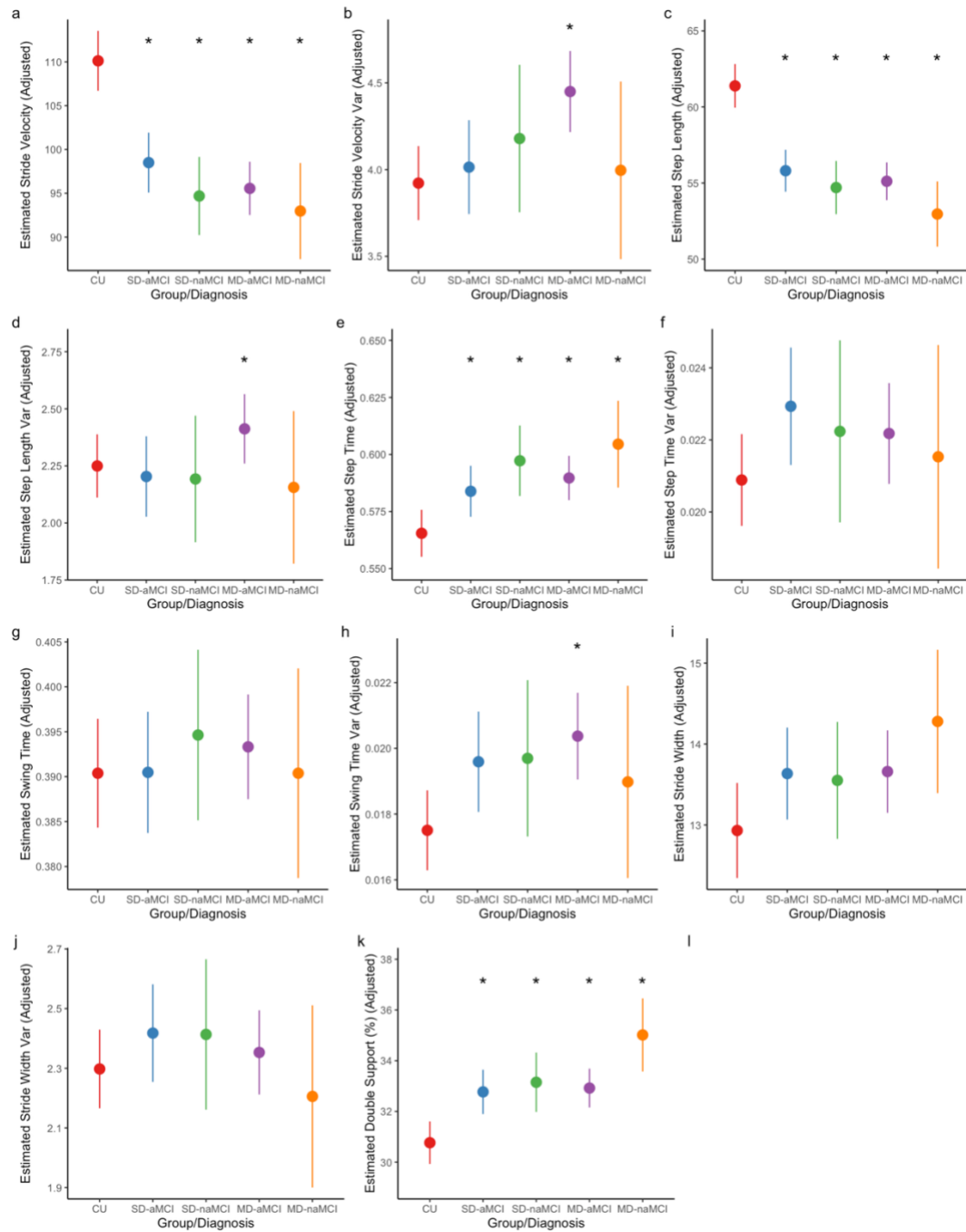


Figure 2: Group differences in EMMs of gait outcomes, averaged across visit and pRBD status. Points represent the EMMs, lines represent the 95% CI. Abbreviations: CU = cognitively unimpaired, SD = single-domain, MD = multi-domain, aMCI = amnesic mild cognitive impairment, naMCI = non-amnesic mild cognitive impairment. * = different from CU.

5.2.2 Main Effects of Time

Stride velocity variability increased over time in all groups regardless of pRBD status ($b = 0.735$, $SE = 0.231$, $p = 0.001$). No other significant main effects of time were found for any gait outcomes. Post hoc differences in EMMs by time are displayed in Figure 3 and Table 6. See Appendix B2: Table B3 for mean and standard deviation values of the gait outcomes at baseline and follow-up, collapsed across group and pRBD status, and Appendix C1: Figure C2 for boxplots depicting raw values of gait outcomes by visit.

Table 7: EMMs (95% CI) of gait outcomes at baseline and follow-up.

Gait Outcome	BL	FU
Stride velocity (cm/s)	99.511 [96.519, 102.503]	97.225 [94.196, 100.253]
Stride velocity var (cm/s)	3.789 [3.496, 4.082]	4.436 [4.135, 4.736]*
Step length (cm)	56.409 [55.217, 57.602]	55.580 [54.375, 56.785]
Step length var (cm)	2.217 [2.026, 2.409]	2.268 [2.072, 2.464]
Step time (s)	0.585 [0.575, 0.596]	0.591 [0.581, 0.601]
Step time var (s)	0.022 [0.020, 0.023]	0.022 [0.020, 0.024]
Swing time (s)	0.389 [0.383, 0.395]	0.395 [0.388, 0.401]
Swing time var (s)	0.020 [0.018, 0.022]	0.019 [0.017, 0.020]
Stride width (cm)	13.324 [12.833, 13.816]	13.898 [13.401, 14.395]
Stride width var (cm)	2.436 [2.265, 2.607]	2.239 [2.064, 2.413]
Double Support (%)	33.063 [32.288, 33.838]	32.787 [32.001, 33.572]

Data is displayed as model-adjusted EMM [lower 95% CI, upper 95% CI]. * indicates the gait outcome is significantly different from BL.

Abbreviations: BL = baseline, FU = follow-up, var = variability.

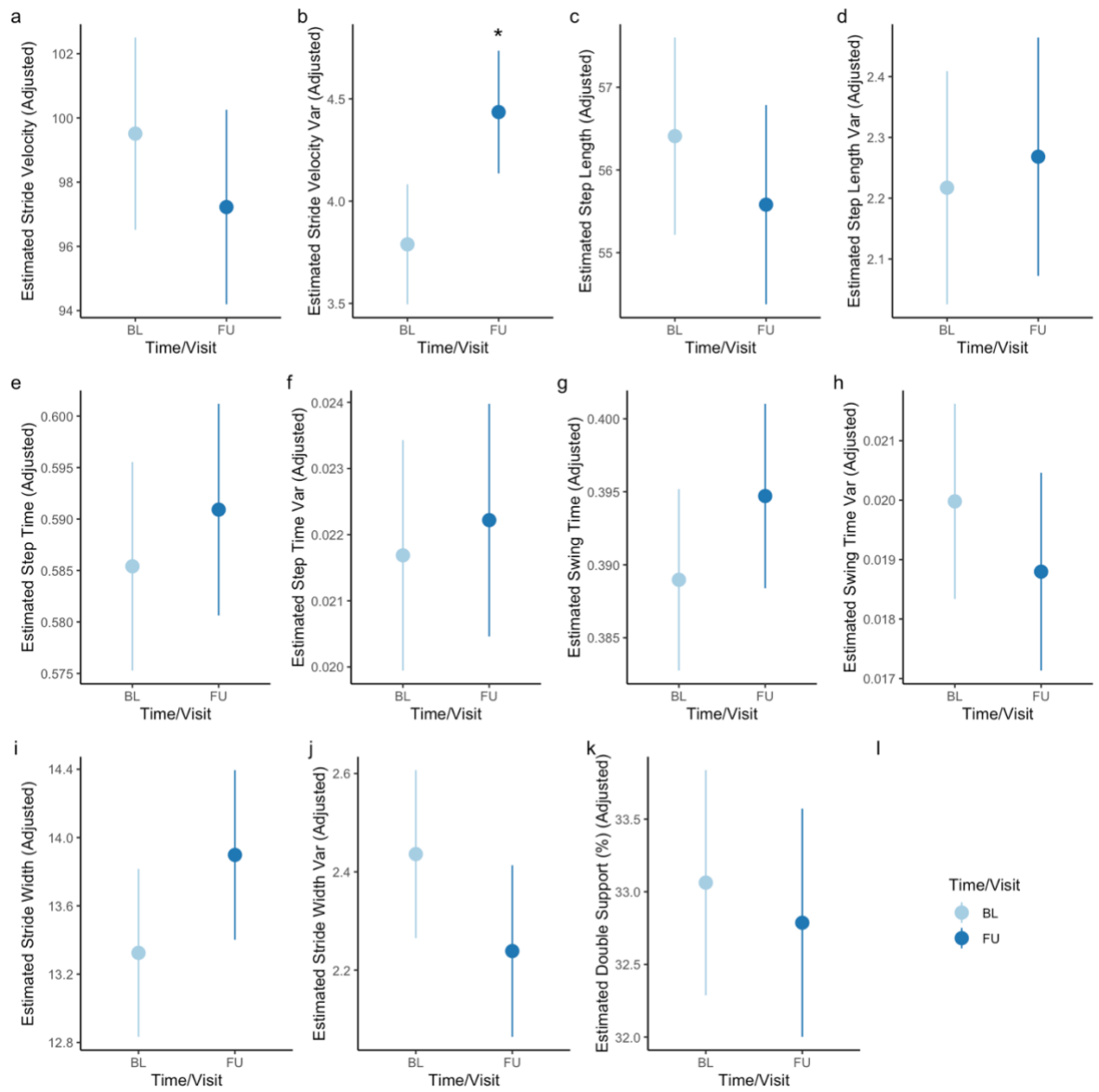


Figure 3: Differences in EMMs of gait outcomes over time, averaged across group and pRBD status. Points represented the EMMs, lines represent the 95% CI. Abbreviations: BL = baseline, FU = follow-up. * = different from BL.

5.2.3 Main Effects of pRBD Status

There was a main effect of pRBD status on stride velocity ($F_{(1, 934.25)} = 8.152, p = 0.004$), step length ($F_{(1, 917.89)} = 13.524, p < 0.001$), stride width ($F_{(1, 920.04)} = 4.912, p = 0.02$), and double support (%) ($F_{(1, 947.86)} = 10.002, p = 0.002$). Individuals with pRBD exhibited decreased stride velocity ($p = 0.004$), decreased step length (< 0.001), greater stride width ($p = 0.02$), and greater double support (%) ($p = 0.002$), compared to individuals without pRBD.

Despite this, the conditional fixed effect coefficients for pRBD status in the linear mixed models were not statistically significant for stride velocity, step length, stride width, nor double support (%). This discrepancy reflects the fact that the fixed effect coefficients of pRBD status from the linear mixed models reflect the effect of pRBD presence in CU individuals at baseline, rather than in the whole sample across time. Consistently, interaction effects between pRBD status and group have been found, which are reported in section 5.2.3. Post hoc differences in EMMs by pRBD status are displayed in Figure 4 and Table 7. See Appendix B2: Table B4 for mean and standard deviation values of gait outcomes of interest for individuals with and without pRBD, and Appendix C1: Figure C3 for boxplots depicting raw values of gait outcomes by pRBD status

Table 8: EMMs (95% CI) of gait outcomes by pRBD status.

Gait Outcome	pRBD–	pRBD+
Stride velocity (cm/s)	101.809 [99.717, 103.900]	94.927 [90.682, 99.172]*
Stride velocity var (cm/s)	4.236 [4.076, 4.396]	3.988 [3.704, 4.273]
Step length (cm)	57.825 [56.969, 58.680]	54.165 [52.407, 55.922]*
Step length var (cm)	2.271 [2.167, 2.375]	4.273 [2.030, 2.399]
Step time (s)	0.581 [0.575, 0.588]	0.595 [0.582, 0.608]
Step time var (s)	0.022 [0.021, 0.023]	0.022 [0.020, 0.024]
Swing time (s)	0.394 [0.390, 0.398]	0.390 [0.382, 0.397]
Swing time var (s)	0.019 [0.018, 0.020]	0.020 [0.018, 0.021]
Stride width (cm)	13.158 [12.807, 13.510]	14.064 [13.343, 14.786]*
Stride width var (cm)	2.398 [2.302, 2.495]	2.277 [2.102, 2.451]
Double Support (%)	31.977 [31.451, 32.503]	33.873 [32.820, 34.926]*

Data is displayed as model-adjusted EMM [lower 95% CI, upper 95% CI]. * indicates the gait outcome is significantly different from pRBD–.

Abbreviations: pRBD– = without probable REM sleep behavior disorder, pRBD+ = with probable REM sleep behavior disorder, var = variability.

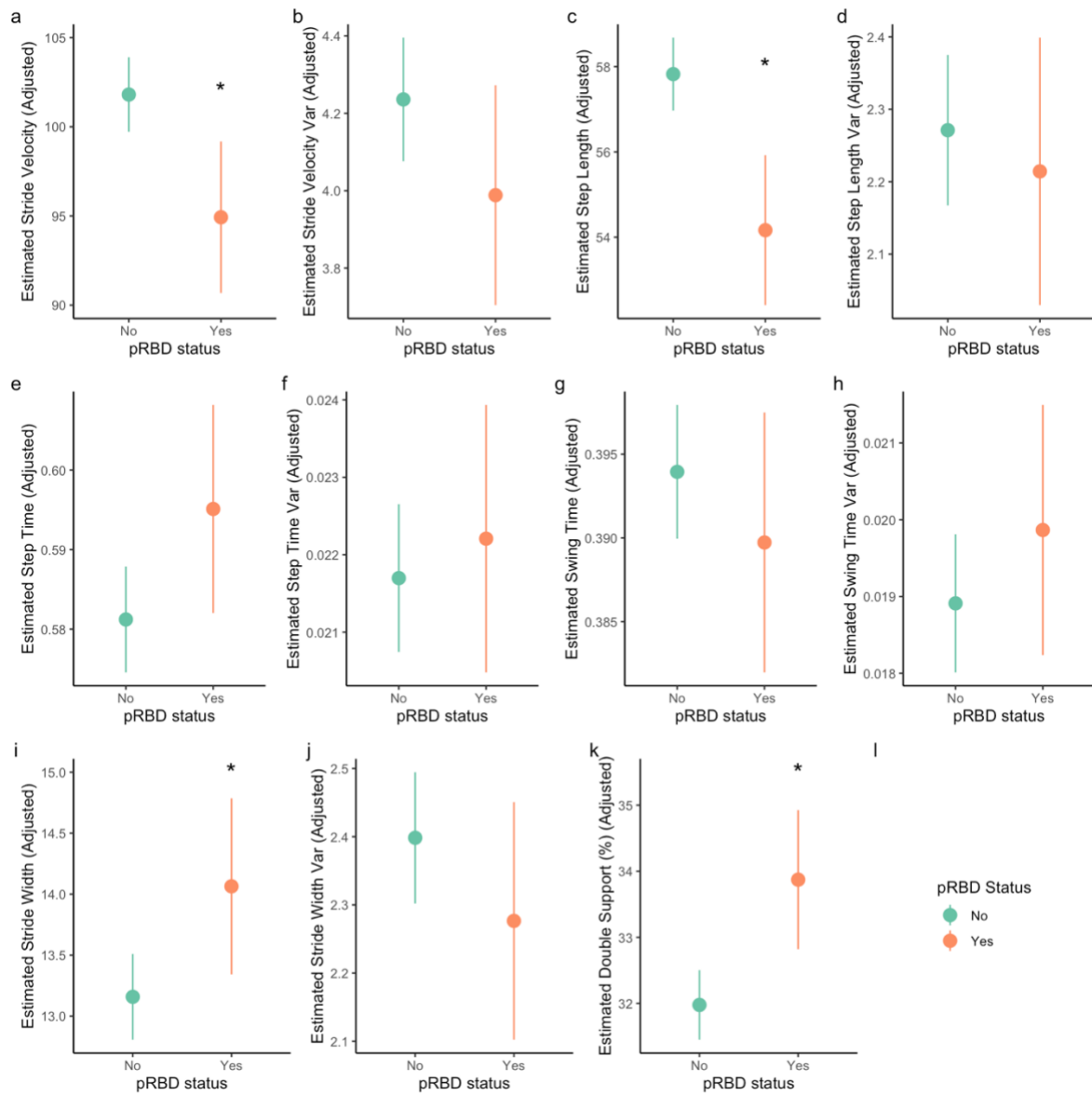


Figure 4: Differences in EMMs of gait outcomes over time, averaged across group and pRBD status. Points represent the EMMs, lines represent the 95% CI. Abbreviations: pRBD = probable REM sleep behavior disorder.

5.2.4 Gait progression in MCI over time: Interaction Effects of Group and Time

The MD-aMCI exhibited reductions in stride velocity ($b = -4.40$, $SE = 1.62$, $p = 0.006$) and step length ($b = -1.34$, $SE = 0.60$, $p = 0.02$), and increases in step time ($b = 0.015$, $SE = 0.006$, $p = 0.01$) over time. Post-hoc comparison of EMMs revealed that step length decreased over time in the MD-aMCI group ($p = 0.02$), as well as the SD-naMCI group ($p = 0.01$). Differences in the EMMs in each group over time are displayed in Figure 5 and Table 8. See Appendix B2: Table B5 for mean and standard deviation values of the gait outcomes of interest for each group at baseline and follow-up (collapsed across pRBD status), and Appendix C1: Figure C4 for boxplots depicting raw values of gait outcomes stratified by group and time.

Table 9: EMMs (95% CI) of gait outcomes by group at baseline and follow-up.

	CU		SD-aMCI		SD-naMCI		MD-aMCI		MD-naMCI	
Gait Outcome	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU
Stride velocity (cm/s)	110.522 [106.582, 114.462]	109.727 [105.793, 113.662]	98.092 [94.068, 102.117]	98.910 [94.668, 103.151]	97.477 [92.120, 102.833]	91.899 [86.284, 97.515]	97.769 [93.985, 101.552]	93.343 [89.729, 96.956]*	93.696 [87.100, 100.293]	92.244 [85.499, 98.989]
Stride velocity var (cm/s)	3.526 [3.181, 3.870]	4.318 [3.974, 4.663]	3.657 [3.253, 4.060]	4.371 [3.937, 4.805]	3.619 [3.029, 4.208]	4.739 [4.109, 5.370]	4.266 [3.884, 4.648]	4.634 [4.275, 4.993]	3.877 [3.146, 4.608]	4.115 [3.380, 4.849]
Step length (cm)	61.438 [59.832, 63.044]	61.333 [59.729, 62.936]	55.723 [54.136, 57.311]	55.893 [54.228, 57.558]	56.123 [54.055, 58.191]	53.280 [51.120, 55.441]*	56.021 [54.523, 57.518]	54.210 [52.773, 55.646]*	52.741 [50.207, 55.275]	53.186 [50.590, 55.781]
Step length var (cm)	2.240 [2.015, 2.465]	2.259 [2.034, 2.484]	2.060 [1.797, 2.323]	2.347 [2.063, 2.631]	2.100 [1.715, 2.485]	2.286 [1.873, 2.698]	2.525 [2.275, 2.774]	2.300 [2.066, 2.534]	2.162 [1.682, 2.641]	2.150 [1.670, 2.630]
Step time (s)	0.564 [0.552, 0.577]	0.567 [0.554, 0.579]	0.587 [0.574, 0.601]	0.580 [0.566, 0.595]	0.590 [0.570, 0.609]	0.605 [0.585, 0.625]	0.585 [0.572, 0.598]	0.594 [0.582, 0.607]*	0.601 [0.577, 0.624]	0.608 [0.584, 0.632]
Step time var (s)	0.021 [0.019, 0.023]	0.021 [0.019, 0.023]	0.024 [0.021, 0.026]	0.022 [0.020, 0.025]	0.021 [0.017, 0.024]	0.024 [0.020, 0.028]	0.021 [0.019, 0.024]	0.023 [0.021, 0.025]	0.022 [0.018, 0.027]	0.021 [0.017, 0.025]
Swing time (s)	0.387 [0.379, 0.395]	0.394 [0.386, 0.402]	0.389 [0.381, 0.398]	0.392 [0.383, 0.401]	0.394 [0.382, 0.406]	0.395 [0.383, 0.408]	0.391 [0.383, 0.399]	0.396 [0.389, 0.404]	0.384 [0.369, 0.399]	0.397 [0.382, 0.412]
Swing time var (s)	0.018 [0.016, 0.019]	0.017 [0.016, 0.019]	0.021 [0.019, 0.023]	0.020 [0.017, 0.022]	0.021 [0.018, 0.024]	0.019 [0.015, 0.022]	0.021 [0.019, 0.023]	0.020 [0.018, 0.022]	0.020 [0.015, 0.024]	0.018 [0.014, 0.022]
Stride width (cm)	12.568 [11.908, 13.228]	13.295 [12.636, 13.955]	13.307 [12.652, 13.962]	13.964 [13.276, 14.651]	13.178 [12.322, 14.033]	13.924 [13.030, 14.819]	13.524 [12.906, 14.141]	13.796 [13.203, 14.388]	14.046 [12.997, 15.095]	14.512 [13.438, 15.587]
Stride width var (cm)	2.386 [2.185, 2.588]	2.209 [2.007, 2.410]	2.597 [2.362, 2.831]	2.239 [1.987, 2.492]	2.459 [2.117, 2.801]	2.368 [2.002, 2.733]	2.417 [2.195, 2.639]	2.289 [2.080, 2.498]	2.322 [1.897, 2.747]	2.089 [1.663, 2.516]
Double Support (%)	31.110 [30.113, 32.107]	30.423 [29.428, 31.419]	33.154 [32.102, 34.205]	32.389 [31.276, 33.502]	32.710 [31.282, 34.138]	33.590 [32.088, 35.092]	32.843 [31.857, 33.829]	32.998 [32.061, 33.936]	35.496 [33.732, 37.261]	34.534 [32.734, 36.334]

Data is displayed as model-adjusted EMM [lower 95% CI, upper 95% CI]. * indicates the gait outcome is significantly different from BL. Abbreviations: CU = cognitively unimpaired, SD = single-domain, MD = multi-domain, aMCI = amnesic MCI, naMCI = non-amnesic MCI, BL = baseline, FU = follow-up, var = variability.

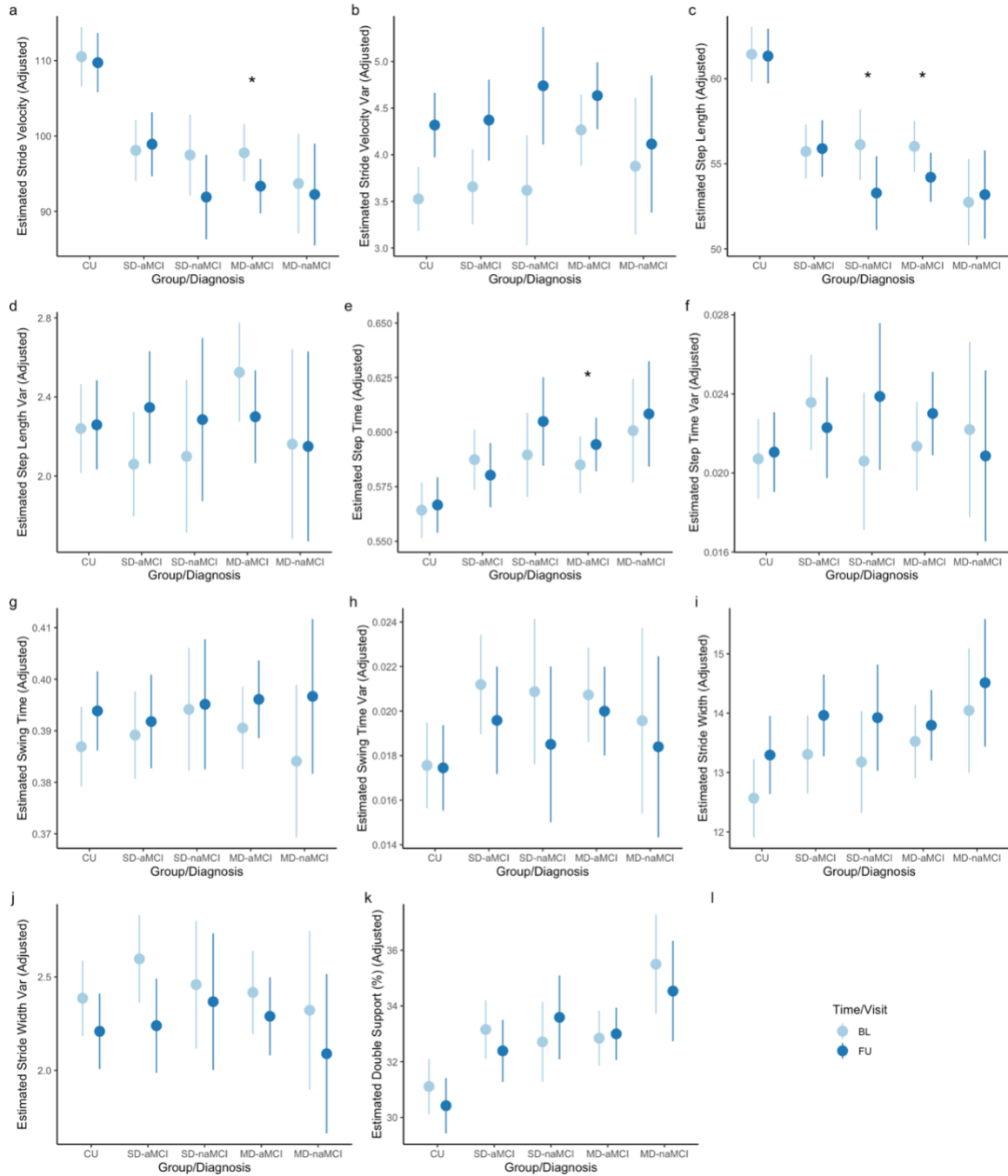


Figure 5: Differences in EMMs of gait outcomes by group over time, averaged across pRBD status. Points represent the EMMs, lines represent the 95% CI. Abbreviations: CU = cognitively unimpaired, SD = single-domain, MD = multi-domain, aMCI = amnesic mild cognitive impairment, naMCI = non-amnesic mild cognitive impairment, BL = baseline, FU = follow-up.

5.2.5 Effect of pRBD on gait in MCI: Interaction Effects of Group and pRBD Status

In MD-naMCI, the presence of pRBD was associated with decreased stride velocity ($b = -20.207$, $SE = 7.44$, $p = 0.006$), decreased step length ($b = -12.629$, $SE = 2.914$, $p < 0.001$), decreased swing time ($b = -0.0341$, $SE = -0.016$, $p = 0.03$), as well as greater stride width ($b = 4.475$, $SE = 1.204$, $p < 0.001$), and increased double support (%) ($b = 7.950$, $SE = 1.956$, $p < 0.001$). Differences in the EMMs in each group subdivided by pRBD status are displayed in Figure 6 and Table 9. See Appendix B2: Table B6 for mean and standard deviation values of the gait outcomes of interest subdivided by pRBD for each group, and Appendix C1: Figure C5 for boxplots depicting raw values of gait outcomes stratified by group and pRBD status.

Table 10: EMMs (95% CI) of gait outcomes by group, subdivided by pRBD status.

	CU		SD-aMCI		SD-naMCI		MD-aMCI		MD-naMCI	
Gait Outcome	pRBD–	pRBD+	pRBD–	pRBD+	pRBD–	pRBD+	pRBD–	pRBD+	pRBD–	pRBD+
Stride velocity (cm/s)	109.791 [107.708, 111.875]	110.458 [103.964, 116.953]	99.886 [97.317, 102.454]	97.117 [90.788, 103.445]	98.186 [94.395, 101.977]	91.190 [83.102, 99.279]	98.574 [95.898, 101.251]	92.537 [87.083, 97.990]	102.607 [97.035, 108.178]	83.333 [73.856, 92.810]*
Stride velocity var (cm/s)	3.961 [3.831, 4.090]	3.883 [3.479, 4.287]	4.246 [4.051, 4.442]	3.782 [3.280, 4.284]	4.361 [3.990, 4.732]	3.997 [3.232, 4.762]	4.478 [4.258, 4.699]	4.422 [4.014, 4.829]	4.133 [3.531, 4.735]	3.859 [3.031, 4.687]
Step length (cm)	61.237 [60.365, 62.108]	61.534 [58.817, 64.251]	56.996 [55.947, 58.046]	54.620 [52.075, 57.164]	56.443 [54.959, 57.927]	52.961 [49.789, 56.132]	56.339 [55.253, 57.425]	53.892 [51.666, 56.118]	58.108 [55.973, 60.244]	47.818 [44.097, 51.539]*
Step length var (cm)	2.168 [2.084, 2.253]	2.331 [2.069, 2.593]	2.274 [2.147, 2.402]	2.132 [1.806, 2.459]	2.323 [2.081, 2.565]	2.062 [1.564, 2.561]	2.466 [2.323, 2.609]	2.359 [2.093, 2.624]	2.124 [1.732, 2.517]	2.187 [1.647, 2.728]
Step time (s)	0.568 [0.561, 0.574]	0.563 [0.544, 0.583]	0.587 [0.579, 0.595]	0.580 [0.560, 0.601]	0.587 [0.574, 0.600]	0.608 [0.580, 0.635]	0.585 [0.576, 0.594]	0.594 [0.577, 0.612]	0.579 [0.559, 0.599]	0.630 [0.598, 0.662]
Step time var (s)	0.021 [0.020, 0.021]	0.021 [0.019, 0.024]	0.023 [0.022, 0.024]	0.023 [0.020, 0.026]	0.021 [0.019, 0.024]	0.023 [0.019, 0.028]	0.022 [0.021, 0.024]	0.022 [0.020, 0.024]	0.021 [0.018, 0.025]	0.022 [0.017, 0.027]
Swing time (s)	0.391 [0.387, 0.395]	0.390 [0.378, 0.401]	0.396 [0.392, 0.401]	0.385 [0.372, 0.397]	0.394 [0.386, 0.403]	0.395 [0.378, 0.412]	0.392 [0.387, 0.398]	0.394 [0.384, 0.405]	0.396 [0.383, 0.408]	0.385 [0.365, 0.405]*
Swing time var (s)	0.018 [0.017, 0.019]	0.017 [0.015, 0.019]	0.021 [0.020, 0.022]	0.020 [0.017, 0.023]	0.018 [0.016, 0.021]	0.021 [0.017, 0.025]	0.019 [0.018, 0.020]	0.022 [0.019, 0.024]	0.018 [0.015, 0.022]	0.020 [0.015, 0.024]
Stride width (cm)	13.126 [12.769, 13.483]	12.737 [11.623, 13.852]	13.263 [12.832, 13.694]	14.007 [12.959, 15.055]	13.289 [12.676, 13.902]	13.813 [12.503, 15.123]	13.354 [12.907, 13.801]	13.965 [13.050, 14.880]	12.760 [11.875, 13.644]	15.799 [14.262, 17.336]*
Stride width var (cm)	2.276 [2.196, 2.356]	2.319 [2.070, 2.569]	2.410 [2.292, 2.528]	2.425 [2.122, 2.729]	2.549 [2.330, 2.768]	2.278 [1.823, 2.732]	2.312 [2.180, 2.443]	2.395 [2.147, 2.642]	2.445 [2.092, 2.798]	1.966 [1.468, 2.463]
Double Support (%)	30.953 [30.442, 31.463]	30.581 [28.989, 32.173]	32.121 [31.474, 32.768]	33.422 [31.805, 35.039]	32.375 [31.378, 33.371]	33.925 [31.804, 36.046]	32.456 [31.776, 33.136]	33.386 [32.012, 34.759]	31.979 [30.486, 33.473]	38.051 [35.578, 40.524]*

Data is displayed as model-adjusted EMM [lower 95% CI, upper 95% CI]. * indicates the gait outcome is significantly different from pRBD-. Abbreviations: CU = cognitively unimpaired, SD = single-domain, MD = multi-domain, aMCI = amnesic mild cognitive impairment, naMCI = non-amnesic mild cognitive impairment, pRBD- = without probable REM sleep behavior disorder, pRBD+ = with probable REM sleep behavior disorder, var = variability.

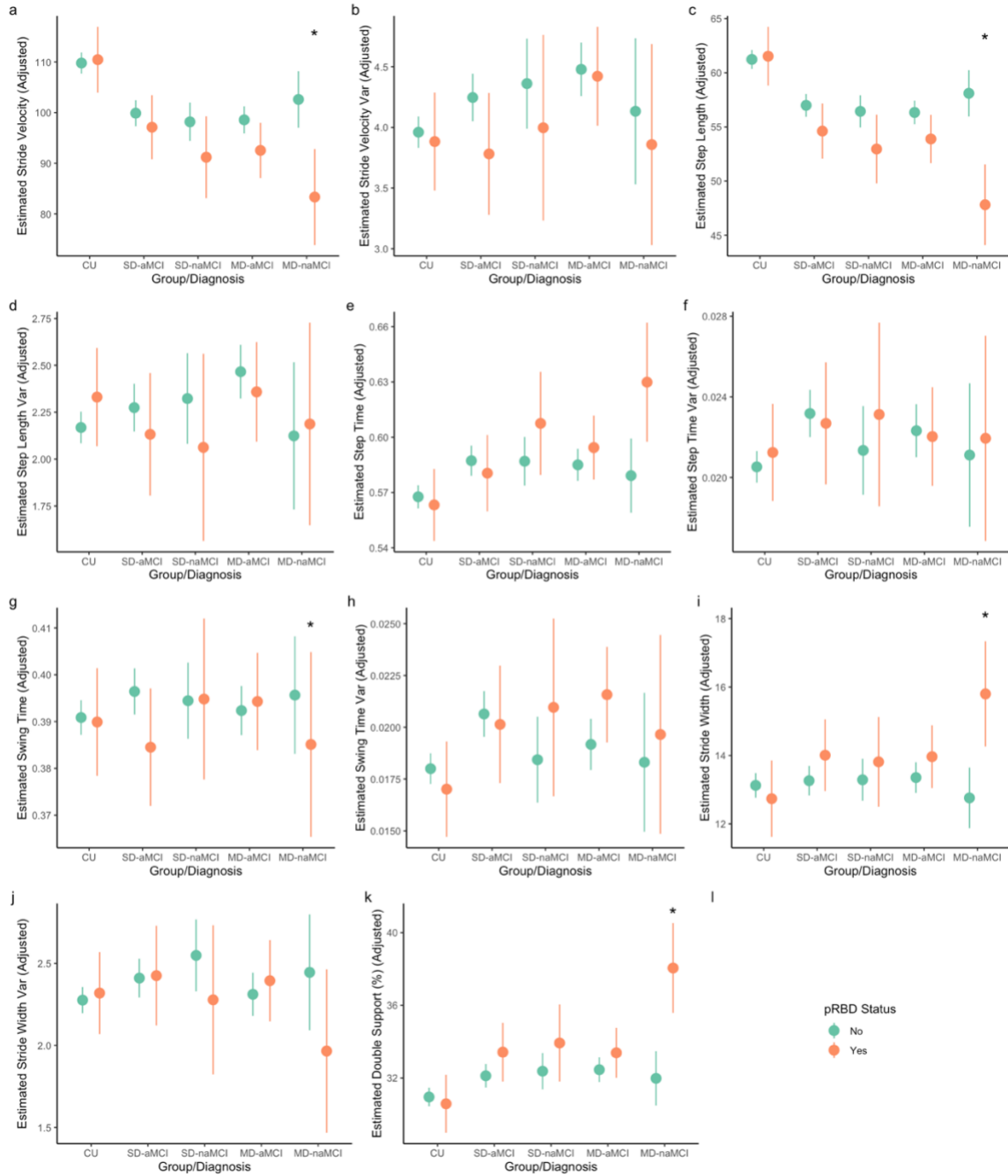


Figure 6: Differences in EMMs of gait outcomes by group subdivided by pRBD status, averaged across visits. Points represent the EMMs, lines represent the 95% CI of each mean. Abbreviations: CU = cognitively unimpaired, SD = single-domain, MD = multi-domain, aMCI = amnesic mild cognitive impairment, naMCI = non-amnesic mild cognitive impairment, pRBD = probable REM sleep behavior disorder.

5.2.6 Effect of pRBD on progression of gait outcomes: Interaction Effects of pRBD status and Time

There were no interaction effects of pRBD status and time on any of the gait outcomes of interest. EMMs for the gait outcomes by pRBD status and group are displayed in Figure 7 and Table 10. See Appendix B2: Table B7 for mean and standard deviation values of the gait outcomes of interest for subjects with and without pRBD for each group (collapsed across time), and Appendix C1: Figure C6 for boxplots depicting raw values of gait outcomes stratified by time and pRBD status.

Table 11: EMMs (95% CI) of gait outcomes by pRBD status at baseline and follow-up.

Gait Outcome	pRBD-		pRBD+	
	BL	FU	BL	FU
Stride velocity (cm/s)	102.946 [100.056, 105.835]	100.672 [97.958, 103.385]	96.077 [91.358, 100.796]	93.777 [88.864, 98.691]
Stride velocity var (cm/s)	3.985 [3.679, 4.291]	4.487 [4.206, 4.767]	3.593 [3.182, 4.004]	4.384 [3.941, 4.827]
Step length (cm)	58.364 [57.230, 59.497]	57.286 [56.215, 58.356]	54.455 [52.538, 56.371]	53.875 [51.890, 55.859]
Step length var (cm)	2.283 [2.083, 2.483]	2.259 [2.076, 2.443]	2.151 [1.883, 2.420]	2.277 [1.988, 2.567]
Step time (s)	0.580 [0.570, 0.590]	0.582 [0.573, 0.592]	0.591 [0.575, 0.606]	0.600 [0.583, 0.616]
Step time var (s)	0.022 [0.020, 0.024]	0.021 [0.020, 0.023]	0.021 [0.019, 0.024]	0.023 [0.020, 0.026]
Swing time (s)	0.393 [0.387, 0.399]	0.395 [0.389, 0.401]	0.385 [0.376, 0.394]	0.394 [0.385, 0.404]
Swing time var (s)	0.019 [0.018, 0.021]	0.018 [0.017, 0.020]	0.021 [0.018, 0.023]	0.019 [0.017, 0.022]
Stride width (cm)	12.813 [12.345, 13.281]	13.504 [13.062, 13.946]	13.836 [13.047, 14.624]	14.293 [13.476, 15.110]
Stride width var (cm)	2.454 [2.276, 2.631]	2.343 [2.180, 2.506]	2.418 [2.177, 2.659]	2.135 [1.876, 2.394]
Double Support (%)	31.982 [31.222, 32.742]	31.971 [31.262, 32.681]	34.144 [32.946, 35.341]	33.602 [32.348, 34.856]

Data is displayed as model-adjusted EMM [lower 95% CI, upper 95% CI]. Abbreviations: pRBD = probable REM sleep behavior disorder; BL = baseline; FU = follow-up; var = variability

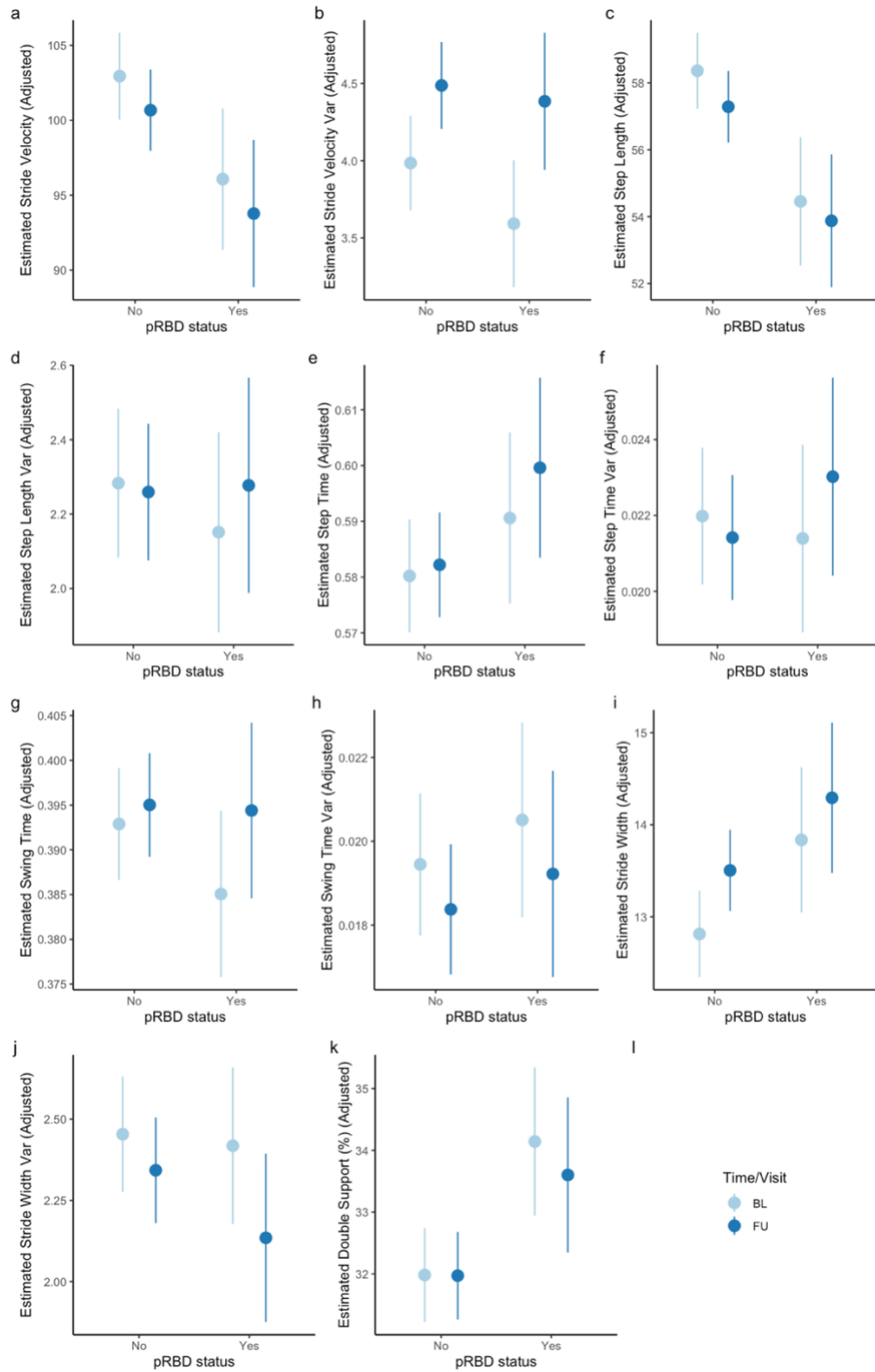


Figure 7: EMMs of gait outcomes subdivided by pRBD status and time, averaged across group. Points represent the EMMs, lines represent the 95% CI. Abbreviations: pRBD = probable REM sleep behavior disorder, BL = baseline, FU = follow-up.

5.2.7 Effect of pRBD on gait progression in MCI subtypes: Interaction Effects of Group, Time, and pRBD Status

There was a significant three-way interaction effect of MCI subtype, time, and pRBD status on swing time ($F_{(4, 853.13)} = 2.808, p = 0.02$). Swing time increased over time in people with MD-naMCI and pRBD ($b = 0.0476, SE = -0.018, p = 0.007$) but did not change in people with MD-naMCI without pRBD ($p = 0.053$). EMMs at baseline and follow-up for each group, in participants with and without pRBD are reported in Tables 11 and 12, respectively. Appendix B2: Tables B8 and B9 show mean and standard deviation of the gait outcomes at baseline and follow-up, for subjects with and without pRBD, respectively. Figures 8 and 9 plot EMMs for mean and variability measures, respectively. Plots depicting average raw change in mean and variability measures are in Appendix C1: Figures C7 and C8.

Table 12: EMMs (95% CI) of the gait outcomes of interest for subjects with pRBD divided by group at baseline and follow-up.

Gait Outcome	CU		SD-aMCI		SD-naMCI		MD-aMCI		MD-naMCI	
	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU
Stride velocity (cm/s)	110.962 [103.933, 117.991]	109.955 [102.925, 116.985]	95.863 [88.825, 102.901]	98.370 [90.975, 105.766]	95.058 [85.750, 104.366]	87.323 [77.325, 97.320]	94.469 [88.157, 100.781]	90.605 [84.600, 96.610]	84.032 [73.782, 94.283]	82.635 [70.996, 94.273]
Stride velocity var (cm/s)	3.459 [2.890, 4.028]	4.308 [3.737, 4.878]	3.340 [2.658, 4.022]	4.223 [3.491, 4.956]	3.347 [2.339, 4.355]	4.647 [3.535, 5.759]	4.242 [3.640, 4.845]	4.601 [4.045, 5.157]	3.575 [2.512, 4.638]	4.142 [2.921, 5.363]
Step length (cm)	61.562 [58.668, 64.456]	61.506 [58.611, 64.400]	54.335 [51.548, 57.123]	54.904 [51.988, 57.821]	54.871 [51.267, 58.475]	51.050 [47.199, 54.901]	54.956 [52.434, 57.477]	52.828 [50.416, 55.240]	46.551 [42.571, 50.530]	49.086 [44.585, 53.586]
Step length var (cm)	2.321 [1.950, 2.692]	2.341 [1.969, 2.713]	1.908 [1.463, 2.353]	2.357 [1.878, 2.835]	1.906 [1.247, 2.565]	2.219 [1.492, 2.946]	2.566 [2.173, 2.959]	2.151 [1.788, 2.514]	2.056 [1.358, 2.754]	2.319 [1.521, 3.116]
Step time (s)	0.561 [0.539, 0.583]	0.565 [0.543, 0.587]	0.587 [0.563, 0.611]	0.574 [0.548, 0.599]	0.595 [0.562, 0.628]	0.620 [0.584, 0.656]	0.593 [0.572, 0.614]	0.596 [0.576, 0.616]	0.617 [0.581, 0.653]	0.643 [0.602, 0.684]
Step time var (s)	0.021 [0.017, 0.024]	0.022 [0.019, 0.025]	0.023 [0.019, 0.027]	0.022 [0.018, 0.027]	0.020 [0.015, 0.026]	0.026 [0.019, 0.032]	0.021 [0.018, 0.025]	0.023 [0.019, 0.026]	0.022 [0.015, 0.028]	0.022 [0.015, 0.030]
Swing time (s)	0.386 [0.372, 0.399]	0.394 [0.381, 0.407]	0.384 [0.369, 0.399]	0.385 [0.369, 0.401]	0.395 [0.375, 0.416]	0.394 [0.372, 0.417]	0.394 [0.381, 0.407]	0.395 [0.382, 0.407]	0.366 [0.344, 0.389]	0.404 [0.379, 0.430]*
Swing time var (s)	0.017 [0.014, 0.020]	0.017 [0.014, 0.020]	0.021 [0.017, 0.025]	0.019 [0.015, 0.023]	0.022 [0.017, 0.028]	0.020 [0.014, 0.026]	0.023 [0.019, 0.026]	0.020 [0.017, 0.023]	0.019 [0.013, 0.026]	0.020 [0.013, 0.027]
Stride width (cm)	12.246 [11.057, 13.435]	13.229 [12.040, 14.418]	13.608 [12.458, 14.758]	14.406 [13.203, 15.610]	13.519 [12.028, 15.009]	14.107 [12.514, 15.701]	13.845 [12.806, 14.884]	14.085 [13.091, 15.078]	15.961 [14.316, 17.607]	15.636 [13.774, 17.498]
Stride width var (cm)	2.476 [2.141, 2.811]	2.163 [1.827, 2.498]	2.759 [2.361, 3.157]	2.091 [1.664, 2.518]	2.332 [1.747, 2.917]	2.224 [1.579, 2.868]	2.488 [2.137, 2.839]	2.301 [1.976, 2.626]	2.037 [1.417, 2.656]	1.895 [1.184, 2.605]
Double Support (%)	30.984 [29.226, 32.742]	30.178 [28.420, 31.936]	34.094 [32.263, 35.924]	32.750 [30.819, 34.681]	33.055 [30.581, 35.530]	34.795 [32.124, 37.466]	33.240 [31.611, 34.869]	33.531 [31.990, 35.072]	39.345 [36.633, 42.057]	36.757 [33.668, 39.846]

Data is displayed as model-adjusted EMM [lower 95% CI, upper 95% CI]. Abbreviations: CU = cognitively unimpaired, SD = single-domain, MD = multi-domain, aMCI = amnesic mild cognitive impairment, naMCI = non-amnesic mild cognitive impairment, BL = baseline, FU = follow-up, var = variability

Table 13: EMMs (95% CI) of the gait outcomes of interest for subjects without pRBD divided by group at baseline and follow-up.

Gait Outcome	CU		SD-aMCI		SD-naMCI		MD-aMCI		MD-naMCI	
	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU
Stride velocity (cm/s)	110.082 [107.376, 112.789]	109.500 [106.810, 112.190]	100.322 [97.165, 103.480]	99.449 [96.077, 102.821]	99.895 [95.101, 104.689]	96.476 [91.662, 101.291]	101.068 [97.529, 104.607]	96.080 [92.773, 99.388]	103.360 [95.374, 111.346]	101.853 [95.530, 108.176]
Stride velocity var (cm/s)	3.593 [3.331, 3.855]	4.328 [4.069, 4.588]	3.973 [3.653, 4.294]	4.519 [4.171, 4.867]	3.890 [3.346, 4.434]	4.832 [4.285, 5.379]	4.290 [3.920, 4.660]	4.667 [4.321, 5.013]	4.179 [3.220, 5.138]	4.087 [3.342, 4.832]
Step length (cm)	61.314 [60.230, 62.398]	61.159 [60.081, 62.238]	57.111 [55.860, 58.363]	56.882 [55.553, 58.210]	57.376 [55.533, 59.219]	55.510 [53.660, 57.361]	57.086 [55.697, 58.474]	55.592 [54.287, 56.896]	58.931 [55.912, 61.950]	57.285 [54.881, 59.690]
Step length var (cm)	2.160 [1.988, 2.331]	2.177 [2.007, 2.347]	2.212 [2.003, 2.421]	2.337 [2.109, 2.565]	2.294 [1.938, 2.649]	2.352 [1.995, 2.710]	2.483 [2.242, 2.725]	2.449 [2.223, 2.674]	2.267 [1.640, 2.894]	1.981 [1.495, 2.467]
Step time (s)	0.567 [0.567, 0.567]	0.568 [0.559, 0.577]	0.587 [0.577, 0.598]	0.587 [0.575, 0.599]	0.584 [0.567, 0.602]	0.589 [0.572, 0.607]	0.577 [0.565, 0.589]	0.593 [0.582, 0.604]	0.585 [0.555, 0.614]	0.574 [0.550, 0.597]
Step time var (s)	0.021 [0.019, 0.022]	0.020 [0.019, 0.022]	0.024 [0.022, 0.026]	0.022 [0.020, 0.024]	0.021 [0.018, 0.024]	0.022 [0.019, 0.025]	0.021 [0.019, 0.024]	0.023 [0.021, 0.025]	0.023 [0.017, 0.029]	0.019 [0.015, 0.024]
Swing time (s)	0.388 [0.383, 0.394]	0.394 [0.388, 0.399]	0.394 [0.388, 0.401]	0.399 [0.391, 0.406]	0.393 [0.382, 0.404]	0.396 [0.385, 0.407]	0.387 [0.379, 0.395]	0.398 [0.390, 0.405]	0.402 [0.383, 0.421]	0.389 [0.375, 0.404]
Swing time var (s)	0.018 [0.017, 0.020]	0.018 [0.017, 0.019]	0.021 [0.019, 0.023]	0.020 [0.018, 0.022]	0.020 [0.017, 0.023]	0.017 [0.014, 0.020]	0.019 [0.017, 0.021]	0.020 [0.018, 0.022]	0.020 [0.015, 0.025]	0.017 [0.013, 0.021]
Stride width (cm)	12.890 [12.444, 13.337]	13.361 [12.917, 13.806]	13.006 [12.489, 13.522]	13.521 [12.972, 14.069]	12.836 [12.074, 13.599]	13.742 [12.976, 14.508]	13.202 [12.629, 13.776]	13.506 [12.968, 14.045]	12.131 [10.879, 13.383]	13.389 [12.392, 14.385]
Stride width var (cm)	2.297 [2.144, 2.450]	2.255 [2.104, 2.406]	2.434 [2.248, 2.619]	2.387 [2.185, 2.589]	2.586 [2.271, 2.900]	2.512 [2.195, 2.828]	2.346 [2.131, 2.561]	2.277 [2.077, 2.477]	2.607 [2.053, 3.161]	2.284 [1.854, 2.714]
Double Support (%)	31.237 [30.539, 31.935]	30.668 [29.975, 31.361]	32.214 [31.392, 33.036]	32.027 [31.144, 32.910]	32.364 [31.080, 33.648]	32.385 [31.095, 33.675]	32.446 [31.516, 33.376]	32.466 [31.600, 33.332]	31.648 [29.478, 33.818]	32.311 [30.602, 34.020]

Data is displayed as model-adjusted EMM [lower 95% CI, upper 95% CI]. Abbreviations: CU = cognitively unimpaired, SD = single-domain, MD = multi-domain, aMCI = amnesic mild cognitive impairment, naMCI = non-amnesic mild cognitive impairment, BL = baseline, FU = follow-up, var = variability

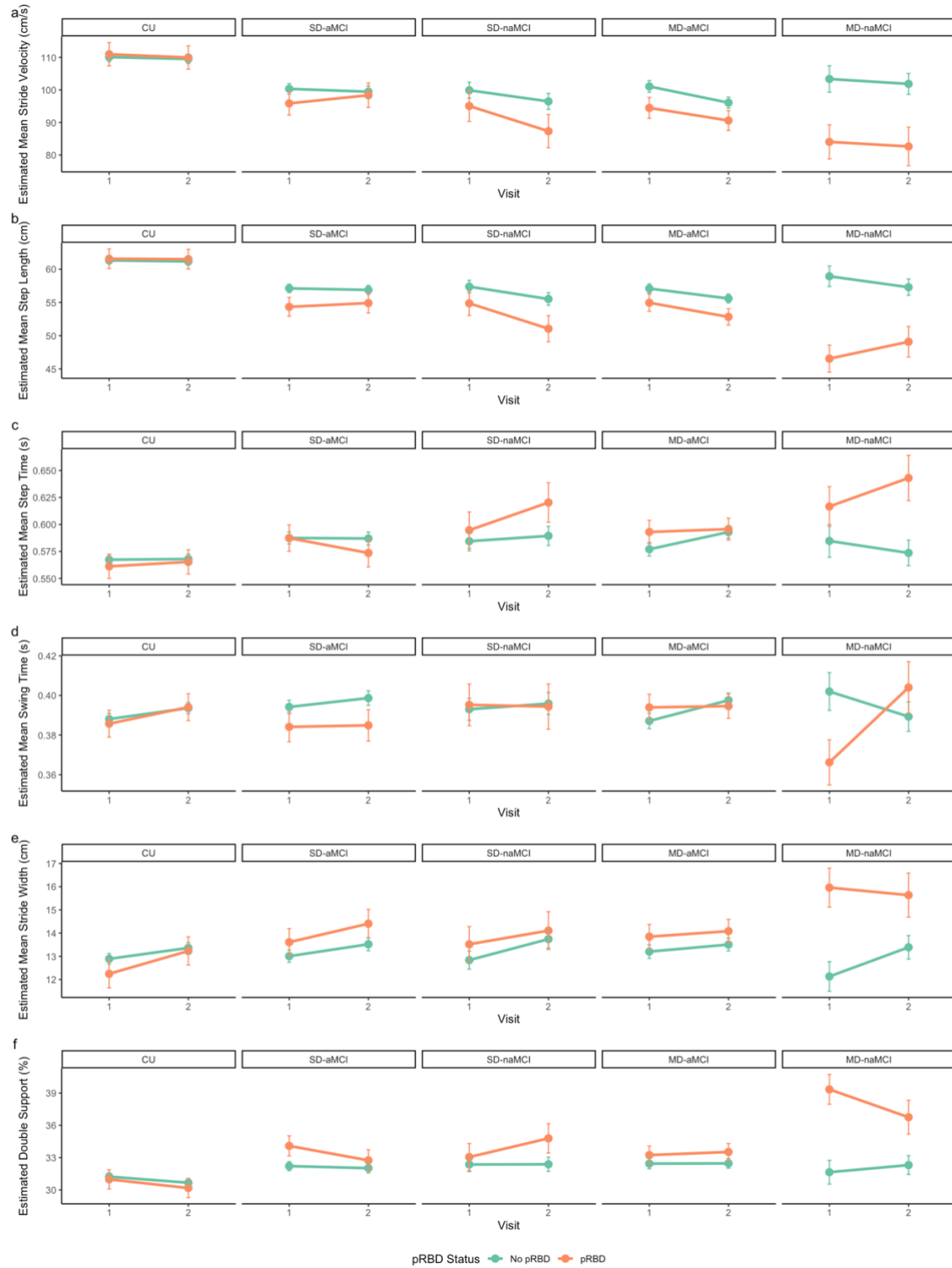


Figure 8: EMMs of mean gait outcomes at baseline and follow-up by group and pRBD status. Points represent the EMMs, lines represent the 95% CI of each mean. Abbreviations: pRBD = probable REM sleep behavior disorder, BL = baseline, FU = follow-up; CU = cognitively unimpaired; aMCI = amnestic MCI; naMCI = non-amnestic MCI; SD = single-domain; MD = multi-domain.

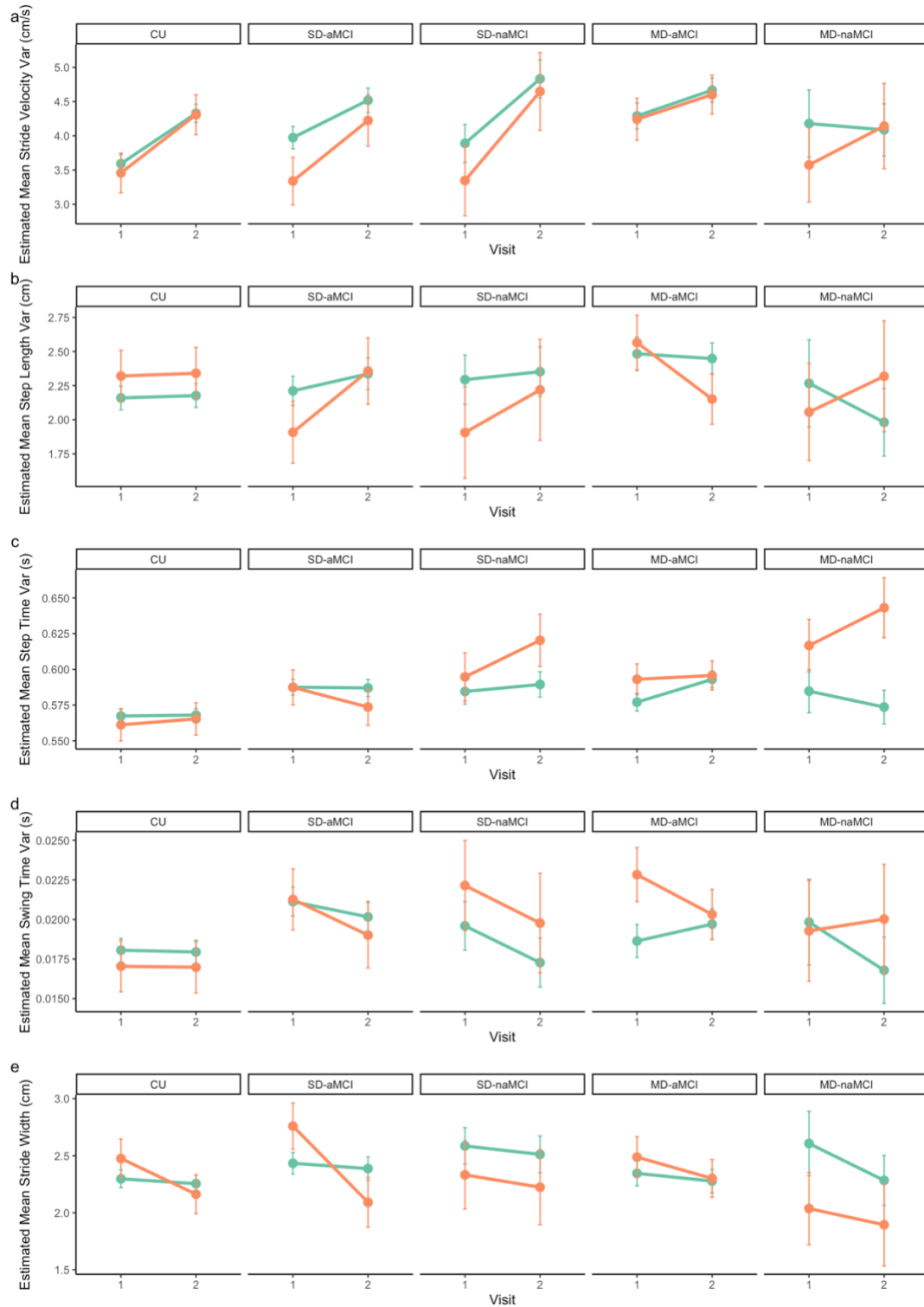


Figure 9: EMMs of mean gait outcomes at baseline and follow-up by group and pRBD status. Points represent the EMMs, lines represent the 95% CI of each mean. Abbreviations: pRBD = probable REM sleep behavior disorder, BL = baseline, FU = follow-up; CU = cognitively unimpaired; aMCI = amnesic MCI; naMCI = non-amnesic MCI; SD = single-domain; MD = multi-domain; var = variability.

5.3 Objective 4

5.3.1 Principal Component Analysis of Gait Variables

Principal component analysis was conducted on 11 gait variables to reduce multicollinearity between them. Parallel analysis indicated that three components should be retained, as their eigenvalues exceeded those of randomly generated data, as shown in Figure 10.

The three retained component account for a total of 67.61% of the variance in gait performance. The first, second, and third components each explained 37.80%, 15.48%, and 14.33% of the variance, respectively.

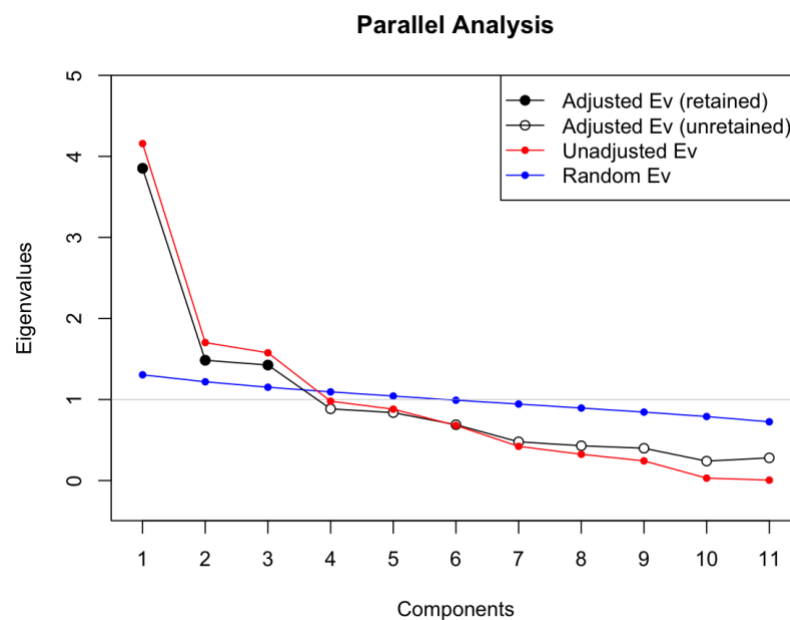


Figure 10: Results of the parallel analysis displayed in scree plot of observed vs random eigenvalues. The eigenvalues from randomly generated datasets are represented in blue, and the eigenvalues from gait data in this study are represented in red (unadjusted) and black (adjusted). Retained components are represented with a filled dot. Unretained components are represented with an unfilled dot.

The first factor was characterized by strong loadings from stride velocity, step length, double support (%), stride width, and step time variability, and was interpreted to represent “pace” The second component showed strong loadings from step time and swing time and was interpreted to represent “rhythm and timing.” The third component had strong loadings from stride velocity variability, step length variability, swing time variability, and stride width variability, and was interpreted to represent gait “variability and stability.” Factor loadings for each principal component are shown in Table 13.

Table 14: Factor loadings from the varimax-rotated principal component analysis.

Gait Outcome	PC1: Pace	PC2: Timing and Rhythm	PC3: Variability and Stability
Stride velocity (cm/s)	-0.89	-0.3	-0.11
Stride velocity var (cm/s)	0.04	-0.28	0.84
Step length (cm)	-0.89	0.1	-0.16
Step length var (cm)	0.14	0.12	0.72
Step time (s)	0.52	0.78	0.03
Step time var (s)	0.52	0.34	0.49
Swing time (s)	-0.09	0.95	0.03
Swing time var (s)	0.44	0.45	0.47
Stride width (cm)	0.5	0.11	-0.04
Stride width var (cm)	-0.26	0.24	0.41
Double Support (%)	0.89	-0.04	0.03

The strongest loadings for each principal component are bolded. Abbreviations: PC = principal component; var = variability.

5.3.2 Baseline Gait Performance as a Predictor of Changes in Cognition in MCI

Significant main effects of time were found for global cognition ($b = -0.282$, 95% CI $[-0.367, -0.202]$, $p < 0.001$), memory ($b = -0.191$, 95% CI $[-0.271, -0.111]$, $p < 0.001$), attention ($b = -0.353$, 95% CI $[-0.467, -0.233]$, $p < 0.001$), and language ($b = -0.295$, 95% CI $[-0.394, -0.194]$, $p < 0.001$), but not visuospatial function ($b = -0.085$, 95% CI $[-0.181, 0.010]$, $p = 0.14$). Average z-scores for the MCI participants in each domain at baseline and follow-up are reported in Table 14. Figure 11 shows change in these z-scores across both visits.

Table 15: Domain-specific cognitive z-scores at baseline and follow-up, with main effects of time from linear mixed models exploring associations between gait factors and change in cognition.

	Baseline	Follow-Up	Linear Mixed Model Results		
			<i>b</i>	95% CI	p-value
Global Cognition	-1.52 ± 0.96	-2.15 ± 0.92	-0.282	$[-0.367, -0.202]$	<0.001
Memory	-1.75 ± 0.89	-1.99 ± 0.98	-0.190	$[-0.271, -0.111]$	<0.001
Attention	-1.36 ± 1.31	-1.90 ± 1.39	-0.352	$[-0.467, -0.233]$	<0.001
Language	-1.27 ± 1.25	-1.72 ± 1.44	-0.295	$[-0.394, -0.194]$	<0.001
Visuospatial Function	-0.82 ± 0.99	-1.09 ± 1.06	-0.085	$[-0.181, 0.010]$	0.14

Cognitive domain z-score data presented as mean ± standard deviation. Significant main effects are indicated by bolded p-values.

The “pace” factor was negatively associated with global cognition ($b = -0.088$, 95% CI [-0.175, -0.001], $p = 0.04$) and attention ($b = -0.252$, 95% CI [-0.387, -0.121], $p < 0.001$). This factor was not significantly associated with memory ($b = 0.073$, 95% CI [-0.016, 0.159], $p = 0.11$), language ($b = 0.070$, 95% CI [-0.205, 0.070], $p = 0.33$), or visuospatial function ($b = 0.058$, 95% CI [-0.164, 0.050], $p = 0.27$). There were no significant interaction effects of the “pace” factor and time on any of the cognitive domain z-scores. Figure 12 shows associations between the pace and stability gait component and each cognitive domain.

On the other hand, the “rhythm and timing” domain was positively associated with memory only ($b = 0.086$, 95% CI [0.009, 0.167], $p = 0.03$), as shown in Figure 13. No interaction effects of the “rhythm and timing” factor and visit were found on any of the cognitive domain z-scores.

Finally, greater gait “variability and stability” scores was associated with lower scores of visuospatial function ($b = -0.221$, 95% CI [-0.313, -0.129], $p = 0.01$), but not global cognition ($b = -0.075$, 95% CI [-0.160, 0.009], $p = 0.08$), memory ($b = -0.005$, 95% CI [-0.084, 0.070], $p = 0.8$), attention ($b = -0.077$, 95% CI [-0.207, 0.053], $p = 0.2$), nor language ($b = -0.012$, 95% CI [-0.110, 0.148], $p = 0.96$). A significant interaction effect of this factor and time was also found on visuospatial function ($b = 0.103$, 95% CI [0.017, 0.188], $p < 0.001$). Post hoc analysis of this interaction effect revealed that greater “gait variability and stability” scores was associated with significantly lower visuospatial function at baseline ($b = -0.20$, 95% CI [-0.294, -0.096], $p < 0.001$), but this association was attenuated and non-significant at follow-up ($b = -0.09$, 95% CI [-0.195, 0.0104], $p = 0.08$). The difference between the slopes at baseline and at follow-up was significant ($b = -0.103$, SE = -0.042, $t(271) = -2.42$, $p = 0.016$). Figure 14 shows relationships between each cognitive domain and the gait variability component.

Results of the linear mixed model are summarized in Table 15. Standardized coefficients (β) are also provided in Table 16.

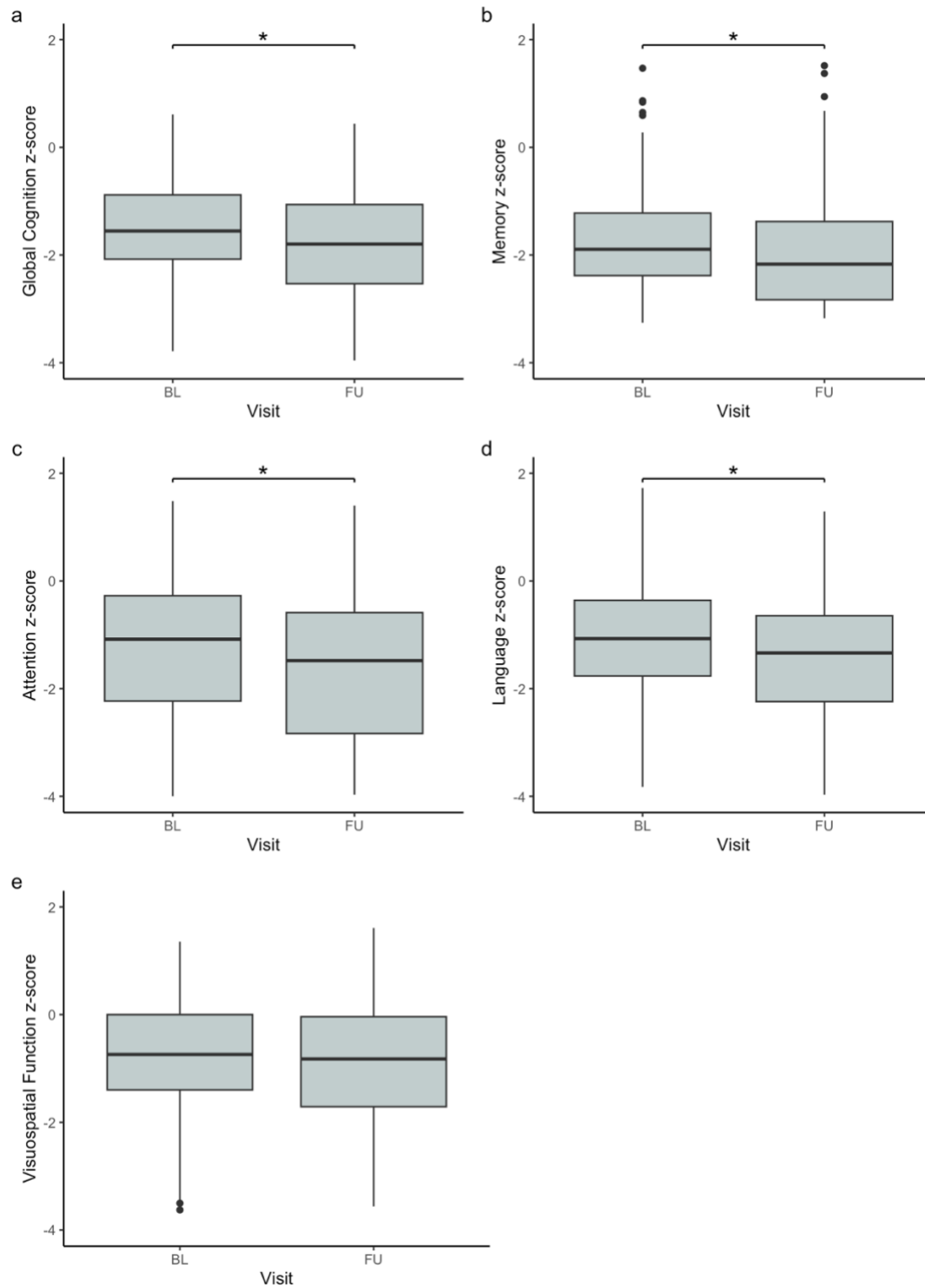


Figure 11: Change in cognitive domains from baseline to follow-up in MCI participants. Plots show changes in a) global cognition, b) memory, c) attention, d) language and e) visuospatial function z-scores from baseline (BL) to follow-up (FU) in individuals with MCI.

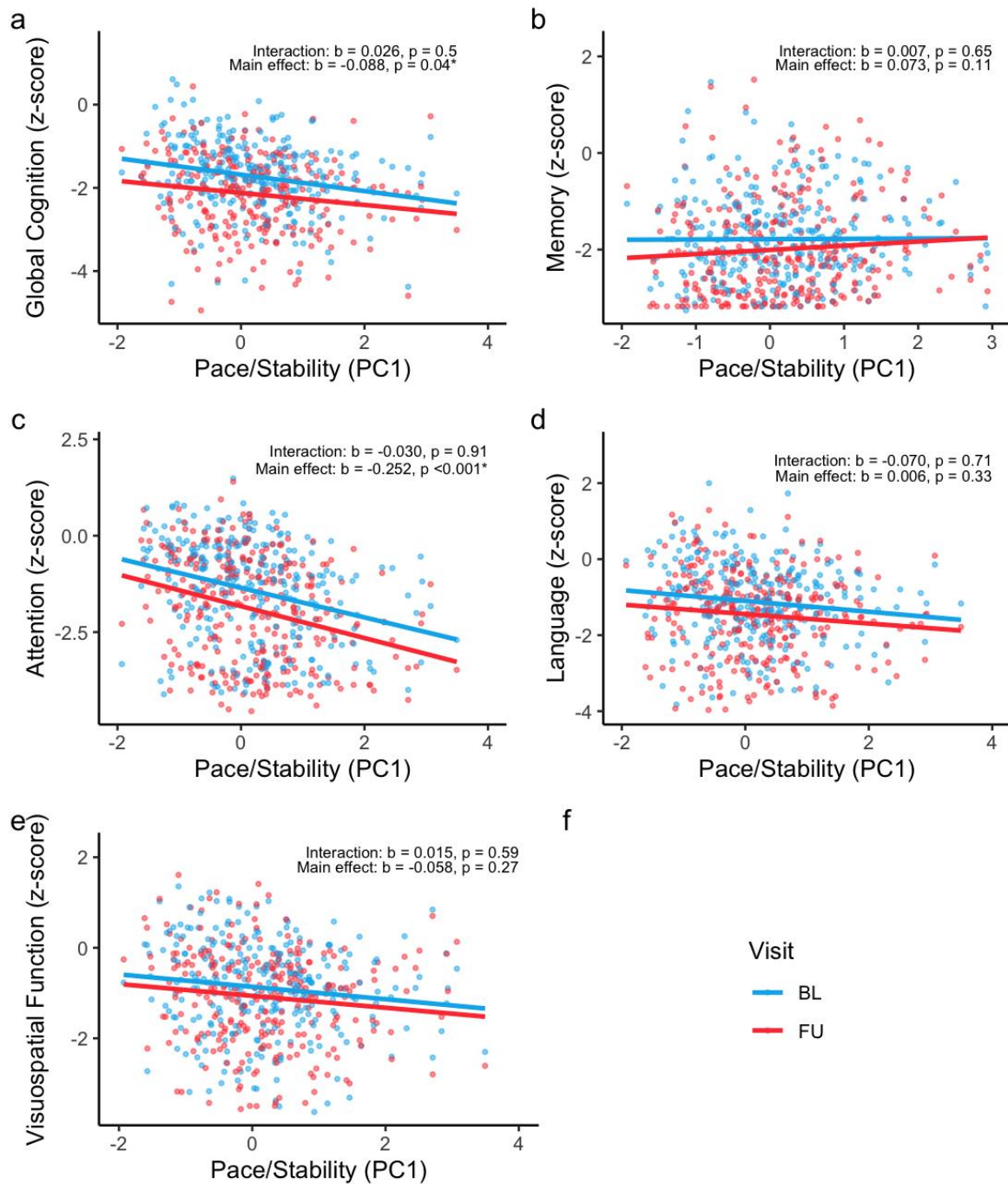


Figure 12: Relationship between the pace and stability gait factor and domain-specific cognitive z-scores at baseline and follow-up. Associations between the pace and stability factor and a) global cognition, b) memory, c) attention, d) language, and e) visuospatial function are shown at baseline (blue) and follow-up (Red). Unstandardized coefficients (b) and p values for main and interaction effect are reported on each graph. * indicates significant relationships. Abbreviations: PC1 = Principal Component 1; BL = baseline; FU = follow-up.

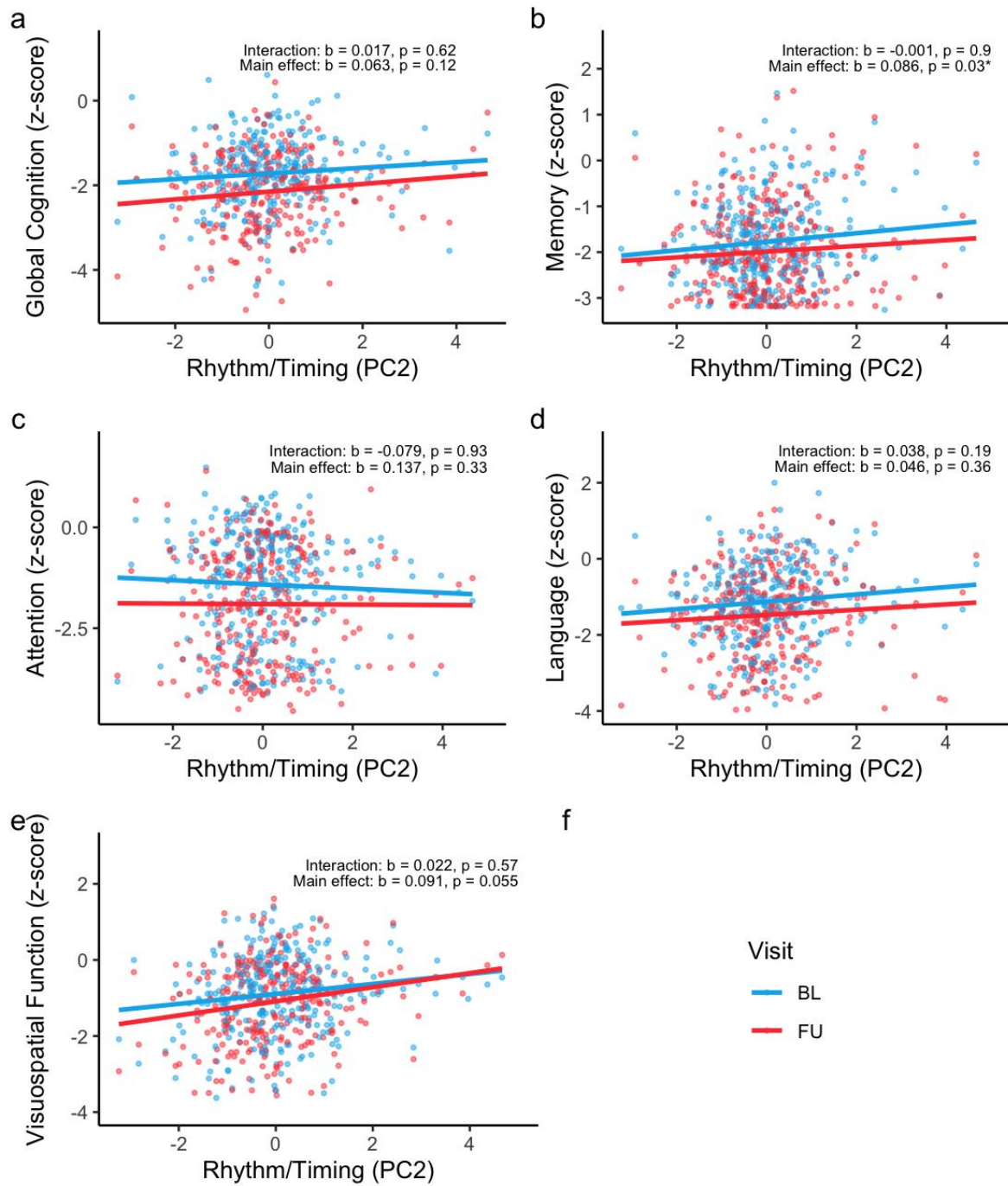


Figure 13: Relationship between the rhythm and timing gait factor and domain-specific cognitive z-scores at baseline and follow-up. Associations between the rhythm and timing gait factor and a) global cognition, b) memory, c) attention, d) language, and e) visuospatial function are shown at baseline (blue) and follow-up (Red). Unstandardized coefficients (b) and p values for main and interaction effect are reported on each graph. * indicates significant relationships. Abbreviations: PC2 = Principal Component 2; BL = baseline; FU = follow-up.

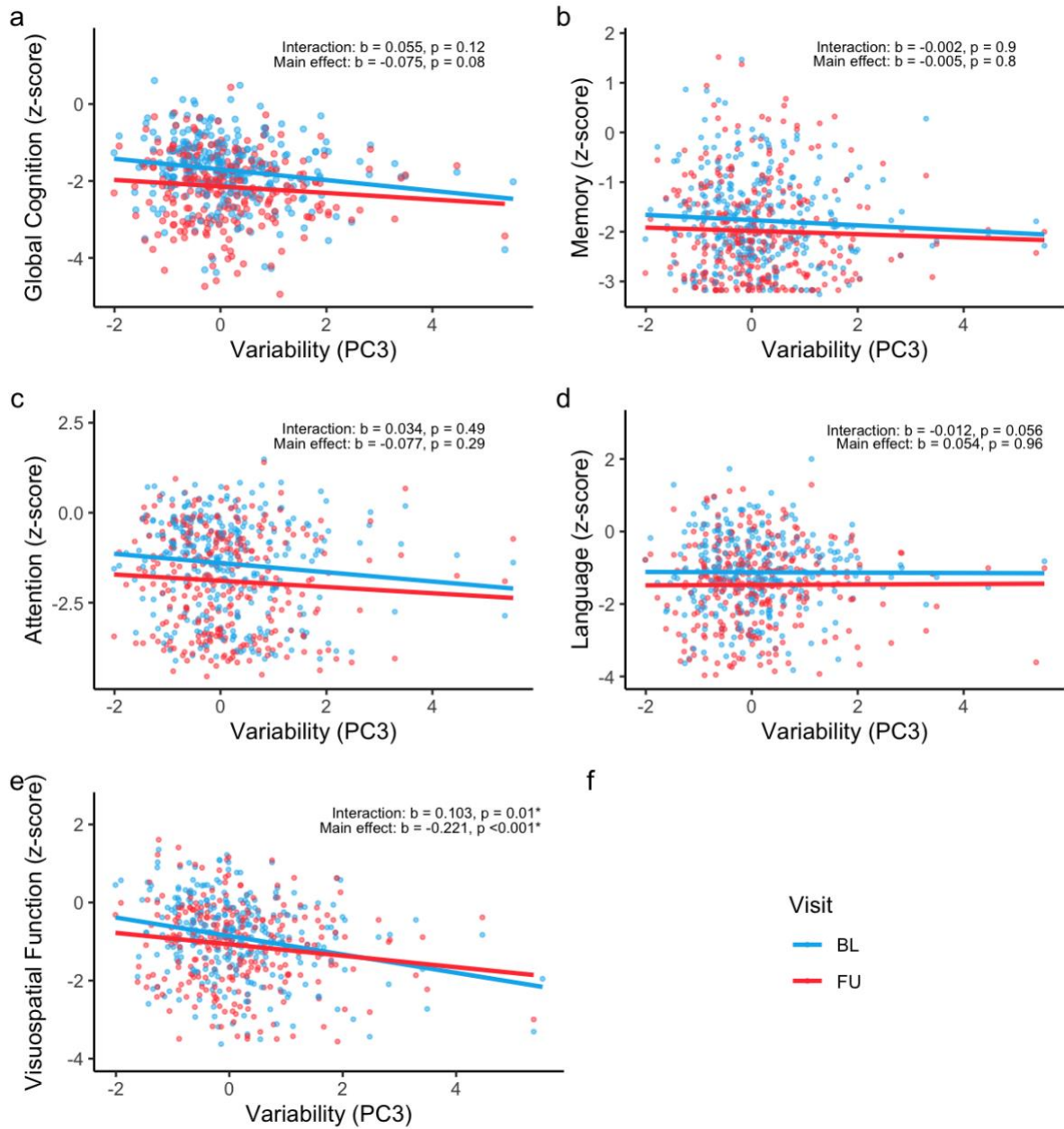


Figure 14: Relationship between the variability factor and domain-specific cognitive z-scores at baseline and follow-up. Associations between the variability factor and a) global cognition, b) memory, c) attention, d) language, and e) visuospatial function are shown at baseline (blue) and follow-up (Red). Unstandardized coefficients (b) and p values for main and interaction effect are reported on each graph. * indicates significant relationships. Abbreviations: PC3 = Principal Component 3; BL = baseline; FU = follow-up.

Table 16: Unstandardized coefficients for associations between each gait factor and cognitive domain z-score assessed with linear mixed models, adjusted for MCI subtype, pRBD status, age, sex, height, and follow-up duration.

	Global Cognition	Memory	Attention	Language	Visuospatial Function
Pace/Stability					
Factor	-0.088 [-0.175, -0.001]	0.073 [-0.016, 0.159]	-0.252 [-0.387, -0.121]	-0.070 [-0.205, 0.070]	-0.058 [-0.164, 0.050]
Factor x Time	0.026 [-0.049, 0.105]	0.007 [-0.064, 0.077]	-0.030 [-0.135, 0.078]	0.006 [-0.080, 0.094]	0.015 [-0.081, 0.103]
Timing/Rhythm					
Factor	0.063 [-0.017, 0.142]	0.086 [0.009, 0.167]	-0.009 [-0.137, 0.116]	0.046 [-0.080, 0.179]	0.091 [0.005, 0.176]
Factor x Time	0.017 [-0.049, 0.087]	-0.001 [-0.060, 0.062]	0.012 [-0.079, 0.111]	0.038 [-0.044, 0.114]	0.022 [-0.053, 0.097]
Variability					
Factor	-0.075 [-0.160, 0.009]	-0.005 [-0.084, 0.070]	-0.077 [-0.207, 0.053]	-0.012 [-0.110, 0.148]	-0.221 [-0.313, -0.129]
Factor x Time	0.055 [-0.017, 0.122]	-0.002 [-0.067, 0.062]	0.034 [-0.065, 0.139]	0.054 [0.028, 0.131]	0.103 [0.017, 0.188]

Data is reported as unstandardized coefficient [lower range of 95% CI, upper range of 95% CI]. Significant associations are bolded.

Table 17: Standardized coefficients for associations between each gait factor and cognitive domain z-score assessed with linear mixed models, adjusted for MCI subtype, pRBD status, age, sex, height, and follow-up duration.

	Global Cognition	Memory	Attention	Language	Visuospatial Function
Pace/Stability					
Factor	-0.10 [-0.19, -0.01]	0.08 [-0.02, 0.17]	-0.19 [-0.29, -0.09]	-0.05 [-0.16, 0.05]	-0.06 [-0.15, 0.04]
Factor x Time	0.03 [-0.06, 0.11]	0.01 [-0.07, 0.08]	-0.02 [-0.10, 0.06]	0.01 [-0.06, 0.07]	0.01 [-0.07, 0.10]
Timing/Rhythm					
Factor	0.08 [-0.02, 0.18]	0.10 [0.01, 0.20]	-0.01 [-0.11, 0.09]	0.04 [-0.07, 0.14]	0.10 [0.00, 0.20]
Factor x Time	0.02 [-0.06, 0.10]	-0.01 [-0.08, 0.07]	0.01 [-0.07, 0.09]	0.03 [-0.03, 0.10]	0.02 [-0.06, 0.11]
Variability					
Factor	-0.09 [-0.19, 0.01]	-0.01 [-0.10, 0.09]	-0.06 [-0.16, 0.04]	0.01 [-0.09, 0.11]	-0.22 [-0.32, -0.13]
Factor x Time	0.07 [-0.02, 0.15]	0.01 [-0.08, 0.07]	0.03 [-0.05, 0.11]	0.04 [-0.02, 0.11]	0.11 [0.02, 0.19]

Data is reported as standardized coefficient [lower range of 95% CI, upper range of 95% CI]. Significant associations are bolded.

Chapter 6: Discussion

6.1 Summary of Findings

The primary and secondary objectives of this study aimed to compare how gait changes over time in different MCI subtypes. It was hypothesized that all individuals with MCI will exhibit decreased stride velocity and step length, and greater step time, swing time, and double support (%) than CU individuals at baseline and over time, but individuals with non-amnesic impairment will also exhibit increased gait variability than CU individuals and the SD-aMCI group. Furthermore, individuals with multi-domain cognitive impairment will exhibit more pronounced gait changes compared to individuals with single-domain cognitive impairment. These hypotheses were partially supported, as all individuals with MCI exhibited decreased stride velocity and step length and increased double support (%) and step time than CU individuals. Moreover, the MD-aMCI group alone had increased variability in stride velocity, step length, and swing time compared to CU individuals. This group also exhibited increases in step time and reduction in stride velocity and step length after a mean follow-up of 16.8 months. Step length also decreased in SD-naMCI over time.

The third objective was to explore how the presence of pRBD influences gait outcomes in individuals with MCI. It was predicted that the presence of pRBD will further exacerbate these gait differences, particularly in individuals with non-amnesic impairment. This hypothesis was partially supported as we found that individuals with MD-naMCI and pRBD exhibited decreased stride velocity, step length and swing time, as well as increased stride width and double support (%). Swing time increased after follow-up in people with MD-naMCI and pRBD.

Finally, the fourth objective of this study was to explore if gait outcomes can predict change in cognitive performance over time in individuals with MCI. It was hypothesized that baseline gait characteristics will predict change in cognitive performance over time in individuals with MCI, mirroring previously reported selective associations between gait and cognition. Results revealed three gait factors representing pace, timing and rhythm, and gait variability and stability, which were associated with specific cognitive domains. The pace component was negatively associated with global cognition and attention. Timing and rhythm was positively associated with memory, and gait variability and stability were negatively associated with visuospatial function. These effects did not change over time with the exception of the association between the variability and stability component and visuospatial function, which weakened and became non-significant at follow-up.

6.2 Gait Differences Between CU individuals and Across MCI Subtypes

This current study demonstrated clear differences in gait between CU participants and participants with MCI. As mentioned previously, various earlier studies revealed that individuals with MCI walk slower, with decreased step length, and increased step time and double support (%) than healthy controls (Choi et al., 2011; Cullen et al., 2019; Du et al., 2023; Goyal et al., 2019; Nascimbeni et al., 2015; Verghese et al., 2007; Yamagami et al., 2023). These findings are further supported by this current study, as individuals with MCI in this sample also exhibited decreased stride velocity and step length, and increased step time and double support (%) compared to CU individuals, regardless of MCI subtype.

Decreased stride velocity, step length and step time highlight that individuals with MCI overall walk slower, by taking longer to take shorter steps, than CU older adults. Previous research has demonstrated that gait slowing precedes cognitive decline, which is in line with this finding in this sample of individuals with MCI (Beauchet et al., 2016; Buracchio et al., 2010; Camicioli et al., 1998). Double support (%) is also related to stride velocity, wherein slower gait velocity is associated with increased double support (%) (Williams & Martin, 2019). However, increased double support (%) in MCI may also reflect compensatory behavior to increase postural stability during walking as base of support is wider and humans have better control of their center of gravity when in double support (Williams & Martin, 2019). This work contributes to a growing body of literature that recognizes gait as a marker of cognitive decline.

While these findings of gait differences between MCI and CU individuals supports previous findings, a novel aim of this work is the comparison of gait over time in all four MCI subtypes. Notably, increased gait variability in step length and stride velocity were observed only in individuals with MD-aMCI compared to CU older adults. Several studies have linked increased gait variability to cognitive dysfunction, particularly in attention and executive function. One study has also previously linked gait variability with impairment in visuospatial function in PD (Amboni et al., 2012; Morris et al., 2016). Individuals with MD-aMCI have impairment in memory and at least one other non-memory domain. Therefore, the non-memory impairment may explain why gait variability is increased in MD-aMCI, but not in SD-aMCI. As mentioned previously, in one study, aMCI was reported to have increased variability in stride time than naMCI (Montero-Odasso et al., 2014). However, the aMCI sample of that study had greater deficits in executive function than naMCI,

indicating the sample included participants with MD-aMCI, which may explain this increase in gait variability (Montero-Odasso et al., 2014). Longitudinally, results showed that the MD-aMCI group also demonstrated significant reductions in stride velocity and step length and increases in step time from baseline to follow-up, but gait outcomes did not change over time in any other groups.

One important difference between the current study and prior research study is in recruitment strategies. MCI participants in the Mayo Clinic Study of Aging were recruited from the general population in the Olmstead County in Minnesota (Roberts et al., 2008). Verghese et al analyzed data in the Einstein Aging Study, which also recruited from the general population in the Bronx community (Verghese et al., 2008). Beauchet et al analyzed data from the Gait and Alzheimer's Interaction Tracking study which recruited people from local memory clinics in Angers, France (Beauchet et al., 2011). Montero-Odasso et al recruited participants in the Gait and Brain study from local clinics in London, Ontario (Montero-Odasso et al., 2014). Finally, Allali et al involved analysis of data from various sources that includes both population-based cohorts and participants recruited from memory clinics from several locations across the world (Allali et al., 2016). It is possible that there are differences between people with MCI recruited through the general population and people with MCI recruited from clinics and hospitals. Particularly, individuals with MCI recruited from clinics and hospitals may be less heterogeneous and more likely to have a neurodegenerative etiology, compared to samples of MCI recruited from population-based cohorts. This is another potential source of difference between studies that might explain why findings regarding how gait differs across MCI subtypes.

It is also important to recognize that while straight-line single-task walking is less cognitively demanding than dual-task walking or walking while navigating obstacles, it is becoming increasingly recognized that even simple walking is not entirely automatic in older adults (Mirelman et al., 2018). This is evidenced by increased gait variability and slower gait while dual-tasking in older adults, suggesting attentional resources are still needed for simple walking (Mirelman et al., 2018). Thus, slowing of gait and increased gait variability in MD-aMCI in the current study may be due to their widespread cognitive impairment, which includes impairment in non-amnestic domains, despite gait being measured through simple walking. However, it is possible that more complex walking tasks may exacerbate slowing of gait or reveal further changes to gait outcomes in this group, and potentially in single-domain MCI subtypes. A variation of tasks, beyond just dual-tasking, may also

be important. For example, using obstacle crossing or reactive stepping can challenge gait, rather than cognition, to better expose problems of gait control more directly (Galna et al., 2009).

As multi-domain impairment in MCI is associated with increased risk of progression to dementia, it was hypothesized that individuals with multi-domain impairment would exhibit slowing of gait and increases in gait variability over time (Michaud et al., 2017). This was partially supported, as only the MD-aMCI demonstrated changes in stride velocity, step length and step time and increased gait variability, but not the MD-naMCI group.

This is surprising as individuals with MD-naMCI have cognitive impairments in multiple non-memory domains, including executive function, attention and visuospatial function which have been linked to slower pace and increased gait variability (Amboni et al., 2012; Morris et al., 2016). This may be due to the limited sample size of the MD-naMCI group in this study, as they were the smallest group in the study, consisting of 20 participants at baseline. As this is a very small sample size, this study may have been underpowered to detect differences between them and other groups, or changes over time in this group. Moreover, the small sample size may mean this is not a representative sample of people with MD-naMCI, which is particularly important given the heterogeneity of MCI.

Additionally, the follow-up duration in this study was relatively short, with an average follow-up of less than two years in all groups. This is important as the course of MCI can be highly variable. Some individuals with MCI advance to dementia, others remain stable with MCI for several years, and some may even revert to normal cognition. These differing trajectories may be impacted by underlying differences in pathology and comorbidities, or by lifestyle factors (Shimada et al., 2019; Xue et al., 2019). As such, change in gait over time may also mirror this heterogeneity, where some participants may show marked slowing of gait over time, while others exhibit relative stability. Consequently, the hypothesis for this aim may not have been supported due to variation in the course of MCI among participants in the study. While MCI subtype was modeled as a time-varying variable in the analyses of this study in an effort to account for variability in clinical trajectories, the variable trajectories of these participants may not have been adequately captured due to limited follow-up duration. Additionally, participants who progressed to dementia after follow-up were not included, which likely limited the overall decline in cognitive function.

Finally, it was hypothesized that gait and its progression would differ between MCI subtypes, however this was not supported as results mostly demonstrated differences between participants with MCI and CU individuals, not across MCI subtypes. While this current study subtyped MCI based on the clinical presentation (i.e., amnesic vs. non-amnesic, single-domain vs. multi-domain), MCI can arise due to a range of underlying etiologies, which may affect gait differently. For example, aMCI is often due to underlying AD pathology, namely amyloid- β and tau deposition in medial temporal regions, but in other cases, it may also be a result of cerebrovascular pathology, previous traumatic brain injury, psychiatric conditions, or systemic medical conditions (Petersen, 2016). These etiologies may contribute to heterogeneity in this sample of participants with MCI, with differing underlying neural mechanisms that may impact cognition and motor control. As a result, gait may be impacted differently across individuals with the same cognitive subtype of MCI. This may explain why the hypotheses were only partially supported.

These hypotheses were informed in part by previous literature comparing gait characteristics across dementia subtypes, such as AD and DLB (Elasfar, Hameed, Boeve, et al., 2025; Fritz et al., 2016; Mc Ardle et al., 2019, 2020). However, MCI represents a prodromal and transient stage, where trajectory toward a specific neurodegenerative disorder is not always certain (Petersen, 2004, 2016). While aMCI is more likely to progress to AD, and naMCI is more likely to progress to non-AD dementias, such as DLB, these are not definitive trajectories, as not all individuals with MCI will progress to dementia or to specifically these dementia subtypes (Petersen, 2004, 2016). In addition, it is difficult to know how close participants are to developing dementia given that cognitive decline does not necessarily decline linearly in people with MCI (Michaud et al., 2017; Roberts et al., 2014).

Therefore, the primary and secondary hypotheses of this thesis may be oversimplifications of the relationship between gait characteristics and MCI subtypes. Without extended follow-up and biomarker confirmation, it remains difficult to distinguish participants who will progress to neurodegenerative conditions, from those with stable MCI, or MCI due to other etiologies. This heterogeneity may partially explain why hypothesized patterns of gait decline were only partially supported in this study.

6.3 Role of pRBD in Gait Changes among MCI subtypes

The third aim of this thesis was to investigate how the presence of pRBD may impact gait characteristics among individuals with MCI, and whether this relationship differs between MCI

subtypes. Previous research has shown that prior to the onset of parkinsonian symptoms and an overt α -synucleinopathy, individuals with iRBD exhibit subtle changes in balance and gait, as well as other motor functions (Del Din et al., 2020; Fereshtehnejad et al., 2019; McDade et al., 2013; Postuma et al., 2006, 2009). Patients with comorbid RBD and MCI are also at risk for early phenocconversion (Arnaldi et al., 2021). Based on this, it was hypothesized the presence of pRBD, particularly in people with naMCI subtypes, will be associated with decreased stride velocity, step length and stride width, and increased step time, swing time, and double support (%), as well as increased gait variability compared to individuals with MCI alone.

In this study, the presence of pRBD was associated with gait differences in individuals with MD-naMCI. Specifically, individuals with this MCI subtype and pRBD exhibited significantly reduced stride velocity, step length, and swing time, as well as increased stride width and double support (%) compared to individuals with MD-naMCI without pRBD. These findings partially support our hypothesis that comorbid pRBD will exacerbate gait changes in individuals with MCI, particularly naMCI groups.

These gait changes of slower gait may reflect bradykinesia-like features, while increased stride width and double support (%) may reflect compensatory strategies for maintaining balance (Peterson & Horak, 2016). This is consistent with prior research that has shown that the presence of pRBD in healthy older adults is associated with gait changes compared to older adults without pRBD (McDade et al., 2013). Notably, parkinsonian gait is characterized by slow gait with shorter steps (Peterson & Horak, 2016). As individuals with RBD are at increased risk of developing PD and DLB, and this risk is further increased in individuals with cognitive impairment and RBD, these gait changes may be early manifestations of parkinsonian symptoms (Arnaldi et al., 2021; Postuma et al., 2019).

The increase in swing time over time may reflect disruption of gait timing, which may be linked to basal ganglia and brainstem dysfunction, which occurs in Lewy body pathology (Adler et al., 2019; Beach et al., 2009; Del Din et al., 2020; Peterson & Horak, 2016). Interestingly, previous research has highlighted that individuals with RBD exhibit disruptions in timing and rhythm aspects of various motor tasks, including gait and tapping tasks, even prior to slowing of motor tasks (Cohen De Cock et al., 2020, 2022; McDade et al., 2013). Del Din et al also demonstrated that swing time

was increased in people with iRBD compared to healthy controls, and it was outcome that most strongly distinguished these groups (Del Din et al., 2020).

However, it is important to consider that although significant, the magnitude of the difference and change in swing time between MD-naMCI with and without pRBD in this study was small and may not reflect a clinically meaningful change. Moreover, there was considerable variability in swing time between participants with MD-naMCI and pRBD, as reflected in the 95% confidence interval of the EMM for swing time in this group in Figure 5G. This is likely due to the limited sample size of seven out of 20 participants with MD-naMCI also having pRBD. Moreover, pRBD was defined using the MSQ. While this questionnaire has demonstrated adequate sensitivity and specificity for detecting pRBD, diagnosis cannot be definitively confirmed without a polysomnography (Boeve et al., 2013). This may further explain variability in certain gait measures, including swing time, as there is the possibility of false positives or undetected pRBD cases in this sample.

It was also hypothesized that stride width will be decreased in individual with MCI and pRBD, particularly multi-domain MCI subtypes. This was informed by previous research demonstrating that individuals with iRBD do not increase their step width during dual-task walking, and because individuals with PD exhibit narrow-based gait (Ehgoetz Martens et al., 2019; Nonnekes et al., 2018; Pistacchi et al., 2017). However, the results found increased step width in individuals with MD-naMCI and pRBD, compared to individuals with MD-naMCI without pRBD. Instead of reflecting early manifestations of parkinsonian gait, this may reflect a compensatory strategy, whereby individuals widen their base of support to improve balance and stability while walking.

Importantly, no significant gait differences associated with the presence of pRBD were observed in any other MCI subtypes (SD-aMCI, SD-naMCI and MD-aMCI) or in CU individuals. Given that it is well-established that RBD is a prodromal marker for α -synucleinopathies, it is likely that individuals with pRBD across all subtypes in this study will develop PD or DLB (Boeve, 2010; Postuma et al., 2019). However, the absence of gait differences between those with and without pRBD in these subtypes suggests these individuals are at an early disease stage, where changes in motor function, or at least gait, are not yet observable.

On the other hand, the specificity of effect in individuals with MD-naMCI may reflect the high risk of early phenoconversion that is seen in individuals with concurrent pRBD and MCI. Furthermore in MCI, multi-domain MCI subtypes are associated with increased risk of progression to

dementia, further suggesting this group may be closer to phenoconversion (Arnaldi et al., 2021). Additionally, cognitive impairment in PD and DLB is most often in non-amnestic domains, particularly executive function, attention and visuospatial deficits (Aarsland, 2016; Goldman & Litvan, 2011; Janvin et al., 2006). Therefore, the combination of pRBD and widespread non-amnestic cognitive impairment could reflect increased underlying α -synuclein burden and proximity to phenoconversion, which might explain why their gait is starting to resemble parkinsonian gait, with bradykinesia-like features, disrupted timing, and compensatory postural adjustments.

In summary, results highlight that the presence of pRBD in MD-naMCI is associated with additional changes in gait, particularly slower and more cautious gait. However, the limited sample size is an important limitation of these results. With only seven total participants with pRBD and MD-naMCI, this may not be a representative sample. This is especially important given the heterogeneity of both of these conditions, which would not be well represented with a limited sample size. Therefore, although this study provides preliminary evidence of associations between pRBD presence and gait changes in individuals with MD-naMCI, results should be interpreted with caution.

6.4 Gait as a Predictor of Change in Cognition in MCI

The final aim of this thesis was to investigate whether baseline gait characteristics can predict change in domain-specific cognitive performance from baseline to follow-up in individuals with MCI. Previous research has demonstrated that motor and cognitive functions are intricately linked and may rely on shared neural resources (Morris et al., 2016; Rosano et al., 2012; Wilson et al., 2019). Additionally, cognitive domains have been independently linked to distinct cognitive domains, leading to the hypothesis of distinct associations between specific cognitive domains and gait factors (Morris et al., 2016).

Using principal component analysis, three distinct gait components were identified, namely pace (e.g., stride velocity, step length, double support (%)), timing and rhythm (e.g., step time, swing time), and gait variability and stability (e.g. step length variability, stride velocity variability). These components were then used in longitudinal models to assess associations with changes in domain-specific cognitive z-scores. The pace component was labeled as such because it had strong loadings from stride velocity, as well as from measures that typically covary with walking speed, such as step length, stride width, and double support (%). These variables reflect the overall speed of gait, making “pace” the most appropriate label. The timing and rhythm component was characterized by strong

loadings from measures of gait cycle timing, including step time and swing time. These outcomes capture the temporal structure of gait and thus were deemed the timing and rhythm factor. Finally, the gait variability and stability component had strongest loadings from measures of variability, such as step length variability and stride velocity variability. These outcomes quantify step-to-step fluctuations and are often interpreted as indicators of dynamic balance control (Hausdorff, 2005; Pieruccini-Faria et al., 2020b). Greater variability in foot placement can signal instability in the anteroposterior direction (step length variability) and mediolateral direction (step width variability) (Bauby & Kuo, 2000; MacKinnon & Winter, 1993; Moe-Nilssen et al., 2010; Stimpson et al., 2018). Prior research has also found that swing time variability is an independent measure of gait speed and can be used as a proxy for unsteadiness in people with PD (Frenkel-Toledo et al., 2005). For these reasons, this component was labeled as “variability and stability”, to reflect both the step-to-step fluctuations of gait and their relevance for dynamic balance control.

Before discussing the results of this analysis, it is worth discussing that some gait characteristics exhibited cross-loading across multiple gait domains, despite orthogonal rotation being applied to the principal component analysis, as shown in Table 11. Particularly, step time variability exhibited cross-loading across the three components. It is not surprising as it directly measures variability, but it also measures in timing and rhythm gait characteristics and has been shown to be related to walking speed in people with PD (Frenkel-Toledo et al., 2005). Inherently, all gait characteristics will be closely associated, so some degree of cross-loading is not surprising. Based on this, these gait characteristics were kept in the model. Importantly, multi-collinearity assumptions were not violated in any of the models.

The pace component was significantly associated with global cognition and attention, regardless of timepoint. Lower baseline scores in this component indicated slower gait, characterized by reduced stride velocity and step length, as well as increased double support (%), stride width, and step time variability. This gait pattern was associated with decreased global cognition and attention. This aligns with previous research that has linked reduced global cognition and attention with slower gait (Morris et al., 2016). Attention and executive control are important cognitive functions for planning, initiating and monitoring gait, so impairments in these domains may result in compensatory walking behavior involving slower, more cautious walking. (Mirelman et al., 2018; Woollacott & Shumway-Cook, 2002).

There was also a weak but positive association between timing and rhythm scores and memory decline. This is counterintuitive given that increased baseline timing and rhythm indicates increased step time and swing time, which suggests slowing of gait, but is associated with better memory scores. Additionally, the relationships between other gait factors and cognition suggests the opposite, for example, slower pace is associated with worse scores of global cognition and attention.

This finding is also contradictory to a previous study by Verghese et al, which found that the rhythm component of gait, characterized by decreased cadence and increased swing time and stance time in their study, predicted future memory decline in healthy older adults (Verghese et al., 2007). One possible explanation for the difference in results is the difference in gait outcomes measured in this current study and their study, as in the present study, the rhythm and timing component is primarily characterized of strong positive loadings from step time and swing time. Additionally, Verghese et al used the Free and Cued Selective Reminding Test to measure memory performance, whereas this study used a composite z-score made up of Logical Memory-II and Visual Reproduction-II from the WMS-R, and the Auditory Verbal Learning Test. Furthermore, their study was in healthy older adults, whereas the population in the present study are individuals with MCI. Follow-up duration was also longer in their study compared to the current study. Given the small effect size and the contradictory findings, these results should be interpreted with caution and further investigation is needed to confirm the relationship between gait rhythm and memory decline reported by Verghese et al (Verghese et al., 2007).

Finally, gait variability and stability was associated with visuospatial function. Increased gait variability has been linked with impaired cognitive function in older adults and individuals with PD, particularly deficits in global cognition, attention and executive function (Amboni et al., 2012; Lord et al., 2014; Morris et al., 2016). However, relatively few studies have explored associations between visuospatial function and gait variability measures, with conflicting results (Amboni et al., 2012; Lord et al., 2014). Research in individuals with posterior cortical atrophy, which is often considered a variant of AD with deficits in visuospatial function, has shown increased gait variability compared to individuals with typical AD, DLB, and CU individuals (Crutch et al., 2012; Mc Ardle, 2025; Mc Ardle et al., 2020). Interestingly, this difference was only found in the lab environment, and not in real-world gait, collected using wearable sensors on the fifth lumbar vertebrae over seven days (Mc Ardle, 2025; Mc Ardle et al., 2020). The authors suggested that given their visuospatial deficits, participants with posterior cortical atrophy may pay more attention to their gait in a novel, unfamiliar

environment, such as a lab environment, leading to slower, more variable, and less automatic gait (McArdle, 2025). These findings suggest that visuospatial deficits may interfere with processing of the environment, which is critical for safe gait, and for adjustments in walking in response to the environment.

This aligns with the results of this current study showcasing that gait variability is associated with visuospatial function in MCI. Early deficits in visuospatial abilities may result in more variable gait, potentially through disrupting the ability to process information about the environment, which may contribute to slower gait, with more volitional control, thereby resulting in increased gait variability (Mirelman et al., 2018; Peterson & Horak, 2016). Deficits in visuospatial processing may contribute to the ability to accurately assess information about the environment, which is essential for the planning of movement (Mirelman et al., 2018). However, in addition to being important for planning of movement, gait also relies on integration of visual and sensory feedback to update and adjust the initial motor plan (Hocking et al., 2011; Patla, 1997). Therefore, it may also be that these individuals with visuospatial deficits experience difficulties with continuous integration of sensory information, resulting in more cognitive resources being needed to monitor and control gait, leading to more variable gait. This association between visuospatial function and increased gait variability has been reported in healthy older adults and in PD (Amboni et al., 2012; Martin et al., 2013).

Importantly, gait variability measures can also be interpreted as indirect indicators of dynamic balance control. Variability in stride length or step time may reflect AP instability, while variability in step width may reflect ML instability (Bauby & Kuo, 2000; Hausdorff, 2005; MacKinnon & Winter, 1993; Moe-Nilssen et al., 2010; Pieruccini-Faria et al., 2020b). Therefore, step-to-step fluctuations in gait may suggest that visuospatial deficits may compromise adjustments needed to maintain stability, leading to more variability in foot placement as individuals are walking. Individuals with impaired visuospatial processing may have difficulty accurately locating their foot relative to the body and the environment, leading to inconsistent placement from step to step. Therefore, the observed association between visuospatial function and gait variability may reflect problems with processing information about the environment as well as reduced dynamic balance control.

Interestingly, the only significant interaction effect between any gait outcome and time on a cognitive domain was found between gait variability and time on visuospatial function, such that,

compared to baseline, the association between gait variability and visuospatial function was weaker and non-significant at follow-up. In addition, visuospatial function was the only cognitive domain that did not show significant decline from baseline to follow-up. The lack of substantial cognitive change may explain why the strength of the association was attenuated at follow-up compared to baseline

This lack of change may be due to limited follow-up duration, or limitations of the cognitive battery, which utilized traditional pen-and-paper neuropsychological assessments to measure performance in each cognitive domains, in particular the Picture Completion Test and Block Design tests were used to measure visuospatial function. Limitations of traditional pen-and-paper assessments of cognition have been highlighted previously in the literature (Allard et al., 2014; Sliwinski et al., 2018). They may lack ecological validity, as they only capture a snapshot of cognitive functioning and do not consider potential sources of within-person variability in cognition, for example, recent changes in sleep quality or exposure to a stressor (Sbordone & Purisch, 1996; Sliwinski et al., 2018). Additionally, these tests may suffer from floor or ceiling effects, which could explain the lack of change in visuospatial function from baseline to follow-up. Practice effects may also play a role. Although more than a year passed between assessments, participants could still have benefited from familiarity with the tasks or from strategies learned during the first exposure to the test (Lichtenberger, 2013).

Moreover, the exclusion of people who develop dementia in follow-up visits may have narrowed the change in cognition from baseline to follow-up. At the same time, excluding participants who reverted to CU individuals would have also excluded individuals that improved, which may have obscured findings if they were included. The exclusion of these groups however may limit generalizability of these findings to individuals with MCI who do not have stable MCI diagnoses and either progress to dementia or revert to normal cognition.

While some of the results of this aim align and confirm results from previous studies that have established similar associations between specific cognitive domains and gait domains, the effect sizes of these relationships are all considerably small. Furthermore, there were no interaction effects between any of the gait factors and time on any of the cognitive domains, with the exception of gait variability and visuospatial function, but even this effect was small and not in the hypothesized direction. This means there is limited evidence that gait outcomes at baseline can predict subsequent change in cognitive function over time in MCI. There are several possible reasons for these findings.

Firstly, as mentioned previously, follow-up duration was relatively short in this study, which may have limited the ability to adequately capture meaningful longitudinal changes in cognition in MCI. This is further complicated by the varying trajectories that MCI can take (Petersen, 2016). Secondly, as discussed previously, the lack of data about the etiology of MCI in these participants means there may be heterogeneity in underlying pathology which may have influenced the associations between gait factors and cognitive performance (Petersen, 2016). Thirdly, gait was assessed on a six-meter walkway, which may not allow for a sufficient number of strides to achieve steady state gait, and therefore reliably capture gait outcomes, particularly gait variability (Hollman et al., 2010). Finally, as mentioned previously, cognition was assessed using traditional pen-and-paper neuropsychological assessments which may lack ecological validity (Allard et al., 2014; Sbordone & Purisch, 1996; Sliwinski et al., 2018). The use of domain-level composite z-scores may have also masked changes captured by specific tests, especially if one test within the domain is more or less sensitive to changes in cognitive performance.

It is also worth noting that the principal component analysis was used to reduce dimensionality and multicollinearity between our gait variables but may have compromised the interpretability of these findings. This was the similar approach used in prior studies investigating whether gait decline can predict future cognitive decline in healthy older adults (Verghese et al., 2007). Rather than using factor analysis, it may be worthwhile to investigate associations between a select few gait variables and specific cognitive domains to improve interpretability of these associations. However, given the gait variables in this study were a priori selected, to avoid bias, select gait variables were not selected again from the eleven gait outcomes selected previously.

In summary, this study identified domain-specific associations between gait outcomes and cognitive function: pace and stability with both global cognition and attention, timing and rhythm with memory, and gait variability with visuospatial function and global cognition. However, there was no evidence to support the predictive value of gait for cognitive decline over time in MCI. The only significant interaction revealed that baseline gait variability was more strongly associated with visuospatial function at baseline than at follow-up. Additionally, weak effect sizes in the current study and contradictory findings to prior research warrant further investigation before firm conclusions can be made.

6.5 Potential Alternative Explanations for Findings

Although this thesis emphasizes the role of cognition in gait, many other factors contribute to gait function and may explain why gait differs in individuals with MCI from healthy aging, so the potential for alternative explanations cannot be ignored.

Firstly, gait is influenced by physical and biomechanical properties, such as lower-limb strength, body composition, joint range of motion, and other anthropometric elements (Beavers et al., 2013). The ability to process and integrate sensory information, particularly, vision, vestibular and proprioceptive information also plays an important role in gait control (Aboutorabi et al., 2016; Osoba et al., 2019). Declines in these sensory systems, and changes in body composition and range of motion often occur with aging, which can contribute to overall slowing of gait (Aboutorabi et al., 2016; Beavers et al., 2013; Osoba et al., 2019).

Musculoskeletal disorders, vascular conditions, neuropathy, and diabetes can also impair mobility (Alam et al., 2017; de Laat et al., 2010; Dixon et al., 2017; McCully et al., 1999; Petrofsky et al., 2005). Cardiovascular and respiratory diseases, such as heart failure and chronic pulmonary obstructive disorder may result in reduced aerobic capacity, which can contribute to slower gait (Panizzolo et al., 2014; Pulignano et al., 2016; Zago et al., 2018). In addition, psychiatric and psychological factors such as anxiety, depression, and fear of falling can influence gait cautiousness and lead to slower gait (Belvederi Murri et al., 2020; Feldman et al., 2019; Norouzzian et al., 2024). This is particularly important given that depression and anxiety are often comorbid with MCI, and individuals with MCI experience falls more often than healthy older adults, so they may be more likely to experience fear of falling, leading them to adopt a cautious and slower gait pattern (Borges et al., 2015, 2015; Ma, 2020; Mirza et al., 2017). Due to limited data availability for this sample, comorbidities and other psychological disorders were not adjusted for in the models, so it is possible they have influenced findings.

Sleep quality is also important to consider, given that individuals with RBD often report poor sleep quality, which may result in fatigue, that could also impact their walking speed (Arnulf et al., 2015; Hu, 2020; Jung & St. Louis, 2016; Milane et al., 2024). The only sleep scale used in the Mayo Sleep Study of Aging was the MSQ to diagnose pRBD, which does not directly address sleep quality (Boeve et al., 2013). Future studies exploring how gait and motor function changes in the presence of

pRBD should measure sleep quality as well as daytime sleepiness, as these factors may impact performance.

Therefore, gait may not solely reflect neurodegeneration but may serve as a general biomarker of aging. Markers such as grip strength, processing speed, and frailty also worsen with age and are associated with both gait performance and cognitive outcomes (Chou et al., 2019; Cui et al., 2021; Ebaid et al., 2017; Eckert, 2011; Orchard et al., 2022; Park & Reuter-Lorenz, 2009; Robertson et al., 2013; Zammit et al., 2019). Therefore, gait changes may be a result of more global age-related changes that are more often comorbid in clinical populations like MCI and RBD compared to healthy aging, rather than dementia risk, specifically. Alternatively, it is possible that gait is still sensitive to dementia risk, but this cannot be ascertained without properly measuring and adjusting for these age-related outcomes that also affect gait.

In this study, the inclusion of age-matched controls and age as a covariate in analyses helped mitigate some of these confounding influences. However, we did not have consistent data on anthropometric measures, comorbidities, mood symptoms, or sleep quality, so we could not adjust for these factors directly. As a result, alternative explanations for gait differences in MCI cannot be ruled out. Therefore, these considerations highlight that gait is shaped by multiple influences, and acknowledging this complexity is important when interpreting gait changes in MCI and their potential as predictors of future cognitive decline.

6.6 Clinical Implications

This thesis provides further evidence that slow gait is characteristic of MCI. Results also suggest that slowing of gait over time and increased gait variability may be specific to multi-domain MCI subtypes. Gait outcomes are also impacted by the co-occurrence of pRBD in MCI. Furthermore, distinct relationships between gait outcomes and specific cognitive domains were found in MCI. These findings have important clinical implications.

Firstly, these findings support a growing body of literature that has identified slowing of gait as an important biomarker for cognitive decline and MCI. Individuals with MD-aMCI demonstrated increased gait variability and a more rapid reduction in gait speed than other MCI subtypes. As multi-domain cognitive impairment is associated with poorer prognosis and faster progression to dementia, these gait markers may help identify individuals that are at high risk of further cognitive decline (Michaud et al., 2017). Similarly, individuals with MD-naMCI and pRBD demonstrated slower gait

with wider steps and increased double support (%). These distinct gait changes may therefore help identify individuals at high-risk of α -synucleinopathies, namely PD and DLB. Therefore, incorporating gait assessment in clinical evaluation of individuals with MCI may allow early identification of individuals with the highest risk of advancement to PD and dementia. As gait can be assessed relatively quickly and non-invasively, for example, using wearable sensors, it may potentially be an important tool, particularly in primary care, or in settings with limited resources (Čepukaitytė et al., 2024; Mc Ardle et al., 2020). This may be particularly helpful in settings where access to neuroimaging or cerebrospinal fluid biomarker testing is limited, as they can be both expensive and relatively invasive.

These findings also have important implications for fall risk in individuals with MCI. Individuals with MCI fall nearly twice as much as older adults without cognitive impairment (Delbaere et al., 2012). Increased gait variability, particularly in step length, has been linked to falls in healthy older adults (Hausdorff, 2007; Pieruccini-Faria et al., 2020a). In this study, individuals with MD-aMCI had increased variability of step length, swing time, and stride velocity, suggesting they may be a subgroup of MCI with elevated risk for falls. Therefore, gait analysis may also be a helpful tool to monitor fall risk in MCI, in order to identify patients who may benefit from fall prevention interventions, such as balance training or home modifications (Cheng et al., 2018).

While the findings from this study did not support the hypothesis that gait at baseline can predict future cognitive decline, cross-sectional associations between specific cognitive domains and gait factors were observed in MCI. Importantly, the limited follow-up duration in this study may have limited the ability to predict meaningful changes in cognition, highlighting the need for larger longitudinal studies with longer and more frequent follow-up to help clarify the temporal relationship between gait and cognitive decline. Nonetheless, these findings suggest gait may be useful as a proxy for cognitive function, that is relatively easy to monitor over time than repeated neuropsychological assessments in individuals with MCI. However, as discussed previously, alternative explanations for this link between gait and cognition are possible, given the increased prevalence of comorbidities that could impact gait in people with MCI.

6.7 Strengths and Limitations

This study has several strengths. This is the first study to investigate gait differences across MCI subtypes with a longitudinal design. Furthermore, previous research comparing gait between MCI

divides MCI into aMCI and naMCI, without accounting for how gait may differ if impairment is in a single domain or multiple domains. This study is also the first to stratify MCI groups by the presence of pRBD, which is important given that RBD is the strongest biomarker for developing α -synucleinopathies, and because previous research has demonstrated the presence of RBD in healthy older adults impacts different gait outcomes. As mentioned, the co-occurrence of MCI and RBD is also associated with increased risk of early phenocconversion.

Additionally, this study examined longitudinal associations between specific gait domains and distinct cognitive domains in MCI. Prior studies have investigated these associations in healthy older adults, but there are limited studies in individuals with MCI. Furthermore, many studies exploring the association between gait and cognition utilize global cognitive measures or limited gait variables. By applying a principal component analysis to derive underlying gait domains and relating these to changes in cognitive performance, this study demonstrated domain-specific relationships between gait and cognition.

Despite these strengths, several limitations should also be addressed. Firstly, sample sizes of the naMCI group (SD-naMCI and MD-naMCI) were relatively small which may have limited statistical power. The sample sizes of the pRBD groups were also limited. Replication in larger studies is important to confirm these findings. Given that no prior research has investigated how gait changes over time across MCI subtypes, or how the presence of pRBD impacts gait in MCI, a priori power was not estimated, as there are no prior effect sizes for the interaction effects in this study. Instead, post hoc sample size estimations based on observed effect sizes in this current study were calculated and are detailed in Appendix A2.

Secondly, although this study was longitudinal, the follow-up duration was limited and may have not been sufficiently long to adequately capture motor and cognitive trajectories in MCI. Longer follow-up durations are important in MCI as cognitive performance can remain stable, improve, or decline.

Thirdly, there was a lack of data about other health conditions and comorbidities that may have impacted gait, such as previous injuries or orthopedic conditions. Information about current medication use was also not available in this dataset, which is important as certain medications could have impacted gait, sleep and cognitive performance.

In addition, RBD was diagnosed using the MSQ, instead of by polysomnography, which is the gold-standard for diagnosis of RBD. While the MSQ has been validated for the diagnosis of pRBD, there is still the possibility of misdiagnosis as it is possible that other sleep disorders are mistaken for RBD by bedpartners (Boeve et al., 2013). Therefore, there may be false positives or unidentified cases of pRBD in this sample, which may have obscured true effects. Given there is a lack of data about comorbidities and medication use, it is also possible individuals have secondary RBD, or RBD due to other causes (Boeve, 2010).

Furthermore, gait was assessed using a 6-meter instrumented walkway. This method of measuring gait is commonly used in similar research, however, this may not be a long enough distance for participants to reach steady-state gait. This is particularly important for measures of gait variability, as they are more accurately captured with continuous steady-state walking for longer distances (Hollman et al., 2010). Variability is increased during acceleration and deceleration phases and therefore, reported variability measures could be inflated and may not reflect true fluctuations in gait outcomes during steady-state gait. Given that participants started and terminated their gait one meter before and after the mat, this may not have given them enough strides to reach steady-state gait, meaning, their acceleration and deceleration may have been captured within the analyzed steps.

Moreover, due to a lack of data on neuroimaging and biomarker data, as well as medical history, this study could not account for heterogeneity in the etiology of MCI. As described previously, MCI can arise due to various causes, such as neurodegenerative pathologies, including β -amyloid deposition and α -synuclein accumulation, as well as cerebrovascular pathology (Petersen, 2016). Psychiatric conditions and systemic medical causes can also lead to MCI symptoms (Petersen, 2016). These varying causes may impact gait differently and may be associated with different trajectories of MCI. As such, the inability to confirm MCI etiology may have introduced heterogeneity in the sample, thereby impacting study findings.

Finally, given the large number of study-wise comparisons conducted, there is an inherent risk of Type I error. For example, in Table 9, approximately 120 confidence intervals were examined. At an alpha level of 0.05, one would expect about six comparisons to be significant by chance alone. This raises the possibility that some observed effects could represent false positives. At the same time, this thesis is the first study to investigate these aims, and therefore a more conservative correction across all tests could have increased the likelihood of Type II error, potentially obscuring

novel findings. To balance these risks, pairwise contrasts were limited to those following significant omnibus tests, Bonferroni correction was applied within each model, and multiple covariates known to affect gait were adjusted for (e.g., age, sex, height). Nonetheless, these results need to be replicated before firm conclusions can be made.

6.8 Future Directions

This study is the first to provide evidence of subtype-specific gait trajectories in MCI, and evidence that the presence of pRBD impacts gait in MCI subtypes. However, the limited sample size in naMCI and pRBD subgroups restricts statistical power and generalizability of these findings. Additionally, longer follow-up is needed to better investigate whether baseline gait can predict subsequent decline in cognitive function, as well as progression to dementia or phenoconversion. Future research should also incorporate imaging and fluid biomarkers to capture and confirm the underlying etiology of MCI, as well as to investigate mechanisms underlying the relationship between gait and cognition.

Another major objective of future studies should be evaluating the prognostic utility of gait for predicting phenoconversion or progression to specific dementia subtypes in MCI. As research has demonstrated that gait outcomes can help distinguish certain dementia subtypes, it will be important to evaluate if they can also identify individuals with MCI that will progress to these subtypes prior to dementia onset (Elasfar, Hameed, Boeve, et al., 2025; Mc Ardle et al., 2019). Similarly, in RBD, it will be important to understand whether certain gait outcomes can allow for prediction of future phenoconversion, and distinguishing PD converters from DLB converters. This will support early intervention, which is important given emerging research into disease-modifying treatments in prodromal disease stages, particularly iRBD (Postuma, 2022).

Another essential future direction involves using neuroimaging to understand neuropathological underpinnings of the relationship between gait outcomes and cognitive domains. While this study contributed to a growing body of literature capturing the relationship between gait outcomes and specific cognitive domains, few studies to date have investigated shared neural substrates between gait and cognition (Byun et al., 2023; Rosano et al., 2012; Sakurai et al., 2014, 2017). This will help improve the understanding of the mechanisms underlying the gait-cognition relationship.

Future work should also consider leveraging wearable sensors to assess gait in the real world. As mentioned previously, assessing gait in a laboratory setting using a six-meter walkway has

limitations, as it may not capture steady-state walking, which requires longer bouts of continuous walking (Hollman et al., 2010). Using wearable sensors to measure gait in real-world settings will address these limitations and provide ecologically valid measures of gait outcomes (Del Din et al., 2020; Mc Ardle et al., 2020). This may enhance sensitivity for detecting subtle changes in gait and mobility, which may be helpful to predict changes in cognition in MCI. In addition, instrumented walkways are relatively expensive and require a large space for setup, which may not be feasible in many clinics. In contrast, wearable sensors can be less expensive and require minimal setup, making them a more feasible and scalable alternative, which can translate more easily to clinical settings and allow for continuous monitoring of gait, compared to instrumented walkways.

Similarly, recently, studies have investigated the potential of conducting neuropsychological assessments using remote or mobile technologies, which may allow for more ecologically valid measures of cognitive function (Allard et al., 2014; Atkins et al., 2022; Geddes et al., 2020; Guimond et al., 2019; Hassenstab et al., 2020; Sbordone & Purisch, 1996; Sliwinski et al., 2018; Thompson et al., 2022; Timmers et al., 2014). Concerns about the ecological validity of traditional pen-and-paper neuropsychological tests have been raised in several studies, as the clinic or laboratory setting in which these tests are typically conducted are different from real-world contexts in which these cognitive functions are used by patients (Sliwinski et al., 2018). Researchers have suggested that cognitive performance measured in the lab can appear better because of social facilitation, or worse because of test anxiety (Guerin, 2010; Sliwinski et al., 2018; Strauss, 2002). For this reason, researchers have started investigating various methods of measuring cognition remotely with repeated assessments by phone or using mobile applications and online websites. These assessments are reported to have good reliability and validity, but limited research has explored how well they correlate with biomarkers of different diseases, or if they can predict important health outcomes, such as conversion to dementia (Allard et al., 2014; Atkins et al., 2022; Geddes et al., 2020; Guimond et al., 2019; Hassenstab et al., 2020; Sbordone & Purisch, 1996; Sliwinski et al., 2018; Thompson et al., 2022; Timmers et al., 2014). Importantly, more research is needed to understand the feasibility of these remote cognitive assessments in older adults and individuals with cognitive impairment.

Research has also investigated the potential of analysis of spoken discourse, for example, with a picture description task, as important tools to identify early cognitive decline (Mueller et al., 2018; Roberts et al., 2021). In AD, it was previously thought that language function deteriorates later in the disease course, however, individuals with aMCI exhibit deficits in spoken discourse prior to

progression to AD (Drummond et al., 2015; Duong et al., 2003; Fleming & Harris, 2008; Mueller et al., 2018). Other research has demonstrated that spoken discourse can be used to identify PD, FTD, LBD, and vascular dementia from normal aging (Ash et al., 2012, 2017; Duong et al., 2003; Hardy et al., 2016; Murray, 2000; Murray & Lenz, 2001; Roberts et al., 2021; Roberts & Post, 2018; Vuorinen et al., 2000). If these methods of measuring cognition can prove more sensitive than traditional neuropsychological assessments, future research should investigate whether gait is predictive of change in cognition as measured with these potentially more ecologically valid assessments of cognition.

Finally, it would also be of interest to explore how more complex walking paradigms impact gait features in different MCI subtypes. Dual-tasking paradigms have been used previously by one study which compared dual-task gait in people with aMCI and naMCI (Montero-Odasso et al., 2014). Dual-tasking has also been shown to uncover further changes in gait and balance in people with iRBD (Ehgoetz Martens et al., 2019). Therefore, using dual-tasking paradigms may help reveal further changes in gait in people with MCI and RBD. Prior research has also shown that the type and difficulty of the secondary task is important, so it might be worthwhile to investigate whether the secondary task has an impact of how gait changes in different MCI subtypes. For example, using a memory test as a secondary task may be more challenging for people with amnesic impairment, whereas using an executive function test as a secondary task may be more challenging for people with non-amnesic impairment. These dual tasks may therefore impact gait differently in different MCI subtypes. This would help understanding if using different dual tasks during clinical assessment of gait can improve sensitivity and specificity of identifying and monitoring disease progression in different MCI subtypes.

On the other hand, dual-tasking alone may not fully capture the range of gait impairments in MCI. Task variation is needed to expose different components of gait regulation. For instance, visuospatial impairments as well as balance control problems may be better exposed using obstacle navigation paradigms (Galna et al., 2009; Hocking et al., 2011). Similarly, using postural threat tasks (e.g., plank paradigms in virtual reality or postural perturbations, such as simulating a slip while walking) may expose the influence of anxiety, which is common in MCI and RBD, as well as problems with reactive postural control (Ehgoetz Martens et al., 2014; Norouzzian et al., 2024; Tang et al., 1998). These tasks directly challenge sensory and psychological components of walking, as well as aspects of balance and motor control directly, rather than only challenging their cognition. These

methods may be more effective at understanding the multiple contributors to gait dysfunction in MCI, which is often assumed to only be a function of their cognitive impairment, but can have other underlying explanations that have not been properly explored. Therefore, using an approach with varying tasks could help determine whether gait changes are primarily driven by problems with gait control, sensory integration, and/or anxiety and fear.

Chapter 7: Conclusion

This thesis aimed to characterize how gait changes over time in MCI subtypes, while examining how the presence of pRBD modifies gait outcomes in MCI, and evaluating whether baseline gait outcomes predict longitudinal changes in domain-specific cognitive performance. Using a longitudinal design, gait outcomes were compared across MCI subtypes from baseline to follow-up, while stratifying by presence of pRBD. Additionally, associations between baseline data-derived gait components and cognitive domain z-scores at baseline and follow-up visits were explored.

The results of this study showed that individuals with MCI subtypes exhibit slower gait (reduced stride velocity, decreased step length, increased step time), and increased double support (%) than CU individuals. However, only individuals with MD-aMCI demonstrated increased gait variability in stride velocity, step length, and swing time. Furthermore, this group demonstrated reductions in stride velocity and step length and increases in step time over time. The presence of pRBD was associated with slower gait, wider steps, and increased double support (%) than MD-naMCI, which are similar to gait features seen in parkinsonism. Moreover, selective associations between gait factors and cognitive domains were reported in this study. Pace and stability was associated with global cognition and attention. Gait variability was associated with global cognition and visuospatial function, though this association weakened at follow-up. However, surprisingly, timing and rhythm components were positively associated with memory scores, highlighting the need for further investigation.

This study is the first to examine gait longitudinally across MCI subtypes, finding that further slowing of gait and gait variability may help identify individuals with MCI with elevated risk of progression to dementia. It is also the first study to investigate how the presence of pRBD impacts gait in MCI, identifying early parkinsonian gait features in individuals likely to develop α -synucleinopathies. This thesis provides additional evidence of distinct relationships between domains of gait and cognition, however, there is no evidence that gait can predict changes in these domains over time, which may be due limited follow-up duration and heterogeneity in the MCI sample.

Overall, these findings further support the notion that gait, and cognition are intricately linked, as well as the growing body of literature recognizing gait as an important marker of cognitive decline and a potential predictor of neurodegeneration. Furthermore, these results suggest that gait assessment should be integrated into clinical evaluation of MCI, particularly for individuals with

multi-domain impairment, and for individuals with pRBD. As emerging research explores the potential for disease-modifying treatments and early interventions for individuals with prodromal disease, identifying biomarkers that can identify and monitor risk of progression to neurodegenerative conditions is paramount. The results of this thesis provide support for the potential clinical utility of gait analysis as a non-invasive and relatively accessible tool for early detection and monitoring of dementia risk in people with MCI. However, replication of these findings in larger studies with longer follow-up, and the integration of neuroimaging and fluid biomarkers is important to confirm findings.

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Appendix A: Supplementary Methods

A1. Z-score transformation for cognitive domain scores

Cognitive domain z-scores were calculated using a reference sample of 3,686 cognitively unimpaired MCSA participants. These participants had enough valid neuropsychological data to calculate at least one of the four domains. This meant they needed both tests for the executive function, language and visuospatial function domains, and at least two out of three tests for the memory domain.

Population-based weights were assigned to each participant in the reference sample based on their age and sex. These weights were based on the 2013 Olmstead County five-year age and sex distribution. These weights were used to calculate a weighted mean and a weighted standard deviation for each test, as well as weighted standard deviation for the domain scores. The weighted mean was subtracted from the raw score, then it was divided by the weighted standard deviation for that test, giving each participant a population z-score.

These population z-scores for each test were then averaged within each domain to obtain a domain-level z-score for each of the four domains for each participant. These domain-level z-scores were then scaled using the weighted standard deviation for each domain-level z-score, such that each domain z-score had a mean of 0 and standard deviation of 1.

Finally, a global cognition z-score was calculated by averaging the domain level z-scores. This score was once again scaled by the weighted standard deviation.

Therefore, the z-scores at the domain and global level can be interpreted as the number of standard deviations above or below the Olmstead County mean.

A2. Post hoc effect sizes and sample size analyses

A2.1. Introduction

As no prior studies have investigated how gait changes over time in all four MCI subtypes, nor investigated how pRBD status impacts gait in individuals with MCI, a priori power could not be estimated as no prior effect sizes for any of these interactions have been published. Given that this is the first study to investigate these aims, calculations for post hoc effect sizes and sample sizes required to detect these effects were conducted. These calculations were performed for the overall group effect, pairwise contrasts between groups, and interactions of group with RBD and time. Stride velocity was selected as the outcome variable for this analysis given how widely used it is in research and clinical settings, and because it showed consistent effects across our analysis.

A2.2. Methods

Post hoc effect sizes were calculated from the observed estimates of the linear mixed model for stride velocity. Pairwise contrasts were extracted using the emmeans package and standardized as Hedge's g . The overall diagnostic group effect was calculated as η^2 from the Type III ANOVA table, and converted to Cohen's f . For the two-way interaction effects, particularly MD-aMCI x time, and MD-naMCI x pRBD, pairwise contrasts (i.e. between BL and FU for MD-aMCI, and with and without pRBD for MD-naMCI) were extracted using the emmeans package and standardized as Hedge's g . Required sample sizes to detect these effects with 80% power and 90% power with an alpha level of 0.05 were calculated using the pwr package in R.

A2.3. Results

The overall main effect of group was significant ($F_{(4, 1131.63)} = 11.784, p < 0.001$). This corresponded to an η^2 of 0.04, or a Cohen's f of 0.20, which is a small-to-moderate effect. This corresponds to 290 participants (58 per group) or 375 participants (75 per group) for 80% or 90% power, respectively.

Pairwise comparisons of the EMMs revealed that CU individuals walk faster than all MCI groups. Cohen's g estimates ranged from small-to-moderate ($g = 0.27-0.42$), which corresponded to 91-279 participants per group for 80-90% power. Full sample size estimates for comparisons between CU and each MCI group are summarized in Table A1. Comparisons between MCI subtypes yielded very small effects ($g < 0.10$), corresponding to very large sample sizes ($n > 1000$).

Pairwise comparisons of the EMMs for the diagnosis x time interaction effect revealed that stride velocity decreased over time in only the MD-aMCI group. This corresponded to a small effect size ($g = 0.14$), which corresponded to 403-539 participants for 80-90% power. For the SD-naMCI group, the

effect was also estimated to be small ($g = 0.11$) and corresponded to a sample size of 571-763 participants for 80-90% power. Comparisons of stride velocity over time in other MCI subtypes yielded very small effects ($g < 0.02$), corresponding to very large sample sizes ($n > 10000$).

Pairwise comparisons of EMMs for the diagnosis x RBD interaction effect revealed that individuals with MD-naMCI and pRBD walked slower than individuals with MD-naMCI without pRBD. This corresponded to a small effect size ($g = 0.18$), which corresponded to 496-663 participants for 80-90% power. Comparisons of stride velocity over time in other MCI subtypes yielded very small effects ($g < 0.1$), corresponding to very large sample sizes ($n > 1000$).

Table A1. Observed effect sizes and estimated sample sizes for main effects, interaction effects, and pairwise comparisons.

Effect/Comparison	Effect size (g or f)*	Interpretation	N per group ($\beta = 0.8$)	N per group ($\beta = 0.9$)
Main effect of group	$f = 0.20$	Small	58	75
CU vs SD-aMCI	$g = 0.30$	Small-moderate	183	244
CU vs SD-naMCI	$g = 0.29$	Small-moderate	179	239
CU vs MD-aMCI	$g = 0.42$	Moderate	91	121
CU vs MD-naMCI	$g = 0.27$	Small-moderate	209	276
MD-aMCI * visit	$g = 0.14$	Small	403	539
SD-naMCI * visit	$g = 0.11$	Small	571	763
MD-naMCI * pRBD	$g = 0.18$	Small	496	663

* for clarity, only effect sizes greater than 0.1 reported.

A2.4. Discussion

The main effect of diagnosis on stride velocity and pairwise comparisons between CU and MCI groups were overall small-to-moderate and would require sample sizes of 290 to achieve 80% power, or 375 to achieve 90% power. On the other hand, comparisons between MCI groups were very small, and would require very large sample sizes to be detected, based on estimations from this study. Similarly, interaction effects on stride velocity with time and pRBD yielded very small effect sizes resulting in extremely large sample sizes, with the exception of the interaction of MD-aMCI and time, SD-naMCI and time, and MD-naMCI with pRBD. Under a balanced design, all other interaction effects would require thousands of participants to achieve adequate power. Given the highly unbalanced groups in this current study (e.g., 382 CU, 180 SD-aMCI, 20 MD-naMCI at baseline), effect size estimates for smaller groups are less certain and should be interpreted cautiously, as they may underestimate true underlying effects. For this reason, only effect sizes greater than 0.1 were reported in detail. Future research with more balanced recruitment across MCI groups is needed to provide more reliable estimates of effect sizes.

Appendix B: Supplementary Data

B1. Additional Participant Demographic Data

Table B1: Participant demographic and clinical information by group and by pRBD status.

	CU (n = 382)		SD-aMCI (n = 180)		SD-naMCI (n = 48)		MD-aMCI (n = 134)		MD-naMCI (n = 20)	
	pRBD–	pRBD+	pRBD–	pRBD+	pRBD–	pRBD+	pRBD–	pRBD+	pRBD–	pRBD+
Age	76.6 ± 8.25	73.41 ± 7.61	77.5 ± 8.25	76.41 ± 6.43	76.6 ± 6.92	71.08 ± 8.9	77.11 ± 7.74	72.45 ± 11.34	74.38 ± 6.76	71.37 ± 8.02
Sex	42.2%	19.4%	42.0%	30.4%	52.6%	10.0%	45.6%	12.9%	36.4%	44.4%
Education	14.32 ± 2.66	15.08 ± 3.07	14.45 ± 2.76	15.75 ± 3.26	13.14 ± 2.31	15.38 ± 2.88	13.97 ± 3.11	14.37 ± 3.21	12.68 ± 2.54	18.43 ± 1.81
CDR	0 (0, 0)	0 (0, 0)	0.5 (0, 1)	0.5 (0, 0.5)	0.5 (0, 0.5)	0.5 (0, 0.5)	0.5 (0, 1)	0.5 (0, 1)	0.5 (0, 0.5)	0.5 (0, 0.5)
MMSE	28.39 ± 2.47	28.97 ± 0.84	26.56 ± 1.82	26.48 ± 1.95	24.79 ± 4.51	27.6 ± 1.43	24.69 ± 3.07	26.06 ± 2.0	25.27 ± 2.65	26.44 ± 1.59
Follow up duration	1.38 ± 0.33	1.4 ± 0.44	1.44 ± 0.45	1.44 ± 0.39	1.35 ± 0.38	1.2 ± 0.32	1.36 ± 0.36	1.44 ± 0.51	1.41 ± 0.43	1.71 ± 1.21
Height	169.4 ± 14.19	173.51 ± 9.35	165.97 ± 25.15	170.93 ± 8.69	161.93 ± 28.81	177.08 ± 6.38	162.69 ± 29.86	173.71 ± 7.6	171 ± 8.66	169.87 ± 9.15

Data presented as mean ± standard deviation unless indicated otherwise below:

* Data is presented as median (range)

Abbreviations: CU = cognitively unimpaired, SD-aMCI = single-domain amnesic mild cognitive impairment; SD-naMCI = single-domain non-amnesic mild cognitive impairment; MD-aMCI = multi-domain amnesic mild cognitive impairment; MD-naMCI = multi-domain non-amnesic mild cognitive impairment; pRBD– = without probable REM sleep behavior disorder; pRBD+ = with probable REM sleep behavior disorder; var = variability

B2. Descriptive Statistics for Raw Data

Table B2: Mean and standard deviation of gait outcomes of interest by MCI subtype (collapsed across time and pRBD status)

Gait Outcome	CU	SD-aMCI	SD-naMCI	MD-aMCI	MD-naMCI
Stride velocity (cm/s)	110.573 ± 22.739	100.757 ± 23.326	99.720 ± 20.588	95.308 ± 22.824	97.359 ± 25.875
Stride velocity var (cm/s)	3.956 ± 1.609	4.091 ± 1.846	4.230 ± 1.525	4.451 ± 1.761	3.932 ± 1.322
Step length (cm)	61.976 ± 10.387	57.715 ± 9.846	57.238 ± 8.959	55.043 ± 10.355	56.411 ± 11.618
Step length var (cm)	2.162 ± 1.024	2.286 ± 1.083	2.308 ± 0.987	2.516 ± 1.131	2.108 ± 1.079
Step time (s)	0.570 ± 0.055	0.589 ± 0.079	0.585 ± 0.064	0.591 ± 0.070	0.601 ± 0.101
Step time var (s)	0.019 ± 0.008	0.024 ± 0.016	0.023 ± 0.013	0.025 ± 0.015	0.022 ± 0.011
Swing time (s)	0.393 ± 0.038	0.398 ± 0.041	0.394 ± 0.040	0.394 ± 0.042	0.398 ± 0.060
Swing time var (s)	0.016 ± 0.008	0.022 ± 0.013	0.020 ± 0.011	0.022 ± 0.013	0.019 ± 0.009
Stride width (cm)	13.356 ± 3.787	13.450 ± 3.518	13.533 ± 3.707	14.121 ± 3.992	13.164 ± 3.876
Stride width var (cm)	2.301 ± 0.938	2.392 ± 0.976	2.474 ± 1.063	2.289 ± 0.945	2.183 ± 0.727
Double Support (%)	30.783 ± 5.043	31.966 ± 5.464	32.321 ± 5.180	33.045 ± 5.587	33.283 ± 6.780

Data is presented as mean ± standard deviation. Abbreviations: CU = cognitively unimpaired, SD-aMCI = single-domain amnesic mild cognitive impairment; SD-naMCI = single-domain non-amnesic mild cognitive impairment; MD-aMCI = multi-domain amnesic mild cognitive impairment; MD-naMCI = multi-domain non-amnesic mild cognitive impairment; var = variability

Table B3: Mean and standard deviation of gait outcomes of interest at baseline and follow-up for all participants (collapsed across group and pRBD status)

Gait Outcome	BL	FU
Stride velocity (cm/s)	106.430 ± 22.907	102.472 ± 24.328
Stride velocity var (cm/s)	3.972 ± 1.616	4.221 ± 1.752
Step length (cm)	60.212 ± 10.274	58.315 ± 10.842
Step length var (cm)	2.239 ± 1.076	2.290 ± 1.054
Step time (s)	0.577 ± 0.067	0.582 ± 0.067
Step time var (s)	0.020 ± 0.012	0.022 ± 0.012
Swing time (s)	0.396 ± 0.039	0.394 ± 0.041
Swing time var (s)	0.018 ± 0.011	0.020 ± 0.011
Stride width (cm)	13.370 ± 3.720	13.687 ± 3.826
Stride width var (cm)	2.342 ± 0.989	2.309 ± 0.912
Double Support (%)	31.204 ± 5.127	32.083 ± 5.600

Data is presented as mean ± standard deviation. Abbreviations: BL = baseline; FU = follow-up; var = variability

Table B4: Mean and standard deviation of gait outcomes of interest for individuals with and without pRBD (collapsed across time and pRBD status)

Gait Outcome	pRBD–	pRBD+
Stride velocity (cm/s)	104.511 ± 23.390	104.092 ± 25.562
Stride velocity var (cm/s)	4.124 ± 1.702	3.928 ± 1.604
Step length (cm)	59.195 ± 10.404	59.673 ± 11.733
Step length var (cm)	2.261 ± 1.069	2.283 ± 1.046
Step time (s)	0.579 ± 0.066	0.588 ± 0.070
Step time var (s)	0.021 ± 0.012	0.022 ± 0.012
Swing time (s)	0.394 ± 0.040	0.397 ± 0.041
Swing time var (s)	0.019 ± 0.011	0.020 ± 0.012
Stride width (cm)	13.411 ± 3.738	14.231 ± 3.927
Stride width var (cm)	2.332 ± 0.939	2.288 ± 1.024
Double Support (%)	31.567 ± 5.302	32.103 ± 5.850

Data is presented as mean ± standard deviation. Abbreviations: pRBD– = without probable REM sleep behavior disorder; pRBD+ = with probable REM sleep behavior disorder; var = variability

Table B5: Mean and standard deviation values of the gait outcomes of interest for each group at baseline and follow-up (collapsed across pRBD status).

	CU		SD-aMCI		SD-naMCI		MD-aMCI		MD-naMCI	
Gait Outcome	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU
Stride velocity (cm/s)	112.047 ± 22.114	109.098 ± 23.283	101.277 ± 22.868	100.136 ± 23.922	106.021 ± 18.407	92.999 ± 20.853	98.999 ± 21.410	92.217 ± 23.568	96.278 ± 30.136	98.190 ± 22.654
Stride velocity var (cm/s)	3.778 ± 1.486	4.133 ± 1.707	4.007 ± 1.693	4.190 ± 2.014	3.935 ± 1.418	4.545 ± 1.587	4.484 ± 1.862	4.422 ± 1.678	4.008 ± 1.294	3.873 ± 1.365
Step length (cm)	62.717 ± 10.070	61.234 ± 10.656	58.071 ± 9.758	57.290 ± 9.966	60.025 ± 8.435	54.265 ± 8.621	56.580 ± 9.628	53.755 ± 10.788	56.386 ± 14.328	56.430 ± 9.323
Step length var (cm)	2.145 ± 1.036	2.178 ± 1.013	2.213 ± 1.022	2.374 ± 1.149	2.227 ± 0.992	2.394 ± 0.986	2.550 ± 1.208	2.487 ± 1.065	2.212 ± 1.275	2.029 ± 0.919
Step time (s)	0.568 ± 0.052	0.571 ± 0.057	0.590 ± 0.085	0.588 ± 0.072	0.574 ± 0.051	0.598 ± 0.073	0.583 ± 0.066	0.599 ± 0.074	0.616 ± 0.127	0.589 ± 0.076
Step time var (s)	0.018 ± 0.008	0.019 ± 0.008	0.024 ± 0.019	0.024 ± 0.018	0.019 ± 0.009	0.027 ± 0.014	0.022 ± 0.010	0.027 ± 0.017	0.022 ± 0.013	0.022 ± 0.009
Swing time (s)	0.394 ± 0.034	0.392 ± 0.042	0.399 ± 0.0415	0.397 ± 0.041	0.396 ± 0.0373	0.392 ± 0.043	0.393 ± 0.043	0.394 ± 0.041	0.404 ± 0.076	0.394 ± 0.045
Swing time var (s)	0.016 ± 0.007	0.017 ± 0.009	0.021 ± 0.014	0.022 ± 0.011	0.019 ± 0.010	0.021 ± 0.011	0.020 ± 0.012	0.023 ± 0.014	0.019 ± 0.011	0.019 ± 0.007
Stride width (cm)	13.186 ± 3.699	13.525 ± 3.869	13.181 ± 3.583	13.771 ± 3.422	13.297 ± 3.531	13.784 ± 3.910	14.174 ± 3.906	14.0769 ± 4.074	13.350 ± 4.132	13.021 ± 3.743
Stride width var (cm)	2.303 ± 0.976	2.300 ± 0.900	2.425 ± 1.031	2.352 ± 0.908	2.499 ± 0.865	2.447 ± 1.249	2.304 ± 1.042	2.276 ± 0.859	2.220 ± 0.716	2.154 ± 0.748
Double Support (%)	30.469 ± 4.648	31.098 ± 5.397	31.729 ± 5.608	32.249 ± 5.291	30.761 ± 4.523	33.985 ± 5.363	32.380 ± 4.794	33.602 ± 6.132	33.697 ± 9.191	32.964 ± 4.278

Data is presented as mean ± standard deviation. Abbreviations: CU = cognitively unimpaired, SD-aMCI = single-domain amnesic mild cognitive impairment; SD-naMCI = single-domain non-amnesic mild cognitive impairment; MD-aMCI = multi-domain amnesic mild cognitive impairment; MD-naMCI = multi-domain non-amnesic mild cognitive impairment; BL = baseline; FU = follow-up; var = variability

Table B6: Mean and standard deviation values of the gait outcomes of interest for subjects with and without pRBD for each group (collapsed across time).

	CU		SD-aMCI		SD-naMCI		MD-aMCI		MD-naMCI	
Gait Outcome	pRBD–	pRBD+	pRBD–	pRBD+	pRBD–	pRBD+	pRBD–	pRBD+	pRBD–	pRBD+
Stride velocity (cm/s)	109.098 ± 23.283	112.047 ± 22.114	100.136 ± 23.922	101.278 ± 22.868	92.999 ± 20.853	106.021 ± 18.407	92.217 ± 23.568	98.999 ± 21.410	98.190 ± 22.654	96.278 ± 30.137
Stride velocity var (cm/s)	4.134 ± 1.707	3.778 ± 1.487	4.191 ± 2.014	4.007 ± 1.693	4.545 ± 1.587	3.935 ± 1.418	4.422 ± 1.678	4.485 ± 1.862	3.873 ± 1.366	4.008 ± 1.294
Step length (cm)	61.235 ± 10.656	62.718 ± 10.070	57.291 ± 9.966	58.071 ± 9.758	54.265 ± 8.621	60.025 ± 8.435	53.755 ± 10.788	56.581 ± 9.628	56.430 ± 9.323	56.386 ± 14.328
Step length var (cm)	2.178 ± 1.013	2.145 ± 1.036	2.374 ± 1.149	2.213 ± 1.022	2.394 ± 0.986	2.227 ± 0.992	2.487 ± 1.065	2.549 ± 1.209	2.029 ± 0.920	2.212 ± 1.275
Step time (s)	0.571 ± 0.058	0.568 ± 0.052	0.588 ± 0.072	0.590 ± 0.085	0.598 ± 0.073	0.574 ± 0.051	0.599 ± 0.074	0.583 ± 0.066	0.590 ± 0.076	0.616 ± 0.127
Step time var (s)	0.019 ± 0.008	0.018 ± 0.008	0.024 ± 0.012	0.024 ± 0.019	0.027 ± 0.015	0.019 ± 0.009	0.027 ± 0.017	0.022 ± 0.010	0.022 ± 0.009	0.023 ± 0.013
Swing time (s)	0.393 ± 0.042	0.394 ± 0.034	0.397 ± 0.041	0.400 ± 0.041	0.392 ± 0.043	0.397 ± 0.037	0.394 ± 0.041	0.393 ± 0.043	0.394 ± 0.045	0.404 ± 0.076
Swing time var (s)	0.017 ± 0.009	0.016 ± 0.007	0.022 ± 0.012	0.021 ± 0.014	0.021 ± 0.011	0.019 ± 0.010	0.023 ± 0.014	0.020 ± 0.012	0.019 ± 0.007	0.020 ± 0.011
Stride width (cm)	13.525 ± 3.869	13.186 ± 3.700	13.771 ± 3.422	13.181 ± 3.583	13.784 ± 3.911	13.297 ± 3.531	14.077 ± 4.074	14.174 ± 3.906	13.021 ± 3.743	13.350 ± 4.132
Stride width var (cm)	2.300 ± 0.900	2.303 ± 0.976	2.352 ± 0.908	2.425 ± 1.031	2.447 ± 1.249	2.500 ± 0.865	2.276 ± 0.859	2.304 ± 1.042	2.154 ± 0.748	2.220 ± 0.716
Double Support (%)	31.098 ± 5.397	30.469 ± 4.648	32.249 ± 5.291	31.729 ± 5.608	33.985 ± 5.363	30.761 ± 4.523	33.602 ± 6.132	32.380 ± 4.794	32.964 ± 4.278	33.697 ± 9.191

Data is presented as mean ± standard deviation.

Abbreviations: BL = baseline; FU = follow-up; pRBD– = without probable REM sleep behavior disorder; pRBD+ = with probable REM sleep behavior disorder var = variability

Table B7: Mean and standard deviation values of the gait outcomes of interest for subjects without pRBD divided by group at baseline and follow-up.

Gait Outcome	pRBD-		pRBD+	
	BL	FU	BL	FU
Stride velocity (cm/s)	106.474 ± 22.715	102.547 ± 23.902	106.163 ± 24.137	102.021 ± 26.864
Stride velocity var (cm/s)	4.012 ± 1.634	4.236 ± 1.762	3.728 ± 1.485	4.129 ± 1.697
Step length (cm)	60.136 ± 10.111	58.254 ± 10.613	60.666 ± 11.243	58.679 ± 12.174
Step length var (cm)	2.236 ± 1.068	2.287 ± 1.070	2.260 ± 1.129	2.305 ± 0.961
Step time (s)	0.576 ± 0.065	0.581 ± 0.067	0.585 ± 0.077	0.590 ± 0.063
Step time var (s)	0.020 ± 0.012	0.022 ± 0.012	0.020 ± 0.011	0.024 ± 0.012
Swing time (s)	0.395 ± 0.038	0.393 ± 0.042	0.398 ± 0.045	0.396 ± 0.036
Swing time var (s)	0.018 ± 0.010	0.020 ± 0.011	0.019 ± 0.014	0.020 ± 0.011
Stride width (cm)	13.256 ± 3.685	13.567 ± 3.788	14.051 ± 3.872	14.412 ± 3.992
Stride width var (cm)	2.331 ± 0.961	2.332 ± 0.917	2.409 ± 1.148	2.167 ± 0.871
Double Support (%)	31.111 ± 4.997	32.024 ± 5.557	31.764 ± 5.842	32.441 ± 5.864

Data is presented as mean ± standard deviation. Abbreviations: BL = baseline; FU = follow-up; pRBD- = without probable REM sleep behavior disorder; pRBD+ = with probable REM sleep behavior disorder var = variability

Table B8: Mean and standard deviation values of gait outcomes of interest for subjects without pRBD divided by group at baseline and follow-up.

Gait Outcome	CU		SD-aMCI		SD-naMCI		MD-aMCI		MD-naMCI	
	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU
Stride velocity (cm/s)	111.465 ± 22.649	108.561 ± 23.563	100.813 ± 22.617	99.074 ± 23.759	104.917 ± 17.996	92.742 ± 15.278	99.751 ± 21.589	93.080 ± 23.257	98.641 ± 14.407	96.867 ± 17.705
Stride velocity var (cm/s)	3.797 ± 1.502	4.130 ± 1.684	4.083 ± 1.714	4.211 ± 2.017	4.099 ± 1.455	4.563 ± 1.603	4.566 ± 1.877	4.506 ± 1.754	4.300 ± 1.505	3.974 ± 1.489
Step length (cm)	62.381 ± 10.171	60.892 ± 10.695	57.849 ± 9.695	56.962 ± 9.834	58.993 ± 8.112	53.813 ± 6.406	56.475 ± 9.674	53.961 ± 10.521	60.377 ± 7.324	55.338 ± 7.408
Step length var (cm)	2.132 ± 1.039	2.165 ± 1.005	2.254 ± 1.025	2.368 ± 1.169	2.308 ± 1.009	2.404 ± 1.015	2.523 ± 1.209	2.564 ± 1.126	2.271 ± 1.000	1.949 ± 0.866
Step time (s)	0.569 ± 0.053	0.571 ± 0.060	0.590 ± 0.084	0.591 ± 0.072	0.569 ± 0.049	0.591 ± 0.071	0.578 ± 0.068	0.595 ± 0.077	0.622 ± 0.071	0.580 ± 0.059
Step time var (s)	0.018 ± 0.008	0.019 ± 0.008	0.024 ± 0.019	0.024 ± 0.012	0.019 ± 0.009	0.026 ± 0.014	0.022 ± 0.010	0.027 ± 0.018	0.024 ± 0.008	0.022 ± 0.008
Swing time (s)	0.394 ± 0.035	0.392 ± 0.043	0.400 ± 0.040	0.398 ± 0.040	0.392 ± 0.037	0.391 ± 0.045	0.390 ± 0.044	0.394 ± 0.042	0.433 ± 0.059	0.388 ± 0.042
Swing time var (s)	0.016 ± 0.007	0.018 ± 0.010	0.021 ± 0.014	0.022 ± 0.012	0.018 ± 0.010	0.020 ± 0.009	0.019 ± 0.009	0.023 ± 0.014	0.022 ± 0.011	0.018 ± 0.005
Stride width (cm)	13.211 ± 3.778	13.501 ± 3.962	13.198 ± 3.600	13.699 ± 3.370	12.996 ± 3.493	13.778 ± 4.125	13.647 ± 3.655	13.599 ± 3.687	12.760 ± 3.135	13.227 ± 3.541
Stride width var (cm)	2.288 ± 0.959	2.311 ± 0.901	2.378 ± 0.945	2.388 ± 0.941	2.567 ± 0.821	2.479 ± 1.205	2.296 ± 1.056	2.300 ± 0.860	2.520 ± 0.677	2.251 ± 0.781
Double Support (%)	30.560 ± 4.771	31.209 ± 5.528	31.674 ± 5.589	32.384 ± 5.162	31.042 ± 4.654	33.620 ± 4.570	32.194 ± 4.892	33.307 ± 6.207	30.484 ± 2.887	33.022 ± 3.463

Data is presented as mean ± standard deviation. Abbreviations: CU = cognitively unimpaired, SD-aMCI = single-domain amnesic mild cognitive impairment; SD-naMCI = single-domain non-amnesic mild cognitive impairment; MD-aMCI = multi-domain amnesic mild cognitive impairment; MD-naMCI = multi-domain non-amnesic mild cognitive impairment; BL = baseline; FU = follow-up; var = variability

Table B9: Mean and standard deviation values of gait outcomes of interest for subjects with pRBD divided by group at baseline and follow-up.

	CU		SD-aMCI		SD-naMCI		MD-aMCI		MD-naMCI	
Gait Outcome	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU
Stride velocity (cm/s)	117.642 ± 15.209	114.269 ± 19.944	104.448 ± 24.815	107.087 ± 24.433	110.217 ± 20.328	94.192 ± 29.126	96.503 ± 20.956	89.446 ± 24.651	93.391 ± 33.365	101.781 ± 34.314
Stride velocity var (cm/s)	3.590 ± 1.328	4.173 ± 1.951	3.491 ± 1.475	4.054 ± 2.045	3.313 ± 1.120	4.462 ± 1.619	4.215 ± 1.815	4.154 ± 1.394	3.651 ± 0.940	3.600 ± 0.999
Step length (cm)	65.952 ± 8.509	64.531 ± 9.813	59.584 ± 10.271	59.443 ± 10.808	63.944 ± 8.915	56.357 ± 10.814	56.933 ± 9.624	53.091 ± 11.727	51.508 ± 10.283	59.395 ± 10.548
Step length var (cm)	2.267 ± 1.005	2.315 ± 1.099	1.937 ± 0.978	2.414 ± 1.036	1.922 ± 0.908	2.351 ± 0.898	2.637 ± 1.221	2.240 ± 0.805	2.140 ± 1.612	2.245 ± 1.095
Step time (s)	0.563 ± 0.036	0.570 ± 0.036	0.588 ± 0.093	0.568 ± 0.064	0.591 ± 0.058	0.628 ± 0.079	0.599 ± 0.054	0.609 ± 0.060	0.609 ± 0.179	0.615 ± 0.111
Step time var (s)	0.016 ± 0.005	0.019 ± 0.008	0.023 ± 0.015	0.022 ± 0.012	0.018 ± 0.010	0.032 ± 0.018	0.023 ± 0.010	0.027 ± 0.013	0.021 ± 0.019	0.024 ± 0.011
Swing time (s)	0.397 ± 0.033	0.398 ± 0.033	0.397 ± 0.053	0.388 ± 0.046	0.414 ± 0.035	0.399 ± 0.034	0.402 ± 0.037	0.396 ± 0.035	0.370 ± 0.084	0.409 ± 0.052
Swing time var (s)	0.013 ± 0.005	0.015 ± 0.006	0.021 ± 0.014	0.020 ± 0.010	0.021 ± 0.010	0.026 ± 0.016	0.025 ± 0.019	0.024 ± 0.013	0.018 ± 0.011	0.022 ± 0.011
Stride width (cm)	12.954 ± 2.869	13.750 ± 2.867	13.061 ± 3.541	14.244 ± 3.803	14.442 ± 3.622	13.813 ± 2.934	15.926 ± 4.256	15.613 ± 4.865	14.071 ± 5.215	12.464 ± 4.502
Stride width var (cm)	2.449 ± 1.135	2.190 ± 0.892	2.745 ± 1.482	2.112 ± 0.621	2.244 ± 1.023	2.298 ± 1.519	2.330 ± 1.010	2.198 ± 0.863	1.853 ± 0.607	1.891 ± 0.626
Double Support (%)	29.593 ± 3.153	30.025 ± 3.813	32.108 ± 5.848	31.365 ± 6.147	29.694 ± 4.020	35.674 ± 8.333	32.996 ± 4.473	34.550 ± 5.865	37.625 ± 9.595	32.807 ± 6.343

Data is presented as mean ± standard deviation. Abbreviations: CU = cognitively unimpaired, SD-aMCI = single-domain amnesic mild cognitive impairment; SD-naMCI = single-domain non-amnesic mild cognitive impairment; MD-aMCI = multi-domain amnesic mild cognitive impairment; MD-naMCI = multi-domain non-amnesic mild cognitive impairment; BL = baseline; FU = follow-up; var = variability

Appendix C: Supplementary Figures

C1. Boxplots showcasing raw values of gait outcomes.

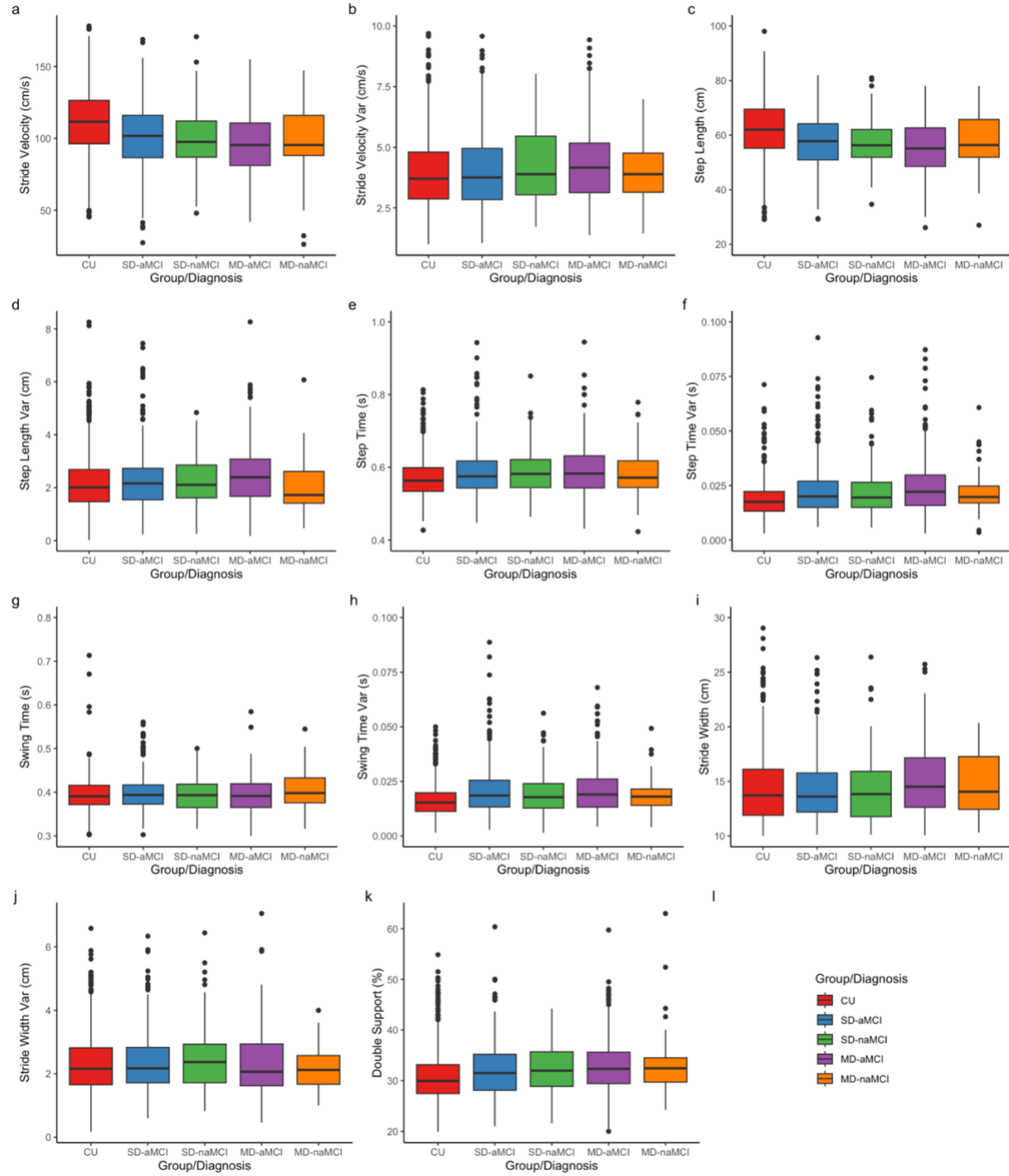


Figure C1: Boxplots of raw values for gait outcomes stratified by diagnosis group.

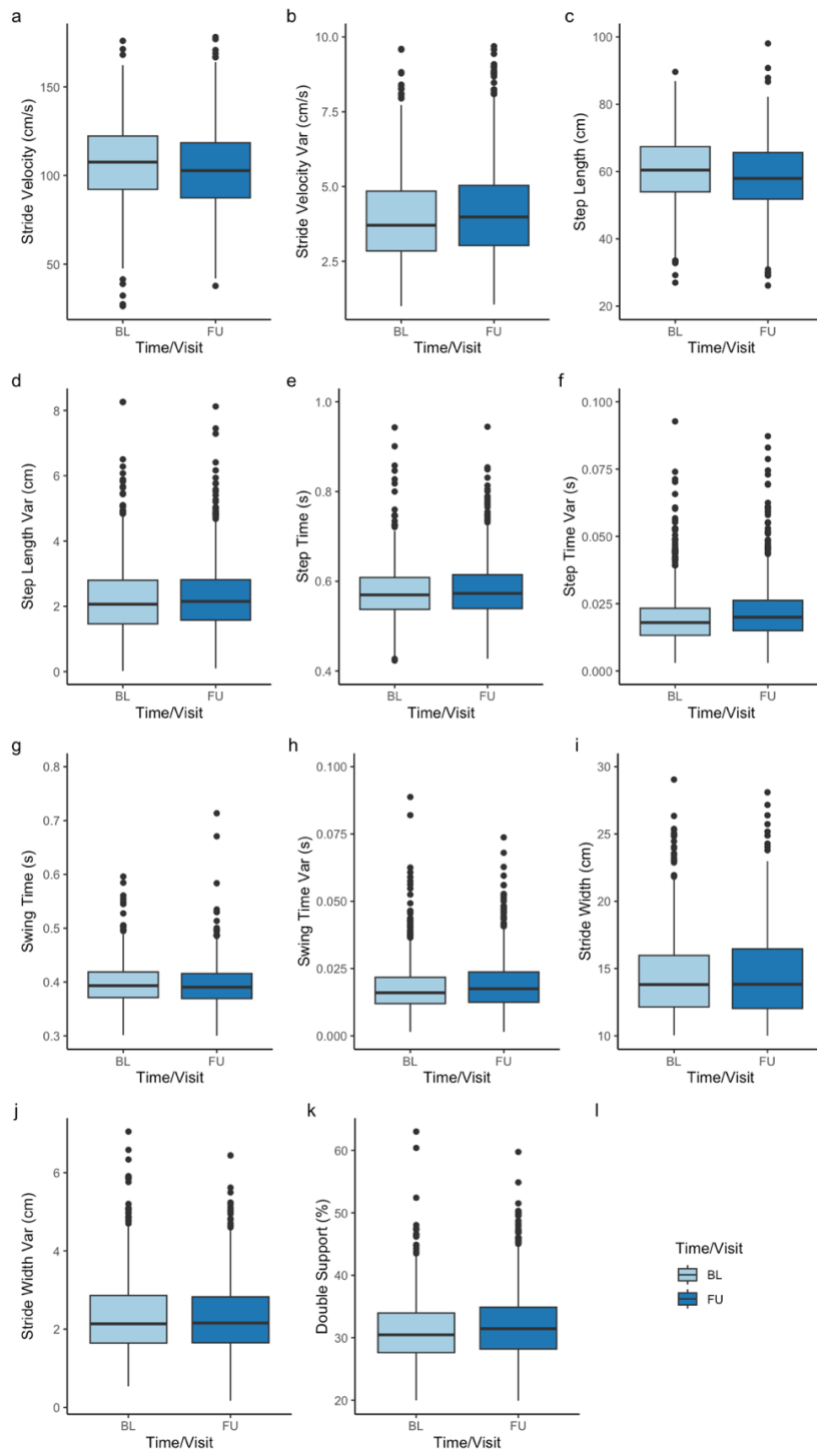


Figure C2: Boxplots of raw values for gait outcomes stratified by time/visit.

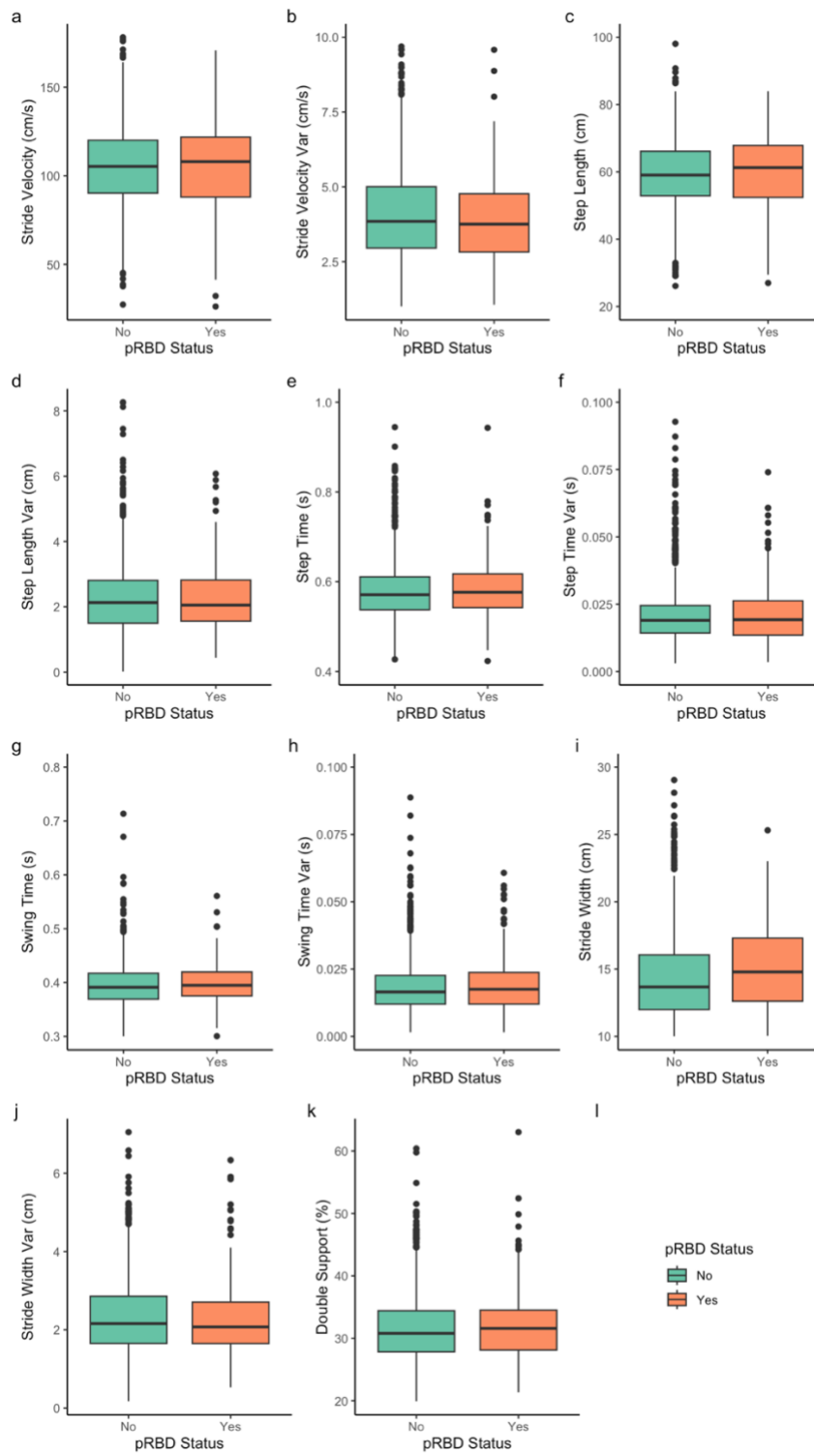


Figure C3: Boxplots of raw values for gait outcomes stratified by pRBD status.

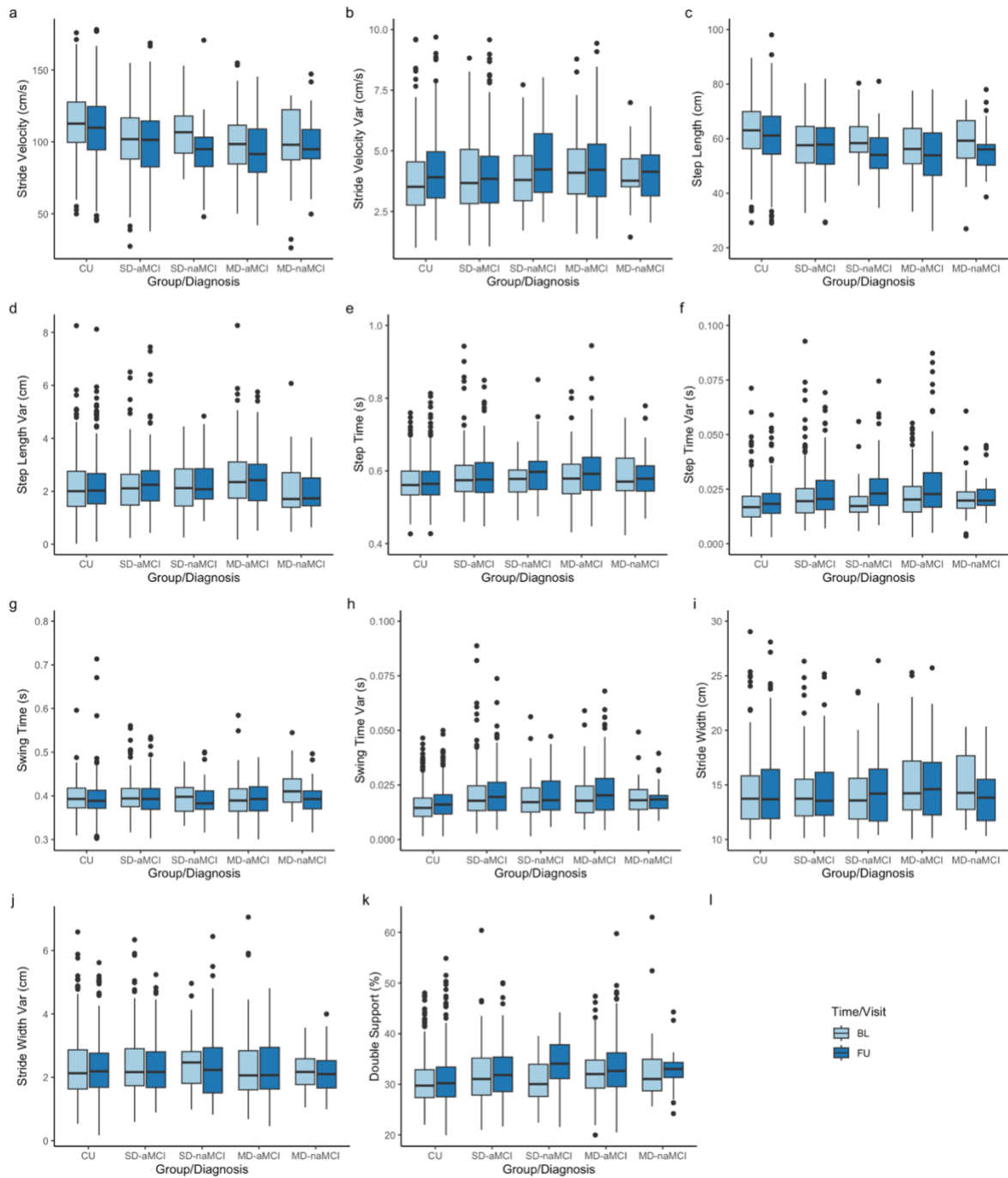


Figure C4: Boxplots of raw values for gait outcomes stratified by group and visit.

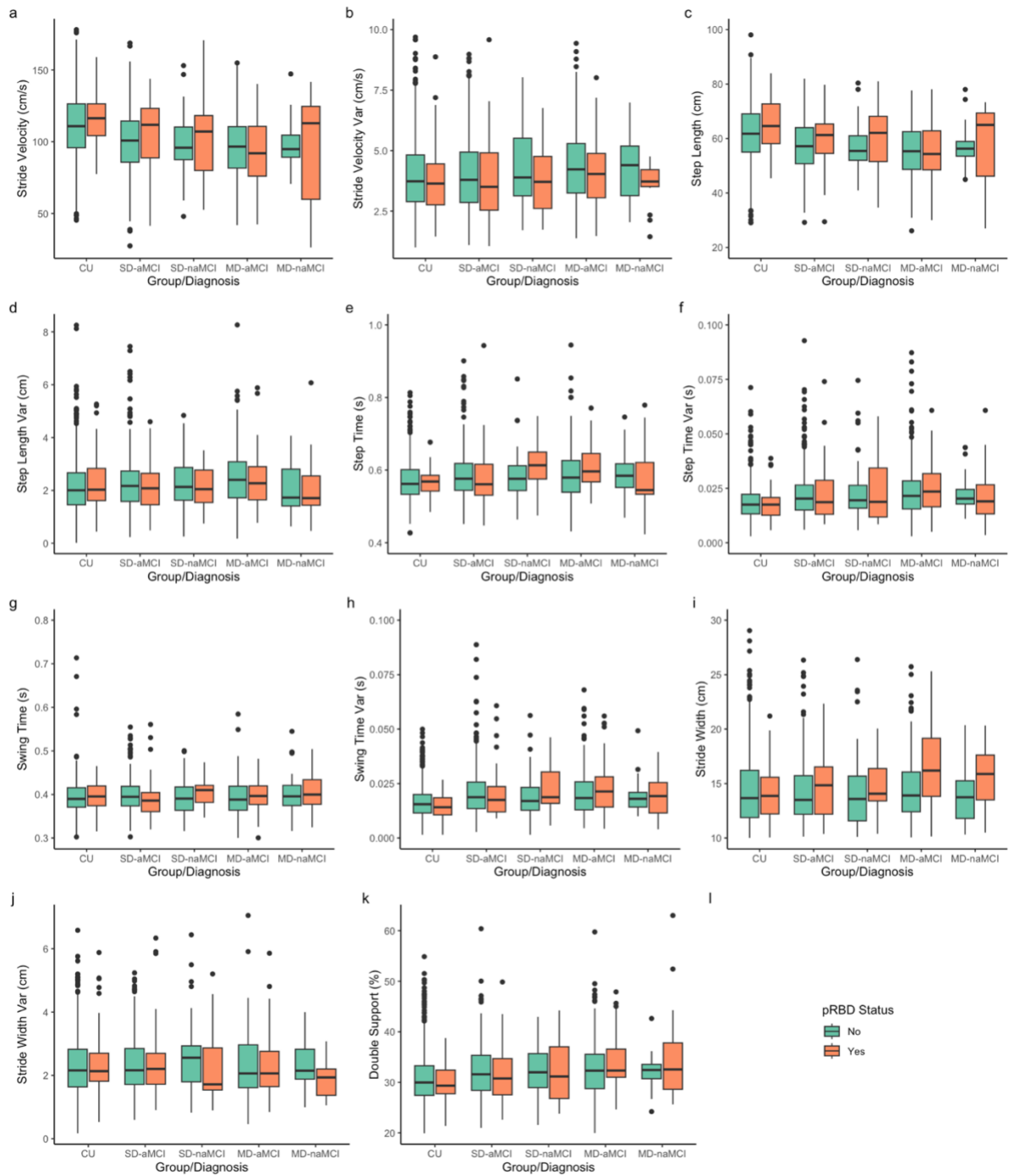


Figure C5: Boxplots of raw values for gait outcomes stratified by group and pRBD status.

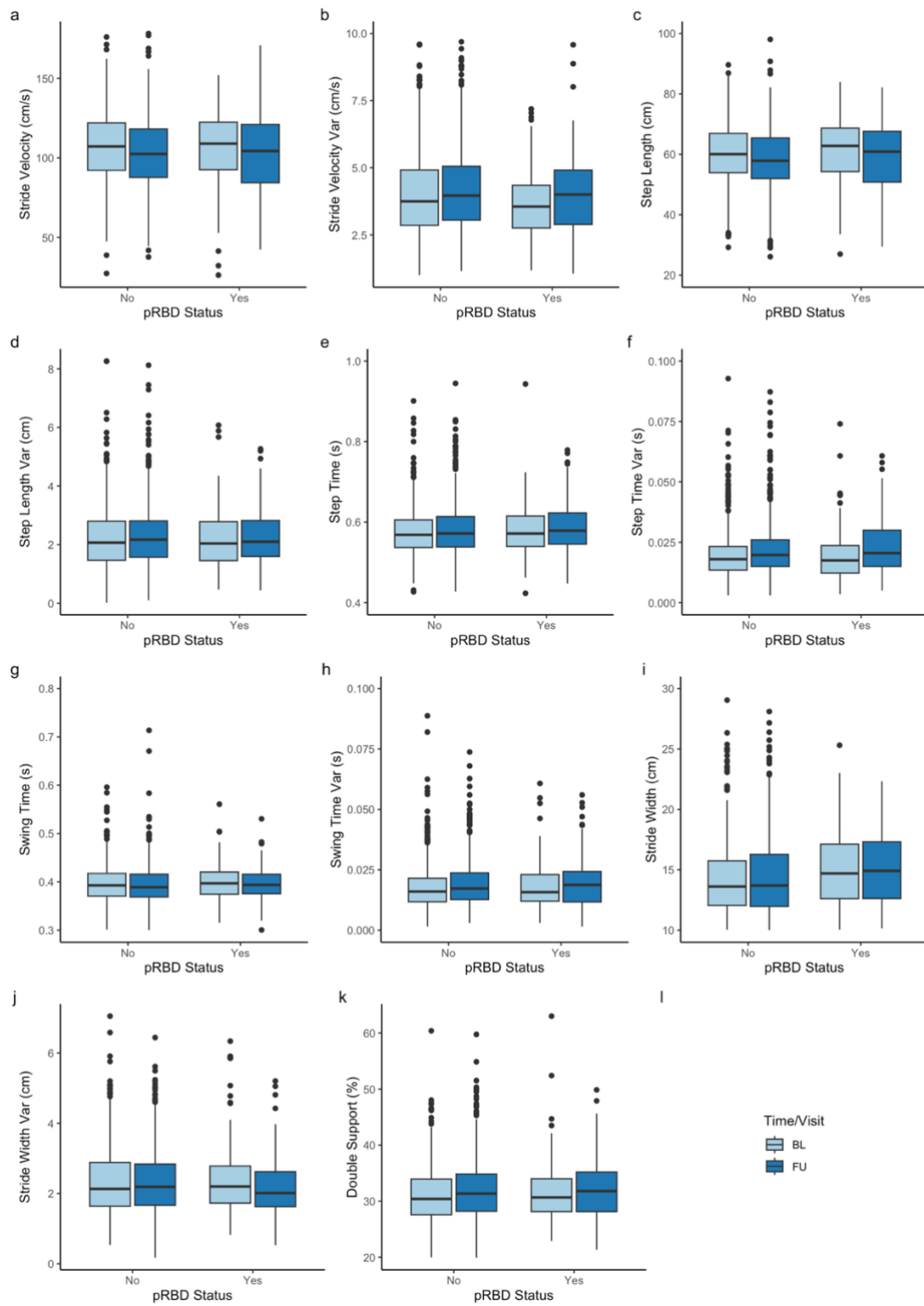


Figure C6: Boxplots of raw values for gait outcomes stratified by pRBD status and time.

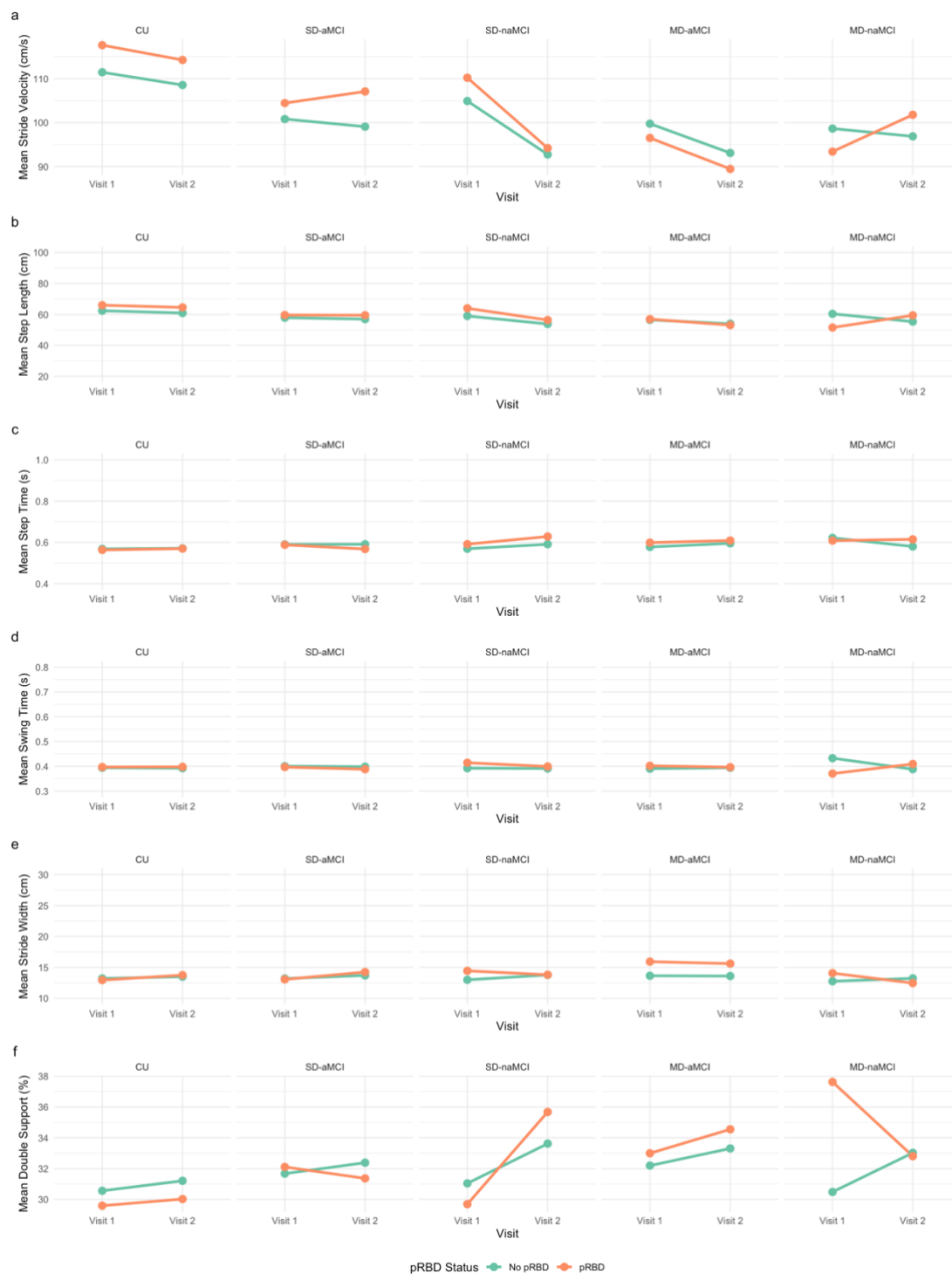


Figure C7: Plots for raw average change in mean gait outcomes for each group stratified by pRBD status.

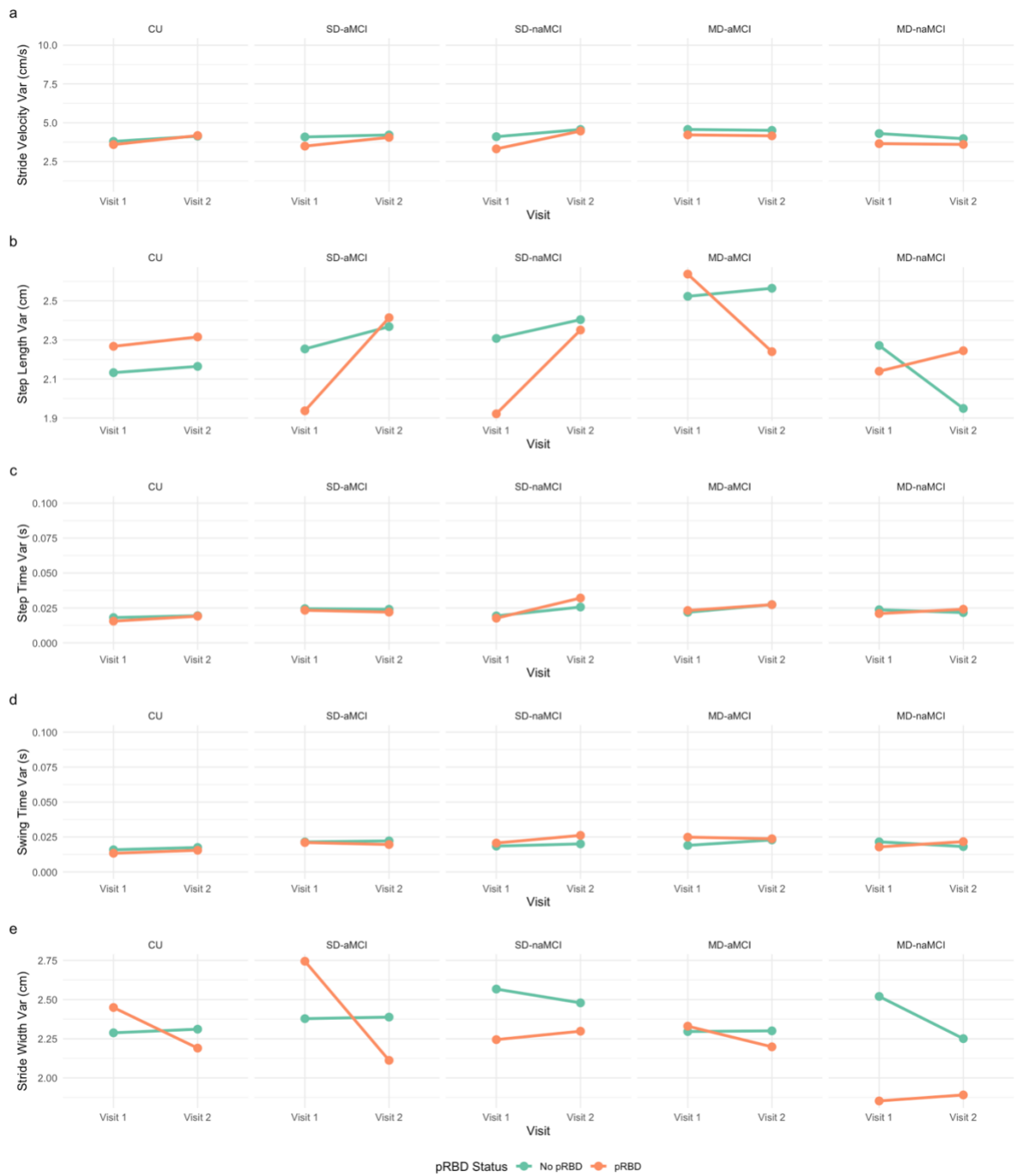


Figure C8: Plots for raw average change in variability gait outcomes for each group stratified by pRBD status.