The Utility Of Novel Clinical Dual Task Assessments For Individuals With Multiple Sclerosis: The Bridge To Understanding Real-World Ambulation

THE UTILITY OF NOVEL CLINICAL DUAL TASK ASSESSMENTS FOR INDIVIDUALS WITH MULTIPLE SCLEROSIS: THE BRIDGE TO UNDERSTANDING REAL-WORLD AMBULATION

A Dissertation Presented

by

Michael VanNostrand

to

The Faculty of the Graduate College

of

The University of Vermont

In Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy
Specializing in Human Functioning and Rehabilitation Science

October, 2023

Defense Date: September 8, 2023
Dissertation Examination Committee:

Susan Kasser, Ph.D., Advisor
Michael S. Cannizzaro, Ph.D., CCC-SLP, Chairperson
Emily L. Coderre, Ph.D.
Peter Callas, Ph.D.
Nancy Gell, PT, Ph.D, M.P.H.
Holger Hoock, DPhil, Dean of the Graduate College

ABSTRACT

The neurodegeneration caused by multiple sclerosis (MS) results in a progressive decline in functioning and quality of life. Mobility impairment is often reported as the most common symptom affecting people with the disease, contributing to about 50% of the population reporting at least one fall in any three-month period. Although the underlying cause of falls in persons with MS is multifaceted, there is mounting evidence that the inclusion of a cognitive task during walking (dual tasking) leads to increased fall risk. Previous research in lab-based environments has highlighted the association between dual task walking and increased stride variability and decreased gait speed, leading to an increase in falls for persons with MS.

While there is mounting evidence that dual task walking in the lab can differentiate between fallers and non-fallers with MS, these findings have not translated into acceptable clinical assessments. These assessments notably lack ecological validity, as they fail to consider key real-world factors, such as concurrent cognitive tasks, movement quality examination, and postural transitions and turns – all of which are problematic for those with MS.

Additionally, changes in real-world ambulation are often attributed to mobility impairment, yet previous research underscores cognition and fear of falling as vital metrics impacting walking. Understanding contributors to real-world mobility is crucial, as they are necessary for both walking and community participation. Therefore, the objective of this project was to: 1) Examine the sensitivity and specificity of both currently used and novel clinical measures at predicting fall status in persons with MS 2) Identify a clinical assessment that is reflective of everyday walking in individuals with MS and 3) Examine the contributions of cognition, ambulation disability, and psychosocial factors to real-world gait quality and quantity.

A total of 27 participants with MS, ranging in age from 40 to 75, were included in the study and underwent cognitive testing. Upon completion, participants performed a series of walking assessments, including the timed up and go (TUG), and three novel clinical assessments: TUG-extended, 25-foot walk and turn, and figure-8 walk. During the performance of the novel assessments, participants concurrently engaged in a verbal fluency cognitive task. At the conclusion of the in-lab session, participants in the study had an inertial sensor placed on their lower back, which they wore in the real world for three days.

Results from the study showed that one of the novel clinical assessments, the 25-foot walk and turn, exhibited increased sensitivity and specificity compared to currently used clinical assessments. Furthermore, the 25-foot walk and turn was the assessment with the highest correlation to real-world captured measures of gait speed and stride variability. Finally, both cognition, namely processing speed, and ambulation disability significantly contributed to real-world measures of gait speed and stride variability. The findings highlight the significance of incorporating cognition into walking assessments for individuals with MS. Cognition emerged as a notable factor impacting real-world measures of gait speed and stride variability. Moreover, integrating cognition into clinical mobility evaluations enhanced ecological validity and ultimately improved the effectiveness at identifying fall status when compared to existing assessments.

ACKNOWLEDGEMENTS

I am filled with gratitude for the individuals who have helped guide my path through this project. I would like to express my appreciation to all the individuals who participated in this project; your dedication and commitment made it all possible.

I am thankful for my committee: Dr. Michael Cannizzaro, Dr. Emily Coderre, Dr. Peter Callas, and Dr. Nancy Gell. The guidance you have generously offered me is deeply valued.

Next, my heartfelt thanks go to the student contributors who played a vital role in this project: John Ramsdell, Sadegh Khodabandeloo, Annika Ligon, Julia Kropiewnicki, and Connor Mcclure. Additionally, I extend special thanks to Natalie Lloyd for her tireless dedication and commitment to this endeavor.

I wish to extend a special note of gratitude to Myeongjin Bae. None of this achievement would have been possible without your help, and I consider myself fortunate to call you both a colleague and a friend.

To my family and friends, whose support has been a pillar of strength, I am immensely thankful for your encouragement throughout this journey.

Finally, my mentor, Dr. Susan Kasser, deserves my deepest appreciation. Sue, your brilliance has served as a guiding light for me. Thank you for your unwavering support and availability whenever I have needed guidance. I am genuinely grateful for the countless hours you have dedicated to my growth as a researcher, writer, and teacher. I thank you for all the life lessons you have taught me that extend well beyond your role as my mentor. I am grateful and honored to have worked with you.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1: INTRODUCTION

Multiple sclerosis overview

Multiple sclerosis (MS) is a chronic, autoimmune neurological disease of the central nervous system (CNS) leading to demyelination and axonal loss.[1] This demyelination process involves the destruction of the protective myelin sheath surrounding nerve fibers, leading to the formation of plaques.[1] These plaques, which arise from relapses, progressively accumulate over time on both the brain and spinal cord, resulting in permanent damage and the worsening of symptoms.[1] Consequently, this process disrupts the normal transmission of signals along the affected nerves, impairing various bodily functions.[2] There is an increased prevalence rate in women compared to men (2.3-3.5:1),[3] with first symptoms typically presenting between the ages of 20 and 40.[4] Notably, research has indicated that approximately one million Americans are currently affected by this condition,[5] with an estimated total economic burden of 85.4 billion dollars, equivalent to $65,612 per person per year.[6]

There is a wide array of symptoms resulting from MS, including muscle weakness, fatigue, depression, cognitive dysfunction, and difficulties with walking and balance.[7] These symptoms significantly affect individuals with the disease and can have profound impacts on their daily lives, leading to increased levels of depression,[8] sedentary behavior,[9] and a decrease in functional independence.[10,11] As a result, individuals with MS report poorer health-related quality of life, which encompasses challenges in family and peer relationships, occupational status, and community participation.[12-15] In fact, approximately 56.5% of the MS population is unemployed, and an individual's ability to remain employed declines by 3% per year after diagnosis.[16] Fatigue, along with mobility-related issues and difficulties with cognition, are frequently reported by individuals with MS as key factors in reducing work hours or leaving their jobs.[17,18] Taken together, the disease course of MS, along with its associated symptoms, imposes a substantial burden on both the healthcare system and the labor force.

Mobility and fall risk

MS has profound consequences on mobility, significantly impacting the daily lives of individuals with the disease. Mobility impairments in MS arise from various factors, including muscle weakness, spasticity, balance problems, and coordination difficulties,[19] leading to an increased reliance on assistive devices and a higher risk of falls.[20] Mobility impairment is widely reported as the most common symptom affecting individuals with MS, with over 90% reporting mobility dysfunction.[21,22] It is frequently cited as the primary factor limiting community participation.[23] Studies consistently demonstrate that the loss of mobility contributes to a significant patient burden and reduced quality of life.[24,25]

As walking becomes more challenging, the risk of falls increases among individuals with MS. Over 50% of ambulant people with MS report at least one fall in any three-month period.[26] Furthermore, of those who report falling, 50% experience injuries and 23% require medical care.[27] Additionally, previous studies have indicated that the MS population is at a higher risk of developing osteoporosis, leading to an increased likelihood of fractures from falls.[28] Falls also have a profound impact on the quality of life of individuals with MS, as they can lead to a loss of functional mobility.[25] Additionally, experiencing a fall increases fear of falling, leading to reduced community participation and physical activity which, in turn, further reduces quality of life.[29-31] Physical activity curtailment and self-isolation contribute to decreased strength, endurance, and range of motion, thereby increasing the risk of future falls and severe injuries.[32,33] The cyclical nature of this process emphasizes the significance of identifying individuals at risk for falls in order to mitigate fear of falling and promote physical activity (figure 1). Given the progressive decline in mobility and its functional consequences over time, it is imperative to identify and address fall risk as important healthcare priorities.

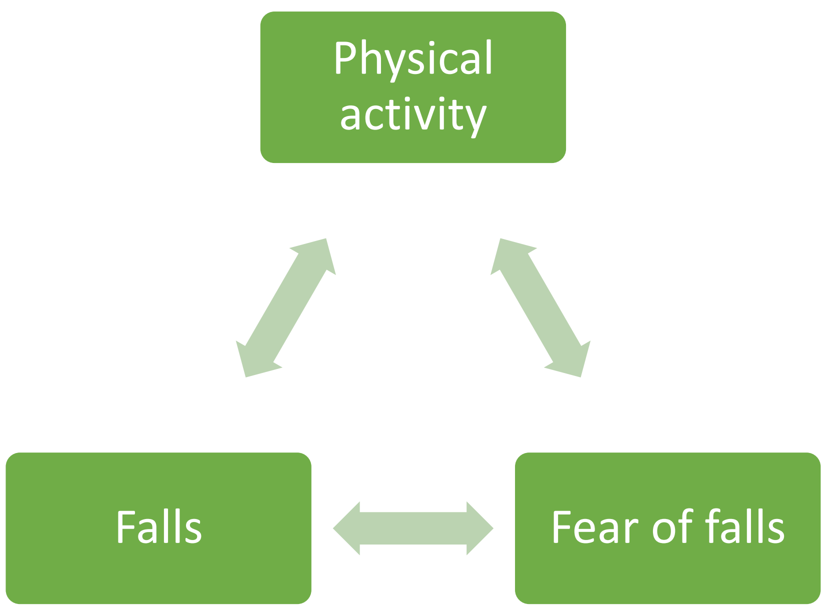

Figure 1. Relationship between falls, fear of falling, and physical activity

However, despite the frequency of falls and injurious falls in this population, they are often under-reported. It has been shown that only about 50% of patients who experience a fall report it to their healthcare provider, resulting in less than half of those with MS receiving information about fall prevention strategies from their healthcare providers.[34] Given the high prevalence of falls and the lack of reporting, there is an urgent health need for assessments that can identify individuals at risk for falls. Further underscoring this need for clinical fall risk assessments, the National Multiple Sclerosis Society emphasizes the importance of developing clinically useful and sensitive quantitative outcome measures that can effectively identify those with MS who are at risk for falls.[35]

Cognitive impairment

While falls are often seen as caused solely by mobility impairment,[36] it has also been well established that cognition plays a key role. Cognition encompasses various domains, such as executive functioning, language, memory, attention, social cognition, and perceptual motor function.[37] In individuals with MS, cognitive impairment is prevalent, with up to 70% of those with the disease experiencing cognitive deficits.[10,38,39] Most commonly, individuals with MS report cognitive problems related to processing speed,[40] executive functioning,[41] and long-term memory.[38] The impact of cognitive impairment on the quality of life for individuals with MS is profound, leading to increased difficulties in completing daily activities,[11] reduced functional independence,[10] higher unemployment rates,[42] and challenges in engaging in social activities.[43]

Processing speed refers to the rate at which the brain processes information and has been identified as the most common cognitive deficit in individuals with MS, affecting over 50% of those with the condition.[38,44-46] This deficit is often observed in conjunction with impairments in other cognitive domains, particularly working and long-term memory.[47,48] Given the prevalence of processing speed deficits and their association with other cognitive functions, it is crucial for clinicians to assess this domain in individuals with MS.

Executive function is a multifaceted domain encompassing goal-directed behavior and the capacity to adapt to environmental changes or demands through planning, anticipating, allocating resources, and responding appropriately (figure 2).[37] Although less common than deficits in processing speed, approximately one-third of individuals with MS experience impairments in executive function.[49] These deficits have a far-reaching impact given the link between executive functions and occupational performance deficits.[49] Moreover, executive dysfunction has been significantly associated with anxiety and depression within this population.[50]

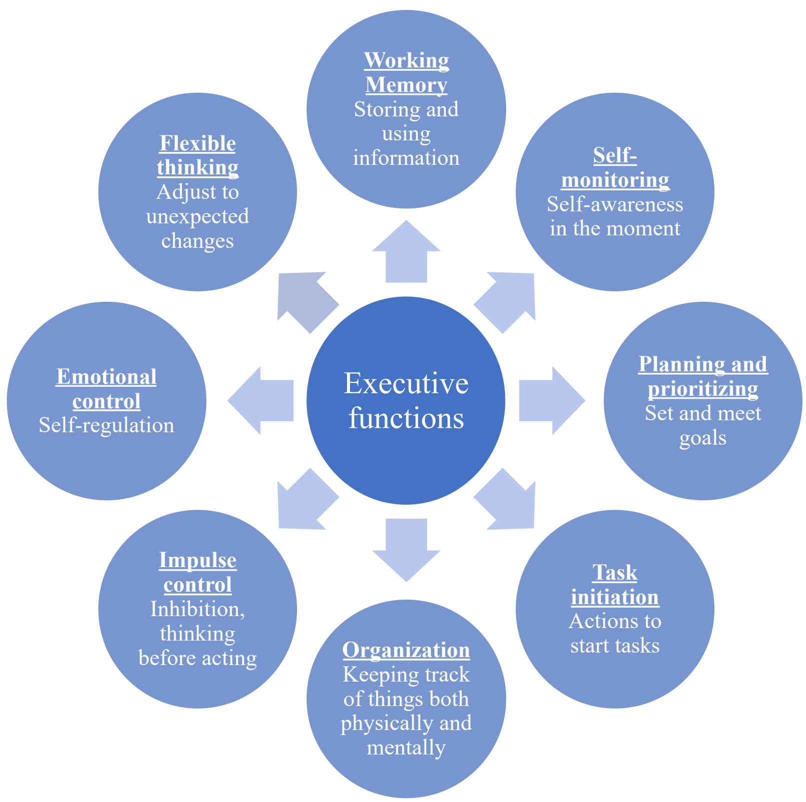

Figure 2. Domains of executive function

Long-term memory is the ability to learn new information, maintain that information, and recall it at a later time. Deficits in long-term memory are prevalent in the population with up to 65% of individuals with MS showing impaired function in this domain.[51] While long-term memory is impaired for individuals for MS, research has shown that the cause of this deficit is more related to the initial learning of the information.[52,53] This difficulty with learning new information results from dysfunction in other cognitive domains, including processing speed, executive functions, and cognitive inhibition.[38]

Given the prevalence of cognitive impairment in individuals with MS, it is crucial to conduct assessments to identify and intervene in those affected. Since cognitive deficits in MS often fall within specific domains, it is essential to use assessments that examine these frequently impaired areas. Among the various cognitive batteries, the short form Brief Repeatable Battery of Neuropsychological Tests (BRB) has been identified as a sensitive and cost-effective screening tool for identifying impairments in major cognitive domains in individuals with MS.[54] The short form BRB consists of the Paced Auditory Serial Addition Test (PASAT), the Symbol Digits Modalities Test (SDMT), and the Selective Reminding Test (SRT). This cognitive battery has demonstrated high sensitivity (78%-94%) and specificity (65%-84%) in identifying individuals with MS experiencing cognitive impairment.[54,55] Furthermore, some cognitive assessment batteries include the Stroop test in conjunction with the short form BRB.[56]

The SDMT is widely used for assessing processing speed in the MS population and is considered the most sensitive metric of cognitive function.[57-60] The PASAT, measuring both processing speed and executive functioning, has commonly been used to identify deficits in these domains.[61-63] The SRT, a memory test distinguishing between short and long-term storage, has also been utilized in MS research, revealing the prevalence of memory dysfunction in the population.[64] Finally, the Stroop test evaluates inhibitory control, requiring individuals to resist interference from distracting information and maintain goal-directed behavior.[65] As there is variability in the presentation of impairments among individuals with MS, there is an increased emphasis on cognitive assessments that evaluate multiple domains of cognition, including executive function, processing speed, and memory.[66]

Cognitive-motor interference

Walking, which is typically an automated motor task for healthy adults,[67] becomes attentionally demanding for individuals with MS, resulting in increased mobility issues.[68] This increased attentional demand is further compounded by existing cognitive deficits often experienced by individuals with the disease.[69] These findings underscore the concept of cognitive-motor interference (CMI), which refers to the decline in cognitive and/or motor performance when both tasks are performed concurrently. Given that these individuals require increased attentional focus on mobility and may experience cognitive decline, they face higher attentional demands when performing mobility and cognitive tasks together compared to healthy controls.[70,71] When the demands of these tasks exceed the limited attentional resources available, CMI will be present.[72] Additionally, given the propensity of individuals with MS to employ a posture-first strategy, or prioritize mobility in the presence of competing attentional demands,[73] dual task assessments that include outcomes related to both mobility and cognition are necessary to effectively identify those with MS who are at risk for falls.

While mobility and cognitive impairments are both prevalent in individuals with MS, they are often studied independently of each other.[74] However, there is a growing understanding that examining the performance of both mobility and cognition concurrently, known as dual tasking, is essential due to their complex and ecologically necessary interaction.[75,76] That is, dual tasking is ecologically necessary as the simultaneous performance of motor and cognitive tasks is an fundamental part of everyday life. In fact, previous research by Shema-Shiratzky et al. has identified the ecological validity of dual tasking in a lab setting. They found that gait speed and stride variability metrics captured while dual tasking in the lab were similar to those same metrics captured in community ambulation.[77]

When individuals with MS engage in concurrent cognitive tasks while walking, they show increased postural sway,[78-81] decreased gait speed,[82-87] reduced step length,[88,89] decreased double limb support time,[88-90] and increased stride variability compared to walking without a concurrent cognitive task.[91-95] While the impact of dual tasking on spatio-temporal parameters of gait are widespread, the impact is not seen solely in the mobility domain. In fact, dual tasking has also been found to result in slowed task performance and increased errors in cognitive performance.[70,96,97] Importantly, dual task impairments in mobility and cognition have been identified as sensitive biomarkers for falls in this population. Increased stride variability,[91,94] decreased gait speed,[86] decrements in cognitive performance, and self-reported difficulties with dual tasking have all been linked to fall risk in individuals with MS.[97,98] Therefore, dual task assessments that consider both motor and cognitive outcomes in people with MS are crucial for gaining a better understanding of their intricate relationship and importance to everyday mobility.[99,100]

Clinical assessments of fall risk

While in-lab assessments, especially dual task walking tests, have demonstrated sensitivity in differentiating between individuals with MS who are fallers and those who are non-fallers, these findings have not yet been effectively translated into clinical evaluations. In fact, research by Cameron et al. revealed that a fall in the previous year was a better predictor of a future fall than the currently used walking and balance assessments.[101] Furthermore, other research utilizing the timed up and go (TUG), a clinical walking assessment routinely used to identify those at risk for falls, was unable to discriminate fallers from non-fallers with MS.[102] These findings were corroborated by a recent meta-analysis that concluded the most commonly used assessments to identify fall risk in MS, such as the TUG, Berg Balance Scale, and Falls Efficacy Scale International, have poor predictive ability.[103] It is worth noting that these assessments lack the ecological validity present in in-lab dual task assessments, which more accurately identified fallers with MS.[86,104] Specifically, both the TUG test and the BERG Balance Scale lack a concurrent cognitive task, limiting their ability to effectively distinguish between fallers and non-fallers with MS.

More recently, clinical assessments of fall risk that have attempted to incorporate a secondary cognitive task have shown mixed results. Notably, the incorporation of serial seven or serial three subtraction has been integrated into the existing TUG, the TUG-cognitive, with the aim of increasing sensitivity to falls. However, both Nilsagard et al.

and Quinn et al. examined the time to completion on the TUG-cognitive and found no difference between fallers and non-fallers with MS.[102,105] Since time to completion did not offer additional insights into the impact of cognition on mobility, researchers have sought to evaluate its effect on mobility more directly. That is, previous studies have examined dual task cost, a measurement of performance decrement under dual task conditions compared to single task performance, calculated as a percentage comparison.[97,106] This provides a better understanding of the impact on mobility caused by the concurrent cognitive task.

$$Dual\ task\ cost\ (\%) = \left(\frac{Single\ task - Dual\ task}{Single\ task}\right) \times 100\%$$

Although dual task cost was initially developed to examine the underlying impact of cognition on mobility, clinical assessments of dual tasking have not yielded promising results in identifying fallers with MS. To date, several studies have utilized dual task cost as an outcome measure for both the TUG and timed twenty-five foot walk (T25FW) but have not found a significant difference between fallers and non-fallers with MS.[107-110] Interestingly, while all these studies included a cognitive component in their fall risk assessment, performance on the subtraction task was not quantified, despite previous research showing the utility of cognitive outcomes in identifying those at risk for falls.[97] Since CMI can manifest as decrements in either mobility or cognition, it may be necessary to examine performance on both the cognitive and motor tasks to effectively discriminate fallers from non-fallers with MS. Additionally, there is limited evidence to suggest that the serial seven subtraction test is effective at identifying cognitive decline in individuals with MS. Previous research has stated that serial seven subtraction performance is heavily influenced by arithmetic skill, and that caution should be exercised when using it as an assessment of cognitive abilities.[111] Furthermore, this cognitive task lacks ecological validity as continuous subtraction is rarely performed in everyday life. However, a verbal fluency task has been identified as an ecologically valid cognitive task that is sensitive in identifying deficits in processing speed and executive functioning in individuals with MS.[112] Furthermore, while language has traditionally been considered intact, recent research by Lebkuecher et al. has revealed a significant relationship between vocabulary and cognitive performance. This underscores the importance of including phonemic verbal fluency cognitive tasks in dual-task fall risk assessments, as they encompass aspects of cognition that have been demonstrated to pose increasing challenges for individuals with MS.[113]

The absence of cognitive outcome measures is not the sole reason current clinical assessments of fall risk lack the ability to effectively identify those with MS at risk for falls. Falls are multifaceted and the current mobility tests are limited in this regard. Specifically, current fall risk assessments lack ecological validity as they fail to incorporate many real-world factors that have been identified as particularly challenging for individuals with MS.[114,115] Since a majority of falls occur during activities of daily living,[114] assessments that include movements required in these contexts are crucial. Therefore, the incorporation of postural transitions and turns,[116-119] which are common everyday tasks that have shown to be increasingly difficult for individuals with MS, is essential in fall risk mobility assessments. Additionally, since stride variability has been identified as a sensitive measure of fall risk and tends to increase after turning,[118] assessments that include turning are vital for fall risk detection.

While in-lab findings have identified dual tasking, postural transitions, and turning as important biomarkers for mobility decline, these findings have not yet translated into clinical application.[103] For example, the T25FW lacks a secondary cognitive task, turns, and postural transitions. Similarly, the TUG, which includes both postural transitions and turns, is traditionally performed without a cognitive task. Moreover, the TUG test is conducted over a short distance, which may not provide sufficient length to ecologically evaluate CMI.[120] As such, there is an urgent need to develop ecologically valid fall risk assessments that incorporate both mobility and cognitive metrics derived from ecologically valid tasks. These assessments should encompass measures of stride variability and should also increase in length and difficulty to effectively distinguish individuals with MS who experience falls from those who do not.

Community participation

Research has shown a correlation between walking and community participation in individuals with MS, in which walking difficulty has been associated with a reduced ability to engage in community activities, such as social roles and work.[121,122] Community participation is a crucial aspect in the lives of individuals with MS, as it encompasses home-based activities, work, and leisure pursuits, which together significantly influence one's overall quality of life.[123] The significance of walking and community participation has been highlighted by Kwiatkowski et al., who found moderate to strong correlations between disability status and social participation.[124] Moreover, walking speed has been shown to be a reliable predictor of both community activity and participation, thereby highlighting the critical importance of community ambulation in various aspects of daily life.[122,125]

Although gait quality metrics (such as gait speed and stride variability) have been studied between individuals with MS and controls,[126] little is known about the relationship between these gait quality measures and community-based walking. While previous research has identified gait speed and stride length as related to real-world gait quantity, such as time spent walking, these findings were based on in-lab mobility measures, providing limited insights into the real-world contexts of walking.[127] Additionally, the focus of these findings has been primarily on pace-related metrics (gait speed and stride length), omitting the examination of the relationship between real-world walking and stride variability. While these findings have contributed to a better understanding of the link between gait quality and mobility, they have notable limitations. Specifically, lab-based mobility assessments occur at a single time point, limiting their ability to capture fluctuations in gait associated with MS, caused by factors like fatigue,[128] medications,[129] or environmental variables. Therefore, there is a pressing need to explore factors associated with both gait quality and quantity, derived from inertial sensors worn in real-world settings.

Instrumentation of real-world walking

Wearable sensors, particularly accelerometers, have played a vital role in enhancing our understanding of the impact of mobility impairment. Inertial sensors offer invaluable insights into both gait quality and quantity metrics as they collect data in real-world settings. Unlike in-lab assessments, which are limited by their cross-sectional nature, accelerometers allow for the collection data in the community for longer periods of time. The integration of accelerometers into research has led to significant progress in the field of dual tasking and MS. Recent studies have demonstrated the ecological validity of dual tasking, with gait features collected during dual tasking in the lab showing similarities to those collected in the community.[77] Moreover, a significant relationship has been observed between cognition, particularly processing speed, and both gait quality and quantity metrics, highlighting the importance of cognition in real-world ambulation.[77] Some studies have further shown that outcomes measured in the lab may not accurately reflect daily walking measures.[130] These findings align with a growing body of evidence suggesting differences between in-lab and real-world walking metrics for both gait quality and quantity in older adults and individuals with other neurological conditions.[77,131,132]

Research by Zijlstra and Hof has identified rhythmic patterns of trunk accelerations correlated with walking, enabling the quantification of gait parameters using an accelerometer placed on the lumbar region.[133] This study revealed that utilizing an inverted pendulum method allows for the quantification of displacements of the lower trunk, leading to the extraction of gait speed and step length metrics.[134] In other words, mean step length and gait speed can be estimated based on the upward and downward movement of the trunk.[134] By utilizing this model, changes in the height of sensor position become dependent on step length.[134] Consequently, when changes in height are quantified, step length can be predicted using the following equation.

$$Step\ length = 2\sqrt{(2lh - h^2}$$

In this equation, *h* represents the change in sensor height during one full step cycle, and *l* denotes the pendulum length, which refers to the distance of the sensor from the ground. The changes in the vertical position of the sensor are determined by double integration of the Y coordinate plane, converting raw acceleration data into position data, as depicted in Figure 3 below. With knowledge of the known step length and sampling rate, the time for each step can be determined, enabling the calculation of gait speed. This method has been previously employed in gait quantification studies involving older adults and individuals with neurological conditions.[77,130,131,133,135,136]

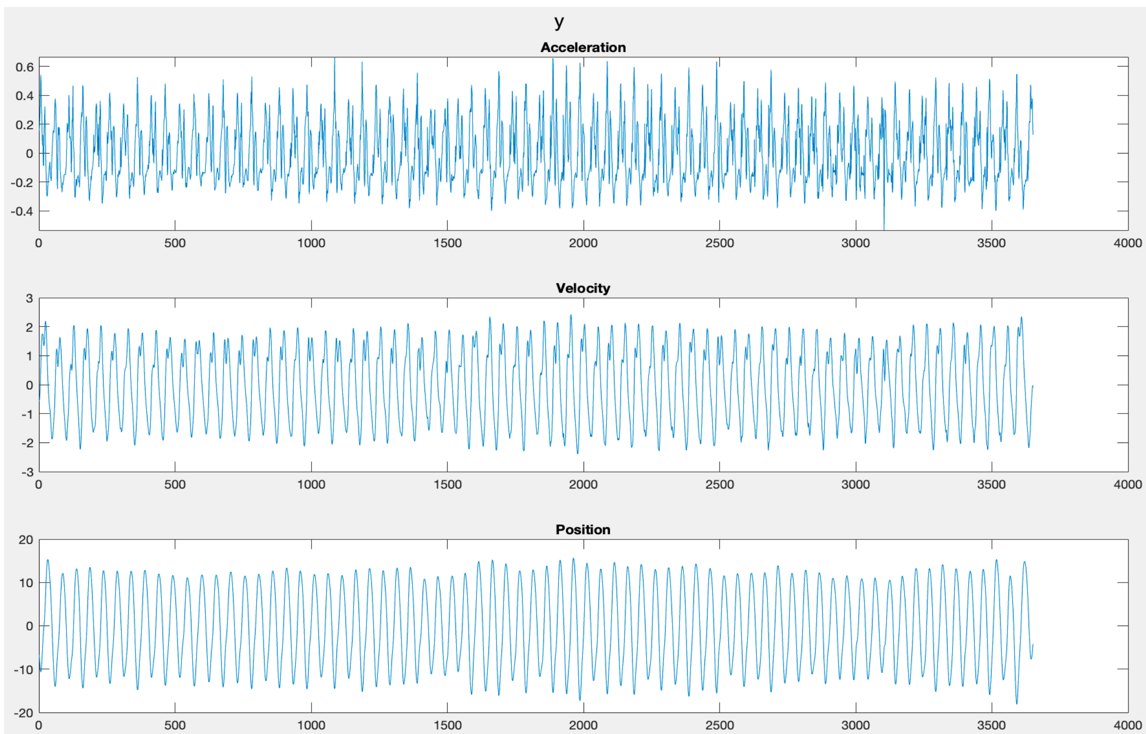

Figure 3: Example of double integration of Y-axis raw acceleration data to position data from one participant during continuous walking utilizing a lumbar accelerometer. The top represents raw data while the bottom represents the sensor position data that will be used in the inverted pendulum calculation to determine step length.

Overall, the findings from previous research emphasize the need to move beyond solely lab-based measures to truly understand mobility and community ambulation in individuals with MS.

Statement of the problem

Currently, clinical mobility assessments lack the ecological validity necessary to reliably and accurately identify individuals with MS who are at risk for falls. The absence of sensitive clinical assessments that are accessible and practical for clinicians hinders the ability to adequately identify potential fallers. As CMI can manifest in decrements of mobility and/or cognition, fall risk assessments that incorporate outcomes of both are imperative. Moreover, dual tasking in the lab has demonstrated sensitivity in predicting falls due to its ecological validity. Therefore, it is imperative to develop and implement mobility assessments that are also ecologically valid. Further underscoring the need for ecologically valid clinical fall risk assessments, the National Multiple Sclerosis Society has emphasized the urgent need for the development of clinically useful and sensitive quantitative outcome measures to identify those with MS who are at risk for falls.

While the association of cognition and mobility with gait quality have been examined in lab settings, little is known about the influence of these factors on real-world walking performance. Understanding contributors to real-world gait quality is crucial, as they necessary for engagement in walking and community-based activities.[137]

Therefore, the objective of this project was to conduct a cross-sectional cohort study to identify a clinically applicable mobility assessment that represents real-world gait metrics and that is accessible in the clinic for identifying fall risk in individuals with MS. Additionally, while it is understood that psychosocial and cognitive factors influence mobility, little is known about their contributions to real-world gait quality and quantity.

The following study aims were evaluated:

1. To examine sensitivity and specificity of both currently used and novel clinical measures at predicting fall status in persons with MS
2. Identify a clinical assessment that is reflective of everyday walking in individuals with MS.
3. Examine the contributions of cognition, ambulation disability, and psychosocial factors to real-world gait quality and quantity metrics.

CHAPTER 2: UTILIZATION OF NOVEL DUAL TASK MOBILITY ASSESSMENTS TO PREDICT FALL STATUS IN INDIVIDUALS WITH MULTIPLE SCLEROSIS

Introduction

The progressive neurodegeneration associated with multiple sclerosis (MS) results in a continual decline in mobility.[93] Mobility impairment is often reported to be the most common and impactful symptom experienced by people with the disease,[138] and several studies have shown that loss of mobility contributes to significant patient burden[24] and reduced functional independence.[25] As walking becomes more difficult, fall risk increases and falls become quite prevalent, with over 50% of ambulant people with MS reporting at least one fall in any 3-month period.[26] Falls have long-term consequences and can result in a loss of functional mobility, which is the most commonly cited problem impacting quality of life and prompting persons with MS to leave the workforce early.[25] As individuals with MS experience a fall, they are more likely to be fearful of falling, reduce community participation and physical activity, all leading to lower quality of life.[29-31] Additionally, this reduction in physical activity and self-isolation leads to reduced strength, endurance, and range of motion, increasing the risk for future falls and increasing the risk for severe injury.[32,33] Given the trajectory of mobility decline and its functional consequences over time, identifying and mitigating fall risk are important health imperatives.

Studies have revealed reduced gait speed and increased stride variability as sensitive gait measures that have been found to differentiate MS fallers from non-fallers.[91,93,94,139-141] Furthermore, the cognitive demands of walking,[142] together with the cognitive dysfunction associated with the disease,[143] put individuals with MS at a higher risk for falling.[144] This is significant given that many daily activities often require the simultaneous performance of both a movement and a cognitive task (dual tasking), and research has shown that dual tasking, reflective of cognitive motor interference, is particularly difficult for those with MS.[83,106] In one study, researchers found that dual tasking not only resulted in decreased walking velocity but was also associated with an increased risk of recurrent falls.[104]

While there is growing evidence that dual task walking in the lab can distinguish between individuals with MS who fall and those who do not,[86,97] these findings have not been translated into sensitive clinical assessments.[101] In fact, previous research found the timed-up-and-go (TUG), a clinical assessment routinely used to identify those at risk for falls, did not sufficiently discriminate between fallers and non-fallers with MS.[102] Additionally, a recent meta-analysis concluded that the most commonly used assessments for identifying fall risk (i.e., the Berg Balance Scale, the TUG, and the Falls Efficacy Scale International) have poor predictive ability for fall risk in persons with MS.[103] As such, these findings further emphasize the need to develop assessments that better predict falls in this population.

The lack of clinical assessments suitable for identifying fall risk in persons with MS may be best explained by the limitations associated with currently used evaluative instruments. Specifically, these assessments lack ecological validity as they do not incorporate many real world factors that have been identified as particularly difficult for individuals with MS.[114,115] Notably, current assessments performed in clinics fail to incorporate competing attentional demands of concurrent motor and cognitive tasks, evaluate the quality of movements, or include postural transitions and turning, all of which have been linked to an increased risk for falls.[91,92,119] As previous research has highlighted the importance of ecologically valid fall risk assessments, new and innovative clinical assessments that relate to real world mobility challenges are essential for earlier detection and intervention.

The cyclical nature of falls leading to future falls and poor life quality highlights the urgent need to provide clinicians with effective assessments that can identify those who are at risk for falls before they occur. As such, the purpose of this study was to examine the ability of novel, dual task fall risk assessments to predict falls in individuals with MS, and to compare these results to the routinely performed TUG test. We hypothesized that the novel clinical assessments (i.e. Timed up and go extended, 25-foot walk and turn, and figure 8 walk) would show increased sensitivity and specificity compared to the currently used TUG test in classifying fallers and non-fallers with MS.

Methods

Participants

To adequately power a logistic regression, we aimed to follow guidelines laid out in previous literature examining the minimum number of events per variable in a given regression analysis to avoid bias.[145] As such, we set a goal to recruit 30 participants for this study aim since three variables were included in the initial regression model for the novel clinical assessments (stride variability, gait speed, verbal fluency outcome measure). Participants from Vermont and Syracuse, New York were enrolled in the study if they had physician-diagnosed MS, reported no to moderate self-reported mobility dysfunction (i.e., 0 to 4 on the Patient Determined Disease Steps; PDDS),[146] and had not experienced an exacerbation of symptoms in the previous month. Individuals were excluded from the study if they reported having any neurological condition (other than MS) that could contribute to significant balance impairment or had a medical diagnosis considered an absolute or relative contraindication to exercise.

Participants who expressed interest in the study and contacted the principal investigator underwent a phone screening to determine eligibility. The study was approved by the Institutional Review Board at the University of Vermont, and informed consent was obtained prior to testing.

Instrumented measures of mobility

Objective measures of mobility were collected using small wireless inertial sensors (OPAL, APDM Inc.) placed on the feet, lumbar, and sternum. Walking outcome measures of interest included both gait speed and stride variability. For stride variability, values can range from 0 to 1 with higher values indicating lower levels of variability, or increased stride symmetry. Both of these measures were calculated in MATLAB (R2022a) using algorithms previously utilized to quantify gait characteristics in individuals with neurological conditions.[77,147] Once properly fitted, participants in the study were instructed to perform the following series of walking assessments: TUG, TUG-extended, 25-foot walk and turn, and figure 8 walk. The four mobility assessments were randomized across participants to control for order effects.

Walking assessments

Timed up and go

Participants were positioned in a standard-height chair with their back against the chair's backrest. Next, they were directed to rise from the seated position, walk a distance of 3 meters to a cone, execute a turn, return to the chair, and resume a seated posture.

Timed up and go extended

Consistent with the research conducted by Evans et al.,[148] participants performed a modified TUG assessment, known as the TUG-extended. Participants began the assessment from a seated position in a stable and standard chair with armrests. They were instructed to stand up from their seated position, walk seven meters at a comfortable pace, make a 180-degree turn, and return to a seated position at the starting point.

25-foot walk and turn

Participants completed a modified version of the 25-foot walk assessment.[149] The trial was conducted similarly to the traditional 25-foot walk, in which participants are instructed to walk a distance of 25 feet. However, in this novel assessment, participants were instructed to walk the 25 feet, make a 180-degree turn, and return to the starting position.

Figure 8 walking

For this task, participants were positioned at the midpoint of a figure 8, with cones placed five feet away both in the anterior and posterior directions. They were instructed to walk in a figure 8 pattern around the cones back to the starting point. The trial concluded once the participant completed one full figure 8.

Cognitive outcome measure

To assess cognitive performance while completing the novel clinical assessments, participants in the study completed the phonemic verbal fluency task, an ecologically valid cognitive task that has shown to be sensitive at identifying deficits in processing speed and executive functions in individuals with MS.[112] Participants were instructed to name as many words as possible that begin with a given letter (i.e. F, A, and S) for the duration of the walking tasks. Letters were randomized across the three walking tasks for all participants. To standardize cognitive performance by time, number of correct utterances was divided by time taken to complete the trial in seconds.

Procedures

During all walking trials, participants received specific instructions to walk at a natural and comfortable pace, allowing their arms to swing naturally by their sides. Moreover, participants were advised not to prioritize either the cognitive or mobility task during all tests. The sequence of both the walking assessments and the concurrent verbal fluency task was randomized for all participants. Prior to conducting mobility testing, baseline demographic information was gathered, including age, sex, year of diagnosis, MS subtype, and history of prior falls.

Analysis

Participants were divided into two groups based on whether or not they had experienced a fall in the previous six months.[34,150,151] Consistent with previous literature, individuals were considered fallers if they reported one or more falls,[105,152] and non-fallers if they did not report a fall within the specified time period. Descriptive statistics between groups were compared using either an independent samples T-test or chi-square test. To compare the gait and cognition variables between fallers and non-fallers for the clinical assessments, an independent samples T-test was conducted, and Cohen's D was included as a measure of effect.

A logistic regression model was utilized with both gait speed and stride variability serving as predictors for each clinical assessment. Additionally, in the three novel assessments, the number of correct utterances per second on the verbal fluency task was incorporated into each model. The area under the receiver operating curve (AUC) was computed from each logistic regression result. The AUC curve plotted the true positive rate against the false positive rate and provided an average sensitivity for each model identifying fallers in the previous six months. AUC outputs were compared across walking trials to determine which mobility assessment more accurately identified fall status.

Results

A summary of descriptive statistics is presented in table 1 below. A total of 27 participants, 14 fallers and 13 non-fallers, were included in the study. No differences were seen between groups for age (p=0.63), years post diagnosis (p=0.32), gender (p=0.24), ambulation status (PDDS; p=0.07), or MS subtype (p=0.26).

A summary of clinical assessment outcomes for each group is presented in Table 2 below. The results indicate no significant differences between groups in terms of gait speed on the TUG (p=0.39, d=0.34), TUG-extended (p=0.39, d=0.34), 25-foot walk and turn (p=0.30, d=0.41), and figure 8 walk (p=0.47, d=0.28). Additionally, no significant differences were found for the TUG (p=0.18, d=0.54), TUG-extended (p=0.13, d=0.61), 25-foot walk and turn (p=0.06, d=0.77), and figure 8 walk (p=0.19, d=0.52) in terms of stride variability. Regarding verbal fluency task performance, a significant difference was observed between groups during the 25-foot walk and turn task (p=0.02, d=0.94), with the fallers group scoring lower on average. However, no significant differences were noted between groups for the verbal fluency task during the TUG-extended (p=0.97, d=0.01) and the figure 8 walk (p=0.58, d=0.22).

Table 1: Descriptive statistics between fallers and non-fallers with MS

Variables	Fallers (N=14)	Non-fallers (N=13)	P-value
Age (years±SD)	60.07±11.31	58.08±10.06	0.63
Years post diagnosis (years±SD)	24.00±15.40	19.23±7.67	0.32
Gender (% female)	92.86	76.92	0.24
PDDS (mean±SD)	2.07±1.33	1.15±1.14	0.07
MS subtype	8 RR, 5 SP, 1 PP	11 RR, 2 SP	0.26

Table 2 Mobility assessment outcomes for both fallers and non-fallers

Test	Metrics	Fallers (N=14)	Non-fallers (N=13)	P-value	Cohen's D
TUG	Gait speed (m/s)	1.04±0.32	1.14±0.27	0.39	0.34
	Stride variability (arbitrary units)	0.57±0.14	0.65±0.16	0.18	0.54
TUG-extended	Gait speed (m/s)	0.87±0.29	0.96±0.27	0.39	0.34
	Stride variability (arbitrary units)	0.46±0.19	0.57±0.17	0.13	0.61
	Verbal fluency (utterances per second)	0.32±0.17	0.32±0.14	0.97	0.01
25-foot walk and turn	Gait speed (m/s)	0.83±0.30	0.95±0.24	0.30	0.41
	Stride variability (arbitrary units)	0.44±0.20	0.59±0.18	0.06	0.77
	Verbal fluency (utterances per second)	0.27±0.12	0.37±0.08	0.02*	0.94
Figure 8 walk	Gait speed (m/s)	0.79±0.27	0.87±0.25	0.47	0.28
	Stride variability (arbitrary units)	0.44±0.20	0.59±0.18	0.19	0.52
	Verbal fluency (utterances per second)	0.33±0.15	0.35±0.10	0.58	0.22

TUG: timed up and go; TUG-extended: timed up and go extended

Contributions of all variables in each regression are presented in Table 3. When all variables were included in the regression analysis, none significantly contributed to predicting fall status ($p \geq 0.14$). The TUG correctly identified 64.30% of fallers and 61.50% of non-fallers, yielding an overall predictive value of 63.00%. The model fit was deemed acceptable (Hosmer and Lemeshow test, $p=0.49$), and the Nagelkerke R^2 was 0.10. The AUC statistic for this model was 0.67 (95% CI, 0.46-0.88; figure 4).

The TUG-extended assessment exhibited an overall predictive value of 51.90% (sensitivity 46.20%, specificity 57.10%). Goodness of fit results indicated that the data did not fit the model well ($p=0.03$). The AUC of the model was 0.63 (95% CI, 0.42-0.85; figure 5), and the Nagelkerke R^2 was 0.13.

The 25-foot walk and turn model demonstrated acceptable fit ($p=0.06$) and a Nagelkerke R^2 of 0.32. Overall, the 25-foot walk and turn correctly identified 71.40% of fallers and had a specificity of 69.20%, resulting in a 70.40% predictive value. The AUC for this model was 0.76 (95% CI, 0.56-0.96; figure 6).

Lastly, the figure 8 walk model exhibited acceptable fit ($p=0.51$) and had an overall predictive value of 63.00% (sensitivity 53.80%, specificity 71.40%). This resulted in an AUC of 0.67 (95% CI, 0.45-0.88; figure 7) and a Nagelkerke R^2 of 0.10.

Table 3: Logistic regression analysis results for clinical mobility assessments

Mobility test	Predictor	B	SE	Wald	P-value
TUG	Gait speed (m/s)	-0.38	1.57	0.06	0.81
	Stride variability (arbitrary units)	-3.61	3.30	1.20	0.27
TUG-extended	Gait speed (m/s)	1.22	2.31	0.28	0.60
	Stride variability (arbitrary units)	-5.05	3.80	1.77	0.18
	Verbal fluency (utterances per second)	-0.55	2.89	0.04	0.85
25-foot walk and turn	Gait speed (m/s)	3.25	3.08	1.11	0.29
	Stride variability (arbitrary units)	-6.08	4.59	1.76	0.19
	Verbal fluency (utterances per second)	-7.28	4.95	2.16	0.14
Figure 8 walk	Gait speed (m/s)	0.54	2.19	0.06	0.81
	Stride variability (arbitrary units)	-4.23	4.04	1.10	0.30
	Verbal fluency (utterances per second)	-0.85	3.25	0.07	0.79

TUG: timed up and go; TUG-extended: timed up and go extended; B: regression coefficient; SE: standard error;

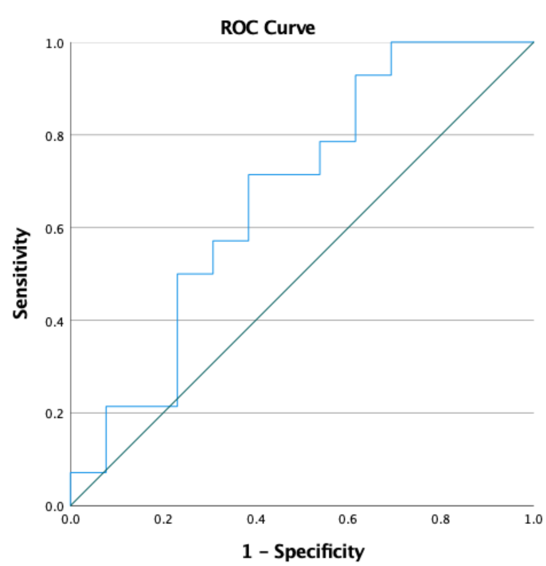

Figure 4: Timed up and go receiver operating curve, AUC 0.67

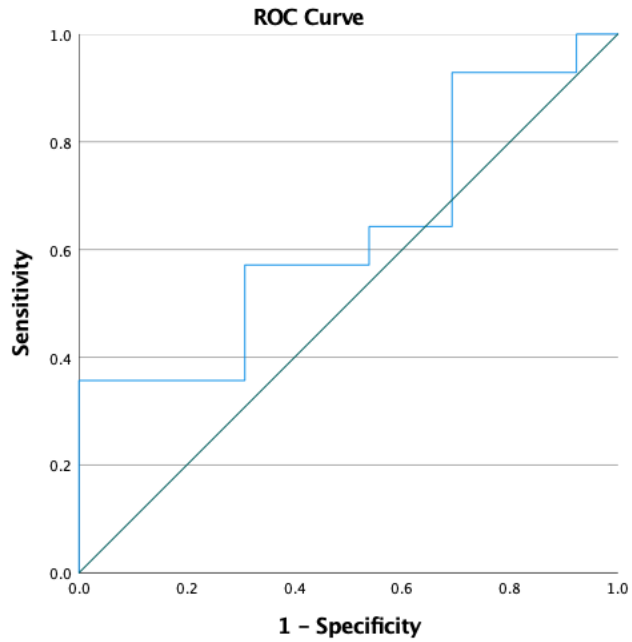

Figure 5: Timed up and go extended receiver operating curve, AUC 0.63

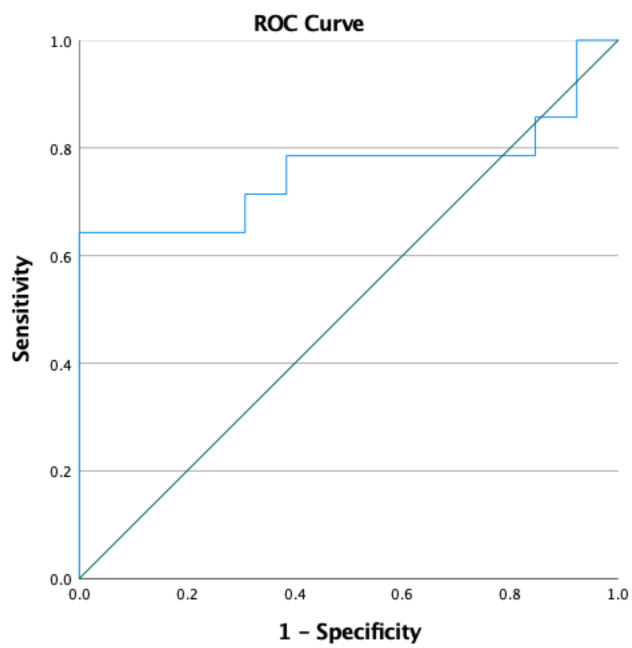

Figure 6: 25-foot walk and turn receiver operating curve, AUC 0.76

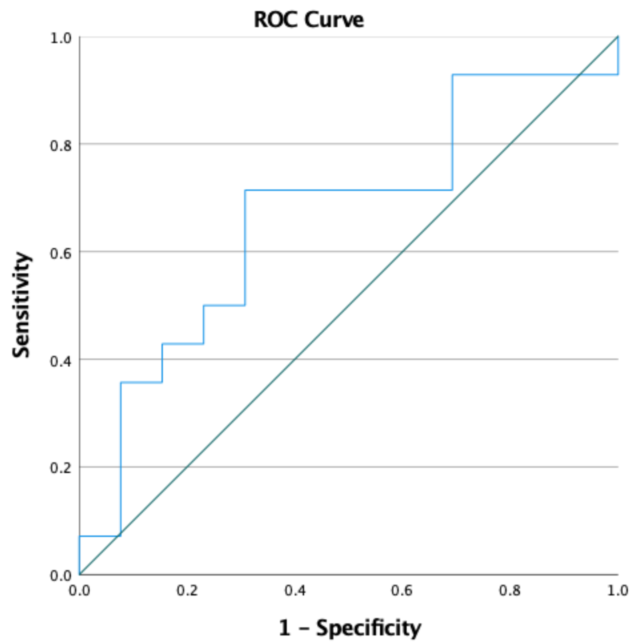

Figure 7: Figure 8 walk receiver operating curve, AUC 0.67

Discussion

Dual tasking is a significant concern for individuals with MS, and previous research has highlighted its impact on mobility and its association with fall risk.[86,97,98] While the intersection of cognitive and motor tasks have been successfully incorporated into lab based mobility assessments, there remains a gap in translating this to clinical application. That is, current mobility assessments lack ecological validity, thus presents a challenge in effectively detecting fall risk for individuals with MS.[103,120] The results obtained from the TUG in our study align with the findings of previous investigations, underscoring its limited effectiveness in identifying individuals with MS who are at risk of falls. Specifically, our study revealed an AUC of 0.67 for the TUG. These outcomes are consistent with prior research, where studies have reported AUC values ranging from 0.46 to 0.67.[102,103,110,153] The results of the present study underscore the urgent need to improve the ecological validity of clinical fall risk assessments for individuals with MS. Specifically, the findings indicate that the TUG test had limited predictive ability,[101,102] while the 25-foot walk and turn exhibited increased sensitivity in identifying fallers. These results emphasize the importance of refining fall risk assessments to improve their accuracy and applicability in clinical settings for individuals with MS.

The results of this study emphasize the significance of considering factors beyond mobility alone when assessing fall risk in individuals with MS. Across all clinical assessments, no significant differences were observed between groups for measures of gait speed or stride variability, although fallers tended to walk slower and display increased stride variability. Notably, cognition did differ between fallers and non-fallers in the 25-foot walk and turn task, and it was the variable that made the most substantial contribution to this model. These findings are consistent with previous studies and underscore the importance of incorporating and quantifying cognitive aspects in mobility assessments for fall risk evaluation.[70,97] The findings from this study suggest that, when faced with simultaneous cognitive and motor tasks, individuals at a higher risk for falls may adopt a "posture-first" strategy. In this strategy, they prioritize maintaining balance and may sacrifice cognitive performance as a protective mechanism against falling.[73] This prioritization approach might explain why, under dual task conditions, no significant differences were observed between groups in mobility measures, while significant differences were seen for cognition.

While the 25-foot walk and turn assessment showed increased sensitivity, particularly due to the cognitive outcome variable, these findings were inconsistent with the results obtained from the other ecologically valid mobility assessments conducted in this study, namely the figure 8 walk and the TUG-extended. While these seemingly contradictory results warrant further investigation, they may likely be best explained by considering the attentional demands of each task. The 25-foot walk and turn involves fewer turns and/or postural transitions compared to the figure 8 walk and the TUG-extended. Previous research has highlighted that both turning and postural transitions are increasingly challenging and require additional resources for individuals with MS.[116,118,119,126,154] Therefore, in the 25-foot walk and turn assessment, non-fallers with MS may have been able to allocate more cognitive resources to prioritize and execute the cognitive aspects of the task effectively, resulting in improved sensitivity in identifying fall risk. On the other hand, in the figure 8 walk and TUG-extended assessments, the increased demands of turning and postural transitions might have led individuals in both faller and non-faller groups to prioritize their mobility over cognition. Consequently, this prioritization may have resulted in similar outcomes for both groups in these assessments.

There are several strengths of the present study. The study included both novel, ecologically valid mobility assessments, and the conventionally used TUG, allowing for comparisons across tasks. Most notably, the incorporation and evaluation of ecologically valid cognitive outcome metrics increased the sensitivity of the 25-foot walk and turn assessment. While the study had important strengths, limitations should be acknowledged. Retrospective falls were utilized as the primary outcome, which may introduce recall bias, as identified in previous research.[155] Additionally, the small sample size did not include the recommended 30 participants to avoid bias, limiting the generalizability of the findings to the entire MS population. Future research should incorporate larger sample sizes and prospective fall risk assessment when evaluating the effectiveness of these clinical assessments in identifying fallers with MS. Lastly, although the study aimed to explore novel assessments for potential use in clinical settings, the metrics used were derived from inertial sensors, which might not be feasible for clinic-based fall risk assessments. Therefore, future research should focus on identifying gait speed and stride variability metrics that are practical for use in routine mobility testing.

Conclusion

The inclusion of ecologically valid constructs from everyday life into dual-task fall risk assessments enhances sensitivity compared to currently used mobility evaluations. As dual task deficits can manifest in either mobility or cognitive performance declines, evaluating both aspects simultaneously is crucial for more accurately identifying individuals at risk for falls. Therefore, future studies should aim to incorporate and assess cognition to improve the accuracy of fall risk identification, enabling earlier and targeted interventions.

Chapter 3: CORRELATION OF NOVEL DUAL TASK CLINICAL ASSESSMENTS TO REAL-WORLD AMBULATION IN PERSONS WITH MULTIPLE SCLEROSIS

Introduction

The neurodegeneration caused by multiple sclerosis (MS) results in a progressive decline in functioning and overall quality of life.[93] Mobility impairment is often reported as the most common symptom affecting people with the disease, with over 90% reporting mobility dysfunction,[21,22] and is frequently reported as the most important factor limiting community participation.[23]

Although the underlying cause of mobility impairment in MS is multifaceted, there is mounting evidence that including a cognitive task during walking (dual tasking) increases the risk of falls.[100] Given that cognitive dysfunction contributes to mobility impairment,[142,156] and over 60% of persons with MS report cognitive dysfunction,[38] it becomes crucial to incorporate cognitive-motor dual task paradigms in functional walking assessments. This highlights the importance of cognitive-motor interference (CMI), which refers to the deterioration in cognitive or motor performance when performed concurrently, and the challenges it poses for individuals with MS. Previous research in lab-based settings has demonstrated that dual task walking increases stride variability and decreases gait speed, leading to an elevated risk of falls in individuals with MS.[82,85,86,157]

Further underlining the importance of existing CMI in individuals with MS, recent research comparing gait quality for individuals with MS in and out of the lab setting found that real-world walking performance was indistinguishable from dual task walking in the lab.[77] In fact, gait speed and stride variability, two metrics commonly used and sensitive for identifying fall risk in individuals with MS, were similar when performed in the lab while dual tasking and when measured in everyday ambulation.[77] These findings reveal the importance of mobility assessments that include cognitive tasks as they are more representative of everyday walking, and employing evaluations that are representative of these real-world contexts are crucial to improving sensitivity and specificity of clinical assessments to accurately identify individuals at risk for falls in the community.

While the inclusion of a cognitive task in mobility assessments is imperative to elucidate walking differences in the population, it is also important to consider further evaluation of mobility challenges that are difficult for individuals with MS. As previous research has identified that a majority of falls in the population occur indoors and during activities of daily living,[114] assessments that include movements typically required in these contexts are crucial. As such, two common everyday movement that have been demonstrated to be more challenging for individuals with MS, postural transitions[116,117] and turning,[118,119] are critical to include in mobility assessments. Since stride variability is a sensitive measure of mobility decline and fall risk, and previous research has shown that stride variability increases after turning,[118] the inclusion of turns in mobility assessments for fall risk detection is vital to identify those with MS who have increased mobility decline. Additionally, previous research has identified sit-to-stand transitions as biomarkers for functional decline and fall risk detection,[116,117] highlighting the importance of including postural transitions in mobility tests.

While in-lab findings have identified dual task walking, postural transitions, and turning as important indicators for mobility performance and disease progression,[104,112,118] these findings have not sufficiently translated to clinical assessments, and early fall risk prediction.[103] For example, the timed 25-foot walk (T25-FW) lacks a cognitive task, turns, and postural transitions. Additionally, while the timed-up-and-go (TUG) includes a postural transition and turn, the test is performed over a short distance and lacks a secondary cognitive task. This may help explain why both tests have poor predictive ability for fall risk.[103] As such, current clinical assessments routinely performed by healthcare practitioners do not incorporate ecologically valid components of mobility that make individuals with MS more susceptible to falls.

To adequately evaluate mobility and CMI in individuals with MS, the incorporation of cognition as well as other ecologically valid constructs of community mobility are vital. As falls are most likely to occur during activities of daily living and in the community, and current functional mobility tests such as the TUG and T25-FW lack the ecological validity necessary to adequately identify those who are risk for falls, assessments that are reflective of and correlate to real-world ambulation are essential to improve mobility assessments and ultimately improve overall quality of life. As such, the goal of this study is to compare novel clinical mobility assessments to real-world community ambulation in individuals with MS. We hypothesize that the ecologically valid construct of the newly developed in-lab walking assessments will result in no differences between in-lab and real-world ambulation for both measures of gait speed and stride variability, and there will be high correlations between them.

Methods

To be eligible, participants had to have physician-diagnosed MS, none to moderate self-reported mobility impairment (0-4 on the Patient Determined Disease

Steps; PDDS), and must not have experienced an exacerbation of symptoms in the previous month. Participants were excluded from the study if they had a neurological disorder or medical diagnosis other than MS that might cause significant balance problems. Individuals who were interested in the study underwent a phone screening to determine eligibility and, if eligible, provided written informed consent prior to testing. All study components had been approved by the Institutional Review Board at the University of Vermont.

In-lab testing

Demographic information, including age, gender, disease duration, MS subtype, and mobility impairment (PDDS), was obtained. All subjects completed walking assessments wearing small wireless motion sensors (OPAL sensors, APDM Inc., Portland, OR, USA) placed on their chest, sacrum, and feet. The OPAL sensors allowed for real-time collection of spatio-temporal aspects of gait and had been validated against motion capture systems to detect minimal changes in movement.[158] Outcome measures included gait speed and stride variability, as previous literature had identified these metrics as measures affected in early stages of MS that could be detected with inertial sensors.[159] Both gait speed and stride variability measurements were derived from similar algorithms used for real-world ambulation, enabling direct comparisons between the two environments.

Once properly fitted with OPAL sensors, subjects were instructed to perform a series of assessments in a randomized order, which included the traditional TUG and other novel assessments including the TUG-extended, 25-foot walk and turn, and figure 8 walk. For the TUG, participants were seated in a standard-height chair and instructed to stand up, walk around a cone 3 meters away on the ground, turn around, and walk back to sit in the chair. Similar instructions were given for the TUG-extended, except for the cone being placed 7 meters away. For the 25-foot walk and turn, participants started standing and were instructed to walk 25 feet, turn around a cone, and walk back to the starting line. In the figure 8 walk, participants started at the midpoint of a figure 8, with cones placed five feet away in the anterior and posterior direction. They were instructed to walk in a figure 8 pattern around the cones, with the trial concluding once the participant completed one full figure 8.

Performance of the three novel clinical assessments included a secondary cognitive task, with participants instructed to perform the F-A-S phonemic verbal fluency task for the duration of each trial. Verbal fluency was selected as it has shown increased ecological validity compared to other cognitive tasks when examining deficits in processing speed and executive functions in individuals with MS.[112] For all walking assessments, participants were instructed to walk at their normal, everyday walking pace, and told to not prioritize either the mobility or cognitive task.

Real-world ambulation data collection

Upon completion of in-lab assessments, subjects were fitted with a small, body-fixed inertial sensor (Axivity AX3, York, UK) taped to their lower back (between lumbar vertebrae 4-5). The AX3 sensor was held in place by hypafix tape and programmed to a sampling frequency of 100 hertz and at a range of ±8 g. The recorded accelerometer data was stored locally on the sensor's internal memory until it was extracted by a research team member. This sensor was used to capture real-world community gait speed and stride variability for three days after in-lab testing. This time period was selected as previous research utilizing bod-fixed inertial sensors identified three days as a sufficient amount of time to capture real-world ambulation data.[135] Subjects were instructed to leave the device on for the following three days and not to deviate from their usual daily activities. Upon completion of the three-day period, sensors were collected from participants and returned to the lab for data extraction and processing.

Real-world ambulation data processing

Unfiltered 3-axis accelerometer data collected on AX3 sensors was exported and analyzed using the MATLAB program (R2022a). Outcome variables of interest, including gait speed and stride variability, were calculated in accordance with algorithms derived by Zijlstra and Hof.[133] These algorithms were designed for optimal use with lower back sensors, and previous research has identified a high correlation between these algorithms and gait metrics calculated via the GaitRite instrumented walkway.[160]

Consistent with previous literature that examined real-world ambulation in populations with neurological disorders, community data was only included for analysis if the walking trial included thirty or more seconds of continuous walking. This criterion ensured that the collected data was representative of an individual's typical gait pattern.[77,131,135] Consequently, the analysis of walking data was conducted in two stages:

1) Identification of walking bouts equal to or exceeding thirty seconds of continuous walking.

2) Application of algorithms to calculate average gait speed and stride variability for the identified bouts in step 1.

Analysis

Descriptive statistics were computed for all variables. To assess whether there was a significant difference between real-world gait metrics and gait metrics from the clinical assessments, a paired sample T-test was used with a p-value less than 0.05 to signal significance. Effect sizes (Cohen's *d*) were calculated between testing environments and interpreted as small ($d < 0.20$), moderate ($d = 0.21\text{-}0.79$), or large ($d > 0.80$).[161] To examine the strength of correlation between in-lab walking and real-world ambulation, a single measurement, two-way mixed effect, absolute agreement intraclass correlation coefficient (ICC) model with all in-lab mobility metrics being compared to at-home walking measures. Specifically, gait speed and stride variability measures derived from in-lab clinical assessments were compared to the corresponding metrics obtained from AX3 sensors worn on the lower back for three consecutive days in the community. Consistent with existing literature, ICC values between 0.75 and 0.90 indicated good reliability, with values greater than 0.90 indicating excellent reliability, both of which are above the threshold for clinical utility.[162]

Results

Table 4 below provides the descriptive statistics for the sample. A total of 20 participants were included in the study. The sample included 16 females and 4 males, ranging in age from 40-75, with an average age of 56.35±8.59.

Table 4: Descriptive statistics

Descriptive statistics	N=20
Age (years±SD)	56.35±8.59
Years post diagnosis (years±SD)	17.00±8.35
Gender (% female)	80%
PDDS [median(range)]	1 (0-4)

Patient Determined Disease Steps (PDDS)

Table 5 below provides results of both the paired samples T-test and ICC analyses. Statistically significant differences were observed in both gait speed and stride variability between real-world ambulation and the traditional TUG. On average, participants exhibited significantly faster gait speed during the TUG than their real-world gait speed ($p<0.01$, $d=0.70$) and demonstrated significantly less variability ($p=0.04$, $d=0.48$).

When examining the novel dual-task clinical assessments in relation to real-world ambulation, significant differences were observed in gait speed for the figure 8 walk test ($p=0.03$, $d=0.53$), indicating slower gait speeds during the figure 8 walk. However, no differences were found between real-world ambulation and the TUG-extended ($p=0.44$, $d=0.18$) or the 25-foot walk and turn ($p=0.37$, $d=0.21$) in terms of gait speed. Additionally, no differences in stride variability were noted between real-world ambulation and the TUG-extended ($p=0.52$, $d=0.15$)., 25-foot walk and turn ($p=0.22$, $d=0.29$)., and figure 8 walk ($p=0.53$, $d=0.15$).

Intraclass correlation coefficient results comparing real-world ambulation with the TUG demonstrated moderate reliability for gait speed (ICC=0.56) and poor reliability for stride variability (ICC=0.41). Comparing the TUG-extended to real-world ambulation, moderate reliability was observed for both gait speed (ICC=0.66) and stride variability (ICC=0.63), respectively. Similar findings were seen in the comparison between the figure 8 walk and real-world ambulation, as the ICC analysis yielded moderate reliability for both gait speed (ICC=0.61) and stride variability (ICC=0.74). Finally, when comparing the 25-foot walk and turn with real-world ambulation, results indicated good reliability for both gait speed (ICC=0.75) and stride variability (ICC=0.81).

Table 5: Accelerometer derived mobility outcome metrics for both real-world ambulation and in-lab clinical assessments and their associated p-values, effect sizes, and reliability statistics with 95% confidence intervals

Metrics	Test	Mean±SD	P-value	Cohen's D	ICC	ICC 95% CI
Gait speed (m/s)	Real-world Ambulation	0.98±0.29	--	--	--	--
	TUG	1.14±0.29	<0.01*	0.69	0.56	0.12-0.81
	TUG-extended	0.93±0.29	0.44	0.18	0.66	0.32-0.85
	25-foot walk and turn	0.93±0.30	0.37	0.21	0.75	0.48-0.89
	Figure 8 walk	0.85±0.27	0.03*	0.53	0.61	0.23-0.83
Stride variability (arbitrary units)	Real-world Ambulation	0.51±0.21	--	--	--	--
	TUG	0.61±0.17	0.04*	0.48	0.41	0.01-0.70
	TUG-extended	0.53±0.20	0.52	0.15	0.63	0.41-0.89
	25-foot walk and turn	0.54±0.21	0.22	0.29	0.81	0.59-0.92
	Figure 8 walk	0.49±0.16	0.53	0.15	0.74	0.46-0.89

*Denotes significant difference ($p<0.05$) from real-world ambulation**,** ICC values in relation to real-world ambulation, TUG: Timed up and go, TUG-extended: Timed up and go extended

Discussion

The limited ecological validity of current clinical assessments highlights the challenges associated with understanding balance and mobility impairments in individuals with MS. Current clinical mobility assessments often fail to incorporate a secondary cognitive task, thereby limiting their ability to reproduce the complexity of real-life scenarios in which dual-tasking is common. Although previous research has underscored the ecological significance of dual-tasking,[83,97,163,164] along with postural transitions[116,117] and turning[118,119] in mobility tests, these findings have yet to be effectively translated into clinical assessments. Consequently, the limited ecological validity of currently employed mobility assessments has resulted in suboptimal predictive capabilities in identifying individuals at risk for falls.

This investigation aimed to directly compare the gait speed and stride variability metrics of the widely used TUG with real-world captured mobility outcomes in individuals with MS. The results revealed significant differences between the TUG test and real-world mobility, with individuals with MS displaying faster gait speed and reduced stride variability during the TUG compared to real-world mobility. These findings suggest that the TUG may not adequately simulate the challenges encountered during everyday walking for individuals with MS. These findings are consistent with previous research by Shema-Shiratzky et al.,[77] which found that real-world mobility metrics were indistinguishable from those during dual task walking in a laboratory setting. Furthermore, Shema-Shiratzky et al. found that real-world mobility was significantly slower compared to self-paced "usual walking" performed in the laboratory. Collectively, these findings indicate the limited ecological validity of currently used mobility assessments, which may lead to better walking performance in controlled laboratory conditions, particularly in the absence of a secondary cognitive task. Given the lack of ecological validity revealed in this study and the poor predictive qualities of the TUG observed in previous studies,[102,105,109,120] future research should focus on deploying mobility assessments that incorporate increased attentional challenges, such as the inclusion of a cognitive task.

Given the lack of ecological validity present in the TUG, this study aimed to investigate the underlying gait metrics of newly developed dual-task clinical assessments, namely the TUG-extended, the 25-foot walk and turn, and the figure 8 walk, by comparing them to real-world ambulation. The results of this study indicate that, in terms of gait speed and stride variability, all three novel clinical assessments had a higher correlation to real-world ambulation compared to the traditional TUG. However, noteworthy differences were observed among the three novel assessments. Specifically, while moderate reliability was observed between the figure 8 walk and real-world ambulation, a significant difference in gait speed was detected. That is, individuals with MS walked significantly slower during the figure 8 walk compared to real-world walking, despite the correlation observed. These findings may be attributed to the challenges associated with turning for individuals with MS, as previous studies have identified increased difficulties with turning in this population.[118,119,126] Given the multiple successive turns in the figure 8 walk test, individuals with MS may have purposely slowed their walking speed to manage this increased difficulty.

While significant differences were observed between real-world mobility and both the TUG and the figure 8 walking test, no differences were found when comparing real-world walking and the TUG-extended and 25-foot walk and turn assessments. These findings suggest that, when performed concurrently with the phonemic verbal fluency task, the latter two tests are comparable to real-world mobility. Further examination of ICC results revealed that although the TUG-extended and the 25-foot walk and turn were not significantly different from real-world walking metrics, their association with real-world ambulation differed. The TUG-extended displayed moderate reliability compared to real-world mobility for both gait speed (ICC=0.66) and stride variability (ICC=0.63). In contrast to all other mobility assessments conducted in this study, which showed poor to moderate reliability when compared to real-world ambulation, the 25-foot walk and turn demonstrated good reliability for both gait speed (ICC=0.75) and stride variability (ICC=0.81) measures. The differences observed between the 25-foot walk and turn and the TUG-extended assessments, in terms of their equivalence to real-world ambulation may be attributed to requirements of the clinical assessments and the methodology utilized to identify walking bouts. The TUG-extended involves postural transitions and turns, both of which necessitate periods of acceleration and deceleration that are not present during the 30 or more seconds of continuous community walking. This consistent variation in speed may have contributed to the higher correlation observed between the 25-foot walk and turn task and community ambulation, in comparison to the TUG-extended. However, it is important to note that both the TUG-extended and the 25-foot walk and turn assessments still displayed moderate to good reliability when compared to real-world ambulation. No significant differences were observed for both measures of gait speed and stride variability, indicating promising potential for these assessments in the context of mobility and fall risk evaluations. These findings warrant further research examining their utility for fall risk detection.

While previous research has identified the verbal fluency task as a cognitively demanding and ecologically valid assessment in dual-task paradigms,[112] this is the first study to administer this assessment in a laboratory setting and compare the results to real-world ambulation. This novel approach provides valuable insights into the ecological validity of the verbal fluency task and bridges the gap between laboratory-based assessments and real-world ambulation. The findings, particularly from the 25-foot walk and turn assessment, suggest that the inclusion of the verbal fluency dual-task paradigm contributes to high levels of ecological validity, potentially improving the effectiveness of detecting mobility impairments. As such, future research should explore incorporating the verbal fluency cognitive task in dual-task clinical assessments, as previously recommended by Abou et al.[120]

Despite the strengths of this study, some limitations should be acknowledged. In the current study, real-world walking was assessed over a period of three days, although consistent with previous research.[77,131,135] While this approach allows for the collection of objective, real-world data, the outcome measure used was median walking, which may not fully capture the daily and day-to-day fluctuations in gait that are observed in this population. Future studies should consider examining changes in mobility outcomes throughout the day to gain a better understanding of other factors such as fatigue and their impact on gait. Additionally, the study included a small sample size of individuals with MS who had mild levels of disability, thus limiting the generalizability of the findings to the larger population. Future research should aim to evaluate mobility outcomes by comparing in-lab assessments to real-world ambulation using a larger, more heterogeneous sample to enhance external validity.

Conclusion

Increasing ecological validity in mobility assessments is crucial for gaining a comprehensive understanding of the challenges encountered during everyday walking for individuals with MS. Comparisons between in-lab mobility assessments and real-world ambulation serve as a bridge that facilitates the identification of tasks that may be more sensitive to fall risk in this population. The findings of this study emphasize the significance of including ecologically valid cognitive tasks into mobility assessments, as these dual task paradigms more accurately represent everyday walking. As the results show, both the 25-foot walk and turn and the TUG-extended assessments, when performed concurrently with a verbal fluency task, displayed similar characteristics to real-world ambulation. These findings suggest the need for future research to employ these assessments, potentially providing a more sensitive assessment for fall risk detection.

CHAPTER 4: EXAMINATION OF CORRELATES TO REAL-WORLD AMBULATION IN PERSONS WITH MULTIPLE SCLEROSIS

Introduction

The progressive neurodegeneration associated with multiple sclerosis (MS) results in a continual decline in mobility.[93] Mobility impairment is often reported to be the most common and impactful symptom experienced by people with the disease,[138] and several studies have shown that loss of mobility contributes to significant patient burden,[24] reduced quality of life,[25,165] and increased fall risk.[33,142] While mobility decline in the population is prevalent, it is not experienced in isolation, as forty-three to seventy percent of individuals with MS also experience cognitive impairment due to their disease.[10,38,39] Previous research has highlighted the association that both cognition and mobility have with walking levels,[126,166] reducing overall functional independence and decreasing community participation.[11,167,168]

Community participation plays a pivotal role in enhancing the quality of life for individuals with MS, encompassing home-based activities, work, leisure activities, and social engagement.[123] Existing studies have consistently highlighted the relationship between an individual's walking capacity and their level of community engagement, with lower levels of walking having a strong correlation with reduced social participation.[121,124,169] However, the significance of walking extends beyond simply walking levels, as walking speed itself has emerged as a telling predictor of both community activity and overall participation.[122,125] These findings underscore the multifaceted influence of walking on an individual’s broader community participation and connections.

Given the importance of walking for community engagement, research has focused on gait quality and stability. Although aspects of real-world gait quality (e.g., gait speed and stride variability) have been examined between MS and controls,[77,126] there is limited knowledge about the relationship between gait quality measures and walking levels in individuals with MS. While previous research has identified gait speed and stride length as significantly correlated with real-world gait quantity, such as time spent walking, these findings were based on in-lab measures, providing limited insight into real-world walking.[127] Additionally, the relationship between stride variability, a known biomarker sensitive for fall prediction in individuals with MS, and real-world gait quantity has not been thoroughly explored. While in-lab findings have been instrumental to the further understanding the relationship between gait quality and gait quantity metrics, they do not come without drawbacks. Specifically, these observations occur at a single moment in time, which means they do not fully capture the gait fluctuations associated with MS, such as differences caused by fatigue,[128] medication,[129] or other environmental variables that may alter gait. As such, understanding the associations between objective measures of gait quality (e.g., gait speed and stride variability) and walking levels in individuals with MS is essential.

While gait quality and quantity have often been viewed as products of mobility impairment,[170] research has shown that they are multifaceted, with cognition and fear of falling playing crucial roles. In fact, previous research has identified the impact of cognition, particularly processing speed, on decrements in real-world ambulation.[77] These findings revealed that decreases in processing speed not only affected community-based gait quality (gait speed and stride variability) but were also significantly correlated with a lower number of steps.[77] While this is true, the study failed to examine other cognitive domains that commonly affect individuals with MS, such as executive functions and long-term memory.[38,41] Further emphasizing the multifaceted nature of community-based walking, previous research has identified that the fear of falling led to activity curtailment in individuals with MS.[171] Although these findings have been instrumental in identifying additional correlates beyond mobility impairment that impact gait quality and quantity, they have been examined independently of one another thereby limiting insight into the contributions they together afford to overall community-based ambulation. Therefore, there is a clear need for a study that incorporates both cognitive functions and fear of falling to understand their contributions to real-world gait quality and quantity outcomes.

Furthermore, recommendations from the International MS Falls Prevention Research Network include outcome measures aiming to increase community and activity engagement, so as to improve the quality of life for individuals with MS.[172] Therefore, the goal of this study was to examine the contributions of cognition, ambulation disability, and fear of falling on real-world gait quality and quantity metrics.

Methods

Participants were eligible for the study if they had physician-diagnosed MS, had none to moderate self-reported mobility dysfunction determined via the Patient Determined Disease Steps (0-4; PDDS),[146] and had no exacerbation of symptoms in the prior month. Individuals were excluded if they had any neurological condition, other than MS, that might have contributed to significant balance impairment.

Cognitive tests

To examine executive functions in areas commonly impaired in individuals with MS, all participants underwent cognitive testing using the short form Brief Repeatable Battery of Neuropsychological Tests (BRB).[54] This battery includes the Paced Auditory Serial Addition Test (PASAT), the Symbol Digits Modalities Test (SDMT), and the Selective Reminding Test (SRT). Additionally, participants underwent the color-word Stroop test, a cognitive test commonly used in conjunction with the short form BRB, as previous studies have shown it to be sensitive for identifying deficits in cognitive inhibition.[56,173] Previous research identified the short form BRB as both an economical screening tool for identifying those with MS who have cognitive impairment,[54] and a screening with acceptable sensitivity (78%-94%) and specificity (65%-84%).[54,174]

As a test that assesses executive functions and processing speed, the PASAT has been frequently used as a cognitive test to evaluate cognitive deficits in these domains.[10,61-63] The PASAT was administered using the protocol described by Rao et al.[10] Participants were presented with an audio recording containing a total of 61 numbers ranging from one to nine, provided at an interval of one every three seconds. Participants were asked to add the first pair of numbers together and state the sum aloud to the research team. When they heard the next number, they were told to add it only to the number directly preceding it played on the audio recording. A practice test was conducted before the trial to familiarize participants with the protocol. The outcome measure was the number of correct additions, which were only considered correct if the correct sum was provided before the next number was presented on the audio recording.

Cognitive processing speed was measured using the SDMT.[59] The test assigns the digits 1-9 to a variety of symbols, which are placed in random order on the page. Participants were asked to match the symbol to its corresponding digit as quickly and accurately as possible for 90 seconds. Research supports the reliability and validity of the SDMT for use with individuals with MS.[57]

As a measure of memory, the SRT differentiates between short and long-term memory. Consistent with previous literature, participants were instructed to recall a list of twelve words over the course of six trials.[175,176] For each consecutive trial, only the words that were missed on the preceding trial were presented to the participant. The test yielded two outcome measures: long-term storage (SRT-LTS), any word that was recalled on two consecutive trials, and consistent long-term retrieval (SRT-CLTR), words recalled consistently throughout learning trials.[55]

To measure cognitive inhibition, the visual Stroop test was administered. Consistent with previous work by Macniven et al., subjects were presented with a list of color-words printed in inconsistent color ink (e.g., the word "red" presented in blue ink).[173] Participants were tasked with identifying the color of the ink rather than the word itself. They were given 30 seconds to complete the task and total number of correct responses was recorded. In this incongruent condition, participants were required to perform the less automated task of identifying the color while inhibiting their expected natural response of reading the word. This phenomenon is known as the Stroop effect, which involves inhibiting the more automated process.[177]

Fear of Falls

Fear of falling was assessed using the Falls Efficacy Scale - International (FES-I).[178] Using a 4-point scale, subjects rated how concerned they were about falling when performing seven activities of daily living. A total score was calculated out of 28 points. The FES-I is a reliable and valid instrument for use with people with MS.[179]

Real-world ambulation data collection

Upon completion of cognitive measures and the survey, subjects were fitted with a tri-axial accelerometer (Axivity AX3, York, UK) to their lower back, between lumbar vertebrae four and five, a location previously shown to be a reliable location for the assessment of real-world walking measures.[133,135] The sensor had a sampling rate of 100 hertz and a range of ±8 g. Participants were instructed to leave the device on for the subsequent three days and not to deviate from their usual daily schedule. Upon completion of the three-day period, sensors were collected from participants, and data stored on the sensor were extracted.

Real-world ambulation data processing

Unfiltered tri-axial accelerometer data were exported and analyzed using algorithms developed in MATLAB program (R2022a). Data analysis occurred in two stages; 1) Detection of all walking bouts equal to or greater than thirty seconds of continuous walking, and 2) Application of tri-axial accelerometer measurements to the walking bouts identified in stage one. We decided to use thirty seconds of continuous walking as the cutoff for inclusion, as this allowed for an examination of an individual's underlying gait quality, as bouts of thirty seconds or greater represented purposeful walking and were consistent with previous literature.[77,131,135] Gait quality outcomes derived from accelerometers included both gait speed and stride variability and were calculated using algorithms designed for optimal use with low back sensors.[133] Consistent with previous literature examining real-world ambulation in populations with neurological disorders,[135] the total amount of time spent purposefully walking throughout the three days was used, as it reflected the total time spent active over the course of the day. It is important to note that in terms of quantifying gait quantity, utilizing this approach underestimated the total time spent walking throughout the three-day period, as periods of walking that lasted less than thirty seconds were not included in the analyses.

Analysis

To examine significant correlates to both gait quality (gait speed and stride variability), Pearson correlations were conducted. As time spent walking was non-parametric, Spearman's rho was used to identify correlated to gait quantity. Variables that were included in correlation analyses include self-reported ambulation status (PDDS), cognition (PASAT, SDMT, SRT-LTS, SRT-CLTR, Stroop), and fear of falling (FES-I). Next, a linear regression with backwards selection was used to identify variables that significantly predicted gait quality and quantity. Only variables that were determined to be significant correlates by either Pearson correlation or Spearman's rho were included in each linear regression. Variables were removed stepwise from the model until all remaining variables had a p-value of <0.05. We examined R^2, B coefficients, T coefficients, and F-statistic. All data analyses were performed in SPSS version 27.0 (SPSS Inc, Chicago, IL).

Results

A total of 20 participants were included in the study. Descriptive statistics for the participants are presented in Table 6 below. The participants had an average age of 56.35±8.59, ranging from 40-75 years old. Walking impairment, as interpreted from the PDDS scores, ranged from 0-4, with a median of 1, indicating minimal walking impairment. Means and standard deviations for cognitive measures and community ambulation metrics are also provided in table 6 below.

Table 6: Descriptive statistics

Descriptive statistics	N=20
Age (years)	56.35±8.59
Years post diagnosis (years)	17.00±8.35
Gender (% female)	80%
PDDS [median(range)]	1 (0-4)
PASAT	40.75±10.40
SDMT	44.45±11.03
SRT-LTS	7.50±3.00
SRT-CLTR	6.20±3.22
Stroop	25.90±4.06
FES-I	28.25±9.87
Gait speed (m/s)	0.98±0.29
Stride variability (arbitrary units)	0.51±0.21
Total time spent walking (s)	1717.68±2044.92

PDDS: Patient Determined Disease Steps; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digits Modalities Test; SRT-LTS: Selective Reminding Test – Long-term Storage; SRT-CLTR: Selective Reminding Test-Consistent Long-term Retrieval; FES-I: Falls Efficacy Scale-International

Table 7 below provides the results of the correlation analyses for both gait quality and quantity metrics. Regarding gait speed, there was a significant correlation with self-reported ambulation status (PDDS; ρ=-0.66, p<0.01), fear of falling (FES-I; ρ=-0.69, p<0.01), and SDMT scores (ρ=0.61, p=0.01). Similar results were observed for stride variability, with significant correlations found with PDDS (ρ=-0.72, p<0.01), FES-I (ρ=-0.67, p<0.01), and SDMT (ρ=0.59, p=0.01). However, no variable showed a significant correlation with total time spent walking when examining the results of the Spearman's rho correlation analysis.

Table 7: Correlation analysis results between gait quality and quantity variables and disease-related characteristics among individuals with MS

	Disability level (PDDS)	PASAT	SDMT	SRT-LTS	SRT-CLTR	Stroop	FES-I	Gait speed	Stride variability
Time spent walking (s)	-0.22	0.11	0.36	0.32	0.35	0.33	-0.24	0.26	0.22
Gait speed (m/s)	-0.66*	-0.20	0.61*	0.20	0.23	0.36	-0.69*	--	--
Stride variability (arbitrary units)	-0.72*	-0.03	0.59*	0.20	0.24	0.30	-0.67*	--	--

*p<0.01; PDDS: Patient Determined Disease Steps; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digits Modalities Test; SRT-LTS: Selective Reminding Test-Long Term Storage; SRT-CLTR: Selective Reminding Test-Consistent Long Term Retrieval; FES-I: Falls Efficacy Scale-International

The dependent variables, gait speed and stride variability, were regressed on the predicting variables PDDS, SDMT, and FES-I using backward selection until all remaining variables had a p-value < 0.05. The results are presented in Table 7 and Table 8 below. The final model for gait speed included both PDDS and SDMT, and these independent variables significantly predicted gait speed ($F(2,17)=14.34$, $p<0.01$). Moreover, the R^2 value was 0.63, indicating that PDDS and SDMT together accounted for 63% of the variance seen in gait speed captured in the real world. Similarly, for stride variability, the final model included both PDDS and SDMT, and these variables significantly predicted stride variability (F(2,17)=18.97, p<0.01). The R^2 value was 0.69, indicating that 69% of the variance in stride variability captured in the real world could be explained by PDDS and SDMT. As there was no significant correlation between time spent walking and the independent variables, no linear regression was conducted.

Table 8: Final gait speed linear regression model results

Gait speed regression	B	T	P-value
PDDS	-0.12	-3.46	<0.01
SDMT	0.01	3	0.01
R^2	0.63		
P-value	<0.01		
F-statistic (2,17)	14.34		

PDDS: Patient Determined Disease Steps; SDMT: Symbol Digits Modalities Test

Table 9: Final stride variability linear regression model results

Stride variability regression	B	T	P-value
PDDS	-0.1	-4.32	<0.01
SDMT	0.01	3.06	0.01
R^2	0.69		
P-value	<0.01		
F-statistic (2,17)	18.97		

PDDS: Patient Determined Disease Steps; SDMT: Symbol Digits Modalities Test

Discussion

The heightened significance of walking for both community participation is consistently demonstrated in MS research.[121,122,124,125] Mobility impairments and reductions in gait speed and stride length have been shown to negatively impact community ambulation in individuals with MS. While previous research has explored correlates of community participation, highlighting the importance of cognition and fear of falling,[77,165,166] few studies have utilized regression analysis to determine the individual contributions of these factors to real-world walking. Moreover, although previous research has found a significant correlation between gait quality features (e.g., gait speed and stride length) and community ambulation,[127] no study has investigated the relationship between gait quality metrics captured in the real-world. Thus, the present study aimed to examine the contributions of cognition, ambulation disability, and fear of falling to gait quality and quantity derived from inertial sensors worn in the real-world.

Results from the study revealed the multifaceted nature of gait quality captured in the real-world. Specifically, the findings highlight a strong relationship between ambulation status, cognition (particularly processing speed), and fear of falling with everyday gait speed and stride variability. These findings confirm and extend upon previous research, emphasizing the importance of these three variables on mobility. In line with the results of Shema-Shiratzky et al., our study also showed significant correlations between disability level and processing speed with real-world gait speed.[77] However, Shema-Shiratzky et al. found weak to moderate relationships between processing speed and mobility outcomes (ρ=0.35-0.40), while our study found a high correlation between disability status, processing speed, and gait quality metrics.

Our findings further underscore the importance of both disability and cognition and their impact on gait quality, as together they explained 63% of the variance in gait speed and 69% of the variance in stride variability. This observation was expected, considering that both mobility and cognition are necessary for performing tasks in daily life. Since Shema-Shiratzky et al. found that dual tasking in the lab is comparable to real-world ambulation,[77] it is reasonable that self-perceived measures of mobility (PDDS) and cognitive measures (SDMT) significantly contribute to real-world ambulation. Although not included in the final linear regression model, our findings also indicated a strong relationship between fear of falling and gait quality, consistent with the results of a recent meta-analysis by Scholz et al.[180] However, fear of falling was dropped from the final model likely due to its overlap with the PDDS, as prior research has demonstrated that increased mobility impairment is associated with increased fear of falls.[168,180-182] Given the strong contributions of ambulation status and cognition to gait quality, interventions should be developed targeting both areas to improve community ambulation.

When examining correlates to gait quantity, our study found no significant relationship with disability level, cognition, fear of falling, or gait quality. All variables yielded small to moderate and insignificant correlations. These findings were unexpected, as they are contrary to the results reported by Shema-Shiratzky et al., who found significant relationships between disability level and cognition with the amount of walking levels.[77] Our results underscore the complexities community ambulation, emphasizing the need for future studies to explore the impact of disability level and cognition on real-world gait quantity.

Interestingly, our study also revealed no significant relationship between gait quality and gait quantity variables, which contradicts the findings of Pau et al.[127] This difference could be attributed to the methods employed for gait quality assessment. In Pau et al., participants were asked to walk as a single tasked in a lab environment and instructed to walk at a comfortable speed for thirty meters. Our study, on the other hand, collected gait quality data simultaneously with real-world gait quantity measurements.

Further research is necessary to evaluate the relationship, or lack thereof, between gait quality and gait quantity in real-world settings.

The lack of significance between all variables and gait quantity may be attributed to the multitude of potential factors involved in ambulation and community participation. Previous research has shown that factors such as mobility impairment,[127] cognition,[166] fatigue,[183] fear of falling,[165] knowledge about the benefits of exercise,[184] and accessibility[184] can influence walking and community participation. The absence of a significant relationship in our study, combined with the mounting evidence suggesting diverse and personal factors to community participation, highlight the importance of tailoring approaches to increasing walking levels based on an individual's specific needs and contexts.

Our study had several noteworthy strengths, including the collection of real-world gait quality data and the analysis of multiple areas of impairment and their contributions to both gait quality and quantity. However, it is important to acknowledge the limitations present in our study when interpreting the results. Namely, only bouts of walking that were thirty seconds or longer were included in the gait quantity metric, meaning any walking under that amount of time was not included. Additionally, the small sample size limits generalizability to the larger population. Finally, as previous research has highlighted the relationship between other variables and mobility metrics, such as fatigue and accessibility,[184] future research should look to incorporate these factors.

Conclusion

Our current study builds upon prior research that has demonstrated the usefulness of wearables in assessing individuals with MS and other neurological conditions.[77,130,131,135,136,185] The results of our study provide insights into how ambulation disability, cognition, and fear of falling influence real-world gait quality in individuals with MS. Furthermore, our findings underscore the significance of examining multiple factors that impact walking and community participation, as these can vary individual to individual. This study provides a foundation for future research to utilize wearables as a valuable tool for evaluating the effectiveness of interventions, particularly in relation to gait quality or quantity. By incorporating wearables, researchers can collect objective, real-world data, leading to a more comprehensive understanding of community mobility and participation outcomes.

CHAPTER 5: DISCUSSIONS AND CONCLUSION

Current mobility assessments utilized for examining fall risk in individuals with MS lack the ecological validity required for the accurate discrimination between fallers and non-fallers. Specifically, frequently utilized clinical mobility evaluations often fail to incorporate a secondary cognitive task, limiting their ability to reproduce the complexity of real-life walking scenarios which predominantly require dual tasking. This lack of ecological validity has consequently resulted in suboptimal prediction of fall risk. Additionally, while previous research has highlighted the effect of dual tasking on gait speed and stride variability, understanding the contributions of mobility, cognition, and fear of falling to real-world gait quality and quantity is crucial. Ultimately, this can aid in the development of more accurate fall risk assessments and the identification of cognitive, mobility, and psychosocial variables that impair community ambulation. As such, this study aimed to bridge the gap between conventional clinical mobility tests and real-world walking by developing more ecological dual task assessments for predicting fall risks and exploring their correlation with real-world outcomes. Moreover, we aimed to identify the contributions of cognition, mobility impairment, and fear of falling on walking quality and quantity in community settings.

As revealed in Chapter 2, the inclusion of metrics beyond gait speed measures is of utmost importance. Presently, fall risk assessments are conducted primarily focusing on time as the sole outcome measure and without a concurrent cognitive task. This approach overlooks the significance of dual tasking and stride variability as potential factors linked to fall risk. Consequently, this limitation hinders the ability to discern fallers from non-fallers, as observed not only in this study but also in previous studies with AUC values ranging from 0.46 to 0.67.[102,103,110,153] These findings are likely due to the lack of ecological validity inherent in commonly employed walking assessments such as the TUG test.

The need for more ecologically valid assessments was further reinforced in Chapter 3, where individuals with MS exhibited significantly higher walking speeds and reduced stride variability during the TUG test in comparison to real-world ambulation. The disparity between the TUG and real-world ambulation highlights a significant gap in mobility assessments, indicating that individuals with MS often exhibit better performance in tasks like the in-lab TUG but that lack the ecological validity of everyday activities. The analysis conducted in Chapter 4 delves deeper into contributing factors that further highlight this incongruency. Specifically, the results of Chapter 4 shed light on the significant role of cognition, particularly processing speed, in relation to gait speed and stride variability. These findings corroborate the findings of Shema-Shiratzky et al. and emphasize the impact of cognition on everyday walking.[77]

Expanding on these earlier findings, our current study highlights processing speed as a key factor contributing to real-world gait speed and stride variability. In conclusion, the limited ability of the TUG test to predict outcomes could be best explained by its lack of real-world relevance. This shortfall stems from its inability to correlate with real-world measures of gait speed or stride variability. Furthermore, the TUG test omits cognitive factors that are crucial in daily life and have a notable impact on gait quality. This study emphasizes the need to develop assessments of increased ecological validity for a more accurate evaluation of fall risk and mobility challenges among individuals with MS.

To address the existing limitations in identifying fall risk among individuals with MS, this study aimed to introduce novel dual task mobility assessments and explore their correlation with real-world ambulation. As such, the current project employed the TUG-extended, the 25-foot walk and turn, and the figure 8 walk, as these tests encompassed some or all dimensions of mobility(i.e., postural transitions and turns) that present significant challenges for individuals with MS.[116-119] Furthermore, this project incorporated a cognitive outcome measure, recognizing that CMI can manifest in either mobility or cognitive decrements, and previous research has demonstrated its sensitivity in detecting fall risk.[97] The results presented in Chapter 2 demonstrate that one of the novel clinical assessments, the 25-foot walk and turn task, exhibited enhanced sensitivity and specificity, yielding an AUC of 0.76 (95% CI, 0.56-0.96). Moreover, the findings indicated that cognitive performance was the most substantial influence on these outcomes, followed by stride variability, and subsequently gait speed. These results underline the importance of extending analysis beyond pace-related metrics, such as gait speed, for predictive purposes in clinical fall risk assessments. Furthermore, the findings highlight the significance of evaluating a cognitive outcome measure within mobility tests, as the inclusion of this outcome in the 25-foot walk and turn resulted in the highest sensitivity and specificity in identifying fall status.

Chapter 3 provides insight into elucidating why the 25-foot walk and turn task emerged as the most effective assessment for identifying fall risk among individuals with MS. Specifically, the 25-foot walk and turn task exhibited the strongest correlation with real-world ambulation, with good reliability for both gait speed (ICC = 0.75) and stride variability (ICC = 0.81). This increased ecological validity could potentially be attributed to the inclusion of turning and increased length of time spent walking, coupled with the concurrent cognitive component. When comparing the 25-foot walk and turn with the TUG, it is important to note that the TUG test is completed within a relatively short timeframe. This shorter duration may be limited in effectively challenging and assessing motor performance. Additionally, the inclusion of the verbal fluency cognitive task in the 25-foot walk and turn increases its potential for greater insight into real-world situations especially as it is a more realistic and ecologically valid representation of daily mobility and cognitive demands.

The results from Chapter 4 highlight the significant impact of processing speed on gait in real-world scenarios, affecting both walking speed and stride variability. As previous research has identified verbal fluency as a cognitive task that examines processing speed performance,[113] the inclusion of a verbal fluency cognitive task into dual task paradigms increases the ecological validity of these assessments. These findings are further supported by a systematic review that highlights the sensitivity and ecological validity of the verbal fluency cognitive task.[99] Taken together, these findings help in understanding why adding the verbal fluency task to the 25-foot walk and turn yielded high correlations to real-world gait quality, ultimately leading to an assessment with an increased ability to identify fall status in individuals with MS.

Furthermore, Chapter 4 emphasizes the importance of incorporating ecologically relevant measures of cognition, namely processing speed, in dual task paradigms as their inclusion replicate real-life walking situations, particularly those challenging for individuals with MS. As discussed in Chapter 4, performance on the SDMT, a commonly used assessment of processing speed,[57,58] exhibited a significant impact on real-world gait quality. These findings, along with previous research demonstrating the strong association between processing speed and real-world mobility,[77,166] underscore the need to incorporate the verbal fluency task into dual task paradigms. In everyday life, individuals often encounter situations that require various cognitive abilities, including processing speed, executive functions, memory, and cognitive inhibition. While this is also true for individuals with MS, the results of this study specifically highlight the distinctive influence of processing speed on gait quality, as it stands out as the singular cognitive measure significantly associated with gait performance.

The real-world results discussed in Chapter 4 align with the findings from Chapter 2, in which cognitive performance stood out as the main factor affecting the 25-foot walk and turn. This emphasizes the need to include cognitive tasks that are relevant to everyday situations in dual task mobility assessments. However, current mobility assessments conducted within research and clinical environments frequently utilize a mental arithmetic task, specifically the serial seven subtraction. Yet, our findings indicate that this approach lacks ecological validity and, according to our results, does not significantly influence real-world ambulation. This may offer a plausible explanation for the ineffectiveness of current mobility assessments that incorporate cognitive tasks, such as the serial seven subtraction test, in distinguishing between individuals with MS who experience falls and those who do not.[102,105,107,108] Therefore, it is imperative that future research and mobility assessments incorporate a cognitive measure of processing speed, such as verbal fluency, given its merits as both ecologically valid and relevant to real world gait quality.

Limitations and future research

While the project's findings have highlighted the necessity to move beyond current clinical fall risk assessments, some limitations should be acknowledged. The small sample size predominantly consisted of individuals with MS displaying mild mobility impairment based on the PDDS scale. To enhance generalizability, future studies should involve a larger, more diverse sample. Additionally, this study primarily focused on gait speed and stride variability, although other evaluations integrating postural transitions and turning could also serve as valuable fall risk indicators. Furthermore, the retrospective classification of fallers and non-fallers using fall history may be influenced by recall bias. Prospective fall monitoring could yield clearer insights into the relationship between assessment performance and fall status. Lastly, the study employed inertial sensors to quantify mobility, but these sensors are not widely accessible in clinics. Future research should pinpoint gait speed and stride variability outcomes that are practical for routine clinical use.

Conclusion

The impact of cognition on everyday mobility is substantial, influencing both gait speed and stride variability. However, current clinical mobility assessments often overlook the inclusion of secondary cognitive tasks, thereby constraining their ability to replicate the real-life situations that often involve dual tasking. Therefore, the objective of this project was to incorporate a concurrent cognitive task into novel mobility assessments, aiming to increase the ecological validity of fall risk evaluations. Our findings underscore the importance of incorporating and assessing processing speed as a measure for fall risk detection, due to its ecological validity and its impact on real-world ambulation, thereby bridging the existing gap between clinical assessments and real-world mobility.

REFERENCES

1. Calabresi PA. Diagnosis and management of multiple sclerosis. *American family physician.* 2004;70(10):1935-1944.
2. Weinshenker BG. Epidemiology of multiple sclerosis. *Neurologic clinics.* 1996;14(2):291-308.
3. Harbo HF, Gold R, Tintoré M. Sex and gender issues in multiple sclerosis. *Ther Adv Neurol Disord.* 2013;6(4):237-248.
4. Romero-Pinel L, Bau L, Matas E, et al. The age at onset of relapsing-remitting multiple sclerosis has increased over the last five decades. *Mult Scler Relat Disord.* 2022;68:104103.
5. Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States: A population-based estimate using health claims data. *Neurology.* 2019;92(10):e1029-e1040.
6. Bebo B, Cintina I, LaRocca N, et al. The Economic Burden of Multiple Sclerosis in the United States: Estimate of Direct and Indirect Costs. *Neurology.* 2022;98(18):e1810-e1817.
7. Newland PK, Thomas FP, Riley M, Flick LH, Fearing A. The use of focus groups to characterize symptoms in persons with multiple sclerosis. *J Neurosci Nurs.* 2012;44(6):351-357.
8. Gay MC, Vrignaud P, Garitte C, Meunier C. Predictors of depression in multiple sclerosis patients. *Acta Neurologica Scandinavica.* 2010;121(3):161-170.
9. Veldhuijzen van Zanten JJCS, Pilutti LA, Duda JL, Motl RW. Sedentary behaviour in people with multiple sclerosis: Is it time to stand up against MS? *Multiple Sclerosis Journal.* 2016;22(10):1250-1256.
10. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology.* 1991;41(5):685-691.
11. Goverover Y, Genova HM, Hillary FG, DeLuca J. The relationship between neuropsychological measures and the Timed Instrumental Activities of Daily Living task in multiple sclerosis. *Mult Scler.* 2007;13(5):636-644.
12. Amtmann D, Bamer AM, Kim J, Chung H, Salem R. People with multiple sclerosis report significantly worse symptoms and health related quality of life than the US general population as measured by PROMIS and NeuroQoL outcome measures. *Disability and health journal.* 2018;11(1):99-107.
13. Morales-Gonzales J, Benito-León J, Rivera-Navarro J, Mitchell AJ, Group GS. A systematic approach to analyse health-related quality of life in multiple sclerosis: the GEDMA study. *Multiple Sclerosis Journal.* 2004;10(1):47-54.
14. Bass AD, Van Wijmeersch B, Mayer L, et al. Effect of Multiple Sclerosis on Daily Activities, Emotional Well-being, and Relationships: The Global vsMS Survey. *Int J MS Care.* 2020;22(4):158-164.
15. Gijbels D, Alders G, Van Hoof E, et al. Predicting habitual walking performance in multiple sclerosis: relevance of capacity and self-report measures. *Multiple Sclerosis Journal.* 2010;16(5):618-626.

16. Minden S, Frankel D, Hadden L, Perloff J, Srinath K, Hoaglin D. The Sonya Slifka longitudinal multiple sclerosis study: methods and sample characteristics. *Multiple Sclerosis Journal.* 2006;12(1):24-38.
17. Simmons RD, Tribe KL, McDonald EA. Living with multiple sclerosis: longitudinal changes in employment and the importance of symptom management. *Journal of neurology.* 2010;257:926-936.
18. Coyne KS, Boscoe AN, Currie BM, Landrian AS, Wandstrat TL. Understanding drivers of employment changes in a multiple sclerosis population. *Int J MS Care.* 2015;17(5):245-252.
19. Browne P, Chandraratna D, Angood C, et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. *Neurology.* 2014;83(11):1022-1024.
20. Kohn CG, Coleman CI, Michael White C, Sidovar MF, Sobieraj DM. Mobility, walking and physical activity in persons with multiple sclerosis. *Curr Med Res Opin.* 2014;30(9):1857-1862.
21. Hemmett L, Holmes J, Barnes M, Russell N. What drives quality of life in multiple sclerosis? *Qjm.* 2004;97(10):671-676.
22. LaRocca NG. Impact of Walking Impairment in Multiple Sclerosis. *The Patient: Patient-Centered Outcomes Research.* 2011;4(3):189-201.
23. van der Feen FE, de Haan GA, van der Lijn I, Heersema DJ, Meilof JF, Heutink J. Independent outdoor mobility of persons with multiple sclerosis - A systematic review. *Mult Scler Relat Disord.* 2020;37:101463.
24. Pike J, Jones E, Rajagopalan K, Piercy J, Anderson P. Social and economic burden of walking and mobility problems in multiple sclerosis. *BMC Neurol.* 2012;12:94.
25. Zwibel HL. Contribution of impaired mobility and general symptoms to the burden of multiple sclerosis. *Adv Ther.* 2009;26(12):1043-1057.
26. Nilsagård Y, Gunn H, Freeman J, et al. Falls in people with MS—an individual data meta-analysis from studies from Australia, Sweden, United Kingdom and the United States. *Multiple Sclerosis Journal.* 2015;21(1):92-100.
27. Peterson EW, Cho CC, von Koch L, Finlayson ML. Injurious Falls Among Middle Aged and Older Adults With Multiple Sclerosis. *Arch Phys Med Rehabil.* 2008;89(6):1031-1037.
28. Cosman F, Nieves J, Komar L, et al. Fracture history and bone loss in patients with MS. *Neurology.* 1998;51(4):1161-1165.
29. Sosnoff JJ, Sandroff BM, Pula JH, Morrison SM, Motl RW. Falls and Physical Activity in Persons with Multiple Sclerosis. *Mult Scler Int.* 2012;2012:315620.
30. Sebastião E, Learmonth YC, Motl RW. Lower Physical Activity in Persons with Multiple Sclerosis at Increased Fall Risk: A Cross-sectional Study. *American Journal of Physical Medicine & Rehabilitation.* 2017;96(5):357-361.
31. Kasser SL, Jacobs JV, Littenberg B, Foley JT, Cardinal BJ, Maddalozzo GF. Exploring physical activity in women with multiple sclerosis: associations with fear of falling and underlying impairments. *Am J Phys Med Rehabil.* 2014;93(6):461-469.

32. Gunn HJ, Newell P, Haas B, Marsden JF, Freeman JA. Identification of Risk Factors for Falls in Multiple Sclerosis: A Systematic Review and Meta-Analysis. *Physical Therapy.* 2013;93(4):504-513.
33. Coote S, Comber L, Quinn G, Santoyo-Medina C, Kalron A, Gunn H. Falls in People with Multiple Sclerosis: Risk Identification, Intervention, and Future Directions. *Int J MS Care.* 2020;22(6):247-255.
34. Matsuda PN, Shumway-Cook A, Bamer AM, Johnson SL, Amtmann D, Kraft GH. Falls in multiple sclerosis. *PM R.* 2011;3(7):624-632; quiz 632.
35. Bebo BF, Allegretta M, Landsman D, et al. Pathways to cures for multiple sclerosis: A research roadmap. *Multiple Sclerosis Journal.* 2022;28(3):331-345.
36. Cattaneo D, De Nuzzo C, Fascia T, Macalli M, Pisoni I, Cardini R. Risks of falls in subjects with multiple sclerosis. *Arch Phys Med Rehabil.* 2002;83(6):864-867.
37. American Psychiatric Association D, Association AP. *Diagnostic and statistical manual of mental disorders: DSM-5.* Vol 5: American psychiatric association Washington, DC; 2013.
38. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *The Lancet Neurology.* 2008;7(12):1139-1151.
39. Benedict RH, Cookfair D, Gavett R, et al. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *J Int Neuropsychol Soc.* 2006;12(4):549-558.
40. Archibald CJ, Fisk JD. Information processing efficiency in patients with multiple sclerosis. *Journal of clinical and experimental neuropsychology.* 2000;22(5):686-701.
41. Arnett PA, Rao SM, Grafman J, et al. Executive functions in multiple sclerosis: an analysis of temporal ordering, semantic encoding, and planning abilities. *Neuropsychology.* 1997;11(4):535-544.
42. Beatty WW, Blanco CR, Wilbanks SL, Paul RH, Hames KA. Demographic, Clinical, and Cognitive Characteristics of Multiple Sclerosis Patients Who Continue to Work. *Journal of Neurologic Rehabilitation.* 1995;9(3):167-173.
43. Hakim EA, Bakheit AM, Bryant TN, et al. The social impact of multiple sclerosis--a study of 305 patients and their relatives. *Disabil Rehabil.* 2000;22(6):288-293.
44. DeLuca J, Chelune GJ, Tulsky DS, Lengenfelder J, Chiaravalloti ND. Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? *Journal of clinical and experimental neuropsychology.* 2004;26(4):550-562.
45. Bergendal G, Fredrikson S, Almkvist O. Selective decline in information processing in subgroups of multiple sclerosis: an 8-year longitudinal study. *European neurology.* 2007;57(4):193-202.
46. van Geest Q, Douw L, van 't Klooster S, et al. Information processing speed in multiple sclerosis: Relevance of default mode network dynamics. *NeuroImage: Clinical.* 2018;19:507-515.
47. Gaudino EA, Chiaravalloti ND, DeLuca J, Diamond BJ. A comparison of memory performance in relapsing–remitting, primary progressive and secondary

progressive, multiple sclerosis. *Cognitive and Behavioral Neurology.* 2001;14(1):32-44.

48. Lengenfelder J, Chiaravalloti ND, Ricker JH, DeLuca J. Deciphering components of impaired working memory in multiple sclerosis. *Cognitive and behavioral neurology.* 2003;16(1):28-39.
49. Preston J, Hammersley R, Gallagher H. The Executive Dysfunctions Most Commonly Associated with Multiple Sclerosis and Their Impact on Occupational Performance. *British Journal of Occupational Therapy.* 2013;76(5):225-233.
50. Julian LJ, Arnett PA. Relationships among Anxiety, Depression, and Executive Functioning in Multiple Sclerosis. *The Clinical Neuropsychologist.* 2009;23(5):794-804.
51. Rao SM, Grafman J, DiGiulio D, et al. Memory dysfunction in multiple sclerosis: Its relation to working memory, semantic encoding, and implicit learning. *Neuropsychology.* 1993;7(3):364.
52. DeLuca J, Barbieri-Berger S, Johnson SK. The nature of memory impairments in multiple sclerosis: acquisition versus retrieval. *J Clin Exp Neuropsychol.* 1994;16(2):183-189.
53. Thornton AE, Raz N, Tucker KA. Memory in multiple sclerosis: contextual encoding deficits. *Journal of the International Neuropsychological Society.* 2002;8(3):395-409.
54. Portaccio E, Goretti B, Zipoli V, Siracusa G, Sorbi S, Amato MP. A short version of Rao's Brief Repeatable Battery as a screening tool for cognitive impairment in multiple sclerosis. *Clin Neuropsychol.* 2009;23(2):268-275.
55. Hansen S, Muenssinger J, Kronhofmann S, Lautenbacher S, Oschmann P, Keune PM. Cognitive screening tools in multiple sclerosis revisited: sensitivity and specificity of a short version of Rao's Brief Repeatable Battery. *BMC Neurology.* 2015;15(1):246.
56. Amato MP, Portaccio E, Goretti B, et al. The Rao's Brief Repeatable Battery and Stroop Test: normative values with age, education and gender corrections in an Italian population. *Mult Scler.* 2006;12(6):787-793.
57. Benedict RH, DeLuca J, Phillips G, et al. Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2017;23(5):721-733.
58. Parmenter BA, Weinstock-Guttman B, Garg N, Munschauer F, Benedict RH. Screening for cognitive impairment in multiple sclerosis using the Symbol Digit Modalities Test. *Multiple Sclerosis Journal.* 2007;13(1):52-57.
59. Smith A. *Symbol digit modalities test.* Western Psychological Services Los Angeles; 1973.
60. Patel VP, Walker LAS, Feinstein A. Deconstructing the symbol digit modalities test in multiple sclerosis: The role of memory. *Multiple Sclerosis and Related Disorders.* 2017;17:184-189.
61. Forn C, Belenguer A, Belloch V, Sanjuan A, Parcet MA, Ávila C. Anatomical and functional differences between the Paced Auditory Serial Addition Test and the

Symbol Digit Modalities Test. *Journal of Clinical and Experimental Neuropsychology.* 2011;33(1):42-50.
62. Forn C, Belenguer A, Parcet-Ibars MA, Ávila C. Information-processing speed is the primary deficit underlying the poor performance of multiple sclerosis patients in the Paced Auditory Serial Addition Test (PASAT). *Journal of Clinical and Experimental Neuropsychology.* 2008;30(7):789-796.
63. Parmenter BA, Shucard JL, Benedict RHB, Shucard DW. Working memory deficits in multiple sclerosis: Comparison between the n-back task and the Paced Auditory Serial Addition Test. *Journal of the International Neuropsychological Society.* 2006;12(5):677-687.
64. Beatty WW, Wilbanks SL, Blanco CR, Hames KA, Tivis R, Paul RH. Memory disturbance in multiple sclerosis: reconsideration of patterns of performance on the selective reminding test. *Journal of Clinical and Experimental Neuropsychology.* 1996;18(1):56-62.
65. Ternes A-M, Clough M, Foletta P, White O, Fielding J. Characterization of inhibitory failure in Multiple Sclerosis: Evidence of impaired conflict resolution. *Journal of Clinical and Experimental Neuropsychology.* 2019;41(3):320-329.
66. Macías Islas MÁ, Ciampi E. Assessment and Impact of Cognitive Impairment in Multiple Sclerosis: An Overview. *Biomedicines.* 2019;7(1):22.
67. Clark DJ. Automaticity of walking: functional significance, mechanisms, measurement and rehabilitation strategies. *Front Hum Neurosci.* 2015;9:246.
68. Srygley JM, Mirelman A, Herman T, Giladi N, Hausdorff JM. When does walking alter thinking? Age and task associated findings. *Brain Res.* 2009;1253:92-99.
69. Benedict RH, Zivadinov R. Risk factors for and management of cognitive dysfunction in multiple sclerosis. *Nature Reviews Neurology.* 2011;7(6):332.
70. VanNostrand M, Belanger B, Purin G, Kasser SL, Cannizzaro M. Cognitive-Motor Interference and Cortical Activation While Walking in Individuals With Multiple Sclerosis. *Motor Control.* 2022;1(aop):1-17.
71. Hernandez ME, Holtzer R, Chaparro G, et al. Brain activation changes during locomotion in middle-aged to older adults with multiple sclerosis. *Journal of the Neurological Sciences.* 2016;370:277-283.
72. Kahneman D. *Attention and effort.* Englewood Cliffs, N.J.: Prentice-Hall; 1973.
73. Yogev-Seligmann G, Hausdorff JM, Giladi N. Do we always prioritize balance when walking? Towards an integrated model of task prioritization. *Mov Disord.* 2012;27(6):765-770.
74. Giannì C, Prosperini L, Jonsdottir J, Cattaneo D. A systematic review of factors associated with accidental falls in people with multiple sclerosis: a meta-analytic approach. *Clin Rehabil.* 2014;28(7):704-716.
75. Al-Yahya E, Dawes H, Smith L, Dennis A, Howells K, Cockburn J. Cognitive motor interference while walking: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* 2011;35(3):715-728.
76. Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture.* 2002;16(1):1-14.

77. Shema-Shiratzky S, Hillel I, Mirelman A, et al. A wearable sensor identifies alterations in community ambulation in multiple sclerosis: contributors to real-world gait quality and physical activity. *J Neurol.* 2020;267(7):1912-1921.
78. Jacobs JV, Kasser SL. Effects of dual tasking on the postural performance of people with and without multiple sclerosis: a pilot study. *J Neurol.* 2012;259(6):1166-1176.
79. Boes MK, Sosnoff JJ, Socie MJ, Sandroff BM, Pula JH, Motl RW. Postural control in multiple sclerosis: effects of disability status and dual task. *J Neurol Sci.* 2012;315(1-2):44-48.
80. Cameron MH, Lord S. Postural control in multiple sclerosis: implications for fall prevention. *Curr Neurol Neurosci Rep.* 2010;10(5):407-412.
81. Maylor EA, Allison S, Wing AM. Effects of spatial and nonspatial cognitive activity on postural stability. *British Journal of Psychology.* 2001;92(2):319-338.
82. Kalron A, Dvir Z, Achiron A. Walking while talking--difficulties incurred during the initial stages of multiple sclerosis disease process. *Gait Posture.* 2010;32(3):332-335.
83. Hamilton F, Rochester L, Paul L, Rafferty D, O'Leary CP, Evans JJ. Walking and talking: an investigation of cognitive—motor dual tasking in multiple sclerosis. *Multiple Sclerosis Journal.* 2009;15(10):1215-1227.
84. Motl RW, Sosnoff JJ, Dlugonski D, Pilutti LA, Klaren R, Sandroff BM. Walking and cognition, but not symptoms, correlate with dual task cost of walking in multiple sclerosis. *Gait & Posture.* 2014;39(3):870-874.
85. Sosnoff JJ, Socie MJ, Sandroff BM, et al. Mobility and cognitive correlates of dual task cost of walking in persons with multiple sclerosis. *Disabil Rehabil.* 2014;36(3):205-209.
86. Wajda DA, Motl RW, Sosnoff JJ. Dual task cost of walking is related to fall risk in persons with multiple sclerosis. *J Neurol Sci.* 2013;335(1-2):160-163.
87. Allali G, Laidet M, Assal F, Armand S, Lalive PH. Walking while talking in patients with multiple sclerosis: The impact of specific cognitive loads. *Neurophysiologie Clinique/Clinical Neurophysiology.* 2014;44(1):87-93.
88. Learmonth YC, Sandroff BM, Pilutti LA, et al. Cognitive Motor Interference During Walking in Multiple Sclerosis Using an Alternate-Letter Alphabet Task. *Arch Phys Med Rehabil.* 2014;95(8):1498-1503.
89. Sosnoff JJ, Boes MK, Sandroff BM, Socie MJ, Pula JH, Motl RW. Walking and thinking in persons with multiple sclerosis who vary in disability. *Arch Phys Med Rehabil.* 2011;92(12):2028-2033.
90. Nogueira LA, Santos LT, Sabino PG, Alvarenga RM, Thuler LC. Walking execution is not affected by divided attention in patients with multiple sclerosis with no disability, but there is a motor planning impairment. *Arq Neuropsiquiatr.* 2013;71(8):521-526.
91. Allali G, Laidet M, Herrmann FR, et al. Gait variability in multiple sclerosis: a better falls predictor than EDSS in patients with low disability. *J Neural Transm (Vienna).* 2016;123(4):447-450.

92. Hsieh KL, Sun R, Sosnoff JJ. Cognition is associated with gait variability in individuals with multiple sclerosis. *Journal of Neural Transmission.* 2017;124(12):1503-1508.
93. Kalron A. Gait variability across the disability spectrum in people with multiple sclerosis. *J Neurol Sci.* 2016;361:1-6.
94. Kalron A. Association between gait variability, falls and mobility in people with multiple sclerosis: A specific observation on the EDSS 4.0-4.5 level. *NeuroRehabilitation.* 2017;40(4):579-585.
95. Socie MJ, Motl RW, Pula JH, Sandroff BM, Sosnoff JJ. Gait variability and disability in multiple sclerosis. *Gait & posture.* 2013;38(1):51-55.
96. Beste C, Mückschel M, Paucke M, Ziemssen T. Dual-Tasking in Multiple Sclerosis - Implications for a Cognitive Screening Instrument. *Front Hum Neurosci.* 2018;12:24.
97. Etemadi Y. Dual task cost of cognition is related to fall risk in patients with multiple sclerosis: a prospective study. *Clinical Rehabilitation.* 2016;31(2):278-284.
98. VanNostrand M, Sogoloff B, Giroux C, Bergmans L, Kasser SL. Predicting falls in adults with multiple sclerosis using patient-reported measures: are perceptions of dual-tasking missing? *Multiple sclerosis and related disorders.* 2022:104115.
99. Postigo-Alonso B, Galvao-Carmona A, Benítez I, et al. Cognitive-motor interference during gait in patients with Multiple Sclerosis: a mixed methods Systematic Review. *Neurosci Biobehav Rev.* 2018;94:126-148.
100. Wajda DA, Sosnoff JJ. Cognitive-Motor Interference in Multiple Sclerosis: A Systematic Review of Evidence, Correlates, and Consequences. *BioMed Research International.* 2015;2015:720856.
101. Cameron MH, Thielman E, Mazumder R, Bourdette D. Predicting falls in people with multiple sclerosis: fall history is as accurate as more complex measures. *Mult Scler Int.* 2013;2013:496325-496325.
102. Quinn G, Comber L, McGuigan C, Galvin R, Coote S. Discriminative ability and clinical utility of the Timed Up and Go (TUG) in identifying falls risk in people with multiple sclerosis: a prospective cohort study. *Clin Rehabil.* 2019;33(2):317-326.
103. Quinn G, Comber L, Galvin R, Coote S. The ability of clinical balance measures to identify falls risk in multiple sclerosis: a systematic review and meta-analysis. *Clinical Rehabilitation.* 2017;32(5):571-582.
104. Etemadi Y. Dual task cost of cognition is related to fall risk in patients with multiple sclerosis: a prospective study. *Clin Rehabil.* 2017;31(2):278-284.
105. Nilsagard Y, Lundholm C, Denison E, Gunnarsson LG. Predicting accidental falls in people with multiple sclerosis -- a longitudinal study. *Clin Rehabil.* 2009;23(3):259-269.
106. Leone C, Patti F, Feys P. Measuring the cost of cognitive-motor dual tasking during walking in multiple sclerosis. *Mult Scler.* 2015;21(2):123-131.
107. Gunn H, Creanor S, Haas B, Marsden J, Freeman J. Risk factors for falls in multiple sclerosis: an observational study. *Mult Scler.* 2013;19(14):1913-1922.

108. Quinn G, Comber L, O'Malley N, McGuigan C, Galvin R, Coote S. An exploration of falls and dual tasking: a prospective cohort study of people with multiple sclerosis. *Topics in Geriatric Rehabilitation.* 2019;35(3):190-198.
109. Quinn G, Comber L, McGuigan C, Hannigan A, Galvin R, Coote S. Risk factors for falling for people with Multiple Sclerosis identified in a prospective cohort study. *Clin Rehabil.* 2021;35(5):765-774.
110. Tajali S, Shaterzadeh-Yazdi M-J, Negahban H, et al. Predicting falls among patients with multiple sclerosis: comparison of patient-reported outcomes and performance-based measures of lower extremity functions. *Multiple sclerosis and related disorders.* 2017;17:69-74.
111. Karzmark P. Validity of the serial seven procedure. *Int J Geriatr Psychiatry.* 2000;15(8):677-679.
112. Rooney S, Ozkul C, Paul L. Correlates of dual-task performance in people with multiple sclerosis: A systematic review. *Gait & Posture.* 2020;81:172-182.
113. Lebkuecher AL, Chiaravalloti ND, Strober LB. The role of language ability in verbal fluency of individuals with multiple sclerosis. *Multiple Sclerosis and Related Disorders.* 2021;50:102846.
114. Carling A, Forsberg A, Nilsagård Y. Falls in people with multiple sclerosis: experiences of 115 fall situations. *Clin Rehabil.* 2018;32(4):526-535.
115. Nilsagård Y, Denison E, Gunnarsson LG, Boström K. Factors perceived as being related to accidental falls by persons with multiple sclerosis. *Disabil Rehabil.* 2009;31(16):1301-1310.
116. Tulipani LJ, Meyer B, Larie D, Solomon AJ, McGinnis RS. Metrics extracted from a single wearable sensor during sit-stand transitions relate to mobility impairment and fall risk in people with multiple sclerosis. *Gait & Posture.* 2020;80:361-366.
117. Tulipani LJ, Meyer B, Fox S, Solomon AJ, McGinnis RS. The Sit-to-Stand Transition as a Biomarker for Impairment: Comparison of Instrumented 30-Second Chair Stand Test and Daily Life Transitions in Multiple Sclerosis. *IEEE Trans Neural Syst Rehabil Eng.* 2022;30:1213-1222.
118. Weed L, Little C, Kasser SL, McGinnis RS. A Preliminary Investigation of the Effects of Obstacle Negotiation and Turning on Gait Variability in Adults with Multiple Sclerosis. *Sensors (Basel, Switzerland).* 2021;21(17):5806.
119. Adusumilli G, Lancia S, Levasseur VA, et al. Turning is an important marker of balance confidence and walking limitation in persons with multiple sclerosis. *PLOS ONE.* 2018;13(6):e0198178.
120. Abou L, Peters J, Fritz NE, Sosnoff JJ, Kratz AL. Motor Cognitive Dual-Task Testing to Predict Future Falls in Multiple Sclerosis: A Systematic Review. *Neurorehabilitation and Neural Repair.* 2022;36(12):757-769.
121. Cattaneo D, Lamers I, Bertoni R, Feys P, Jonsdottir J. Participation Restriction in People With Multiple Sclerosis: Prevalence and Correlations With Cognitive, Walking, Balance, and Upper Limb Impairments. *Arch Phys Med Rehabil.* 2017;98(7):1308-1315.

122. Kierkegaard M, Einarsson U, Gottberg K, von Koch L, Holmqvist LW. The relationship between walking, manual dexterity, cognition and activity/participation in persons with multiple sclerosis. *Mult Scler.* 2012;18(5):639-646.
123. Bertoni R, Jonsdottir J, Feys P, Lamers I, Cattaneo D. Modified Functional Walking Categories and participation in people with multiple sclerosis. *Multiple Sclerosis and Related Disorders.* 2018;26:11-18.
124. Kwiatkowski A, Marissal J-P, Pouyfaucon M, Vermersch P, Hautecoeur P, Dervaux B. Social participation in patients with multiple sclerosis: correlations between disability and economic burden. *BMC neurology.* 2014;14:1-8.
125. Paltamaa J, Sarasoja T, Leskinen E, Wikström J, Mälkiä E. Measures of physical functioning predict self-reported performance in self-care, mobility, and domestic life in ambulatory persons with multiple sclerosis. *Arch Phys Med Rehabil.* 2007;88(12):1649-1657.
126. Shah VV, McNames J, Mancini M, et al. Quantity and quality of gait and turning in people with multiple sclerosis, Parkinson's disease and matched controls during daily living. *J Neurol.* 2020;267(4):1188-1196.
127. Pau M, Porta M, Coghe G, Cocco E. What gait features influence the amount and intensity of physical activity in people with multiple sclerosis? *Medicine (Baltimore).* 2021;100(9):e24931.
128. Ibrahim AA, Küderle A, Gaßner H, Klucken J, Eskofier BM, Kluge F. Inertial sensor-based gait parameters reflect patient-reported fatigue in multiple sclerosis. *J Neuroeng Rehabil.* 2020;17(1):165.
129. Behm K, Morgan P. The effect of symptom-controlling medication on gait outcomes in people with multiple sclerosis: a systematic review. *Disability and Rehabilitation.* 2018;40(15):1733-1744.
130. Hillel I, Gazit E, Nieuwboer A, et al. Is every-day walking in older adults more analogous to dual-task walking or to usual walking? Elucidating the gaps between gait performance in the lab and during 24/7 monitoring. *Eur Rev Aging Phys Act.* 2019;16:6.
131. Galperin I, Hillel I, Del Din S, et al. Associations between daily-living physical activity and laboratory-based assessments of motor severity in patients with falls and Parkinson's disease. *Parkinsonism Relat Disord.* 2019;62:85-90.
132. Del Din S, Godfrey A, Mazzà C, Lord S, Rochester L. Free-living monitoring of Parkinson's disease: Lessons from the field. *Movement Disorders.* 2016;31(9):1293-1313.
133. Zijlstra W, Hof AL. Assessment of spatio-temporal gait parameters from trunk accelerations during human walking. *Gait & Posture.* 2003;18(2):1-10.
134. Zijlstra W, Hof AL. Displacement of the pelvis during human walking: experimental data and model predictions. *Gait & Posture.* 1997;6(3):249-262.
135. Weiss A, Herman T, Giladi N, Hausdorff JM. Objective assessment of fall risk in Parkinson's disease using a body-fixed sensor worn for 3 days. *PLoS One.* 2014;9(5):e96675.

136. Weiss A, Sharifi S, Plotnik M, van Vugt JP, Giladi N, Hausdorff JM. Toward automated, at-home assessment of mobility among patients with Parkinson disease, using a body-worn accelerometer. *Neurorehabilitation and neural repair.* 2011;25(9):810-818.
137. Ezeugwu V, Klaren RE, Hubbard EA, Manns PT, Motl RW. Mobility disability and the pattern of accelerometer-derived sedentary and physical activity behaviors in people with multiple sclerosis. *Preventive medicine reports.* 2015;2:241-246.
138. Larocca NG. Impact of walking impairment in multiple sclerosis: perspectives of patients and care partners. *Patient.* 2011;4(3):189-201.
139. Sosnoff JJ, Weikert M, Dlugonski D, Smith DC, Motl RW. Quantifying gait impairment in multiple sclerosis using GAITRite™ technology. *Gait & Posture.* 2011;34(1):145-147.
140. Pilutti LA, Dlugonski D, Sandroff BM, et al. Gait and six-minute walk performance in persons with multiple sclerosis. *J Neurol Sci.* 2013;334(1-2):72-76.
141. Givon U, Zeilig G, Achiron A. Gait analysis in multiple sclerosis: Characterization of temporal–spatial parameters using GAITRite functional ambulation system. *Gait & Posture.* 2009;29(1):138-142.
142. Amboni M, Barone P, Hausdorff JM. Cognitive contributions to gait and falls: evidence and implications. *Mov Disord.* 2013;28(11):1520-1533.
143. Winkelmann A, Engel C, Apel A, Zettl U. Cognitive impairment in multiple sclerosis. *Official Journal of the European Neurological Society.* 2007;254(2):II35-II42.
144. Kalron A. The relationship between specific cognitive domains, fear of falling, and falls in people with multiple sclerosis. *Biomed Res Int.* 2014;2014:281760.
145. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *Journal of Clinical Epidemiology.* 1996;49(12):1373-1379.
146. Hohol MJ, Orav EJ, Weiner HL. Disease steps in multiple sclerosis: a longitudinal study comparing disease steps and EDSS to evaluate disease progression. *Mult Scler.* 1999;5(5):349-354.
147. Moe-Nilssen R, Helbostad JL. Estimation of gait cycle characteristics by trunk accelerometry. *J Biomech.* 2004;37(1):121-126.
148. Evans T, Jefferson A, Byrnes M, et al. Extended “Timed Up and Go” assessment as a clinical indicator of cognitive state in Parkinson's disease. *Journal of the Neurological Sciences.* 2017;375:86-91.
149. Kieseier BC, Pozzilli C. Assessing walking disability in multiple sclerosis. *Mult Scler.* 2012;18(7):914-924.
150. Kalron A, Aloni R, Givon U, Menascu S. Fear of falling, not falls, impacts leisure-time physical activity in people with multiple sclerosis. *Gait Posture.* 2018;65:33-38.
151. Prosperini L, Kouleridou A, Petsas N, et al. The relationship between infratentorial lesions, balance deficit and accidental falls in multiple sclerosis. *Journal of the neurological sciences.* 2011;304(1-2):55-60.

152. Ytterberg C, Einarsson U, Holmqvist LW, Peterson EW. A population-based study of fall risk factors among people with multiple sclerosis in Stockholm county. 2013.
153. Dibble LE, Lopez-Lennon C, Lake W, Hoffmeister C, Gappmaier E. Utility of disease-specific measures and clinical balance tests in prediction of falls in persons with multiple sclerosis. *J Neurol Phys Ther.* 2013;37(3):99-104.
154. Kralj A, Jaeger RJ, Munih M. Analysis of standing up and sitting down in humans: definitions and normative data presentation. *Journal of biomechanics.* 1990;23(11):1123-1138.
155. Coote S, Sosnoff JJ, Gunn H. Fall Incidence as the Primary Outcome in Multiple Sclerosis Falls-Prevention Trials: Recommendation from the International MS Falls Prevention Research Network. *Int J MS Care.* 2014;16(4):178-184.
156. Winkelmann A, Engel C, Apel A, Zettl UK. Cognitive impairment in multiple sclerosis. *J Neurol.* 2007;254 Suppl 2:II35-42.
157. Sosnoff JJ, Sandroff BM, Motl RW. Quantifying gait abnormalities in persons with multiple sclerosis with minimal disability. *Gait & Posture.* 2012;36(1):154-156.
158. Mancini M, King L, Salarian A, Holmstrom L, McNames J, Horak FB. Mobility Lab to Assess Balance and Gait with Synchronized Body-worn Sensors. *J Bioeng Biomed Sci.* 2011;Suppl 1:007.
159. Spain RI, St George RJ, Salarian A, et al. Body-worn motion sensors detect balance and gait deficits in people with multiple sclerosis who have normal walking speed. *Gait Posture.* 2012;35(4):573-578.
160. Godfrey A, Del Din S, Barry G, Mathers JC, Rochester L. Instrumenting gait with an accelerometer: a system and algorithm examination. *Med Eng Phys.* 2015;37(4):400-407.
161. Cohen J. *Statistical power analysis for the behavioral sciences.* Academic press; 2013.
162. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J Chiropr Med.* 2016;15(2):155-163.
163. Veldkamp R, Kalron A, Baert I, et al. Differential effects and discriminative validity of motor and cognitive tasks varying in difficulty on cognitive–motor interference in persons with multiple sclerosis. *Multiple Sclerosis Journal.* 2021;27(12):1924-1938.
164. Leone C, Patti F, Feys P. Measuring the cost of cognitive-motor dual tasking during walking in multiple sclerosis. *Multiple Sclerosis Journal.* 2014;21(2):123-131.
165. Vister E, Tijsma ME, Hoang PD, Lord SR. Fatigue, Physical Activity, Quality of Life, and Fall Risk in People with Multiple Sclerosis. *Int J MS Care.* 2017;19(2):91-98.
166. Motl RW, Gappmaier E, Nelson K, Benedict RH. Physical activity and cognitive function in multiple sclerosis. *Journal of Sport and Exercise Psychology.* 2011;33(5):734-741.
167. Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology.* 1991;41(5):692-696.

168. Khalil H, Al-Shorman A, El-Salem K, et al. Fear of falling in people with multiple sclerosis: which clinical characteristics are important? *Physical therapy.* 2017;97(7):698-706.
169. Söylemez B, Çetİşlİ-Korkmaz N, Tekİn S, Bİr LS, Şenol H. The effect of balance, walking capacity, and fear of falling on the level of community integration in individuals with Multiple Sclerosis: A cross-sectional study. *Physiotherapy theory and practice.* 2023:1-7.
170. Kohn CG, Coleman CI, Michael White C, Sidovar MF, Sobieraj DM. Mobility, walking and physical activity in persons with multiple sclerosis. *Current Medical Research and Opinion.* 2014;30(9):1857-1862.
171. Peterson EW, Cho CC, Finlayson ML. Fear of falling and associated activity curtailment among middle aged and older adults with multiple sclerosis. *Mult Scler.* 2007;13(9):1168-1175.
172. Finlayson M, Peterson E, Matsuda PN. Participation as an Outcome in Multiple Sclerosis Falls-Prevention Research: Consensus Recommendation from the International MS Falls Prevention Research Network. *Int J MS Care.* 2014;16(4):171-177.
173. Macniven JA, Davis C, Ho MY, Bradshaw CM, Szabadi E, Constantinescu CS. Stroop performance in multiple sclerosis: information processing, selective attention, or executive functioning? *J Int Neuropsychol Soc.* 2008;14(5):805-814.
174. Hansen S, Muenssinger J, Kronhofmann S, Lautenbacher S, Oschmann P, Keune PM. Cognitive screening tools in multiple sclerosis revisited: sensitivity and specificity of a short version of Rao's Brief Repeatable Battery. *BMC Neurol.* 2015;15:246.
175. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology.* 1974;24(11):1019.
176. Boringa JB, Lazeron RH, Reuling IE, et al. The brief repeatable battery of neuropsychological tests: normative values allow application in multiple sclerosis clinical practice. *Mult Scler.* 2001;7(4):263-267.
177. Stroop JR. Studies of interference in serial verbal reactions. *Journal of experimental psychology.* 1935;18(6):643.
178. Yardley L, Beyer N, Hauer K, Kempen G, Piot-Ziegler C, Todd C. Development and initial validation of the Falls Efficacy Scale-International (FES-I). *Age Ageing.* 2005;34(6):614-619.
179. van Vliet R, Hoang P, Lord S, Gandevia S, Delbaere K. Falls Efficacy Scale-International: A Cross-Sectional Validation in People With Multiple Sclerosis. *Arch Phys Med Rehabil.* 2013;94(5):883-889.
180. Scholz M, Haase R, Trentzsch K, Weidemann ML, Ziemssen T. Fear of falling and falls in people with multiple sclerosis: A literature review. *Mult Scler Relat Disord.* 2021;47:102609.
181. Mazumder R, Lambert WE, Nguyen T, Bourdette DN, Cameron MH. Fear of Falling Is Associated with Recurrent Falls in People with Multiple Sclerosis: A Longitudinal Cohort Study. *Int J MS Care.* 2015;17(4):164-170.

182. Kasser SL, Jacobs JV, Littenberg B, Foley JT, Cardinal BJ, Maddalozzo GF. Exploring physical activity in women with multiple sclerosis: associations with fear of falling and underlying impairments. *American journal of physical medicine & rehabilitation.* 2014;93(6):461-469.
183. Ploughman M. Breaking down the barriers to physical activity among people with multiple sclerosis – a narrative review. *Physical Therapy Reviews.* 2017;22(3-4):124-132.
184. Ploughman M. Breaking down the barriers to physical activity among people with multiple sclerosis–a narrative review. *Physical Therapy Reviews.* 2017;22(3-4):124-132.
185. Frechette ML, Meyer BM, Tulipani LJ, Gurchiek RD, McGinnis RS, Sosnoff JJ. Next Steps in Wearable Technology and Community Ambulation in Multiple Sclerosis. *Current Neurology and Neuroscience Reports.* 2019;19(10):80.