Self-reported, Performance-based and Technologically-measured Walking Capacity in Gait Vulnerable Populations: Similarities and Differences Across Age and Disability Levels

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This work is dedicated to my mom (Vidya Mate), dad (Kamalakar Mate), brother (Vinayak), sister (Kadambari), my dearest niece (Hrishika) and also to all my past and present teachers and mentors who have shaped my life.

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ABBREVIATIONS

6MWT	Six-minute Walk Test
7dPAR	7-day physical activity recall
9HPT	Nine-hole Peg Test
25FW / T25FW	25 Foot Walk / Timed 25 Foot Walk
ABC	Activity-specific Balance Confidence Scale
ADLs	Activities of Daily Living
BBS	Berg Balance Scale
CI	Confidence Interval
ClinRO	Clinically reported outcomes
CSPPS	Continuous Summary Physical Performance Score
CV	Coefficient of Variation
DASH	Disability of the Arm, Shoulder and Hand
DGI	Dynamic Gait Index
EDSS	Expanded Disability Status Scale
EMG-BFB	Electromyogram Biofeedback
EQ-5D-3L	EuroQoL Five-Dimensions Three-Levels
EXSE	Exercise Self-Efficacy scale
FIM	Functional Independence Measure
FR	Function Reach
FSS	Fatigue Severity Scale
GDS	Geriatric Depression Scale
GLTEQ	Godin Leisure-Time Exercise Questionnaire
HADS	Hospital Anxiety and Depression Scale

HWP	Habitual Walking Performance
IADL	Instrumental Activities of Daily Living
IPAQ	International Physical Activity Questionnaire
IPAQ-E	International Physical Activity Questionnaire for Elderly
IQR	Inter Quartile Range
LEFS	Lower Extremity Function Scale
LMSQOL	Leeds Multiple Sclerosis Quality of Life Scale
mCAFT	Modified Canadian Aerobic Fitness Test
METs	Metabolic Equivalents
MFIS	Modified Fatigue Impact Scale
MHI	Mental Health Index
MMSE	Mini-Mental State Examination
MSFC	Multiple Sclerosis Functional Composite
MS	Multiple Sclerosis
MSQLI	Multiple Sclerosis Quality of Life Inventory
MSSE	Multiple Sclerosis Self-Efficacy Scale
MSWS-12	Multiple Sclerosis Walking Scale
OARS	Older Americans Resource and Services Disability subscale
OR	Odds Ratio
PADLS	Performance test of Activities of Daily Living
PBMSI	Preference Based Multiple Sclerosis Index
PD	Parkinson's Disease
PDDS	Patient Determined Disease Steps
PDQ	Perceived Deficit Questionnaire

PerfO	Performance Outcomes
PFI	Physical Function Index
PPT / mPPT	Physical Performance Test / modified Physical Performance Test
PRO	Patient Reported Outcomes
QoL	Quality of Life
QSPPS	Quartile Summary Physical Performance Score
RAND-36	Research ANd Development
SD	Standard Deviation
SE	Standard Error
SF-36	Short Form-36
SGBA	Sex and Gender Based Analysis
SPPB	Short Physical Performance Battery
SPS	Social Provisions Scale
SRO	Self-reported Outcomes
SWLS	Satisfaction With Life Scale
T25FW	Timed 25-Foot Walk
TechO	Technologically measured Outcomes
TUG	Timed Up and Go
US-FDA	United States Food and Drug Administration
ZIP	Zero-inflated Poisson

ABSTRACT

Physical activity is an important way to maintain good health for older adults and people with neurodegenerative conditions such as Parkinson's Disease (PD) and Multiple Sclerosis (MS). Walking is one of the most commonly performed and recommended physical activity. Aging and neurodegenerative conditions predispose people to gait vulnerability that limit walking activities and restrict opportunities for achieving health benefits from walking. The Canadian Physical Activity Guidelines for older adults recommend at least 150 minutes of moderate- to vigorous-intensity aerobic physical activity per week, in bouts of 10 minutes or more with an additional 2 days of muscle and bone strengthening activities. Brisk walking is one of the recommended modes to achieve moderate intensity physical activity.

Two aspects of walking need to be considered: what the person can do (walking capacity) and what they do do (walking performance). Information on walking capacity is typically obtained by measuring performance in a clinical setting and by asking the individuals about activity (self-report) and/or free-living monitoring using accelerometers (technology). It is not known how these three sources of information provide concordant or discordant information among gait vulnerable populations, in this case older adults and people with PD and MS.

The objective of this thesis is to contribute evidence towards how the different sources of information about walking (self-report questionnaires, performance tests, and technologically assessed) provide convergent or divergent information about walking capacity and walking performance among people with health conditions that lead to gait vulnerability. As is typical for theses in the Faculties of Medicine and Science, this thesis is built around manuscripts.

The first manuscript aimed to estimate the extent to which sex/gender differences affect the relationships between tests of physical performance and self-reports about function in everyday life activities among people with MS. The second manuscript aimed to estimate, for people with

MS, the extent to which walking capacity tested in laboratory, using 6MWT, is reproduced during 7 days of free-living step monitoring using an accelerometer and how this relationship is affected by age, gender, motivation, exercise enjoyment and barriers to participation. The third manuscript tested whether walking among older adults is modifiable by external auditory feedback using a technology - Heel2Toe sensor. Auditory feedback was provided to correct stepping pattern during outdoor walking. This objective was achieved using a pre-post design with 5 training sessions. The fourth and last manuscript targeted the relationship between indicators of step quality and cadence among seniors, people with PD and MS. The data for this manuscript came from the Heel2Toe sensor that was deployed during walking assessments for people with MS, PD and seniors. The objective of this manuscript was to estimate, across seniors and people with MS and PD, the extent to which heel-to-toe stepping pattern (good steps), angular velocity and coefficient of variation at heel strike using the Heel2Toe sensor separately explained variation in cadence.

This thesis highlights the lack of ecological validity among commonly used performance tests (manuscript 1), shows the discrepancy between walking capacity and free-living walking performance among people with MS (manuscript 2), demonstrates that gait in seniors shows adaptation to auditory feedback using Heel2Toe sensor (manuscript 3), and illustrates how gait quality parameters of proportion of good steps and angular velocity are not predictive of cadence in seniors, people with MS and PD.

ABRÉGÉ

L'activité physique est un moyen de maintenir une bonne santé pour les personnes âgées et les personnes atteintes de maladies neurodégénératives telles que la maladie de Parkinson et la Sclérose en Plaques (SP). Les lignes directrices canadiennes en matière d'activité physique pour les personnes âgées recommandent au moins 150 minutes d'activité physique aérobique d'intensité modérée à vigoureuse par semaine, en périodes de 10 minutes ou plus. La marche est l'une des activités recommandées pour réaliser une activité physique d'intensité modérée.

Deux aspects de la marche doivent être considérés : ce que la personne peut faire (capacité à la marche) et ce qu'elle fait (performance à la marche). Les informations sur la capacité à la marche sont obtenues en observant la performance dans un cadre clinique sur des tests tels que le test de marche de six minutes (6 MWT). L'information sur la performance à la marche est obtenue en demandant aux personnes concernées les activités qui leur limite et / ou à travers la surveillance de personnes dans leur vie de tous les jours à l'aide d'un accéléromètre. On ne sait pas comment ces sources d'information fournissent des informations concordantes ou discordantes chez les personnes âgées, les personnes atteintes de la maladie de Parkinson et de SP.

L'objectif de cette thèse est de contribuer sur comment les différentes sources d'information sur la marche fournissent des informations convergentes ou divergentes sur la capacité de marche et la performance de marche chez les personnes ayant des problèmes de santé menant à une vulnérabilité à la marche. Les données pour ces quatre projets font parties d'analyses secondaires de données existantes et de la collecte de données primaires. Comme c'est le cas pour les thèses dans les Facultés de Médecine et de Sciences, la thèse est construite autour de manuscrits.

Le premier manuscrit visait à estimer la mesure dans laquelle les différences de sexes/genres affectent la relation entre les tests de performance physique et les tests d'autoévaluations concernant le fonctionnement dans les activités de la vie quotidienne chez les personnes atteintes

de SP. Le deuxième manuscrit visait à estimer, pour les personnes atteintes de SP, la mesure dans laquelle la capacité à la marche testée en laboratoire, en utilisant le 6MWT, est reproductible pendant 7 jours de surveillance en utilisant un accéléromètre et comment cette relation est influencée par l'âge, le sexe, la motivation, le plaisir de l'exercice et les obstacles à la participation. Le troisième manuscrit testait si la démarche chez les personnes âgées est modifiable à l'aide d'une technologie de rétroaction (capteur Heel2Toe). La rétroaction auditive a été fournie pour corriger la qualité des pas pendant la marche extérieure. Cet objectif a été atteint en utilisant une méthode de recherche pré-post avec 5 sessions de formation. Le quatrième manuscrit visait à établir la relation entre les indicateurs de la qualité des pas et la cadence chez les personnes âgées, les personnes atteintes de la maladie de Parkinson et de SP. Les données pour ce manuscrit proviennent du capteur Heel2Toe. L'objectif de ce manuscrit était d'estimer, chez les personnes âgées et les personnes atteintes de la maladie de Parkinson et de SP, la variation du rythme de marche du talon a l'orteil, la vitesse angulaire et le coefficient de variation de l'attaque du talon en utilisant la capteurHeel2toe.

Cette thèse a souligné le manque de validité écologique parmi les tests de performance couramment utilisé (manuscrit 1), la divergence entre la capacité à la marche et la performance à la marche libre chez les personnes atteintes de SP (manuscrit 2), la démarche chez les personnes âgées montre une adaptions à la rétroaction auditive en utilisant le capteur Heel2Toe (manuscrit 3), et les paramètres de qualité de marche de la vitesse angulaire ne prédisent pas la cadence chez les personnes âgées.

ACKNOWLEDGEMENTS

This work represents a collaboration of many people and would not have been possible without the support of several dedicated experts. First and foremost, I would like to express my sincerest gratitude to my supervisor and mentor, Prof. Nancy E. Mayo for her support, dedication, and guidance throughout this program. She is the most dedicated person I have ever known, who has instilled in me qualities of ethical statistical analysis. Dr. Mayo is a lady of quotes. One of her quotes, “Do you want an answer or do want the right answer?” illustrates her commitment to doing science with an inquiring and honest mind, and not just for results. Another quote she often expresses is in response to students’ questions: “There are no stupid questions but there are stupid answers and I will try not give you one”. I have been extremely fortunate to have this life-time opportunity to work for and learn from her. She is an incredibly patient human being when it comes to teaching. She has always supported all my endeavours, no matter what they were, and provided me with many opportunities to learn, network and collaborate. In addition, her enthusiasm and energy is contagious.

I would also like to extend my thanks to my committee members, Dr. Jose Morais and Dr. Sara Ahmed. Dr. Morais is one of the most pleasant people I know who has always welcomed me to his clinic with a warm smile. He has referred to me the patients I needed to complete my recruitment. Dr. Ahmed has always extended her support to me throughout this journey with her expertise, knowledge and warm manner.

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PREFACE

Statement of Originality

As a physical therapist I was interested in walking, particularly use of technology to assess and treat gait impairments and to improve walking capacity. This thesis work arose out of my interest in integrating walking and technology for rehabilitation of people with health conditions. This work was developed with an overarching theme on how different sources of information on walking differ among gait vulnerable population. Walking literature is well-established, however, use of patient/self-reported outcome is relatively recent. My interest in working with health outcomes, particularly those related to walking and use of technology to assess and improve walking patterns led to these four linked manuscripts. I was fortunate to work with the Heel2Toe sensor and analyse data from accelerometers as part of an exercise trial for Multiple Sclerosis. The Heel2Toe sensor was developed by Dr. Mayo's team and will eventually be a part of the Walk-Well Toolkit that will become commercially available. I was involved in testing of the sensor on three populations, developing the business canvas, and liaising with companies to commercialize this device.

Contributions of Authors

The manuscripts in this thesis are the work of Kedar Mate with guidance from Dr. Nancy Mayo. The first manuscript analysed data from an existing database that was collected by Dr. Ayse Kuspinar for a study on Gender and Life Impact of Multiple Sclerosis. Dr. Sara Ahmed agreed to be on my thesis committee to provide her considerable expertise on measuring health outcomes to enrich this thesis work. Drs. Kuspinar and Ahmed are co-authors on this manuscript and provided feedback on the manuscript. The manuscript is under peer-review with *Archives of Physical Medicine and Rehabilitation journal.*

The second manuscript used the data from a Canadian Institutes of Health Research (CIHR) funded randomized controlled trial (RCT) on Role of Exercise in Modifying Outcomes for People with Multiple Sclerosis (MSTEP; PI: Dr. Mayo). Accelerometer data from the baseline data on people with MS were available for analysis. This manuscript will be submitted to the *Journal of Clinical Epidemiology*. I was one of the blinded evaluators for this trial and helped with analysis of accelerometer data for 3-month time points that will be published in the main trial paper by Dr. Mayo.

The data for the third manuscript was obtained from a feasibility study on Heel2Toe sensor on six older adults. I designed the protocol, selected the outcomes, conducted baseline and post-training evaluation, trained the participants at their homes in using the Heel2Toe sensor, and processed the data from the Heel2Toe using MATLAB© software. Mr. Abou-Sharkh helped with a few training sessions. The paper is co-authored by Dr. Jose Morais who referred patients for participation in this study and provided feedback on the manuscript. This manuscript is under review with the journal of *Rehabilitation and Assistive Technologies Engineering.*

The data for the fourth manuscript was obtained from three different projects. Heel2Toe sensor was deployed during the walk test for people with MS recruited for CIHR-funded RCT on 'Role of Exercise in Modifying Outcomes for People with Multiple Sclerosis' (MSTEP; PI: Dr. Mayo). Data from people with Parkinson’s was collected as a part of pilot study on a novel Approach to Clinical Assessment and Personalized Intervention in Early Parkinson’s Disease (PI: Dr. Jelena Djordjevic). Data on older adults was collected during the development and testing of Heel2Toe sensor and additional sample (n=17) was collected by me. The paper will be submitted to *NeuroRehabilitation*.

The idea for this thesis arose from my discussion with Dr. Mayo. I contributed original thought and work on all of the projects that went into this thesis. Dr. Mayo oversaw all aspects of this thesis work and provided expert feedback on methodology and statistical analysis. She also helped with addressing reviewer's comments.

Thesis Organization and Overview

This thesis consists of four manuscripts of which the first three are submitted to scientific journal and are under-going peer review. The fourth manuscript is completed will be submitted in a month. This thesis is organized based on guidelines from Graduate and Postdoctoral Studies (GPS) and requirements of Library and Archives Canada: the work therein is organized as per below:

Chapter 1 outlines the background for this work and provides details on three gait vulnerable populations that were under study for this project.

Chapter 2 summarizes the importance of walking for health, sources of information, and comprehensive literature review.

Chapter 3 presents the rationale and objectives of this thesis.

Chapter 4 is Manuscript 1, titled: "Comparison of Common Performance-Based Tests to Self-report in People with Multiple Sclerosis: Does Sex or Gender Matter?"

Chapter5 links manuscript 1 to 2.

Chapter 6 is Manuscript 2, titled, "Ecological Validity of Clinically Assessed Walking Capacity among People with Multiple Sclerosis".

Chapter 7 links manuscript 2 to 3.

Chapter 8 is Manuscript 3, titled, "Real-Time Auditory Feedback Induced Adaptation to Walking among Seniors using Heel2Toe Sensor: A Proof-of-Concept Study".

Chapter 9 links manuscript 3 to 4.

Chapter 10 is Manuscript 4, titled, "Putting the Best Foot Forward: Relationships between Indicators of Step Quality and Cadence in Three Gait Vulnerable Population".

Chapter11 presents overall discussion of the findings, ideas for future direction, and conclusion.

References, figures, and tables are presented at the end of each manuscript. Referencing style reflects the journal guidelines. All projects were approved by the Research Ethics Board of the McGill University Health Centre and all the participants signed an informed consent form.

CHAPTER 1: BACKGROUND

International Classification of Functioning (ICF), defines “capacity” as what an individual can do in a ‘standardized’ environment and “performance” as what the person actually does in his or her ‘current’ (usual) environment [1]. In other words, capacity is “can do” and performance is “does do” [2]. In the context of walking, performance is the ability to use that capacity to achieve goals such as walking for activities of daily living, work, recreation, leisure, and health promotion.

The terminology surrounding walking varies considerably among disciplines. Gait, walking and ambulation are terms that are widely used, often interchangeably, but are conceptually different. Walking is a rhythmic, dynamic, aerobic activity involving large skeletal muscles [3] usually done for recreational purpose or as an exercise. Gait on the other hand is the manner of walking. The term ambulation is used for the action of walking about (http://medical-dictionary.thefreedictionary.com/ambulation) with no stipulation as to how. Stepping is the action of the lifting one foot off the ground and placing it elsewhere, producing a locomotor displacement for centre of mass and is a feature of very slow walking speed. The inconsistent use of these terms creates confusion among researchers and clinicians as to what is being assessed and treated, and why.

Gait speed is recognized as a the 6th vital sign [4] but speed alone is not sufficient for walking performance [5, 6] nor for participation in social roles [7]. The most relevant aspect of walking is walking competency, the elements of which include walking at adequate speed so as to navigate intersections, walking the distances for the purpose of activities of daily living, negotiating curbs, turning the head while walking and maintaining balance, maintaining stability when faced with unexpected perturbation, and demonstrating anticipatory strategies to avoid obstacles [8, 9]. In order to be a competent walker, the components need to be optimal. These aspects of walking competency span outcomes ranging from parameters of gait quality to strolling, sauntering, walking forwards, backwards, sideways [10] to walking for recreation and leisure. Walking, when done well features an upright posture, rhythmical movements and counter rotation of trunk, arms and legs with optimal spatiotemporal gait parameters. An important feature of efficient walking is the functional walking speed and ability to voluntarily modulate speed while remaining safe. In order to achieve efficient walking an individual needs good posture, musculoskeletal flexibility, peripheral and core strength, power, static and dynamic balance, attention and arm swing.

Aging and the presence of degenerative neurological conditions render people vulnerable for gait deviations. Gait vulnerability is defined as a physiological health state or disease that results in the person being at an increased risk of developing deviation in gait parameter/s, limitation in walking capacity, and/or sustaining walking for purposes of health promotion. This limits older adults and people with chronic neurological health conditions from maintaining a healthy lifestyle through meeting the Canadian Physical Activity Guidelines (http://www.csep.ca/en/guidelines/get-the-guidelines). The Canadian Physical Activity Guidelines for Older Adults recommends 150 minutes of moderate intensity exercise over a week in bouts of 10 minutes (http://www.csep.ca/en/guidelines/get-the-guidelines). Walking at a pace of 100 steps per minute for 10 minutes, twice a day would meet this guideline. Despite capacity to walk at this pace, it is rare for the North American senior to do this for more than a few minutes a day [5, 6]. Achieving these physical activity guidelines would require seniors to develop efficient walking. Maintaining a level of physical fitness is also critical to prevent secondary health conditions such as health disease, osteoporosis, obesity and diabetes. These conditions may directly or indirectly impact participation in physical activity and lead to a vicious cycle of inactivity, physical limitation, and more inactivity. This thesis focuses on three gait vulnerable populations: seniors, and people with Multiple Sclerosis (MS) and people with Parkinson's Disease (PD) with the global aim of comparing and contrasting sources of information on walking capacity and walking performance.

1.1 Older Adults

An estimated 13.9% of Canada's 35 million people are over the age of 65 (4.7 million) and this section of the population is on rise (Statistics Canada, 2010). Keeping older persons active for as long as possible is an achievable goal owing to an increase in research on healthy aging and the availability of technologies that older persons can use to monitor and increase activity. The current and future senior populations have expectations for active aging (http://www.who.int/ageing/active_ageing/en/), that is, maintaining an active life style even with a health condition.

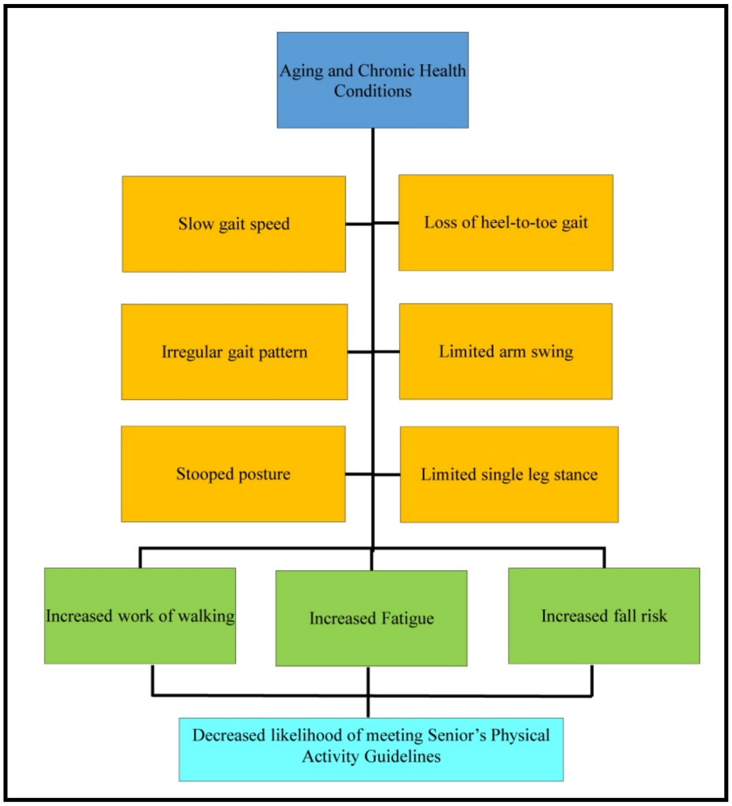
Seniors represent a population predisposed to chronic health conditions frequently associated with comorbidities and a mix of chronic health conditions. These complex health conditions increase risk of gait vulnerability among seniors. Disabled or not, active aging requires physical activity. The most common disability among seniors and persons with chronic health conditions is of walking [11]. Yet, the most accessible and safe way to be physically active is by walking. Achieving these physical activity guidelines would require seniors to develop an efficient walking pattern, that is, a pattern that is safe, reproducible, and sustainable. For older adults and people with health conditions, maintaining adequate walking capacity and a healthy level of physical activity could mean a difference between health and illness.

Other important health goals for seniors are maintaining bone density and muscle strength as these are implicated in falls and injuries from falls [12]. Osteoporosis is silent until it has progressed to vertebral micro-fractures, making early detection and pharmacotherapy essential

[13]. However, weakness is manifest as difficulty in supporting body weight for long durations (for example standing), rising from a chair or toilet seat, and climbing stairs. Declining muscle strength can be improved by targeted exercises and putting muscles to work by maintaining an optimal level of physical activity.

Brisk walking is the most accessible physical activity for seniors that is recommended by Osteoporosis Canada for prevention of osteoporosis [14-16], but people with a poor gait pattern will have difficulty achieving and sustaining walking targets. One of the most common gait abnormalities limiting walking is the loss of a heel-to-toe stride and the full foot is in contact with the surface at initial contact. As a consequence, the stride shortens and there is more flexion of the trunk and hips, and gait speed slows [17-20]. This slow, unstable, shuffling pattern increases work of walking, fatigue, and risk of falls, hip fracture and prevents walking from producing a health benefit [17-20]. This poor gait pattern is a result of a myriad of factors including easily modifiable factors such as poor footwear, inattention, and deconditioning from a sedentary life style to features of physiological aging such as psychomotor slowing, poor balance, and inability to generate sufficient power for push-off, leading to fear of falling and falls.

Figure 1 shows different features of inefficient walking among older adults and those with health conditions that produce gait vulnerability, such as MS and PD, two conditions under study in this thesis.



1.2 Multiple Sclerosis (MS)

MS is one of the most common neurodegenerative conditions affecting a large proportion of young adults who are at the peak of their career and family development in North America [21, 22]. The prevalence of MS in Canada is estimated at 240 per 100,000 and there are between 55,000 to 75,000 Canadians living with MS, making Canada among the highest-ranking countries in the world for MS prevalence [23-26]. The estimated healthcare cost for a Canadian with MS is reported to range from $7,500-$35,000 annually depending on the severity of the disease, and lifetime costs of MS care average $1.6million dollars per person [27]. The most commonly reported challenges with MS are fatigue and difficulty walking [28] making it crucial for people with MS to develop optimal walking pattern. Falls are very common for people with MS with 1 in 3 people reporting a fall each month with half of the falls receiving no medical attention. A few reasons reported by people with MS who fell were balance problems, lower limb weakness, and inattention [29-34]. As the average life-expectancy of people with MS is approaching values seen in the general population, aging with MS is now an important agenda [35, 36]. Keeping physically active will be a key ingredient to aging with MS.

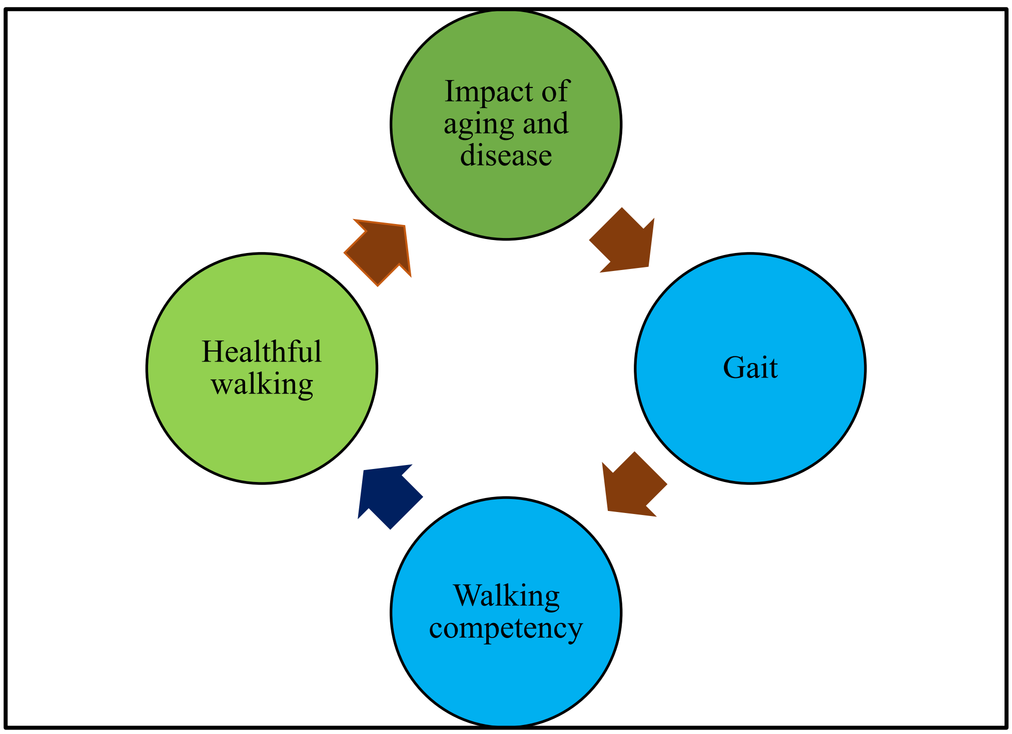
1.3 Parkinson's Disease (PD)

The worldwide prevalence of PD ranges from 57 to 230 per 100,000 and with increasing age and life expectancy, the prevalence of PD is projected to increase, the term "Parkinson pandemic" has been used to direct attention to this global health trend [37-39]. The disability associated with Parkinson's accounts for a large and growing proportion of the disability from non-communicable diseases [40, 41]. One important suggestion to target this global health care need is to improve physical activity among people with Parkinson's disease.

Parkinson's disease is a neurodegenerative movement disorder of the central nervous system primarily because of decrease in dopaminergic neurons, primarily affecting older persons. The characteristics are hypokinesia (reduced movement), akinesia (absent movement), tremor, rigidity and postural instability [42]. Predominant motor symptoms include tremor, slowness and stiffness, impaired balance and rigidity [43]. People with Parkinson's disease manifest motor impairments such as freezing in mid-activity and difficulty starting and stopping walking. In addition, they have an abnormal gait pattern, characterized by stooped posture, reduced arm swing and trunk rotation, short shuffling steps, and absence of heel strike. All of these lead to poor foot clearance during stepping, thereby increasing the risk of falls, and increasing the work and effort of walking [44-47]. These impairments are barriers to walking competency and health promoting walking.

1.4 Commonality Between Older Adults, People with MS and PD

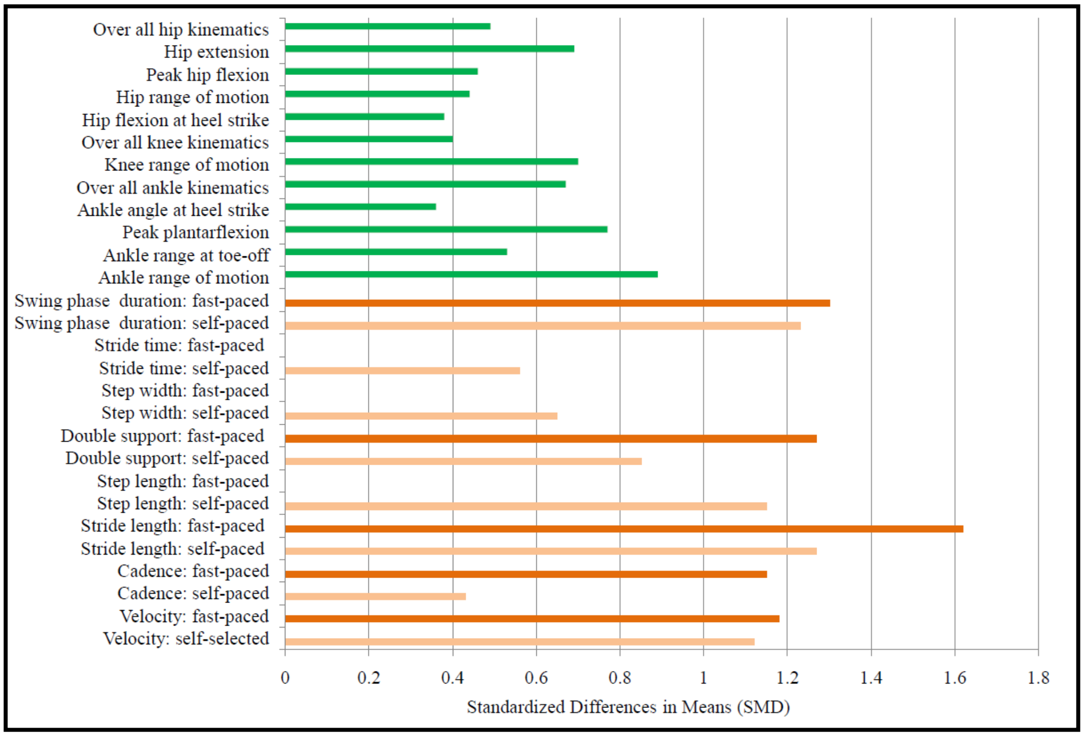
The cause of neuro-degenerative conditions such as MS and PD is multifactorial, including genetic and environmental factors. People with MS and PD now live longer and with treatment show less rapidly declining trajectories of disability [31, 48]. Aging and the presence of degenerative neurological conditions render people vulnerable for gait deviations. This limits older adults and people with chronic neurological health conditions from maintaining a healthy lifestyle by meeting the Canadian Physical Activity Guidelines [49, 50]. Maintaining a level of physical fitness is also critical to prevent secondary health conditions such as heart disease, osteoporosis, obesity and diabetes [51-56]. These conditions directly and indirectly affect the components needed for healthful walking (**Figure 2**).



CHAPTER 2: MEASURING WALKING

The introductory chapter highlighted the challenges for healthful walking for three populations (seniors, MS, and PD) and shows that the common activity needed to promote health for all of these conditions is walking. All three populations under study have characteristic gait patterns that are uniquely different from young adults. A systematic review and meta-analysis on quantitative age-related gait parameters including 29 cross-sectional studies and baseline data from clinical trials [57], found that young and older adults had small by statistically significant differences in ankle angle at heel strike (-0.36) but no differences in mid-stance peak flexion, and peak flexion during swing. Comber et. al. conducted a similar systematic review and meta-analysis on gait parameters in people with MS (EDSS 1.8 to 4.5) compared to healthy adults [58]. The results of which are shown in Figure 3. A total of 41 studies (32 were included in the meta-analysis) showed that people with MS had lower values on gait velocity, stride length, and swing phase duration under both fast and self-selected conditions, whereas step length, step width and stride time values were lower on self-selected condition (there was insufficient data to estimate under fast paced condition). The double support duration was higher under both fast and self-selected conditions. Summary estimates on all spatiotemporal gait parameters indicated that people with MS had lower values compared to healthy control. Additionally, people with MS showed greater variability on lower limb joint angles, muscle activation, torque, power, and ground reaction forces.

Figure 3 shows the Standardized Differences for Young Individuals compared with Seniors (Green) and People with MS (Orange) from the two Systematic Reviews.



There has been no systematic review on gait parameters in people with PD. Gait impairments in people with PD are of two types: episodic and continuous. As the name implies, episodic gait disturbances present randomly and include festinating and freezing gait [59-61]. Continuous gait disturbances on the other hand are persistent gait impairments such as hypokinetic gait, characterized by short steps, reduced arm swing and trunk rotation, increased double support, decreased stride length and speed with normal cadence [46, 62-66]. People with PD have challenges with gait initiation, turning particularly in narrow hallways, and stopping [67]. The gait parameters differ depending on whether the gait was assessed before or during the peak effect of the medication ("on" or "off" period) [68, 69].

Gait vulnerable populations share similar challenges with gait and walking and with remaining as active as possible. Walking can be of different types: walking for recreation or exercise, walking to reach a destination which includes active travel, non-motorized travel, transportrelated physical activity, destination-oriented walking, and utilitarian walking [70]. Walking in context of rehabilitation is to reduce secondary effects of sedentariness from accidents or illness and to promote function and prevent falls. However, the activity of walking goes beyond function and rehabilitation treatment target to a meaningful way to promote health.

Walking is the most common method of maintaining an active lifestyle, it requires no equipment, no specialized environment, and can be physically and cognitively challenging particularly when walking outdoors [71]. Walking is one of the most common cost-effective, low-impact, (minimal strain on joints) exercise modality that is accessible to all people and recommended by health care professionals. Walking is not only a functional activity but also the main way for many people to remain healthy. Canadian longitudinal study on aging (CLSA) reports walking to be the most accessible activity for older adults to engage in physical activity [72]. CLSA reports that around 62.9% of women and 69.8% of men between the age of 65-85 engaged in walking for more than 3 days a week [72]. As an exercise, sustained fast walking will target cardio-vascular functional capacity and endurance and for people with limited capacity or reserve the effort of walking could be an exercise in itself. Walking for the purpose of health promotion is targeted towards meeting recommendations from physical activity guidelines. Walking is the most practical method of meeting physical activity guidelines for seniors and people with disability.

The health promoting aspect of walking is derived from walking at a certain intensity such that it stimulates breathing and heart rate. Walking at a health promoting intensity requires that the time of double support (both feet in contact at the same time) is shorter than the swing time [73]. A study using data from National Health and Nutrition Examination Survey (NHANES) shows that adults spent less than a minute walking at health promoting intensity despite the capacity to do so [5, 74]. The Canadian Physical Activity Guidelines for physical activity recommends participation in moderate to vigorous intensity exercises in bouts of 10 minutes up to cumulated 150 minutes per week (http://www.csep.ca).

2.1 Sources of Information

Information on walking capacity and walking performance is obtained from clinical tests or asking patients to report on how often and how well they can do certain activities. Information on walking performance in the community can only be inferred from questioning the person but wearable technologies, such as accelerometers, provide more representative information as these are worn for several days at a time and hence capture more than a snap shot of walking performance.

Information on walking performance in the community can only be inferred from questioning the person but wearable technologies, such as accelerometers, provide more representative information. These devices are typically worn for several days and hence capture more than a few minutes of walking performance. This is in contrast to walking tests done clinically, such as the 6MWT, which captures only 6 minutes of a person's day-time walking. Values on the 6MWT may not represent real-world function. Each of these different sources of information provides overlapping yet unique information on walking. Mayo et. al (2017) have collated definitions for different sources of information [75].

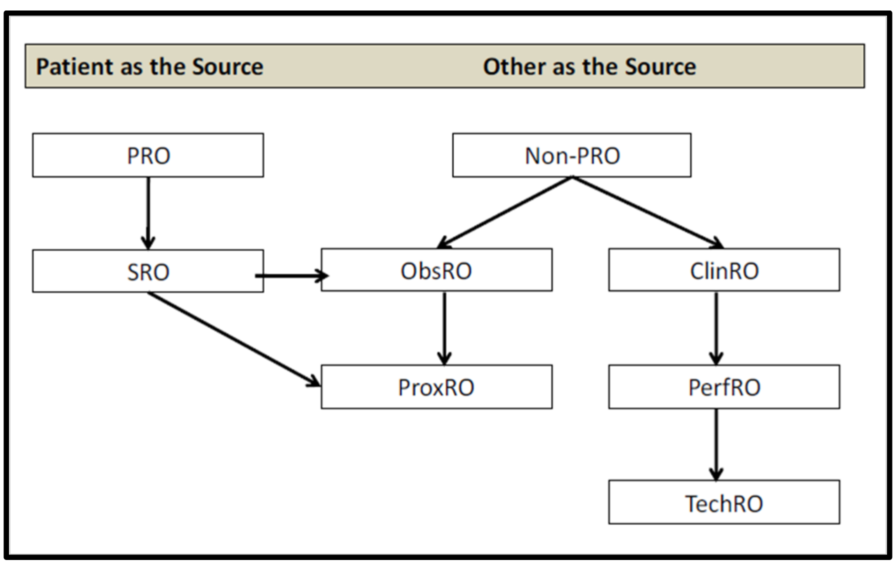
2.1.1 Patient-reported outcomes (PRO): A PRO is a measurement of any aspect of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else [76]. PRO captures symptoms such as pain severity, fatigue, and nausea but also constructs such as walking difficulty as only the person themselves can say how difficult an activity is. A PRO can be measured by self-report or by interview, provided that the interviewer records only the patient's response and does not interpret responses.

2.1.2 Self-reported Outcomes (SRO): A SRO is a measurement of any aspect of patient's health that comes from the person themselves but could also be validated from other sources such as observed performance tests. Self-reported outcome captures constructs such as need for assistance when walking and limitations in long walking distances, for example [75]. People can report on these but sometimes for the purposes of safety, validation is important.

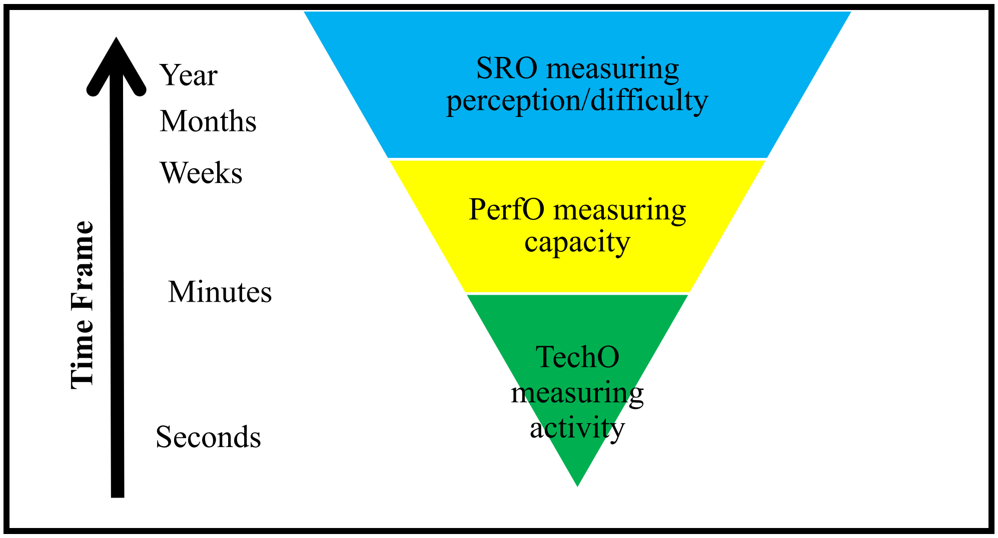
2.1.3 Performance outcomes (PerfO): A PerfO is a measurement based on a task(s) performed by a patient according to instructions that are administered by a health care professional. Performance outcomes require patient cooperation and motivation [75]. These include tests of completion or timing for example, measures of gait speed (timed 25 foot walk test), memory recall, or other cognitive tests.

2.1.4 Technologically measured outcomes (TechO): TechOs are those that measure health outcomes such as a pedometer counting steps or accelerometers [75].

The relation between different sources of information is shown in **Figure 4** [75].



PRO, SRO, PerfO, and TechO that a focus of this thesis, capturing information on different time frames as shown below in **Figure 5**. Clinically reported outcomes (ClinRO) are not usually used to gather information to quantify walking capacity or performance but can be used for judging gait impairments.



2.2 Beauty lies in the "eye of the beholder"

Measuring walking capacity and performance requires integration of different sources of information. Walking is a complex activity, features of which are important to different people. To illustrate, rehabilitation professionals are interested in walking speed, endurance, quality of walking, dual task costs during walking, among others that are commonly measured assessed by using performance tests done in a clinical setting. Timed 25-foot walk (T25FW); 2-minute, and 6-minute walk tests (6MWT) are examples. These tests are conducted at participant's self-selected or comfortable pace and at fast pace. The 6MWT is a test of functional walking capacity, measured as the total distance covered in 6 minutes.

Gait researchers are mostly focused on spatiotemporal gait parameters such as kinematics of gait and these are measured using instrumented walkways and motion capture systems. For people themselves, how they perform in a clinical setting is not as relevant as how they perform in their life. Walking as a function necessary to carry out activities of daily living and concerns about difficulty or effort in walking is more important. From a broad public health perspective, walking is an inexpensive way to maintain health and mobility. Given that many different aspects of walking are important depending on the context, one source of information may not provide as complete a picture and different sources of information should be viewed as complementary to each other. Moreover, how each source of information, SRO/PRO, PerfO and TechO, provides concordant and discordant information is rather more important. Discrepancies between SRO and PerfO highlights a perception-action gap – in other words, failure to notice loss of ability to perform tasks at the same level of proficiency. SRO could over-or under-estimate functional ability.

Performance tests are validated measures that are reproducible, responsive to change, [77] but require trained personnel, standardized environment, and special equipment. Although performance tests are accurate, they tend to capture only a few seconds or minutes of a person's walking day. Tests carried out in clinical settings may reflect a person's best or maximal performance and may overestimate functional capacity. SRO/PRO on the other hand capture self-perceived walking performance that are important to people themselves such as limitations or difficulty in walking, walking without or with an aid, among others. The advantages of SRO/PRO are ease of administration, low cost and no need for trained personnel. Discordance between SRO/PRO and PerfO could indicate a perception-action gap where a person feels that he/she is performing better than that shown by the standardized tests or vice a versa.

The literature on the relationships between SRO, PerfO, and TechO is not amenable to a systematic search as there is no consistency in how these terms are used in the literature. For this literature review, I relied on hand searching, known authors, and database searching using combinations of the following key words: validity, self-report, physical function, mobility, physical activity, seniors and sensors.

Table 1: Literature on use of SRO, PerfO, and TechO to measure physical activity among three populations

Author	Year	Type of study	Sample size/no. of studies	Construct	SRO	Proxy	PerfO	TechO	Relationship
<u>Seniors</u>									
Portegijs [78]	2017	Study	174	Physical activity	x			x	Moderate correlation between self-report sedentary behaviour and physical activity with step count (-0.28, 0.49)
Nawrocka [79]	2017	Study	61	Physical activity			x	x	6 senior women performed vigorous physical activity (>6 MET). 36% met Global Recommendation for Physical Activity for Health. Women who met the guidelines performed better on some performance tests on Senior Fitness Test battery
Dayton [80]	2016	Study	23	Physical function, ADLs and recreation	x		x		PerfO measures declined 1-month post total hip arthroplasty whereas SRO score improved. Weak correlations between SRO and PerfO at 6-months.
Visser [81]	2014	Study	138	Physical activity	x			x	5.8% of the sample reached the threshold of everyday physical activity guidelines (30 min per day). Women > men with poor walking performance, lower social support and self-efficacy incorrectly reported adherence to physical activity guidelines
Syddall [82]	2014	Study	1729	Walking speed	x		x		SRO walking speed and strongly associated with performance test on walking speed. Both men and women were more accurate (narrow 95% CI) at higher than slower walking speeds.
Sun [83]	2013	Systematic review	53 studies	Physical activity	x			x	Increase in age was associated with lower physical activity particularly among women across high income countries
Hurtig-	2010	Study	54	Physical	x			x	Weak to moderate correlation between

Wennlöf [84]				activity					IPAQ-E (SRO) and accelerometer counts (TechO). Spearman's rank correlation coefficient ranged from -0.337 to 0.471
Harris [85]	2009	Study	238	Physical activity	x			x	2.5% of the participants reached targeted physical activity guidelines. Self-report physical activity predicted average accelerometer daily count
Nieves [86]	2007	Study	216	Mobility	x		x		Established meaningful change between SF-36, single item on ADLs and mobility (SRO) and continuous summary physical performance score (CSPPS) and quartile summary physical performance score (QSPPS) (PerfO)
Coman [87]	2006	Systematic review	18 studies	Mobility	x		x		Weak to moderate correlation between SRO and PerfO across different studies
Brach [88]	2004	Study	3075	Physical function	x		x		Moderate to strong relationship between SRO and PerfO
Rogers [89]	2003	Study	57	ADL	x	x	x		Concordant between proxy rating and self-report. Discordant between PerfO tested in clinic and when tested at home
Harada [90]	2001	Study	87	Physical activity	x		x	x	Moderate to weak correlation between SRO, PerfO and TechO. Overall correlations ranged between -0.004 and 0.46 between three outcome measures for total physical activity. These values ranged from -0.00076 to 0.54 for moderate activities.
Sager [91]	1992	Study	247	ADLs	x		x		Disagreement between 2 sources of information in 55% on at least one and 33% in at least 2 or more ADLs. Greater age (>84), poor cognition (MMSE≥24), and presence of depression (GDS≥25) reported greater disagreement.
PD									

Del Din [92]	2017	Study	342	Gait			x	x	Fallers and non-fallers differed on total walking time (s), number of steps, bouts per day and mean bout length (s)
Nero [93]	2016	Study	91	Physical activity	x		x	x	34% of the variance in total physical activity measured by accelerometer (TechO) were explained by physical function (SRO), balance, dyskinesia and motor impairments. Moderate correlations between overall physical activity and brisk walking (TechO) with gait speed, balance and mobility (SRO)
Nero [94]	2015	Study	31	Walking speed			x	x	Walking speed ≤1.0 m/s had a accelerometer count of ≤ 328 and ≤470 for every 15 sec. These values were ≥730 and ≥851 counts for every 15 sec for walking speeds >1.3 m/s
Dontje [95]	2013	Study	467	Physical activity	x		x		82% of the participants did not meet the 10 min bout criteria whereas only 17.3% partially and only 3% fully met the physical activity recommendations.
Tanji [96]	2008	Study	79	ADLs	x		x		Moderate association between OARS (SRO) and performance tests. PerfO included Physical Performance Test (PPT), modified Physical Performance Test (mPPT), Short Physical Performance Battery (SPPB), Performance Test of Activities of Daily Living (PADL), Berg Balance Scale (BBS), Timed Up and Go (TUG), and Functional Reach (FR). Correlation between OARS best total and PerfO ranged from -0.56 to 0.44
Shulman [97]	2006	Study	76	ADLs	x		x		Performance and self-report on walking and dressing showed greatest concordance (kappa 0.28 and 0.32 respectively)
MS									
Kruger [98]	2017	Study	56	Physical activity	x			x	Moderate correlation between SRO lower limb mobility and step count (r=-0.44), mean

									METs (-0.22), active METs (0.75), light physical activity (-0.74), moderate physical activity (-0.44) and vigorous physical activity (-0.31). Sample consisted of people with MS and healthy control. Moderate association between self-report IPAQ and SWAmini (TechO).
Pau [99]	2016	Study	105	Walking			x	x	Weak to moderate correlations (range -0.616 to 0.772) were estimated between T25FW and spatiotemporal gait parameters from sensors.
Stellmann [100]	2015	Study	30	Mobility			x	x	An average of 2.61 bouts of 2 minutes and 0.35 bouts of 6 minutes per day were observed per person over 210 person-days of monitoring
Stuifbergen [101]	2014	Study	60	Physical function	x		x		Total score on Incapacity Status Scale (SRO) and MSFC (PerfO) were moderately correlated (r=-0.59 to -0.74) over time.
Motl [102]	2013	Study	256	Physical activity	x		x	x	Moderate correlations were observed between accelerometer data with SRO and PerfO: PDDS (-0.55), MSWS-12 (-0.62) scores, T25FW (0.59) and oxygen consumption during 6MWT (0.63)
Weikert [103]	2012	Study	66	Walking	x		x	x	Moderate correlation between TechO: accelerometer with PerfO: 6MWT (0.761), TUG (-0.674) and TechO with SRO:GLTEQ (0.587) and IPAQ (0.649)
Motl [104]	2011	Study	49	Physical activity	x			x	Moderate correlation between peak oxygen consumption and accelerometer counts (r=0.69) and GLTEQ (r=0.63)
Cavanaugh [105]	2011	Study	21	Physical activity	x		x	x	Moderate to strong correlation between MSWS-12, ABC, MFIS (SRO), TUG, 6MWT, DGI, BBS, (PerfO) and accelerometer (TechO)

Motl [106]	2010	Study	26	Walking	x		x	x	Moderate to strong correlation between SRO (MSWS-12, PDDS), PerfO (6MWT distance) and TechO (accelerometer and oxygen consumption during 6MWT) range r=-0.427 to 0.847
Weikert [107]	2010	Study	269	Physical activity and mobility	x			x	Accelerometer output correlated with SRO GLTEQ (r=0.36) IPAQ (r=0.34), MSWS-12 (r=-0.37) and PDDS (r=-0.40).
Gijbels [108]	2010	Study	50	Physical function	x		x		Correlations between 2 and 6 MWT and habitual walking performance (HWP) were low (0.35, 0.43 respectively) for people with mild MS (EDSS: 1.5-4.0) and moderate (0.73, 0.73 respectively) for people with moderate MS (EDSS: 5.5-6.5). Univariate regression analysis showed that only 6MWT predicted for HWP (R^2=0.187) among people with mild MS whereas 2MWT, 6MWT and 25FW predicted HWP among moderate MS (R^2=0.532, 0.527 and 0.387 respectively)
Motl [109]	2009	Study	292	Physical activity	x			x	Moderate to strong correlations between physical activity and SRO measures of QoL (range -0.85 to 0.73)
Motl [110]	2009	Study	133	Domains of life	x			x	Moderate correlations between SRO and TechO (ranged from r=-0.22 to 0.74)
Snook [111]	2009	Study	74	Physical activity and mobility	x			x	Weak to moderate associations between self-report physical activity and mobility with accelerometer measured walking
Motl [110]	2008	Study	133	Domains of life	x			x	Moderate correlations between SRO and accelerometer across different levels of EDSS
Klassen [112]	2008	Study	36	Physical activity	x			x	Moderate correlations between accelerometer output and physical activity diary scores (range 0.59 to 0.74

Hale [113]	2008	Study	47	Physical activity	x			x	Overall moderate correlation between SRO and PerfO across different study population (people with PD, MS, stroke and healthy control)
Gosney [114]	2007	Study	196	Physical activity	x			x	GLTEQ (SRO) correlated moderately with pedometer (TechO) (r=0.51) and accelerometers (r=0.53). IPAQ correlated moderately with pedometer (r=0.32) and accelerometer (r=0.36).
Kos [115]	2007	Study	29	Physical activity	x			x	Moderate correlation between SRO physical activity and actigraph worn at ankle (r=0.57) and at wrist (r= 0.59)
Motl [116]	2006	Study	30	Physical activity	x			x	Moderate to strong correlation between GLTEQ, 7dPAR (SRO) with accelerometer and pedometer (TechO). Correlation coefficient ranged from 0.44 to 0.93
Ng [117]	1997	Study	32	Physical activity	x			x	Moderate association between SRO and TechO. Sample consisted of people with MS and healthy control

For seniors, 12 studies and two systematic reviews were identified for review. All used at least one of the three sources of information (SRO/PRO, PerfO, TechO) on the target constructs: physical function, mobility, activities of daily living (ADLs), recreation, or walking speed. The sample size across these studies ranged from 23 to several thousand participants. Studies included in the systematic reviews had larger sample sizes as these studies were data from the national surveys that are routinely employed in European and North America. Thirteen articles used SRO that was associated with either PerfO (9 studies) or TechO (7 studies). One study, in addition to SRO and PerfO, had a proxy outcome measure. All studies demonstrated weak to moderate associations between the SROs and the PerfOs or TechOs.

In people with PD, six studies were identified for review. All demonstrated moderate associations between SROs and PerfOs. Four of these six studies were aimed at measuring physical activity or ADLs. Two of the six studies measured gait or walking speed using PerfO and TechO.

There has been greater interest in measuring physical activity and/or walking for people with MS compared to seniors or people with PD. This is understandable because walking was one of the most frequently reported disabilities among people affected by MS [28, 118-120]. Even early on in the MS disease course, approximately 75% of people with MS were observed clinically to have some type of walking impairment [121, 122]. For PD, walking, thinking, stiffness, slowness, and tremor are important; for seniors (women), memory, vision, and medication side effects dominate as health concerns [12, 123].

For people with MS, 21 studies targeting physical activity, mobility or walking constructs were identified for review: 19 of these 16 studies associated SRO with PerfO or TechO; eight studies correlated PerfO with TechO. SROs used in these studies were Incapacity Status Scale (ISS), Patient Determined Disease Steps (PDDS), Multiple Sclerosis Walking Scale (MSWS), Godin

Leisure-Time Exercise Questionnaire (GLTEQ), International Physical Activity Questionnaire (IPAQ), Stanford 7-day Physical Activity Recall Scale (7dPAR), Activity-specific Balance Confidence Scale (ABC), and Modified Fatigue Impact Scale (MFIS). PerfOs included individual tests of physical performance or score on Multiple Sclerosis Functional Composite scale. TechO in these studies were one of the two wearable biosensing devices, either an accelerometer or Actigraphy, to monitor physical activity in real-life.

Accelerometers are typically small sized piezoelectric based sensors that are attached to body surface either at thigh, wrist, ankle or waist and usually worn over a 7-day period [124]. The usual duration of data collection with biosensing devices is for 7-days which is considered a 'gold standard' for obtaining a valid measure of free-living physical activity [125, 126]. Accelerometers record data between 20 to 100 Hertz [127] and the outputs provide information on recording time, step count, metabolic equivalents, and times spent in sedentary activity, upright, stepping and transition time. Data from the accelerometer could be summarized by time periods; 15 seconds epochs, hourly, daily or weekly. Accelerometers have been shown to be an ecologically valid measure of free-living among people with MS [128]. On the other hand, activity monitors such as ActiGraphy are piezo-resistive based technology, in addition to capturing daily activity, they provide a finer gradation of the raw data (1 second epoch) [129, 130].

The magnitude of associations across these three sources of information varied widely with correlations ranging from near 0 to 0.8. None of the three sources of information by themselves accurately captured physical constructs, indicating that more than one source of information is advantageous. Studies consistently demonstrate that people with MS are less ambulatory compared to healthy controls [103, 108, 131, 132].

CHAPTER 3: RATIONALE AND OBJECTIVES

Rationale

Physical activity is an important way to maintain good health for older adults and people with neurodegenerative conditions such as Parkinson's Disease (PD) and Multiple Sclerosis (MS). Walking is one of the most commonly performed and recommended physical activities. Aging and neurodegenerative conditions predispose people to gait vulnerability that limit walking activities and restrict opportunities for achieving health benefits from walking. The Canadian Physical Activity Guidelines for older adults recommend at least 150 minutes of moderate- to vigorous-intensity aerobic physical activity per week, in bouts of 10 minutes or more with an additional 2 days of muscle and bone strengthening activities. Brisk walking is one of the recommended modes to achieve moderate intensity physical activity.

Two aspects of walking need to be considered: what the person can do (walking capacity) and what they do do (walking performance). Information on walking capacity is typically obtained by measuring performance in a clinical setting on such tests as two- and six-minute walk test (2 and 6MWT) (performance-based outcomes). Information on walking performance is also typically obtained by asking the individuals about activity (self-report) and/or free living monitoring using accelerometer (technology). It is not known how these three sources of information provide concordant or discordant information among gait vulnerable populations, here seniors and people with PD and MS.

Objectives

The objective of this thesis is to contribute evidence towards how the different sources of information about walking (self-report questionnaires, performance tests, and technologically assessed) provide convergent or divergent information about walking capacity and walking performance among people with health conditions that lead to gait vulnerability. The data for these four projects came from secondary analyses of existing data and from primary data collection that I carried out independently. As is typical for theses in the Faculties of Medicine and Science, this thesis is built around manuscripts.

The first manuscript aimed to estimate the extent to which sex/gender differences affect the relationships between tests of physical performance and self-reports about function in everyday life activities among people with MS. Data for this study came from an existing database. The study showed that few performance tests are ecologically valid, and their extent of ecological validity is different for women and men.

The second manuscript aimed to estimate, for people with MS, the extent to which walking capacity tested in a laboratory, using 6MWT, is reproduced during 7 days of free-living step monitoring using an accelerometer and how this relationship is affected by age, gender, motivation, exercise enjoyment and barriers to participation. This study showed that walking bouts of ≥5 minutes were not associate across any category of 6MWT but were associated with mood and exercise barrier. The third manuscript tested whether walking among older adults is modifiable by external auditory feedback using a technology, the Heel2Toe sensor, developed by Dr. Mayo's team. Auditory feedback was provided to correct stepping pattern during outdoor walking. This objective was achieved using a pre-post design with 5 training sessions. All 6 participants showed improvement in their spatiotemporal parameters and had a positive experience with the device.

The fourth and last manuscript targeted the relationship between indicators of step quality and cadence among seniors, people with PD and MS. The data for this manuscript came from the Heel2Toe sensor that was deployed during walking assessments for people with MS, PD and seniors. The objective of this manuscript was to estimate, across seniors and people with MS and PD, the extent to which heel-to-toe stepping pattern (good steps), angular velocity and coefficient of variation at heel strike using Heel2Toe sensor separately explained variation in cadence. The results showed that they did not.

This thesis highlights the lack of ecological validity among commonly used performance tests (**manuscript 1**), shows discrepancies between walking capacity and free-living walking performance among people with MS (**manuscript 2**),demonstrates that gait in seniors shows adaptation to auditory feedback using Heel2Toe sensor (**manuscript 3**), and illustrated how gait quality parameters of proportion of good steps and angular velocity are not predictive of cadence in seniors, people with PD and MS (**manuscript 4**).

CHAPTER 4: MANUSCRIPT 1

Comparison of Common Performance-Based Tests to Self-report in People with Multiple Sclerosis: Does Sex or Gender Matter?

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Abstract

Objective: To estimate the extent to which sex/gender differences affect the relationships between tests of physical performance and self-reports about function in everyday life activities. Ecological validity is an important psychometric property when choosing tests of physical function, as they need to relate to everyday function. In Multiple Sclerosis (MS) tests of strength, balance, exercise capacity, manual dexterity, gait speed, and walking capacity are commonly used but the extent to which they relate to everyday function is understudied and the extent to which ecological validity of these tests differ between women and men is unknown.

Design: A cross-sectional analysis was conducted on a random sample of men and women recruited for a study on the life-impact of MS. Correlations between pairs of performance tests of physical function (PerfO) and self-report items (SRO) pairs of variables with theoretical coherence were calculated and gender effects identified using linear regression.

Setting: Participants were recruited from a random sample of patients from the three largest MS clinics in the greater Montreal area.

Participants: The sample comprised of 140 women and 48 men with MS

Interventions: Not applicable

Results: The mean age of the participants was 43 (SD:10). Sixty PerfO and SRO items yielded 165 theoretically linked pairs separately for women and men. Of these, 77 pairs of the performance tests related strongly to everyday function and an additional 203 showed moderate correlations. Thirty-one pairs had a statistically significant interaction with gender with men having higher correlations than women (n=27/31).

Conclusion: The results support the ecological validity for physical performance tests, particularly balance tests and particularly for men. The observation that many indicators of everyday function derived from SROs were related to physical performance supports the routine use of SROs in clinical practice to guide therapy to meet the needs of clients with MS.

Keywords: self-reported outcomes, performance outcomes, sex/gender, Multiple Sclerosis, ecological validity

Abbreviations:

6MWT- six-minute walk test,

9HPT - nine-hole peg test,

DASH-disability of the arm, shoulder and hand,

EDSS-Expanded Disability Status Scale,

EQ-5D-3L-EuroQol five-dimension three-levels,

IADL - instrumental activities of daily living,

IQR-interquartile range,

MFSC-Multiple Sclerosis Functional Composite Index,

mCAFT - modified Canadian Aerobic Fitness Test.

MSQLI - MS Quality of Life Inventory,

MS - Multiple Sclerosis,

OR-odds ratio,

PRO - patient reported outcomes,

PerfO-performance outcomes,

PBMSI-Preference Based MS Index,

RAND-36-Research ANd Development,

SRO- self-reported outcomes,

T25FW-timed 25-foot walk,

US-FDA- United States Food and Drug Administration

Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory, demyelinating disease of the central nervous system that affects young adults during the most productive years of their life [1]. Canada has the highest prevalence of MS in world, with over 240 per 100,000 individuals [2]. There are four distinct clinical types of MS reported by the United States National Multiple Sclerosis Society: these are relapsing-remitting MS, primary and secondary progressive, and progressive relapsing. A fifth type, clinically isolated syndrome, is now recognized [3]. Women are three times more likely to develop MS than men [4-6] and men are more severely affected than women [7] even today with new generation disease modifying drugs [8].

People with MS typically experience sensory disturbances, muscle weakness, increased muscle tone, and fatigue [9]. These impairments lead to limitations in physical function, physical activity, work, sports, and other everyday activities. At one or more times in the life-course of MS, patients will be seen in rehabilitation, where assessments of physical performance are carried out using standardized clinical tests. Commonly used performance tests cover domains such as strength, balance, exercise capacity, manual dexterity, gait speed, and walking capacity. The extent to which these relate to everyday life activities is a topic of increasing interest as the Food and Drug Administration (US-FDA) recommends, for drug trials, the use of outcome measures that reflect the patient's perspective [10]. If this is true for drug studies, it is even more crucial for studies of rehabilitation interventions as the only aim is to improve function in everyday life.

Everyday function is most often assessed by asking people to report on activities such as walking distance, climbing stairs, and doing house hold tasks. There are a number of validated and widely used self-report measures of physical function. In the context of MS, the Short-Form General Health Survey (SF-36) is commonly used as it is part of the MS Quality of Life

Inventory (MSQLI) [11]. The Disability of the Arm, Shoulder and Hand (DASH) has also been used in the context of MS [12].

Ecological validity is a term that refers to the degree to which results on a test obtained under controlled experimental conditions are related to those obtained in real world environments [13, 14]. This aspect of validity is particularly important for tests of physical function as performance is often considered the gold standard for assessing physical function. However, the results of these tests are often difficult to interpret with respect to how an individual will function in their usual environment, which is of course, what is important for the patients. The interpretation and impact on everyday function will also differ by sex/gender given that physical capacity is often greater for men than women, but performance of everyday activities may be affected by gender.

According to the Gender, Sex and Health Research Guide from the Canadian Institute of Health Research (CIHR), sex refers to the "biological and physiological characteristics that distinguish females from males" [15]. Sex differences are seen on tests of physical capacity. Gender, in contrast, is related to "socially constructed roles, relationships, behaviours, relative power, and other traits that societies ascribe to women and men" [15]. Gender differences can be seen in what people with MS choose to do in their lives. In the context of this paper, we consider the biological composition of an individual to be more likely to determine performance on physical function tests, whereas we consider gender is more likely to influence responses on self-report questionnaires.

These differences would indicate the importance of considering sex and/or gender when measuring disability in MS. While some studies have queried the relationship between performance tests and everyday functioning [16, 17], none have addressed differences by sex/gender. Stuifbergen et. al. compared a performance based measure (the Multiple Sclerosis

Functional Composite [MSFC] Index) and a self-report measure of functional limitation (the Incapacity Status Scale (ISS)] over five time points in 60 participants with MS [17]. The relationship between the MSFC total scores and the ISS total score was reported as moderate to strong (r=-0.59 to -0.74) at all of the time points. The Gross and Fine Motor Subscales of the ISS had moderate to strong relationships (*r*= -0.51 to -0.76) with the MSFC total score [17]. Goldman et al. interviewed 159 patients with MS on their ability to perform instrumental activities of daily living (IADL) and the Timed 25-foot Walk Test (T25FW). Patients with T25FW of 6 to 8 seconds, compared to those who covered 25 foot distance in less than 6 seconds, required walking aid and assistance in IADL and were likely to be unemployed, whereas patients with T25FW ≥8 seconds were more likely to be unable to perform ADL and were unemployed. Patients with 6-8 seconds on T25FTwere more likely to be unemployed, walk with an aid and need assistance with IADL whereas patients with T25FW ≥8 seconds were unemployed with a 70% likelihood of being unable to perform IADL tasks such as house cleaning, grocery shopping, cooking etc [16]. Paltamaa et al. studied relationship between clinically measured physical function and self-reports among ambulatory people with MS and showed that the Box and Block Test, Berg Balance Scale and 6MWT were significantly associated with reported limitations in self-care, mobility and domestic life (OR range 1.01 - 2.15).

Identifying whether there are sex/gender differences would help with the interpretation of values on performance tests for women and men. Ultimately, the information could be used to design better sex/gender targeted interventions for people with MS whose ultimate goal is to improve function in everyday life rather than a value on a test.

Objective

The purpose of this study is to estimate the extent to which sex/gender differences affect the relationships between tests of physical performance and self-reports about function in everyday life activities. We hypothesize that not all PerfOs will have the same relationship to SROs in women and men with MS.

Methods

Study Design

A cross-sectional analysis was carried out on data arising from a project on gender differences in the life-impact of people with MS. Results arising from the study have been published previously [18-24]. In brief, a random sample of men and women diagnosed after 1995, when diagnostic criteria was updated to include imaging and disease modifying drugs were available, was selected from three largest MS clinics in the greater Montreal area [23]. All assessments were carried out at a single visit by trained personnel. Ethical approval was obtained from Research Ethics Boards of the participating sites.

Participants

The individuals included in the study were over the age of 18 years and diagnosed with MS after 1995. This represented 52% of those identified from the data base. Recruitment ended when the target sample size had been reached. The time period was chosen to coincide with secular changes in the diagnosis and treatment of MS leading to the label of the *New MS* [23]. This distinction is important in the context of research to reduce survival bias arising from selective retention of only those people doing well from earlier cohorts where diagnosis and treatment differed. People with a recent relapse (preceding month), severe cognitive impairments, and/or preexisting health conditions affecting functioning were excluded [21, 25].

Measurement Framework

The measures chosen for the study were selected based on the World Health Organization International Classification of Functioning framework [26]. Performance measures covered the domains of impairment and activity limitations, while the self-report measures were of activity only.

Table 1 lists the measures used. The testing methods for the PerfO followed standardized protocols previously reported in the literature [27-33]. Four SRO outcome measures were used covering the domains of physical function, upper limb activity, and mobility, from “Research And Development Corporation” (RAND-36), DASH, EuroQol five-dimension three-levels (EQ-5D-3L), Preference Based MS Index (PBMSI) questionnaires [12, 34-36]. The measures RAND-36 (Physical Function Index), EQ-5D-3L and PBMSI items are scored from 1, 2, or 3 with a score of 3 being the best, and DASH items are scored from 5 to 0 with 0 being no difficulty. PerfO included balance items from EQUI scale, modified Canadian aerobic fitness test, grip strength (dominant hand), vertical jump, push-up, partial curl-up, gait speed (comfortable and fast), six-minute walk test (6MWT) and nine-hole peg test (9HPT). One additional measure was included, the Perceived Deficits Questionnaire (PDQ) which is a 20-item self-report measure of cognitive difficulties [37]. This measure was included to identify whether indicators of cognitive impairment could explain results on the other measures.

Data analysis

Correlations were performed between pairs of variables that were theoretically linked based on the construct they represented using Statistical Analysis System® 9.4 software [38]. Three types of correlations were performed depending on the measurement scale of the variables. Pairs of two continuous variables were analyzed using Pearson product moment correlation, pairs of one continuous and one ordinal variable were analyzed using polyserial correlations, and pairs of two ordinal variables were analyzed using polychoric correlations [39]. The effects of gender on the relationships between performance tests and self-report measures were analyzed with linear regression with the model including a term for the interaction between gender and the performance items. The level of significance was set at p = ≤ 0.05. The correlations between self-reported cognitive difficulties and physical function measures were also estimated. The linear regression models above were retested for the effect of cognition on the associations.

<u>Results</u>

Of the 364 people randomly selected to be sent recruitment letters, 52% agreed to the study and there were no significant differences between responders (n = 188) and non-responders (n = 176) on age, sex, MS severity, date of diagnosis, medication management, and duration of symptoms [22]. The characteristics on the 140women and 48 men are presented in Table 2. The study participants were mostly young adults (mean age: 43; SD:10) with an average time since diagnosis of 6.2 years (SD: 3.6). The median Expanded Disability Status Scale (EDSS) was 2 (IQR 1-3 for women and 1-5 for men). Women and men did not differ on any characteristics, except MS type.

Among 60 items included for analysis, 165 theoretically linked PerfO and SRO pairs were correlated separately for women and men (total 330 pairs). Figure 1 gives the distribution of these correlations across the different PerfOs overall and according to the strength of correlation and presence of gender interactions. Most pairs (n=150) involved one of the 9 balance items from EQUI scale; of these pairs, 55 (10 for women and 45 for men) were strongly correlated with one or more SRO items and 18 of the 55 pairs had a statistically significant interaction with gender with men having higher correlations than women (n=64/77). Only moderate correlations with SROs were observed for vertical jump, push-ups, step-test, 9HPT, and grip strength. There were no gender interactions for pairs of SRO and gait speed, 6MWT, and step test. Overall, when there were gender interactions, men had higher correlations between PerfOs and SROs. All the correlations are provided in Supplementary Table 1.

Table 3 presents, for each PerfO, the SRO that had the greatest difference in the magnitude of the correlation coefficients between women and men. Only pairs with significant gender interactions are shown; most of the 95% CI did not overlap. For example, the correlation between standing balance (PerfO) and preparing a meal (SRO) was 0.14 for women and 0.83 for men. Of the 9 most discriminating pairs with gender interactions, 7 pairs were with DASH items, one with bathing and dressing from the RAND-36 and one with the mobility dimension from the EQ-5D-3L. In all of these pairs, the correlations for men were higher (range: 0.64 - 0.94) than for women (range: 0.14 - 0.74).

Table 4 shows the extent to which PerfO tests contribute to the person's rating of physical function on the SRO items. Only pairs with strong correlations (r=≥0.8) are shown [40]. To illustrate, standing balance, tandem stance, comfortable and fast gait speed, and 6MWT were highly correlated with the SRO item, limitation in walking several blocks. Pairs with gender interactions are shown in bold font.

The relationship between cognition, as reflected by scores on the PDQ (higher values indicate more impairment), and 10 performance tests as assessed Pearson correlation coefficient were all low (<-0.3). For women 2/10 correlations were ≤-0.2. PDQ and 6MWT was -0.2 and that of PDQ with 9HPT was -0.26. For men, these correlations were -0.0061 and -0.301 respectively. Additionally, for men the correlation between PDQ and VO_2 peak was -0.203. Thus, out of the 20 correlations, 4 (2 each for women and men) were between -0.2 and -0.3. All the others were near 0. The relationship between SRO and PerfO in the linear regression models did not change after including PDQ scores.

Discussion

The results of this study showed that almost half (70/165; see Figure 1) of the performance tests related strongly to everyday function and 88/165 (53%) showed moderate correlations indicating ecological validity for these tests in MS. When there were statistically significant differences in the strength of the associations between women and men (31/165 pairs), the relationships were almost always (27/31) stronger for men. This suggests that performance in men maybe a stronger determinant of everyday function than it is for women. This discrepancy arose primarily from items related to everyday function involving the upper body. This is perhaps because women are more likely to undertake these tasks regardless of their physical capacity (see Table 3) and self-report no or little limitation or difficulty (gender effect) [41-43]. This may be a source of fatigue for women. Exercises targeting strength of the upper body may be of benefit to women in their daily lives. An area that needs further investigation.

These results also showed that multiple PerfOs linked strongly to SROs of everyday function (see Table 4) indicating specific treatment targets when people identify limitations in their everyday functioning. For example, if limitations in outdoor walking (several blocks) are identified, the treatment should target at least, balance, gait speed, and functional walking capacity although other variables not measured in this study may also apply. These result support the use of SROs routinely in clinical practice to guide therapy to meet the needs of clients with MS. Ecological validity is a relatively new psychometric property more often reported in relation to cognitive tests [13]. The systematic review suggested that the strength of the relationships between neuropsychological tests and everyday outcome function is moderate across different populations and outcomes [13] and has not yet been studied in the context of physical tests.

The measures with the strongest ecological validity were balance tests with 65% of pairs showing strong correlations with SROs (see Figure 1). The next strongest PerfOs were the 6MWT (64% of pairs with strong correlations); gait speed and curl-ups each showed 50% of pairs with strong correlations. The strong relationship between balance and everyday function emphasizes the need for interventions for balance. The most commonly used PerfOs in MS are the T25FW test and the 9HPT, as both of these are in the test battery of the MS Quality of Life Inventory. Gait speed and the 6MWT both relate to mobility as does the T25FW indicating that the degree of ecological validity of the former tests likely apply to the later.

In contrast, the 9HPTand grip strength showed no high correlations. Nevertheless, they are widely used in practice and research, but do not have the same ecological validity as do the gait tests. Interestingly, capacity to do push-ups was more related to arm activities than the usual tests of 9HPT and grip strength. The PerfOs measuring functional walking capacity (6MWT) and mobility (gait speed - comfortable and fast) and upper limb function (9HPT) are sub-maximal in effort. Four PerfOs demand maximal effort (vertical jump, push-ups, curl-ups, and Step test), constructs rarely if ever assessed clinically or in research. Yet, for the most part, these tests demonstrate ecological validity because they are all moderately correlated with SROs. These more demanding tests could be important to assess for more highly functioning individuals as they also correlated with more demanding functional activities such as walking more than a kilometer, climbing several flights of stairs, heavy household tasks, and as well as vigorous and sports activities (see Supplementary Table 1).

Half of the PerfOs (9/18 see Figure 1) showed gender interactions (see Table 3). Five of the gender interactions were with balance items, with men showing much stronger correlations than women despite reporting more challenges with functional activities (see Supplementary Table 1). This indicates that balance may be a more important determinant for physical function in everyday life for men than for women, supporting the need for personalized therapy by gender.

The US-FDA emphasizes the need to have outcomes that reflect the patient's perspective. These can be patient- or self-reported (PRO or SRO) [44] or performance-based as long as they relate to function in everyday life. In other words, the PerfOs have to demonstrate ecological validity. This paper suggests a portfolio of PerfOs with ecological validity in MS.

Limitations

This study had a number of strengths including its sampling strategy to minimize selection and survival bias. For example, those who entered the study and those declining or not traced did not differ on important clinical characteristics [18]. A number of limitations are also important to note. These data are only cross-sectional and the predictive validity of these performance tests for future everyday function cannot be inferred from the data presented here. Future qualitative work on the women and men's perceptions of how PerfO and SROs are related is warranted. The focus of this paper was on the relationship between PerfO and SRO for constructs related to physical function. We did not analyze these relationships for cognitive constructs. The 9HPT (or other measures of manual dexterity) are often included in the neuropsychological test batteries. Thus, the correlation between the SRO of cognitive difficulties with the 9PHT was expected. While these results are of interest and perhaps warrant a separate paper, we present only a brief summary in the results section to allay concerns that the results were affected by cognition which theyweren't.

Conclusions

Ecological validity is an important psychometric property to consider when choosing a PerfO for research. The results of this study support the ecological validity for physical performance tests, particularly balance tests and particularly for men. Only one test showed no ecological validity and that was the modified Canadian Aerobic Fitness Test (mCAFT) measuring exercise capacity and only for women. In clinical practice, ecological validity would suggest treatment targets and whether these targets would differ for men and women.

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Figure 1: Number of correlations between performance tests and self-report item pairs, overall, with strong or moderate correlation, and with significant gender interactions.

Table 1: Tests of Physical Performance and Self-report variables

Variable	Construct	Unit/coding
Physical Performance Tests		
Impairment Domain		
EQUI scale	Balance	3 point clinician reported ordinal scale (higher score is better)
modified Canadian Aerobic Fitness Test	Submaximal Exercise capacity	Oxygen cost per liter per minute for each stage of step test
Grip strength [147]	Muscle strength	Kilograms
Vertical jump	Lower extremity power	Centimeters
Push-up	Core strength	Count
Partial curl-up	Core strength	Count
Activity Domain		
Gait speed (comfortable/fast)	Mobility	Meters per second
Six-minute walk test	Functional walking capacity	Distance in meters
Nine-hole peg test	Dexterity	Pegs per second
Self-Report		
Activities		
	Items; Descriptor	Unit/coding
Physical Function Index (PFI) from RAND-36 [162]	10; Limitation	3 point ordinal scale (higher score is better)
Disability of the Arm, Shoulder and Hand (DASH)	20; Difficulty	Reverse scored from the original: 5 point ordinal scale (higher scores are better)
Mobility dimension of EQ-5D-3L	1; Problem	3 point ordinal scale (lower score is better)
Walking dimension of Preference-based MS Index	1; Ability	3 descriptors on walking ability

RAND-36: Research ANd Development Corporation
EQ-5D-3L: EuroQol - five dimensions - 3 levels

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Table 2: Demographic and Clinical Characteristics of study participants (N=188)

Variables	Mean ± SD or N (%) or median (IQR)	
	Women (n=140)	Men (n=48)
Age (years)	42.6 ± 9.7	44 ± 11.6
Years since diagnosis	6.1 (3.4)	6.6 (3.9)
Type of MS (%):		
Relapsing–remitting*	78 (56)	20 (41)
Secondary progressive	5 (4)	2 (4)
Primary progressive	1 (0.7)	2 (4)
Primary relapsing	4 (3)	4 (8)
Clinically isolated syndrome	6 (4)	3 (6)
MS severity (EDSS)	2 (IQR: 1-3)$	2 (IQR: 1-5)$
Employed	90 (65)	32 (65)

* chi-square statistic: 4.6924 (1df); p = 0.03
$ chi-square statistic: 20.4781 (16df); p=0.1995

Table 3: The Self-Report Measure with the Largest Significant Sex/Gender Correlation Differential for Each Performance Measure

Item-Pair	Women		Men	
	Item Score Mean (SD)	Correlation (95% CI)	Item Score Mean (SD)	Correlation (95% CI)
Standing balance: unsupported standing with narrow stance (0,1,2)	1.92(0.30)	---	1.68(0.66)	---
Prepare a meal (DASH: 5-0)	1.4(0.8)	0.14 (-0.02, 0.29)	1.5(1.0)	0.83 (0.71, 0.91)
Lean forward: lean forward with an outstretched arm (0,1,2)	1.7(0.5)	---	1.5(0.7)	
Garden or yard work (DASH: 5-0)	2.0(1.2)	0.57 (0.45, 0.67)	2.4(1.5)	0.94 (0.89, 0.97)
Pick-up: pick up an object from the floor (0,1,2)	1.8(0.5)	---	1.6(0.7)	---
Garden or yard work (DASH: 5-0)	2.0(1.2)	0.35 (0.19, 0.49)	2.4(1.5)	0.86 (0.76, 0.92)
Rotate: turn quickly on the spot (0,1,2)	1.7(0.5)	---	1.5(0.7)	---
Garden or yard work (DASH: 5-0)	2.0(1.2)	0.50 (0.36, 0.61)	2.4(1.5)	0.92 (0.86, 0.95)
Tandem stance: standing with one foot in front of the other such that the heel of one foot touches the toes of the other (0,1,2)	1.4(0.7)	---	1.2(0.9)	---
Problems with mobility (EQ5D)	1.3(0.5)	0.74 (0.65, 0.81)	1.5(0.5)	0.94 (0.89, 0.97)
Push-ups: test of muscle endurance (count)	2.9(5.2)	---	6.2(6.8)	---
Garden or do yard work (DASH: 5-0)	2.0(1.2)	0.42 (0.27, 0.55)	2.4(1.5)	0.76 (0.61, 0.86)
Partial curl-ups: test of muscle endurance (count)	10.0(10.7)	---	13.7(12.1)	---
Bathing or dressing yourself (RAND-36: 1,2,3)	2.7(0.5)	0.48 (0.34, 0.59)	2.6(0.6)	0.89 (0.81, 0.94)
Nine-Hole Peg test: manual dexterity (pegs/sec):	0.4(0.0)	---	0.4(0.0)	---
Pull over a sweater (DASH: 5-0)	1.1(0.4)	0.34 (0.18, 0.48)	1.2(0.6)	0.73 (0.56, 0.84)
Grip strength: average grip strength (kg)	61.1(17.0)	---	89.6(26.4)	---
Recreational activities which require little effort e.g. card playing, knitting (DASH: 5-0)	1.2(0.5)	0.29 (0.13, 0.43)	1.3(0.8)	0.64 (0.43, 0.78)

Table 4: Treatable Contributors to Self-reported Physical Function: Strong Correlations (r≥0.8) and 95% Confidence Intervals between Self-Reported and Performance Tests of Physical Function for Women and Men with MS

Self-report	Women	Men
Walking several blocks (RAND-36)		
Standing balance	0.86 (0.81, 0.89)	0.87 (0.78, 0.92)
Tandem stance	0.79 (0.72, 0.84)	0.94 (0.89, 0.97)
Gait speed comfortable/fast	0.67 (0.57, 0.75)/ 0.72 (0.63, 0.79)	0.85 (0.75, 0.91)/ 0.90 (0.83, 0.94)
6-minute walk test	0.74 (0.65, 0.81)	0.88 (0.79, 0.93)
Walking more than a kilometre(RAND-36)		
Standing balance	0.75 (0.67, 0.81)	0.86 (0.76, 0.92)
Tandem stance	0.79 (0.72, 0.84)	0.95 (0.91, 0.97)
Gait speed comfortable/fast	0.56 (0.43, 0.66)/ 0.69 (0.59, 0.76)	0.88 (0.79, 0.93)/ 0.83 (0.71, 0.91)
6-minute walk test	0.64 (0.59, 0.76)	0.86 (0.76, 0.92)
Climb several flights of stairs(RAND-36)		
Tandem stance	0.79 (0.72, 0.84)	0.96 (0.93, 0.98)
Sit-to-stand	0.82 (0.76, 0.86)	0.92 (0.86, 0.95)
Gait speed comfortable/fast	0.67 (0.57, 0.75)/ 0.85 (0.79, 0.89)	0.77 (0.62, 0.86)/ 0.91 (0.84, 0.95)
6-minute walk test	0.70 (0.61, 0.77)	0.88 (0.79, 0.93)
Bathing or dressing yourself (RAND-36)		
Sit-to-stand	0.67 (0.57, 0.75)	0.91 (0.84, 0.95)
Nudge	0.64 (0.59, 0.76)	0.82 (0.69, 0.89)
Lean forward	**0.68 (0.58, 0.76)**	**0.94 (0.89, 0.97)**
Partial curl-ups	**0.48 (0.34, 0.59)**	**0.89 (0.81, 0.94)**
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf (RAND-36)		
Nudge	0.73 (0.64, 0.79)	0.82 (0.69, 0.89)
Lean forward	0.72 (0.63, 0.79)	0.86 (0.76, 0.92)
Rotate	0.76 (0.68, 0.82)	0.82 (0.69, 0.89)
Vigorous activities such as running, lifting heavy objects, participating in strenuous sports (RAND-36)		
Lean forward	0.73 (0.64, 0.79)	0.83 (0.71, 0.91)
6-minute walk test	0.63 (0.52, 0.72)	0.85 (0.75, 0.91)

Problems with mobility (EQ5D)		
Tandem stance	**0.74 (0.65, 0.81)**	**0.94 (0.89, 0.97)**
Gait speed comfortable/fast	0.70 (0.61, 0.77)/ 0.74 (0.65, 0.81)	0.83 (0.71, 0.91)/ 0.93 (0.88, 0.96)
6-minute walk test (distance)	0.69 (0.59, 0.76)	0.94 (0.89, 0.97)
How would you best describe your ability to walk without or with a walking aid? (PBMSI)		
Tandem stance	**0.84 (0.78, 0.88)**	**0.90 (0.83, 0.94)**
Gait speed comfortable/fast	0.81 (0.74, 0.86)/ 0.75 (0.67, 0.81)	0.79 (0.65, 0.87)/ 0.75 (0.59, 0.85)
Standing balance	0.84 (0.78, 0.88)	0.75 (0.59, 0.85)
6-minute walk test (distance)	0.82 (0.76, 0.86)	0.78 (0.64, 0.87)
Prepare a meal (DASH)		
Standing balance	**0.14 (-0.02, 0.29)**	**0.83 (0.71, 0.91)**
Push open a heavy door (DASH)		
Nudge	0.52 (0.38, 0.63)	0.83 (0.71, 0.91)
Lean forward	0.55 (0.42, 0.65)	0.82 (0.69, 0.89)
Push-ups	0.57 (0.45, 0.67)	0.83 (0.71, 0.91)
Place an object on a shelf above your head (DASH)		
Lean forward	0.47 (0.33, 0.59)	0.81 (0.68, 0.89)
Do household chores e.g. washing floors, wash walls (DASH)		
Standing balance	0.55 (0.42, 0.65)	0.90 (0.83, 0.94)
Sit-to-stand	0.49 (0.35, 0.61)	0.95 (0.91, 0.92)
Pick-up	0.43 (0.28, 0.56)	0.82 (0.69, 0.89)
Rotate	0.52 (0.38, 0.63)	0.88 (0.79, 0.93)
Partial curl-ups	0.50 (0.36, 0.61)	0.81 (0.68, 0.89)
Garden or yard work (DASH)		
Standing balance	0.41 (0.26, 0.54)	0.95 (0.91, 0.97)
Sit-to-stand	0.41 (0.26, 0.54)	0.93 (0.88, 0.96)
Lean forward	**0.57 (0.45, 0.67)**	**0.94 (0.89, 0.97)**
Pick-up	**0.35 (0.19, 0.49)**	**0.86 (0.76, 0.92)**
Rotate	**0.50 (0.36, 0.61)**	**0.92 (0.86, 0.95)**
Make a bed (DASH)		
Lean forward	**0.64 (0.59, 0.76)**	**0.83 (0.71, 0.91)**
Pick-up	**0.55 (0.42, 0.65)**	**0.81 (0.68, 0.89)**
Rotate	**0.67 (0.57, 0.75)**	**0.88 (0.79, 0.93)**

Carry heavy object e.g. > 10lbs (DASH)		
Standing balance	**0.81 (0.74, 0.86)**	**0.65 (0.45, 0.78)**
Change a light bulb (DASH)		
Lean forward	0.77 (0.69, 0.83)	0.90 (0.83, 0.94)
Standing with eyes open and head extended	0.72 (0.63, 0.79)	0.83 (0.71, 0.91)
Sit-to-stand	0.74 (0.65, 0.81)	0.80 (0.67, 0.88)
Wash your back (DASH)		
Rotate	**0.51 (0.37, 0.62)**	**0.83 (0.71, 0.91)**
Recreational activities which require little effort (e.g., card playing, knitting, etc.) (DASH)		
Rotate	**0.43 (0.28, 0.55)**	**0.84 (0.73, 0.91)**
Recreational activities in which you take some force or impact through your arm, shoulder or hand e.g., golf, hammering, tennis (DASH)		
Lean forward	0.63 (0.52, 0.72)	0.86 (0.76, 0.92)
Rotate	0.67 (0.57, 0.75)	0.87 (0.78, 0.92)
Recreational activities in which you move your arm freely e.g., playing frisbee, badminton (DASH)		
Rotate	0.73 (0.64, 0.79)	0.81 (0.68, 0.88)
Manage transportation e.g. getting from one place to another (DASH)		
Standing balance	0.58 (0.46, 0.68)	0.81 (0.68, 0.88)
Rotate	**0.68 (0.58, 0.76)**	**0.83 (0.71, 0.91)**
6-minute walk test	0.63 (0.52, 0.72)	0.80 (0.67, 0.88)

significant interaction (p≤0.05) are shown in bold

Figure 1: Number of correlations between performance tests and self-report item pairs, overall, with strong or moderate correlation, and with significant gender interactions

	Balance items (n=9)[$]	Gait speed (n=2)[*]	6MWT	Vertical jump	Push-up	Curl-up	Step test	9HPT	Grip strength
N correlation pairs (N=165 per gender)	75	20	11	9	11	6	5	12	16
N strong correlation Women/Men ($r \Rightarrow 0.8$; n=13/64)	10/45	2/9	1/6	0	0/1	0/3	0/0	0/0	0/0
N moderate correlation Women/Men ($r = \geq 0.5 \leq 0.79$; n=109/94)	52/27	18/11	9/5	9/9	7/13	2/4	0/5	7/10	5/9
N significant gender interactions (n=31)	18	0	0	4	2	2	0	2	3
N gender interactions with correlation men > women (n=27)	16	0	0	2	2	2	0	2	3

[*]Includes comfortable and fast gait speed
[$] 9 balance items from EQUI scale

Supplementary Table1: Correlation between indicators of balance performancefrom the EQUI scale (scored 0-2, higher is better) and tests of physical performance with related self-report physical function among Women and Men with MS. Highlighted ones are not significant

Self-report	Women		Men	
	Item Score Mean (SD)	Correlation	Item Score Mean (SD)	Correlation
Standing balance: unsupported standing with narrow stance	1.92 (0.30)	---	1.68(0.66)	---
Walking several blocks (RAND-36)	2.3(0.7)	0.86	2.1(0.8)	0.87
Walking one block (RAND-36)	2.6(0.6)	0.84	2.3(0.8)	0.81
Walking more than a kilometre (RAND-36)	2.1(1.2)	0.75	1.9(0.8)	0.86
Climb one flight of stairs (RAND-36)	**2.6(0.6)**	**0.95**	**2.5(0.7)**	**0.59**
Lifting or carrying groceries (RAND-36)	2.2(1.2)	0.75	2.4(0.7)	0.74
How would you best describe your ability to walk without or with a walking aid (PBMSI)	1.2(0.4)	0.84	1.4(0.7)	0.75
Problems with mobility (EQ5D)	1.3(0.5)	0.80	1.5(0.5)	Did not converge
Prepare a meal (DASH)	**1.4(0.8)**	**0.14**	**1.5(1.0)**	**0.83**
Carry a shopping bag or briefcase (DASH)	**1.5(1.0)**	**0.75**	**1.7(1.1)**	**0.65**
Carry heavy object e.g. > 10lbs (DASH)	**2.0(1.2)**	**0.81**	**1.8(1.2)**	**0.65**
Manage transportation e.g. getting from one place to another (DASH)	1.5(0.9)	0.58	2.0(1.2)	0.81
Do household chores e.g. washing floors, wash walls (DASH)	2.2(1.3)	0.55	2.3(1.3)	0.90
Garden or yard work (DASH)	2.0(1.2)	0.41	2.4(1.5)	0.95
Wash or blow your hair (DASH)	1.4(0.8)	0.33	1.2(0.6)	0.59
Sit-to-stand: standing from a chair without support	1.2(0.2)	---	1.7(0.57)	---
Bending kneeling or stooping (RAND-36)	2.4(1.1)	0.74	2.3(0.7)	0.68
Bathing or dressing yourself (RAND-36)	2.7(0.5)	0.67	2.6(0.6)	0.91
Climb one flight of stairs (RAND-36)	2.6(0.6)	0.90	2.4(0.7)	0.80
Climb several flights of stairs (RAND-36)	2.1(0.8)	0.82	2.06(0.8)	0.92
Recreational activities which require little effort for e.g., card playing, knitting (DASH)	**1.2(0.5)**	**0.23**	**1.3(0.8)**	**0.75**
Manage transportation e.g. getting from one place to another (DASH)	1.5(0.9)	0.61	2.0(1.2)	0.78
Do household chores e.g. washing floors, wash walls (DASH)	2.2(1.3)	0.49	2.31(1.37)	0.95
Garden or yard work (DASH)	2.0(1.2)	0.41	2.4(1.5)	0.93
Change a light bulb overhead (DASH)	1.8(1.3)	0.74	1.9(1.3)	0.80
Nudge:	1.7(0.6)	---	1.5(0.8)	---
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing	2.3(1.2)	0.73	2.2(0.8)	0.82

golf (RAND-36)				
Vigorous activities such as running, lifting heavy objects, participating in strenuous sports (RAND-36)	1.6(1.2)	0.73	1.6(0.8)	Did not converge
Bathing or dressing yourself (RAND-36)	2.7(0.5)	0.64	2.6(0.6)	0.82
Lifting or carrying groceries (RAND-36)	2.2(1.2)	0.69	2.4(0.7)	0.69
Push open a heavy door (DASH)	1.6(0.8)	0.52	1.4(0.9)	0.83
Lean forward: lean forward with an outstretched arm	1.7(0.5)	---	1.5(0.7)	
Bending kneeling or stooping (RAND-36)	2.4(1.1)	0.69	2.3(0.7)	0.79
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf (RAND-36)	2.3(1.2)	0.72	2.2(0.8)	0.86
Vigorous activities such as running, lifting heavy objects, participating in strenuous sports (RAND-36)	1.6(1.2)	0.73	1.6(0.8)	0.83
Bathing or dressing yourself (RAND-36)	**2.7(0.5)**	**0.68**	**2.6(0.6)**	**0.94**
Push open a heavy door (DASH)	1.6(0.8)	0.55	1.4(0.9)	0.82
Place an object on a shelf above your head (DASH)	1.5(0.9)	0.47	1.5(0.9)	0.81
Garden or yard work (DASH)	**2.0(1.2)**	**0.57**	**2.4(1.5)**	**0.94**
Make a bed (DASH)	**1.3(0.7)**	**0.64**	**1.6(1.1)**	**0.83**
Change a lightbulb overhead (DASH)	1.8(1.3)	0.77	1.9(1.3)	0.90
Recreational activities in which you take some force or impact through your arm, shoulder or hand e.g., golf, hammering, tennis (DASH)	1.9(1.2)	0.63	2.3(1.5)	0.86
Pick-up: pick up an object from the floor	1.8(0.5)	---	1.6(0.7)	---
Lifting or carrying groceries (RAND-36)	2.2(1.2)	0.61	2.4(0.7)	0.59
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf (RAND-36)	2.3(1.2)	0.62	2.2(0.8)	0.56
Vigorous activities such as running, lifting heavy objects, participating in strenuous sports (RAND-36)	1.6(1.2)	0.50	1.6(0.8)	0.55
Bathing or dressing yourself (RAND-36)	2.7(0.5)	0.63	2.6(0.6)	0.77
Make a bed (DASH)	**1.3(0.7)**	**0.55**	**1.6(1.1)**	**0.81**
Carry a shopping bag or briefcase (DASH)	1.5(1.0)	0.63	1.7(1.1)	0.62
Carry heavy object e.g. > 10lbs (DASH)	2.0(1.2)	0.63	1.8(1.2)	0.61
Do heavy household chores e.g. wash walls or floors (DASH)	2.2(1.3)	0.43	2.3(1.3)	0.82
Garden or yard work (DASH)	**2.0(1.2)**	**0.35**	**2.4(1.5)**	**0.86**
Recreational activities in which you move your arm freely e.g., playing frisbee, badminton (DASH)	2.0(1.3)	0.63	2.4(1.5)	0.60

Stand with eyes closed: stand with feet together, eyes closed for more than 20 seconds	1.6(0.6)	---	1.5(0.7)	---
Wash your back (DASH)	**1.4(0.8)**	**0.47**	**1.6(1.1)**	**0.68**
Put on a pullover sweater (DASH)	1.1(0.4)	0.29	1.2(0.6)	0.62
Rotate: turn quickly on the spot	1.7(0.5)	---	1.5(0.7)	---
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf (RAND-36)	2.3(1.2)	0.76	2.2(0.8)	0.82
Vigorous activities such as running, lifting heavy objects, participating in strenuous sports (RAND-36)	1.6(1.2)	0.70	1.6(0.8)	Did not converge
Bathing or dressing yourself (RAND-36)	2.7(0.5)	0.74	2.6(0.6)	0.89
Do heavy household chores e.g. wash walls or floors (DASH)	2.2(1.3)	0.52	2.3(1.3)	0.88
Make a bed (DASH)	**1.3(0.7)**	**0.67**	**1.6(1.1)**	**0.88**
Garden or yard work (DASH)	**2.0(1.2)**	**0.50**	**2.4(1.5)**	**0.92**
Wash your back (DASH)	**1.4(0.8)**	**0.51**	**1.6(1.1)**	**0.83**
Recreational activities in which you take some force or impact through your arm, shoulder or hand e.g., golf, hammering, tennis (DASH)	1.9(1.2)	0.67	2.3(1.5	0.87
Recreational activities in which you move your arm freely e.g., playing frisbee, badminton (DASH)	2.0(1.3)	0.73	2.4(1.5)	0.81
Manage transportation e.g. getting from one place to another (DASH)	**1.5(0.9)**	**0.68**	**2.0(1.2)**	**0.83**
Stand with eyes closed and head extended: stand with eyes closed, feet together and head extended for 5 sec	1.4(0.8)	---	13.3(0.9)	---
Change a light bulb overhead (DASH)	1.8(1.3)	0.72	1.9(1.3)	0.83
Place an object on a shelf above your head (DASH)	1.5(0.9)	0.71	1.5(0.9)	0.73
Push open a heavy door (DASH)	1.6(0.8)	0.57	1.4(0.9)	0.68
Put on a pullover sweater (DASH)	1.1(0.4)	0.36	1.2(0.6)	0.60
Wash your back (DASH)	1.4(0.8)	0.48	1.6(1.1)	0.64
Tandem stance: standing with one foot in front of the other such that the heel of one foot touches the toes of the other	1.4(0.7)	---	1.2(0.9)	---
Walking one block (RAND-36)	2.6(0.6)	0.88	2.3(0.8)	0.90
Walking several blocks (RAND-36)	2.3(0.7)	0.79	2.1(0.8)	0.94
Climb several flights of stairs (RAND-36)	2.1(0.8)	0.79	2.06(0.8)	0.96
Walking more than a kilometre (RAND-36)	2.1(1.2)	0.79	1.9(0.8)	0.95
Climb one flight of stairs (RAND-36)	2.6(0.6)	0.78	2.4(0.7)	0.86
How would you best describe your ability to walk without or with a walking aid (PBMSI)	**1.2(0.4)**	**0.84**	**1.4(0.7)**	**0.90**

Problems with mobility (EQ5D)	**1.3(0.5)**	**0.74**	**1.5(0.5)**	**0.94**
Do heavy household chores e.g. wash walls or floors (DASH)	2.2(1.3)	0.64	2.3(1.3)	0.72
Recreational activities in which you take some force or impact through your arm, shoulder or hand e.g., golf, hammering, tennis (DASH)	**1.9(1.2)**	**0.71**	**2.3(1.5)**	**0.77**
Recreational activities in which you move your arm freely e.g., playing frisbee, badminton (DASH)	2.0(1.3)	0.72	2.4(1.5)	0.69
Tests of Physical Performance				
Gait speed comfortable/fast: functional gait speed	1.1(0.3)/ 1.5(0.5)	---	1.1(0.4)/ 1.6(0.7)	---
Walking one block (RAND-36)	2.6(0.6)	0.72/0.77	2.3(0.8)	0.80/0.87
Walking several blocks (RAND-36)	2.3(0.7)	0.67/0.72	2.1(0.8)	0.85/0.90
Walking more than a kilometre (RAND-36)	2.1(1.2)	0.56/0.69	1.9(0.8)	0.88/0.83
Climb several flights of stairs (RAND-36)	2.1(0.8)	0.67/0.85	2.0(0.8)	0.77/0.91
Lifting or carrying groceries (RAND-36)	2.3(1.2)	0.57/0.66	2.4(0.7)	0.72 /0.79
How would you best describe your ability to walk with or without a walking aid (PBMSI)	1.2(0.4)	0.75/0.81	1.4(0.7)	0.75/0.79
Problems with mobility (EQ5D)	1.3(0.5)	0.70/0.74	1.5(0.5)	0.83/0.93
Carry a shopping bag or briefcase (DASH)	1.5(1.0)	0.60/0.67	1.7(1.1)	0.67/0.74
Recreational activities in which you take some force or impact through your arm, shoulder or hand e.g., golf, hammering, tennis (DASH)	1.9(1.2)	0.56/0.66	2.3(1.5)	0.72/0.79
Recreational activities in which you move your arm freely e.g., playing frisbee, badminton (DASH)	2.0(1.3)	0.59/0.68	2.4(1.5)	0.69/0.74
6-minute walk test (distance): test of submaximal exercise capacity	462.1(148.3)	---	433.5(225.2)	---
Walking several blocks (RAND-36)	2.3(0.7)	0.74	2.1(0.8)	0.88
Climb several flights of stairs (RAND-36)	2.1(0.8)	0.70	2.0(0.8)	0.88
Walking more than a kilometre (RAND-36)	2.1(1.2)	0.64	1.9(0.8)	0.86
Vigorous activities such as running, lifting heavy objects, participating in strenuous sports (RAND-36)	1.6(1.2)	0.63	1.6(0.8)	0.85
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf (RAND-36)	2.3(1.2)	0.68	2.2(0.8)	0.77
Problems with mobility (EQ5D)	1.3(0.5)	0.69	1.5(0.5)	0.91
How would you best describe your ability to walk without or with a walking aid (PBMSI)	1.2(0.4)	0.82	1.4(0.7)	0.78
Recreational activities which require little effort e.g. card playing, knitting (DASH)	1.2(0.5)	0.43	1.3(0.8)	0.72
Recreational activities in which you take some force or impact through your arm, shoulder or hand e.g., golf, hammering, tennis (DASH)	1.9(1.2)	0.64	2.3(1.5)	0.79

Recreational activities in which you move your arm freely e.g., playing frisbee, badminton (DASH)	2.0(1.3)	0.67	2.4(1.5)	0.74
Manage transportation e.g. getting from one place to another (DASH)	1.5(0.9)	0.63	2.0(1.2)	0.80
Vertical jump test: test of lower extremity power	17.0(9.5)	---	23.1(18.0)	---
Bending, kneeling, or stooping (RAND-36)	2.4(1.1)	0.61	2.3(0.78)	0.59
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf (RAND-36)	2.3(1.2)	0.68	2.2(0.8)	0.72
Vigorous activities such as running, lifting heavy objects, participating in strenuous sports (RAND-36)	1.6(1.2)	0.58	1.6(0.8)	0.66
Do heavy household chores e.g. wash walls, wash floors (DASH)	2.2(1.3)	0.55	2.3(1.37)	0.70
Place an object on a shelf above your head (DASH)	**1.5(0.9)**	**0.60**	**1.5(0.9)**	**0.72**
Change a light bulb overhead (DASH)	**1.8(1.3)**	**0.68**	**1.9(1.3)**	**0.71**
Garden or do yard work (DASH)	2.0(1.2)	0.54	2.4(1.5)	0.71
Recreational activities in which you take some force or impact through your arm, shoulder or hand e.g., golf, hammering, tennis (DASH)	**1.9(1.2)**	**0.65**	**2.3(1.5)**	**0.60**
Recreational activities in which you move your arm freely e.g., playing frisbee, badminton (DASH)	**2.0(1.3)**	**0.67**	**2.4(1.5)**	**0.52**
Push-ups: test of muscle endurance	2.9(5.2)	---	6.2(6.8)	---
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf (RAND-36)	2.3(1.2)	0.48	2.2(0.8)	0.71
Lifting or carrying groceries (RAND-36)	2.3(1.2)	0.42	2.4(0.7)	0.69
Bending, kneeling, or stooping (RAND-36)	2.4(1.1)	0.47	2.3(0.78)	0.69
Push open heavy door (DASH)	1.6(0.8)	0.57	1.4(0.9)	0.83
Make a bed (DASH)	**1.3(0.7)**	**0.54**	**1.6(1.1)**	**0.76**
Place an object on a shelf above your head (DASH)	1.5(0.9)	0.43	1.5(0.9)	0.70
Carry a shopping bag or brief case (DASH)	1.5(1.0)	0.53	1.7(1.1)	0.62
Carry heavy object e.g. > 10lbs (DASH)	2.0(1.2)	0.50	1.8(1.2)	0.62
Do heavy household chores e.g. wash walls or floors(DASH)	2.2(1.3)	0.51	2.3(1.3)	0.73
Recreational activities in which you take some force through your arm, shoulder or hand e.g. golf, hammering, tennis (DASH)	1.9(1.2)	0.49	2.3(1.5)	0.55
Garden or do yard work (DASH)	**2.0(1.2)**	**0.42**	**2.4(1.5)**	**0.76**
Partial curl-ups: test of muscle endurance	10.0(10.7)	---	13.7(12.1)	---

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf (RAND-36)	**2.3(1.2)**	**0.44**	**2.2(0.8)**	**0.83**
Vigorous activities such as running, lifting heavy objects, participating in strenuous sports (RAND-36)	1.6(1.2)	0.45	1.6(0.8)	0.67
Bending, kneeling, or stooping (RAND-36)	2.4(1.1)	0.45	2.3(0.78)	0.74
Bathing or dressing yourself (RAND-36)	**2.7(0.5)**	**0.48**	**2.6(0.6)**	**0.89**
Recreational activities in which you move your arm freely e.g., playing frisbee, badminton (DASH)	2.0(1.3)	0.50	2.4(1.5)	0.68
Do heavy household chores e.g. wash walls or floors(DASH)	2.2(1.3)	0.50	2.3(1.3)	0.81
Modified Canadian Aerobic Fitness Test: oxygen cost/litres/min for each stage of step test	1.39(0.21)	---	1.91(0.26)	---
Walking several blocks (RAND-36)	2.3(0.7)	0.31	2.1(0.8)	0.69
Climbing several flights of stairs (RAND-36)	2.1(0.8)	0.42	2.0(0.8)	0.76
Walking more than a kilometre (RAND-36)	2.1(1.2)	0.31	1.9(0.8)	0.60
Vigorous activities such as running, lifting heavy objects, participating in strenuous sports (RAND-36)	1.6(1.2)	0.30	1.6(0.8)	0.57
Problems with mobility (EQ5D)	1.3(0.5)	0.35	1.5(0.5)	0.58
Nine-Hole Peg test (pegs/sec): manual dexterity	0.4(0.0)	---	0.4(0.0)	---
Bathing or dressing yourself (RAND-36)	2.7(0.5)	0.57	2.6(0.6)	0.77
Open a tight or new jar (DASH)	2.0(1.1)	0.51	1.5(1.0)	0.76
Place an object on a shelf above your head (DASH)	1.5(0.9)	0.51	1.5(0.9)	0.74
Change a light bulb overhead (DASH)	1.8(1.3)	0.62	1.9(1.3)	0.74
Pull over a sweater (DASH)	**1.1(0.4)**	**0.34**	**1.2(0.6)**	**0.73**
Use a knife to cut food (DASH)	1.2(0.5)	0.63	1.4(0.8)	0.68
Wash your back (DASH)	**1.4(0.8)**	**0.40**	**1.6(1.1)**	**0.66**
Wash or blow your hair (DASH)	1.4(0.8)	0.46	1.2(0.6)	0.63
Prepare a meal (DASH)	1.4(0.8)	0.48	1.5(1.0)	0.62
Recreational activities which require little effort e.g. card playing, knitting (DASH)	1.2(0.5)	0.54	1.3(0.8)	0.53
Write (DASH)	1.5(0.8)	0.68	1.5(1.0)	0.47
Turn a key (DASH)	1.1(0.5)	0.43	1.2(0.6)	0.47
Grip strength: average grip strength	61.1(17.0)	---	89.6(26.4)	---
Bathing or dressing yourself (RAND-36)	**2.75(0.5)**	**0.32**	**2.6(0.6)**	**0.63**
Lifting or carrying groceries (RAND-36)	2.3(1.2)	0.49	2.4(0.7)	0.56
Carry heavy object e.g. > 10lbs (DASH)	2.0(1.2)	0.53	1.8(1.2)	0.42
Carry a shopping bag or briefcase (DASH)	1.5(1.0)	0.41	1.7(1.1)	0.38
Recreational activities which require little effort e.g. card playing, knitting (DASH)	**1.2(0.5)**	**0.29**	**1.3(0.8)**	**0.64**

Make a bed (DASH)	1.3(0.7)	0.30	1.6(1.1)	0.50
Open a tight or new jar (DASH)	2.1(1.1)	0.53	1.5(1.0)	0.55
Place an object on a shelf above your head (DASH)	1.5(0.9)	0.39	1.5(0.9)	0.47
Change a light bulb overhead (DASH)	1.8(1.3)	0.49	1.9(1.3)	0.48
Pull over a sweater (DASH)	1.1(0.4)	0.42	1.3(0.6)	0.29
Use a knife to cut food (DASH)	1.2(0.5)	0.32	1.4(0.8)	0.40
Wash your back (DASH)	1.4(0.8)	0.41	1.6(1.1)	0.51
Write (DASH)	1.5(0.8)	0.54	1.5(1.0)	0.58
Turn a key (DASH)	1.1(0.5)	0.54	1.2(0.6)	0.63
Prepare a meal (DASH)	**1.4(0.8)**	**0.41**	**1.5(1.0)**	**0.60**
Push open a heavy door (DASH)	1.6(0.8)	0.58	1.4(0.9)	0.47

significant interaction ($p \leq 0.05$) are shown in bold

CHAPTER 5: INTEGRATION OF MANUSCRIPT 1 AND 2

The first manuscript established a relationship between some SROs and PerfOs among people with MS. One of the findings applicable to walking was the correlation between the items: walking a kilometer (SRO) and 6MWT test. The correlation coefficient was 0.64 for women and 0.86 for men. The second manuscript links 6MWT to information on actual walking performance during everyday activities as captured using an accelerometer (TechO).

The next chapter presents the second manuscript is titled, "Ecological Validity of Clinically Assessed Walking Capacity is People with MS". The global aim of this manuscript is to contribute evidence towards the ecological validity of clinically assessed walking capacity in people with MS. Specifically, the objective of this study is to estimate for people with MS the extent to which walking capacity tested in laboratory, using 6MWT, is reproduced during 7 days of free-living step monitoring using an accelerometer. This manuscript is submitted to the Journal of Clinical Epidemiology.

CHAPTER 6: MANUSCRIPT 2

Ecological Validity of Clinically Assessed Walking Capacity among People with Multiple Sclerosis

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Abstract

Objective: Ecological validity is an important psychometric property while assessing function. In people with Multiple Sclerosis (MS) how a person performs in clinical settings and natural environment can be quite different. In people with MS walking is the most frequently assessed and also recommended way to maintain health in view of a progressive disease. To estimate among people with MS the extent to which walking capacity tested in laboratory, using six minute walk test (6MWT), is reproduced during 7 days of monitoring using an accelerometer.

Study design: This is a cross sectional analysis of baseline data from a randomized controlled trial that consisted of 98 women and 27 men with MS.

Results: A total of 869 patient-days of accelerometer data were available with an average of 7 days of recording. The total number steps taken per day was greater, on average, for people with higher walking capacity (6MWT >600 meters). There was no trend for increasing rate of walking bouts of ≥5 minutes across categories of the 6MWT but higher rates were associated with better mood and fewer exercise barrier.

Conclusion: For people with MS walking capacity was more related to step count than to duration of walking bouts.

Keywords: walking capacity, walking performance, ecological validity, walking bouts, six minute walk test, Zero-inflated Poisson model

What is new?

- Assessment of patient's walking performance in real-life is a important clinical outcome
- Supplement clinical tests of walking capacity (6MWT) with a performance outcome on walking
- Important to recommend increase duration of walking and address issues related to mood and exercise barriers

Introduction

Ecological validity is defined as the degree to which results on a test obtained under controlled experimental conditions are related to those obtained in real world environments (1, 2). In the context of Multiple Sclerosis (MS), how a person functions when tested clinically and when they are in their natural environment can be quite different. This difference can affect how the result of a particular functional test is interpreted, important not only for clinical care but also in context of clinical trials where functional outcomes provide evidentiary support for new interventions (3). As clinical and experimental interventions are not targeted to improve a test but to improve the person in their environment, the degree to which the test results are reproduced in a natural environment is an important psychometric property. Ecological validity is rarely assessed primarily because it is very difficult to obtain accurate information on the person's function in their everyday environment. Today, new technology such as triaxial accelerometers makes the assessment of real world function easier particularly for mobility constructs (4, 5). In MS, mobility, particularly walking is the most frequently conducted clinical assessment as it forms the basis for the Expanded Disability Status Scale (EDSS) rating and most trials of MS interventions use a walking test, most often the 25foot Walk Test (25FWT) (3). Sampling only a few seconds out of an infinite time span will introduce misclassification such that some low functioning people may perform higher from time to time in their real environment and some others may make their best effort clinically and be unable to reproduce this outside. It maybe that, over time, the test improved, but the patient did not.

Capacity is what the person can do and performance is the ability to use that capacity to achieve goals such as walking for activities of daily living, work, recreation, and health promotion. Performance implies a sustained activity and physical activity guidelines recommends 150 minutes per week of moderate to vigorous intensity of physical activity which translates to minimum walking bouts of 10 minutes. Walking capacity is key to being able to engage in health promoting activities as walking is one of the recommended forms of physical activity even for people with disabilities (6). Physical activity has been shown in several meta-analyses as effective for improving many health outcomes for people with MS (7-13).

Several studies have related walking tests with habitual everyday walking with the aim of identifying whether these performance outcomes (PerfOs) could be used to identify those likely to be physically active. Stellmann et.al. probed whether the results of the 2 and 6minute walk tests (2MWT, 6MWT) conducted clinically was reproduced by 2 or 6 minutes of uninterrupted walking during 7 days of monitoring with accelerometer(14). Among 30 people with MS, EDSS< 7, an average of 2.61 bouts of 2 minutes and 0.35 bouts of 6 minutes per day were observed per person over 210 person-days of monitoring (14). Gijbelset. al. estimated the extent to which leg muscle strength, walking balance, EDSS and self-report physical function were able to predict habitual walking performance (HWP) recorded using an activity monitor for 7 consecutive days (15). Walking capacity was measured using Timed Up and Go (TUG), T25FW, 2 and 6 MWT. People with MS were grouped as mild MS (EDSS 1.5-4.0) and moderate MS (EDSS 4.5-6.5). HWP was indicated by stride count. The correlations between 2 and 6MWT and HWP were low (0.35, 0.43 respectively) for people with mild MS and moderate (0.73, 0.73 respectively) for people with moderate MS. Univariate regression analysis showed that only 6MWT predicted for HWP (R^2=0.187) among people with mild MS whereas 2MWT, 6MWT and 25FW predicted HWP among moderate MS (R^2=0.532, 0.527 and 0.387 respectively). In a sample of 256 ambulatory people with MS, Motl and colleagues correlated EDSS, Patient Determined Disease Steps (PDDS), Multiple Sclerosis Walking Scale (MSWS-12), T25FW, and oxygen consumption on six-minute walk test with step counts measured over seven days of accelerometer data (16). Moderately strong correlations were observed between these clinical outcomes with the accelerometer data: EDSS (-0.52), PDDS (-0.55), MSWS-12 (-0.62) scores, T25FW (0.59) and oxygen consumption (0.63) (16).

Several other studies associated self-report and performance tests with accelerometer data among people with MS. It is common to report the accelerometer output as mean step count, a metric that does not adequately represent walking performance during the day (14, 16-18). In a typical day people may engage in low intensity walking behavior for activities of daily living as well as higher intensity walking for exercise, continuously, or interspaced with the rest periods. Walking intensity is typically reported as cadence (steps per unit time). The relationship between cadence and effort is expressed as metabolic equivalents (METs). For example, cadence of 100 steps minute is equivalent to 3 METs, which is classified as moderate intensity effort and is the pace recommended to meet Canadian Physical Activity Guidelines (19). In addition, there are other factors that act as barriers or facilitators to translating walking capacity to walking performance, such as mood, motivation, fatigue and the environment (20-22).

Knowing the difference between capacity and performance can indicate targets for therapy, particularly rehabilitation therapies. The assumption that clinical capacity is sufficient to indicate walking performance may not hold; clinically assessed walking capacity may lack ecological validity. The global aim of the study is to contribute evidence towards the ecological validity of clinically assessed walking capacity in people with MS. Specifically, the objective of this study is to estimate for people with MS the extent to which walking capacity tested in laboratory, using 6MWT, is reproduced during 7 days of free-living step monitoring using an accelerometer and how this relationship is affected by age, gender, motivation, mental health, exercise enjoyment and barriers to participation.

Methods

Study design

The data for this study came from the first assessment of people with MS recruited for a trial on 'Role of Exercise in Modifying Outcomes for People with Multiple Sclerosis' (23). 98 women and 27 men diagnosed with *new* MS (post-1995) were assessed at baseline on 6-minute walk test (6MWT) and were subsequently fitted with an accelerometer on the right thigh to be worn for 7 consecutive days. Ethical approval was obtained from Ethics Review Board of McGill University Health Center Research Institute at Montreal Neurological Institute.

Study population

Participants for the trial were recruited from two university hospital MS clinics. To be included, people had to be diagnosed with MS after 1994, aged between 19 to 65 years and be independent in ambulation without use of walking aid (PDDS stage: Early Cane). Participants were excluded if they: (1) were already exercising three or more time per week; (ii) had any additional illness that restricted their function; (iv) had experienced a relapse during the past 30 days; and (iv) showed difficulty reading, understand or speaking either French or English. Only people diagnosed after 1994 were included so as to have more homogeneous group of participants with respect to diagnostic criteria and access to disease modifying therapies (4, 24, 25).

Measures

The full measurement strategy is given in the published protocol (23). Walking capacity was measured using an MS specific standardized protocol for 6MWT (26) which asks the person to walk as fast as possible to measure fatigability (ratio of last to first minute distance). The person is allowed to rest if needed but timing continues.

Free-living physical activity was measured using accelerometer (activPAL)^{3TM}. The activPAL employed in this study is a 53×37×7mm in size, weighs 15gms at a sampling frequency of 20Hz (one reading of acceleration every 1/20th of a second). Accelerometer outputs include time spent standing, and time spent talking steps expressed as time spent in different cadence bands (10-20, 20-30...90-100 etc.). Accelerometers have been shown to have excellent psychometric properties in people with MS and are considered a feasible and acceptable tool to measure physical activity in this population (4, 5, 27).

According to a behavioral model, an activity like walking for health promotion requires Capacity, Opportunity (time and safe space to practice) and Motivation (COM-B) (20-22). In the context of this paper, capacity is 6MWT, opportunity is barrier to walking and motivation is self-efficacy, exercise enjoyment, vitality and mood. For this study, baseline information on age, sex, and disability status was relevant as was information related to factors affecting free-living walking performance including mood, motivation, exercise barriers and benefits, self-efficacy, exercise enjoyment, and mental health. Exercise self-efficacy has shown to be a valid measure with test-retest reliability of >0.85 (28). Scores on the Exercise Benefits and Barriers Scale have been shown to be an independent predictor of exercise engagement (7). Exercise barriers and self-efficacy were used in the model as total scores, exercise enjoyment was used as a single item question measured on a continuous scale from 0 to 10. Information on vitality and mood was obtained from the Vitality and Mental Health Index (MHI) (high score is better) subscales from Research ANd Development (RAND-36).

<u>Statistical Methods</u>

To relate the distance covered during 6MWT to community-based walking performance which is measured by cadence and time spent walking, 5 different distance categories were created (<300m, 300-400m, 400-500m, 500-600m, >600m) and average cadence was estimated within these categories. The cadence from the accelerometer was grouped into cadence bands based on meaningful categories from the literature (1-19--incidental movement, 20-39--sporadic movement, 40-59--purposeful movement, 60-79--slow walking, 80-99--medium walking, 100-119--brisk walking, >120--fast walking) (29, 30). Both linear and quantile (median; 0.5) regression models were tested on the following walking outcomes: mean number of steps (per person per day), mean number of these steps at ≥brisk (≥100 steps), and cumulative time per week spent walking at ≥brisk. An assumption of the linear regression model, multivariate normality (normality access levels of the explanatory variable, here the categories of the 6MWT used to infer cadence), did not hold and therefore the quantile regression model was also used.

Contiguous steps from accelerometer data were grouped into bouts of < and ≥5 minutes. Appendix A shows the distribution of the step count from accelerometer for 125 participants with valid accelerometer data. Counts of the number of walking bouts of ≥5 minutes (per person-days of measurement) have a Poisson distribution and, as there was a preponderance of zeros, a Zero-inflated Poisson (ZIP) model was used. All models were tested univariately (only categories of 6MWT) and multivariately with adjustment for age, sex, and variables related to COM-B (vitality, mental health, exercise barriers, self-efficacy, and exercise enjoyment). Also, all the models were tested for the linear effect of 6MWT categories.

Results

Table 1 displays the demographic characteristics of the study population. The sample was comprised of adults with mean age of 45.4 years (SD: 10), predominantly women (78%) and with a diagnosis of the relapsing-remitting type of MS (67%). Table 1 also gives the means and SDs of the study variables. For the RAND-36 subscales normative values from the Canadian population are also given. The values for the Physical Function Index, Mental Health Index, and Vitality subscales of the RAND-36 were 72.5, 67.5 and 48.9, respectively, compared to norms of 88, 77 and 66 respectively.

Table 2 presents the distribution of daily steps, cadence, and proportion of time spent walking at different intensities, according to the level of the 6MWT assessed clinically. A total of 869 patient-days of accelerometer data were available with an average of 7 recording days, 12 hours per day. The value on the 6MWT was converted to cadence to be comparable with accelerometer data which is based on cadence. People with the smallest6MWT distance (<300 meters) walked an average of 4130 (SD:906) steps per day. Approximately 10% of steps were classified as incidental (<39 steps per minute); 18% of steps were classified as purposeful (40-59 steps per minute), 30% of steps were at slow walking (60-79 steps per minute) and medium walking (80-99 steps per minute) and only 11% of steps were at brisk walking and above (>100 steps per minute). In the community, 30% of the steps were at the same cadence band (shaded box) as the 6MWT value (concordant cadence band) and 42% of the steps were at a higher cadence. For the people in the other 6MWT groups, as the laboratory measured cadence increased the proportion of steps at or exceeding this band decreased. For people in 6MWT groups with 300->400 meters, 400->500 meters, 500->660 meters and ≥600 meters, the percent of steps at the concordant band were 32.8%, 29.3%, 12.2% and 20.5%, respectively. The proportion of steps greater than clinically measured cadence was 42.6%, 27.4%, 7.9%, 0% and 0%. Also shown in Table 2 is that the distribution of the duration of walking bouts did not differ by walking capacity.

The average duration of vertical time (standing and stepping time) per day increased across the groups who walked <300 to group >600 meters, there was no difference in the proportion of time allocated to longer bouts of walking. Figure 1 displays the data in Table 2 as a stacked bar graph showing the proportion of steps at different cadence bands contributing towards the recommended total of 10,000 steps for healthy people. On the x-axis are the five groups of distances walked during 6MWT and the y-axis is number steps.

Table 3 shows the results of linear, quantile and ZIP regression analysis, both unadjusted and adjusted models, comparing walking outcomes of mean number of steps, number of steps at ≥brisk, cumulated time per week at ≥brisk, and number of 5 minute bouts across the five categories of walking cadence, derived from the 6MWT. The first row, repeated from Table 2, gives the category specific means for daily steps followed by the results of linear regression, unadjusted and adjusted. The regression parameters indicate by how much people in each categories of cadence differed from the highest cadence group. For example, people who walked <300 m (cadence ~70 steps/min), had an average number of steps per day of 4130 (SD: 906). The estimated difference from the highest cadence group (≥600 m) was -3315steps (se: 1363), unadjusted, and -3417 steps (se:1489) adjusted. People in any category of <500 m showed statistically lower daily step counts than the highest value, unadjusted and adjusted.

The distribution of daily step counts was not normally distributed consistently across categories of 6MWT cadence values necessitating an alternate model, quantile regression at the median. The median values are presented. The regression parameters are interpreted as the estimated difference from the median of the highest group. 95% CI that excluded the null value of 0 indicate statistical significance. The unadjusted quantile models show similar results to the linear models but for the adjusted quintile model, only the lowest 6MWT cadence (<300 m.) was significantly different from the highest level of walking capacity.

The mean and median values for the outcome number of steps at ≥brisk cadence (≥100 steps) for people who walked a distance of <300 m on 6MWT was 463 (SD: 490) and 328, respectively. The unadjusted and adjusted linear regression estimate difference, compared to 6MWT category of ≥600 m, on number of steps at ≥brisk cadence was -3347 (se: 847) and -3323 (se: 956) respectively. These estimates for quantile regression were -3044, and -3009 respectively. Both the models yielded similar results: only people in the 6MWT category of <500 m were not significantly different from the people in referent category in both the adjusted linear and quantile models.

For the outcome of cumulated time at ≥brisk cadence, the means across categories of 6MWT ranged from 17.4 to 34.2 minutes; the medians ranged from 17.4 to 27.6 minutes. For the linear regression model, the unadjusted and adjusted estimates of the difference for 6MWT category of <300 m compared with the highest category (6MWT of >600) was 18 (se: 18). The unadjusted linear models were statistically significant for two categories, 6MWT 300-<400 and 400 to <500m; whereas the unadjusted quantile regression model was significant for those two categories and also for people who walked 500 to <600 m. None of the adjusted linear and quantile models were significant for this outcome.

The linear test for trend across categories of the 6MWT revealed significant trends (<p=0.005) for increasing step counts across increasing levels of cadence as inferred from these categories. There was no effect of any of the adjustment variables on these of step counts. Data presented in Supplementary Table 1.

The total number of bouts of ≥5 minutes over 7 days ranged from 209 for all the persons in the lowest 6MWT category to 1030 for all those in the highest category. Per person, the median values across the 6MWT categories were 36, 41, 48, 66, and 71, respectively; the overall mean (median) per person was 57 (56.5). The rates per 1000 waking hours were 10.36 for the lowers 6MWT category and 11.44 for the highest. The unadjusted and adjusted RRs for the lowest three categories were similar to each other and statistically lower than the highest category. There was no significant trend for increasing rates of walking bouts of ≥5 minutes (p=0.2) across categories of 6MWT. For lowest category, the RR is interpreted as reducing the expected number of bouts by 0.59, where the expected number is the overall mean.

There were significant effects of mood (MHI) and exercise barriers on these ≥5 minute walking bouts. People who differed on the MHI by 10 points (higher is better mood) had a higher than expected number of walking bouts by a factor of 1.03 (95%: 1.00 - 1.05); people who differed by one exercise barrier (more is worse) had a lower than expected number of walking bouts by a factor of 0.96 (95% CI: 0.93 - 0.99). Supplemental table 1 shows the estimates for linear, quantile and ZIP regression analysis (adjusted and unadjusted) values for all variables under study.

Discussion

The results of this study showed that people with MS spent only a proportion (20.5%-72.5%; see Table 2 concordance or greater) of their usual day walking at a pace equivalent to the pace assessed clinically using a walking performance test. Not surprising people with more severe walking disability (6MWT <300 m) showed more consistency between free-living walking and that assessed clinically (72.5% of steps ≥ clinically measured 6MWT) as they have limited capacity to increase their walking pace. However, people with MS with greater walking capacity (≥500 meters on 6MWT) rarely walked at the measured pace outside of the clinic (12.2% - 20.5%; see Table 2). The clinically assessed walking test used here was the 6MWT, and Table 2 also shows that this duration of walking was rare in the community and when performed, the cadence was much lower than that assessed clinically. Although, the total number steps taken per day was greater, on average, for people with higher walking capacity, they did not distribute these steps towards walking for longer durations. To illustrate, people who walked less than <300 m spent an average of 50.7% of their daily upright time (standing and stepping) walking in short bouts of 1 minute, similar to those with higher capacity.

People differed on their mean and median values of all three walking outcomes by the five categories 6MWT distance (significant test for trend) although there were some non-significant differences for specific categories compared to the highest category (see Table 3). When mean and median values were tested, there were differences in the conclusions about the contrasts obtained from the linear and the quantile models (Table 3). This highlights that it is important to choose the model that matches the data.

However, the results for the number of ≥5 minute bouts differed: there was no trend for increasing rates of 5 minute bouts (Table 3) across categories of 6MWT. This finding is important and points out that in spite of the greater number of steps and brisk steps across the categories of the 6MWT, people of different capacities did not walk for longer. The ecological validity of the clinically assessed 6MWT translates more to number of steps, number of steps at ≥brisk, and cumulated time per week at ≥brisk but does not translate to greater engagement in health promoting walking as shown by the effects on 5 minute bouts (see Table 3). Two variables from the COM-B model were associated with walking bouts, better mood and fewer barriers. It would be important before recommending increase duration of walking that issues related to mood and exercise barriers are addressed.

The COM-B variables were not significantly associated with the step count variables. This suggests that translation of walking capacity to performance is perhaps more complex and could be mediated by variables other than the ones studied here. Thielman et. al. analyzed data from Canadian Health Measures Surveys on neighbourhood walkability and accelerometer measured physical activity in 7180 respondents (31). The study found that people with access to walkable neighbourhoods were able to accumulate approximately half to two-thirds of the amount recommended in Canadian physical activity guidelines compared to people with access to least walkable area (31).

In a report(17) summarizing data from 786 people with MS, accumulated across several studies, Motl et. al., linked disability level to steps per day measured using accelerometers. There was an incremental decline in average number of steps per day with increasing disability measured using Patient Determined Disease Steps (PDDS). People without activity limiting MS related disability (PDDS=0) walked on average 7500 steps per day, people with some activity limitation from MS but no walking disability(PDDS 1 and 2) walked on average 6600 steps per day, people with walking disability walked on average 5200 steps per day, people needing a unilateral walking aid walked on average 3500 steps per day and people needing bilateral support walked on average 2000 steps per day. These data support that approximately 1000 steps per day could be considered clinically important differences (CID)(32). In our study, steps per day ranged from 4130 for people walking <300 meters in 6 minutes (equivalent to some walking disability) to 7446 for people walking > 600 meters in 6 minutes and are concordant with those from Motl et al. Thus, the results of laboratory tests of walking capacity for people with MS are not an accurate reflection of walking performance needed to go beyond activities of daily living and to achieve the health benefits of walking.

The health benefits of physical activity (33) in terms of physical, cardiovascular and mental health are well known and apply to people even with disabilities. There is a great interest in measuring and promoting physical activity among people with disabilities such as MS. Use of technology, such as wearable sensors, have increased in popularity for promoting physical activity among vulnerable populations. Walking could be an effort for people with disability because self-initiated walking at an intensity and duration that is health promoting requires capacity, opportunity and motivation (34). We showed here that capacity is more related to step counts than duration of walking and that mood and barriers affect duration rather than step counts.

The results of this study have implications for evaluating the effects of therapeutics for MS as walking capacity is a key outcome (25 foot walk test) in most trials (17, 18). Simply testing once in a clinical setting may overestimate the real-world gains from the intervention leading to incorrect conclusions about the real benefits of the intervention. The participants may improve of what they can do but not on what they do do in the real world. The latter outcome is harder to measure as it requires the use of technology. However, these outcomes are more patient relevant and reflect real world experience.

Understanding that people with MS when tested in clinical setting cannot reproduce the walking performance in real life is a first step towards designed targeted interventions to promote physical activity.

Limitations

This study has several limitations. Similar to other studies that have looked into measuring walking among people with MS, this study was a planned analysis of people recruited into an exercise trial. This limits generalizability of this study's findings as people may have been more motivated to exercise and have less exercise barriers than the general MS population. This may explain why none of the COM-B variables were associated with walking outcomes except duration. In addition, not all variables affecting the real life performance were available, notably neighbourhood walkability.

Conclusion

What people with MS can do and what they do do is not the same. In the community, people only occasionally reproduced the same walking capacity as tested clinically. Although there was an association between clinically assessed walking capacity and technologically assessed step counts, there were very few bouts of walking duration of ≥ 5 minutes and this rate was independent of clinically assessed capacity. This study provided support for the ecological validity of clinically assessed walking tests for step count but not for health promoting walking bouts. Closing the gap between tested walking capacity and community walking performance could be an achievable physical activity goal for people with MS.

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Table 1: Demographic characteristics of the study population (n=125)

Variables	Mean ± SD or N (%)
Age (years)	45.4 (10.0)
Women / Men	98/27 (78/22)
Years since diagnosis	6.1 (3.4)
Type of MS (%):	
Relapsing–remitting	84 (67)
Secondary progressive	3 (0.2)
Primary progressive	3 (0.2)
Primary relapsing	3 (0.2)
RAND-36 subscales (0-100) [Norm]	
Physical Function Index [88]	72.5 (23.3)
Mental Health Index [77]	67.5 (16.5)
Vitality [66]	48.9 (20.9)
Exercise barrier (0-4)	2.2 (1.1)
Self-efficacy (20-70)	51.6 (10.5)
Exercise enjoyment (0-10)	6.6 (2.5)

Table 2. Distribution of daily steps, cadence, and duration of bouts of walking according to levels clinically assessed walking capacity (6MWT)

	Levels of 6MWT distance				
	<300 m (cadence~70steps/min)	300 to <400 m (cadence ~83steps/min)	400 to <500 m (cadence ~107steps/min)	500 to <600 m (cadence ~130steps/min)	≥600 m (cadence >142steps/min)
Patient days	28	119	269	322	131
Mean days of recording	7	7	6.9	7	6.9
No. of patients	4	17	39	46	19
Mean no. of steps per day(SD)	4130 (906)	4366 (2176)	5100 (2684)	6620 (2357)	7446 (2695)
N (%) ofsteps at specific cadence bands					
0-39(incidental)	390 (9.4)	371 (8.7)	331 (6.5)	404 (6.1)	389 (5.2)
40-59 (purposeful)	748 (18.1)	591 (13.6)	631(12.4)	726 (10.9)	716 (9.6)
60-79 (slow)	1238 (29.9)	768 (17.6)	833(16.3)	976 (4.7)	959 (12.9)
80-99 (medium)	1289 (31.3)	1491 (32.3)	1409 (27.6)	1596 (24.1)	1570 (21.1)
100-119 (brisk)	396 (9.7)	1007 (23.2)	1492 (29.3)	2108 (31.9)	2280 (30.6)
>120 (fast)	66 (1.6)	190(4.4)	402 (7.9)	808 (12.2)	1529 (20.5)
% ≥ concordant band	72.5	59.9	37.2	12.2	20.5
Average upright time (standing + stepping) hours/day	4.3	6.2	8.8	8.0	8.6
Duration of walking bouts (values are % of time)					
<1min	50.7	47.6	46.9	45.9	46.9
≥1 to <2 mins	21.3	20.5	20.5	20.8	20.3
≥2 to <3mins	14.7	13.8	13.8	14.1	13.4
≥3 to <4 mins	4.6	5.9	5.9	5.8	5.5
≥4 to <5 mins	3.7	4.5	4.5	4.4	4.5
≥5 to <6 mins	1.3	2.2	2.2	2.1	2.2
≥6 to <10 mins	2.5	3.9	3.9	4.6	4.3
≥10 mins	0.5	1.9	1.9	2.2	2.7

Recording from 09:00 a.m. to 09:00p.m.

Figure 1: Proportion of steps at different cadence bands contributing towards recommended target steps (10,000 per day)

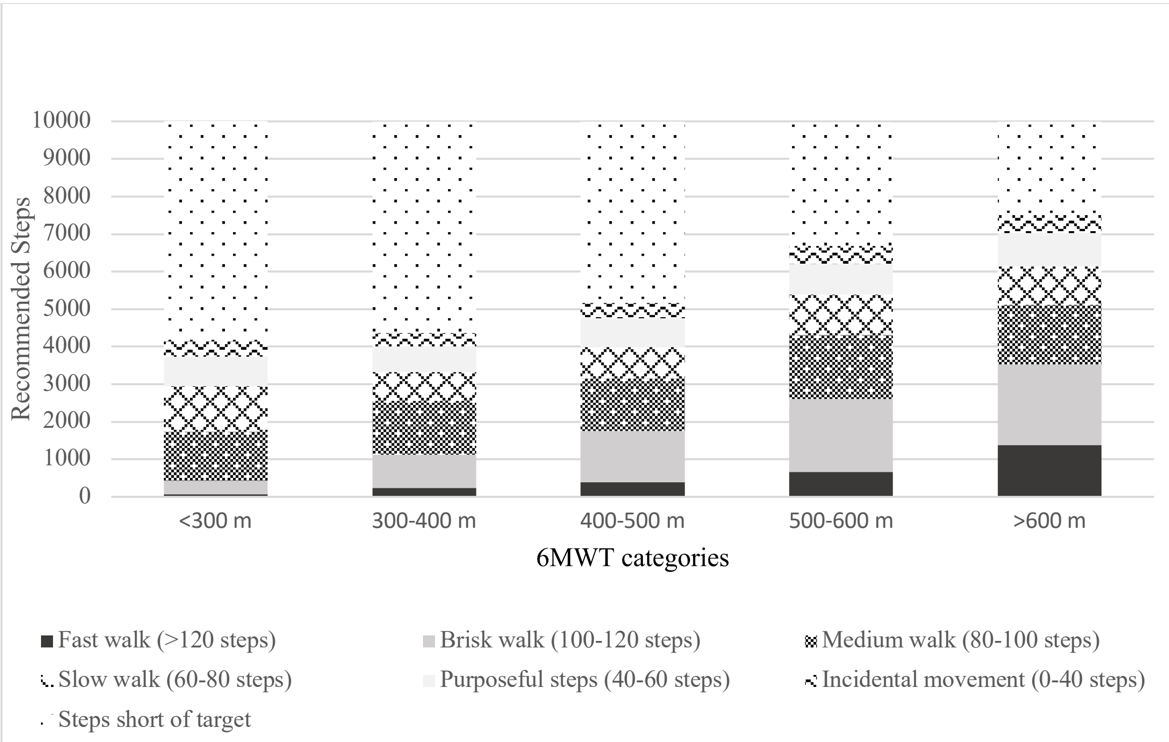


Table 3: Linear, quantile and zero-inflated Poisson regression analysis (adjusted and unadjusted) on mean number of steps, number of steps are brisk or more, cumulated time per week at brisk or more and number of 5 minute bouts.

	6MWT distance				
	<300 m (cadence~70steps/min)	300 to <400 m (cadence ~83steps/min)	400 to <500 m (cadence ~107steps/min)	500 to <600 m (cadence ~130steps/min)	≥600 m (cadence >142steps/min)
Mean no. of steps per person per day [SD]	4130(906)	4366(2176)	5100(2684)	6620(2357)	7446(2695)
β (se) unadjusted	**-3315 (1363)**	**-3079 (847)**	**-2345 (718)**	-825 (694)	Referent
β (se) adjusted	**-3417(1489)**	**-2276(986)**	**-1973(865)**	-418(825)	Referent
Quantile regression β (95% CI)					
Median	4306	4325	5425	6898	7844
Unadjusted	**-3072.6 (-4773.2, -2379.3)**	**-3081.4 (-4559.9, -2083.3)**	**-2176.8 (-4078.8, -290.2)**	-940.5 (-2248.4, 814.7)	Referent
Adjusted	**-3379.4 (-6881.1, -1963.6)**	-3304.1 (-5086.9, 219.8)	-1485.9 (-4392.4, 1932.2)	-804.1 (-2332.4, 2270.8)	Referent
N (SD) ofsteps at brisk or more	463 (490)	1197 (913)	1894 (1438)	2916 (1654)	3810 (1915)
β (se) unadjusted	**-3347(847)**	**-2613(526)**	**-1915(446)**	**-893 (431)**	Referent
β (se) adjusted	**-3323(956)**	**-2164(633)**	**-1584(555)**	-551(530)	Referent
Quantile regression β (95% CI)					
Median	328	1017	1585	2507	3637
Unadjusted	**-3044.0 (-3732.1, -2434.8)**	**-2571.7 (-3068.9, -1751.2)**	**-964.3 (-3054.5, -1340.1)**	**-1120.6 (-1993.2, -543.9)**	Referent
Adjusted	**-3009.3 (-3957.7, -1907.1)**	**-1929.9 (-3673.6, -642.8)**	**-1298.9 (-2809.3, -149.4)**	-450.8 (-2467.4, 819.5)	Referent
Cumulated time* (min) per week ≥brisk: mean	17.4	19.8	25.2	29.4	34.2
β (se) unadjusted	-16.8 (15.6)	**-14.4 (5.4)**	**-9.0 (4.8)**	-4.8 (4.2)	Referent
β (se) adjusted	-20.4 (17.4)	-12.1 (6.4)	-5.1 (5.7)	-2.2 (5.3)	Referent
Quantile regression β (95% CI)					

Median	17.4	18.6	19.2	24.6	27.6
Unadjusted	-0.2 (infty)	-0.1 (-0.2, -0.1)	-0.1 (-0.3, -0.03)	-0.05 (-0.2, -0.0004)	Referent
Adjusted	-0.2 (infty)	-0.1 (-0.2, 0.01)	-0.1 (-0.2,0.03)	-0.04 (-0.2,0.05)	Referent
5 minute bouts	209	680	1626	2324	1030
Total number	6160	10683	22912	31788	12088
Median	36	41	48	66	71
Bouts per person-waking time (12hours)	20160	81360	171360	214560	90000
Crude rate per 1000 waking hours	10.36	8.35	9.49	10.83	11.44
Crude rate per 12 waking hours	0.12	0.10	0.11	0.13	0.14
$Rate ratio OR (95% CI)					
Unadjusted	**0.59 (0.52, 0.67)**	**0.66 (0.60, 0.73)**	**0.78 (0.72, 0.84)**	0.99 (0.92, 1.07)	Referent
Adjusted	**0.61 (0.53, 0.69)**	**0.66 (0.59, 0.73)**	**0.73 (0.66, 0.79)**	0.96 (0.87, 1.04)	Referent

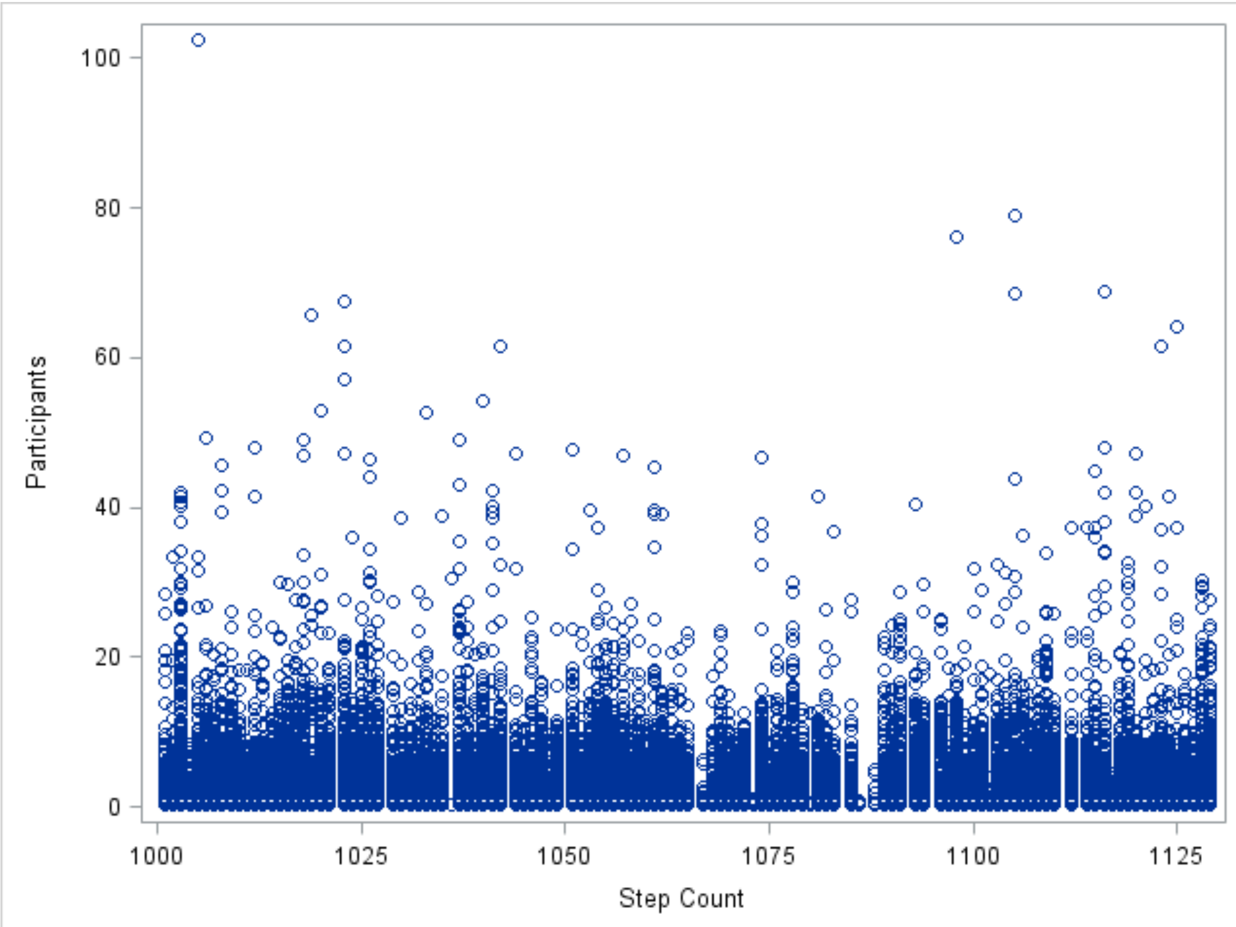
* non-contiguous minutes
$ RR from Zero-inflated Poisson (ZIP) model
Significant model effects are shown in bold
βadjusted for age, sex, mental health, vitality, self efficacy, exercise barriers, and enjoyment
se = standard error
CI – 95% confidence interval
MHI - Mental Health Index

Supplementary Table 1: Adjusted and unadjusted values linear, quantile and zero-inflated Poisson regression analysis for each outcome and predictor

	Unadjusted		Adjusted	
	β (se)	95% CI	β (se)	95% CI
Mean no. of steps per day				
<300 m	**-3315 (1363)**	-4678,-1952	**-3417(1489)**	**-4906, -1928**
300-<400 m	**-3079 (847)**	-3926,-2232	**-2276(986)**	**-3262, -1290**
400-<500 m	**-2345 (718)**	-3063,-1627	**-1973(865)**	**-2838, -1108**
500-<600 m	-825 (694)	-1519, -131	-418(825)	-1243, 407
≥600 m	Referent	---	Referent	---
Age (decade)			-228.1 (300.4)	-528.5, 72.3
Women vs. Men			-215.8 (700.1)	-915.9, 484.3
Vitality (per 10 units)			6.5 (178.4)	-171.9, 184.9
Mental Health (per 10 units)			153.3 (204.1)	-50.8, 357.4
Exercise barriers (per barrier)			96.5 (282.2)	-185.7, 378.7
Self-efficacy (per 10 units)			-151.7 (310.4)	-462.1, 158.7
Exercise enjoyment (per unit)			178.8 (125.8)	53, 04.6
N (%) of steps at brisk or more				
<300 m	**-3347(847)**	**-4194, -2500**	**-3323(956)**	**-4279, -2367**
300-<400 m	**-2613(526)**	**-3139, -2087**	**-2164(633)**	**-2797, -1531**
400-<500 m	**-1915(446)**	**-2361, -1469**	**-1584(555)**	**-2139, -1029**
500-<600 m	**-893 (431)**	**-1324, -462**	-551(530)	-1081,-21
≥600 m	Referent	---	Referent	---
Age (decade)			-345.3 (192.9)	-475.2, -215.4
Women vs. Men			25.5 (449.6)	-424.1, 475.1
Vitality (per 10 units)			77.4 (114.6)	-37.2, 192
Mental Health (per 10 units)			62.1 (131.1)	-69, 193.2
Exercise barriers (per barrier)			21.4 (181.2)	-159.8, 202.6
Self-efficacy (per 10 units)			-179.3 (199.4)	-378.7, 20.1
Exercise enjoyment (per unit)			48.05 (80.8)	-32.75, 128.85
Cumulative time (min) per week at brisk or faster walking				
<300 m	-16.8 (15.6)	-32.4, -1.2	-20.4 (17.4)	-37.9, -2.9
300-<400 m	**-14.4 (5.4)**	**-19.8, -9.0**	-12.1 (6.4)	-18.8, -5.7
400-<500 m	**-9.0 (4.8)**	**-13.8, -4.2**	-5.1 (5.7)	-10.8, 0.5

500-<600 m	-4.8 (4.2)	-9.0, -0.6	-2.2 (5.3)	-7.5, 3.0
≥600 m	Referent	---	Referent	---
Age (decade)			**-0.4 (0.2)**	**-0.6, -0.2**
Women vs. Men			3.9 (4.8)	-0.9, 8.7
Vitality (per 10 units)			0.1 (0.1)	0.02, 0.2
Mental Health (per 10 units)			-0.08 (0.1)	-0.2, -0.06
Exercise barriers (per barrier)			-0.8 (1.9)	-2.8, 1.1
Self-efficacy (per 10 units)			0.04 (0.2)	-0.2, 0.2
Exercise enjoyment (per unit)			-0.3 (0.8)	-1.1, 0.6
Rate ratio	OR	95% CI	OR	95% CI
<300 m	**0.59**	**(0.52, 0.67)**	**0.61**	**(0.53, 0.69)**
300-<400 m	**0.66**	**(0.60, 0.73)**	**0.66**	**(0.59, 0.73)**
400-<500 m	**0.78**	**(0.72, 0.84)**	**0.73**	**(0.66, 0.79)**
500-<600 m	0.99	(0.92, 1.07)	0.96	(0.87, 1.04)
≥600 m	Referent	---	Referent	---
Age (decade)			1.0	(0.98, 1.04)
Women vs. Men			0.96	(0.89 1.03)
Vitality (per 10 units)			0.99	(0.98, 1.00)
Mental Health (per 10 units)			**1.03**	**(1.00, 1.05)**
Exercise barriers (per barrier)			**0.96**	**(0.93, 0.99)**
Self-efficacy (per 10 units)			1	(0.97, 1.03)
Exercise enjoyment (per unit)			1.0	(0.99, 1.02)

Appendix A: Distribution of Step Count across 7 days of Recording for the Study Participants (n=129)



CHAPTER 7: INTEGRATION OF MANUSCRIPT 2 AND 3

The second manuscript demonstrated the gap between clinically assessed walking capacity using 6MWT and free-living walking performance in people with MS and that this relationship is not predicted by sex, mood, motivation, exercise barriers, self-efficacy and exercise enjoyment. In other words, the second manuscript focused on the relationship between PerfO and TechO.

The third manuscript focuses more on walking and asks the question as to whether technology can be used to modify gait. The gait modifications would be assessed using technology (TechO) and, although not strongly emphasized, whether people can detect this modification themselves (SRO). Specifically, the question is whether gait is modifiable/adaptive in response to auditory feedback. This hypothesis was tested using a feasibility pre-post study design with 6 older adults who were trained using a feedback device. The next manuscript is titled, “Real-Time Auditory Feedback Induced Adaptation to Walking among Seniors using Heel2Toe Sensor: A Proof-of-Concept Study”. This objective of this study was to contribute evidence towards the feasibility and efficacy potential for home use of a sensor that provides real-time feedback for good heel strike when walking. The Heel2Toe sensor is feedback technology developed by Dr. Mayo’s team based on principles of neuroplasticity and motor learning. The sensor provides an auditory feedback for each “good” step, in which the heel strikes first.

This manuscript has been reviewed, revised and resubmitted to the Journal of Rehabilitation Assistive Technologies and Engineering. The following paper is the resubmission.

CHAPTER 8: MANUSCRIPT 3

Real-Time Auditory Feedback Induced Adaptation to Walking among Seniors using Heel2Toe Sensor: A Proof-of-Concept Study

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Abstract

Introduction

Evidence shows that gait training in older adults is effective in improving gait pattern, but effects abate with cessation of training. During gait training therapists use a number of verbal and visual cues to place the heel first when stepping. This simple strategy changes posture from stooped to upright, lengthens the stride, stimulated pelvic and trunk rotation and facilitates arm swing. These principles guided the development of Heel2Toe sensor that provides real-time auditory feedback for each 'good' step, in which the heel strikes first.

Objective

The objectives of this feasibility study of the is to contribute efficacy potential for home use of the Heel2Toe sensor were to estimate changes in gait parameters after 5 training sessions using the sensor.

Methods

A pre-post study, with a five-day training period in the person's residence, was carried out on a purposive sample of six seniors. Proportion of good steps, angular velocity at each step, and cadence, over a 2 minute period were assessed as was usability and experience.

Results

All gait parameter: proportion of good steps, angular velocity and duration of walking bouts improved. Coefficient of variation of angular velocity reduced indicating consistency of stepping.

Conclusion

Efficacy potential and feasibility of the Heel2Toe sensor were demonstrated.

Keywords: Heel2Toe sensor, angular velocity, auditory feedback, walking, older adults

Introduction

Gait and walking are terms that are used interchangeably in literature but are conceptually different creating confusion among researchers and clinicians as to the interpretation and application of findings from research papers. Walking is a rhythmic, dynamic, aerobic activity involving large skeletal muscles (1), for accomplishment of everyday activities, recreation, or exercise. Gait on the other hand is the manner of walking and has been extensively studied to derive parameters for normal and deviant patterns (2, 3). Aging renders people vulnerable to gait deviations that impair efficient walking and limits the likelihood of achieving health promoting walking targets. Physical activity guidelines for seniors recommends a target of 150 minutes of moderate intensity exercise accumulated over one week in bouts of 10 minutes (4). Walking is the most practical exercise as it requires no equipment, no specialized environment (5) and, produces many physical and cognitive health benefits from the mental stimulation of exploring new avenues or neighborhoods. Maintaining a level of physical activity is also critical to prevent secondary health conditions including cardiovascular disease, osteoporosis, obesity and diabetes (6). These conditions themselves impact participating in physical activity and lead to a vicious cycle of inactivity, physical limitation, and more inactivity. Promoting healthful walking is not only good for the body, it is good for the brain (6, 7). Despite capacity to walk at a health promoting pace when tested clinically, it is rare for the North American senior to do this in the real world for more than a few minutes a day (8-10).

Reasons for failure to use walking capacity to achieve health promoting walking targets include fear of falling or age-related gait abnormalities (11, 12). These are known to cascade into a slow, unstable, shuffling pattern that increases work of walking, fatigue, risk of falls and, hip fracture (13-16). There is considerable evidence on how to improve seniors' gait (17-24) and evidence shows that gait training is effective in improving gait pattern (18-20, 25) but effects abate with cessation of training (25). Hence alone, gait training will not translate into the sustained behavioral change needed for physical activity guidelines to be met.

A few technologies to improve walking among seniors are commercially available or in development stage. A review on various footwear-based gait monitoring systems showed that all devices did not provide real-time feedback and needed post processing to obtain results on walking performance results (26). Systematic review on use of electromyogram feedback (EMG-BFB) to enhance motor recovery in people post-stroke showed modest effect of EMG-BFB and physical therapy compared to physical therapy alone (27). A previous systematic review synthesized effectiveness of the available technologies that provide different types of feedback (28). Of the included studies, 2 studies used auditory feedback. One of those two studies used a sensor embedded in a GAITRite which provided auditory feedback during weight transfer, but it is not clear whether the feedback was for errors or correct transfer (29). Second study used locomotor training with a robotic-gait orthotic for people with spinal cord injury (30). Though this systematic review is comprehensive in synthesizing literature on available technologies to assist functional recovery, our real-time auditory feedback for “good steps” is a novel innovation applicable in seniors.

Natural aging results in a walking pattern that deviates from optimal, is slower, and requires more effort. Eventually seniors choose to walk less and, superimposed with illness or injury, can accelerate this downward cascade and lead to permanent disability and premature mortality. It is hard to sustain walking for a long duration of time with incorrect stepping pattern. During gait training therapists use many of verbal and visual cues to emphasize stepping with heel first. This simple strategy changes posture from stooped to upright (31), lengthens the stride, stimulated pelvic and trunk rotation and facilitates arm swing. But once verbal cueing ceases, patients frequently revert to an inefficient foot-flat gait (32, 33).

For walking to become more normalized, people must relearn the motor sequences of good walking but also to develop the needed adjuncts to efficient walking; flexibility, strength, power, core stability, balance, and trunk rotation indicated by arm swing. Therapy can work on the adjuncts, but motor learning requires instruction, practice, and feedback. The 2013 review by Sigrist et al. frames motor learning as a lasting change of motor performance caused by training in which the parameters of a "motor program" are developed and there is a gradual reduction of the variability in the newly developed motor program stimulated by sensory feedback loops (34). The phenomenon underlying motor learning is neural plasticity (35-37). A 2014 review of this topic indicates that motor learning takes place with active practice of a skill and that this activity-dependent neural plasticity can be induced by both lengthy-extensive and brief-intensive practice. The authors of this review state: "To maximize human brain fitness and motor functions signaled by the quality of life and independence in daily activity, habitual cognitive and motor learning or practice is required across the lifespan, particularly for older adults" (37) The literature supports the benefit of augmented or extrinsic feedback for motor learning (35). In particular sonification for correct movement sequences have been shown to enhance motor learning in elite athletes, for novices, it is less useful if they have no idea of the correct movement (34, 38-40). Neuroscience literature suggests that the auditory system is fast processing sensor system with reaction times 20-50 milliseconds faster than visual system. Auditory feedback, such as metronome beats and music, can induce short term adaptation in neurological populations like stroke, Parkinson's Disease, Huntington's conditions (41-49). These studies, however, employed an external feedback process, that means, the auditory feedback was not controlled by the participants, but the participants had to match their stepping pattern to the externally feedback device. It is well established that knowledge of performance is a strongly associated with skill acquisition and motor learning compared to knowledge of results (50, 51).

These principles guided the development of Heel2Toe sensor, a sensing and a biofeedback device that provides auditory feedback for each 'good' step, in which the heel strikes first. Pilot work on Heel2Toe has demonstrated that it is highly accurate (52, 53). The purpose of this project was to bridge this gap of absent feedback outside clinical setting and equip seniors to practice correct gait at convenience. The hardware and algorithm underlying generation of auditory feedback from the Heel2Toe sensor in described elsewhere (52, 53). Pilot work on Heel2Toe has demonstrated that it is highly accurate to improve walking in clinical setting (52, 53).

Objective

The purpose of this study is to contribute evidence towards the feasibility and efficacy potential for home use of a sensor that provides real-time feedback for good heel strike when walking. Specifically, the objectives were: (a) to identify the extent of the (i) immediate response to the feedback; (ii) carry over when walking without feedback; and (iii) peak response to feedback and (b) to identify pleasures and challenges to using the feedback sensor.

Methods

Study Design

A pre-post study design, with a five-day training period, was employed to identify feasibility issues and estimate efficacy potential of Heel2Toe sensor when deployed for walking in the community.

Participants

A purposive sample of six people, 4 women and 2 men, over the age of 70 years, were identified from geriatric services at Montreal General Hospital. Participants were identified by geriatrician or other healthcare professionals and included if they had no limitation in walking without an aid and no cognitive impairments. Ethical approval was obtained from Ethics Review Board of McGill University Health Centre Research Institute.

<u>Measures</u>

Participants were assessed on physical performance tests and self-report measures. Standard physical performance tests (https://www.sralab.org/) included gait speed, 30 second chair stand and 2 minute walk without and with auditory feedback. The self-report questionnaires including single items on perceived walking speed, 8 items from lower extremity function scale (LEFS), life space mobility and, activity specific balance confidence (54-56). As the LEFS has a Rasch-based scoring system, any subset of items can be used to form a total score. Here the 8 most relevant items were chosen with a total score ranging from 0 to 32 with 32 indicating no difficulty on any item.

Post-training outcomes additionally included questions about system usability and a semi-structured interview on challenges and pleasures of using the Heel2Toe sensor. The interview was conducted separately with each participant.

<u>Intervention</u>

The intervention involved a therapist visiting participant's residence to provide walking training with the Heel2Toe sensor, for 5 sessions over 2 weeks. The training involved walking in the participant's neighbourhood with the sensor. The duration of the training was determined by the participants themselves based on interest and tolerance. On each training day, persons were instructed to walk for at least 15 minutes with the sensor at a comfortable pace and taking rests when needed. The training was accompanied with home exercises targeting flexibility and strength at ankle, knee and, hip joints with particular focus on core strength and trunk rotation. At the end of the training a semi-structured interview was conducted with all participants.

<u>Analysis</u>

The gait signals recorded with the Heel2Toe sensor were analysed using Matlab (version R2017b)®. The gait parameters extracted for each person over the entire walking period were proportion of good steps (%), total walking time (seconds), and average cadence (steps per minute). Angular velocity (degrees per second) at ankle joint during heel strike was extracted for each step and averaged over the walking duration yielding mean, SD, and coefficient of variation (an indicator of consistency of stepping).

<u>Results</u>

Table 1 shows the characteristics and level of physical activity of the participants before the training. The score on 30-second chair rise test ranged from 0 to 12 for 6 participants. The self-reported walking speed ranged from normal to very slow walking. Every person had at least one of the LEFS items with difficulty rated as extreme or quite a bit. All but one person had items rated with no difficulty. Total scores ranged from 11 to 26 out of maximum 32 (for these 8 items). Life space mobility scores ranged from 48 to 126 out of a total 140 mobility-days. A score of 28 days means no movement outside of home in the past 28 days, score of 56 means mobility outside of house but within the yard, porch or apartment building.

Table 2 shows data indicative of an immediate response to auditory feedback on proportion of good steps, angular velocity and cadence. Participant A produced 0 good steps without any feedback pre-training. With auditory feedback the participant could produce more 50% good steps maintaining same average cadence. This was reflected in an increased in angular velocity to this participant and all others whereas cadence showed more variability among participants. Participant B produced almost twice the proportion of good steps with an increase in angular velocity and no loss in cadence. Four out of six participants showed only a small increase in the proportion of good steps with feedback and all were over 80% without feedback. But all of these showed large increases in angular velocity with stable cadence.

Figure 1 shows the duration (minutes) of intervention time over 5 training days. To illustrate, the participant A, who was the most disabled, walked with the sensor for 4.5, 3.7, 9.4, 7.4 and 5.6 minutes on days 1 through 5. However participant D, who walked for about 12 minutes on day one, had 2 days in which they walked for 30 minutes. All participants increased the time spent walking with the sensor over the intervention period. Out of the 30 intervention-days, 10 minute or more bouts of continuous walking were observed on 21 of the intervention-days and 5/6 persons achieved 10 minute bouts by end of treatment.

Table 3 shows the carry over effects after 5 days of training with the sensor when walking without feedback for a 2 minute period. Post-training gait was assessed within one week. For example, Participant A produced 0% of good steps pre-training but produced 28% good steps at the end of training. He also showed a gain in angular velocity of -32 degrees per second, without a decrease in cadence (+6 steps per minute). The aim of these data was to show that the people could transfer the gains made using real time feedback on stepping pattern into their usual walking without feedback. Overall, there was a positive impact on gait parameters.

Figure 2 shows the response to 5 days of training with auditory feedback on proportion of good steps and cadence. Overall, 5 of 6 participants achieved 90% of good steps without slowing a slowing of cadence, in fact, cadence increased by more than 10% in half of the subjects. Figure 3 shows the response to 5 days of training on mean angular velocity and consistency of angular velocity as indicated by the coefficient of variation. The angular velocity is improved (more negative is better) post training for all the 6 participants. The coefficient of variation also reduced for all the participants post-training, proportional to the increase in angular velocity.

The information collected on system usability and on challenges and pleasures of using the Heel2Toesensor were helpful in identifying areas for improvement. The results from the Usability Scale are given in Supplemental Table 1. Only 8 of the original 10 questions were applicable as one was not understood and one referred to their impression of how other people would be able to use the sensor. Overall, 38 item-responses were available: 25 favorable, 4 neutral, and 9 unfavorable. No one feature was consistently rated “unusable” but one issue raised was about the intrusiveness of the sound while walking in public. This is easily solved by earphones. The question on confidence was inconsistently answered because the trainer was always present during these training sessions.

The aim of semi-structured interviews was to capture the experiences of the participants while walking with Heel2Toe sensor in the community and recommendations for subsequent sensor development and upgrading. Participants expressed that the sensor was enjoyable, stimulating, beneficial, and easy to use while training outside home. The participants had a few recommendations to make the sensor more user-friendly. First, clipping the sensor to the shoe was recommended over a strap to accommodate older adults with back pain and limited trunk mobility. The clip also offers flexibility of use with any shoe. Second, the sensor should be available to connect via an iPad that offers a larger display for app. Third, the sensor and app combination should be affordable and accompanied by an exercise manual.

Discussion

We found that the Heel2Toe sensor was feasible to use in the community setting with older adults and that they improved many gait parameters after only 5 training sessions with an average total training time of 73 minutes (range 43 to 114). Proportion of good steps and angular velocity improved without any detriment to cadence. All 6 participants showed longer duration of time spent in walking from the initial training days. However, the most dramatic effect was seen for duration of walking bouts which frequently exceeded 10 minutes (Figure 1) such that most (5 of 6; see Table 3) participants would now be capable of meeting the Canadian Physical

Activity Guidelines of 150 minutes of moderate to vigorous activity (required walking cadence ≥100 steps per minute) per week in bouts of 10 min.

All participants post-training showed reduction in coefficient of variation of angular velocity, a parameter indicating inconsistency of stepping pattern. Prior to training the coefficient of variation ranged from 23% to 59%. Previous studies have shown a higher coefficient of variation in step width, and stance and stride time among older adults is associated with increased occurrence of falls (57-59) with the suggestion that a treatment target is to reduce coefficient of variation with exercise interventions. After 5 days of training the range was from 9% to 49%.

We purposely chose a sample of people diverse in physical function. Two people were quite frail (A and B). Person A was severely limited in mobility (see Table 1) yet he improved on proportion good steps, and degree and consistency of angular velocity (Table 3 and Figures 2 and 3). Person B also improved on these parameters. The most functional walker, Person D, showed no change as she was high on all parameters but enjoyed the experience of the sensor and could see how it would prevent deterioration.

How did the sensor achieve these outcomes? One hypothesis is that the auditory feedback acts as a positive reinforcement to a rhythmic stepping pattern. With symmetrical walking, each good step produces a “beat” that is repeated with periodicity. To produce the rhythmic pattern (the “beat”), the participants modified their stepping pattern so as to maintain the rhythm. In the long run, auditory cues could enhance cortical motor excitability. This has previously been studied with upper limb movements and walking tasks that required persons synchronizing to an external auditory cue (60-63). The underlying basis of auditory motor synchronization is that brain poses anticipatory tendency for a rhythm and this anticipation guides subsequent movements (64, 65).

The Heel2Toe sensor provides direct positive auditory feedback which could be perceived as rewarding stimulating neural plasticity and also increasing the pleasure in walking stimulating behaviour change. Ultimately, the aim is to improve health promoting walking rather than just functional walking so older people can derive pleasure and health benefit from walking. The sensor is not designed to be worn all the time but to be worn to practice optimal walking with the aim that this would carry over into other walking activities. As it is linked to a smart phone, and the sensor is very small (size of a matchbox), it could be worn for longer periods of time.

Fear of falling and age or illness-related changes co-occur in most seniors and can induce an inefficient and dangerous gait pattern (11, 12). To normalize walking, people must relearn motor sequences of good walking and develop needed adjuncts to efficient walking: flexibility, strength, power, core stability, balance, and arm swing. Therapy targets adjuncts but motor learning requires instruction, practice, and feedback. Motor learning is framed as a lasting change of performance occurring with training in which parameters of a "motor program" are developed and consolidated. Early on, forming the motor program of the "to-be-learned task" can occur rapidly but is very attention-demanding. Later, the motor program is refined, improving error detection/correction mechanisms, reducing movement variability. Finally, movements become highly automatized, skilled, and consistent and the motor program is now relatively permanent (42).

The phenomenon underlying motor learning is mostly due to neural plasticity (42, 44). A review of this topic (44) indicates that motor learning takes place with active practice of a skill and that this activity-dependent neural plasticity can be induced by both lengthy-extensive and brief-intensive practice. The literature supports the benefit of augmented feedback for motor learning (42, 45-47). In particular sonification for correct movement sequences has been shown to enhance motor learning in elite athletes (45); but is less useful for novices who have no idea of the correct movement. Walking is a natural way to get about (1) and, as older persons are not novices to walking but have lost the expertise with age, their walking pattern should respond to auditory feedback. This type of "positive" feedback has been shown effective in the short term to improve gait pattern in people post-stroke (48). It is superior to auditory alarms signalling incorrect movements as feedback for good movement is more motivating (45).

This solution to poor gait is unique in that there is positive reinforcement, in real time, which stimulates motor learning of correct gait. The Heel2Toe sensor provides information in real-time, in other words, knowledge of performance and not just knowledge of after-the-fact results, which is provided by most other technologies in the field today. This is a completely novel and original approach to gait enhancement. There have been other approaches to monitor step counts but these have not attempted to improve gait quality. The review of the literature conducted by our team did not find any study focusing on feedback related to gait quality and ankle kinematics.

Finally, qualitative interview from this project suggests readiness of seniors to adopt technology as long as it is simple and user-friendly. This project is timely and relevant to increasing proportion of older population and builds upon the potential of technology to stimulate innovation thereby advancing Canadian economic and social development. An increasing proportion of older adults use smart phones (66, 67) and this proportion is likely to increase as technologically savy cohorts age.

This sensor could be on the foot of every person who needs to maintain or improve optimal gait. By formally practicing gait improvement with positive auditory feedback, people could develop the habit of walking better leading to walking more often and for longer.

The sensor is in development and refinements to the algorithm will be made such as to provide different thresholds for the feedback to occur (low, medium, and high angular velocity). An instructional manual and video are in production to optimize the participants capacity to use the Heel2Toe sensor. The plan is to develop a full scale trial now that there is some data that people can change their gait with the device.

Implications/Conclusions

The results of this study have future implications in exploring the neural basis of auditory-motor synchronisation during walking, application of motor learning principles to enhance walking performance and technology design of wearable sensors for older adults. Understanding the neural basis of auditory motor synchronization will help design interventions to use auditory feedback to improve walking symmetry. The application of motor learning principles to enhance walking performance based on movement generated auditory feedback and long term effects on skill acquisition, an area yet to be explored. The qualitative interviews from this study suggest that, when designing wearable sensors targeted to seniors, the technology should be human centred design, simple and easy to use, provide real-time meaningful feedback, have a software program that requires minimal pre-processing (zero effort) prior to use, and have the option for technical support and/or supervision from a rehabilitation professional (68).

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Table 1: Characteristics and Physical Activity Level of the Participants at Study Entry

ID (Women/Men) Characteristics/Activity level	A (M)	B (F)	C (W)	D (F)	E (W)	F (M)
Age (years)	80	73	87	83	85	86
Physical Performance Tests						
Self-report walking speed$	Very slow	Stroll	Stroll	Normal	Very slow	Normal
30 second sit to stand (n)	0	12	7	9	10	12
Norms (n)#	10	10	9	8	8	8
Self-report Questionnaires						
Lower Extremity Functional Scale* (LEFS) (scored from 0-extremity difficulty to 4-no difficulty)						
Walking a mile	1	2	0	4	0	3
Running on even ground	0	0	2	1	0	2
Squatting	2	2	1	3	4	3
Standing for 1 hour	2	1	0	4	2	3
Climbing 10 stairs	2	3	3	4	4	3
Heavy household activities	0	1	1	4	2	4
Getting in and out of bath	3	0	4	2	4	4
Light household activities	2	2	4	4	4	4
Total Score	12	11	15	26	20	26
Life Space Mobility (number of days out of past 28 days)^						
been to other rooms besides the bedroom	28	28	28	28	28	28
been to area outside home	6	28	28	28	28	15
been to places in your neighborhood	6	28	15	28	28	5
been to places outside neighborhood within town	6	28	10	28	28	2
been to places outside town	2	2	2	10	14	2
Total Score (out of possible 140 patient days)	48	114	83	122	126	52
Activity Specific Balance Confidence Scale (0 - no confidence to 100% - full confidence)						
Walk around the house	90	60	80	100	95	100
Walk across a parking lot	90	50	100	100	100	100
Walk in a crowded mall	95	50	75	90	100	100

$ Self-report walking speed: Unable to walk, Very slow, Stroll at an easy pace, Normal speed, Fairly brisk, Fast

*Selected item of lower extremity function scale (LEFS)

Center for Disease Control

^ A score of 28 days means no movement outside of home in the past 28 days, score of 56 means mobility outside of house but within the yard, porch or apartment building., score of 84 means going to places in neighborhood, score 112 means going to places outside neighborhood but within town and, score of 140 means going to places outside town.

Table 2: Immediate adaptation to auditory feedback at pre-training

ID	%good steps over a 2-minute walk period		Angular velocity (more negative is better)		Cadence (steps per minute)	
	Without feedback	With feedback	Without feedback	With feedback	Without feedback	With feedback
A	0	56	-48	-102	70	69
B	43	82	-97	-128	95	102
C	80	83	-147	-157	97	95
D	84	97	-145	-186	110	95
E	92	92	-165	-173	113	110
F	93	99	-163	-213	96	95

Figure 1: Time (minutes) spent walking with the sensor during each training day

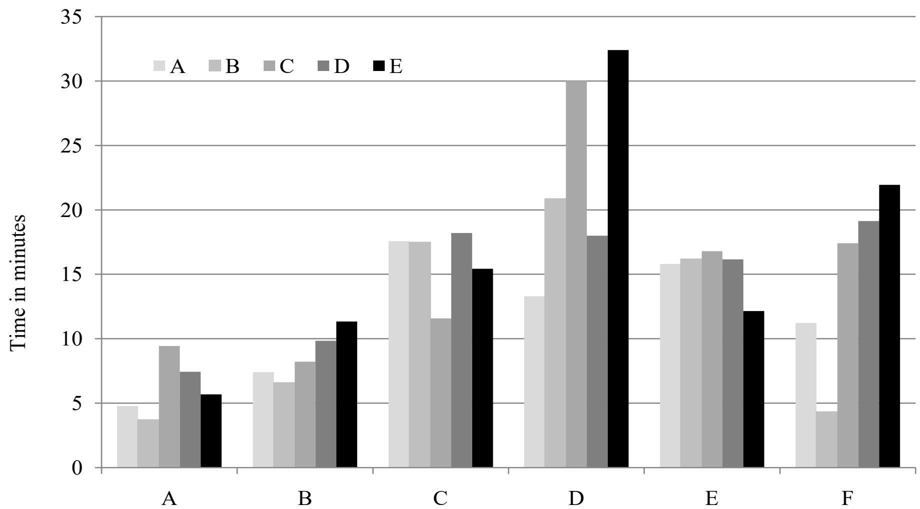


Table 3: Carry over effects after 5 training sessions with Heel2Toe sensor on gait parameters measured without feedback.

ID	Cadence % good steps without feedback over 2 minute walk period		Angular velocity add starting as well		Cadence (steps per minute)	
	Starting	Change	Starting	Change	Starting	Change
A	0	+28	-48	+32	70	+6
B	42	+37	-97	+28	95	+8
C	79	+9	-148	+15	97	+3
D	84	+13	-145	+82	110	+10
E	92	+2	-166	+10	113	-8
F	93	+5	-164	+86	96	+13

Figure 2: Response to 5 days of training on Mean % Good Steps and Cadence

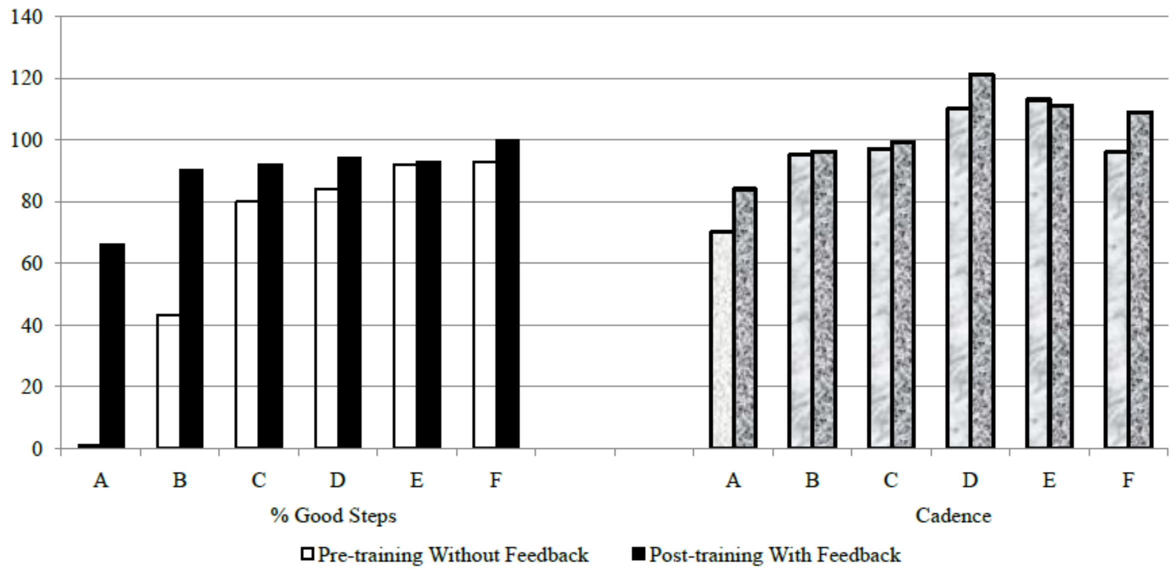
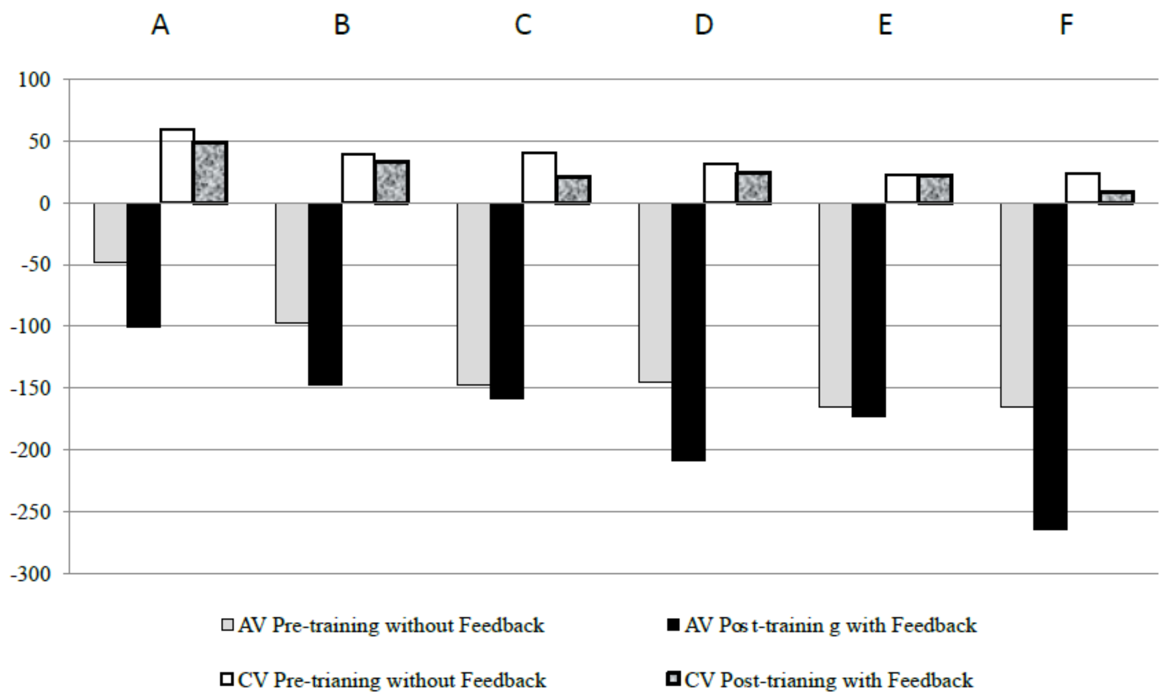


Figure 3: Response to 5 days of training on Mean Angular Velocity (AV) and Coefficient of Variation (CV)



Supplementary Table 1: Items Scores on System Usability Scale

Item (8 of 10 original questions)*	Responses across participants
Higher is better	
Use it frequently	4 3 5 _ 5 4
Easy to use	4 1 1 _ 5 5
Functions integrated	5 1 3 _ 1 _
Confidence in using	5 1 _ _ 1 4
Lower is better	
Too complex	1 1 1 _ 1 1
Need assistance to use	1 1 1 _ 1 1
Cumbersome or awkward	1 1 5 _ 2 1
Need to learn a lot before using	1 5 1 _ 2 5

*Two questions were omitted because of understanding (too much inconsistency with sensor) and applying to what other people might think (I would imagine most people would learn to use this very quickly). Missing data is indicated by _. Of the 18 item-responses for the 4 questions where higher is better, 10/18 were at the two highest agreement levels and 6 were at the lowest. Of the 20 item-responses for 4 items where lower is better 15/20 were at the best level and 3/20 were at the poorest level.

CHAPTER 9: INTEGRATION OF MANUSCRIPT 3 AND 4

The third manuscript demonstrated that gait among older adults in modifiable in response to auditory feedback using Heel2Toe sensor. It also showed that what people reported on their walking speed (SRO) was not fully concordant with that measured using a TechO suggesting that qualitative work needs to be done to understand what underlies people reporting they walk very slowly or normally. The next manuscript focused solely on the outcomes of TechO and their relationships with the aim of identifying key contributors to cadence. Cadence is the outcome most relevant for walking and removes the variation in gait speed that arises from differences in height. For a given gait speed, a very short person would have a higher cadence than a very tall person and the short person might be walking at a health promoting pace. It is more relevant to encourage people to walk at a specific cadence rather than to walk at a given gait speed, although they are obviously related. Thus, my next step was to see whether there is any relationship between parameters of step quality (proportion of good steps, angular velocity) and cadence among seniors, people with MS and PD. The manuscript is titled, “Putting the best foot forward: Relationships between indicators of step quality and cadence in three gait vulnerable population”. The objective of this manuscript is to establish the relationship between cadence, good steps, angular velocity and co-efficient of variation and whether this relationship is same across the health conditions, older adults, people with PD and MS.

CHAPTER 10: MANUSCRIPT 4

Putting the Best Foot Forward: Relationships between Indicators of Step Quality and Cadence in Three Gait Vulnerable Population

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<u>Abstract</u>

Background

Aging and neurological conditions like Multiple Sclerosis (MS) and Parkinson's disease (PD) make people vulnerable for gait impairments, limit function, and restrict sustained walking needed for health promotion. Walking to meet physical activity guidelines requires adequate cadence which is difficult to achieve with gait vulnerable populations.

Objective

The objective of this study is to estimate, for seniors and people with MS or PD, the extent to which cadence is associated with heel-to-toe stepping pattern (good steps), angular velocity of ankle at heel strike and its variability.

Methods

A cross-sectional regression analysis was performed on data collected during walking tests using the Heel2Toe sensor.

Results

Health condition (MS=57, PD=27, seniors=56) had an association with cadence, independent of age and sex. Only angular velocity showed a significant relationship with cadence such that every -50^{o} difference in angular velocity (more negative is better) increased of $\approx$3.5 steps per minute.

Conclusion

Adequate angular velocity occurs with an optimal heel-to-toe movement. This heel-to-toe gait can easily be targeted during therapy, but technology would be an asset to sustain the relearned

movement during everyday activities, Technology that provides real-time feedback for steps with adequate angular velocity at heel strike could be a valuable therapeutic adjunct.

Keywords: cadence, angular velocity, coefficient of variation, Multiple Sclerosis, Parkinson's Disease, seniors

Introduction

Many key gait parameters are required to produce a gait that is rhythmic, reproducible and sustainable. Gait quality is affected by neurological integrity, balance, power and is manifested in ability to produce consistent steps. The ability to walk safely for function, recreation and health promotion depends on producing good quality steps. Two key parameters of good quality steps are angle of ankle at heel strike and consistency. The former is a function of stride length which is shortened if balance is poor and contributes to foot scuffing while walking. The latter (consistency) depends on gait automaticity which when lost increases the attentional requirements of walking (Hollman, Kovash, Kubik, & Linbo, 2007; Lajoie, Teasdale, Bard, & Fleury, 1996). Aging and neurological conditions like Multiple Sclerosis (MS) and Parkinson's disease (PD) make people vulnerable for gait impairments and this is manifested by inconsistent stepping, wide base of support, lack of heel-to-toe stepping, among others (Crenshaw, Royer, Richards, & Hudson, 2006a; Hausdorff, Cudkowicz, Firtion, Wei, & Goldberger, 1998). Lack of heel to toe stepping pattern leads to dangerous shuffling gait that is often seen with seniors and people with PD (Alcock, Galna, Lord, & Rochester, 2016). For people with MS, walking for a sustained duration results in fatigue in leg muscles particularly in antigravity foot muscles (ankle dorsiflexors) that produces foot drop and increases work of walking and risk of falls (Benedetti et al., 1999; Martin et al., 2006; Matsuda et al., 2011; Schwid, Covington, Segal, & Goodman, 2002; Scott, van der Linden, Hooper, Cowan, & Mercer, 2013). People with MS and PD are prone to gait vulnerability and less likely to meet physical activity guidelines for health promotion because of unsafe, effortful and inefficient gait.

Physical activity guidelines recommend 150 minutes of moderate to vigorous intensity physical activity over a week in bouts of 10 minutes (http://www.csep.ca/en/guidelines/get-the-guidelines). This translates to cadence of 100 steps a minute for bouts of 10 minutes, twice a day.

Another indication of activity is steps per day and 10,000 or more steps per day would classify a person as 'active' whereas individuals who take >12,500 steps per day are classified as ‘highly active’(Tudor-Locke & Bassett, 2004). It is well established that in order to gain health benefits from walking, intensity of walking performance in crucial. Conventionally, people are asked to walk faster but walking faster could be achieved by either increasing the cadence or step length or both (Grieve & Gear, 1966; Lamoreux, 1970; Murray, Kory, & Clarkson, 1969). Cadence, a gait parameter that is easily understood by the patients, is increasingly used as a treatment outcome and rehabilitation goal. However, a high cadence with short stride length is often a feature of Parkinsonian gait so there is an optimal ratio between cadence and stride length. That optimal ratio may that when the stride length permits adequate heel-to-toe gait. This would lead to a hypothesis that the greater the degree of heel strike, shown by large angular velocity, the greater will be the cadence, but that his may not hold for people with PD. An optimal heel strike could only be achieved with sufficient step length and ankle dorsiflexion during the preceding swing phase in a gait cycle. The foot flat event succeeding a heel strike is a result of eccentric control of ankle dorsiflexor muscles. The rate at which foot slaps the walking surface is directly related to the extent of ankle dorsiflexion and eccentric control of dorsiflexor muscles. The eccentric control of ankle dorsiflexors at heel strike to foot flat is recorded as angular velocity degrees per second (°/sec). Typical values of angular velocity at running speed of 3.5 ± 0.1 meters per second is around 514°/sec (n=24) (Heidenfelder, Sterzing, Bullmann, & Milani, 2008). Literature is scant with respect to typical values of angular velocity for walking and the methodology for obtaining these values differs. One study reported angular velocity values to be 167.3 (SD: 41.9) for 30 women age 70.4 (SD: 2.4) and 161.2 (SD: 52) for 19 women 78.4 (SD: 2.7) using motion 3D motion analysis system (Afiah, Nakashima, Loh, & Muraki, 2016).

Adequate cadence is only one feature of health promoting walking, sustained walking is another. Irregular gait pattern could interfere with sustainability. Some degree of variability is physiologic to human biology and is demonstrated in heart beats, respiration, blood flow and gait. Systems are designed work efficiently within a limit of variability as too much or too little variability is counterproductive. Gait variability has been a focus of scientific enquiry in last the decade. Typically, in healthy subjects, walking at slower gait speeds, and consequently slower cadence, increases variability of kinematic and kinetic parameters of motion at knee, hip and ankle joint. In other words, faster steps are more consistent than slower steps. Gait that is externally paced is also more consistent that self-paced gait, demonstrated by less variability among lower limb joint co-ordination when walking on treadmill compared to when walking over ground (Wheat, Milner, & Bartlett, 2003).

Variability in gait parameters has been shown to be associated with falls in seniors and is a feature of gait in people with MS and PD (Beauchet, Dubost, Herrmann, & Kressig, 2005; Brach, Berlin, VanSwearingen, Newman, & Studenski, 2005; Bryant et al., 2011; Crenshaw, Royer, Richards, & Hudson, 2006b; Owings & Grabiner, 2004; Schrager, Kelly, Price, Ferrucci, & Shumway-Cook, 2008; Socie & Sosnoff, 2013). Variability is also tested in other gait parameters. Increased variability in stride time and length, swing and stance time, and base width has been associated with falls in seniors, Alzheimer's and PD (Lamoth et al., 2011; Schaafsma et al., 2003; Sheridan, Solomont, Kowall, & Hausdorff, 2003). Coefficient of variation, the ratio of variability (SD) to the mean, is an indicator of variability (Abdi, 2010).

In this study, we used the Heel2Toe sensor to capture angular velocity at heel strike and cadence. The Heel2Toe sensor is a device that is a combination of an accelerometer and a gyroscopeconstructed from off the shelf components comprising a Shimmer 2r motion module with six degree of freedom sensor comprising a 3-axis accelerometer (Freescale MMA7361) and a 3 axis gyroscope (InvenSense 500 series MEMS Gyros). The module also incorporates a microcontroller, 8 channels of 12 bit A/D. The sensing module is attached to the side of the subject's right foot using a strap or clip and sensor signals are streamed via Bluetooth to the biofeedback module that runs a real-time algorithm that discriminates good from poor steps using an algorithm based on an angular velocity boundary. When this boundary is crossed, the appropriate real-time feedback is generated. The sensor is, shown in Figure 1, has been shown to be valid and reliable tool in detecting good and bad heel strike events (Vadnerkar et al., 2014; Vadnerkar et al., 2017). The output from the sensors include cadence, proportion of good steps, and angular velocity among other gait parameters. Figure 1 shows the position of Heel2Toe sensor on the foot that runs a real-time algorithm that discriminates good from poor steps with 94% accuracy (Vadnerkar et al., 2014; Vadnerkar et al., 2017) and generates an auditory feedback signal via a Bluetooth connection to a smartphone. No auditory feedback is generated if the step does not pass the angular velocity of =50^{o} per second. The relationship between cadence, good steps and angular velocity in people with seniors, MS, and PD is yet to be established.

Objective

The objective of this study is to estimate, across three populations defined by health condition (seniors, and people with MS or PD), the extent to which cadence is associated with heel-to-toe stepping pattern (good steps), angular velocity and CV of angular velocity at heel strike using Heel2Toe sensor. We hypothesize that the relationship between cadence and proportion of good steps, angular velocity and coefficient will be different among the three populations, with the PD sample showing different relationships than the senior or MS samples.

Methods

Study Design

This is a cross-sectional analysis of data collected withHeel2Toe sensor during clinical walking tests.

Participants

Data on seniors was available (n=40) from previous validation study on Heel2Toe sensor. Additional data (n=17) on seniors was added. People with MS (n=57) were recruited for a randomized controlled trial on Role of Exercise in Modifying Outcomes for People with MS (Mayo et al., 2013).To be included in the trial, diagnosis of MS had to be done after 1994, age between 19 to 65 years and be independent in ambulation without use of walking aid. Participants were excluded if they: (1) were already exercising three or more time per week; (ii) had any additional illness that restricted their function; (iv) had experienced a relapse during the past 30 days; and (iv) showed difficulty reading, understand or speaking either French or English(Jacobs et al., 2000; Marriott, Miyasaki, Gronseth, & O'Connor, 2010; Polman et al., 2006). Data from people with PD (n=26) were collected as a part of pilot study on a novel Approach to Clinical Assessment and Personalized Intervention in Early Parkinson's Disease. Heel2Toe was deployed during clinical walk tests. For people with MS, the sensor was incorporated during six-minute walk test; for seniors and people with PD the sensor was used during a 2 minute walk test.

Data Extraction and Statistical Methods

The raw data from the sensor was exported and variables of interested extracted using MATLAB 2017b (The MathWorks, Inc., Natick, Massachusetts, United States). The variables analyzed from the Heel2Toe sensor were cadence (steps per minute), good steps (%), angular velocity (degrees per second). The values for angular velocity are in negative representing the extent of ankle dorsiflexion and subsequent plantarflexion, more negative values are better. Patients' characteristics were summarized with using mean and standard deviation (SD) and proportions, where appropriate. Pearson product moment correlations were performed, separately for each population, between pairs of continuous variables: proportion of good steps, angular velocity, coefficient of variation, and cadence. Multiple linear regression was carried out with cadence as the outcome variable. The other variables in the model included health condition, age and sex as adjustment variables, and each of the gait quality variables separately. The interaction with health condition and age was tested. The results are displayed as beta (β), standard error (se), and 95% confidence intervals (CI).

Diagnostics, including Kolmogorov-Smirnov test, residual-by-predicted plots, and scatter plots were generated to verify the assumptions of normality, homoscedasticity, linearity. All the analysis were performed using Statistical Analysis System® 9.4 software (Institute, 2014).

Results

Data on a total of 140 people were available for analyses: 57 people with MS, 27 with PD and 56 seniors. Table 1 displays the characteristics of the three sample populations with mean and standard deviation (SD) for cadence, proportion of good steps and angular velocity.

Table 2 shows the Pearson product moment correlation coefficients between angular velocity, CV of angular velocity and proportion of good steps with cadence across three health conditions. For the seniors group the correlation coefficients between cadence and angular velocity, CV of angular velocity, and % good steps were -0.49, 0.25 and 0.41, respectively. For people with PD and MS, these coefficients were somewhat lower. Age was correlated moderately with cadence (r= -0.59) and ankle angular velocity (r=0.57), less strongly with % good steps (0.34), and weakly with CV of angular velocity (r=-0.17).

Table 3 shows the results of multiple linear regression analysis on the average cadence as the outcome. The preliminary model included only age and sex and, while age was significantly associated with cadence (β: -5.4; se; 0.7), sex was not (β: -1.2; se: 2.3). Model 1 retained age and sex and added health condition with the senior group as the referent category. Three other models were tested. Models 2, 3 and 4 also included age and sex and each of the other explanatory gait variables separately (% good steps, angular velocity and CV of angular velocity). All of the four models showed a statistically significant main effect for health condition with no interaction with age. Of the variables related to gait quality, only angular velocity showed a significant relationship with cadence. Every -50^{o} difference in angular velocity (more negative is better) was associated with an increase of ≈3.5 steps per minute.

Discussion

The mean values for cadence, % good steps and angular velocity were highest for people with MS (mean age 48 years), next highest for people with PD (mean age 71 years) and lastly seniors (mean age 82 years). Age and health condition were strongly related and, as shown in Table 3, age was a significant predictor of cadence, but not when health condition was in the model. This suggests that health condition has an association with cadence that is independent of age.

The results of linear regression analysis show that cadence was not predicted by % good steps or by CV of angular velocity (see Table 3) but was predicted by degree of angular velocity. Previous research suggests that humans prefer to walk at certain speed and cadence so as to optimize the metabolic cost of walking (Donelan, Kram, & Kuo, 2001). In this study, it seems that this preference for optimal cadence holds across health conditions and is not influenced by consistency in the quality of the steps (% good steps or consistency and CV of angular velocity). However, CV is influenced by angular velocity which is linked to cadence through stride length. With an increase in stride length, comes a sharper angle at heel strike and *vice versa*. Heel strike would seem to be a primary therapeutic target followed by consistency in the quality of the steps.

Of the three populations, people with MS, who were younger and who had already signed up to join an exercise study, had the best values for cadence and for gait quality. However, they still showed the same high degree of variability in angular velocity suggesting that consistency in heel strike would be a therapeutic target even for those with good values on the other parameters.

Targeting gait quality would be important preparation for reaching targets for health promoting walking. This study suggests showed that therapy to improve walking should target angular velocity of the ankle joint. Practicing heel-to-toe gait pattern is often incorporated into gait training. There are some technologies that are commercially available that provide feedback for one or more of these gait quality parameters. Technology alone cannot translate to improve walking unless accompanied by educational material to improve the persons capacity to benefit from the technology. For example, for people with MS, balance, core and peripheral muscle strength, and endurance are affected. In a recent paper, Mate et al (Paper 1 of this thesis), showed that people reported less limitations in walking activities when they had better balance, quadriceps strength, leg power, and endurance. It is important one walks well before walking long.

Limitations

This study has several limitations. The three populations were selected as convenience samples as participants were enrolled in other studies. Nevertheless, this is the largest sample to date that has information on these gait parameters. The Heel2Toe technology is relatively new and is only one way of extracting gait parameters. Future studies could compare outputs from Heel2Toe with other motion capture systems and validate this relationship in different samples including healthy populations of different ages.

Conclusion

Of the three indicators of gait quality studied here, only angular velocity had a relationship with cadence in these three populations. Angular velocity is an easily targeted parameter during therapy, but to sustain the relearned movement during everyday activities, technology would be an asset. A technology preference would be for real-time feedback for steps with adequate angular velocity at heel strike.

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Figure 1: Shows the position of Heel2Toe sensor on the foot

Table 1: Characteristics of study participants

Variables	Mean ± SD or N (%)		
	MS	PD	Seniors
No. of subjects	57	27	56
Age (years)	48.1 ± 9.9	71.0 ± 6.9	82.6±8.7
Sex (Women/Men)	39 / 17	10 / 12	6 / 13
Time since diagnosis	7.4 (5.9)	6.0 ± 4.1	---
Cadence (no. of steps per minute)	120.1 (12.6)	110.1 (10.2)	97.4 (14.5)
% good steps	89.9 (5.1)	73.7 (29.5)	72.6 (29.5)
Angular Velocity (^{o}/ sec)	-220.6 (52.1)	-159.6 (57.3)	-141.3 (57.2)

Table 2: Correlation of Angular Velocity, Coefficient of Variation of Angular Velocity and Proportion of Good Steps with Cadence across three Health Conditions

Group	MS (n=57)	PD (n=27)	Seniors (n=56)	Age (n=140)
	r (95% CI)			
Angular Velocity	**-0.35** **(**-0.56, -0.10)	-0.06 (-0.33, 0.43)	**-0.49** **(-0.67, -0.26)**	0.57 (0.45, 0.67)
CV angular velocity	0.16 (-0.40, 0.10)	-0.19 (-0.54, 0.21)	0.25 (-0.01, 0.48)	-0.17 (-0.33, -0.005)
Good steps (%)	0.16 (-0.40, 0.10)	-0.17 (-0.52, 0.23)	**0.41** **(0.16, 0.61)**	**-0.34** **(-0.48, -0.19)**
Age				

CI: Confidence interval; those that exclude 0

Table 3: Linear regression models with explanatory variables for cadence

	β (se)	(95% CI)
Model 1: R^2		0.45
Health condition		
Seniors	Referent	
MS	**20.4 (5.7)**	**14.7, 26.1**
PD	**14.9 (4.2)**	**10.7, 19.1**
Age (per decade)	1.8 (2.1)	-0.3, 3.9
Sex (men v/s women)	-0.2 (0.1)	-0.3, -0.1
Model 2*: R^2		0.46
Health condition		
Seniors	Referent	
MS	**20.1 (5.7)**	**14.4, 25.8**
PD	**15.1 (4.2)**	**10.9, 19.3**
% good Steps per 10%	0.4 (0.6)	-0.2, 1.0
Model 3*: R^2		0.51
Health condition		
Seniors	Referent	
MS	**18.7 (5.5)**	**13.2, 24.2**
PD	**14.8 (3.9)**	**10.9, 18.7**
Angular velocity (°/sec) per 10°	**-0.7 (0.2)**	**-0.5, -0.9**
Model 4*: R^2		
Health condition		0.47
Seniors	Referent	
MS	**20.2 (5.6)**	**14.6, 25.8**
PD	**14.3 (4.1)**	**10.2, 18.4**
CV of angular velocity per 0.1	1.9 (1.1)	0.8, 3.0

*Adjusted for age and sex in a multiple linear regression model

Significant results (where 95% CI exclude the value of 0) are shown in bold

CHAPTER 11: DISCUSSION

The overall objective of this PhD thesis work is to contribute evidence towards how the different sources of information about walking (SRO, PerfO and TechO) provide convergent or divergent information about walking capacity and walking performance among people with health conditions that lead to gait vulnerability. This overall objective was achieved through four linked manuscript, two of which are under-peer review, one is submitted, and the last manuscript will be submitted for publication in due course.

Clinical decisions and outcomes in clinical trials are often based on tests of physical performance that are carried out with standard procedures and instructions. Performance on these outcomes may not accurately reflect what people do in their daily lives. This hypothesis was tested in the first manuscript where commonly used performance tests (PerfOs) were correlated with SRO measures in people with MS and tested whether this relationship was same for women and men.

The data available yielded 165 pair-wise comparisons for women and men. In some fields, multiple comparisons are frowned upon and researchers often use a Bonferroni correction to set a p-value threshold for statistical significance lower than the traditional value of 0.05 by a factor related to the number of comparisons. In this case, this would mean setting the p-value for significance at 0.0003 for women and men. The focus here was the magnitude of the estimate rather than whether it differed from null. This hypothesis does not need to tested as the items correlated were chosen to have theoretical coherence. When estimating parameters, the estimate of the parameter does not depend on the number of parameters estimated [133]. Nevertheless, we focused on estimates ≥0.8 as indicating ecological validity and, in this sample size, the probability that 0.8 is non-zero is <0.0001. In Tables 3 and 4 of manuscript 1, the item-pairs presented had at least one correlation ≥0.8 for women or men.

The key findings from the first manuscript were that half of the PerfO tests in people with MS showed moderate correlations (≈0.5) with SRO items with the correlations stronger for men than women. The balance items (from EQUI scale) were most strongly related to SRO followed by 6MWT. 9HPT and grip strength, PerfOs that are commonly used in clinical practice, were not strongly correlated with SROs. PerfO of maximal performance such as vertical jump (leg power), push-ups (upper body strength), curl-ups (core strength) and step tests (cardiovascular endurance) correlated with SRO supporting their ecological validity. The first manuscript highlighted that not all tests of physical performance are related to how a person reports on their function in everyday life and that the relationship between SRO and PerfO is not same across women and men with MS. Furthermore, tests of balance, upper body and core strength, leg power, and tests for cardiovascular endurance should be included to monitor progress in people with MS and in research. This is important because clinicians and researchers need to select outcomes that are related to person's real-life. Treatment should improve activities in daily life and not just tests in the clinic or laboratory. The gender difference was particularly important for two reasons, MS affects women and men differentially and second, women and men have different gender roles in daily life. If there was a differential relationship between PerfO and SRO the treatment target would need to match what women and men do in their daily life. The differential sex/gender relationship observed for women and men with MS, aligns with Canadian Institute of Health Research's Sex and Gender-Based Analysis (SGBA) in Research Action Plan commitment to address sex and gender differences in health research.

Another aspect of the first manuscript was to relate PerfO items to SRO items, a relationship not yet explored in research. This manuscript provided a list of PerfO items that relate to commonly used SROs of physical function in people with MS. This is important because, SROs are increasingly used as one of the main outcomes in clinical trials and are also gaining popularity for routine clinical practice. However, we do not yet know what PerfO items should be targeted so to have an impact on those self-reported activity limitations/difficulties. For example, people reported less limitation in walking more than a kilometer (SRO item) when they had better values on the PerfO items standing balance, tandem stance, comfortable and fast gait speed and 6MWT. Interventions could be targeted to improve standing balance and tandem stance, components that could improve gait speed, and functional walking capacity, and ultimately translating to less limitation in walking long distances. SROs are increasingly used in research as confirmatory outcomes and, unless we know what PerfO items to target to change these self-report items, it will be hard to expect any shift in SRO response.

Manuscript 1 found that the distance walked on the 6MWT was one PerfO that related to how people reported their everyday function. The second manuscript looked at whether this 6MWT distance as measured in the clinical or laboratory setting related to physical activity in the community. For this manuscript, I linked results from the 6MWT to data from accelerometers.

This was an entirely different learning experience. The vast amount of data available from accelerometers proved a challenge for data management and analysis. Typically, studies using accelerometer data report mean step count over the recording period, usually 7 days. One of Dr. Mayo's quotes is very apt here, ‘data like vegetables, should be served raw’. I learned how to best deal with the raw data to produce meaningful metrics for walking capacity and also walking performance. The mean step count may not be an accurate representation of daily lives, when one may engage in high intensity activities such as sports or low intensity activities such as walking around the house. I had to consider step counts at different intensities, not only as an overall step count. I also had to create walking bouts, something not typically done with accelerometer data.

An additional challenge was that the data on step count was not normally distributed (skewed toward left). Skewed data needs to be dealt with appropriately fitting regression models. Here I used quantile regression which models the effect of explanatory variables on the median or other distribution cut-point and contrasted these results to those from linear regression which makes inference from the mean. Other parameters that can be derived from accelerometer data include counts of bouts of activity. This is a more relevant outcome for health promotion as the physical activity guidelines stipulate 150 minutes of moderate to vigorous aerobic activity accumulated over one week in bouts of 10 minutes or more. Bouts are counts of events are best modeled using a Poisson model but because there was excess of zeros in this data, negative binomial or zero-inflated Poisson (ZIP) models were more optimal [134]. As the denominator for the walking bouts was not people but person-time in view, Poisson model was needed and in particular the ZIP model.

The results of this study showed that people with MS spent variable proportion (20.5%-72.5%) of their usual day walking at a pace equivalent to the pace assessed clinically. Not surprising people with more severe walking disability (6MWT <300 m) showed more consistency between free-living walking and that assessed clinically (72.5% of steps ≥ clinically measured 6MWT) as they have limited capacity to increase their walking pace. However, people with MS with greater walking capacity (≥500 meters on 6MWT) rarely walked at the measured pace outside of the clinic (12.2% - 20.5%; see Table 2 of Manuscript 2). Although, the total number steps taken per day was greater, on average, for people with higher walking capacity, they did not distribute these steps towards walking for longer durations. To illustrate, people who walked less than <300 m spent an average of 50.7% of their daily upright time (standing and stepping) walking in short bouts of 1 minute and those with greater capacity for walking showed similar results.

The striking finding from this project was that people across all abilities of 6MWT did not engage in health promoting walking as measured using 5 minute bouts. The crude rate of walking bouts per 1000 hours of waking time ranged from 8.35 to 11.44 with no trend for increasing rates with increasing capacity (see Table 3 of Manuscript 2).

The manuscript uncovered the gap that ability to perform well on walk tests during clinical visits does not translate into health promoting walking performance. Walking performance measured by step counts was not explained by variables related to behaviour (COM-B) [2-4]: exercise self-efficacy, barriers, fatigue, motivation, and mood. However, walking bouts was explained by mood and exercise barriers underlining the importance of assessing and optimizing these concerns before making recommendations that the person may not be able to realize.

The fact that only mood and exercise barriers were associated with producing walking bouts of five minutes or more indicates that there may be other factors that limit translation of walking capacity to engaging in health promoting walking. Other possible factors that could be studied in future projects could include opportunity for time and space, walkability, that is built environment such as parks that provide opportunity to practice high intensity walking etc.

The third manuscript is an example of the link between TechO and SROs, although this point was not emphasized in the manuscript *per se* owing to the need to target the journal audience. The TechOs were the cadence, proportion of good steps, angular velocity of at heel strike, and variability of the latter. The SRO was the person's self-perceived walking speed. The context for this link was a single-arm pilot study of changes occurring following 5 training sessions using the Heel2Toe feedback device. The results showed that all of the TechO gait parameters improved and that people also reported walking at a faster pace. However, the main focus of the manuscript in terms of publication was results of the training.

The study provided evidence to support gait adaptation in response to short duration intensive training session with Heel2Toe sensor combined with exercises. The main message from this manuscript is that gait in older adults is modifiable in response to real-time auditory feedback. All 6 participants showed improvements in at least one gait parameter. Heel2Toe sensor is advantageous over other device available in the market as it provides real time auditory feedback and opportunity for repetitive practice that is necessary for motor learning and neuroplasticity. Older adults have not lost their skill to walk, however, as a result of age-related musculoskeletal changes, gait becomes inefficient. Home exercise plan with training with real-time feedback from Heel2Toe sensor to correct steps provided the necessary stimulus to re-learn the optimal gait pattern. An interesting gait parameter that has recently being of enquiry is angular velocity at heel strike. As per my knowledge, Heel2Toe sensor is the only device that uses angular velocity at ankle during heel strike as a source for generating auditory feedback.

This project also provided me with an insight into conducting semi-structured interviews, a skill that will be useful in future research career. I acknowledge that this was a not a randomized controlled trial, however, the use of Heel2Toe sensor as feedback device to improve gait among older adults provides is an early indication of potential therapeutic treatment option that could be available to rehabilitation professional working with older adults to improve gait. I see this device available to therapist in clinics and rehabilitation centers to provide short duration intensive training with optimal gait pattern. There are numerous future implementation plans for this sensor and some of them are already in pipeline. I am involved with these new projects that will lead to eventually to commercialization of this sensor as part of a Walk-Well Toolkit. My involvement with testing Heel2Toe sensor provided me opportunities outside academia such as developing a business canvas, talking to stakeholders who are not typical researchers, showcasing our device at conferences, searching for potential funding opportunities that bridge the gap of technology in the lab to technology in the market.

The fourth manuscript reports on the relationship between cadence and proportion of good steps, angular velocity and coefficient of variation of angular velocity and also whether this relationship was same across seniors, people with MS or PD. Data for this manuscript came from the Heel2Toe sensor that was deployed in three populations that were recruited for different projects. Multiple linear regression analysis showed significant main effect of health condition that was independent of age. This project was important for two reasons; first, cadence is increasingly recognized as an important target to achieve and maintain health as it is easily understood by people. Walking intensity is typically expressed as metabolic equivalents (METs) and the conversion of cadence to walking intensity is known. For example, cadence of 100 steps minute is equivalent to 3 METs. This focus on cadence is easier for people to implement themselves and will help people monitor their intensity of walking.

Extrapolating from the findings that angular velocity was associated with cadence might suggest that practicing heel-to-toe gait pattern could a way of improving cadence. Therapists use this strategy clinically with limited carryover into every day activity [5-7]. There are some technologies that are commercially available that provide feedback for one or more of these gait quality parameters. Technology alone cannot not translate to improve walking unless accompanied by educational material to improve the persons capacity to benefit from the technology. It is important one walks well before making recommendations for walking long.

Research limitations and future directions

It is not possible to address all the questions related to walking in seniors, people with PD or MS. This thesis was an attempt to address some of those questions. Not every permutation and combination of outcome measures on the three populations is reported and studied in this thesis.

Use of SROs is increasing in research settings and clinical trials and will soon be implemented in routine data collection within the healthcare system. It is important that SRO chosen are ecologically valid. The Heel2Toe sensor is currently tested in people with PD and eventually will be deployed in stroke population. The ultimate aim of all these projects involving Heel2Toe is to make the device available to general public who wishes to improve their gait. The sensor will be accompanied with a Walk-Well Workbook and a video, products that are in preparation and I am involved in the development of the content.

Concluding statement

This thesis work highlights a novel working the area of walking in seniors, people with MS or PD. The findings from these four manuscripts answered some questions but raised many more that will need future work. This thesis is not the end of this work but a beginning for new and exciting projects in the area of walking for gait vulnerable populations.

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