

THESIS

REHABILITATIVE TARGETS TO INCREASE PHYSICAL ACTIVITY IN PATIENTS WITH
MULTIPLE SCLEROSIS

Submitted by

Nathaniel B. Ketelhut

Department of Health and Exercise Science

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Master's Committee:

Advisor: Thorsten Rudroff

Brian Tracy

Raoul Reiser II

Aga Burzynska

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ABSTRACT

REHABILITATIVE TARGETS TO INCREASE PHYSICAL ACTIVITY IN PATIENTS WITH MULTIPLE SCLEROSIS

Background: Physical activity has been shown to have positive effects on the disease symptoms of multiple sclerosis. However, patients with multiple sclerosis are less active than their healthy counterparts. Previous studies of the predictors of physical activity in this patient population have been limited in their translation to the rehabilitative setting.

Objective: To identify behavioral and functional predictors of physical activity in patients with multiple sclerosis to provide targets for rehabilitative specialists.

Methods: A total of 16 behavioral and functional tests were conducted and physical activity was objectively measured for one week. A stepwise multiple regression analysis was performed to identify the strongest predictors of moderate-to-vigorous physical activity and total activity/day.

Results: The stepwise procedure converged on a model for moderate-to-vigorous physical activity ($R^2=0.35$, $P=0.001$) that included total leg strength of the less-affected side (partial $r=0.42$, $P=0.016$) and Falls Efficacy Scale-International score (partial $r=-0.37$, $P=0.033$). The model for total activity ($R^2=0.41$, $P<0.001$) included five-times sit-to-stand performance (partial $r=-0.42$, $P=0.014$) and total leg strength of the less-affected side (partial $r=0.35$, $P=0.049$).

Conclusion: Rehabilitative specialists aiming to improve physical activity in patients with multiple sclerosis should implement exercise programs that combine balance and strength training of the legs.

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LIST OF ABBREVIATIONS

9-HPT – 9-Hole Peg Test
COP – Centers of Pressure
DXA – Dual-Energy X-ray Absorptiometry
EDSS – Expanded Disability Status Scale
FES-I – Falls Efficacy Scale-International
FSS – Fatigue Severity Scale
MAS – Modified Ashworth Scale
MFIS – Modified Fatigue Impact Scale
MS – Multiple Sclerosis
MVPA – Moderate-to-Vigorous Physical Activity / Day
PASAT-3” – 3 Minute Paced Auditory Serial Addition Test
PD – Parkinson’s Disease
PDDS – Patient Determined Disease Steps
PwMS – Patients with Multiple Sclerosis
PwPD – Patients with Parkinson’s Disease

1. LITERATURE REVIEW

1.1 Introduction to Multiple Sclerosis

Multiple Sclerosis (MS) is an autoimmune disease that leads to inflammation and demyelination in the central nervous system [1]. MS is most common in Caucasians of northern European descent and women are at least 2-3 times more likely to develop the disease than men [2]. MS affects an estimated 2.3 million people worldwide [3] and is the most common disabling neurological disease of young adults in the US [4]. Disease progression usually follows 1 of the following 4 courses, with each more disabling than the last: relapsing remitting, primary progressive, secondary progressive, and progressive relapsing [5].

Demyelination of the central nervous system leads to a wide variety of disease symptoms that are unpredictable and different for everyone. These symptoms include fatigue, weakness, walking difficulties, spasticity, vision impairments, cognitive changes, autonomic dysfunction, temperature sensitivity, and many others [3]. For many years, patients with MS (PwMS) were told to avoid strenuous activity for fear of worsening neurological symptoms due to overheating and increased fatigue [6-7]. However, it is now understood that the side effects following strenuous activity are only temporary, and that physical activity is both safe and effective in the treatment of disease symptoms [6,8].

1.2 Physical Activity in Multiple Sclerosis

Many studies have investigated the impact of physical activity on a variety of factors in PwMS. One study using optical coherence tomography found that physical activity was positively associated with the thickness of the retinal nerve fiber layer and total macular volume, which are each markers of neuronal integrity of the anterior visual pathway [9]. Other studies

have found that physical activity is positively correlated with cardiovascular health and mobility [10-13]. Physical activity has also been shown to be associated with cognitive function [14-15], fatigue and depression [16], potential slowing of disease progression [17], and most importantly, overall quality of life [18-19].

Unfortunately, PwMS continue to be less active than their healthy counterparts despite the many benefits discussed above. A meta-analysis showed that the magnitude of difference in physical activity between PwMS and non-diseased individuals approached 1 standard deviation [20]. Another study involving a secondary analysis of objectively measured physical activity in 800 PwMS and 137 healthy controls found that PwMS get less than 20 min of moderate-to-vigorous physical activity (MVPA) / day, which is approximately 13 min less than the healthy controls [21]. The 2008 Physical Activity Guidelines for Americans recommend at least 30 min of MVPA / day or 150 min of MVPA / week for optimal health benefits [22]. The secondary analysis above found that less than 20% of PwMS were meeting these guidelines. This inactivity is worsened by evidence showing a further reduction in physical activity over time in PwMS [23].

Together, the health benefits associated with an active lifestyle and the high rate of physical inactivity in PwMS have led to studies investigating the reasons for reduced physical activity in this patient population. The majority of these studies are correlational in nature and attempt to identify MS-related factors that are associated with lower activity levels. A combination of original research, reviews, and meta-analyses have identified many predictors of physical activity in MS including: disease duration [21], disability level [21,24], walking ability [24-26], fall risk [27], overall symptoms [26,28-29], self-efficacy [23-24], employment status [21,24], education level [21,24], gender [25,30], age [30], body mass index [30], and several

others. Unfortunately, many of these studies were limited due to self-reported physical activity and only including a minimal number of factors in each study. Furthermore, nearly all of these predictors, such as age, gender, disease duration, employment status, and education level are unchangeable in the rehabilitation setting and do not provide targets for rehabilitative specialists aiming to improve physical activity in PwMS.

1.3 Exercise in Multiple Sclerosis

Implementing an exercise regimen is a common technique to increase physical activity [31]. As a result, many studies have investigated the efficacy of exercise programs in PwMS that include both aerobic and resistance training at a variety of intensities and disease severities. Multiple review articles on exercise in MS have all concluded that exercise is safe and that no study has found a chronic worsening of symptoms following an exercise regimen [5-6,32]. Furthermore, it has been repeatedly demonstrated that PwMS respond to resistance and aerobic training with improvements in strength and cardiorespiratory fitness [33-35]. The improvements in strength have been attributed to increased rate of force development and muscle cross sectional area [36] as well as increased neural drive [37] following resistance training, while the mechanisms of improved cardiorespiratory fitness remain uncharacterized. Potential mechanisms could be improved cardiac output and cardiac autonomic control. However, one study did find that cardiac autonomic control was not improved following 6 months of aerobic and resistance training [38]. Future studies are needed to determine the mechanisms of improved cardiorespiratory fitness in PwMS.

While the underlying mechanisms remain fairly unknown, increased strength and cardiorespiratory fitness has been associated with improvements in fatigue [32,34,39], depression [39], disease severity [40], walking [34,39], and quality of life [34,39]. Importantly,

exercise has even been shown to reduce the inflammatory response of MS in several studies [41-42]. However, the effect of exercise on other common factors of MS, such as cognition, remains unclear [43].

Other types of exercise have also been investigated in PwMS. For example, aquatic training and yoga have been shown to improve fatigue and depression [44]. Studies investigating high intensity resistance and aerobic training have also concluded that it is safe and effective at treating the symptoms of MS [40,45]. Together, these studies clearly demonstrate that many forms of exercise are potential treatments of disease symptoms for PwMS. It is currently recommended that PwMS engage in a combination of aerobic and resistance training for optimal benefits and that PwMS at varying disability levels can benefit from exercise [46].

1.4 Exercise in Parkinson's Disease

Parkinson's (PD) is another degenerative disease of the central nervous system that leads to impaired movement and reduced physical activity [47]. Physical activity and exercise has been shown to have beneficial effects on overall physical performance and balance [48] as well as strength and walking speed [49-50]. However, the beneficial effects of exercise on cognitive function are limited [51-52]. Future studies are still needed to fully establish exercise recommendations for patients with PD (PwPD) [53].

1.5 Comparing Multiple Sclerosis and Parkinson's Disease

Comparing physical activity and its respective predictors in PwMS and PwPD could provide important information for rehabilitative specialists aiming to improve physical activity in patients with neurological disorders. Unfortunately, only one study was found that measured physical activity in both PwMS and PwPD [54]. Furthermore, the challenge of comparing physical activity in these two groups is expanded by the inconsistent sampling and reporting

methods in the PD literature. Several studies used questionnaires to quantify physical activity [55-57], while others objectively measured physical activity but reported the data in steps [58-60], mean vector magnitude [54], or kcal / day [61] instead of min of activity / day. One study did report activity as min / day, but categorized intensity based on cut points derived for healthy individuals rather than PD-specific cut points [62]. While these differences present a challenge to comparing physical activity between PwMS and PwPD, it does appear that there may be differences in physical activity between the groups.

Hale and colleagues [54] measured physical activity in 11 PwMS and 7 PwPD and found that the PwPD were approximately 21% less active over 7 days than the PwMS. Furthermore, one study found that PwPD spent 98% of their day in sedentary activity [61], while another study reported that PwMS spent approximately 90% of their day in “static activity” [63]. Regardless of the difference between PwMS and PwPD, it is commonly accepted that both groups are less active than their healthy counterparts [20-21,56,59].

The increased rate of physical inactivity in these two patient populations should theoretically put each group at increased risk of activity-related comorbidity. While the comorbidity literature does appear to be limited for both diseases, the available data does support the hypothesis that PwMS and PwPD have a high prevalence of comorbidity. One study surveyed 2399 PwMS and found that 22.5% were overweight and 19.4% of responders were obese [64]. Furthermore, the overweight and obese individuals were at greater risk of other comorbidities such as diabetes, hypertension, and cardiovascular disease. However, these rates are lower than the 2014 national average for overweight (35%) and obese (29%) [65]. A study with 194 PwPD found that 23% of the participants had metabolic syndrome, but they did not report the prevalence of overweight or obesity in their sample [66]. Again, this is actually lower

than the national prevalence of metabolic syndrome (33%) from 2003-2012 [67]. These findings suggest that factors other than physical activity may be influencing the prevalence of activity-related comorbidities in these neurological disorders.

While it may appear that PwMS and PwPD are not actually at an increased risk of activity-related comorbidities, the beneficial impact of physical activity on disease symptoms make it important to understand the predictors of physical activity in each of these populations. As previously discussed, the predictors of physical activity in PwMS are highly varied and not fully understood. Similar results have been found in the PD literature, with factors such as disease severity [56,59-61], age [59,61], gender [61], cognition [55,59], balance [58-59], fall risk [57], and walking ability [56,58] being common predictors of physical activity. These predictors are very similar to those found in PwMS, but more research is needed for both diseases to determine whether neuromuscular factors such as strength, power, and motor control contribute to physical activity.

1.6 Conclusions

It is clear that physical activity has a positive influence on disease symptoms of MS. Exercise in a variety of forms is a safe and effective means of increasing physical activity for PwMS, as well as improving strength and cardiorespiratory fitness. It is still unknown whether physical activity in PwMS differs from other neurological disorders such as Parkinson's disease, but it does appear that physical activity is influenced by similar factors in these disorders. Future studies are needed that include multiple neurological disorders to better understand the factors that influence physical activity in order to provide rehabilitative targets for specialists aiming to improve the lives of patients with neurological disorders.

2. INTRODUCTION

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system that affects more than 2.3 million people worldwide and has 100,000 new cases each year [2]. The symptoms of MS are highly varied, but frequently include a more-affected side and impaired walking, balance, strength, fatigue resistance, and cognition [5,68-71]. These symptoms often lead to reduced physical activity, which can increase the risk of comorbidities such as heart disease, obesity, and diabetes mellitus [5]. As a result, much research has focused on the efficacy of exercise in modifying the symptoms of MS.

Recent reviews that summarized the findings of over 50 clinical trials of exercise training in patients with MS (PwMS) demonstrated that exercise is both safe and beneficial for this patient population [32,34,39]. These benefits include improved strength, walking performance, aerobic capacity, balance, quality of life, depressive symptoms, perception of fatigue, disease severity, and potentially relapse rate [34,39]. Despite these benefits, PwMS continue to be less physically active than their healthy counterparts [20].

Several studies have attempted to determine the reasons for lower physical activity by identifying its predictors in PwMS. These investigations have identified factors such as physical activity-related self-efficacy and sociodemographic factors [24], walking speed and gender [25], as well as years since diagnosis, cardiovascular comorbidities, and the ability to walk independently [72]. Unfortunately, most of these factors have limited applicability in the physical rehabilitation setting, which may prevent rehabilitative specialists from directly targeting factors that may improve physical activity. Furthermore, these studies usually only focused on one or two factors that could affect physical activity (i.e. sociodemographic and self-

efficacy). Therefore, the purpose of this study was to test a wide variety of factors and identify the strongest behavioral and functional predictors of physical activity in PwMS to provide targets for rehabilitative specialists.

3. METHODS

3.1 Participants

Participants were recruited through the Center for Neurorehabilitation Services in Fort Collins, CO. Inclusion criteria included a confirmed diagnosis of MS, aged 21-75 years, and the ability to ambulate at least 100 m. Exclusion criteria included a relapse of disease symptoms, change in medication, or hospitalization within the last 3 months, a condition unrelated to MS that would exacerbate fatigue, any contraindications to exercise, and pregnancy. All participants signed informed consent approved by the Colorado State University Institutional Review Board and were in accordance with the Declaration of Helsinki.

3.2 Testing

A total of 16 tests were conducted in the morning hours over the course of 3 visits in an effort to reduce the effect of fatigue on task performance. The first visit was conducted at the Center for Neurorehabilitation Services and included the completion of 5 questionnaires, grip strength measurements, and spasticity assessment. The second and third visit were conducted in the Human Performance and Clinical Research Laboratories at Colorado State University. The second visit was composed of several tests examining lower/upper body and cognitive function. Strength assessments of the knee extensors and flexors of each leg were performed during the third visit. Finally, physical activity was measured for one week between the first and second visit, and a whole body dual-energy X-ray absorptiometry (DXA) scan was performed at the second or third visit (depending on time availability).

3.3 Questionnaires

Disability status was measured using the Patient Determined Disease Steps (PDDS) [73], and perceived fatigue levels were evaluated using the Fatigue Severity Scale (FSS) [74] and Modified Fatigue Impact Scale (MFIS) [75]. Perceived risk of falling while performing a variety of tasks was assessed using the Falls Efficacy Scale-International (FES-I) [76], and their handedness was measured with Appendix II of the Edinburgh Handedness Inventory [77].

3.4 Grip Strength

Maximal voluntary hand grip strength was assessed using a hydraulic JAMAR 5030J1 hand dynamometer (Sammons Preston Rolyan, Bolingbrook, IL). Measurements were performed with the participant in a standardized posture [78]. The dynamometer was adjusted for each participant to control for hand size, and strong verbal encouragement was given while the participant performed 2-5 maximal trials with each hand. Testing was stopped once 2 scores within 5% were achieved. Trials were alternated between hands to provide 60 sec of rest between trials for each hand.

3.5 Modified Ashworth Scale

Spasticity of the quadriceps, hamstrings, and adductors was assessed bilaterally by a certified physical therapist using the Modified Ashworth Scale (MAS) [79]. The scale ranging from 0-4 (which includes a value of 1+ between scores of 1 and 2) was converted to a 0-5 scale. The resulting values were summed to obtain an overall score ranging from 0-30 [79].

3.6 Physical Activity Assessment

Physical activity was measured using ActiGraph model GT3X+ accelerometers (Pensacola, FL). The accelerometer was worn on an elastic belt above the self-reported non-dominant hip and was initialized using the low-frequency extension feature and a sampling rate

of 30 Hz [80-81]. The data was downloaded with an epoch of 15 sec and accelerometer counts in the vertical axis was analyzed in counts per minute (cpm) [80]. Wear time was validated with the following criteria: minimum of 10 hours / day, a minimum of 4 valid days, at least 1 weekend day [82]. Time in moderate-to-vigorous physical activity / day (MVPA) was determined using cut-points as described [81]. Total physical activity was determined by summing MVPA and light physical activity. Since the cut points for disability status were determined using the Expanded Disability Status Scale (EDSS) scores, PDDS scores were converted to EDSS scores [83]. Wear logs were completed by the participants to verify accelerometer data.

3.7 Timed 25-FT Walk Test

Four trials of the timed 25 FT walk test were completed, and the time to complete the first two trials was averaged [79]. All four trials were completed while wearing unobtrusive inertial measurement units on each leg (data to be published elsewhere).

3.8 9-Hole Peg Test and Paced Auditory Serial Addition Test

Complete instructions for the 9-HPT and PASAT-3” can be found at www.nationalmssociety.org. Briefly, the 9-HPT asks patients to place and remove pegs from a 3x3 grid of holes as quickly as possible. The PASAT-3” requires patients to continuously add the last two numbers spoken on a standardized recording for 3 minutes.

3.9 Postural Stability

Postural stability was assessed using two Bertec 4060-10 force platforms (Columbus, OH) mounted edge-to-edge and flush to the surrounding floor surface. Participants were instructed to quietly stand with one foot completely on each platform, looking straight ahead with their head erect, arms at their sides, and knees extended but not locked. Participants were instructed to remain as still as possible throughout four 60 sec trials; 2 trials with eyes open

followed by 2 trials with eyes closed. Approximately 2 min of rest was provided between each trial, during which the participant could sit or stand. Ground reaction forces and moments were recorded at 100 Hz, from which the system internally computed centers of pressure (COPs). To ensure a consistent stance width between trials and across participants, stance width was set to 10% of the participant's standing height. Net COP path lengths in the anterior-posterior and medial-lateral axes were computed over the entire trial using custom MatLab code (Natick, MA) and normalized to % standing height to account for inter-subject size variations within the group.

3.10 Sit-to-Stand

Two trials of the five-times sit-to-stand test were performed, and the faster of the two trials was recorded [84]. The participants were instructed to rise from a seated to standing position and return to a seated position as quickly and safely as possible 5 times with their arms folded across their chest throughout the test. Approximately 3 min of rest was provided between trials.

3.11 Timed-Up-and-Go

Participants were seated in a chair and instructed to stand, walk 3 m with the use of their usual assistive devices, walk around a taped mark on the ground, and return to a seated position in the chair [85]. The participants were instructed to walk as quickly, but as safely as possible, and use of the arms during the standing and sitting stages was permitted. Two timed trials were completed and the average was recorded.

3.12 Dual-Energy X-Ray Absorptiometry

Whole body DXA (Discovery-W, Hologic, Bedford, MA) scans were performed to measure body composition and bone density of each participant. Quality control using a

phantom was performed daily and the machine is calibrated according to manufacturer's recommendations.

3.13 Leg Strength

Maximal Voluntary Contractions of the knee extensors and flexors were used to measure lower body strength. This was performed using a modified weight-stack machine with the ability to lock the participants' knee at 90° of flexion. A strap was wrapped around the ankle to hold a force transducer (LCHD-250, Omegadyne, Inc. Sanbury, OH) between the lower leg (just above the lateral malleolus) and the resistive arm of the machine. A second strap was wrapped around the waist of the participant to maintain posture. Strong verbal encouragement was given as the participant was told to push (knee extension) or pull (knee flexion) against the force transducer with maximal effort. Participants were instructed to push or pull as hard as they could to achieve maximal force, hold for 3 sec, and then relax. Each leg was tested using 2-5 trials until peak forces between the two greatest trials were within 10%. The order of testing for the more- and less-affected leg was counterbalanced based on subject ID number. Knee extensors were tested first.

3.14 More- and Less-Affected Sides

The more- and less-affected sides of the body were determined from asymmetric total leg strength: knee extensor force (N) + knee flexor force (N). A symmetry index was then determined for each participant using the following equation [86]:

$$\frac{R \text{ total leg strength (N)} - L \text{ total leg strength (N)}}{0.5 (R \text{ total leg strength (N)} + L \text{ total leg strength (N)})} \times 100\%$$

Asymmetric total leg strength was defined as a symmetry index greater than $\pm 10\%$, since differences in strength between sides of the body of less than $\pm 10\%$ are considered normal [87].

The self-reported more- and less-affected side of the body was used to determine the more- and less-affected sides when the symmetry index was within $\pm 10\%$.

3.15 Statistical Analysis

Pearson correlations between all variables and MVPA and total activity were performed (Table 1). Variables that were significantly correlated with MVPA or total activity were then entered into a stepwise multiple regression analysis to determine the strongest predictors of MVPA and total activity, respectively. Variables that were significantly correlated with MVPA but represented by a more general measure were not included as factors in the regression analysis (i.e. total leg strength represents both knee extensor and knee flexor strength). The goodness-of-fit of the models is reported as the squared multiple correlation (R^2). The relative importance of each predictor was estimated with the partial correlation (r).

All regression analyses were performed using SPSS software (version 23.0; IBM Corp, Armonk, NY) and the significance level for all statistical analyses was set at $P \leq 0.05$. Data are reported as mean (standard deviation) and physical activity data are reported as min / day.

Table 1. Correlations of functional / anthropometric measures with MVPA and total activity

Variables	Mean (SD)	Pearson Correlation MVPA	P - Value	Pearson Correlation Total Activity	P - Value
MVPA (min / day)	29.1 (20.1)				
Total Activity (min / day)	236.9 (63.0)				
MFIS	30.7 (15.5)	- 0.345	0.046 ^a	- 0.173	0.327
FSS	3.7 (1.8)	- 0.274	0.117	- 0.024	0.894
FES-I	27.2 (9.4)	- 0.457	0.007 ^b	- 0.334	0.054
Total Spasticity	2 (0-13)	- 0.174	0.326	- 0.225	0.200
MA Hand Grip (kg)	31 (9)	0.302	0.083	0.150	0.397
LA Hand Grip (kg)	33 (8)	0.260	0.137	0.092	0.605
Avg. Hand Grip (kg)	32 (8)	0.301	0.084	0.131	0.461
Walking Speed (m / sec)	1.4 (0.4)	0.436	0.010 ^b	0.531	0.001 ^b
MA 9-Hole Peg Test (sec)	24.5 (5.2)	- 0.253	0.148	- 0.196	0.266
LA 9-Hole Peg Test (sec)	24.1 (7.2)	- 0.365	0.034 ^a	- 0.472	0.005 ^b
Avg. 9-Hole Peg Test (sec)	24.3 (5.7)	- 0.349	0.043 ^a	- 0.390	0.022 ^a
PASAT	41.4 (13.7)	0.013	0.942	- 0.125	0.481
Sit-to-Stand (sec)	13.3 (6.6)	- 0.461	0.006 ^b	- 0.573	< 0.001 ^b
TUG (sec)	8.9 (4.0)	- 0.435	0.010 ^b	- 0.431	0.011 ^a
BMD T-Score	-0.2 (1.4)	0.123	0.490	0.198	0.261
BMD Z-Score	0.1 (1.1)	0.041	0.816	0.114	0.521
Body Fat (%)	35.2 (8.3)	- 0.306	0.079	- 0.301	0.084
Anteroposterior Path Length EO (% height)	40.1 (17.6)	- 0.229	0.194	- 0.201	0.254
Anteroposterior Path Length EC (% height)	75.1 (43.4)	- 0.118	0.506	- 0.026	0.882
Mediolateral Path Length EO (% height)	22.8 (13.4)	0.132	0.455	0.156	0.378
Mediolateral Path Length EC (% height)	31.6 (22.7)	- 0.042	0.812	0.185	0.296
MA KE Strength (N / kg)	4.8 (1.8)	0.455	0.007 ^b	0.488	0.003 ^b
MA KF Strength (N / kg)	1.8 (1.0)	0.342	0.048 ^a	0.489	0.003 ^b
LA KE Strength (N / kg)	5.5 (1.8)	0.538	0.001 ^b	0.475	0.004 ^b
LA KF Strength (N / kg)	2.2 (1.0)	0.318	0.067	0.527	0.001 ^b
MA Total Strength (N / kg)	6.6 (2.6)	0.491	0.003 ^b	0.518	0.002 ^b
LA Total Strength (N / kg)	7.7 (2.6)	0.442	0.009 ^b	0.528	0.001 ^b

^a $P \leq 0.05$, ^b $P \leq 0.01$. Total spasticity reported as median (range). MFIS: Modified Fatigue Impact Scale; FSS: Fatigue Severity Scale; FES - I: Falls Efficacy Scale - International; MA: more-affected side; LA: less-affected side; PASAT: Paced Auditory Serial Addition Test; TUG: Timed-Up-and-Go; BMD: bone mineral density; EO: eyes open; EC: eyes closed; KE: knee-extensor; KF: knee-flexor.

4. RESULTS

A total of 38 participants completed the study and 4 were excluded from the final analysis. Three participants were excluded because they did not meet the requirements for accelerometer wear time validation and 1 was excluded due to ActiGraph sampling error. Therefore, the final sample included 34 participants (gender: 26 W, 8 M, age: 53.8 (12.4) years, height: 1.69 (0.11) meters, weight: 72.9 (17.3) kilograms, disease duration: 13.7 (8.6) years), PDDS: 2 (0-6), self-reported subtype: 29 relapsing remitting, 2 secondary progressive, and 3 not provided a subtype by their neurologist, MVPA (range): 4-76 min / day, total activity (range): 94-367 min / day). The more- / less-affected side of 20 participants was objectively determined from total leg strength ($SI \geq 10\%$). One participant was unable to complete the sit-to-stand test and was given a score of 35.0 sec, which was approximately one standard deviation greater than the slowest performance of those who were able to complete the task [88]. The same participant was unable to complete the 9-HPT on the more-affected side and was given a score of 38.8 sec based on the same criteria. Group average values for all variables are reported in Table 1.

4.1 Prediction of MVPA

Based on their correlation with time in MVPA, the following factors were used to predict MVPA: MFIS, FES – I, walking speed, 9-HPT on the less-affected side, average 9-HPT of each hand, sit-to-stand performance, TUG, and total leg strength of the more- and less-affected sides (Table 1). Based on stepwise selection, MVPA was best predicted by the total leg strength of the less-affected side and FES – I score and ($R^2 = 0.35$, $P = 0.001$; Fig 1A). The equation for the predicted MVPA was: $25.077 + (3.178 \times \text{total leg strength of the less affected side}) + (-0.751 \times \text{FES – I score})$. Figure 1B-C shows the partial correlations between the predictors and MVPA.

Total leg strength of the less-affected side was positively correlated with MVPA (partial $r = 0.42$, $P = 0.016$; Fig 1B), whereas perceived fall risk was negatively associated with MVPA (partial $r = -0.37$, $P = 0.033$; Fig 1C).

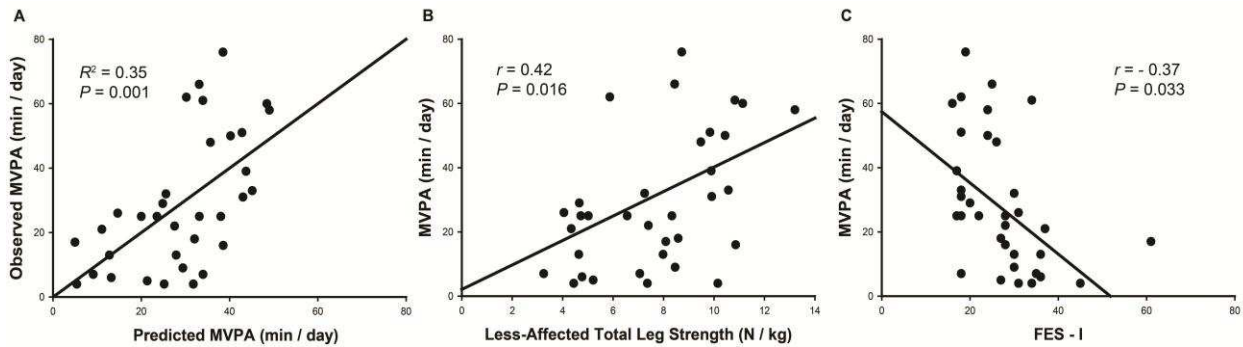


Figure 1. Prediction of Moderate-to-Vigorous Physical Activity / day (MVPA). (A) MVPA was moderately predicted by the linear combination of the total leg strength of the less-affected side and the Falls Efficacy Scale – International (FES – I) score. (B) Participants with greater total leg strength of the less-affected side exhibited greater MVPA. (C) Participants with lower perceived fall risk, as assessed by the FES - I score, had greater MVPA.

4.2 Prediction of Total Activity

Based on their correlation with total activity, the following factors were used to predict total activity: walking speed, 9-HPT on the less-affected side, average 9-HPT of both hands, sit-to-stand performance, TUG, and total leg strength of the more- and less-affected sides (Table 1). Based on stepwise selection, total activity was best predicted by sit-to-stand performance and total leg strength of the less-affected side ($R^2 = 0.41$, $P < 0.001$; Fig 2A). The equation for the predicted total activity was: $230.373 + (-4.009 \times \text{sit-to-stand performance}) + (8.203 \times \text{total leg strength of the less-affected side})$. Figure 2B-C shows the partial correlations between the predictors and total activity. Time to complete the sit-to-stand test was negatively associated with total activity (partial $r = -0.42$, $P = 0.014$; Fig 2B), whereas total leg strength of the less-affected side was positively correlated with total activity (partial $r = 0.35$, $P = 0.049$; Fig 2C).

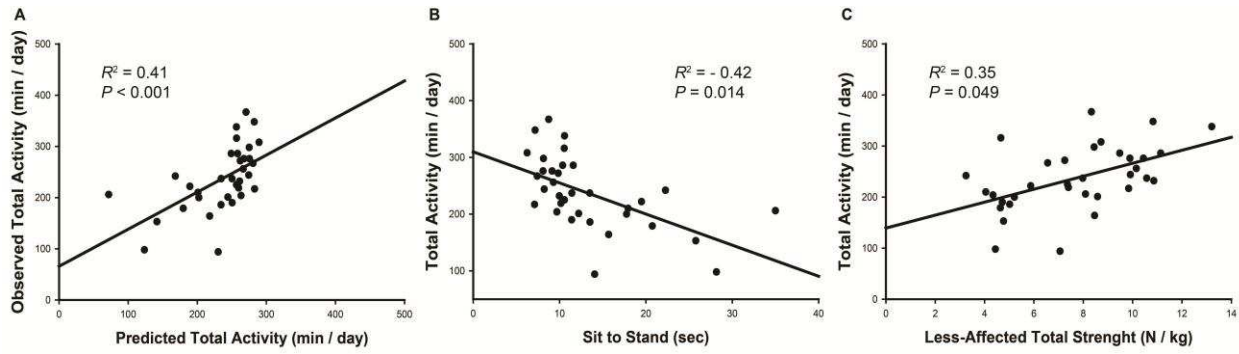


Figure 2. Prediction of total activity. (A) Total activity was moderately predicted by the linear combination of sit-to-stand performance and total leg strength of the less-affected side. (B) Participants with lower performance on the sit-to-stand test exhibited lower total activity. (C) Participants with greater total leg strength of the less-affected side exhibited greater total activity.

5. DISCUSSION

This study included a wide variety of behavioral and functional assessments in order to identify which factors are most predictive of physical activity in PwMS. These findings indicate that combined strength of the less-affected knee extensors and knee flexors and perceived risk of falling are key predictors of MVPA in this patient population. Furthermore, sit-to-stand performance and total strength of the less-affected leg are the primary predictors of total activity. Unlike previous studies, this investigation tested a wider range of functional and behavioral symptoms and used PwMS at varying levels of disability. Furthermore, this is the first study to our knowledge that provides targets for rehabilitation that include the consideration of a more- and less-affected side.

Much work has been performed over the last decade to characterize fall risk and to develop effective interventions to reduce the incidence of falls in PwMS [89]. These studies have revealed that fall risk in MS is multifactorial and includes aspects such as disease subtype, gender, disability, balance, perceived levels of fatigue, and cognitive function [90-94]. Furthermore, falls have been shown to occur early in the disease course and can even occur prior to the detection of locomotor or balance impairment [95]. Rehabilitative programs aimed at improving balance using a variety of modalities, including virtual reality, exergaming, surface perturbation training, and traditional exercise, have been shown to reduce the incidence of falls in PwMS [89,96]. However, it is important to understand that perceived risk of falling may differ from clinical assessments of fall risk. Our data indicate that perceived risk of falling influences physical activity, especially at the moderate-to-vigorous intensity, but we are unable

to associate this risk with any clinical assessment of fall risk. Factors such as strength and power may play an important role in a patient's confidence to avoid falls.

Leg strength is obviously an important factor in a patient's ability to perform activities of daily living and to live an active lifestyle. Unfortunately, PwMS have been shown to have reduced and imbalanced leg strength compared to their healthy counterparts [69]. Our study further supports the importance of assessing bilateral strength differences, with over half of our PwMS displaying asymmetric leg strength. The results of this study indicate that maintaining or improving leg strength on the less-affected side may allow PwMS to overcome the impairments of the more-affected leg and engage in more physical activity. This is supported by evidence from our previous studies showing increased reliance on the less-affected side during walking [97-98]. However, each leg may need a minimal strength in order to perform activities of daily living and to be physically active, so strength training of both legs is still recommended. This is supported by our current data in that leg strength of both limbs is correlated to MVPA and total activity (Table 1). While total leg strength of the less-affected side was a predictor of both MVPA and total activity, sit-to-stand performance was unique to total activity. This is important because the ability to rise from a seated position may dictate whether an individual is able to perform physical activity at a low intensity, such as activities of daily living. Preserving this ability is critical to maintaining an individual's quality of life and independence. The sit-to-stand test can also indirectly assess power since it requires the patients to perform the task as quickly as possible. This power is likely needed to rise from a seated position or even catch themselves during a fall. Strength training is an important first-step in developing the necessary power to perform activities of daily living and other light physical activity.

Although each of the models were only moderate in strength, the findings are very important given the number of factors that determine physical activity independent of disability status. It is estimated that seemingly healthy adults spend ~ 55% - 70% of their waking hours in sedentary behavior [99]. Our findings indicate that for PwMS, 35% of the variability in MVPA and 41% of the variability in total activity can be explained by factors that are treatable in the rehabilitation setting.

5.1 Limitations

A primary limitation of this study is the sample size, which limits the generalizability of the results and prevents us from determining gender-specific and MS sub-type specific predictors of physical activity. Secondly, the assessment of fall risk was limited to a single questionnaire and quiet standing, and did not include dynamic assessments such as surface perturbation or step reaction testing. We were also did not directly measure limb power capabilities, which likely contributes to physical activity. Finally, psychological and sociodemographic factors such as physical activity-related self-efficacy and access to safe spaces to exercise were not assessed.

5.2 Future Directions

Interventional studies are needed to test the effects of reduced fall risk, increased leg strength, power, and improved sit-to-stand performance on physical activity in this patient population. Future studies are also needed to determine the optimal type/amount of physical activity for PwMS.

5.3 Conclusions

These preliminary findings suggest that a patient's perceived risk of falling, total leg strength on their less-affected side, and sit-to-stand performance are important factors in their likelihood and ability to perform physical activity. While total leg strength of the less-affected

side was a predictor of both forms of physical activity, perceived fall risk appears to be an important factor in whether a patient performs physical activity at a moderate-to-vigorous intensity, and the ability to rise from a seated position is important to be active at a light intensity. Therefore, rehabilitative specialists should implement exercise programs that combine strength training of both legs and balance training to reduce fall risk and improve the patients' ability to rise from a seated position. Furthermore, maintaining or improving the strength of the less-affected leg may allow patients to overcome the impairment of the more-affected leg to continue to perform MVPA.

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