THESIS

NO ASSOCIATION OF LEG STRENGTH ASYMMETRY WITH WALKING PERFORMANCE, FATIGABILITY OR FATIGUE IN MULTIPLE SCLEROSIS

Submitted by

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ABSTRACT

NO ASSOCIATION OF LEG STRENGTH ASYMMETRY WITH WALKING PERFORMANCE, FATIGABILITY OR FATIGUE IN MULTIPLE SCLEROSIS

Background: One of the first signs of Multiple Sclerosis (MS) is weakness on one side of the body, which is associated with an increased reliance on the stronger leg during walking as indicated by asymmetric muscle activity. The role of leg strength asymmetry on walking performance, fatigue and fatigability is unknown in people with MS (PwMS).

Objective: The purpose of this cross-sectional study was to determine whether leg strength asymmetry is associated with walking performance, objective measures of fatigability, or subjective perceptions of fatigue during a 6-minute walk test (6MWT).

Methods: Maximal knee extensor strength was assessed in 19 PwMS, and a symmetry index was calculated based on the objectively defined more- and less-affected leg. Walking ability was determined by measuring the total distance covered during a 6MWT and fatigability by calculating the change in distance covered between minutes six and one. Perceptions of fatigue were assessed by obtaining ratings of perceived exertion (RPE) using the modified Borg 10-point scale during the first and the final minute of the 6MWT.

Results: PwMS covered less distance ($P=0.01$) and perceived greater exertion ($P<0.01$) during minute six compared to minute one. Maximal knee extensor strength was different between the more- and less-affected side ($P<0.01$). The magnitude of asymmetry did not correlate with walking performance, fatigability, or perceptions of fatigue.

Conclusions: Maximal knee extensor strength asymmetry may not play an important role in walking performance, fatigability or fatigue in PwMS. Future asymmetry studies should include the flexor muscles and measures of sensory function.

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1. INTRODUCTION

1.1 Multiple Sclerosis

An estimated 2.3 million people worldwide are currently diagnosed with multiple sclerosis (MS) *(Browne et al. 2014),* which is an inflammatory autoimmune disease of the central nervous system (CNS) *(Noseworthy et al. 2000)* manifested by a demyelination and neurodegeneration of the brain and spinal cord (*Chaudhuri et al. 2013, Kindred et al. 2014*). As a result, the travel of information between the CNS and the periphery is often slowed or blocked, leading to various symptoms depending on the location of the damage (*Schmierer et al. 2000)*. People with MS (PwMS) commonly demonstrate reduced walking capacity and greater fatigability *(Kent-Braun et al. 1994)*, defined as a decrease in performance over time *(Rudroff et al. 2016)*. Up to 92% of PwMS also report that fatigue, defined as subjective sensations of weariness and an increasing sense of effort *(Kluger et al. 2013)*, negatively impacts their quality of life (*Branas et al. 2000*). Another early symptom of MS is weakness on one side of the body, particularly in the lower limbs *(White and Dessendorfer, 2005)*. Due to this unilateral weakness, PwMS often have a more- and less-affected side of the body which results in a variety of asymmetries, including measures of power, strength and muscle activity *(Chung et al. 2008, Kalron et al. 2011*, *Ketelhut et al. 2017, Rudroff et al. 2014a).*

1.2 Asymmetries in PwMS

Chung et al. (2008) found greater power asymmetries in the knee extensors of PwMS compared to healthy controls *(Chung et al. 2008)*. Participants with greater power asymmetries also demonstrated slower walking speeds during normal and brisk walking, as well as greater perceptions of fatigue. Moreover, Ketelhut et al. (2017) demonstrated that the strength of the less-affected leg is positively associated with physical activity, and that the strength of the more-affected leg is an independent predictor of sedentary time *(Ketelhut et al. 2017)*. Our preliminary findings show that PwMS also have strength asymmetries and greater muscle activity in the less-affected leg during walking *(Rudroff et al. 2014a)*, as indicated by glucose uptake using positron emission tomography/computed tomography (PET/CT) scans and the glucose analogue [^{18}F]-fluoro-deoxy-glucose ([^{18}F]-FDG). PwMS may therefore overcompensate the less-affected side during activity, which could be a potential mechanism contributing to the early onset of muscle fatigability and the subsequent reduction in walking performance.

In contrast to these preliminary findings suggesting an important role of asymmetries regarding walking performance in PwMS, Kalron (2016) did not find an association between walking ability and vertical ground reaction force (VGRF) symmetry in PwMS *(Kalron 2016)*. However, an important finding of that particular study was that PwMS did not demonstrate asymmetric VGRF. Since no other symmetry measurement was made, the influence of strength asymmetries remained uninvestigated. Despite evidence indicating the involvement of the knee extensor muscles in healthy and pathological gait *(Broekmans et al. 2013, Ivanenko et al. 2004, Winter 1991)*, no study to date has explored the influence of leg strength asymmetries on walking performance, fatigability or perceptions of fatigue in PwMS. As a result, the purpose of this study was to determine whether leg strength asymmetries are associated with walking performance, fatigability, and perception of fatigue during a 6-minute walk test (6MWT) in PwMS. We hypothesized that PwMS with greater strength asymmetries would cover less distance during the 6MWT, would be more fatigable, and would perceive greater levels of fatigue.

2. METHODS

2.1 Participant recruitment

Participants were recruited using the database of the Integrative Neurophysiology Laboratory at Colorado State University. Inclusion criteria included a confirmed diagnosis of MS, aged 21-75 years, self-reported asymmetries (≥2 on a 1-5 scale), and the ability to walk for 6 minutes. To be included in the study, participants were limited be moderately disabled, as indicated by a Patient Determined Disease Step (PDDS) score between 0 and 6. The PDDS allows the determination of disability status based on participants' self-report and was previously found to strongly correlate ($\rho = 0.78$) with the Expanded Disability Status Scale (EDSS) *(Learnmonth et al. 2013)* which is commonly used in MS. Exclusion criteria included contraindications to exercise, pregnancy, a relapse of symptoms within the last 60 days, any concurrent neurological disorder that would exacerbate fatigue, and a change of medication within the previous 45 days. All participants completed an online screening form and signed informed consent approved by the Colorado State University Institutional Review Board and were in accordance with the Declaration of Helsinki. All visits occurred in the morning hours to minimize the effect of time of day on fatigue *(Streckis et al. 2014)* and participants were instructed to avoid exercise and caffeine prior to testing. Upon completion of the consent form, participants performed leg strength testing, a 6-minute walk test and filled out the Fatigue Severity Scale (FSS).

2.2 Leg strength testing

Maximum leg strength was assessed by performing isometric maximal voluntary contractions (MVCs) of the knee extensors. Participants were positioned at 90 degree flexion of the hip, knee, and ankle joints in a custom-built chair that allows for the attachment of a linear force transducer (Noraxon, Scottsdale, AZ, USA) linked to an ankle strap superior to the lateral malleolus. Following a standardized laboratory protocol *(Ketelhut et al. 2017, Kindred et al. 2015, Rudroff et al. 2014a ;2014b)*, participants achieved maximum force production over a 3s increase, followed by maintenance for 3s, and subsequent relaxation. Each leg was tested 2-5 times with at least one minute of rest between attempts. The measurement order was counterbalanced based on the participants' self-reported more- and less-affected side. Testing was completed when force production no longer increased across attempts and the two highest scores were within 10% *(Ketelhut et al. 2017)*.

2.3 Symmetry Index

The more- and less-affected sides were objectively determined based on asymmetric knee extensor strength. To determine the magnitude of leg strength asymmetry the following symmetry index (SI) *(Ketelhut et al. 2017, Sadeghi et al. 2000)* was used:

$$\frac{Less\ affected\ leg\ strength\ (N) - More\ affected\ leg\ strength}{0.5\ (Less\ affected\ leg\ strength\ (N) + More\ affected\ leg\ strength\ (N))}\ x\ 100$$

Asymmetric leg strength was defined as a SI greater than ±10%, since differences in strength between sides of the body of less than ±10% are considered normal *(Ithurburn et al. 2015)*. Participant self-report was used when the SI was within 10%.

2.4 Walking performance

Participants performed a 6MWT with their normal assistive devices in a cordoned off hallway with two cones placed 30m apart. Participants were instructed to walk as quickly but safely as possible and were verbally encouraged to cover the greatest amount of distance. Walking distance was recorded every minute.

During the 6MWT, participants wore two smart devices (Apple iPod 6th generation, Apple, CA) strapped superior to the lateral malleolus using a neoprene sleeve and Velcro® to measure spatiotemporal gait variables (Figure 1).

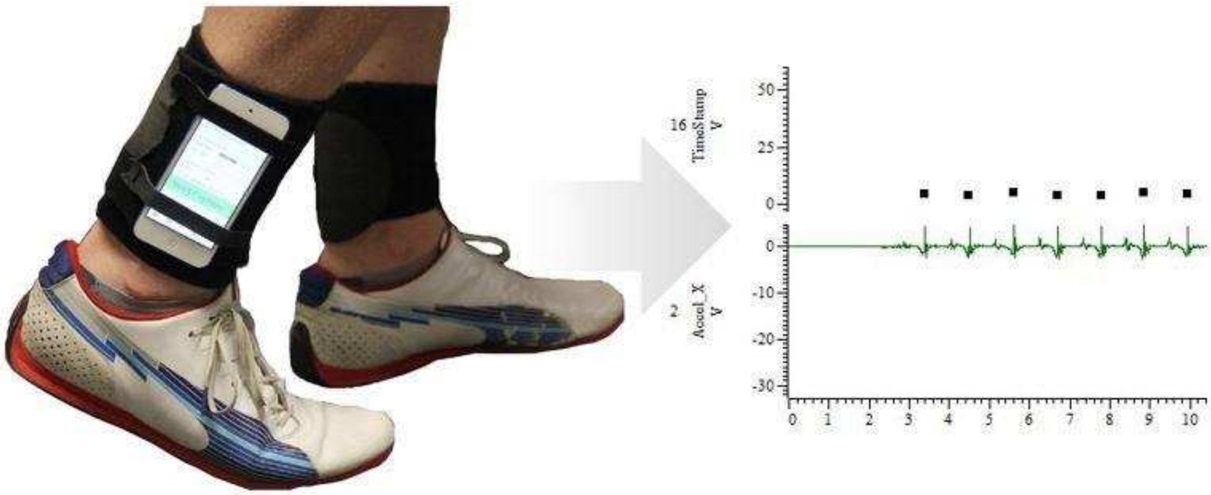

Figure 1. Smart Device placement during the 6MWT and subsequent data analysis. The bottom channel of the figure shows the forward acceleration derived from the iPod, while the upper channel indicates the time stamps (black dots) associated with each peak acceleration.

Using the application Sensor Data (Wavefront Labs) tri-axial acceleration was recorded at a sampling rate of 100 Hz. The raw data was uploaded onto a local web-server and accessed through an IP address using the Sensor Data application. Each leg was exported and analyzed individually using Spike2 (Cambridge Electronic Design Limited, Version 7.18 x86) software. Individual gait variables were calculated based on the procedure described below.

2.4.1 Procedure to calculate measures of walking performance

First, a new memory channel was created to identify and mark gait cycles with a time stamp (Figure 1) using the peak detection tool in Spike2. To ensure accurate detection of the peak forward acceleration (toe off) of each gait cycle, all data was also visually inspected after it was processed. Since previous gait analyses excluded gait cycles prior to and after a turn *(Capela* *et al. 2014, Mariani et al. 2010)* in order to account for the slowing of walking speed and reduction in stride length, we also manually removed the gait cycles associated with a turn from the raw data gathered from the smart device. These gait cycles were not included in any subsequent analysis. Turns were visually identified and confirmed using the pitch acceleration. After visual inspection, the newly created channel indicating the time stamps of individual gait cycles was exported to Microsoft Excel (Redmond, WA) for further analysis.

Stride duration *(s)* for each leg was calculated by subtracting time stamps of one gait cycle from its preceding gait cycle. Based on each individual stride duration, cadence *(steps/min)* was calculated. We divided each stride duration by 60 seconds, computed the average, and subsequently added the average of both legs to obtain cadence. To derive additional measures of walking performance, we calculated walking speed (distance covered / 360s; *m/s*). Finally, by multiplying walking speed and stride duration, stride length (*m*) was derived.

2.5 Fatigability and fatigue

Fatigability was assessed by calculating the percentage change in distance covered between minutes six and one (distance walked index, $DWI_{6\text{-}1}$) *(Leone et al. 2016)*. Subjective perceptions of fatigue were assessed using the Fatigue Severity Scale (FSS) *(Krupp et al. 1989)* and by obtaining ratings of perceived exertion (RPE) using the modified Borg 10-point scale during the first and the final minute of the 6MWT *(Borg 1982)*.

2.6 Statistical analysis

Statistical analyses were completed using SPSS 24® (IBM Corp, Armonk, NY). Paired t-tests were used to assess differences in walking performance and RPE between minutes one and six of the 6MWT, as well as the strength of the more- and less-affected leg. Pearson correlations were performed to assess associations between leg strength SI and measures of walking performance, fatigability (DWI_{6-1}) and perception of fatigue. For all analyses, the significance level was set to $P \leq 0.05$ and data are reported as mean±standard deviation.

3. RESULTS

Participant characteristics are reported in Table 1. From the 48 people who filled out the online screening form, nineteen participants were determined eligible and included in the final sample. Three participants used assistive devices (2 bilateral, 1 unilateral) during the 6MWT. However, results remained unchanged after excluding these participants, which is why they were included in the final sample.

Table 1. Participant characteristics.

n	19 (7 men)
Age (years)	53.74 ± 9.7
BMI (kg/m^2)	24.04 ± 5.2
PDDS	3 (0-6)
Self-reported asymmetries (1-5)	4 (2-5)
Disease duration (years)	14.26 ± 8.1
Fatigue Severity Scale Score (0-7)	5.30 (1.28)

Data are reported as mean ± standard deviation. PDDS and self-reported asymmetries are reported as median (range). BMI: Body Mass Index; PDDS: Patient Determined Disease Steps.

The distance covered during minute one was greater than during minute six (P=0.01) demonstrating fatigability during the 6MWT with an average DWI_{6-1} of -7.57±13.3%. This reduction in distance covered was accompanied by a decrease in stride length from minute one to minute six ($P<0.01$) while cadence remained unchanged (P=0.07) (Table 2).

Table 2. Walking performance during the 6-minute walk test.

Variable	Mean (SD)	Minute 1	Minute 6	Change (%)	P-value
Distance (m)	428 (130)	75 (22)	71 (22)	-7.57 (13.3)	0.01
Cadence (steps/min)	111 (25)	114 (23)	111 (25)	-3.32 (25.1)	0.07
Stride length (m)	1.26 (0.18)	1.32 (0.18)	1.24 (0.17)	-5.43 (5.92)	<0.01
Stride duration (s)	1.17 (0.49)	1.14 (0.37)	1.16 (0.46)	1.04 (6.46)	0.44
Walking speed (m/s)	1.19 (0.36)	1.25 (0.36)	1.18 (0.36)	-5.82 (10.43)	0.02

Data are reported as mean (standard deviation; SD).

The more- and less-affected side was objectively determined for 14 participants (SI≥10%) and was based on self-report for the remaining five. The knee extensor MVC forces for the less-affected side were greater than for the more-affected side (376.2±112.0 N and 304.8±85.6 N respectively; $P<0.01$). On average, the knee extensor strength SI was 21.2±12.3%.

No measure of walking performance or its percentage change from minute one to six was associated with the magnitude of leg strength asymmetry or individual leg strength (Table 3). Similarly, average RPE significantly increased by 62% from minute one to six (Min 1: 4.32±2.03 and Min 6: 6.32±2.16; $P<0.01$). No significant association was found between the knee extensor strength SI and walking ability (r=-0.09, $P=0.70$; Figure 2A), fatigability ($r=0.26$, $P=0.29$; Figure 2B) or measures of fatigue (RPE: $r=0.18$, $P=0.47$, Figure 2C and FSS: $r=-0.14$, $P=0.58$, Figure 2D).

Table 3. Pearson correlations of leg strength asymmetry and individual leg strength with measures of walking performance.

	Leg strength SI		**LA Leg strength**		**MA Leg strength**	
Variable	*r*	*P-value*	*r*	*P-value*	*r*	*P-value*
Distance	-0.09	0.70	0.05	0.84	0.13	0.59
DWI_{6-1}	0.26	0.29	0.14	0.56	0.03	0.91
Cadence *(steps/min)*	-0.08	0.76	-0.18	0.47	-0.12	0.63
$Cadence_{6-1}$	0.05	0.84	0.12	0.62	0.09	0.71
Stride length *(m)*	-0.12	0.64	0.31	0.14	0.42	0.08
Stride $length_{6-1}$	0.42	0.07	0.09	0.71	-0.11	0.67
Stride duration *(s)*	0.02	0.92	0.14	0.56	0.12	0.62
Stride $duration_{6-1}$	-0.06	0.82	-0.18	0.47	-0.15	0.53
Walking speed *(m/s)*	-0.13	0.59	0.05	0.84	0.15	0.53
Walking $speed_{6-1}$	0.27	0.27	0.16	0.52	0.04	0.89

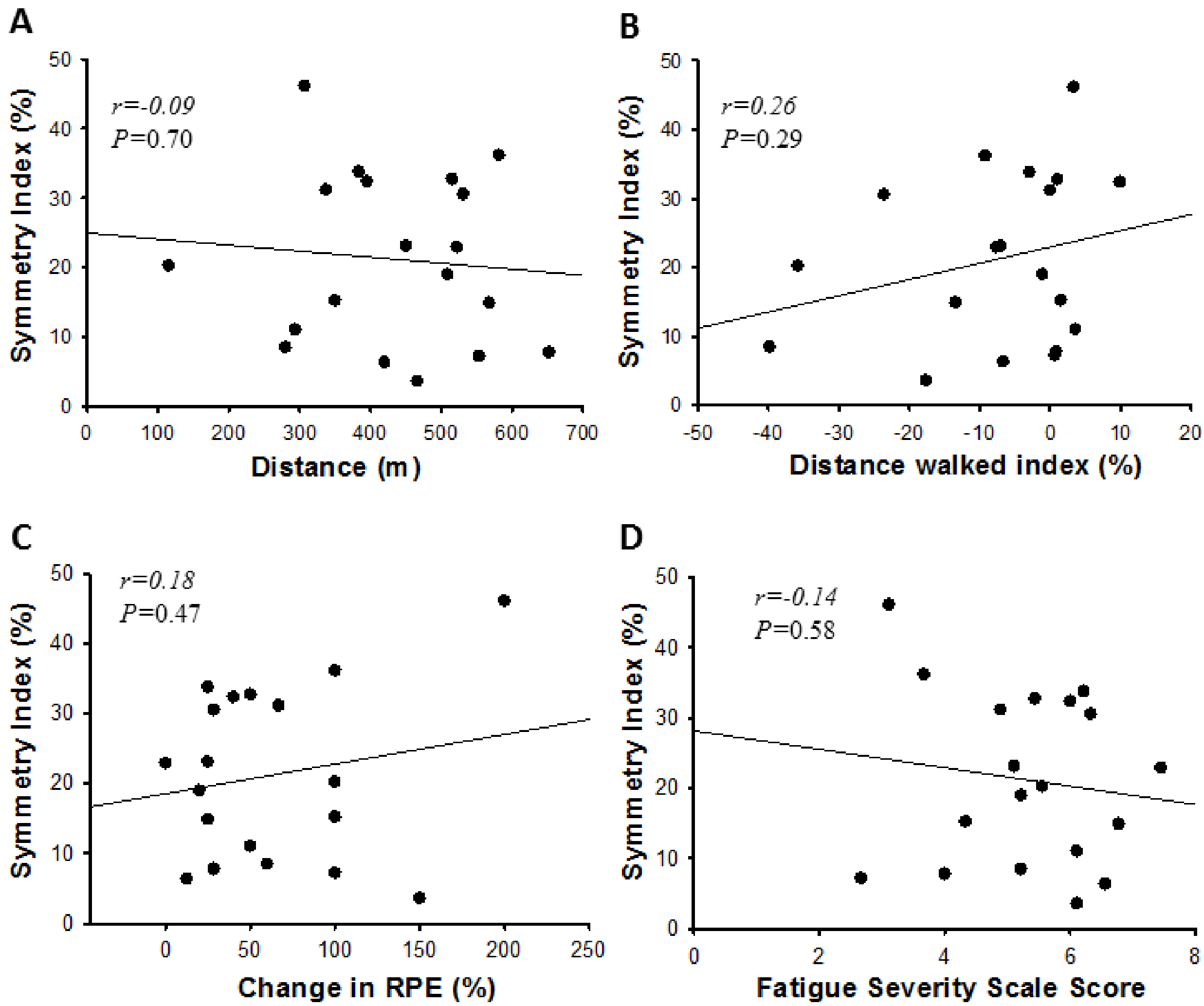

Figure 2. Pearson correlations of leg strength asymmetry with walking ability, fatigability and measures of fatigue. No association was found between leg strength asymmetry (symmetry index) and **(A)** walking ability (distance), **(B)** fatigability (distance walked index), or **(C) & (D)** subjective perceptions of fatigue.

4. DISCUSSION

The aim of this study was to determine the association between leg strength asymmetry and walking performance, fatigability and perceptions of fatigue in PwMS. Participants demonstrated asymmetric leg strength between the objectively defined more- and less-affected side of the body, fatigability and increasing perceptions of fatigue during a 6MWT. However, the magnitude of leg strength asymmetry (SI) did not correlate with walking performance, fatigability, or perceptions of fatigue.

We confirmed previous findings of leg strength asymmetries in PwMS *(Chung et al. 2008, Ketelhut et al. 2017),* but the lack of associations between measures of walking performance, fatigability or fatigue and the strength SI suggests that leg strength asymmetries may not play an important role in prolonged walking performance. On average, the strength of SI in our sample was 21.2±12.3%, which is similar to previous work (*Chung et al. 2008)*. However, it is unknown to what extent asymmetries alter with disease progression and whether a greater asymmetries than the average magnitude reported in this study has a more pronounced impact on activities of daily living in PwMS.

Chung et al. (2008) showed that power asymmetries negatively influence walking speed during short bouts of walking (25ft walk test) *(Chung et al. 2008)*. However, in this study leg strength asymmetry did not correlate with measures of walking performance. One reason for this discrepancy may be the difference in walking tasks (25ft vs. 6-minute walk test). It is also important to note that the correlation achieved by Chung et al. (2008) entailed both, healthy controls and PwMS, and that no associations were reported for the individual groups. As the current study did not have a control group, we were unable to perform a similar correlation and only investigated the influence of strength asymmetries on walking performance in PwMS.

Therefore, it remains uncertain whether the general correlation of asymmetry and walking speed during short bouts of walking also holds true for longer duration walking tests, and whether the previous association also exists in PwMS only.

Another reason that may explain a lack of correlation between asymmetries and walking performance in the current study is the use of strength rather than power in the assessment of asymmetries. Due to its static nature, maximal isometric strength may not be as good of a predictor as isokinetic or dynamic movements regarding walking performance *(Broekmans et al. 2013)*. In the aging literature, for instance, lower extremity power is suggested to be a better predictor of physical function than strength *(Bean et al. 2002)*. Future research should thus consider power rather than strength as a determinant of symmetry in PwMS, which may help clarify the impact of asymmetries on walking ability, fatigability and perceptions of fatigue.

While Ketelhut et al. (2017) demonstrated the importance of individual leg strength for measures of physical activity *(Ketelhut et al. 2017)*, we did not find similar associations with measures of walking performance, fatigability or perceptions of fatigue. Although Broekmans et. al. (2013) indicated an association of both knee extensor and flexor strength with walking in PwMS, knee flexor strength may actually relate better to walking capacity *(Broekmans et al. 2013).* This is further in alignment with our previous findings *(Rudroff et al. 2014a)* demonstrating greater knee flexor muscle activity, indicated by glucose uptake, during walking in PwMS compared to controls. However, due to equipment limitations, we were unable to assess the strength of the flexor muscle groups. More research investigating the leg flexor muscles is needed to determine the association between lower limb asymmetries and walking ability, fatigability and perceptions of fatigue in MS.

Finally, questions arise regarding current testing batteries to determine asymmetries in PwMS. Similar to this study, most laboratories do not consider sensory function in their assessment of symmetry. However, the demyelination associated with MS may not only slow efferent signals into the periphery but also afferent feedback to the CNS, such as proprioception. The ability to maintain postural control, for instance, is suggested to be highly influenced by proprioceptive feedback (*Gandolfi et al. 2014, Fling et al 2014).* As a consequence, it seems plausible that the inability to appropriately interpret and integrate sensory feedback could also contribute to the impaired walking ability that has been reported in PwMS. Therefore, measures of sensory function, such as proprioception, should also be included in future symmetry assessments of PwMS. Including flexor muscle groups, power symmetry assessment and measures of sensory function in future testing batteries for PwMS may provide more clarity regarding the influence of lower limb asymmetries on walking performance, fatigability and perception of fatigue.

4.1 Limitations

One limitation of this study is the relatively small sample size, which limits the generalizability of the results. In addition, the lack of control group prohibited comparisons between healthy adults and PwMS and the performance of associations between strength asymmetry of PwMS and healthy adults with measures of walking performance as previously done *(Chung et al. 2008)*. Also, the measurement of asymmetry was solely based on maximum isometric voluntary contractions and did not include isokinetic or dynamic movements, demonstrating differences to the nature of walking. Lastly, the primary outcome variable of the 6MWT – total distance covered – was heavily reliant on the participant’s maximum effort. Although instructions were standardized and all participants were equally encouraged throughout the task, the motivation to cover the greatest amount of distance during the 6MWT may have varied across subjects, which could have influenced our findings. Finally, it is possible that age-related factors may contribute to the outcomes of the study, given the large age range of 35-65.

4.2 Future directions

Future studies may measure power rather than strength when assessing lower limb asymmetries in PwMS and should consider the use of a variety of walking tasks. Also, measures of sensory function should be incorporated in future batteries to determine the impact of lower limb asymmetries in PwMS. Longitudinal studies are needed to determine whether asymmetries become more severe with disease progression, and whether a greater magnitude of asymmetry may have a more pronounced impact in PwMS.

4.3 Conclusions

This study confirms previous findings of asymmetric leg strength during maximal isometric contractions in PwMS. However, the magnitude of leg strength asymmetry was not associated with walking performance, fatigability or measures of fatigue. Future lower limb asymmetry studies should include the flexor muscles and measures of sensory function in their asymmetry assessment. Longitudinal studies should investigate the change in leg strength asymmetry with disease progression, and their role during activities of daily living in PwMS. Together with improved batteries to assess asymmetries, this may then provide more clarity regarding the impact of lower limb asymmetries in PwMS.

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6. LIST OF ABBREVIATIONS

6MWT – 6-Minute Walk Test

CNS – Central Nervous System

DWI – Distance walked index

EDSS – Expanded Disability Status Scale

[^{18}F]-FDG – 18-fluorodeoxyglucose

FSS – Fatigue Severity Scale

MVC – Maximal Voluntary Contraction

MS – Multiple Sclerosis

PET/CT – Positron Emission Tomography / Computed Tomography

PDDS – Patient Determined Disease Steps

PwMS – People with Multiple Sclerosis

RPE – Ratings of Perceived Exertion

SI – Symmetry Index

VGRF – Vertical Ground Reaction Force