Gait & Posture 74 (2019) 231–235

Contents lists available at ScienceDirect

Gait & Posture

journal homepage: www.elsevier.com/locate/gaitpost

# The association between gait variability with the energy cost of walking depends on the fall status in people with multiple sclerosis without mobility aids

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ARTICLE INFO

*Keywords:*
Multiple sclerosis
Gait variability
Energy cost of walking
Falls

ABSTRACT

*Background:* Falls, gait variability and increased energy cost of walking are common in people with multiple sclerosis (PwMS). However, no studies have as yet examined this triple association in PwMS or in other neurological populations.
*Research question:* Does a relationship exist between gait variability, falls and the energy cost of gait in PwMS?
*Methods:* This cross sectional study included 88 PwMS (50 women), mean age 39.8 (S.D = 13.0) and mean disease duration of 6.2 (SD = 8.2) years since diagnosis. Energy expenditure during walking was collected via a portable metabolic device (COSMED K5, COSMED Srl, Roma, Italy). Gait variability was measured by an electronic walkway (GAITRite™). Participants were divided into groups based on fall history (fallers and non-fallers). Differences between groups in terms of energy expenditure measures and gait variability metrics were determined by the analysis of variance test. The relationship between gait variability and energy cost of walking was examined by the Pearson's correlation coefficient test.
*Results:* Thirty-three PwMS were classified as fallers and 55 as non-fallers. Non-significant differences between groups were observed in the energy expenditure measures, including cost of walking. Fallers demonstrated higher step length variability compared with non-fallers (4.58 (S.D. = 2.42 vs. 3.40 (S.D. = 1.40); p-value = 0.005). According to the Pearson's correlation coefficient analysis, a significant relationship was found between step length variability and energy cost of walking in the non-fallers group (Rho = 0.372, P-value = 0.006) and the total group (Rho = 0.296, p-value = 0.005), but not in those PwMS with a history of falls.
*Significance:* We demonstrated a significant relationship between increased gait variability and energy expenditure while walking only in MS patients without a history of falls. This is important as there is evidence of the clinical relevance of increased gait variability, poor fitness level and high risk of falling in the MS population.

## 1. Introduction

Gait variability, reflecting the stride-to-stride fluctuations in walking, is elevated in people with multiple sclerosis (PwMS) compared to healthy adults [1]. Gait variability is evident even in patients with mild MS, significantly increasing once the patients reach a level of moderate disability [2]. Gait variability has been characterized by different physiologic factors that include neural control, muscle function, postural control, cardiovascular changes and mental health [3].

Recently, Sebastiao et al. [4] presented evidence of a positive association between gait variability and the energy cost of walking in 86 PwMS. According to the multivariate analysis, disability, stance time variability and step length variability 38% explained the variance in energy cost of walking. The relationship between elevated gait variability and increased energy expenditure while walking is not limited to PwMS, it has also been demonstrated in stroke victims [5], and adults with Down Syndrome [6].

As widely known, falls are a significant issue in PwMS,

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https://doi.org/10.1016/j.gaitpost.2019.09.021
Received 7 May 2019; Received in revised form 27 August 2019; Accepted 18 September 2019
0966-6362/ 

affecting > 50% within a 6-month period [7]. Previous research has shown that elevated gait variability is associated with an increased risk of falling in PwMS [8,9]. Additionally, energy cost of gait was found related to spasticity of the lower limbs, a risk factor for falling in moderately disabled PwMS [10]. Taken together, this information suggests a possible link between falls, energy cost of gait and gait variability in PwMS. To date, no studies examining this triple association in PwMS has been found in the Pubmed database.

We believe that exploring the relationship between gait variability, falls and the energy cost of gait, might be beneficial to medical professionals engaged in physical rehabilitation of PwMS. Firstly, it will help clarify if elevated gait variability is related to an increase in the energy cost of walking. Furthermore, does the relationship differ between fallers and non-fallers? Secondly, it might facilitate in improving current physical activity programs focused on reducing falls in the MS population by combining or modifying new and traditional components into the program. Interestingly, a rehabilitation program based on balance and strength training to reduce the rate of falls in the elderly, demonstrated significant correlations between a decreased risk of falling, decreased gait variability and improved energy expenditure metrics while walking [11]. Therefore, the objective of this study was twofold; (1) to examine the relationship between energy cost of walking and gait variability in PwMS, and (2) examine if the relationship differs according to the fall history of the MS participants.

## 2. Methods

### 2.1. Study design and participants

This cross-sectional study included 88 PwMS (50 women and 38 men), average age 39.8 (SD = 13.0), all treated with immunomodulatory drugs. Retrospective data were extracted from the Sheba MS Center's computerized database, a population-based registry documenting demographic, clinical and imaging data of all consecutive PwMS followed at the center. The database includes over 3500 patients out of approximately 6000 patients in Israel. Since 2012, the instrumented gait assessment has been part of the routine evaluation of patients at the Center. To date, the database includes over 900 gait assessment records. Since 2016, evaluation of the energy expenditure while walking, via a portable device, was added to the routine. A computerized questionnaire was employed to assist in selecting PwMS according to the following inclusion criteria: (1) a neurologist-confirmed diagnosis of definite MS according to the revised McDonald criteria [12]; (2) walking without a mobility aid, equivalent to < 6.0 on the Expanded Disability Status Scale (EDSS) [13]; (3) relapse-free for at least 90 days prior to testing; (4) patient had undergone an instrumented gait test via the GAITRite electronic walkway; (5) patient filled out a fall history questionnaire; (6) patient had undergone assessment of energy expenditure while walking with a portable metabolic device; and (7) outcome measures assessed within a 3-month interval and no relapse. Exclusion criteria included: (1) orthopedic disorders that could negatively affect balance and walking; (2) pregnancy; (3) blurred vision; (4) cardiovascular disorders; (5) respiratory disorders; (6) taking steroids or fampridine. The integrity of the data registry was evaluated by a computerized logic-algorithm-questioning process identifying data entry errors. The study was approved by the Sheba Medical Center's Research Ethics Committee (Ethics Ref: 5596-08/244811) confirming extraction of demographical, clinical, gait including energy expenditure data for analysis and full exemption of written or verbal consent from the study participants. Therefore, the individual data will not be made available in order to protect the participants' identity.

### 2.2. Energy expenditure while walking

Energy expenditure was measured separately at rest and during comfortable walking. Gas exchange values were acquired continuously by open spirometry and indirect calorimetry during each test period. Measurements were collected via a portable metabolic device using breath-by-breath technology (COSMED K5, COSMED Srl, Roma, Italy). Participants breathed through a Hans Rudolph face mask (Kansas City, Missouri) equipped with inspiratory valves. Prior to each test, the oxygen and carbon dioxide analyzers and the flow turbine were calibrated according to the COSMED K5's manufacturer's instructions. The COSMED unit was placed in a comfortable harness and worn on the shoulders. Data from each subject were telemetrically transferred to a laptop and analyzed by the COSMED software. Additionally, individual information (ie, height, weight and age) were inputted into the unit's software. Participants were asked to avoid eating 4 h prior to measurements, not to consume alcohol or engage in exercise during the 24 h prior to testing.

Oxygen consumption at rest was calculated by averaging 30 s $VO_2$ values (mL/ kg*min) over a 5-minute period of seated rest; higher values indicated a greater rate of resting energy expenditure. The subjects then participated in a 6-minute walking trial performed along an indoor 30 m corridor. The location allowed homogeneity in terms of temperature and humidity. The participants were instructed to "walk at your own comfortable speed". No encouragement or feedback was provided while walking. Cederberg et al [14] (2019) suggest these conditions if the intention is to reflect more daily activity mobility. Gas exchange values were calculated by averaging 30-second values over the final 3 min (minutes 4–6). Research studies have confirmed that the last 3 min of a 6-minute period of walking on a treadmill with a predetermined speed, yields a steady-state of $VO_2$ in PwMS [15]. Net $VO_2$ ($VO_{2walk}$-$VO_{2sit}$) was used to calculate the cost of walking (ml $O_2\,kg^{-1}\,m^{-1}$) during the preferred walking speed. Cost of walking = ($VO_{2walk}$-$VO_{2sit}$)/speed of walking (m/s) [16].

### 2.3. Gait variability

Gait variability was measured by the GAITRite™ electronic walkway, version 4.0.3 (CIR Systems, Inc. Haverton, PA, USA). The system integrates footprints and provides spatio-temporal parameters. In the present study, we extracted the variability of step time and step length expressed by the coefficient of variation (CV) (CV = SD/mean). The CV (%) is operationalized as a measure of relative gait variability [17]. This parameter was selected in line with previous studies demonstrating their relevance in gait difficulties in the MS population [18,19]. Step time variability in healthy individuals, mean age 69.7 (S.D = 3.6) years, has been estimated at 2.3% (S.D. = 1.0) [20].

A single valid walking trial was defined once the participant independently walked in one direction, at his/her self-selected speed, across the electronic mat without stopping. Each participant performed six consecutive walking trials, with each walking trial estimated between 4–6 gait cycles. At each pass, the step time variability score was individually calculated. The values from all trials were consequently averaged to produce the final results.

### 2.4. Statistical analysis

Participants were divided into groups based on fall history (fallers and non-fallers).

Input of fall history data were recorded when the patient answered the question: "Have you fallen during the past year?" A fall was defined as an event where the participant unintentionally came to rest on the ground or a lower level [21]. A faller was defined as a participant who had experienced at least two falls during the previous year [22]. All data were normally distributed according to the Kolmogorov-Smirnov test. Box plots determined outliers for each outcome. Group differences in MS type, gender distribution and fall status were determined by the chi-square test. Differences between groups in terms of age, disease duration, BMI, EDSS, EDSS subcategories, energy expenditure measures

**Table 1**
Demographics and Clinical Measures of the MS Study Sample (n = 88).

| Variable | Mean (SD) | | | |
|---|---|---|---|---|
| | Total group (n = 88) | Fallers (n = 33) | Non-fallers (n = 55) | *P*-value |
| Age (years) | 39.8 (13.0) | 42.1 (12.0) | 38.5 (13.5) | 0.201 |
| *Gender* | | | | 0.226 |
| Females | 50 | 16 | 34 | |
| Males | 38 | 17 | 21 | |
| Height (cm) | 170 (9.7) | 171 (10.6) | 169 (9.0) | 0.511 |
| Weight (kg) | 71.9 (16.8) | 70.5 (14.5) | 72.9 (18.5) | 0.582 |
| BMI (kg/m$^2$) | 24.6 (4.6) | 23.8 (3.8) | 25.2 (4.9) | 0.227 |
| Disease duration (years) | 6.2 (8.2) | 8.2 (9.5) | 4.9 (7.0) | 0.083 |
| EDSS (score) | 2.0 (1.5) | 2.5 (1.5) | 1.7 (1.4) | 0.065 |
| Pyramidal | 1.1 (1.1) | 1.7 (1.3) | 0.8 (0.9) | 0.001* |
| Cerebellar | 0.7 (0.9) | 1.0 (1.1) | 0.5 (0.7) | 0.007* |
| Sensory | 0.6 (0.9) | 0.7 (0.9) | 0.5 (0.8) | 0.306 |

BMI, body mass index; EDSS, expanded disability status scale; MS, multiple sclerosis.

and gait variability metrics were determined by the analysis of variance test. The relationship between gait variability and energy cost of walking was examined by the Pearson's correlation coefficient test. Correlation analysis was computed while controlling for disability (in terms of the EDSS) in the total sample and separately in the fallers and non-fallers groups. All analyses were carried out using the SPSS software (IBM SPSS Statistics for Windows, Version 25.0 Armonk, NY, USA: IBM Corp). All reported P values were two-tailed. The level of significance was set at $P < 0.05$.

## 3. Results

The mean disease duration of the total sample was 6.2 (S.D = 8.2) years since diagnosis. The mean EDSS score was 2.0 (S.D = 1.5; range 0–5.5) indicating minimal neurological disability. Thirty-three PwMS were classified as fallers and 55 as non-fallers. MS fallers demonstrated a higher neurological disability level in the pyramidal and cerebellar EDSS categories compared to non-fallers. Other participants' related clinical scores are outlined in Table 1.

Non-significant differences between groups were observed in the energy expenditure measures, including cost of walking. Fallers demonstrated higher step length variability compared with non-fallers (4.58 (S.D. = 2.42 vs. 3.40 (S.D. = 1.40); p = 0.005). Main outcome measures are presented in Table 2. According to the Pearson's correlation coefficient analysis, a significant relationship was found between step length variability and energy cost of walking in the non-fallers group (Rho = 0.372, p = 0.006) and the total group (Rho = 0.296, p = 0.005), but not in PwMS with a fall history. The results of the correlation analysis are presented in Table 3. The relationship between step length variability and energy cost of walking in the non-fallers group is illustrated in Fig. 1.

**Table 3**
Pearson's Correlation Analysis (Rho, P value) Between Energy Cost of Walking with Gait Variability Parameters.

| Variable | Total group (n = 88) | Fallers (n = 33) | Non-fallers (n = 55) |
|---|---|---|---|
| | Cost of walking (ml $O_2$ kg$^{-1}$ m$^{-1}$) | | |
| Step time CV | 0.161 (0.136) | 0.119 (0.508) | 0.159 (0.251) |
| Step length CV | 0.296 (0.005)* | 0.185 (0.303) | 0.372 (0.006)* |

CV, Coefficient of variation.
* P value < 0.05.

## 4. Discussion

The main finding of the present study was an association between gait variability and energy cost of walking in people with mild MS, which is in agreement with Sebastiao et al.'s [4] findings (2018). Nevertheless, our study adds novel information. According to the current data, the relationship between gait variability and energy expenditure during walking exists only in PwMS without a history of falls. No associations between gait variability parameters and energy expenditure measures were demonstrated in the MS fallers group.

Due to the present study's cross-sectional design, we were unable to claim a specific cause-effect relationship between falls, gait variability and energy cost of gait. Furthermore, to the best of our knowledge, there are no previous studies examining the triple association between gait variability, energy cost of walking and falls in PwMS. Therefore, we provided related evidence from studies performed on elders. Cirprandi et al. [23] (2017) reported that gait variability was significantly and inversely associated with the level of physical activity in healthy women, specifically, elder women with increased gait variability tended to participate in fewer physical activities. Wang et al.'s [24] clinical trial (2015) also contributes to this issue. The authors demonstrated that a 12-week combined exercise program, including 20 min of endurance training, reduced stride time/length variability in elders. Finally, females who were classified as fallers, demonstrated increased energy cost of walking compared to non-fallers [25]. Incorporating this information suggests that there is a link between increased risk of falls, gait variability and elevated energy expenditure while walking. However, the exact contribution of each factor can be determined only by a future longitudinal study.

Nevertheless, we offer several explanations for our findings. Firstly, PwMS who ambulate with increased variability between steps, expend more energy than normal in order to control the body's irregular center of mass sway. Elevated energy expenditure while walking may lead to a significant increase in fatigue, which by itself is a risk factor of falling in MS [26].

An additional explanation for our findings involves the patient's fall status. Risk of falling is multifactorial in PwMS [27]. Previous studies

**Table 2**
Energy Expenditure and Gait Measures in the MS Subgroups.

| Variable | Mean (SD) | | | |
|---|---|---|---|---|
| | Total group (n = 88) | Fallers (n = 33) | Non-fallers (n = 55) | *P*-value |
| Energy expenditure measures | | | | |
| Sitting - $VO_2$ rate (mL/kg*min) | 4.55 (1.39) | 4.50 (1.21) | 4.57 (1.50) | 0.824 |
| Walking - $VO_2$ rate (mL/kg*min) | 12.17 (2.87) | 12.50 (3.20) | 11.98 (2.67) | 0.414 |
| Cost of walking (ml $O_2$ kg$^{-1}$ m$^{-1}$) | 0.118 (0.037) | 0.126 (0.043) | 0.114 (0.033) | 0.128 |
| Gait parameters | | | | |
| Step time CV (%) | 3.80 (1.81) | 4.14 (1.84) | 3.59 (1.77) | 0.168 |
| Step length CV (%) | 3.84 (1.92) | 4.58 (2.42) | 3.40 (1.40) | 0.005* |
| Walking speed (m/min) | 65.47 (12.64) | 64.66 (13.16) | 65.96 (12.41) | 0.642 |

CV, Coefficient of variation.

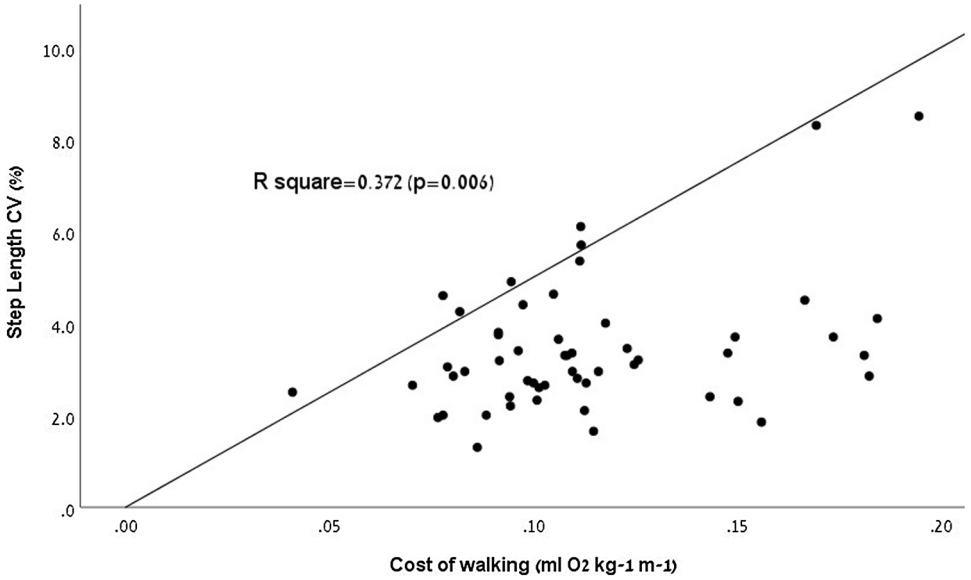


**Fig. 1.** The relationship between step length variability and energy cost of walking in the non-fallers group.

have reported many risk factors for falling in PwMS such as poor static and dynamic balance, spasticity, and sensory deficits. From a feasibility standpoint, it was not possible to control all confounders in our study, therefore, there is a reasonable chance that some of the confounders masked the relationship between gait variability and energy expenditure measures in the fallers group. On the contrary, because these cofounders do not exist in participants classified as non-fallers, the relationship between gait variability and energy expenditure measures was notable, specifically, statistically significant. Perhaps the lack of correlation between energy expenditure and gait variability should alert medical professionals, as it may be an initial sign of a motor and/or sensory disturbance, indicating an increased risk of falling.

Irrespective, of our explanations, future longitudinal research is needed to clarify these assumptions. Defining which of the three factors (falls, increased gait variability, or elevated energy expenditure while walking) is the initial trigger might improve physical rehabilitation programs in people with mild MS. Furthermore, it would be of interest to examine the effect of a focused exercise program on the other symptoms, i.e., the effect of a program focusing on reducing gait variability and the energy cost of walking.

Should be noted that the lack of association between gait variability and energy expenditure in the fallers group may be due to the study protocol. The energy expenditure was measured while patients were instructed to walk at their own comfortable speed. We speculate that a submaximal walking test, using maximum speed, might have revealed an association between gait variability and energy expenditure. However, only by future research can this assumption be proven.

This study is not without limitations. Firstly, as presented earlier, the cross-sectional design does not provide causal inferences. Secondly, the methodology for reporting falls was based on a self-report of previous falls instead of prospectively. In the same context, although the included PwMS presented with only mild memory impairment, recall bias could still affect self-reporting of falls. Furthermore, some may argue that the selection of two falls per year masked the results of those PwMS who experienced a single fall per year, as those patients were classified as non-fallers. We note that while the term "fall" is relatively well defined, there is no consensus as to the definition of a MS faller. Some studies consider $\geq 1$ fall occurring during the past 12-months [21], while others classify a faller as one who fell $\geq 2$ times during a 3-month period, hence, we consider the present definition of a faller to be within the range of previous publications. Another point worth noting refers to the walking speed calculation needed for the Cw formula. In the present study, walking speed was computed according to the total distance during the 6MWT, while the energy expenditure analysis was based solely on the last 3 min. There is a possibility that the walking speed was different between the first and last 3-minutes, consequently affecting the Cw scores. Although we cannot rule this out, changes in walking speed are not expected while walking at a comfortable pace. Additionally, the level of spasticity and fatigue, related to our main outcome measures, was not controlled in the study, although it is rarely significant in mild MS. Our study was limited to patients with a relapsing-remitting form of disease, minimal and mild disability. Therefore, our conclusions cannot be confirmed in progressive MS or patients with moderate and severe disabilities. Finally, the present sample size was relatively small, however, our data should serve as sample size calculations for future trials.

## 5. Conclusions

We provide evidence of a relationship between increased gait variability and energy expenditure while walking in people with mild MS. The novelty of the current study was the focus on the fall status of the sample. We demonstrated a significant relationship only in those patients without a history of falls. This is important as there is evidence of the clinical relevance of increased gait variability, poor fitness level and high risk of falling in the MS population. Nonetheless, future studies addressing these symptoms are needed to improve our understanding of this issue, including the effect of targeted rehabilitation programs.

## Contributors

Alon Kalron contributed to the conception and design of the study, analysis and interpretation of data, drafting the article and final approval of the version to be submitted. Roy Aloni collected the data, contributed to the interpretation of data, revising the article critically for important intellectual content and final approval of the version to be submitted. Uri Givon contributed to the interpretation of data, revising the article critically for important intellectual content and final approval of the version to be submitted. Shay Menascu contributed to the analysis and interpretation of data, drafting the article and final approval of the version to be submitted. All authors approved the final article.

## Identifying material

The current study design was cross-sectional. We evaluated retrospective data collected from the Multiple Sclerosis Center, Sheba Medical Center, Tel Hashomer, Israel's computerized database. The study was approved by the Sheba Institutional Review Board.

## Funding source

This research did not receive any specific grant from funding agencies in the public, commercial or not-or-profit sectors

## Declaration of Competing Interest

There are no financial and personal relationships with other people or organizations that could inappropriately influence this work.

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