Changes in Gait Characteristics During and Immediately After the 6-Minute Walk Test in Persons With Multiple Sclerosis: A Systematic Review

Peer-reviewed author version

ABASIYANIK, Zuhal; Kahraman, Turhan; VELDKAMP, Renee; Ertekin, Ozge; Kalron, Alon & FEYS, Peter (2022) Changes in Gait Characteristics During and Immediately After the 6-Minute Walk Test in Persons With Multiple Sclerosis: A Systematic Review. In: Physical therapy, 102 (7) (Art N° pzac036).

DOI: 10.1093/ptj/pzac036
Handle: http://hdl.handle.net/1942/37962

TITLE: Changes in gait characteristics during and immediately after the six-minute walk test in persons with multiple sclerosis: A systematic review

Running title: 6-Minute Walk Test in Multiple Sclerosis

Zuhal Abasıyanık[1,2,3] PT, MSc; Turhan Kahraman[3] PT, PhD; Renee Veldkamp[1,4] PhD; Özge Ertekin[5] PT, PhD; Alon Kalron[6] PT, PhD; Peter Feys[1,4] PT, PhD

[1]REVAL Rehabilitation Research Center, Faculty of Rehabilitation Sciences, Hasselt University, Hasselt, Belgium
[2]Graduate School of Health Sciences Dokuz Eylül University, Izmir, Turkey
[3]Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Izmir Katip Celebi University, Izmir, Turkey
[4] UMSC, Hasselt-Pelt, Belgium
[5] School of Physical Therapy and Rehabilitation, Dokuz Eylül University, Izmir, Turkey
[6] Department of Physical Therapy, School of Health Professions, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Corresponding author: Zuhal Abasıyanık
REVAL Rehabilitation Research Center, Faculty of Rehabilitation Sciences, Hasselt University, Martelarenlaan 42, Agoralaan 1, 3500 Hasselt, Belgium; Graduate School of Health Sciences, Dokuz Eylül University, Inciralti, Izmir 35340, Turkey; Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Izmir Katip Celebi University, Izmir, Turkey
e-mail: zuhal.abasiyanik@uhasselt.be, Tel.: +90 2323293535; Fax: +90 2323860888
ORCID ID: 0000-0003-3086-8102

Email addresses of co-authors:
Turhan Kahraman: turhan.kahraman@yahoo.com, ORCID ID: 0000-0002-8776-0664
Renee Veldkamp: renee.veldkamp@uhasselt.be, ORCID ID: 0000-0002-7317-2431
Özge Ertekin: ozge.pt@gmail.com, ORCID ID: 0000-0001-9935-0673
Alon Kalron: alkalron@gmail.com, ORCID ID: 0000-0001-7999-0868
Peter Feys: peter.feys@uhasselt.be, ORCID ID: 0000-0002-5680-5495

PROSPERO Registration ID: CRD42020205773

Number of words
  Abstract: 298
  Total: 4262
Number of figures: 2
Number of tables: 3
Number of supplementary tables: 1
Number of references: 56

Changes in gait characteristics during and immediately after the six-minute walk test in persons with multiple sclerosis: A systematic review

Abstract

Objective: There is limited information about the gait pattern during prolonged walking in persons with multiple sclerosis (pwMS). The aim of this review was to report on gait metrics during and immediately after the 6-Minute Walk Test (6MWT) in pwMS with different levels of disability.

Methods: The systematic search was performed in three databases (PubMed, Web of Science, and SCOPUS) using keywords related to multiple sclerosis and 6MWT. Studies that reported on quantitative gait outcomes before and after the 6MWT or multiple time points during the 6MWT were included. The Hedges' g effect size (ES) was calculated to determine the magnitude of change in each gait parameter.

Results: Fourteen studies (n=534 pwMS, n=166 healthy controls) were eligible. Five studies investigated gait parameters prior to and immediately after the 6MWT. Nine studies collected gait measures during the 6MWT. Speed (ES=-0.43 to 0.19), cadence (ES=-0.46 to 0.16), step length (ES=-0.46 to 0.14), stability (ES=-0.35 to 0.33), regularity (ES=-0.25 to -0.15) decreased in most studies. In the majority of included studies, there was an increase in step time (ES=0 to 0.35), stance period (ES=0.12 to 0.58), double support phase (ES=0.03 to 0.62), variability (ES=-0.19 to 1.13), and asymmetry (ES=-0.79 to 0.62) following the 6MWT. The kinetic and kinematic [mainly in dorsiflexion angle (ES=-0.08 to -0.36)] features of gait were also negatively changed after six minutes of walking. There were increases in walking speed, cadence, step length, stride length, and stride time after 6MWT in the assessment at a comfortable speed. Changes in the majority of spatiotemporal parameters were more pronounced in moderate-severely disabled pwMS compared with mild disability.

Conclusion: Most quantitative gait parameters deteriorated during the 6MWT, especially in moderately-severely disabled pwMS.

Impact: The deterioration of the gait patterns should be considered when designing therapeutic interventions to increase sustained walking capacity.

Keywords: Multiple Sclerosis, Walking, Gait, 6-Minute Walk Test, Fatigue, Fatigability

Introduction

Multiple sclerosis (MS) is a neurodegenerative disease that typically results in worsened walking. Persons with MS (pwMS), even with mild disability, show impaired gait characteristics compared to healthy controls in laboratory-based assessments.[1] Walking has been reported as one of the highest priorities in pwMS, even in the early stages of the disease.[2] Therefore, assessment of walking ability is a key component of clinical management of pwMS.

Many clinical tests are used to evaluate walking in pwMS. These include short tests such as Timed-25 Foot Walk (T25FW) and 10-Meter Walk Test (10MWT) or long tests such as 6-Minute Walk Test (6MWT) and 2-Minute Walk Test (2MWT).[3] Long walk tests are considered to have greater ecological validity in terms of reflecting real-life mobility.[4–7] The 6MWT is the most widely used valid and reliable clinical test to assess walking capacity in pwMS.[8] Although the 6MWT has originally been conceived and conventionally been used to measure cardiorespiratory fitness, its main use has been to assess walking capacity rather than aerobic capacity in pwMS with motor impairments.[9] Furthermore, some studies suggested that biomechanical changes can occur during the 6MWT, such as kinematics and kinetics of gait.[10,11] Therefore, the 6MWT has become one of the most commonly used tools to allowing to measure walking-related fatigability.[6] Walking-related fatigability, defined as the magnitude of declined task performance over time[12] is a common problem in pwMS affecting approximately half of the patients with moderate-severe disability.[13] Following the sustained motor task, peripheral changes and reduced central neural drive may lead to deterioration in motor performance. The deterioration may be more pronounced as prolonged nerve conduction caused by demyelination and axonal loss already exists in pwMS.[14,15] Several studies have applied the 6MWT as a fatiguing motor task to investigate the effects of prolonged walking on muscle strength, gait, balance, reaction time, and spasticity in pwMS.[16–19] Reduction of speed or distance during or after the 6MWT has been described in many studies, including pwMS. [4,10,13,16,20,21]Although monitoring the change in distance and speed is significant, it does not explain gait deterioration during prolonged walking.

Knowledge regarding which gait parameters are affected by prolonged walking can provide new insights on fatigability and improve physical rehabilitation intervention programs. Monitoring the changes in gait parameters throughout the 6MWT or after performing the 6MWT can provide insight into compensatory strategies, neuromuscular deficits, and possible gait markers of fatigability in pwMS. Therefore, the main purpose of this systematic review was to explore the changes in quantifiable gait measures during and after the 6MWT in pwMS.

Methods

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[22] The study protocol was registered on PROSPERO (ID=CRD42020205773).

Data Sources and Searches

Two authors (ZA & TK) independently screened the articles published up to the 8th of March 2021 using three databases; PubMed, Web of Science, and SCOPUS. The following search terms were used: ("Six minute walk test" OR "Six minute walk" OR "6-minute walk test" OR "6-minute walk" OR "6 min walk test" OR "6 min walk" OR "6 MWT" OR "6 MW") AND ("Multiple Sclerosis" OR "MS"). Filters were set to include "Humans" and "English".

Study Selection

The studies were first screened based on the title and abstract level. The entire text was read if the abstract did not provide sufficient information. Two authors (ZA & TK) independently screened the full texts of the remaining articles for eligibility. Reference lists of included articles were further checked to identify any other relevant studies that fit the inclusion criteria. Co-authors were consulted in case of any disagreements.

We included only full-length original studies that (1) performed the 6MWT in adults with MS, (2) included quantitative gait measures (e.g., spatial-temporal parameters, kinetics, and kinematics), (3) time assessment of gait was before and after or recorded during multiple time points (e.g., min 6 and min 1) or reported changes between these time points. Low-quality studies, based on scores equal to or above 65% according to the quality assessment checklist, were excluded from this review since they may be a potential source of bias. Additionally, studies applied to concurrent motor or cognitive tasks during the 6MWT were excluded. The corresponding author was contacted in case of uncertainty regarding the content of the study.

Data extraction and Quality Assessment

Data extracted from the studies included: (1) sample size, (2) demographic and clinical characteristics of the participants, including age, sex, type of MS , disability level, and disease duration, (3) 6MWT procedure (instructions, environmental conditions, length of the pathway, use of rest breaks, use of assistive devices), (4) methods and measurement tools assessing gait, (5) gait measures (spatial-temporal parameters, kinetics, and kinematics), (6) if available pre- (or time period-1/onset) or post- (or time period-2/end) 6MWT values for each gait parameter, *p*-values describing the differences between periods within one group, and *p*-values presenting group, time, group by time interactions between the study groups. In cases were a study involved more than one assessment of 6MWT (e.g., before and after an intervention program), only the baseline (or initial gait assessment) was extracted. Since there was no universally used classification for disability status, there were quite different approaches for defining disability severity in included articles. To present more consistent results, we grouped the disability levels based on EDSS according to the classification suggested by Learmonth et al., which is widely used in the MS population (EDSS range 0-3.5 for mild disability, 4.0-5.5 for moderate, and 6 or above for severe neurological disability).[23] In addition, groups categorized as having a moderate or severe disability were consolidated into one group as a moderate-to-severe group. Moderate and severe neurological disability exhibits difficulties with walking, although mild disability indicates expression of impairments based on different functional system scores of EDSS.[23]

Assessment of the methodological quality of each study was conducted based on the Downs and Black checklist.[24,25] The checklist includes 27 questions relating to the quality of reporting (10 items), external validity (3 items), internal validity (13 items), and statistical power (1 item). Items 6, 8, 14, 15, 19, 23, 24, and 26 were not applicable for evaluating observational studies; therefore, they were removed as done in previous similar systematic reviews.[6,25] The score was converted to a percentage value for each study, a higher total score indicating a higher methodological quality. Scores equal or above 65% indicate sufficient quality. The quality assessment was performed independently by two authors (ZA & TK). A third reviewer was consulted in cases of inconsistency.

Data Synthesis and Analysis

Changes in gait metrics were analyzed by interpreting the effect size (ES) and *p*-values. Hedges' g was used to calculate the ES in order to determine whether the magnitude of change in gait measures following the 6MWT is significantly relevant. Hedges' g values were calculated by dividing the difference between the mean value at post /termination of the 6MWT and the pre/initial with the pooled standard deviations for the specific gait measure for each individual study. According to Cohen's classification, the ES was classified: between 0.20 and 0.49 as small, between 0.50 and 0.79 as moderate, and ≥0.8 as large.[26] We calculated the combined mean, SD, and ES for the consolidated groups for each study[26] and used combined ES when presenting the changes in the disability subgroups in the figure. In case of a single study, the ESs were reported as Cohen's d.[27] Results are grouped according to the specific gait parameter and further compared according to the level of disability.

Due to the relatively large heterogeneity of the gait assessment methods, differences in 6MWT administration, assessments in different time periods during the 6MWT, and the low number of studies, we could not perform a meta-analysis with a pooled effect size.

Role of the Funding Source

This study was supported by the Special Research Fund (BOF number: BOF20BL13). The funders played no role in the design, conduct, or reporting of this study.

Results

From searching the electronic databases, 1907 articles were identified after removing duplicates. Following title and abstract screening, 85 articles were assessed in full-text. After the assessment of the full-texts, three studies had insufficient data; therefore, their corresponding authors were contacted. One study was excluded because of an identical patient group as another study included in this review. One study was included after gathering information provided by the authors.[28] One study was excluded due to the absence of essential quantitative gait measures. Fourteen studies were included in the final analysis. The study flow chart is presented in Figure 1.

Quality assessment

The results for quality assessment of the included studies are shown in Supplementary Table 1. All studies had sufficient methodological quality (>65%) with scores ranging from 68% to 84%. Main shortcomings were: not reporting the subpopulation representative for the entire population (item 12), unspecified recruitment periods (item 22), and not mentioning possible confounders (item 25).

Study characteristics

Descriptive characteristics of participants across studies are presented in Table 1. Five studies assessed gait prior and immediately after the 6MWT.[10,11,20,29,30] Nine studies recorded changes during the 6MWT.[28,31–38] The review was based on 534 pwMS (n=143 prior-after the 6MWT, n=391 during the 6MWT) and 166 healthy controls (HCs) (n=59 prior-after the 6MWT, n=107 during the 6MWT). The mean Expanded Disability Status Scale (EDSS) of the pwMS in the studies ranged from 1.5 to 4.5. Three studies divided pwMS according to the level of disability based on the EDSS score.[29,31,32] One study divided participants according to their walking speed[30], another study divided participants according to the use of an assistive device.[33] Thirteen articles reported disability status based on the EDSS and one based on the Patient Determined Disease Steps Scale (PDDS) which is a patient-reported outcome of disability in MS and usually used as a surrogate of EDSS. The majority of the studies (13 out of 14) were cross-sectional. One study assessed gait parameters before and after an 8-week intervention program[11]. For this study, we extracted baseline values only.

A full description of the 6MWT experimental procedure and gait assessments are detailed in Table 2. With regard to instruction during the 6MWT, all studies aimed at the maximum performance (n=9; "as fast as possible" according to Goldman et al.[4] vs. n=5; "maximum distance"). Regarding the gait assessment method, wearable sensors (n=8), GAITRite electronic walkway (n=2), 3D motion capture (n=2), and the electrogoniometer (n=1) were used. The prior-immediately after the 6MWT studies used two different assessment methods to examine changes in gait parameters, including fastest speed (n=1), comfortable speed (n=1), both fastest and comfortable speed conditions (n=2). One study reported no information on pace instruction. The most common spatiotemporal gait measures recorded were speed, cadence, step length, step width, step time, single support, and double support time. In our study, gait parameters are grouped as (1) key spatiotemporal, (2) variability and asymmetry, (3) stability and regularity, and (4) kinematic and kinetic (Table 3 A-D).

Changes in key spatiotemporal parameters of gait

Spatiotemporal gait parameters changed negatively during and following the 6MWT. Walking speed (n=9 studies, 307 pwMS), cadence (n=9, 246 pwMS), and step length (n=6, 154 pwMS), stride length (n=1, 19 pwMS) were mostly decreased, while increases were observed in step time (n=3, 99 pwMS), stride time (n=1, 19 pwMS), stance period (n=1, 54 pwMS), step width (n=2, 72 pwMS), double support phase (n=5, 142 pwMS), and single support phase (n=1, 11 pwMS) after and during the 6MWT in pwMS. Changes in speed, step length, step time, step width, double support phase were greater in studies assessing gait prior and immediately after the 6MWT compared with studies assessing gait during the 6MWT. An exception was cadence that decreased more in studies assessing gait during the 6MWT (Table 3-A, Figure 2-A).

When the comfortable speed and fastest speed conditions of the before-and-after-the-6MWT studies are examined separately, the increase in double support phase was more significant in the fastest speed condition (n=3, 113 pwMS).[10,29,30] Speed (n=4, 132 pwMS),[10,20,29,30] cadence (n=4, 132 pwMS),[10,20,29,30] step length (n=3, 113 pwMS),[10,29,30] stride length (n=2, 51 pwMS),[10,20] and stride time (n=1, 19 pwMS)[20] parameters did not change or improved when gait was evaluated at comfortable speed but worsened in the fastest speed condition (Table 3-A, Figure 2-A).

Several studies reported gait parameters according to disability levels. These studies observed slower speed (n=4, 157 pwMS),[29–31,33] decreased cadence (n=4, 157 pwMS),[29–31,33] shorter step length (n=3, 99 pwMS),[29,30,33] and an increase in step time (n=2, 72 pwMS),[29,33] stance period (n=1, 54 pwMS),[29] step width (n=1, 54 pwMS),[29] and double support (n=3, 99 pwMS)[29,30,33] in patients with greater disability (Table 3-A; Figure 2-A).

One study (86 pwMS) presented an algorithm named the dynamic time warping (DTW) aimed to assess gait deterioration by measuring the similarity between gait cycles.[28] DTW scores increased between minutes 3 and 6 in pwMS with both mild (Cohen's d = 0.786, $p<0.001$) and moderate disability (Cohen's d=0.374, $p<0.001$).[28]

Changes in variability, asymmetry, regularity, and stability parameters of gait

All studies examining gait variability collected data during the 6MWT. Gait variability measures (double support, step width, step time, stride time, and step length) increased during the 6MWT (n=4, 180 pwMS).[31–33,36] Gait asymmetry measures (single support, step time, swing time, and step length) increased following the 6MWT in pwMS (n=3, 124 pwMS)[29,31,36] (Figure 2-B). Due to the heterogeneity of the outcome measures, we could not compare before-after and during the 6MWT protocols for asymmetry and variability parameters.

Several studies reported gait variability and asymmetry parameters at different disability levels. Step time, step length, swing time, and single support asymmetry increased in pwMS with moderate-to-severe disability (n=3, 124 pwMS).[29,31,36] In contrast, these asymmetry measures did not change or decrease in pwMS with mild disability (n=2, 112 pwMS).[29,31] Gait variability (step length, step time, step width, and double support) increased in pwMS with moderate-to-severe disability and decreased in those with mild disability (n=1, 18 pwMS).[33] An exception was stride time variability that increased in both pwMS with mild and moderate-to-severe disability (n=3, 162 pwMS)[31,32,36] (Table 3-B).

None of the included studies examined gait stability and regularity before and immediately after 6MWT. Step and stride regularity decreased during the 6MWT in both pwMS with mild and moderate-to-severe disability (n=1, 58 pwMS).[31] Sample entropy, reflecting the complexity of walking, increased in pwMS with mild disability, and decreased in pwMS with moderate-to-severe disability (n=1, 58 pwMS).[31] In terms of gait stability, assessed by local dynamic stability, pwMS were less stable during the 6MWT compared to HCs, and the change in the vertical accelerations of the trunk was significant (n=2, 101 pwMS).[34,35] Gait stability, assessed using harmonic ratio, decreased during the 6MWT in pwMS (n=1, 12 pwMS)[36] (Figure 2-B). Bilateral coordination of gait, assessed by the phase coordination index, worsened minute by minute during the 6MWT and was more pronounced in pwMS with moderate-to-severe disability ($p<0.0001$) (n=1, 92 pwMS)[32] (Table 3-C).

Changes in the kinematics of gait

The largest effect sizes were observed for the reduced ankle dorsiflexion angle of the affected limb at initial contact and increased knee extension angle during stance after the 6MWT (n=2, 43 pwMS).[10,11] Additionally, knee flexion during stance was increased in the stronger leg compared with the weaker leg of pwMS (and HCs) (n=2, 43 pwMS).[10,11] Maximum ankle plantarflexion increased at loading response and decreased during swing following the 6MWT in pwMS (n=3, 58 pwMS)[10,11,37] (Table 3-D).

One study measured the total range of motion in the hip, knee, and ankle joints (sagittal plane) and found a 4.9%, 4.5%, and 7.7% decrease in the range of motion of the hip, knee, and ankle joints, respectively (n=1, 9 pwMS). Additionally, gait variability increased by 1.2%, 2.3%, and 2.2% in the hip, knee, and ankle joints.[38]

Changes in the kinetics of gait

Several changes occur in terms of gait kinetics in both limbs of pwMS following the 6MWT. These changes include increases in maximum hip extensor and flexor moment in the stance phase, maximum hip power generation during early stance, and maximum hip power absorption during midstance. Furthermore, both pwMS and HCs demonstrated an increase in maximum knee flexor moment at the initial contact and stance. Additional changes concerning the knee included an increase in maximum knee extensor moment, maximum knee power generation during mid-stance, maximum knee power absorption during early stance, and maximum knee power absorption during late swing in pwMS, and slightly greater in HCs. Changes in ankle kinetics included a decrease in maximum ankle dorsiflexion moment during early stance, maximum ankle plantarflexion during late stance in the affected leg in pwMS. Increased maximum ankle power absorption during early stance and decreased maximum ankle power generation during stance were found in both limbs (n=2, 43 pwMS).[10,11] (Table 3-D)

Discussion

In this systematic review, we present novel aspects regarding the walking behaviour following and during the 6MWT in pwMS. Our results suggest that following the 6MWT, deterioration occurs in spatiotemporal, variability, asymmetry, regularity, stability, kinetics, and kinematics metrics of gait. Additionally, we found that the deterioration in most gait parameters is more pronounced in moderate-to-severely disabled pwMS compared with mildly disabled.

Interestingly, although the 6MWT is a standard test in pwMS, we noticed variations in terms of administration protocols and assessment methods between studies. The present review included studies of different designs, those evaluating gait prior to and immediately after the 6MWT and studies monitoring gait parameters during the test. Changes in spatiotemporal parameters (i.e., walking speed, step length, step time, step width, and double support phase) were more prominent when gait was assessed prior to and immediately after the 6MWT compared with studies assessing gait during the 6MWT. In studies examining gait prior to and immediately after 6MWT, gait analysis was performed with different walking speed instructions. PwMS could maintain or improve walking speed, cadence, step length, stride length, and stride time in the assessments at a comfortable speed.[10,20,30] On the other hand, these parameters are negatively affected by the six minutes of walking when instructed to walk fast. It supports the knowledge that walking assessment at a comfortable speed may not detect prolonged walking-induced changes in pwMS.[39]

The deterioration in the majority of spatiotemporal parameters of gait was more pronounced in moderate-severely disabled pwMS.[29–31,33] This finding is in agreement with previous studies showing that fatigability is related with level of disability.[13,20,31,38] This finding might be explained by the reduced central motor drive following sustained tasks, which gets worse as the level of disability increases.[40] Worth noting, when assessing gait by the DTW method, (i.e. indicating similarity between contralateral strides), the deterioration in gait is noticeable in mildly disabled pwMS as well.[28] However, due to the relatively large heterogeneity between studies along with variations in disability categorization, further investigations on this issue are still needed.

Another novel observation of our review concerns the increase in gait asymmetry and variability during the 6MWT solely in pwMS with a moderate-to-severe disability. Sosnoff et al. reported that gait variability was elevated in minimally disabled pwMS compared with HCs, while Kalron et al. found that gait variability increased in relation to the level of disability.[41,42] These findings are in agreement with those of Kalron et al., demonstrating that gait variability increases throughout the 6MWT more in pwMS with moderate-to-severe disability compared to mild disability. Noteworthy, gait variability and asymmetry are associated with the neural control of walking. Elevated gait variability is related to higher energetic costs and increased risk of falls in the neurologic population, including pwMS.[43–45] Recently, Shiratzky et al. demonstrated that greater asymmetry and variability during the 6MWT was associated with fall history in pwMS.[31] Thus, the increase in gait variability and asymmetry after and during the 6MWT (in other terms, sustained walking) might explain the high prevalence of falls in the MS population. Still, risk factors for falls are multifactorial in pwMS;[46] therefore, additional longitudinal studies are still needed in order to clarify this relationship.

In a similar context, regularity of gait, reflecting acceleration consistency, was reported by Shema-Shiratzky et al. The authors found that regularity of steps and strides decreased over the 6MWT, suggesting that prolonged walking might be the cause of inconsistency in the gait pattern in pwMS.[31] Moreover, a decrease in the sample entropy (i.e., the complexity of walking) in moderately-to-severely disabled pwMS suggests that prolonged walking reduces gait complexity in more disabled pwMS.[31] Previously, it has been suggested that a decrease in gait complexity corresponds with difficulties adapting mobility in daily life activities, additionally it might help identify elders who are at increased risk of falls.[47]

The local dynamic stability parameter measured during the 6MWT is often used to assess dynamic balance. According to our findings, pwMS with mild to moderate disability were less stable in the last 3-min of the 6MWT than HCs.[34] We believe that this finding is important for clinicians in the field, as it supports the usage of the 6MWT to detect difficulties in maintaining stability while walking, which tend to occur only after a few minutes of walking. Moreover, the harmonic ratio of the pelvis and head, another metric of gait stability, decreased during the 6MWT in pwMS while increased in HCs, supporting the belief that sustained walking contributes to instability while walking in pwMS.[36] In the same context, deterioration in bilateral coordination of gait, expressed by the phase coordination index, across the 6MWT has been assessed in pwMS.[32] Previously, the local dynamic stability metric has been found associated with falls and found appropriate for trials assessing the impact of rehabilitation on the risk of falls in pwMS.[48] These metrics may be useful to detect patients at risk of falls and/or evaluate the efficacy of treatment programs.

As for kinematic measures, we speculate that the change in ankle kinematics during the 6MWT suggests that prolonged walking uncovers weakness and/or reduced endurance of the dorsi-flexor muscle group.[10,11,37] This result is significant for health professionals involved in physical rehabilitation in pwMS. We believe that a successful treatment plan for this gait abnormality involves early detection. Worth noting, in many cases, drop foot occurs only after walking a relatively long distance/time; therefore, it may not be noticed during short walking tests. Furthermore, the increase in power absorption in the hip, knee, and ankle joints may suggest that prolonged walking during the 6MWT reveals muscle weakness and/or poor neuromuscular control.[10,11] However, compensatory kinetic changes were also observed after 6MWT, such as increased hip extension moment and hip power generation, which are considered to occur to preserve the support of the trunk and forward progression. Additionally, in order to compensate for reduced ankle power at push-off, hip flexion moment might have increased to assist toe-clearance in swing and forward momentum.[10,11] These changes and compensatory strategies highlight the need for strengthening and balance training or orthotic interventions in pwMS.[49,50] However, worth noting, the kinetic and kinematic data in relation to the 6MWT should be considered with caution due to the fact that only a few studies investigated these domains in pwMS.[10,11,37]

Limitations

Several important points should be considered while interpreting the results of this systematic review. First, testing procedures of the 6MWT varied between studies, including instructions on the walking speed. Secondly, studies that monitored gait metrics during the 6MWT used different time intervals (i.e., each minute, 2-min, 3-min). Additionally, the categorization of disability subgroups was inconsistent between studies. Each study based the definition of mild, moderate and severe disability on different EDSS cut-off scores. For these reasons, we were unable to conduct a meta-analysis, and it limited the interpretation of the evidence. Therefore, we highly recommend for clinical use and future research standardized 6MWT administration protocol as provided by Goldman et al.[4] and the American Thoracic Society.[51] Nevertheless, it might be interesting to compare the effects of different instructions regarding walking speed on the performance of the 6MWT. Future instance, it may be argued that instructing the participant to walk as fast as possible might reflect fatigability better compared to asking the patient to walk at a normal pace. Furthermore, if the tester aims to detect changes in spatiotemporal parameters of gait due to prolonged walking, it may be recommended to measure gait parameters before and immediately after the 6MWT rather than measuring these metrics during the 6MWT. Additionally, although the reliability of changes in several gait parameters during the execution of 6MWT has been shown in one study for inertial sensors in pwMS,[38] more studies are needed to present data on the test-retest reliability and validation of spatiotemporal as well as variability, asymmetry, and regularity gait characteristics as a marker of fatigability in pwMS. Without a doubt, the use of additional methods to capture this common symptom is warranted and can potentially improve health management in the MS population. Future research is encouraged to examine the relationship between changes in gait metrics during sustained walking with community ambulation and/or fall risk.

Conclusion

We reviewed the knowledge regarding the effect of prolonged walking on gait characteristics in pwMS. The 6MWT is a powerful tool expressing the impact of fatigability in terms of deterioration in spatiotemporal, variability, asymmetry, regularity, stability, kinetic, and kinematic gait features in pwMS. We note that most of these changes depend on the level of disability. The present findings suggest that for the majority of pwMS (excluding mildly disabled), it is preferable to assess gait prior to and immediately after the 6MWT compared with measuring gait changes during the test. Additionally, requesting the patients to walk at a fast-walking speed might prove better compared with normal walking speed. However, these assumptions need further exploration in a larger sample of pwMS consisting of different disability levels. This information should be of great assist for future trials testing therapeutic interventions to increase sustained walking capacity and decrease the risk of falling in pwMS.

Author Contributions

Conceptualization: ZA, RV, PF; Methodology: ZA, RV, PF; Data curation: ZA, TK; Supervision: PF; Visualization: ZA, TK; Writing-original draft: ZA; Writing – review & editing: ZA, TK, RV, ÖE, AK, PF

Funding

This study was supported by the Special Research Fund (BOF number: BOF20BL13).

Systematic Review Registration

This systematic review was registered in PROSPERO (ref no. CRD42020205773).

Disclosure

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

References

1. Nogueira LAC, Teixeira L, Sabino P, Filho HA, Alvarenga RMP, Thuler LC. Gait characteristics of multiple sclerosis patients in the absence of clinical disability. . *Disabil and Rehabil.* 2013;35:1472-1478.

2. Heesen C, Böhm J, Reich C, Kasper J, Goebel M, Gold SM. Patient perception of bodily functions in multiple sclerosis: Gait and visual function are the most valuable. *Mult Scler.* 2008;14:988-991.

3. Soler B, Ramari C, Valet M, Dalgas U, Feys P. Clinical assessment, management, and rehabilitation of walking impairment in MS: an expert review. *Expert Rev of Neurother*. 2020;20:875-886.

4. Goldman MD, Marrie RA, Cohen JA. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. *Mult Scler.* 2008;14:383-390.

5. Stellmann JP, Neuhaus A, Götze N, et al. Ecological validity of walking capacity tests in multiple sclerosis. *PLoS One*. 2015;10:1-11.

6. van Geel F, Moumdjian L, Lamers U, Bielen H, Feys P. Measuring walking-related performance fatigability in clinical practice: A systematic review. *Eur J Phys Rehabil Med*. 2020;56:88-103.

7. Gijbels D, Alders G, van Hoof E, , et al. Predicting habitual walking performance in multiple sclerosis: Relevance of capacity and self-report measures. *Mult Scler*. 2010;16:618-626.

8. Goldman MD, Motl RW, Rudick RA. Possible clinical outcome measures for clinical trials in patients with multiple sclerosis. *Ther Adv Neurol Disord.* 2010;3:229–239.

9. Sandroff BM, Pilutti LA, Motl RW. Does the six-minute walk test measure walking performance or physical fitness in persons with multiple sclerosis? *NeuroRehabilitation.* 2015;37:149–155.

10. McLoughlin JV, Barr CJ, Patritti B, Crotty M, Lord SR, Sturnieks DL. Fatigue induced changes to kinematic and kinetic gait parameters following six minutes of walking in people with multiple sclerosis. *Disabil Rehabil*. 2016;38:535-543.

11. Barr CJ, Patritti BL, Bowes R, Crotty M, McLoughlin J v. Orthotic and therapeutic effect of functional electrical stimulation on fatigue induced gait patterns in people with multiple sclerosis. *Disabil Rehabil Assist Technol*. 2017;12:560-572.

12. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses. *Neurology*. 2013;80:409-416

13. Leone C, Severijns D, Doležalová V, et al. Prevalence of walking-related motor fatigue in persons with multiple sclerosis: Decline in walking distance induced by the 6-minute walk test. *Neurorehabil Neural Repair*. 2016;30:373-383.

14. Manjaly ZM, Harrison NA, Critchley HD, et al. Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2019;90:642-651.

15. Vucic S, Burke D, Kiernan MC. Fatigue in multiple sclerosis: Mechanisms and management. *Clin Neurophysiol*. 2010;121:809-817.

16. Ramari C, Moraes AG, Tauil CB, von Glehn F, Motl R, de David AC. Knee flexor strength and balance control impairment may explain declines during prolonged walking in women with mild multiple sclerosis. *Mult Scler Relat Disord*. 2018;20:181-185.

17. Barr C, McLoughlin J, Lord SR, Crotty M, Sturnieks DL. Walking for six minutes increases both simple reaction time and stepping reaction time in moderately disabled people with Multiple Sclerosis. *Mult Scler Relat Disord*. 2014;3:457-462.

18. McLoughlin J v., Barr CJ, Crotty M, Sturnieks DL, Lord SR. Six minutes of walking leads to reduced lower limb strength and increased postural sway in people with Multiple Sclerosis. *NeuroRehabilitation*. 2014;35:503-508.

19. Karpatkin H, Babyar S, DiCarrado S, et al. Increases in fatigue do not change spasticity scores in persons with multiple sclerosis. *Neurodegener Dis Manag*. 2018;8:143-150.

20. Drebinger D, Rasche L, Kroneberg D, et al. Association Between Fatigue and Motor Exertion in Patients With Multiple Sclerosis—a Prospective Study. *Front Neurol*. 2020;11:208

21. van Geel F, Veldkamp R, Severijns D, Dalgas U, Feys P. Day-to-day reliability, agreement and discriminative validity of measuring walking-related performance fatigability in persons with multiple sclerosis. *Mult Scler.* 2020;26:1785-1789.

22. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62:1006-1012.

23. Motl RW, Learmonth YC. Neurological disability and its association with walking impairment in multiple sclerosis: brief review. *Neurodegener Dis Manag.* 2014;4:491–500.

24. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52:377-384.

25. Severijns D, Zijdewind I, Dalgas U, Lamers I, Lismont C, Feys P. The Assessment of Motor Fatigability in Persons with Multiple Sclerosis: A Systematic Review. *Neurorehabil Neural Repair*. 2017;31:413-431.

26. Durlak JA. How to select, calculate, and interpret effect sizes. *J Pediatr Psychol.* 2009;34:917-928.

27. Douglas Altman, David Machin, Trevor Bryant MG. Statistics with Confidence. 2000. 28–31.

28. Engelhard MM, Dandu SR, Patek SD, Lach JC, Goldman MD. Quantifying six-minute walk induced gait deterioration with inertial sensors in multiple sclerosis subjects. *Gait Posture*. 2016;49:340-345.

29. Escudero-Uribe S, Hochsprung A, Izquierdo-Ayuso G. Gait pattern changes after six-minute walk test in persons with multiple sclerosis. *Physiother Res Int*. 2019;24:1-10.

30. Feys P, Severijns D, Vantenderloo S, Knuts K, Hannes D, Gijbels D, et al. Spatio-temporal gait parameters change differently according to speed instructions and walking history in MS patients with different ambulatory dysfunction. *Mult Scler Relat Disord*. 2013;2:238-246.

31. Shema-Shiratzky S, Gazit E, Sun R, et al. Deterioration of specific aspects of gait during the instrumented 6-min walk test among people with multiple sclerosis. *J Neurol. 2019;266:3022-3030*

32. Plotnik M, Wagner JM, Adusumilli G, Gottlieb A, Naismith RT. Gait asymmetry, and bilateral coordination of gait during a six-minute walk test in persons with multiple sclerosis. *Sci Rep*. 2020;10:1-11.

33. Socie MJ, Motl RW, Sosnoff JJ. Examination of spatiotemporal gait parameters during the 6-min walk in individuals with multiple sclerosis. *Int J Rehabil Res*. 2014;37:311-316.

34. Arpan I, Fino PC, Fling BW, Horak F. Local dynamic stability during long-fatiguing walks in people with multiple sclerosis. *Gait Posture*. 2020;76:122-127.

35. Caronni A, Gervasoni E, Ferrarin M, et al. Local Dynamic Stability of Gait in People with Early Multiple Sclerosis and No-to-Mild Neurological Impairment. *IEEE Trans Neural Syst Rehabil Eng* 2020;28:1389-1396.

36. Psarakis M, Greene DA, Cole MH, Lord SR, Hoang P, Brodie M. Wearable technology reveals gait compensations, unstable walking patterns and fatigue in people with multiple sclerosis. *Physiol Meas*. 2018;39:075004

37. van der Linden ML, Andreopoulou G, Scopes J, Hooper JE, Mercer TH. Ankle Kinematics and Temporal Gait Characteristics over the Duration of a 6-Minute Walk Test in People with Multiple Sclerosis Who Experience Foot Drop. *Rehabil Res Pract*. 2018:1260852

38. Taborri J, Studer V, Grossi P, et al. Reliability and Repeatability Analysis of Indices to Prolonged Walking. *Sensors*. 2020;20:1-19.

39. Gijbels D, Dalgas U, Romberg A, et al. Which walking capacity tests to use in multiple sclerosis? A multicentre study providing the basis for a core set. *Mult Scler.* 2012;18:364-371.

40. Wolkorte R, Heersema DJ, Zijdewind I. Reduced voluntary activation during brief and sustained contractions of a hand muscle in secondary-progressive multiple sclerosis patients. *Neurorehabil Neural Repair*. 2016;30(4):307–316.

41. Sosnoff JJ, Sandroff BM, Motl RW. Quantifying gait abnormalities in persons with multiple sclerosis with minimal disability. *Gait Posture*. 2012;36:154-156.

42. Kalron A. Gait variability across the disability spectrum in people with multiple sclerosis. *J. Neurol. Sci.* 2016;361:1–6.

43. Sebastião E, Bollaert RE, Hubbard EA, Motl RW. Gait Variability and Energy Cost of Oveground Walking in Persons with Multiple Sclerosis: A Cross-Sectional Study. *Am J Phys Med Rehabil*. 2018;97:646–650.

44. Kalron A. Association between gait variability, falls and mobility in people with multiple sclerosis: A specific observation on the EDSS 4.0-4.5 level. *NeuroRehabilitation.* 2017;40:579–585.

45. Kalron A, Aloni R, Dolev M, Frid L, Givon U, Menascu S. The relationship between gait variability and cognitive functions differs between fallers and non-fallers in MS. *J Neural Transm*. 2018;125:945–952.

46. Gunn HJ, Newell P, Haas B, Marsden JF, Freeman JA. Identification of risk factors for falls in multiple sclerosis: A systematic review and meta-analysis. *Phys. Ther.* 2013;93:504–513.

47. Ihlen EAF, Weiss A, Bourke A, Helbostad JL, Hausdorff JM. The complexity of daily life walking in older adult community-dwelling fallers and non-fallers. *J Biomech*. 2016;49:1420-1428.

48. Tajali S, Mehravar M, Negahban H, van Dieën JH, Shaterzadeh-Yazdi MJ, Mofateh R. Impaired local dynamic stability during treadmill walking predicts future falls in patients with multiple sclerosis: A prospective cohort study. *Clin Biomech*. 2019;67:197-201.

49. Cameron MH, Wagner JM. Gait abnormalities in multiple sclerosis: Pathogenesis, evaluation, and advances in treatment. *Curr Neurol Neurosci Rep*. 2011;11:507-515.

50. Miller L, McFadyen A, Lord AC, et al. Functional Electrical Stimulation for Foot Drop in Multiple Sclerosis: A Systematic Review and Meta-Analysis of the Effect on Gait Speed. *Arch Phys Med Rehabil*. 2017;98:1435-1452.

51. Crapo RO, Casaburi R, Coates AL, Enright PL, MacIntyre NR, McKay RT, et al. ATS statement: Guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166:111-117.

52. Moe-Nilssen R, Helbostad JL. Estimation of gait cycle characteristics by trunk accelerometry. *J Biomech.* 2004;37:121-126.

53. Dingwell JB, Cusumano JP, Cavanagh PR, Sternad D. Local dynamic stability versus kinematic variability of continuous overground and treadmill walking. *J Biomech Eng*. 2001;123:27-32

54. Plotnik M, Giladi N, Hausdorff JM. A new measure for quantifying the bilateral coordination of human gait: Effects of aging and Parkinson's disease. *Exp Brain Res*. 2007;18:561-570.

55. Bellanca JL, Lowry KA, VanSwearingen JM, Brach JS, Redfern MS. Harmonic ratios: A quantification of step to step symmetry. *J Biomech*. 2013;46:828-831.

56. Costa M, Peng CK, Goldberger AL, Hausdorff JM. Multiscale entropy analysis of human gait dynamics. *Physica A*. 2003:53-60.

Table 1. Descriptive characteristics of participants across studies

Study	Population groups	Number of participants	Female/Male	Age (years) Mean±SD / Median (range)	EDSS Mean±SD / Median (range/IQR)	Disease duration (years)	Clinical course of MS (RR/SP/PP)
Studies assessing gait prior and immediately after the 6MWT							
Escudero-Uribe et al.[29]	pwMS (Mild)	23	15/8	39.7±7.3	2.4±0.8	7.3±5.1	22/0/1
	pwMS (Moderate to severe)	31	22/9	46.21±7.85	5.3±0.9	12.5±6.9	15/10/6
	HC	25	13/12	42.5±12.4	N/A	N/A	N/A
Feys et al.[30]	pwMS [Mild (“CW”)]	9	3/6	46.22±10.15	2.89±0.86 (range: 1.5-4.0)	7.33±4.21	6/3/0
	pwMS [Moderate to severe (“LCW&MLCW”)]	18	7/11	49.38±10.11	4.75±1.9	13.77±9.69	5/5/8
McLoughlin et al.[10]	pwMS	32	24/8	50.3±9.9	3.6±0.6 (range:3.0-6.0)	8.2±7.9	NR
	HC	10	7/3	45.1±14.0	N/A	N/A	N/A
Drebinger et al. [20]	pwMS	19	8/11	50.5±9.5	3 (range:1.0–6.0)	NR	NR
	HC	24	12/12	47.1±17.1	N/A	N/A	N/A
Barr et al.[11]	pwMS (Mild to moderate)	11	7/4	47 (range: 34-60)	3.5 (range:3.0-4.0)	NR	NR
Studies assessing gait during the 6MWT							
Shema-Shiratzky et al.[31]	pwMS (Mild)	34	23/11	49.0±11.2	2.5 (IQR:2-3)	13.8±10.9	NR
	pwMS (Moderate to severe)	24	18/6	48.9±8.0	5.25 (IQR:4-6)	13.6±7.5	NR
Socie et al.[33]	pwMS [Mild (“IA”)]	10	8/2	43.6±9.1	1.6±1.5[a]	NR	NR
	pwMS [Moderate to severe (“AA”)]	8	6/2	51.5±13.4	4.5±0.5[a]	NR	NR
	HC	10	8/2	50.6±12.0	N/A	N/A	N/A
Van der Linden et al.[37]	pwMS (Moderate to severe)	15	10/5	54.9±7.7	NR (range:4.0-6.0)	NR	4/4/7
Psarakis et al.[36]	pwMS (Moderate to severe)	12	9/3	52±9.1	4.25 (IQR:1.1)	NR	NR
	HC	12	8/4	55.8±12.23	N/A	N/A	N/A
Arpan et al.[34]	pwMS (Mild to moderate)	25	20/5	51.1±1.6	3.5 (range:2.5-5.0)[b]	NR	NR
	HC	10	6/4	47.6±3.3	N/A	N/A	N/A
Plotnik et al.[32]	pwMS (Mild)	86	70/16	46.16±11.08	2.5 (range:0-4.0)	10.59±7.51	82/2/2
	pwMS (Moderate to severe)	6	6/0	54.1±11.2	5.5 (range:5.0–6.5)	12.3±12.6	6/0/0
Caronni et al.[35]	pwMS (Mild)	76	51/25	38.6±10.2	1.5 (IQR:1.0-2.0)	3.16±1.59	NR
	HC	20	13/7	36.2±9.0	N/A	N/A	N/A
Engelhard et al.[28]	pwMS (Mild)	86	73/13	46 [38–52]	2.5 (IQR:2.0–3.5)	NR	NR
	HC	29	20/9	40 [32–48]	N/A	N/A	N/A
Taborri et al.[38]	pwMS (Mild to moderate)	9	6/3	45±5	NR (range:1.0-4.0)	NR	9/0/0
	HC	26	NR	45±9	N/A	N/A	N/A

[a]PDDS, [b]Self-reported EDSS
Abbreviations: 6MWT, 6-Minute Walk Test; EDSS, Expanded Disability Status Scale; PDDS, The Patient Determined Disease Steps; pwMS, persons with multiple sclerosis; HC, healthy controls; RR, relapsing remitting; SP, secondary progressive; PP, primary progressive; CW, community walkers; LCW, limited community walkers; MLCW, most limited community walkers; IA, Independently ambulatory; AA, Ambulatory with assistance; NR, not reported; N/A, not applicable

Table 2. Specifications of the experimental procedure and outcome measures

Study	Experimental procedure	6MWT administration details	Gait assessment method	Gait outcomes	6MWT distance (m)
Studies assessing gait prior and immediately after the 6MWT					
Escudero-Uribe et al.[29]	Pre-6MWT and post-6MWT assessment	Course: 35 m Instruction: "walk as fast as you comfortably can for 6 minutes, without running or jogging" (Goldman et al.) Encouragement: Participants were informed of the time that had elapsed every minute Rest: NR Assistive device: allowed	Device: Electronic walkway (GAITRite) Pathway: 8 × 0.61 m instrumented walkway system Instruction for gait speed: "walk as fast as you comfortably can" Trials: Average of two trials	Spatiotemporal gait parameters	pwMS (mild disability) = 503±75 pwMS (moderate disability) = 331±51 pwMS (severe disability) = 189±40 HC = 616±38
Feys et al.[30]	Pre-6MWT and post-6MWT assessment	Course: NR Instruction: "as much distance as you can in six-minute" Encouragement: NR Rest: NR Assistive device: NR	Device: Electronic walkway (GAITRite) Pathway: 90 cm wide and 5.18 m long Instruction for gait speed: "walk as fast as you can" and usual speed Trials: Average of two trials for each condition	Spatiotemporal gait parameters	pwMS (CW) = 581.6± 68.5 pwMS (LCW) = 425.1±133.6 pwMS (MLCW) = 188.2± 109.9
McLoughlin et al.[10,20]	Pre-6MWT and post-6MWT assessment	Course: Modified 6MWT protocol in 10 m course Instruction: ''walk as fast as you comfortably can, bearing in mind that you will be walking for six minutes" Encouragement: NR Rest: NR Assistive device: allowed	Device: 3D motion gait analysis (Vicon MX3 motion capture system; Vicon, Oxford, UK), External ground reaction forces: four force plates (AMTI, Watertown, MA) Pathway: NR Instruction for gait speed: comfortable speed Trials: Average of three trials	Spatiotemporal gait parameters Joint kinematics and kinetics (external joint moments and powers)	NR (available on graphs)
Drebinger et al.[20]	Pre-6MWT and post-6MWT assessment	Course: NR Instruction: NR (Goldman et al. was referenced) Encouragement: NR Rest: NR Assistive device: allowed	Device: Wireless inertial sensors (Opal™, APDM) Pathway: 2 x 15-m walkway with U turn around a cone. Instruction for gait speed: comfortable speed and at max walking speed Trials: Average of two trials	Spatiotemporal gait parameters	pwMS = 490.1±134.6 HC = 657.2± 87.4
Barr et al.[11]	Pre-6MWT and post-6MWT assessment	Course: Modified 6MWT protocol in 10 m course, Instruction: NR (Goldman et al. was referenced) Encouragement: NR Rest: NR Assistive device: NR	Device: 3D motion gait analysis (Vicon MX3 motion capture system; Vicon, Oxford, UK), External ground reaction forces: force plates (AMTI, Watertown, MA) Pathway: NR Instruction for gait speed: NR Trials: Average of three trials	Spatiotemporal gait parameters joint kinematics and kinetics (external joint moments and powers)	pwMS = 372±114
Studies assessing gait during the 6MWT					
Shema-Shiratzky et al.[31]	Measurements were taken during 6MWT Change between min 1 and min 6	Course: NR Instruction: "cover the maximal distance during 6 min" (ATS) Encouragement: No specific instructions regarding gait speed or specific encouragement during the test. Rest: allowed (i.e., while standing) Assistive device: allowed	Device: Wireless inertial sensors (Opal™, APDM)	Spatiotemporal gait parameters	pwMS (mild disability) = 434.8±80.4 pwMS (moderate disability) = 291.0±102.3
Socie et al.[33]	Measurements were taken during 6MWT Changes between min 1-2 and min 5-6	Course: 30 m Instruction: "walk as far and as fast as safely possible in 6 min" (Goldman et al.) Notice: each minute passed Rest: NR Assistive device: NR	Device: Electronic walkway (GAITRite)	Spatiotemporal gait parameters	pwMS (IA) = 522±104 pwMS (AA) = 237±127 HC = 607±87
Van der Linden et al.[37]	Measurements were taken during 6MWT Changes between first 10 and last 10 laps	Course: Adapted 6MWT protocol: a rectangular course of 32 m in length (10 m long and 6m wide) Instruction: "cover as much distance as possible over a period of 6 minutes" Rests: allowed Assistive device: NR	Device: Electrogoniometer (SG110A, Biometrics Ltd., Newport, UK)	Cadence and ankle kinematics	pwMS = 263±79
Psarakis et al.[36]	Measurements were taken during 6MWT Changes between first and last laps	Course: 20 m Instruction: "walk as far as possible for six minutes" Encouragement: Standardized encouragement given at 1, 3 and 5 minutes Rests: allowed Assistive device: NR	Device: Wireless inertial sensors (Opal™, APDM)	Spatiotemporal gait parameters, gait compensation, and gait stability	pwMS= 330±112 HC = 506±82.64
Arpan et al.[34]	Measurements were taken during 6MWT Percent changes in local dynamic stability from minute 1 to 6	Course: 20 m Instruction: "at their fastest speed, aiming to cover as much distance as possible" (Goldman et al.)	Device: Wireless inertial sensors (Opal™, APDM)	Local dynamic stability (short term Lyapunov exponent)	pwMS = 452±17 HC = 585±27

Plotnik et al.[32]	Measurements were taken during 6MWT Time effects was analyzed each 1-min interval	Course: 15 m (50-foot) Instruction: NR (Goldman et al. was referenced) Encouragement: NR Rest: NR Assistive device: NR	Device: Wireless inertial sensors (Opal™, APDM)	Spatiotemporal parameters: Gait variability (stride time variability), gait symmetry, and bilateral coordination of gait (Phase coordination index)	pwMS (mild disability) = 253.4±5.4[a] pwMS (moderate disability) = 211.3±8.3 [a] pwMS (severe disability) = 141.6±17.2 [a]
Caronni et al.[35]	Measurements were taken during 6MWT Changes between Min 1-3 and Min 4-6	Course: 30 m Instruction: "at fastest speed, and to cover as much distance as possible" (Goldman et al.) Encouragement: NR Rest: NR Assistive device: NR	Device: Wireless inertial sensors (MTw, XSens, NL)	Speed and local dynamic stability (short term Lyapunov exponent)	pwMS = 558.5±78.3 HC = 635.9±85.4
Engelhard et al.[28]	Measurements were taken during 6MWT Changes between first two minutes and Min 6	Course: 75-foot Instruction and encouragement: according to Goldman et al. Rest: NR Assistive device: NR	Device: ActiGraph GT3X accelerometer	Dynamic time warping (DTW) algorithm	pwMS = 1574 [1352–1873] [a] HC = 2009 [1793–2166] [a]
Taborri et al.[38]	Measurements were taken during 6MWT Changes between first minute and the remaining five minutes	Course: 15 m Instruction and encouragement: "select the speed in order to cover the maximum distance possible during the six minutes" Rest: allowed Assistive device: usin external aid was an exclusion criterion	Device: Wireless inertial sensors (MTw, XSens, NL)	Range of motion (ROM) of hip, knee,and ankle joints, variability and symmetry index of ROM	pwMS = 359±40 HC = 572±16

Abbreviations: [a] Distance reported in feet; 6MWT, 6-Minute Walk Test; pwMS, persons with multiple sclerosis; HC, healthy control, CW, community walkers; LCW, limited community walkers; MLCW, most limited community walkers; IA, Independently ambulatory; AA, Ambulatory with assistance; NR, not reported

Table 3 A. Changes in key spatiotemporal parameters

Study	Study groups	Speed (m/s or cm/s)		Cadence (steps/min)		Step length (m or cm)		Stride length (m)		Step time (sec)		Stride time (sec)		Stance period (%gait cycle)		Step width (cm)		Double support phase (%gait cycle or sec)		Single support phase (%gait cycle)	
		ES	Pre/Onset Post/End	ES	Pre/Onset Post/End	ES	Pre/Onset Post/End	ES	Pre/Onset Post/End	ES	Pre/Onset Post/End	ES	Pre/Onset Post/End	ES	Pre/Onset Post/End	ES	Pre/Onset Post/End	ES	Pre/Onset Post/End	ES	Pre/Onset Post/End
Studies assessing gait prior and immediately after the 6MWT																					
Escudero-Uribe et al.[29]	Mild	0.01	132.0±21.1 132.2±18.7	-0.02	114.8±8.2 114.6±7.8	0.03	68.8±7.9 69.0±7.3	/	/	0	0.53±0.04 0.53±0.04	/	/	0.12	62.5±1.7 62.7±1.6	0.04	9.6±2.2 9.7±2.2	0.03	25.2±3.4 25.3±3.1	/	/
	Moderate to severe	-0.43	78.27±23.10 67.63±25.82¶	-0.36	93.51±15.23 87.37±18.79¶	-0.46	49.37±8.76 45.06±9.90¶	/	/	0.35	0.66±0.12 0.71±0.16¶	/	/	0.58	67.47±2.85 69.37±3.63¶	0.20	11.89±4.15 12.72±4.18	0.62	35.09±5.83 39.75±8.80	/	/
	HC	0.04	163.1±12.3 163.6±11.5	0.03	124.7±5.2 124.9±6.0	0.03	78.6±6.3 78.8±6.4	/	/	0	0.48±0.02 0.48±0.02	/	/	0	60.5±1.2 60.5±1.3	0.23	8.5±2.6 9.1±2.7	0	21.3±2.4 21.3±2.6	/	/
Feys et al.[30]	Mild[a]	/	1.40 1.40	/	113.84 112.99	/	73,45 73.95	/	/	/	0.68 0.85	/	/	/	/	/	/	/	46.62 48.01	/	/
	Moderate to severe[a]	/	0.82 0.81	/	94.19 88.28	/	51.63 52.53	/	/	/	0.56 0.56	/	/	/	/	/	/	/	29.14 29.63	/	/
	Mild[b]	/	2.12 2.10	/	150.06 147.43	/	84.72 85.77	/	/	/	0.68 0.80	/	/	/	/	/	/	/	40.45 40.98	/	/
	Moderate to severe[b]	/	1.18 1.08	/	111.27 103.65	/	60.38 59.43	/	/	/	0.44 0.45	/	/	/	/	/	/	/	23.19 24.49	/	/
Barr et al.[11]	pwMS (Mild to moderate)	-0.07	1.18±0.25 1.16±0.28	-0.02	106.9±10.8 106.7±11.3	-0.22	0.66±0.09 0.64±0.09	-0.05	1.31±0.20 1.30±0.19	/	/	/	/	/	/	/	/	0.06	30.3±3.6 30.5±3.6	0.04	32.9±2.8 33.0±2.8
Drebinger et al.[20]	pwMS[a]	0.19	1.231±0.23 1.278±0.25*	0.16	110.412±11.39 112.335±12.91*	/	/	0.15	1.330±0.17 1.355±0.17	/	/	-0.11	1.099±0.12 1.084±0.15*	/	/	/	/	/	/	/	/
	HC[a]	0.70	1.381±0.18 1.511±0.19*,**, ***	0.64	117.912±7.18 122.776±7.90*,**, ***	/	/	0.46	1.403±0.16 1.474±0.15	/	/	-0.66	1.022±0.06 0.982±0.06*,**, ***	/	/	/	/	/	/	/	/
	pwMS[b]	-0.20	1.630±0.29 1.568±0.32**	-0.13	127.138±12.40 125.418±14.33**	/	/	-0.27	1.529±0.19 1.487±0.19	/	/	0.14	0.954±0.10 0.970±0.12**	/	/	/	/	/	/	/	/
	HC[b]	0.07	1.911±0.22 1.928±0.23	0.09	141.032±8.58 141.835±8.50	/	/	0.01	1.628±0.18 1.630±0.18	/	/	-0.08	0.854±0.05 0.850±0.05	/	/	/	/	/	/	/	/
McLoughlin et al.[10]	pwMS	0.06	1.14±0.29 1.16±0.36	0.1	108.8±12.35 110.2±15.89	0.14	0.62±0.12 0.64±0.16	0	1.24±0.23 1.24±0.27	/	/	/	/	/	/	/	/	0.15	0.33±0.11 0.35±0.15	/	/
	HC	0.83	1.50±0.19 1.65±0.17¶	1.09	118.38±7.59 125.83±5.95¶	0.61	0.75±0.07 0.79±0.06	0.36	1.52±0.14 1.57±0.14	/	/	/	/	/	/	/	/	-0.63	0.24±0.04 0.22±0.02	/	/
Studies assessing gait during the 6MWT																					
Shiraztky et al.[31]	Mild	0.13	1.40±0.28 1.44±0.32**	-0.11	114.8±13.1 113.2±15.6*,**,***	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	Moderate to severe	-0.18	0.99±0.31 0.93±0.35**	-0.26	99.2±18.2 94.3±19.3¶*,**,***	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	All	0	1.23±0.35 1.23±0.41**	-0.15	108.3±17.1 105.4±19.5¶*,**,***	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Socie et al.[33]	Mild	-0.07	150±30.3 147.8±31.3¶,**	-0.09	121.3±11.4 120.2±12.1¶**	0.05	73.9±8.9 74.4±9.1**	/	/	0	0.50±0.05 0.50±0.05**	/	/	/	/	0	10.8±2.0 10.8±2.3**	0.03	26.9±6.6 27.1±7.3	/	/
	Moderate to severe	-0.09	68.7±36.2 65.4±36.7¶**	-0.19	88.0±19.8 84.7±23.2¶,**	-0.1	46.2±17.0 44.6±16.3**	/	/	0.2	0.72±0.17 0.76±0.23¶**	/	/	/	/	-0.12	12.7±5.1 12.1±4.5**	0.05	39.3±24.5 40.9±34.0	/	/
	HC	-0.17	173.7±24.8 169.5±24.9¶	-0.17	128.7±11.7 126.6±13.1	-0.07	81.0±8.6 80.4±9.0	/	/	0.22	0.47±0.04 0.48±0.05	/	/	/	/	-0.21	9.9±1.4 9.6±1.4	0.04	24.4±4.7 24.6±4.7	/	/
Van der Linden et al.[37]	pwMS (Moderate to severe)	/	/	-0.46	49±6 46±7¶	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Psarakis et al.[36]	pwMS (Moderate to severe)	-0.3	0.97±0.35 0.87±0.32*,**	-0.25	101.82±19.91 96.37±23.39*,**	-0.27	55.63±10.56 52.89±9.56**	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	HC	-0.28	1.5±0.28 1.42±0.29*,**	-0.16	123.30±8.02 121.94±8.04*,**	-0.31	72.57±10.12 69.27±10.94**	/	/	/	/	/	/	/	/	/	/		/	/	/
Caronni et al.[35]	pwMS (Mild)	/	2.08 [2.00-2.16] 1.96 [1.88-2.03] †*	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	HC	/	2.25 [2.10-2.39] 2.13 [2.04-2.21] †*	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/

[a]Walking with usual speed, [b]Walking with fastest speed, ¶ presents significant changes between time periods, * presents significant time (fatiguing task) effects (using ANOVA), ** presents significant group effects (using ANOVA), *** presents significant group x time interaction (using ANOVA), †Least squares mean [95%CI], / presents data not available.
Values are mean ± standard deviation unless otherwise reported.
Abbreviations: ES, Effect size; 6MWT, 6-Minute Walk Test; pwMS, persons with multiple sclerosis; HC, healthy control

Table 3 B. Changes in gait variability and asymmetry parameters

Study	**Study groups**	**Step length asymmetry (cm)**		**Step time asymmetry (% or ms)**		**Single support asymmetry (%gait cycle)**		**Swing time asymmetry**		**Step length variability (%)**		**Step time variability (%)**		**Stride time variability (% or ms)**		**Step width variability (%)**		**Double support variability (%)**		**Gait asymmetry (%)**	
		ES	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**
Studies assessing gait prior and immediately after the 6MWT																					
Escudero-Uribe et al.[29]	Mild	0	1.9±0.6 1.9±1.5	-0.2	12.0±10.0 10.0±10.5	-0.79	1.3±0.8 0.8±0.4	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	Moderate to severe	0.63	2.39±1.58 3.80±2.70	0.39	46.19±39.78 70.29±77.05¶	0.53	2.39±2.33 4.08±3.84¶	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	HC	-0.21	1.8±1.2 1.6±0.6	-1.07	15.0±8.0 8.0±4.5¶	0	0.7±0.4 0.7±0.4	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Studies assessing gait during the 6MWT																					
Shiraztky et al.[31]	Mild	/	/	/	/	/	/	-0.04	4.86±4.99 4.67±5.00	/	/	/	/	0.29	3.65±1.72 4.35±2.89*,**	/	/	/	/	/	/
	Moderate to severe	/	/	/	/	/	/	0.08	9.36±10.93 10.22±11.54	/	/	/	/	0.41	4.68±2.45 5.80±2.96*,**	/	/	/	/	/	/
	All	/	/	/	/	/	/	0.03	6.77±8.27 7.03±8.77	/	/	/	/	0.34	4.07±2.10 4.95±2.98*,**	/	/	/	/	/	/
Socie et al.[33]	Mild	/	/	/	/	/	/	/	/	-0.11	2.3±1.0 2.2±0.9	-0.09	2.7±1.1 2.6±1.1	/	/	-0.04	20.1±7.8 19.7±9.2	-0.19	4.7±2.2 4.3±1.9	/	/
	Moderate to severe	/	/	/	/	/	/	/	/	0.38	8.9±5.5 12.8±13.5	0.95	4.7±1.7 9.4±6.8	/	/	0.64	17.1±10.5 30.8±28.5	1.13	5.2±1.6 9.4±5.0	/	/
	HC	/	/	/	/	/	/	/	/	-0.14	1.9±0.9 1.8±0.5	-0.65	2.7±1.1 2.1±0.7	/	/	-0.27	21.1±10.5 18.7±7.1	-0.45	4.0±1.1 3.5±1.1	/	/
Psarakis et al.[36]	pwMS, (Moderate to severe)	/	/	0.26	8.5±9.13 10.97±9.56**	/	/	/	/	/	/	/	/	0.11	51.00±47.06 56.09±44.79**	/	/	/	/	/	/
	HC	/	/	-0.68	2.71±1.75 1.65±1.32**	/	/	/	/	/	/	/	/	-0.59	21.56±8.69 16.44±8.62**	/	/	/	/	/	/
Plotnik et al.[32]	Mild	/	/	/	/	/	/	/	/	/	/	/	/	/	2.14±0.39	/	/	/	/	/	4.87±1.97*
	Moderate to severe	/	/	/	/	/	/	/	/	/	/	/	/	/	4.5±0.4	/	/	/	/	/	22.6±3.5*, ***

¶ presents significant changes between time periods, * presents significant time (fatiguing task) effects (using ANOVA), ** presents significant group effects (using ANOVA), *** presents significant group x time interaction (using ANOVA), / presents data not available.
Values are mean ± standard deviation unless otherwise reported.
Abbreviations: ES, Effect size; 6MWT, 6-Minute Walk Test; pwMS, persons with multiple sclerosis; HC, healthy control; IA, Independently ambulatory; AA, Ambulatory with assistance

Table 3 C. Changes in gait stability and regularity parameters

Study	Study groups	Step regularity		Stride regularity		Local dynamic instability estimate		Local dynamic stability - Vertical		Local dynamic stability – Anterior-posterior		Local dynamic stability - Mediolateral		Phase Coordination Index		Harmonic rate - Vertical		Harmonic rate – Anterior-posterior		Harmonic rate - Mediolateral		Sample entropy	
		ES	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**	**ES**	**Pre/Onset Post/End**
Studies assessing gait during the 6MWT																							
Shiraztky et al.[31]	Mild	-0.21	0.77±0.13 0.74±0.15*,**	-0.17	0.78±0.10 0.76±0.13*,**	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	0.11	1.92±0.43 1.97±0.50*,**,***
	Moderate to severe	-0.15	0.53±0.21 0.50±0.20*,**	-0.25	0.59±0.20 0.54±0.19*,**	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	-0.11	1.73±0.47 1.68±0.46*,**,***
	All	-0.15	0.67±0.20 0.64±0.21¶,*,**	-0,16	0.70±0.18 0.67±0.19*,**	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	0.04	1.83±0.45 1.85±0.50*,**,***
Psarakis et al.[36]	pwMS (Moderate to severe) - pelvis	/	/	/	/	/	/	/	/	/	/	/	/	/	/	-0.24	1.51±0.33 1.42±0.41**	-0.11	1.43±0.19 1.40±0.34**	-0.14	1.0±0.13, 0.98±0.16**	/	/
	HC-pelvis	/	/	/	/	/	/	/	/	/	/	/	/	/	/	0.38	2.13±0.20 2.20±0.17**	0.22	1.90±0.18 1.95±0.26**	0.26	1.43±0.21 1.49±0.25**	/	/
	pwMS (Moderate to severe) - head	/	/	/	/	/	/	/	/	/	/	/	/	/	/	-0.27	1.54±0.27 1.46±0.32**	0.33	1.22±0.15 1.27±0.15**	-0.35	1.05±0.20 0.99±0.14**	/	/
	HC-head	/	/	/	/	/	/	/	/	/	/	/	/	/	/	0.11	2.36±0.27 2.39±0.28**	-0.11	1.61±0.17 1.59±0.19**	0.47	1.34±0.15 1.44±0.26**	/	/
Arpan et al.[34]	pwMS (Mild to moderate)	/	/	/	/	/	n=8 (-1 to -21% decrease) n=3 (no change) n=14 (4 to 43% increase) ***	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	HC	/	/	/	/	/	N=9 (-4 to -20% decrease)	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Plotnik et al.[32]	Mild	/	/	/	/	/	/	/	/	/	/	/	/	/	4.39±1.3*	/	/	/	/	/	/	/	/
	Moderate to severe	/	/	/	/	/	/	/	/	/	/	/	/	/	10.2±1.5*,***	/	/	/	/	/	/	/	/
Caronni et al.[35]	pwMS (Mild)	/	/	/	/	/	/	/	0.759 [0.733-0.785] 0.728 [0.698-0.758†*	/	0.693 [0.667-0.720] † NR NS	/	0.758 [0.732-0.783] † NR NS	/	/	/	/	/	/	/	/	/	/
	HC	/	/	/	/	/	/	/	0.708 [0.679-0.737] 0.677 [0.626-0.729] †*	/	0.613 [0.559-0.667] † NR NS	/	0.676 [0.624-0.728] † NR NS	/	/	/	/	/	/	/	/	/	/

¶ presents significant changes between time periods, * presents significant time (fatiguing task) effects (using ANOVA), ** presents significant group effects (using ANOVA), *** presents significant group x time interaction (using ANOVA), †Least squares mean [95%CI], / presents data not available. NR, not reported; NS, not significant.
Values are mean ± standard deviation unless otherwise reported.
Abbreviations: ES, Effect size; 6MWT, 6-Minute Walk Test; pwMS, persons with multiple sclerosis; HC, healthy control

Footnotes

- Step and stride regularity: The step regularity and stride regularity parameters are index scores used to determine the consistency in the acceleration waveform ranging from 0 to 1. These parameters are calculated using an unbiased autocorrelation between the original acceleration signal and the acceleration signal phase-shifted to the average step time and average stride time.[52]
- Local dynamic stability: Local dynamic stability is a measure of the ability of the of the locomotor system to control small internal or external perturbations during walking. [53]
- Phase Coordination Index: It is a metric for quantifying bilateral coordination of gait based on the degree of consistency and accuracy in the left-right stepping coordination.[54]
- Harmonic rate: It is a measure used to assess dynamic gait stability and is extracted from trunk accelerations in the anteroposterior, vertical, and mediolateral directions.[55]

- Sample Entropy: Sample entropy can be defined as the average level of complexity (irregularity) in a time series.[56]

Table 3 D. Changes in kinematic and kinetic gait parameters

Study design				Studies assessing gait prior and immediately after the 6MWT									Studies assessing gait during the 6MWT		
Study				**McLoughlin et al.**[10]						**Barr et al.**11			**Van der Linden et al.**[37]		
Study groups				**pwMS**			**HC**			**pwMS**			**pwMS**		
			Side	**ES**	**Pre/Onset**	**Post/End**	**ES**	**Pre/Onset**	**Post/End**	**ES**	**Pre/Onset**	**Post/End**	**ES**	**Pre/Onset**	**Post/End**
Kinematics	Hip	Max hip extension in stance (°)	More	-0.03	-11.50±10.52	-11.85±10.46	-0.05	-16.28±9.01	-16.71±8.26	0.15	-10.0±3.8	-9.5±2.9	/	/	/
			Less	-0.019	-11.69±9.81	-11.88±10.05	/	/	/	0.03	-10.6±4.3	-10.5±3.6	/	/	/
		Max hip flexion in swing (°)	More	0.08	32.84±9.09	33.56±8.76	0.38	34.90±5.73	37.20±6.45	0.12	34.0±6.9	34.8±6.2	/	/	/
			Less	0.14	33.71±8.89	34.98±9.12	/	/	/	0.14	36.1±6.8	37.0±5.9	/	/	/
	Knee	Max knee flexion in stance (°)	More	0.16	18.55±6.73	19.64±6.93	0,32	18.51±6.85	20.34±4.08	0.07	20.9±5.0	21.3±5.6	/	/	/
			Less	0.28	19.40±6.84	21.35±7.23	/	/	/	0.12	21.5±5.9	22.2±5.7*	/	/	/
		Max knee extension in stance (°)	More	-0.24	0.98±6.50	-0.63±7.02	-0.27	-2.43±4.31	-3.55±4.04	-0.31	1.0±5.8	-0.9±6.4	/	/	/
			Less	-0.09	1.16±6.74	0.50±7.25	/	/	/	-0.05	2.0±4.2	1.8±4.3	/	/	/
		Max knee flexion in swing (°)	More	-0.07	52.63±12.15	51.72±12.46	0.05	60.56±5.13	60.83±6.18	-0.09	49.2±14.2	47.9±13.5	/	/	/
			Less	-0.09	59.55±7.13	58.91±7.61	/	/	/	0.12	61.5±3.8	62.0±4.6	/	/	/
	Ankle	Ankle dorsiflexion at initial contact (°)	More	-0.26	5.71±4.65	4.49±4.54*	0.18	6.80±3.53	7.45±3.85	-0.36	5.3±5.6	3.3±5.3*	-0.26	-7.6±4.6	-9±6.2
			Less	-0.08	7.82±4.09	7.47±4.15	/	/	/	-0.29	8.8±4.8	7.4±4.8	/	/	/
		Max ankle plantarflexion in early stance (°)	More	/	/	/	/	/	/	-0.31	-2.1±4.7	-3.7±5.5*	/	/	/
			Less	/	/	/	/	/	/	-0.25	1.2±4.5	0.1±4.4*	/	/	/
		Max ankle dorsiflexion in midstance (°)	More	-0.12	16.01±3.07	15.58±4.01	-0.05	13.30±3.76	13.12±3.65	-0.08	16.4±3.3	16.1±3.9	/	/	/
			Less	-0.02	15.48±3.43	14.95±3.39	/	/	/	-0.11	16.3±3.3	15.9±3.8	/	/	/

		Max ankle plantarflexion in late stance (°)	More	-0.10	-5.22±8.51	-6.07±8.01	-0.07	-18.08±5.39	-18.41±4.36	-0.09	-2.8±6.6	-3.5±9.1	/	/	/
			Less	-0.04	-10.32±8.01	-10.64±8.65	/	/	/	-0.07	-13.6±3.7	-13.9±4.9	/	/	/
		Max ankle dorsiflexion in swing (°)	More	-0.14	8.20±4.23	7.61±3.95	0.04	8.32±4.02	8.49±4.07	-0.27	8.7±4.7	7.3±5.6*	-0.2	-0.4±7.6	-2.0±8.7¶
			Less	0.05	9.76±4.28	9.96±4.33	/	/	/	-0.30	10.9±3.7	9.8±3.6	/	/	/
Kinetics	Hip	Max hip extensor moment in stance (Nm/kg)	More	0.33	0.97±0.35	1.11±0.48	0.37	1.17±0.38	1.31±0.37	0.05	0.87±0.37	0.89±0.45*	/	/	/
			Less	0.36	1.06±0.38	1.22±0.51	/	/	/	0.22	1.23±0.39	1.33±0.51	/	/	/
		Max hip flexor moment in stance (Nm/kg)	More	-0.14	-0.91±0.33	-0.96±0.37*	-0.70	-1.12±0.28	-1.31±0.26¶	-0.05	-1.06±0.22	-1.07±0.21	/	/	/
			Less	-0.17	-0.96±0.36	-1.02±0.35	/	/	/	-0.10	-0.93±0.26	-0.96±0.31	/	/	/
		Max hip power generation in early stance (W/kg)	More	0.33	0.94±0.54	1.16±0.79	0,36	1.04±0.52	1.30±0.88	0,2	0.77±0.44	0.87±0.56*	/	/	/
			Less	0.43	0.91±0.53	1.20±0.80	/	/	/	0.31	1.22±0.46	1.40±0.67	/	/	/
		Max hip power absorption in midstance (W/kg)	More	-0.36	-0.83±0.42	-1.01±0.57*	-0.63	-1.11±0.45	-1.45±0.61¶	-0.10	-0.88±0.36	-0.92±0.41	/	/	/
			Less	-0.15	-0.95±0.52	-1.03±0.56	/	/	/	-0.15	-0.92±0.44	-0.98±0.33	/	/	/
		Max hip power generation in late stance (W/kg)	More	0.06	1.44±0.69	1.48±0.73	1.19	1.98±0.32	2.49±0.51¶	-0.02	1.71±0.83	1.69±0.72	/	/	/
			Less	0.30	1.51±0.52	1.69±0.66	/	/	/	-0.04	1.92±0.72	1.89±0.63	/	/	/
	Knee	Max knee flexor moment at initial contact (Nm/kg)	More	-0.28	-0.39±0.16	-0.44±0.19*	-0.13	-0.54±0.15	-0.56±0.15	/	/	/	/	/	/
			Less	-0.24	-0.45±0.19	-0.50±0.22	/	/	/	/	/	/	/	/	/
		Max knee extensor moment in stance (Nm/kg)	More	0.10	0.35±0.30	0.38±0.28	0.34	0.44±0.29	0.54±0.29¶	-0.04	0.62±0.22	0.61±0.25	/	/	/
			Less	0.23	0.33±0.25	0.39±0.27	/	/	/	0.05	0.41±0.24	0.42±0.20	/	/	/
		Max knee flexor moment in stance (Nm/kg)	More	-0.24	-0.42±0.17	-0.45±0.16	-0.44	-0.52±0.13	-0.58±0.14¶	-0.22	-0.28±0.21	-0.33±0.24*	/	/	/
			Less	-0.24	-0.42±0.16	-0.46±0.17	/	/	/	-0.05	-0.38±0.22	-0.39±0.19	/	/	/
		Max knee power absorption in early stance (W/kg)	More	-0.18	-0.81±0.75	-0.96±0.90	-0.57	-1.52±0.86	-2.15±1.30	-0.16	-0.88±0.59	-0.99±0.81*	/	/	/
			Less	-0.28	-0.80±0.79	-1.04±0.90	/	/	/	-0.04	-0.86±0.48	-0.88±0.44	/	/	/
		Max knee power generation in midstance (W/kg)	More	0.15	0.58±0.61	0.68±0.73	0.56	0.91±0.53	1.29±0.80	0.19	0.74±0.41	0.83±0.55	/	/	/
			Less	0.15	0.61±0.74	0.72±0.73	/	/	/	0.28	0.66±0.34	0.76±0.38	/	/	/

		Max knee power absorption in late swing (W/kg)	More	-0.10	-1.10±0.63	-1.17±0.71	-0.28	-1.66±0.71	-1.85±0.64	0.11	-0.96±0.61	-0.89±0.65	/	/	/
			Less	-0.28	-1.43±0.54	-1.61±0.71	/	/	/	-0.07	-1.56±0.55	-1.60±0.61	/	/	/
	Ankle	Max ankle dorsiflexor moment in early stance (Nm/kg)	More	0.13	-0.11±0.07	-0.10±0.08	-0.4	-0.20±0.05	-0.22±0.05¶	0.55	-0.13±0.09	-0.09±0.05	/	/	/
			Less	-0.12	-0.11±0.08	-0.12±0.09	/	/	/	0.15	-0.14±0.06	-0.13±0.07	/	/	/
		Max ankle plantar flexor moment in late stance (Nm/kg)	More	-0.04	1.38±0.24	1.37±0.27	0,38	1.59±0.17	1.66±0.20	-0.28	1.33±0.23	1.26±0.27	/	/	/
			Less	0.18	1.50±0.21	1.54±0.23	/	/	/	-0.11	1.56±0.18	1.54±0.19	/	/	/
		Max ankle power absorption in stance (W/kg)	More	-0.30	-0.91±0.40	-1.05±0.52	-0.23	-0.77±0.27	-0.83±0.26	-0.16	-1.02±0.46	-1.09±0.41	/	/	/
			Less	-0.35	-0.74±0.29	-0.85±0.34	/	/	/	-0.19	-0.81±0.27	-0.87±0.35*	/	/	/
		Max ankle power generation in stance (W/kg)	More	0.10	2.37±1.10	2.49±1.30	0.58	4.42±0.89	4.98±1.03¶	-0.26	2.27±0.91	2.03±0.93	/	/	/
			Less	0.10	3.13±1.25	3.26±1.41	/	/	/	-0.23	3.99±0.81	3.78±1.01	/	/	/

¶ presents significant changes between time periods, * presents significant time (fatiguing task) effects (using ANOVA), ** presents significant group effects (using ANOVA), *** presents significant group x time interaction (using ANOVA), †Least squares mean [95%CI], / presents data not available. more, more affected side; less, less affected side
Values are mean ± standard deviation
Abbreviations: ES, Effect size; 6MWT, 6-Minute Walk Test; pwMS, persons with multiple sclerosis; HC, healthy control

Figure legends

Figure 1 Flowchart of the study

Figure 2 A. Changes in key spatiotemporal parameters **B.** Changes in gait asymmetry, variability, stability, and regularity parameters