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Walking fatigability indices correspond with perception of changes in gait speed and quality during an instrumented 6-minute walking test in people with multiple sclerosis

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Abstract

Background: People with MS (pwMS) present changes in gait speed and quality during a 6-min walking test (6MWT). It is unknown whether these changes are clinically meaningful.

Objective: To examine the relationships between pwMS-perceived changes in gait speed and quality with walking fatigability indices.

Methods: Forty-five pwMS (EDSS: 4.0; 51 ± 11 years) performed the 6MWT. Sensor-based fatigability indices were calculated by comparing gait quality and the distance walked between the first/last minute of the 6MWT. Perceived changes in speed, smoothness, balance, ankle, knee and hip movement, attention, spasticity and pain were reported after the 6MWT using a questionnaire (Likert-type). The minimal important change (MIC) was calculated using an anchor-based approach. Spearman's rank correlations (pwMS-perceived changes x fatigability indices) were calculated.

Results: More than half of pwMS reported changes in speed, smoothness, balance, or ankle position after the 6MWT. Significant MICs were found for most gait quality fatigability indices, as well as significant correlations with perceived changes, particularly for distance, speed, cadence, stride length, double support, step duration variability, and toe-off angle.

Conclusion: PwMS perceived changes in gait speed and quality. The MIC values complement existing cut-off scores, facilitating the identification of walking fatigability and its use in clinical trials.

Keywords

Minimal importance change, meaningful, fatigue, fatigability, gait, inertial measurement units

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Introduction

Walking is one of the most valuable body functions for people with multiple sclerosis (pwMS).[1,2] In a survey, self-reported problems with walking involved excessive energy expenditure, loss of balance, dragging the foot on the ground (i.e., foot-drop), being unable to walk fast, and getting rapidly fatigued.[2] These self-reported features can be captured by instrumented gait measurements. Lower gait speed[3] and impairments in several gait domains, such as balance, variability, rhythm, pace, and kinematics,[3–6] are well-documented in the literature. These walking impairments are associated with self-reported walking limitations, as measured by instruments such as the 12-item Multiple Sclerosis Walking Scale (MSWS-12), particularly in individuals with moderate-to-severe pwMS.[7,8]

In recent years, it is aware that walking (impairment) in pwMS can transiently worsen following sustained effort, a phenomenon known as walking fatigability (WF), affecting more than 60% of pwMS.[9–11] Walking fatigability manifests as a decrease in walking distance (i.e., distance walking fatigability-DWF), a decrease in gait quality (i.e., gait quality fatigability- GQF) or both.[10] This was done by investigating changes in distance walked or gait quality (e.g., step duration variability or foot-drop by means of foot-strike or toe-off angle), comparing the last and first minute in a 6-min walking test (6MWT). Cut-off scores of fatigability indices have been proposed to identify pwMS presenting abnormal fatigability, based on discriminative analysis with healthy subjects.[11–13]

Importantly, the concept of fatigability (i.e., state fatigue: a decrease in performance given a task) is different from the fatigue (i.e., trait fatigue: a feeling of lack of energy) normally captured by self-report questionnaires.[14] Considering that state and trait fatigue are poorly correlated in the motor and cognitive domains,[15–17] in this study, we focus on fatigability and, more specifically, in the walking domain.

A previous study showed that pwMS perceived that their gait pattern, muscle strength, pain, and spasticity increased after performing a 6MWT.[18] However, it is unknown whether the fatigability indices of gait parameters are meaningful (i.e., correspondence to perceived changes in pwMS). The importance of investigating this relationship is twofold: it can provide further validation of objectively measured changes (fatigability indices), and it might identify self-perceived fatigability issues not yet captured by objective measurements.[7] Also, it is unknown how large a change in DWF or GQF must be to be minimally perceptible to pwMS (i.e., minimal important change-MIC).[19] While traditionally, MICs are used to document clinically important changes in walking in a longitudinal perspective or after an intervention, in this study, the methodology is applied to examine perceived changes in the walking distance and gait quality during a 6MWT. While one might argue that the use of the MIC methodology in a cross-sectional study is unusual, we consider it appropriate given that we are looking for gait speed and quality changes within a task (i.e., over time in a 6MWT) that are minimally perceived and important for pwMS.[19] Our results can inform whether the cut-off value of walking fatigability indices, reported elsewhere,[12,13] corresponds to the minimal threshold for a change to be perceived by pwMS, providing a more fine-tuned and valid metric for uptake in clinical practice and research.

Considering the lack of questionnaires in the literature for investigating perceived changes in distance and gait quality within a task, we developed a Likert-type questionnaire, called "perception of gait change (PGC)", with questions on several gait domains (e.g., speed, balance, attention) which are affected in pwMS during prolonged walking,[20] items from the MSWS-12,[21] and recently reported additional gait modules, focusing in gait quality.[22] Therefore, the objective of this study is to determine the relationship of perceived changes in walking speed and gait quality with fatigability indices in pwMS after a 6MWT protocol. We also provide MIC values by applying an anchor-based approach in relation to an external criterion (i.e., a questionnaire asking about how much pwMS perceived their changes comparing the end with the beginning of the 6MWT).

Methods

Participants

PwMS were recruited through REVAL Rehabilitation Research Centre and Belgian MS centres (Noorderhart-Pelt and National MS Centre-Melsbroek), and social media. Participants were informed about the study procedures and signed an informed consent (#B1152024000007). Participants were included if they (i) present a MS diagnosis (McDonald criteria 2017),[23] (ii) had an Expanded Disability Status Scale (EDSS) score of 1–6.5 or a minimum score of 2 on at least one in the items 7, 10, 11 or 12 of the MSWS-12, (iii) were between 18 and 65 years old, (iv) could walk for 6 min without resting, (v) were not pregnant, (vi) did not present cognitive impairment that could interfere with understanding the instructions, (vii) and did not have musculoskeletal conditions interfering with walking.

Experimental procedure

We report secondary analysis of a study investigating the mechanisms of WF in pwMS (NCT06672484). Participants completed questionnaires for general characterisation and performed tests. The questionnaires included: MSWS-12[21] and an extended version of the MSWS-12 with 10 questions encompassing gait quality,[22] Falls Efficacy Scale International (FES-I), Pittsburgh

Fatigability Scale (PFS),[24] Modified Fatigue Impact Scale (MFIS), Fatigue Scale for Motor and Cognitive Functions (FSMC), the Brief Pain Inventory (BPI, short form), Multiple Sclerosis Spasticity Scale 88 (MSWS-88, section 5 and 6) and Brief Self-Control Scale (BSCS). Additionally, the Timed 25-Foot Walk (T25FW) and the Symbol Digit Modalities Test (SDMT) were performed.

Six-Minute walking test

Participants were instructed to safely walk as fast as possible to cover a maximal individual distance for 6 min on a 25-m walkway with turns at both ends. No verbal encouragement was provided to the participants; however, they were informed every minute that lapsed during the test.[25] PwMS were allowed to use their own assistive device. The distance walked minute-by-minute and the total distance were recorded.

The participants were instructed to stop at the end of the 6MWT, where a researcher would then ask about their perception of gait change. Before and after the 6MWT, the participants were asked about their perceived effort with the Borg scale (0–10).

Gait characteristics measurement

Gait characteristics were measured by eight inertial measurement units (IMU's- OPAL, APDM, 128 Hz, Clario®, Portland, US) placed on standardised body positions: sternum, lumbar, two on the lateral side of the thigh, two on the medial side of the tibia, and two on the foot. The Moveo Explore software (Clario®) processed the data on a gait-cycle-by-gait-cycle basis. The data were then split and averaged at the minute level for each gait characteristic (Matlab, V.2023a). To quantify changes in selected gait characteristics and in the distance walked, a fatigability index was calculated by comparing the average of the last and first minutes of the 6MWT. More precisely, we calculated the distance walked index (DWI)[11,12] and the fatigability index for each of the gait characteristics.[13] The following variables, which were shown to be reliable during the 6MWT for pwMS,[13] were used: gait speed, cadence, step duration and its variability, double support, and toe-off and foot-strike angle.

Perception of gait change questionnaire (PGC)

Participants were asked to compare their gait at the end of the 6MWT with the beginning by completing the PGC. The participants were not informed about the content of the questions beforehand to prevent their attention from being focused on their gait during the test, rather than performing the 6MWT as instructed.

The questionnaire included nine questions regarding gait speed, smoothness, balance, the movement of the ankle, hip and knee, attention, spasticity, and pain. The questions were inspired considering different components, including (i) specific questions of the MSWS-12, its recent 'gait' extension (i.e., gait speed, smoothness, attention and related to lower limb kinematics),[21,22] and (ii) MS-related symptoms (i.e., spasticity and pain)[18] and known abnormal gait quality fatigability characteristics, at the end of the 6MWT (e.g., toe-off angle or step duration variability).[10,13] A Likert-type style as follows was adopted: −3 (very much worse), −2 (worse), −1 (little worse), 0 (no change), 1 (little improved), 2 (improved) and 3 (very much improved). The PGC is in the appendix.

Reliable fatigability indices of gait quality[10,13] were retained and related to the following questions of the PGC: speed (DWI, gait speed, cadence, step duration and stride length), balance (double support and step duration variability), ankle, knee, hip (toe-off and foot-strike angle) and attention (step duration variability). The allocation of questions and variables was based on reasoning and previous studies. For example, the DWI, gait speed, cadence, step duration and stride length are strictly related to speed modulation. Double support and step duration variability were related to the balance aspect of walking,[26] and toe-off and foot-strike angle can reflect changes in the ankle, knee, and hip position.[27] Lastly, step duration variability related to the attention question comes from insights that it is associated with higher cortical activity in the prefrontal region (i.e., use of more attentional resources).[28,29] Questions on spasticity and pain were not related to any gait characteristics and came from a previous study that found an increase in these clinical symptoms after the 6MWT,[18] while smoothness had an exploratory character, as no study has demonstrated changes within a 6MWT setup in pwMS. Therefore, we did not match these three questions to any specific gait characteristic.

Statistical analysis

RStudio (2023.12.1) was adopted for all statistical analyses. The Shapiro-Wilk test was used for the data normality check.

Clinical and anthropometric characteristics and Borg were reported as average ± standard deviation or median [interquartile range] depending on the normality of the distribution. Pre versus post 6MWT on the Borg report was compared by a paired Wilcoxon test.

We reported the frequency with which people perceived their changes for each question. Following, walking fatigability indices (DWI and gait quality) were correlated with the respective question of the PGC by Spearman's rank correlation (rho, 95% confidence interval). Correlations were interpreted as negligible (0–0.1), weak (0.1–0.39), moderate (0.4–0.69), strong (0.7–0.89), and very strong (0.9–1.0),[30] and Bonferroni corrections for multiple comparisons were applied.

Table 1. Average ± standard deviation and median [IQR] for anthropometric and clinical outcomes.

Variables	pwMS (n = 45)
EDSS score (0-10)	4 [3.5]
Age (years)	51.1 ± 11.2
Sex (F/M)	30/15
Body mass (kg)	74.4 ± 15.9
Height (cm)	170.9 ± 9.2
T25FW (s)	5.51 [3.37]
6MWT (m)	412.62 ± 168.59
DWI (%)	-10.69 ± 12.94
MSWS-12 (pts, 12–60)	42.5 [24.75]
MSWS-12 (%)	70.83 [41.25]
Gait module (pts, 10–50)	22.5 [17.25]
SDMT (pts)	52.39 ± 13.96
MFIS-total (pts, 0–84)	43.24 ± 15.38
MFIS-Physical (pts, 0–36)	19.5 ± 8.33
MFIS-Cognitive (pts, 0–40)	17.93 ± 9.46
MFIS-Psychosocial (pts, 0–8)	4 [3]
PFS-P (pts, 0–50)	25.52 ± 11.14
PFS-C (pts, 0–50)	20.5 ± 13.01
FSMC (pts, 20–100)	69.35 ± 15.38
FES-I (pts, 16–64)	35 [16.75]
BSCS (pts, 13–65)	43.59 ± 6.81
BPI severity (pts, 1–10)	2.625 [2.69]
BPI interference (pts, 1–10)	1.86 [3.43]
BPI walking (pts, 1–10)	1 [4]
MSSS-88 section 5 (pts, 0–40)	23.5 [17]
MSSS-88 section 6 (pts, 0–40)	22 [17.75]

Note. Expanded Disability Status Scale (EDSS), female (F), male (M), centimetres (cm), timed-25 foot walking test (T25FW), Symbol Digit Modalities Test (SDMT), Modified Fatigue Impact Scale physical (MFIS), Fatigue Scale for Motor and Cognitive Functions (FSMC), Brief Pain Inventory (BPI), Multiple Sclerosis Spasticity Scale 88 (MSWS-88) section 5 and 6 which refer to the impact of spasticity in the walking ability and body movements and Brief Self-Control Scale (BSCS).

The MIC was used to identify the minimal change that a population (pwMS) perceives based on an external criterion (i.e., the PGC) after the 6MWT. An anchor-based approach was used[31,32]

$$Y(t) = \alpha + \beta_1 * Y(t_0) + \beta_2 * minimally\ worsened + \beta_3 * worsened + \varepsilon$$

Y(t) represents the fatigability indices of each of the gait characteristics and distance walked; these are the dependent variables. The independent variables ($Y(t_0)$) correspond to the baseline values (i.e., the fatigability indices at minute 1, which means 0%). The dummy variables β_2 and β_3 represent the groups that reported "minimally worse" or "worse"/"very much worse", respectively. The reference group is the pwMS group that reported no change or improvement on the external criteria (i.e., in the PGC); their intercept coefficient is α. The intercept of the "minimally worsened" group is considered the MIC.

Results

Forty-six participants were recruited, but one was excluded due to severe spasticity, preventing completion of the 6MWT.

Table 1 shows the characteristics of the 45 included participants. Our cohort was composed of mild to severe disabled pwMS (EDSS), the majority were females (2:1 ratio), with abnormal fatigue (FSMC and MFIS), with high concern about falling (FES-I), with relevant perceived walking limitations (MSWS-12), with mild impact of pain and spasticity on walking ability (BPI and MSSS-88), and moderate self-control ability (BSCS). Lastly, pwMS reported increased perceived effort (Borg) at the end of the 6MWT compared with the beginning (pre: 1[2.5] vs post: 4[4], $Z = 982$, $p < .001$).

Answer distribution in the PGC

Overall, more than 50% of pwMS perceived that their speed, smoothness, balance, ankle movement, or attention worsened at the end of the 6MWT compared to the beginning. Knee and hip movements, pain, or spasticity were perceived as worsened after the 6MWT in 47%, 40%, 37.8%, and 40% pwMS, respectively (Figure 1).

Correlation and minimal importance change

The distribution of fatigability indices for each of the PGC questions is shown in Figure 2. Table 2 presents the MIC values for fatigability indices and correlation coefficients with the questions. The average and standard error, minute-by-minute, along with the respective fatigability index, of each gait characteristic, are presented in supplementary Figure S1.

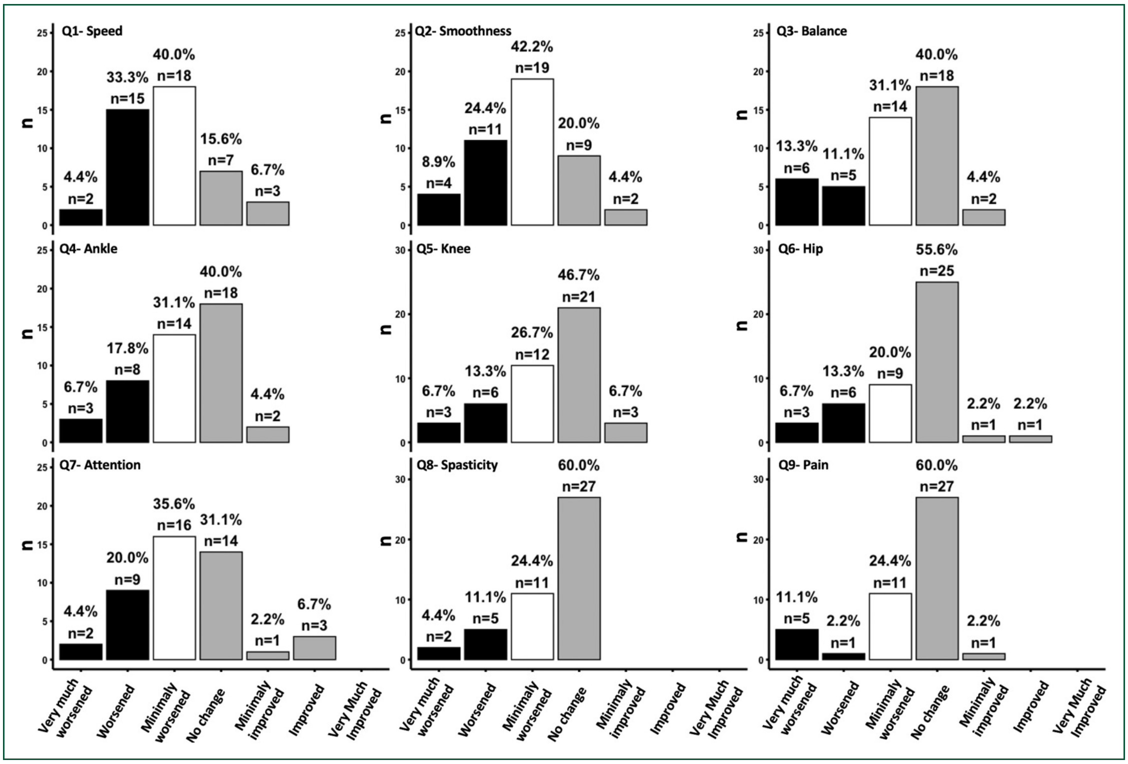

Figure 1. Frequency distribution of the answers of the people with multiple sclerosis to each question about the perception of changes after the 6MWT.

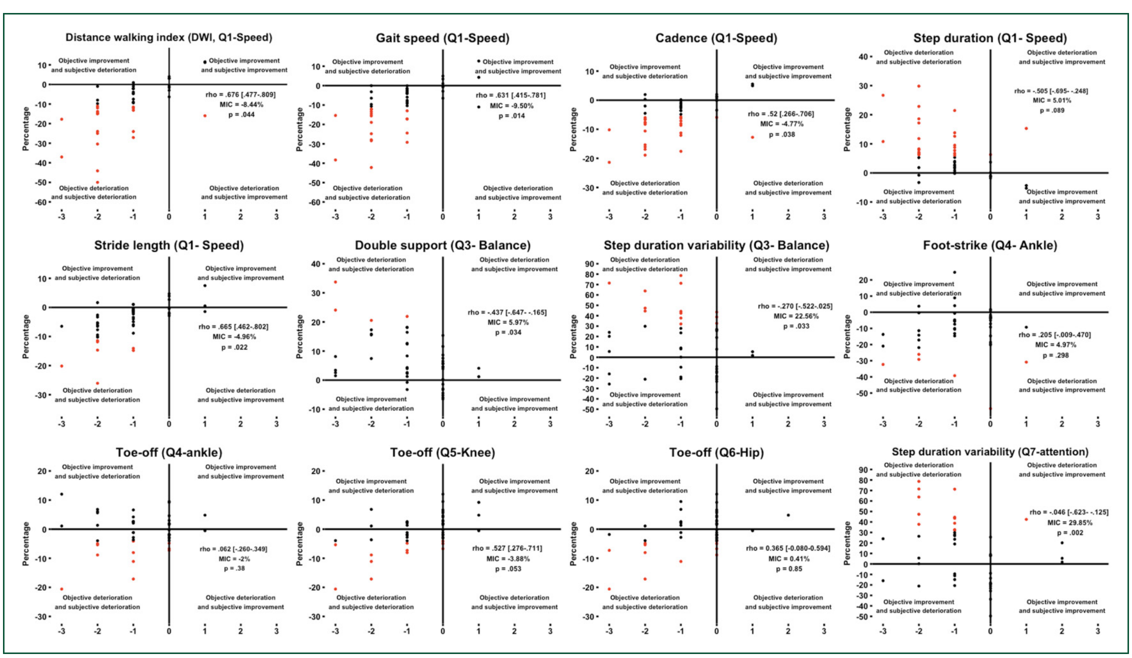

Figure 2. Scatter plot of the changes in distance walked (DWI) or gait quality fatigability indices versus the answers in the PGC questionnaire. Black dots mean people with multiple sclerosis not presenting with walking fatigability (i.e., no abnormal changes exceeding the cutoff score), red dots mean people with multiple sclerosis presenting with walking fatigability (i.e., exceeding the cutoff score published elsewhere[12,13]).

Table 2. Minimal importance change (MIC), along with its p-value of the DWI and the gait fatigability indices using the anchor-based approach.

Question		MIC %	MIC p-value	rho (95% CI)	Correlations p-value (unadjusted)	Correlations p-value (adjusted)
Speed	**DWI**	**−8.44**	**.044**	**.676 [.477-.809]**	**<.001**	**<.001**
	Gait speed	**−9.50**	**.014**	**.632 [.415-.781]**	**<.001**	**<.001**
	Cadence	**−4.77**	**.039**	**.521 [.269-.707]**	**<.001**	**<.003**
	Step duration	5.01	.090	**−.506 [-696- -.249]**	**<.001**	**<.005**
	Stride length	**-4.96**	**.022**	**.666 [.463-.803]**	**<.001**	**<.001**
Balance	**Double support**	**5.97**	**.034**	**-.437 [-.648- -.165]**	**.003**	**<.037**
	Step duration variability	**22.56**	**.033**	-.270 [-.522-.025]	.072	1.000
Ankle	**Toe-Off**	-2.00	.383	.062 [-.236-.349]	.685	1.000
	Foot-strike	4.98	.299	.205 [-.094-.47]	.176	1.000
Knee	**Toe-Off**	**-3.88**	**.053**	**.528 [.277-.711]**	**<.001**	**<.003**
	Foot-strike	4.50	.370	-.021 [-.312-.275]	.893	1.000
Hip	**Toe-Off**	0.41	.849	**.365 [.080-.595]**	**.014**	.192
	Foot-strike	3.17	.561	-.119 [-.399-.181]	.437	1.000
Attention	**Step duration variability**	**29.84**	**.002**	**-.349 [-.583- -.062]**	**.019**	.082

Spearman's rank correlation (rho), along with its p-value between the perception of gait change and its corresponding fatigability indices, is reported.
Note. In **bold,** the significant minimal importance change and correlations are highlighted.
bove half of pwMS

Significant MICs were observed for DWI, gait speed, cadence and stride length (speed question), double support and step duration variability (balance question), toe-off angle (knee question) and step duration variability (attention question).

There were significant associations between the subjective perceived changes and the objective changes. Specifically, moderate correlations were observed for cadence, gait speed, step duration and stride length (speed question), double support (balance question), and toe-off angle (knee question). In addition, weak correlations were observed for toe-off angle (hip question) and step duration variability (attention question).

Discussion

This is the first study to investigate whether perception of distance walking and gait quality changes reflect corresponding fatigability indices during a 6MWT in pwMS. Notably, the PGC indicates that more than 50% of pwMS reported perceived deterioration in speed, smoothness, balance, and ankle movement. We provide MIC for these fatigability indices for distance walked/gait speed and gait quality changes, using an anchor-based approach during the 6MWT. Our results show that the perceived changes are associated with the fatigability indices related to speed, balance, lower limb joint kinematics at the knee level, and attention and confirmed by significant MIC values. Although only two correlations were not significant after Bonferroni correction, some caution should be considered when interpreting the results for those variables.

The MICs were generally close to our previously reported cut-off scores for walking fatigability indices using discriminative analysis of healthy people (Figure 3).[12,13] Specifically, we found similar MIC versus the fatigability indices for DWI,[12] gait speed, cadence, toe-off, and step duration variability.[13] On the other hand, larger MIC differences were observed for stride length, double support, and step duration variability. Cut-off values and MIC provide complementary information as they allow differentiation

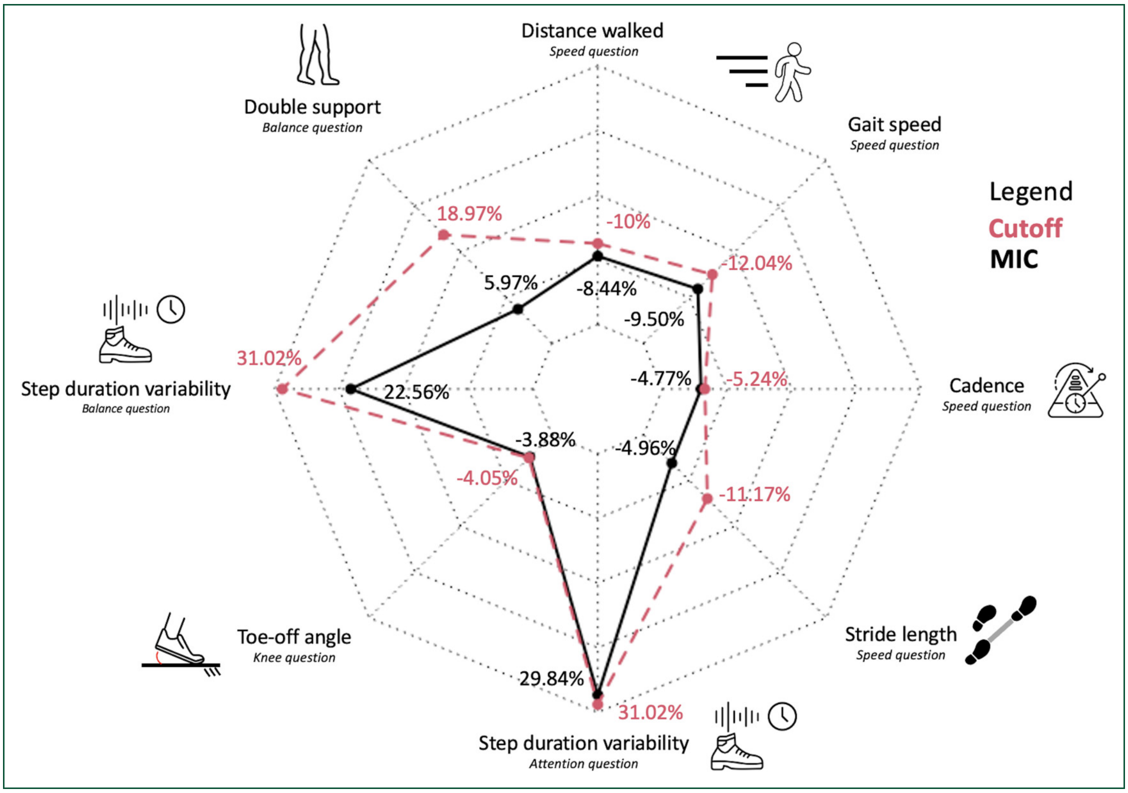

Figure 3. Overview of the significant minimal importance change values (MIC) with their respective cutoff score (average ± 2 standard deviations). Cut-offs provided in van Geel et al.[12] and in Santinelli et al.[13].

between groups and whether it is abnormal (i.e., exceeding the cutoff score), important (i.e., the minimal threshold to be relevant for the person), and maybe early detection of WF. A lower MIC value for a fatigability index than the cut-off score indicates that changes are perceived and might signal an early sign of moving towards an abnormal WF. In our previous work, cut-off scores were defined as the average ±2SD of HC values.[12,13] This conservative approach ensures high specificity and certainty in identifying abnormal cases. However, it may also result in misclassification, with some true positives being classified as negative (i.e., reduced sensitivity). Since the MIC values of some gait quality characteristics (stride length, double support and step duration variability) are consistently and substantially lower than the established cut-offs, they may detect changes in individuals who do not exceed the cut-off. Therefore, future studies should consider applying alternative methods for determining cut-offs with greater sensitivity (e.g., receiver operating characteristic-ROC). In clinical practice, MIC values may facilitate the identification of early walking fatigability and support timely intervention.

Questions in the PGC could be used in a clinical setting. PwMS' perceptions of changes in gait domains can indicate whether an instrumented 6MWT is recommended to examine the manifestation of GQF. Instrumental gait analysis performed using a motion capture system (either optical or IMU-based) might not be suitable for the daily routine in specialised MS centres. Hence, having a first screening including pwMS perception of gait changes might optimise care. The PGC can be incorporated into clinical decision-making to personalise assessment and rehabilitation programs, as it directs attention to the gait domains where pwMS perceive changes. In fact, this goes in line with the global patient reported outcomes for MS initiative (PROMs), where patient-reported outcome measures are suggested as essential for treatment and decision-making.[33] For the latter, we acknowledge, however, that the PGC has not been extensively validated, but was used as a tool to anchor perceptions for various gait-related domains.

The significant associations between the GQF indices and the subjective changes indicate that pwMS can perceive whether their gait has changed due to fatigability. The appearance of signs and symptoms when walking for a prolonged period might require some sort of conscious effort and bring awareness to the way one is walking,[34] which may lead pwMS to adopt different strategies to finish the 6MWT safely.[35] Consequently, these increases in awareness of the way of walking might cause an increase in the utilisation of brain resources,[29] which may impact their attention capacity. In fact, 60% of pwMS reported some degree of attention worsening at the end of the 6MWT, which must probably have been due to a lack of capacity in using neural resources due to fatigability. Nevertheless, this should be interpreted cautiously and needs further confirmation.

When analysing lower limb kinematics, one surprising finding was the significant association between the toe-off angle and perceived changes in the knee and hip. We expected the toe-off and foot-strike angle to be closely (or strongly) related to the perception at the ankle level. Toe-off angle estimation is calculated as the angle between the foot position relative to the floor, so the magnitude of plantar flexion at the toe-off preceding the swing phase. However, a reduction in the toe-off angle can also indicate a decreased knee flexion or hip extension, which would compromise a proper push-off moment.[27] Therefore, the toe-off metric reflects a large contribution of knee and hip position, rather than the ankle control alone.

Interestingly, there is an apparent difference in the ability of pwMS to perceive changes in gait related to speed or joint movement estimation. Gait speed and related spatial-temporal parameters estimation rely on different sensory afferences, such as vision, vestibular, and somatosensory (i.e., proprioception).[36] Having information from different sources, mainly vision, as pwMS rely mostly on that sensory source of information,[37] might help to a better estimation of speed-related parameters (e.g., optical flow provided by the visual system). Also, the distance walked changes had the greatest correlation with perception. Although they were unaware of the questionnaire's content beforehand, we cannot exclude the possibility that pwMS may have attempted to recall the number of corridors walked per minute at the beginning versus the end of the 6MWT once the questions were posed, particularly given that each elapsed minute was announced. Nevertheless, we followed standardised instructions for the 6MWT,[25] as it was unknown what the impact would be on pwMS perception while performing the 6MWT in silence. Future studies should investigate such a question. On the other hand, joint movement estimation might rely mainly on proprioception information during walking when joints are out of the visual field. PwMS normally have impairments in their estimation of joint movement given disruptions in proprioception pathways,[38,39] which may be exacerbated by fatigability, thereby affecting their ability to distinguish joint movement performance after walking for a long period.[40]

Methodological considerations apply. First, our questionnaire requires participants to compare their late state with their initial state, which introduces a recall bias. Our decision not to inform participants about the questionnaire before the commencement of the 6MWT was to avoid participants' focusing their attention on their walking distance or gait quality during the test, which could lead to an adapted pace, a change in their walking pattern, and an overload on their cognitive capacity. Future studies could investigate whether informing participants in advance about the questions and their content would change the correlation coefficients and MIC scores. As several significant MICs and associations were observed, the recall bias might have been minimal on participants' ability to report changes. Second, our questionnaire comprises different questions as anchors. However, we did not aim to validate the PGC. In the absence of established instruments for perceived change, MIC studies frequently rely on purpose-developed anchor questions tailored to the construct under investigation (see[31,32,41]). Some anchors that correlate $\geq$0.30 with the change score give more support for its use and validity in future research.[42] The current questionnaire is not ready yet for a composite score. Further validation, including data in HC and item redundancy analyses, is needed. Finally, the stratification by different levels of disability could be important for MIC values, considering that the magnitude of walking fatigability differs between disability levels.[9] Nevertheless, our sample size is limited, preventing stratification by disability level.

In conclusion, the present study showed that pwMS' perception of gait changes is correlated to objective gait fatigability indices, with stronger associations on speed-related variables. This was also reflected in significant MICs for several fatigability indices. Specifically, similar values were observed for the DWI, gait speed, cadence, step duration, toe-off and step duration variability. The combination of significant correlations and MICs, which means the correspondence of one perception with objective measurements, suggests that these metrics are relevant for pwMS. The current results further support the implementation of these metrics (i.e., fatigability indices) in rehabilitation and randomised controlled trials.

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Data statement

The data used to support the findings of the present study are available through the corresponding author upon request.

Supplemental material

Supplemental material for this article is available online.

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