BMC Neurology

RESEARCH

Open Access

Middle-range scores from the patient determined disease steps scale reflect varying levels of walking dysfunction in multiple sclerosis

Robert Motl[1*], Whitney Neal[2], Deborah Backus[3], Jeffrey Hebert[4], Kevin McCully[5], Francois Bethoux[6], Prudence Plummer[7], Alexander Ng[8], John Lowman[2], Hollie Schmidt[9], Robert McBurney[9] and Gary Cutter[10]

Abstract

Background Multiple sclerosis (MS) is a leading cause of neurological disability among young and middle-aged adults worldwide, and disability is measured using a variety of approaches, including patient reported outcome measures (PROMs) such as the Patient Determined Disease Steps (PDDS) scale. There is limited evidence for the validity of inferences from the middle-range of scores on the PDDS (i.e., 3 "gait disability" – 6 "bilateral support"), but that range of scores seemingly represents moderate disability characterized by varying levels of walking dysfunction.

Purpose The current study examined whether the middle-range of scores from the PDDS reflect varying levels of walking dysfunction among people with MS.

Method Participants ($N = 374$) completed the Patient Determined Disease Steps (PDDS) scale, Multiple Sclerosis Walking Scale-12 (MSWS-12), timed 25-foot walk (T25FW), six-minute walk (6 MW), Modified Fatigue Impact Scale (MFIS), and Multiple Sclerosis Impact Scale-29 (MSIS-29), and underwent a neurological exam for generating an Expanded Disability Status Scale (EDSS) score as part of screening and baseline data collection for a clinical trial of exercise training in MS. We undertook a series of linear trend analyses that examined differences in the outcomes of EDSS, T25FW, 6 MW, MSWS-12, MFIS subscales, and MSIS-29 subscales across the 4 levels of PDDS scores (i.e., 3–6).

Results There were statistically significant and strong linear trends for EDSS ($F_{1,370} = 306.1$, $p < .0001$, $\eta^2 = 0.48$), T25FW ($F_{1,370} = 161.0$, $p < .0001$, $\eta^2 = 0.32$), 6 MW ($F_{1,370} = 178.9$, $p < .0001$, $\eta^2 = 0.34$), and MSWS-12 ($F_{1,370} = 97.0$, $p < .0001$, $\eta^2 = 0.24$). There was a strong correlation between PDDS and EDSS scores ($r_s = 0.695$, 95% CI = 0.643, 0.748). Both PDDS and EDSS scores had strong correlations with walking outcomes, yet weaker correlations with measures of fatigue and QOL.

Conclusion The PDDS could serve as a simple, inexpensive, and rapidly administered PROM for remote screening and early detection of walking dysfunction for initial eligibility into clinical trials and practice for managing mobility-specific disability in MS.

*Correspondence:
Robert Motl
robmotl@uic.edu

Full list of author information is available at the end of the article

Registration The study was registered on ClinicalTrials.gov on March 19, 2018 (NCT03468868).

Keywords Neurological disability, Walking, Validity, Multiple sclerosis, Neurological disease, Patient reported Outcome measure

Introduction

Multiple sclerosis (MS) is a leading cause of neurological disability among young and middle-aged adults worldwide [1], and disability is measured using a variety of approaches, including patient reported outcome measures (PROMs) [2]. The Patient Determined Disease Steps (PDDS) scale was developed by researchers affiliated with the NARCOMS registry as a PROM for disability in MS [3]. The PDDS was adapted from the physician administered Disease Steps scale [4] that provided a simple, reproducible assessment of disability administered by neurologists who were not MS specialists. The PDDS has nine ordinal levels ranging between 0 (no disability) and 8 (bedridden) [3] and PDDS scores have been converted into Expanded Disability Status Scale (EDSS) scores [5] as well as classifications of mild, moderate, or severe disability [6], although there is debate regarding the PDDS as a surrogate for the EDSS [7]. There has been increasing evidence for the validity of PDDS scores as a measure of mobility disability in MS [8], yet validation of PROMs (e.g., PDDS) is an ongoing and evolving process [9].

To date, there is limited focus on the meaning of the middle range of scores from the PDDS (i.e., 3 "gait disability" – 6 "bilateral support"), yet this range of scores seemingly reflects moderate disability characterized by varying levels of walking dysfunction in a manner comparable with the EDSS (Table 1). The focus on the middle range of PDDS scores is important since the middle range of EDSS scores of 4 through 6.5 (i.e., moderate disability) is often indicative of the onset of mobility disability [10] and a likely irreversible course of disease progression [11] in MS. This middle range of EDSS scores further is a focus of inclusion criteria for persons with walking dysfunction into clinical trials of pharmacological and/or rehabilitation therapies [12, 13]. The same middle range of PDDS scores may provide an alternative for the EDDS during screening and provide insights into the need for clinical rehabilitation that slows functional decline in people with MS. If the middle range of PDDS scores can identify levels of walking dysfunction, the PDDS may serve as a simple, first-stage screening tool for the detection of walking dysfunction and inform treatment-related decisions.

The current study examined whether levels of middle-range scores from the PDDS scale reflect varying levels of walking dysfunction using baseline data from a clinical trial of exercise training for people with MS [14]. We hypothesized that higher PDDS scores between the range of 3 "gait disability" and 6 "bilateral support" would be selectively accompanied by the linear worsening of scores from walking-specific outcomes, but not measures of fatigue and quality of life (QOL). If our hypothesis is correct, the PDDS could serve as a simple, inexpensive, and rapidly administered PROM for screening people with walking limitations into clinical trials and practice for improving mobility-related disability in MS.

Methods

Registration, protocol, and regulatory oversight

The data were from screening and baseline phases of a multicenter comparative effectiveness clinical trial examining exercise training in people with MS; the full study is described in a protocol paper [14]. The study was registered on ClinicalTrials.gov on March 19, 2018 (NCT03468868), approved by the Shepherd Center Institutional Review Board (i.e., Human Ethics) on September 1, 2018 (IRBNet ID Number: 1130891-103), and overseen by a data safety and monitoring board. All participants provided written informed consent for participation per our IRB approval.

Participants and relevant procedures

Participants were recruited in waves through eight collaborating centers in the United States between 2018 and 2022. Recruitment occurred via research and clinical databases, direct contact with patients by providers and other clinical or research staff, word-of-mouth, social media (i.e. Facebook, Twitter), members of the study advisory board, patient advocates, local NMSS chapters, iConquerMS, and other partners. Those who were interested in participating contacted the nearest research coordinator who described the study and its procedures, answered questions, and initiated the three-phase screening process.

The first phase of screening took place over the telephone and involved basic eligibility criteria (i.e., self-reported diagnosis of MS, age, ability to travel to the site, relapse status, falls history, cognitive status and other comorbidities). Participants who passed the first screening then verbally consented for undertaking and recording the survey responses in the second phase of screening while on the telephone. The second screening included the Multiple Sclerosis Walking Scale-12 (MSWS-12) [15] and PDDS [3], and screened participants for walking dysfunction operationalized as MSWS-12 scores of 25–75 and PDDS scores of 3–6 for initial inclusion in the main trial. Those who passed the two-part telephone screening were invited for the third phase of screening for

Table 1 Patient determined disease steps (PDDS) scale and expanded disability status scale (EDSS) rating elements

PDDS		EDSS	
Score	Disability Level	Score	Disability Level
0	Normal	0	Normal neurological examination
1	Mild disability	1-1.5	No disability
2	Moderate disability	2-2.5	Minimal disability
3	Gait disability	3-3.5	Mild disability
4	Early cane	4-4.5	Moderate disability
5	Late cane	5-5.5	Increasing limitation in ability to walk
6	Bilateral support	6-6.5	Walking assistance is needed
7	Wheelchair/scooter	7-7.5	Confined to wheelchair
8	Bedridden	8-8.5	Confined to bed/chair
		9-9.5	Completely dependent
		10	Death due to MS

final eligibility and this occurred on-site typically within 1 month of the initial telephone screening for inclusion. The participant initially provided written informed consent and then completed the Timed 25-Foot Walk (T25FW) [16] and 6-Minute Walk (6 MW) [17], and underwent a neurological exam for generating an EDSS score [18]. We screened for T25FW values of 6–300 s and EDDS scores of 4.0-6.5 as our final inclusion criteria for walking dysfunction. Those who were eligible then completed the MSWS-12, as an outcome of the main trial and included in the analyses in this paper, along with Modified Fatigue Impact Scale (MFIS) [19] and Multiple Sclerosis Impact Scale-29 (MSIS-29) [20] via computer assessment using a HIPPA-compliant web-based portal.

Measures

PDDS

The PDDS was administered over the telephone. The PDDS contains one item with nine ordinal levels with descriptors ranging from 0 (Normal) through 8 (Bedridden) [3, 8].

The following clinical measures were administered in-person.

EDSS

The EDSS was administered by Neurostatus-certified examiners using the Neurostatus scoring grid, and consisted of seven (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral) neurological functional systems. The scores from the functional systems plus ambulatory status were combined into a composite EDSS score ranging between 0 (Normal neurological examination) through 10 (Death caused from MS) [18].

T25FW

The T25FW was administered based on standard instructions [16]. The participant walked across a marked, 25-foot path as quickly and as safely as possible on two consecutive trials. The tester recorded the time per trial in seconds. T25W scores were averaged across the two trials, and then converted into walking speed (feet/second).

6MW

The 6 MW was administered using standard instructions for MS [17]. The participant walked as far and as fast as possible, and the participant was allowed to take rests as needed, but while remaining upright without external support. The tester recorded total distance walked over the 6-minute period in feet.

The following PROMs were administered using a trial-specific HIPPA-compliant web-based portal.

MSWS-12

The MSWS-12 [15] is a PROM of walking dysfunction that contains 12 items rated on a 5-point scale with anchors of 1 (not at all) and 5 (extremely) based on a 2-week period. Overall MSWS-12 scores range between 0 and 100 points with higher scores reflecting greater walking impairment.

MFIS

Fatigue was measured by the MFIS [19], a 21-item measure of the physical, cognitive, and psychosocial impact of fatigue on daily life over the past four weeks. Higher scores reflect greater perceptions of fatigue across subscales.

MSIS-29

QOL was measured using the MSIS-29 [20]. The MSIS-29 is a 29-item, disease-specific measure of mental and physical domains of QOL over the past 4 weeks developed for people with MS, and higher scores reflect worse QOL.

Data analyses

Data analyses were conducted using IBM SPSS Statistics, Version 29.0.1. Analyses started with descriptive statistics reported as mean (standard deviation), median (interquartile range), or frequency (%), as appropriate for the measurement type per variable. This was followed by a series of linear trend analyses examining differences across the 4 levels of PDDS scores in the outcomes of EDSS, T25FW, 6 MW, MSWS-12, MFIS subscales, and MSIS-29 subscales. The linear trend analyses essentially tested if the values of the EDSS, T25FW, 6 MW, MSWS-12, MFIS subscales, and MSIS-29 subscales increased or decreased in a linear manner (i.e., straight line) across values of the PDDS scores. The 4 levels of PDDS scores varied between 3 and 6 and reflected (3) "gait disability," (4) "early cane," (5) "late cane," and (6)"bilateral support."

Table 2 Descriptive characteristics of the overall sample of persons with multiple sclerosis (MS) and subgroups per level of patient determined disease steps (PDDS) scale score

		Subgroups Based on PDDS Scores			
Variable	Overall (*N* = 374)	PDDS 3 (*n* = 103)	PDDS 4 (*n* = 124)	PDDS 5 (*n* = 91)	PDDS 6 (*n* = 56)
Age (years)	50.9 (9.6)	50.2 (9.9)	50.3 (10.3)	52.6 (8.8)	50.6 (8.6)
Sex (N/% female)	282/75.4%	85/82.5%	92/74.2%	67/73.6%	38/67.9%
Race (N/% Caucasian)	242/64.7%	74/71.8%	85/81.7%	57/62.6%	26/46.4%
Ethnicity (N/% Hispanic)	17/4.5%	5/4.9%	5/4.0%	3/3.3%	4/7.1%
MS Type (N/% RRMS)	258/69.0%	83/80.6%	87/70.2%	56/61.5%	32/58.9%
Duration (years)	12.5 (10.2)	10.6 (10.4)	12.6 (9.6)	13.7 (11.0)	13.5 (9.1)

Note Values for age and disease duration are mean (standard deviation). RRMS = relapsing-remitting multiple sclerosis

We provided eta-squared (η^2) as an estimate of effect size for the linear trend analyses, and values of 0.01, 0.06, and 0.14 were applied for interpreting the values as small, moderate, or large, respectively [21]. The adjusted alpha for judging statistical significance was set as 0.005 based on multiple outcomes in the linear trend analyses (i.e., 0.05/9). We further estimated the correlation between PDDS and EDSS scores, and correlations between PDDS and EDSS scores with T25FW, 6 MW, MSWS-12, MFIS subscale, and MSIS-29 subscale scores using Spearman's rho rank-order correlation coefficients (r_s) along with 95% confidence intervals (CI) for comparability with previous research on the validity of PDDS scores in MS. The standard guidelines of 0.1, 0.3, and 0.5 were applied for interpreting the correlations as small, moderate, or large, respectively [21]. We tested the differences in correlations between the PDDS and EDSS with T25FW, 6 MW, MSWS-12, MFIS subscale, and MSIS-29 subscale scores using Fisher's z-statistic.

Results

Sample characteristics

The demographic and clinical characteristics of the overall sample and subsamples by PDDS scores are provided in Table 2. There were no statistically significant differences in age (p = .29), sex (p = .23), race (p = .21), ethnicity (p = .88), or disease duration (p = .14) across levels of PDDS scores, but there was a significant difference in MS type (p = .003) such that the percent of persons with relapsing-remitting MS was lower with higher PDDS scores.

Table 3 Descriptive statistics for outcomes across patient determined disease steps (PDDS) scale scores in the sample of 374 persons with MS

Outcome Variable	PDDS Score (sample size)			
	3 (*n* = 103)	4 (*n* = 124)	5 (*n* = 91)	6 (*n* = 56)
EDSS (0–10)	4.4 (0.5)	5.2 (0.9)	5.9 (0.7)	6.2 (0.4)
T25FW (f/s)	3.3 (0.7)	3.0 (0.7)	2.3 (0.8)	1.9 (0.8)
6 MW (f)	1188 (297)	1014 (367)	751 (271)	551 (281)
MSWS-12 (0-100)	46.3 (20.0)	62.2 (19.0)	69.9 (20.2)	76.4 (16.3)
MFIS-Physical (0–30)	19.1 (7.8)	20.6 (7.3)	21.6 (7.2)	20.4 (8.1)
MFIS-Cognitive (0–40)	15.4 (9.5)	14.9 (8.9)	15.2 (9.8)	12.2 (8.0)
MFIS-Psychosocial (0–8)	3.5 (2.3)	4.0 (2.1)	4.2 (2.1)	4.0 (2.3)
MSIS-29 Physical (0-100)	28.8 (36.2)	37.9 (51.6)	43.8 (55.1)	43.6 (56.3)
MSIS-29 Mental (0-100)	28.1 (36.5)	30.3 (38.2)	27.0 (36.0)	23.5 (34.5)

Note Values for outcome variables are mean (standard deviation). EDSS = Expanded Disability Status Scale; T25FW = Timed 25-Foot Walk; 6 MW = Six Minute Walk; MSWS-12 = Multiple Sclerosis Walking Scale-12; MFIS = Modified Fatigue Impact Scale; MSIS-29 = Multiple Sclerosis Impact Scale-29

Linear trend analysis

The descriptive statistics from the linear trend analyses on the 9 outcomes are provided in Table 3. There were statistically significant and strong linear trends for EDSS ($F_{1,370}$ = 306.1, p < .0001, η^2 = 0.48), T25FW ($F_{1,370}$ = 161.0, p < .0001, η^2 = 0.32), 6 MW ($F_{1,370}$ = 178.9, p < .0001, η^2 = 0.34), and MSWS-12 ($F_{1,370}$ = 97.0, p < .0001, η^2 = 0.24), and the linear trends are presented graphically in Fig. 1 along with boxplots for T25FW, 6 MW, and MSWS-12 in Fig. 2; the boxplots identify noteworthy individual variability in T25FW, 6 MW, and MSWS-12 scores across PDDS scores. The were no statistically significant linear trends for physical ($F_{1,370}$ = 1.6, p = .20, η^2 = 0.02), cognitive ($F_{1,370}$ = 3.8, p = .05, η^2 = 0.01), and psychosocial ($F_{1,370}$ = 1.8, p = .18, η^2 = 0.02) subscale scores of the MFIS. There was a statistically significant, albeit small linear trend for MSIS-29 physical subscale scores ($F_{1,370}$ = 14.2, p < .001, η^2 = 0.05), but not MSIS-29 mental subscale scores ($F_{1,370}$ = 1.3, p = .26, η^2 = 0.01). The results regarding linear trends between PDDS and EDSS, 6 MW, T25FW, MSWS-12, and MSIS-29 physical subscale scores were unchanged when controlling for MS type as a covariate of PDDS scores.

Bivariate correlation analysis

There was a strong correlation between PDDS and EDSS scores (r_s = 0.695, 95% CI = 0.643, 0.748). Figure 3 presents frequency histograms of EDSS scores per level of PDDS scores, and there was a general shift in the distribution of EDSS scores with higher PDDS scores. The correlations between PDDS and EDSS scores with T25FW,

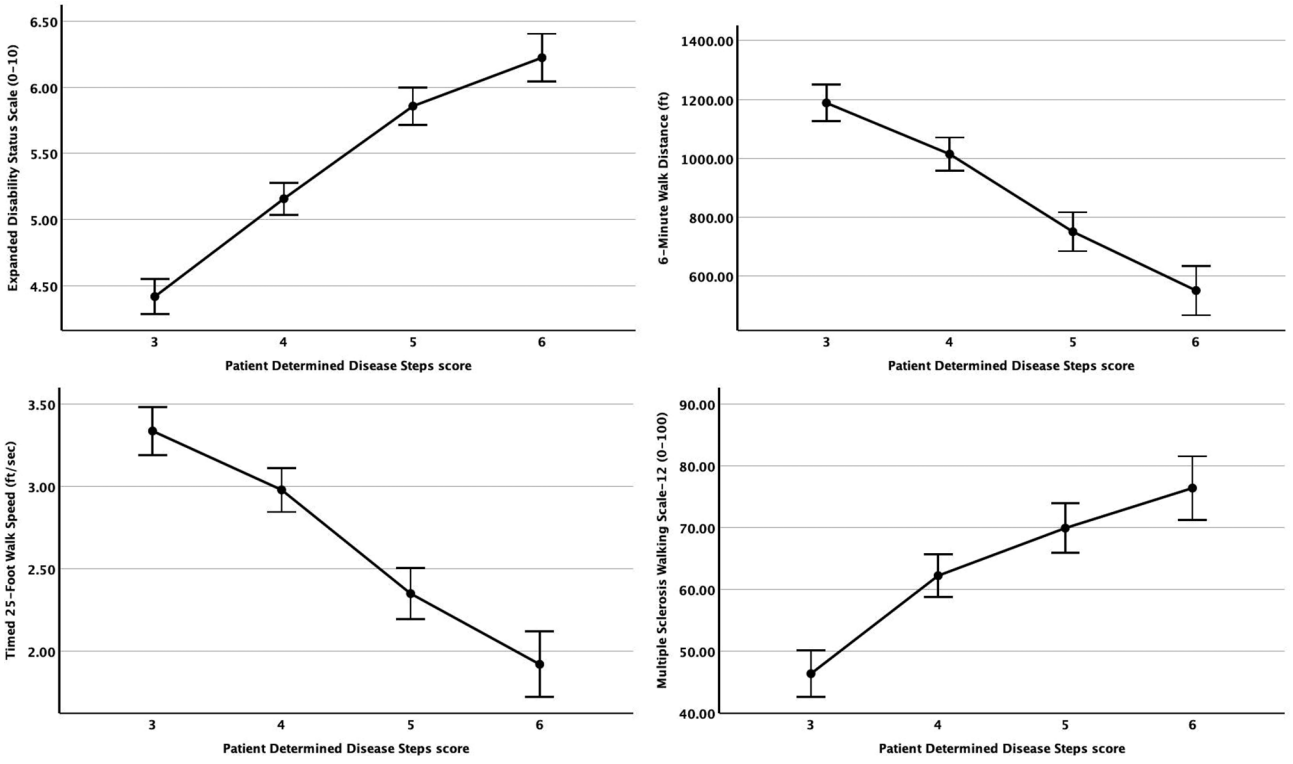

Fig. 1 Linear trend for Expanded Disability Status Scale, Timed 25-Foot Walk, Six-Minute Walk, and Multiple Sclerosis Walking Scale-12 scores across Patient Determined Disease Steps scale scores of 3 through 6 in the sample of 374 persons with MS. Values are mean along with standard error bars

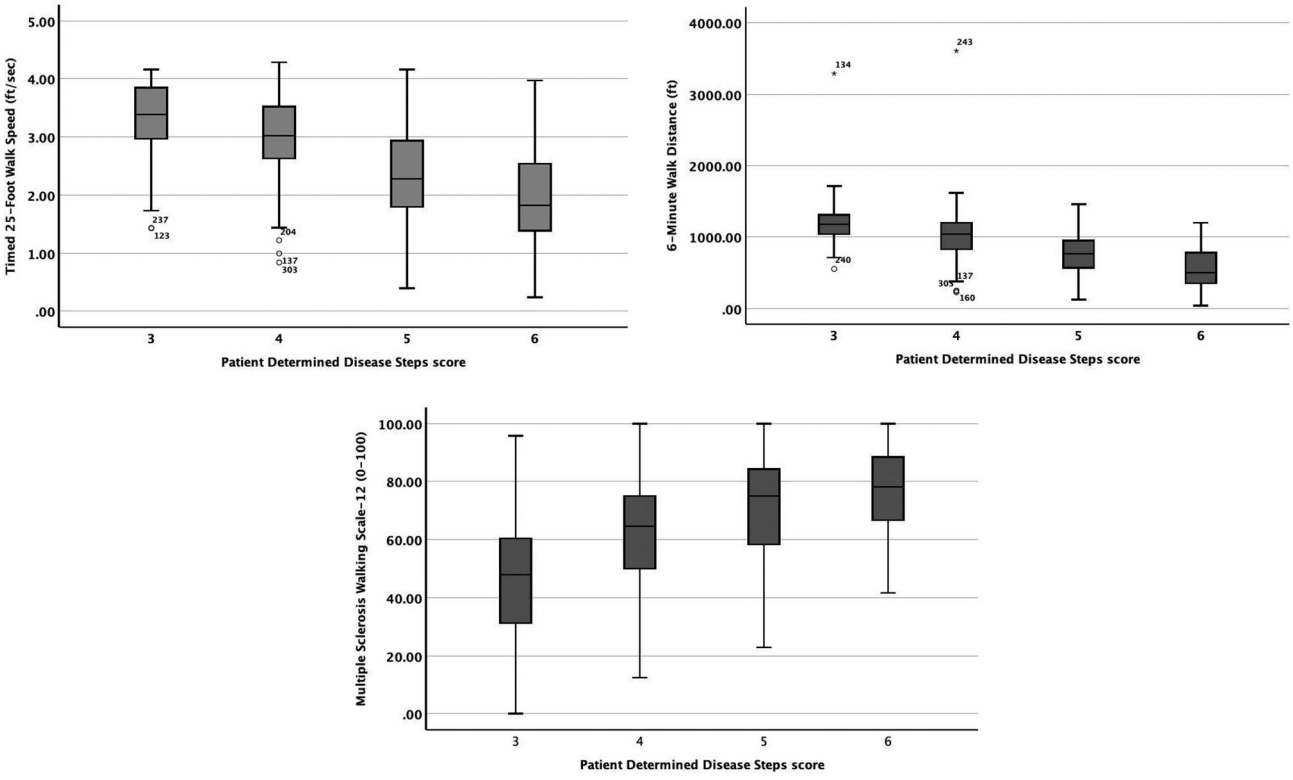

Fig. 2 Box plots for Timed 25-Foot Walk, Six-Minute Walk, and Multiple Sclerosis Walking Scale-12 scores across Patient Determined Disease Steps scale scores of 3 through 6 in the sample of 374 persons with MS

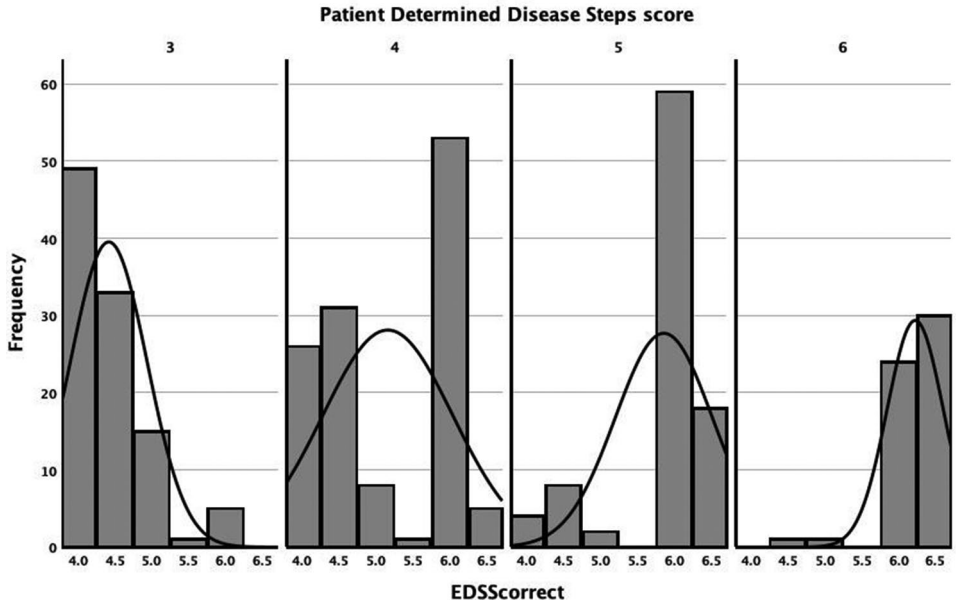

Fig. 3 Frequency histograms of Expanded Disability Status Scale scores across Patient Determined Disease Steps scores of 3 through 6 in the sample of 374 persons with MS

Table 4 Bivariate correlations between patient determined disease steps (PDDS) and expanded disability status scale (EDSS) scores with other outcomes in the sample of 374 persons with MS

Outcome Variable	PDDS	EDSS	Fisher's z	*p*-value
T25FW (f/s)	−0.555 (−0.625, −0.485)	−0.622 (−0.684, −0.600)	2.135	0.016
6 MW (f)	−0.634 (−0.695, −0.573)	−0.705 (−0.756, −0.654)	2.527	0.006
MSWS-12 (0-100)	0.481 (0.403, 0.559)	0.517 (0.442, 0.592)	1.052	0.146
MFIS-Physical (0–30)	0.084 (−0.017, 0.185)	0.066 (−0.035, 0.167)	0.445	0.328
MFIS-Cognitive (0–40)	−0.084 (−0.185, 0.017)	−0.120 (−0.220, −0.020)	0.893	0.186
MFIS-Psychosocial (0–8)	0.092 (−0.008, 0.193)	0.070 (−0.031, 0.171)	0.545	0.293
MSIS-29 Physical (0-100)	0.307 (0.215, 0.399)	0.252 (0.157, 0.347)	1.422	0.078
MSIS-29 Mental (0-100)	−0.051 (−0.153, 0.051)	−0.071 (−0.172, 0.030)	0.494	0.311

Note Values are Spearman rho rank-order correlation coefficients (95% confidence intervals) along with *z*-values and *p*-values for comparisons of correlations between PDDS and EDSS and outcome variables. T25FW=Timed 25-Foot Walk; 6 MW=Six Minute Walk; MSWS-12=Multiple Sclerosis Walking Scale-12; MFIS=Modified Fatigue Impact Scale; MSIS-29=Multiple Sclerosis Impact Scale-29

6 MW, MSWS-12, MFIS subscale, and MSIS-29 subscale scores are in Table 4, and there were significant differences in the correlations between EDSS and PDDS with T25FW and 6 MW based on Fisher's z and associated *p*-values. Nevertheless, PDDS and EDSS scores both had expected strong correlations with measures of walking dysfunction, yet weaker correlations with measures of fatigue and QOL, such that higher PDDS and EDSS scores were associated with greater levels of walking dysfunction, but less so with fatigue and QOL.

Discussion

This study examined whether higher middle-range scores from the PDDS scale reflected greater levels of walking dysfunction among persons with MS. The results were consistent with the hypothesis that higher PDDS scores within the range of 3 "gait disability" and 6 "bilateral support" would be selectively accompanied by the linear worsening of scores from measures of mobility/walking dysfunction, but not measures of fatigue and QOL. Indeed, the linear trend analysis, boxplots, and bivariate correlations all suggested that higher PDDS scores were associated with higher levels of mobility disability based on EDSS, T25FW, 6 MW, and MSWS-12 in this sample that was prescreened for presence of walking dysfunction for a clinical trial of exercise training in MS. The results collectively indicate that the PDDS scale could serve as a simple, inexpensive, and rapidly administered PROM for screening people with walking dysfunction into clinical trials and therapies for managing mobility disability in MS.

Some studies have examined differences in mobility and walking outcomes across broad categories of disability based on PDDS scores (e.g., mild, moderate, or severe) in MS [22–24]. For example, one study reported differences in 6 MW performance and oxygen cost of walking between persons with MS categorized with "no gait disability" defined as PDDS scores of 0–2 (i.e., mild disability) and persons

categorized with "gait disability" defined as PDDS scores of 3–8 (i.e., moderate or severe disability) [23]. Another study reported differences in T25FW, 6 MW, and **Six-Spot Step Test** scores among subgroups of "mildly impaired/no gait issues" defined as PDDS scores of 0–2, "gait disability" defined as a PDDS scores of 3, "cane users" defined as PDDS scores of 4–5, and "bilateral support/wheelchair" defined as PDDS scores of 6–7 [24]. One final study reported differences in simple and complex walking while talking tasks between subgroups of "low" and "high" PDDS scores of 0–3 and 4–6, respectively [22]. To our knowledge, the current study is the first to examine differences in mobility and walking outcomes within the middle range of PDDS scores indicative of moderate disability and onset of walking dysfunction. Our findings provide novel data indicating that higher middle range scores on the PDDS reflect greater levels of mobility disability, providing novel evidence for the validity of the middle range of PDDS scores as a measure of walking disability in MS. These results overcome a noted limitation of previous research on the validity of the PDSS that has seemingly been biased by the presence of extreme scores in the lower and/or upper ranges [7]. We do note that despite the strong concordance between higher PDDS scores and worsening mobility disability expressed based on group-level analyses as displayed in Fig. 1, the box-plots in Fig. 2 suggest a large degree of individual-level variability in mobility disability per level of the PDDS. This strong overall association, but limited prediction for individuals does not diminish the value of the PDDS, but does indicate that it cannot replace direct measures of walking dysfunction such as T25FW and 6 MW in people with MS.

We further estimated associations between PDDS scores with EDSS, T25FW, 6 MW, and MSWS-12 for comparison with previous research examining the validity of this scale in MS. The evidence for the validity of PDDS scores has recently been summarized in a review indicating that PDDS scores correlated strongly with EDSS ($|r|$=0.73), T25FW ($|r|$=0.63), 6 MW ($|r|$=0.67), and Timed Up and Go ($|r|$=0.62) across 5 studies involving 458 persons with MS who were generally in the mild or moderate range of disability based on PDDS scores [8]. We further note a recent study indicating that PDDS scores were moderately correlated with EDSS (r=.45) and weakly correlated with T25FW (r=.20) in a sample of 983 persons with MS who had mild disability based on PDDS scores [7]. We provide evidence that PDDS scores were associated with T25FW (r=–.555), 6MW (r=–.634), and MSWS-12 (r=.481), and the pattern of correlates was comparable with EDSS scores, despite the small statistically significant differences based on a large sample size. There further was concordance, albeit not absolute, between PDDS and EDSS scores (r=.695), and this further reinforces that these scales are correlated, but not isomorphic and interchangeable (i.e., PDDS is not a surrogate for EDDS) [7, 25]. The stronger correlation between PDDS and EDSS in the current study that other research [7] is likely based on the level of disability such that we included those with moderate disability (EDSS of 4.0-6.5) and walking dysfunction, whereas the other study included people with mild disability (EDSS of less than 4.0). Nevertheless, our results and other research collectively provide evidence for the validity of inferences from the PDDS as a measure of walking mobility in MS.

The strengths of this study include a large sample of persons with MS, and a unique focus on the middle range of the PDDS scores as reflecting mobility disability. There are some noteworthy limitations. The analysis was only performed using cross-sectional data, and future analysis should examine the comparative ability and sensitivity of the PDDS versus the EDSS for capturing changes in walking dysfunction over time. The sample was recruited and screened for inclusion into an exercise training clinical trial, and perhaps the unique features of this study design and resulting sample biased the outcomes and the results might not be applicable ou02?>

Overall, our results derived using baseline data from a clinical trial of exercise training in persons with MS indicated that PDDS scores between the range of 3 "gait disability" and 6 "bilateral support" were incrementally accompanied by the linear worsening of scores from measures of mobility/walking dysfunction, but not measures of fatigue and QOL. The linear trend analysis, boxplots, and bivariate correlations all suggested that higher PDDS scores were associated with greater levels of mobility disability based on EDSS, T25FW, 6 MW, and MSWS-12, and this was supported based on correlation and frequency analyses. Such results collectively support the middle range of PDDS scores as a simple, inexpensive, and rapidly administered PROM for screening samples of people with walking dysfunction into focal clinical trials and therapies targeting mobility disability in persons with MS.

Abbreviations

EDSS	Expanded Disability Status Scale
IRB	Institutional Review Board
MFIS	Modified Fatigue Impact Scale
MS	Multiple Sclerosis
MSIS-29	Multiple Sclerosis Impact Scale
NMSS	National MS Society
PDDS	Patient-Determined Disease Steps
PROMs	Patient Reported Outcome Measures
QOL	Quality of Life
6 MW	Six-Minute Walk
T25FW	Timed 25-Foot Walk

Acknowledgements

N/A.

Author contributions

Robert Motl wrote the main manuscript; Whitney Neal critically revised the main manuscript; Gary Cutter guided the data analysis for the manuscript; Deborah Backus, Jeffrey Hebert, Kevin McCully, Francois Bethoux, Prudence Plummer, Alexander Ng, John Lowman, Hollie Schmidt, and Robert McBurney (all remaining authors) reviewed and revised the manuscript.

Funding
This work was supported through a Patient-Centered Outcomes Research Institute (PCORI) Project Program Award (MS-1610-36999). The study sponsor had no role in study design.

Data availability
The final dataset will be posted at clinicaltrials.gov, and will be available from the corresponding author through written request.

Declarations

Ethics approval and consent to participate
The trial was successfully registered on ClinicalTrials.gov on March 19, 2018 (NCT03468868), and three institutional review boards approved the study protocol on September 1, 2018. The main institutional review board for study oversight was Shepherd Center (IRBNet ID Number: 1130891-103). All participants provided written informed consent for participation per our IRB approval.

Consent for publication
N/A.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Kinesiology and Nutrition, University of Illinois at Chicago, 1919 West Taylor St, Applied Health Sciences Building, Room 506J, Chicago, IL 60612, USA
[2]Department of Physical Therapy, University of Alabama at Birmingham, Birmingham, AL, USA
[3]Shepherd Center, Atlanta, GA, USA
[4]School of Medicine, University of Colorado Anschutz Medical Campus, Denver, CO, USA
[5]Department of Kinesiology, University of Georgia, Athens, GA, USA
[6]Mellen Center for MS, Neurological Institute, Cleveland Clinic, Cleveland, Oh, USA
[7]Department of Physical Therapy, MGH Institute of Health Professions, Boston, MA, USA
[8]Program in Exercise Science, Department of Physical Therapy, Marquette University, Milwaukee, WI, USA
[9]Accelerated Cure Project for Multiple Sclerosis, Boston, MA, USA
[10]Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL, USA

Received: 9 May 2024 / Accepted: 19 September 2024
Published online: 10 October 2024

References

1. Segal BM. 66 – multiple sclerosis. In: Rich RR, Fleisher TA, Shearer WT, Schroeder HW, Frew AJ, Weyand CM, editors. Clinical immunology: principles and practice. 5th ed. Elsevier; 2019. pp. 891–e9021.
2. Kieseier BC, Pozzilli C. Assessing walking disability in multiple sclerosis. Mult Scler. 2012;18:914–24.
3. Rizzo MA, Hadjimichael O, Preiningerova J, et al. Pravelence and treatment of spasticity reported by multiple sclerosis patients. Mult Scler. 2004;10:589–95.
4. Hohol MJ, Orav EJ, Weiner HL. Disease steps in multiple sclerosis: a simple approach to evaluate disease progression. Neurology. 1995;45:251–5.
5. Marrie RA, Cutter G, Tyry T, et al. Does multiple sclerosis-associated disability differ between. Races? Neurol. 2006;66:1235–40.
6. Marrie RA, Horwitz R, Cutter G, et al. Comorbidity delays diagnosis and increases disability at diagnosis in MS. Neurology. 2009;72:117–24.
7. Foong YC, Merlo D, Gresle M, et al. The patient-determined disease steps scale is not interchangeable with the expanded Disease Status Scale in mild to moderate multiple sclerosis. Eur J Neurol. 2024;31:e16046.
8. Marrie RA, McFadyen C, Yaeger L, et al. A systematic review of the validity and reliability of the patient-determined disease steps scale. Int J MS Care. 2023;25:20–5.
9. Messick S. Validity of psychological assessment: validation of inferences from persons' responses and performances as scientific inquiry into score meaning. Am Psychol. 1995;50:741–9.
10. Confavreux C, Vukusic S, Moreau T, et al. Relapses and progression of disability in multiple sclerosis. N Engl J Med. 2000;343:1430–80.
11. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain. 2003;126:770–82.
12. Goldman MD, Motl RW, Rudick RA. Possible clinical outcome measures for clinical trials in patients with multiple sclerosis. Ther Adv Neurol Disord. 2010;3:229–39.
13. Baird JF, Sandroff BM, Motl RW. Therapies for mobility disability in persons with multiple sclerosis. Expert Rev Neurother. 2018;18:493–502.
14. Motl RW, Backus D, Neal WN, et al. Rationale and design of the STEP for MS Trial: comparative effectiveness of supervised versus Telerehabilitation Exercise Programs for multiple sclerosis. Contemp Clin Trials. 2019;81:110–22.
15. Hobart JC, Riazi A, Lamping DL, et al. Measuring the impact of MS on walking ability: the 12-item MS walking scale (MSWS-12). Neurology. 2003;60:31–6.
16. Motl RW, Cohen JA, Benedict R, et al. Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. Mult Scler. 2017;23:704–10.
17. Goldman MD, Marrie RA, Cohen JA. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. Mult Scler. 2008;14:383–90.
18. Kurtzke JF. Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33:1444–52.
19. Ritvo PG, Fischer JS, Miller DM, et al. MSQLI: multiple sclerosis quality of Life Inventory: a user's Manual. New York, NY: National Multiple Sclerosis Society; 1997.
20. Hobart J, Lamping D, Fitzpatrick R, et al. The multiple sclerosis impact scale (MSIS-29): a new patient-based outcome measure. Brain. 2001;124:962–73.
21. Cohen J. A power primer. Psychol Bull. 1992;112:155–9.
22. Henning DA, Edwards EM, Ansara M, et al. Validating the walking while talking test to measure motor, cognitive, and dual-task performance in ambulatory individuals with multiple sclerosis. Mult Scler Relat Disord. 2021;54:102123.
23. Sandroff BM, Pilutti LA, Dlugonski D, et al. Comparing two conditions of administering the six-minute walk test in people with multiple sclerosis. Int J MS Care. 2014;16:48–54.
24. Skjerbaek AG, Dalgsa U, Stenagar E, et al. The six-spot step test is superior in detecting walking capacity impairments compared with short- and long-distance walk tests in persons with multiple sclerosis. Mult Scler J Exp Transl Clin. 2023;9:20552173231218127.
25. Learmonth YC, Motl RW, Sandroff BM, et al. Validation of patient determined disease steps (PDDS) scale scores in persons with multiple sclerosis. BMC Neurol. 2013;13:37.

Publisher's note