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The six spot step test is superior in detecting walking capacity impairments compared to short- and long-distance walk tests in persons with multiple sclerosis

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Abstract

Background: Walking capacity is important not only to persons with multiple sclerosis but also to clinical practice and research. The present study aims to compare the extent of impairments (relative to healthy controls) across three commonly used walking capacity outcomes in persons with multiple sclerosis.

Methods: In a two-hospital cross-sectional study, walking capacity was assessed using the timed-25-foot-walk-test (timed 25-ft walk test; 'walking speed'), the six-minute-walk-test ('walking endurance') and the six-spot-step-test ('walking balance and coordination'). Data were compared to normative reference data in healthy controls.

Results: A total of 228 persons with multiple sclerosis (68% females) were involved in the study: age 53.7 ± 11.6 y (range 26–81 y); patient-determined-disease-steps 3 [IQR; 1; 4] (range 0–7); time since diagnosis 12.6 ± 9.9 y (range 0–49 y); MS-phenotype (relapse remitting MS, secondary progressive MS, primary progressive MS) 146/39/41; and co-morbidity $n = 80$ (35%). Compared to healthy controls, deficits were observed across all walking capacity outcomes ($p < 0.001$): timed 25-foot walk test −26 [−30; −23]%, 6 minute-walk-test −36 [−39; −32]% and six-spot-step-test −44 [−47; −40]%. Deficits differed across walking capacity outcomes ($p < 0.001$).

Conclusion: Altogether, persons with multiple sclerosis performed substantially worse than healthy controls across all three walking capacity outcomes. The results showed that the six-spot-step-test was superior to the timed 25-foot walk test and the 6 minute-walk-test in detecting walking capacity impairments in persons with multiple sclerosis.

Keywords: Multiple sclerosis, timed 25-foot walk test, six minute walk test, six spot step test, multiple sclerosis walking scale-12, normative reference data

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Introduction

In multiple sclerosis (MS), walking difficulty is a common symptom, which affects daily life and ultimately limits independent living.[1] Walking impairment is reported in nearly 75% of all persons with MS (pwMS),[2,3] and therefore improvements in walking are often a key target in rehabilitation. Furthermore, studies in MS are increasingly recognising improvements in walking capacity as a primary efficacy endpoint in medical trials.[4,5]

Whilst the 12-item MS walking scale (MSWS)[6] is the most frequently used patient-reported outcome of the impact of MS on the individual's walking ability in MS research, a variety of walking capacity outcomes are used interchangeably in pwMS.[7] Specifically, the use of short-distance walk tests (e.g., timed 25-foot walk test (T25FWT)[8] to reflect walking speed) is well-established and has previously been compared with and discussed alongside the use of long-distance walk tests (e.g., the six-minute walk test (6MWT)[9] to

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reflect walking endurance[10–12]). Moreover, the six-spot step test (SSST)[13] was developed to capture other dimensions of walking (i.e., coordination and balance). In addition, it was recently shown that the SSST has better discriminative validity regarding disability and disease progression than the timed up-and-go test (TUG) and T25FWT.[5] Taken together, as more outcome measures of walking capacity are implemented and validated in MS, a comprehensive evaluation is warranted. Thus, the objective of this study was to compare walking capacity in pwMS across three commonly used walking capacity outcomes representing different dimensions of walking (i.e., walking speed, walking endurance, and walking coordination/balance, respectively), when expressed relative to available data from healthy controls (HC). As a secondary objective, the association between walking capacity (i.e., T25FWT, 6MWT, SSST) and walking ability (i.e., MSWS), impact of self-perceived disease severity, MS type, as well as time since diagnosis (TSD) were investigated.

Methods

Study design

The present two-hospital cross-sectional study compared three objectively assessed walking capacity measures in Danish MS patients and the extent of impairments in relation to available reference data from HC. Next, self-perceived walking ability and disease severity were also assessed. The study is part of an ongoing cohort study, investigating long-term changes in physical function (upper body function, processing speed and memory, walking ability, and walking capacity) alongside health-related quality of life in Danish MS patients.

Study recruitment took place at the Danish MS Hospitals that offer MS patients individualized and effective multidisciplinary rehabilitation (MDR).[14] In brief, patients with a need for MDR and a definite diagnosis of MS[15] are referred to the MS Hospitals via general practitioners or specialised MS neurologists. The Danish MS Hospitals are overseen by the Danish Health Authorities.

Participants

Clusters of 10 patients referred to 2 to 3 weeks of inpatient MDR at one of two Danish MS Hospitals (Ry and Haslev) were randomly—and blinded to the investigators—recruited from the patient admission lists of both hospitals. This was prior to each admission time between March 2022 and February 2023. Recruitment and randomisation were done by one secretary controlling all incoming referrals at both hospitals. From the admission lists, and sorted by date of birth, coin flips were made until 10 patients (from pools of 36 and 52 patients, respectively) from each hospital were selected (i.e., subjects getting 'tails') and consented to participate. This procedure was repeated prior to every admission time.

Inclusion criteria were: (1) willingness to participate (including written consent); (2) definite diagnosis of MS according to the McDonald criteria[15]; and (3) patient-determined disease step (PDDS)[16] score ≤ 7 (i.e., preserve of sufficient capacity to complete at least one of the three walking capacity tests).

The local ethical committee decided that no ethical approval was required to conduct this study (Local ethical committee in the Region of Central Denmark reference: 39/2021, project number 1-10-72-1-21). The study was conducted between February 18 2022, and February 3 2023.

Prior to admission, information on patient demographics and characteristics was obtained from the patients' medical records and stored using the RedCap electronic data capture tools hosted at [Aarhus University].

Patient demographics. Sex, age, height and body mass (height and body mass were used to calculate body mass index) and co-morbidities (defined as having one or more additional diseases: Diabetes, hypertension, depression, psychological disorder, osteoporosis, Crohn's disease, colitis ulcerous, lung disorders, or other chronic diseases).

MS characteristics. TSD, MS disease severity (PDDS), MS type, relapse remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS) and self-perceived walking ability (i.e., using the MSWS).

During the first week of admission, tests were performed on walking capacity, which included the T25FWT, 6MWT, and SSST (representing walking speed, walking endurance, as well as walking balance and coordination, respectively). All comparative normative reference values were extracted post-assessment. As done previously by Hvid et al., 2020,[17] reference values on the T25FWT and the 6MWT were based on data merged from several studies to have the most comprehensive reference values possible,[18–21] while data on SSST were

derived from several studies (three published studies[22–24] and three ongoing studies). When merging these data, reference values were weighted according to participant numbers of the respective studies across predefined age groups (20–29, 30–39, 40–49, 50–59, 60–69, 70+y).

Patient-reported outcomes

The PDDS is a patient-reported outcome (PRO) that assesses disability in MS, which was developed by the North American Research Committee on MS. Patients are asked to rate themselves in one of nine ordinal levels ranging between 0–2 (normal to moderate disability), 3 (gait disabilities), 4–6 (in need of walking aids) and 7–8 (a wheelchair user or bedridden). Although the PDDS is a simple self-perceived measure, it has shown a good correlation with the expanded disability status scale.[16]

The MSWS-12 is a PRO that measures self-perceived walking limitations and compensation strategies during walking in daily life. It consists of 12 questions describing situations that are considered to impact walking. Each item is scored from 1 'not at all' to 5 'extremely.' Scores are summed to generate a total score that can be transformed into a scale with a range of 0 to 100. High scores indicate a greater impact of MS on walking.[6]

Procedures

Walking capacity outcomes were administered by experienced physiotherapists who were trained to provide testing according to the protocol. Furthermore, the applied test instructions followed the original procedures of the T25FWT,[8] 6MWT[9] and SSST[13] in order to increase the reliability and validity of the study results.

In short, for the T25FWT, the patient is instructed to walk 25 ft as quickly as possible but safely in a clearly marked 25-ft course (7.62 m). The task is administered twice with the average time as the test result. Patients may use assistive devices and in case of falls, measurement errors or a completion time above 180 s, the test is discontinued.[8]

During the 6MWT, the patient is instructed to walk as far as possible in six minutes on a 30-m lane, with marks at each end clearly indicating where to turn. Patients are allowed to use assistive devices during the test and to rest (while standing) if needed. However, if sitting rest is needed, this discontinues the test. Total distance (*m*) undertaken in six minutes or until the test is discontinued is applied as the test result.[9]

In the SSST, the patient is instructed to walk as quickly as possible, but safely, in a criss-cross lane of 6 m, while kicking five wooden blocks from circles marked on the floor. The task is done twice using the dominant foot and twice using the non-dominant foot. Assistive devices are allowed and the average time (s) from the four runs are used as the test result. Failure to complete the test in less than 180 s or not being able to complete subsequent test runs within less than five minutes of rest leads to discontinuation. Failing to kick out a wooden block from any of the five circles or any measurement errors occurring during the test causes a new test run.[13]

The testing of the patients was organised with respect to other planned rehabilitation activities during the inpatient stay, and when appropriate, typically spread over a few days in order to reduce potential influence from mental and/or physical fatigue. All data collection was performed in settings that eliminated unnecessary interference (i.e., from other people, noise, activities). The use of walking aids and orthosis were allowed if necessary and were registered. Standardised test instructions were strictly followed and learning effects were minimised through familiarisation test(s) being conducted once for the T25FW and twice for the SSST. Deviations from original test procedures were noted and ultimately a test was terminated and/or repeated dependent on specific procedures related to the single test.

Statistics

Statistical analyses were performed using linear mixed models in STATA (IC 17, StataCorp, College Station, TX, USA). Descriptive statistics included patient demographics (number of subjects, gender and age) and MS characteristics (TSD [y], PDDS [score] and MS type). Normal distribution of data was checked using histograms and q–q-plots. This was met for all walking capacity outcomes, except for SSST, which was subsequently transformed from seconds to rounds/s (=1/SSST) as a proxy measure of speed. Data in text, tables and figures are presented as mean ± SD (MSWS [score], T25FWT [m/s], 6MWT [m] and SSST [rounds/s]), whereas absolute differences (between MS and HC) as well as deficits (i.e., the difference in percentage between MS and HC calculated as individual values for each pwMS in relation to HC mean values) are presented as mean (95%CI). To further elaborate on these three general outcomes, z-scores are provided (calculated as the difference between individual values for each pwMS and HC mean values,

divided by mean HC SD values). Data on MS was further divided into subgroups across PDDS ($PDDS_{0-2}$ = mildly impaired/no gait issues, $PDDS_3$ = gait disability, $PDDS_{4-5}$ = cane users, $PDDS_{6-7}$ = bilateral support/wheelchair), TSD (TSD_{0-2} y, TSD_{3-10} y, TSD_{11-20} y, TSD_{21+} y) and MS type (RRMS, SPMS, PPMS). To accentuate the differences between MS and HC across all three walking capacity outcomes, percentage deficits were calculated by expressing individual values for each MS patient in relation to the mean values of HC (adjusted for sex and age by groups: 20–29, 30–39, 40–49, 50–59, 60–69, 70–79 and 80–89 y). When comparing absolute values between MS and HC, group (MS, HC) was set as a fixed effect. When comparing absolute values as well as deficit values within MS, subgroup was set as a fixed effect and patient identity (ID) as a random effect. Simple linear regression was carried out to explore the association between walking ability (MSWS) and all three walking capacity outcomes. To explore the influence of PDDS, TSD and MS type, respectively, multiple regression (adjusting for PDDS, TSD and MS type) was carried out in relation to the deficits in each of the three walking capacity tests. Level of significance was set at $p < 0.05$.

Results

Patient demographics

From 472 possible patients, 331 responded to the invitation and 241 accepted (73%). A total of 228 pwMS entered the study (68% females). Mean age was 53.7 ± 11.6 y (range 26–81 y) and mean body mass index was 26.8 ± 6.1 kg/m^2 (range 17.3–49.9 kg/m^2).

MS characteristics

PDDS was 2.9 ± 1.9 (range 0–7) and TSD was 12.6 ± 9.9 y (range 0–49 y). A total of $n = 146$ had RRMS, $n = 39$ had SPMS, $n = 41$ had PPMS and $n = 2$ were missing data. A full overview is displayed in Table 1.

Healthy controls

Available data from HC were based on $N = 1197$ (age 47.0 ± 2.8 y; 62% females) for the T25FWT,[18,19] $N = 1070$ (age 45.0 ± 24.2 y; 51% females) for the 6MWT[20,21] and $N = 253$ (age 51.6 ± 23.6 y; 71% females) for the SSST (three published studies[22–24] and three ongoing studies).

Walking capacity

In pwMS, mean values of the T25FWT, 6MWT and SSST were 1.37 ± 0.55 m/s ($n = 227$), 416 ± 163 m ($n = 219$) and 0.108 ± 0.054 rounds/s ($n = 223$), respectively. Self-perceived walking ability (MSWS) was 35.6 ± 13.7points (n = 222). Absolute walking capacity values all differed between MS and HC, in favour of HC (T25FWT −0.54 [−0.59; −0.49] m/s [$p < 0.05$], 6MWT −222 [−236; −208] m [$p < 0.05$] and SSST −0.077 [−0.085; −0.069] rounds/s [$p < 0.05$]) (Table 2, Figure 1).

Substantial deficits (i.e., individual pwMS data relative to mean normative reference data from HC, stratified according to sex and age) across all walking capacity outcomes were observed (T25FWT −26 [−30; −23]% [$p < 0.05$], 6MWT −36 [−39; −32]% [$p < 0.05$], and SSST −44 [−47; −40]% [$p < 0.05$]). The magnitude of deficits differed across walking capacity outcomes (T25FWT vs. 6MWT −10 [−15; −4]% [$p < 0.05$], T25FWT vs. SSST −17 [−22; −12] % [$p < 0.05$] and 6MWT vs. SSST −8 [−13; −2]% [$p < 0.05$]) (Figure 2).

Table 1. Demographic and disease-related characteristics.

Number of patients, *n*	228
Females, *n* (%)	156 (68%)
Age, y (mean ± SD, (range))	53.7 ± 11.6 (26–81)
BMI, kg/m^2 (mean ± SD, (range))	26.8 ± 6.1 (17.3–49.9)
Comorbidity, (yes), *n* (%)	80 (35%)
Disease severity	
PDDS score (median [IQR], (range))	3 [1;4] (0–7)
Time since diagnosis, y (mean ± SD, (range))	12.6 ± 9.9 (0–49)
Time since symptoms, y (mean ± SD, (range))	17.1 ± 12.3 (0–54)
MS type, (RRMS/SPMS/PPMS/missing), (*n*)/(%)	(146/39/41/2)/(64, 17, 18, <1)%

RR: relapse remitting; SP: secondary progressive, PP: primary progressive, PDDS: patient determined disease steps, IQR: interquartile range; MS: multiple sclerosis; BMI: body mass index. (p25, p75).

Table 2. Walking capacity and ability in Danish MS patients and healthy controls.

	MS	HC
Walking capacity		
T25FWT, (m/s)	1.37 ± 0.55 (0.07–2.78)	1.91 ± 0.28[a]
6MWT, (m)	416 ± 163 (8–755)	638 ± 83[b]
SSST, (rounds/s)	0.108 ± 0.054 (0.007–0.272)	0.184 ± 0.037[c]
Walking ability		
MSWS	35.6 ± 13.7 (12–60)	not applicable

MS: patients with multiple sclerosis; HC: reference values from healthy controls; T25FWT ($N = 227$): timed 25-foot walk test; 6MWT ($N = 219$): six-minute walk test; SSST ($N = 223$): six-spot-step-test; MSWS: multiple sclerosis walking scale (12-Item). All data is presented as mean ± SD (range).
[a]Derived from Bohannon (1997) and Bohannon & Wang (2018) ($n = 1197$).
[b]Derived from Tveter et al. (2014) and McKay et al. (2017) ($n = 1070$).
[c]Derived from Brincks & Callesen (2022), Sieljacks et al. (2020), Riemenschneider et al. (2021) and three ongoing studies ($n = 253$).

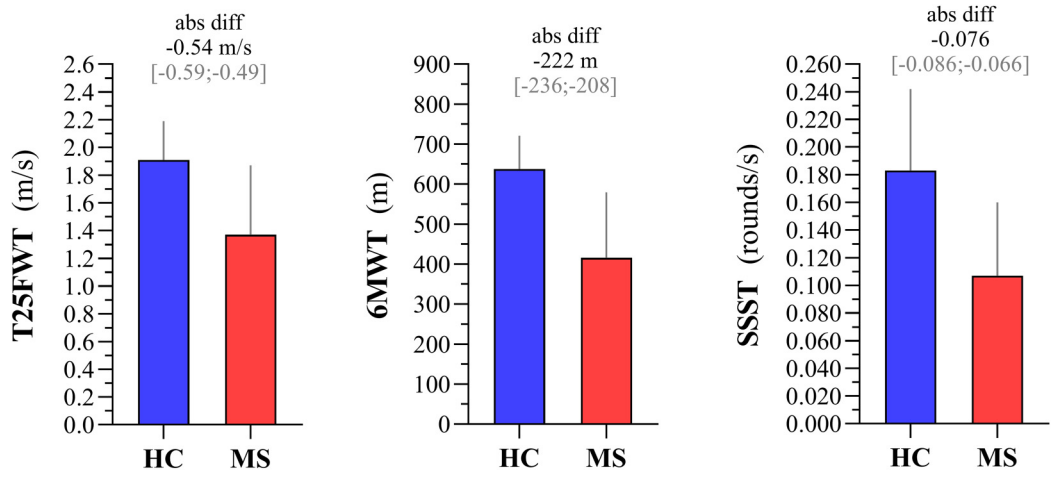

Figure 1. Walking capacity in MS patients and Healthy Controls (HC).

Subgroup-analysis

Deficits in subgroups ($PDDS_{0–2}$, $PDDS_3$, $PDDS_{4–5}$, $PDDS_{6–7;}$ $TSD_{0–2}$, $TSD_{3–10}$, $TSD_{11–20}$, TSD_{21+}, RRMS, SPMS, PPMS) are shown in Figure 3 (absolute values are displayed in Supplemental Tables 1–3). Within each walking capacity outcome, all PDDS subgroups differed from each other ($p < 0.05$) (Figure 3A). Deficits within each PDDS subgroup were overall shown to follow a pattern where SSST > 6MWT > T25FWT. Adjusting for age, sex, TSD and MS type did not affect these findings. Within each walking capacity outcome, $TSD_{0–2}$ and $TSD_{3–10}$ differed from $TSD_{11–20}$ and TSD_{21+}, respectively ($p < 0.05$) (Figure 3B). Hence, deficits in $TSD_{0–2}$ and $TSD_{3–10}$ were comparable, as were deficits in $TSD_{11–20}$ and TSD_{21+}. Within each TSD subgroup, deficits were overall shown to follow a pattern where SSST > 6MWT ≈ T25FWT. Adjusting for age, sex, MS type and PDDS subgroup did not affect these findings. Lastly, within each walking capacity outcome, RRMS differed from SPMS and PPMS ($p < 0.05$) (Figure 3C). Hence deficits in SPMS and PPMS were comparable. Within each MS type, deficits were overall shown to follow a pattern where SSST > 6MWT > T25FWT. Adjusting for age, sex, TSD and PDDS subgroup did not affect these findings.

Associations

Simple linear regression analysis showed that all walking capacity outcomes were strongly to very strongly associated with walking ability, and to a comparable extent, $r = 0.73$ ($p < 0.001$) for T25FWT and MSWS, $r = 0.77$ ($p < 0.001$) for 6MWT and

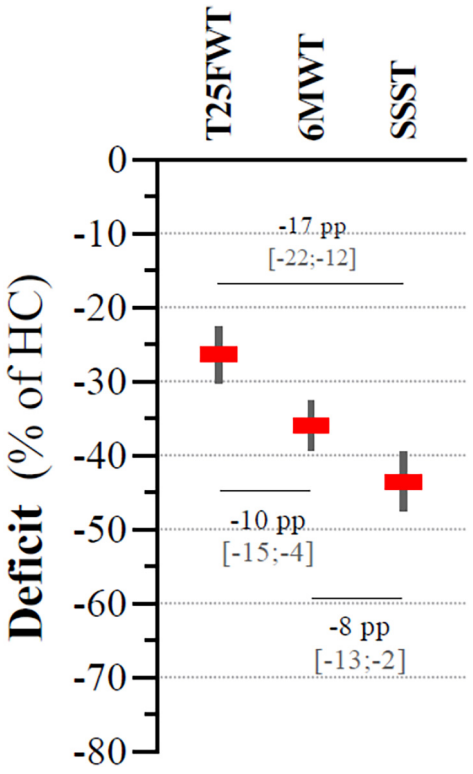

Figure 2. Differences (deficit) in T25FWT, 6MWT, and SSST between MS patients and HC, with HC serving as a reference. Corresponding *z*-scores were −1.90 [−2.15; −1.64], −2.14 [−2.35; −1.92], and −2.52 [−2.76; −2.28] for T25FWT, 6MWT, and SSST, respectively.
HC: healthy controls; 6MWT: six minute-walk-test; SSST: six-spot-step-test; T25FWT: timed 25-foot walk test; MS: multiple sclerosis.

MSWS and $r = 0.72$ ($p < 0.001$) for SSST and MSWS. Multiple linear regression analysis showed that deficits in T25FWT were explained ($r^2 = 0.53$, $p < 0.05$) by PDDS (β value = –0.60) and MS type (β value = −0.20) but not TSD (β value = 0.05), deficits in 6MWT were explained ($r^2 = 0.57$, $p < 0.05$) by PDDS (β value = −0.67) and MS type (β value = −0.16) but not TSD (β value = 0.03) and deficits in SSST were explained ($r^2 = 0.47$, $p < 0.05$) by PDDS (β value = −0.52), MS type (β value = −0.20) and TSD (β value = 0.14). The standardised β values revealed that PDDS and, to some extent, MS type were the main factors explaining deficits across all walking capacity outcomes.

Discussion

This study compared data from pwMS to normative reference data from HC across three walking capacity outcomes reflecting different dimensions of walking (i.e., walking speed, walking endurance, as well as walking coordination and balance). The results showed that pwMS performed substantially worse than HC across all walking capacity outcomes and that the deficits seen in SSST were most prominent, followed by 6MWT and T25FW, respectively.

Our analysis demonstrated that the SSST, in comparison to 6MWT and T25FWT, was the superior outcome measure in detecting deficits in walking capacity in pwMS. One explanation for this may relate to the construct of the SSST as this outcome is somewhat more complex and captures more dimensions (i.e., balance and coordination) of walking capacity compared to short- and long-distance walk tests (evaluating walking speed and endurance, respectively). Hence, elements of coordination and balance that are important in daily walking behaviour are likely better captured by the SSST, and this is what distinguishes the SSST from other walking outcomes.[13,25] Further, Fritz et al.[26] noted that the dual tasks involved in the SSST is relevant to functional ambulation as they require similar skills such as the ability to navigate obstacles, shift weight, and, at the same time, maintain an adequate speed to interact with the surrounding environment. While it captures additional elements in comparison to short- and long-distance walk tests, the SSST is still associated with other timed walking capacity tests (e.g., TUG, T25FWT, 6MWT). Previous studies have reported very acceptable psychometric properties of SSST (i.e., concurrent validity,[26] test–retest agreement and reliability,[27] responsiveness[28]), including within-day, day-to-day and inter-rater agreement.[27] Although the responsiveness needs further validation,[28] the increasing use and validation of the SSST confirms its potential as an important clinical outcome measure.

Our study findings emphasise a number of aspects that deserve to be elaborated on. First, few previous studies have comprehensively evaluated walking capacity (i.e., the use of short- and long-distance walk tests only appear insufficient). Our results show that deficits increase when more complex tests of walking capacity are applied (i.e., SSST). Second, if important dimensions of walking capacity are not addressed, impairments may be overlooked thus leaving pwMS and their caregivers with reduced information to decide on timely rehabilitation and medical treatment. In line with this, Jensen et al,[29] investigated the effect of Fampridine on different walking outcome measures and found that the SSST was more responsive to the effect of fampridine than the T25FWT. Going forward, researchers should further investigate the psychometric properties (e.g., validity, reliability and

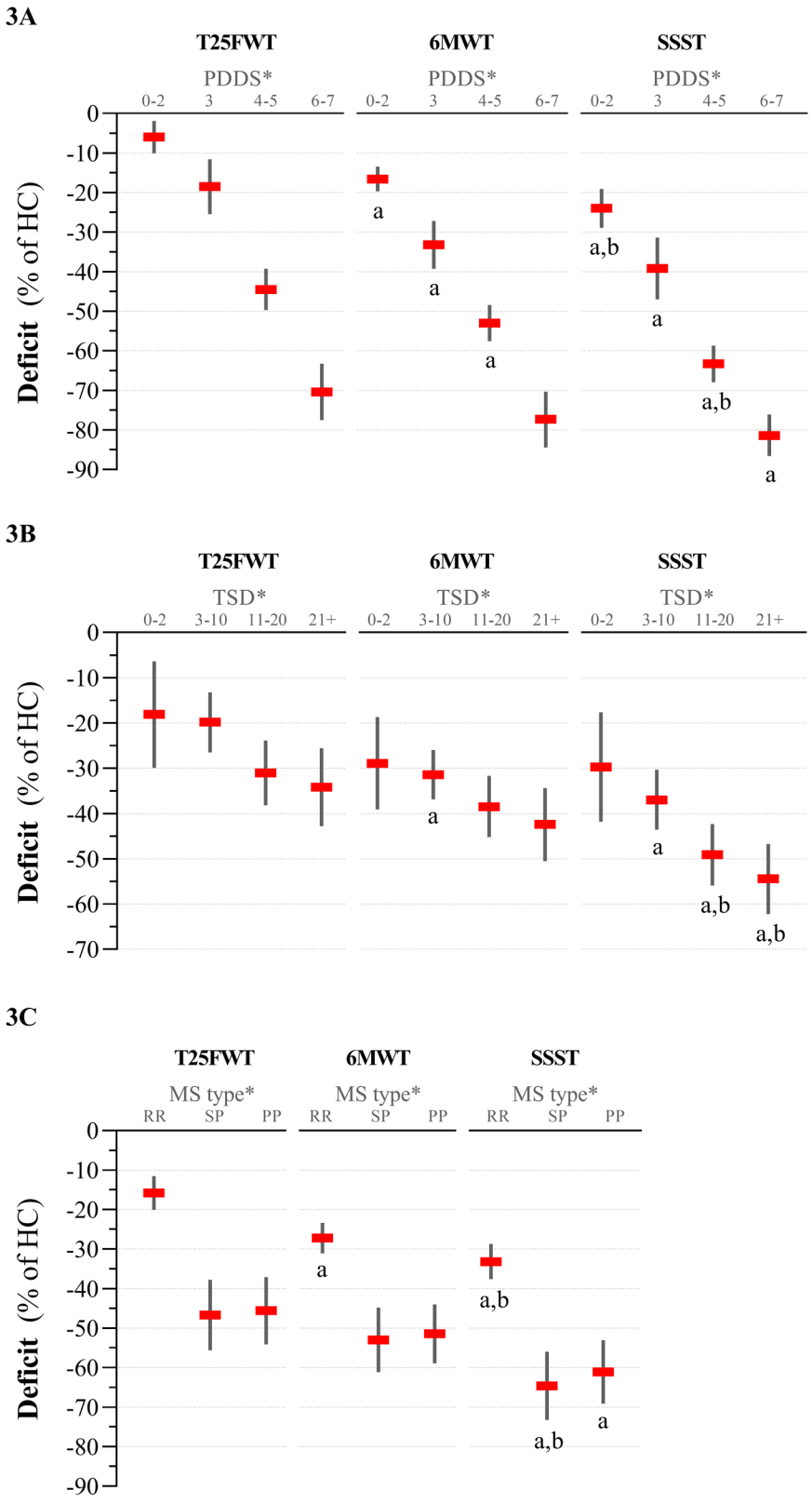

Figure 3. Differences (deficit) in T25FWT, 6MWT and SSST between MS patients and HC across subgroups (PDDS, 3A, TSD, 3B, and MS type, 3C). *a* = statistical difference from T25FWT ($p < 0.05$), *b* = statistical difference from 6MWT ($p < 0.05$). HC: healthy controls; 6MWT: six minute-walk-test; SSST: six-spot-step-test; T25FWT: timed 25-foot walk test; MS: multiple sclerosis; PDDS: patient-determined disease step; TSD: time since diagnosis.

responsiveness) and the interrelations between these frequently used walking capacity outcomes in order to guide clinicians in their use.

Notably, our study found substantial deficits even in mildly impaired pwMS ($PDDS_{0–2}$) who did not report having walking disabilities. To emphasise this further, in pwMS having PDDS = 0 ($n = 23$ pwMS; categorised as having normal physical function) deficits corresponded to −5 [−14; 3]% ($p < 0.05$) in T25FWT, −14 [−21; −8] % ($p < 0.05$) in 6MWT and −23 [−35; −1]% ($p < 0.05$) in SSST (data not shown). Substantial deficits were also found in those pwMS who had had the disease for 0–2 yr. These observations are in overall agreement with the review from Thrue et al.,[30] reporting deficits of 14% in walking capacity (pooled data across different outcomes) in pwMS early into their disease (mean disease duration < 5 y), stressing that 'time matters in MS'. Our study adds more evidence to this discussion, since non- to mildly impaired pwMS showed pronounced deficits across outcome measures, also emphasising the need for regular screening programs and interventions (e.g., physical rehabilitation/exercise) as previously suggested.[30]

Since walking capacity and disease severity are closely related, PDDS (which is based on self-perceived walking ability and the need for assistive devices) was, as expected, the main factor explaining walking deficits across all three outcome measures. MS type and TSD were also shown to independently explain walking deficits, yet to a much lesser extent than PDDS. This might be explained by the heterogeneous nature of MS characterised by a highly individual disease course recognised by the unique dissemination in space and time.[15]

Study limitations

The study has some limitations. First, only patients admitted to Danish MS Hospitals were recruited, which may have affected the generalisability of the study findings. Indeed, this population of patients were all in need of rehabilitation at the time of recruitment and therefore may be characterised by more pronounced walking impairments than the average population of pwMS. However, patients are often referred to the Danish MS Hospitals for reasons other than mobility issues (e.g., energy management or cognitive issues). In addition, the study population represented the adult lifespan and most disease severity levels: From early diagnosed patients to advanced MS, including all MS types, suggesting that the sample might not be that different from the general MS population. Second, the deficits found in this study may not reflect actual walking impairments in pwMS, as it was not based on clinical thresholds of walking capacity impairments but rather expressed as the absolute percentage difference in pwMS as compared to published normative reference data. Future studies establishing well-founded clinical thresholds are nevertheless warranted. Third, deficits were calculated based on published normative reference data from different studies (i.e., across different reference populations and countries). It is thus likely that some differences (basic participant characteristics, cultures, etc.) 'contaminated' our deficit calculations. It would have been more ideal, if our reference data could have been extracted from the Danish background population; however, published study data with large numbers of representatives on these three walking capacity outcomes do not exist.

Clinical perspectives

Importantly, all three walking capacity outcomes were strongly associated with walking ability, supporting the idea that objectively assessed walking capacity is of importance to pwMS. Based on our findings, clinicians and researchers should ideally evaluate walking capacity in pwMS comprehensively, i.e., by applying a battery of tests that capture different dimensions of walking impairments. Further, the SSST offers a sensitive option when aiming to capture walking deficits, especially at the very early stages of MS. Moreover, the SSST is simple, performs efficiently, and does not require much space, adding further relevance to its use in daily clinical practice.

Conclusion

PwMS performed worse than HC across three common walking capacity outcomes (i.e.,T25FWT, 6MWT, SSST) reflecting different dimensions of walking (i.e., walking speed, walking endurance, as well as walking coordination and balance). The results showed that the SSST was superior to short- and long-distance walk tests (6MWT and T25FWT) in detecting walking capacity impairments in pwMS. While all three walking capacity outcomes were able to capture walking impairments, the SSST showed the most pronounced deficits.

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Supplemental material

Supplemental material for this article is available online.

References

1. Reich DS, Lucchinetti CF and Calabresi PA. Multiple sclerosis. *N Engl J Med* 2018; 378: 169–180. DOI: 10.1056/NEJMra1401483.
2. Green R, Cutter G, Friendly M, et al. Which symptoms contribute the most to patients' perception of health in multiple sclerosis? *Mult Scler J Exp Transl Clin* 2017; 3: 2055217317728301. 20170905. DOI: 10.1177/2055217317728301.
3. Heesen C, Haase R, Melzig S, et al. Perceptions on the value of bodily functions in multiple sclerosis. *Acta Neurol Scand* 2018; 137: 356–362. 20171203. DOI: 10.1111/ane.12881.
4. Goodman AD, Brown TR, Krupp LB, et al. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *Lancet* 2009; 373: 732–738. DOI: 10.1016/s0140-6736(09)60442-6.
5. Jensen HB, Nielsen JL, Ravnborg M, et al. Effect of slow release-fampridine on muscle strength, rate of force development, functional capacity and cognitive function in an enriched population of MS patients. A randomized, double blind, placebo controlled study. *Mult Scler Relat Disord* 2016; 10: 137–144. 20160914. DOI: 10.1016/j.msard.2016.07.019.
6. 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: 31–36. DOI: 10.1212/wnl.60.1.31.
7. Santisteban L, Teremetz M, Irazusta J, et al. Outcome measures used in trials on gait rehabilitation in multiple sclerosis: a systematic literature review. *PLoS One* 2021; 16: e0257809. 20210930. DOI: 10.1371/journal.pone.0257809.
8. Rudick RA, Cutter G and Reingold S. The multiple sclerosis functional composite: a new clinical outcome measure for multiple sderosis trials. *Mult Scler* 2002; 8: 359–365. DOI: 10.1191/1352458502ms845oa.
9. Goldman MD, Marrie RA and Cohen JA. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. *Mult Scler* 2008; 14: 383–390. 20071017. DOI: 10.1177/1352458507082607.
10. Gijbels D, Eijnde BO and Feys P. Comparison of the 2- and 6-minute walk test in multiple sclerosis. *Mult Scler* 2011; 17: 1269–1272. 20110603. DOI: 10.1177/1352458511408475.
11. Feys P, Bibby B, Romberg A, et al. Within-day variability on short and long walking tests in persons with multiple sclerosis. *J Neurol Sci* 2014; 338: 183–187. 20140109. DOI: 10.1016/j.jns.2014.01.001.
12. 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. 20110927. DOI: 10.1177/1352458511420598.
13. Nieuwenhuis MM, Van Tongeren H, Sørensen PS, et al. The six spot step test: a new measurement for walking ability in multiple sclerosis. *Mult Scler* 2006; 12: 495–500. DOI: 10.1191/1352458506ms1293oa.
14. Boesen F, Nørgaard M, Skjerbæk AG, et al. Can inpatient multidisciplinary rehabilitation improve health-related quality of life in MS patients on the long term – The Danish MS Hospitals Rehabilitation Study. *Mult Scler* 2020; 26: 1953–1957. 20191105. DOI: 10.1177/1352458519884244.
15. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17: 162–173. 20171221. DOI: 10.1016/s1474-4422(17)30470-2.
16. 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: 20130425. DOI: 10.1186/1471-2377-13-37.
17. Hvid LG, Feys P, Baert I, et al. Accelerated trajectories of walking capacity across the adult life span in persons with multiple sclerosis: an underrecognized challenge. *Neurorehabil Neural Repair* 2020; 34: 360–369. 20200304. DOI: 10.1177/1545968320907074.
18. Bohannon RW. Comfortable and maximum walking speed of adults aged 20–79 yrs: reference values and determinants. *Age Ageing* 1997; 26: 15–19. DOI: 10.1093/ageing/26.1.15.
19. Bohannon RW and Wang YC. Four-meter gait speed: normative values and reliability determined for adults participating in the NIH Toolbox Study. *Arch Phys Med Rehabil* 2019; 100: 509–513. 20180806. DOI: 10.1016/j.apmr.2018.06.031.
20. Tveter AT, Dagfinrud H, Moseng T, et al. Health-related physical fitness measures: reference

values and reference equations for use in clinical practice. *Arch Phys Med Rehabil* 2014; 95: 1366–1373. 20140305. DOI: 10.1016/j.apmr.2014.02.016.
21. McKay MJ, Baldwin JN, Ferreira P, et al. Reference values for developing responsive functional outcome measures across the lifespan. *Neurology* 2017; 88: 1512–1519. 20170322. DOI: 10.1212/wnl.0000000000003847.
22. Brincks J and Callesen J. A study of the discriminative properties of the six-spot step test in older adults at risk of falling and those not at risk. *Physiother Theory Pract* 2023; 39(12): 2715–2722. DOI: 10.1080/09593985.2022.2094844.
23. Sieljacks PS, Søberg CA, Michelsen AS, et al. Lower extremity muscle strength across the adult lifespan in multiple sclerosis: implications for walking and stair climbing capacity. *Exp Gerontol* 2020; 139: 20200724. DOI: 10.1016/j.exger.2020.111025.
24. Riemenschneider M, Hvid LG, Ringgaard S, et al. Study protocol: randomised controlled trial evaluating exercise therapy as a supplemental treatment strategy in early multiple sclerosis: the Early Multiple Sclerosis Exercise Study (EMSES). *BMJ Open* 2021; 11: e043699. 20210112. DOI: 10.1136/bmjopen-2020-043699.
25. Sandroff BM, Motl RW, Sosnoff JJ, et al. Further validation of the six-spot step test as a measure of ambulation in multiple sclerosis. *Gait Posture* 2015; 41: 222–227. 20141023. DOI: 10.1016/j.gaitpost.2014.10.011.
26. Fritz NE, Jiang A, Keller J, et al. Utility of the six-spot step test as a measure of walking performance in ambulatory individuals with multiple sclerosis. *Arch Phys Med Rehabil* 2016; 97: 507–512. 20151111. DOI: 10.1016/j.apmr.2015.10.100.
27. Callesen J, Richter C, Kristensen C, et al. Test-retest agreement and reliability of the six spot step test in persons with multiple sclerosis. *Mult Scler* 2019; 25: 286–294. 20171220. DOI: 10.1177/1352458517745725.
28. Pommerich UM, Brincks J, Skjerbæk AG, et al. The subjective minimal important change for the six spot step test in people with multiple sclerosis – The Danish MS Hospitals Rehabilitation Study. *Acta Neurol Belg* 2022; 122: 893–901. 20220615. DOI: 10.1007/s13760-022-01991-4.
29. Jensen H, Ravnborg M, Mamoei S, et al. Changes in cognition, arm function and lower body function after slow-release fampridine treatment. *Mult Scler* 2014; 20: 1872–1880. 20140522. DOI: 10.1177/1352458514533844.
30. Thrue C, Riemenschneider M, Hvid LG, et al. Time matters: early-phase multiple sclerosis is accompanied by considerable impairments across multiple domains. *Mult Scler* 2021; 27: 1477–1485. 20200702. DOI: 10.1177/1352458520936231.