

Personalised inpatient multidisciplinary rehabilitation elicits clinically relevant improvements in physical function in patients with multiple sclerosis – The Danish MS Hospitals Rehabilitation Study

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Abstract

Purpose: Evidence of the effects of inpatient multidisciplinary rehabilitation (MDR) on physical function in patients with multiple sclerosis (MS) is limited, particularly whether clinically relevant improvements can be achieved. The aim of this study, therefore, was to investigate the effects of personalised inpatient MDR on the physical function of MS patients.

Methods: Embedded in the Danish MS Hospitals Rehabilitation Study, a pragmatic study was performed in MS patients undergoing four weeks of inpatient MDR specifically targeting physical function. Outcomes were assessed at baseline ($n = 142$), at discharge ($n = 137$) and at six months follow-up ($n = 126$) using the six-minute walk test (6MWT), six-spot step test (SSST), five times sit to stand test (5STS), nine-hole peg test (NHPT), dynamic gait index (DGI) and 12-item MS walking scale (MSWS).

Results: From Baseline-to-Discharge, significant and clinically relevant improvements were found in all measures of walking capacity (6MWT, SSST, 5STS, DGI and MSWS; $p < 0.05$) along with significant (but not clinically relevant) improvements in upper extremity function (NHPT; $p < 0.05$). Whilst comparable improvements were observed within subgroups of MS phenotype (relapsing-remitting [RR] vs. secondary + primary progressive [SP + PP]), disease severity (moderate [EDSS_{2.5–5.5}] vs. severe [EDSS_{6.0–7.5}]) and age (young/middle-aged [Age_{24–59}] vs. old [Age_{60–65}]), an attenuated adaptation was nevertheless observed for 6MWT in the most affected and vulnerable subgroups (i.e. SP + PP, EDSS_{6.0–7.5} and Age_{60–65}). The significant improvements in walking capacity and upper extremity function persisted at six months follow-up but did not exceed anymore the thresholds regarded as clinically relevant.

Conclusion: The results provide novel evidence that personalised inpatient MDR targeting physical function in MS patients elicits significant and clinically relevant improvements in physical function.

Keywords: Multiple sclerosis, physical functional performance, rehabilitation

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory degenerative autoimmune disease of the central nervous system that is notably heterogeneous in clinical progression and symptomatic presentation.¹

These symptoms include a variety of impairments in physical function, which appear to be particularly predominant in the lower extremities.² As a result, walking impairments in MS patients are often reported in objective short, long and complex

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walking tests, as well as in subjective walking measures, such as the MS walking scale (MSWS).^{3–5} Moreover, walking capacity is regarded by MS patients as one of the most important bodily functions of relevance to quality of life.^{6,7}

The treatment of MS aims not only to slow the progression of the disease (e.g. by minimising the number and severity of relapses and reducing the extent of neurodegeneration)⁸ but also to relieve and manage symptoms. To achieve this, the treatment of MS commonly consists of a combination of disease-modifying drugs and multidisciplinary rehabilitation (MDR), defined as a coordinated intervention delivered by a team of health care personnel across different professions/occupations.⁹ Regarding physical function, one of the primary objectives of MDR in MS patients is to maintain or even improve current levels of physical function.

MS rehabilitation interventions are studied in both isolated experimental and pragmatic real-world settings. Whilst isolated experimental interventions (e.g. exercise therapy) have shown very positive results in terms of counteracting MS symptoms and physical impairments,¹⁰ pragmatic real-world MDR studies evaluating more complex interventions are fewer and show more divergent results, with both positive and neutral findings being reported.^{11–14} The evidence provided by these pragmatic real-world MDR studies is generally limited by their small sample sizes along with highly divergent and less well-described interventions. Moreover, few of these MDR studies have specifically focused on improving physical function, they rarely have a long-term (\geq six months) follow-up period, and none of them have put their findings into the context of clinical cut points (i.e. whether the interventions elicited clinically relevant improvements).

Our group carried out a four-week inpatient MDR study that includes a six-month follow-up period (the Danish MS Hospitals Rehabilitation Study), and it found improvements in health-related quality of life (HRQoL) in a large representative population of MS patients.^{15,16} The present study is conducted as a supplementary analysis to investigate how physical function was affected in a subset of these MS patients. The primary aim was to evaluate the effects of personalised inpatient MDR, specifically targeting physical function in MS patients at discharge and at six months follow-up. A secondary aim was to evaluate the effects of MDR in subgroups of MS phenotype, disease severity and age.

Methods

This pragmatic longitudinal cohort study was part of the Danish MS Hospitals Rehabilitation Study ($n = 427$), with the overall aim of improving the functioning and daily living of all MS patients, including mastery of and coping with the disease (primary study outcome: HRQoL) (for further details, see Refs.^{15,16}). The four-week inpatient MDR programme with 20 days of scheduled rehabilitation (weekdays only) was individually tailored, with all MS patients being assigned to one of five focus areas (resilience, cognitive function, energy, physical function and personal needs) at admission on the basis of their current disease state and specific goal(s), under guidance and support from the case manager handling the patient. In addition to the personalised rehabilitation support by a case manager, a team of MS specialists (i.e. neurologists, neuropsychologists, clinical psychologists, social workers, occupational therapists, physiotherapists, nutritional therapists, dietitians and nurses) helped facilitate the inpatient MDR programme.

The present study included $n = 142$ MS patients from the original study population who completed the four-week inpatient MDR programme specifically aiming to improve physical function (one of the five focus areas). Assessments of physical function were carried out at baseline, discharge and at six months follow-up (from the baseline). Subgroups were established based on MS phenotype (relapsing-remitting: RR; secondary and primary progressive: SP + PP), disease severity (based on the expanded disability status scale (EDSS) score; moderate: EDSS_{2.5–5.5}; severe: EDSS_{6.0–7.5}) and age (young/middle-aged: Age_{24–59} years; old: Age_{60–65} years). These disease characteristics, which also included whether MS patients received disease-modifying drug treatment (DMT) at study enrolment, were extracted from medical records. All participants gave their written informed consent prior to participation. The ethics committee of Region Midtjylland (M-20110178) approved the study in accordance with the Helsinki Declaration, and it was registered at www.controlled-trials.com (ISRCTN05245917).

Assessment of physical function

Physical function was assessed using objective and subjective measurements. The objective measurements included the six-minute walk test (6MWT) to evaluate walking endurance,¹⁷ the six-spot step test (SSST) to evaluate coordination and dynamic balance during walking,¹⁸ the five times sit to

stand test (5STS) to evaluate the muscle function of the lower extremities (of relevance to walking),¹⁹ and the nine-hole peg test (NHPT) to evaluate the patient's manual dexterity.²⁰ The subjective measurements included the 12-item multiple sclerosis walking scale (MSWS) which is the patient's rating of the impact of MS on walking ability,²¹ and the dynamic gait index (DGI), which is the therapist's rating of dynamic balance whilst walking.²²

Content of personalised multidisciplinary rehabilitation (MDR)

For MS patients choosing physical function as their focus area, the following MDR services were offered (differentiated according to personal goals): physiotherapy and occupational therapy (individual and group based), inter-disciplinary classes, nursing, coaching, psychotherapy, educational programmes, conversations with a caregiver, teaching, supervision and counselling. In addition to these supervised planned/structured MDR services, all MS patients were instructed to perform goal-oriented semi-supervised self-training. The exact content of the self-training activities was decided in agreement with the case manager and recorded (in minutes) by the patient and subsequently validated by the case manager. The physical aspects of the MDR included basic exercise modalities, such as mobility training, gait training, balance training, aerobic training, resistance training, motor therapy/training of the arms/hands and hippotherapy, supported by educational activities with a focus on a healthy lifestyle. An individually composed and reconciled programme with an overall functional purpose in areas meaningful to each patient was also applied. Specifically, functional and task-specific training was performed in surroundings similar to the patient's own home environment, with an emphasis on strategies to complete activities safely and successfully, e.g. mastering transfer strategies using relevant aids, carrying groceries up/down the stairs or riding a bike. Furthermore, motor automaticity was stimulated using dual task activities to lower the brain-cost, i.e. walking and standing whilst performing a secondary demanding task, such as playing with a balloon, dribbling a ball, reciting tables and playing word games. The total volume of the physical aspects of the MDR with/without self-training is presented as minutes per day calculated from the total number of minutes divided by the entire MDR inpatient stay in days.

Statistics

All statistical analyses were performed using Stata version 14.2 (StataCorp LP, Texas, USA). Data were tested for normal distribution, and, if missing, appropriate transformations were carried out (6MWT: no transform, DGI: no transform, MSWS: no transform, SSST: log transform, STS5: log transform, NHPT: inverse transform). For all outcomes, an intention-to-treat linear mixed effects model was conducted to compare the differences between all available data at each time point (missing values were thus taken into account) and to compare the calculated change values between time points (requiring *intact* matched data across time points). Participant ID was set as a random effect, and the outcome (demographic as well as physical function) was set as a fixed effect. The data in the tables are presented as a mean [95% confidence interval (CI)]; normally distributed) or median [interquartile range (IQR); non-normally distributed). The data in the figures are presented as a mean [95%CI] (normally distributed). It is noted that because of the statistical approach, the data presented in Table 2 (i.e. mean values at each time point) may differ slightly from those in Figure 1(a) and (b) (i.e. mean change values between time points). Potential associations between adaptations in *pure* walking capacity outcomes (i.e. 6MWT, DGI, MSWS and SSST) were tested using Pearson's correlation analysis. Furthermore, potential associations (i.e. dose-response) between the total volume of the physical aspects of the MDR (minutes per day) and adaptations in physical function were tested using Pearson's correlation analysis. Statistical significance was set at $p < 0.05$.

We also evaluated our outcomes in relation to established clinical cut points, i.e. whether the personalised MDR elicited individual clinically relevant improvements. The cut points used based on the perspectives of the MS patients were as follows: 6MWT = 21.6 m (minimal important change),²³ MSWS = -10.4 (minimal important change),²³ 5STS = -2.03 s (minimal important change),²⁴ DGI = 1.36 (minimal important change),²⁴ NHPT = -24% (i.e. not an absolute value in s) as an average of the dominant and non-dominant hand (minimal detectable change)²⁵ and SSST = -1.4 s (minimal important change) (non-published data established by Uwe Pommerich; acceptance from data owners: Danish MS Hospitals, including co-authors AGS, MN and FB). Based on the listed cut points, the MS patients were classified into the categories of improvers (positive changes at or beyond cut point values), maintainers (changes not

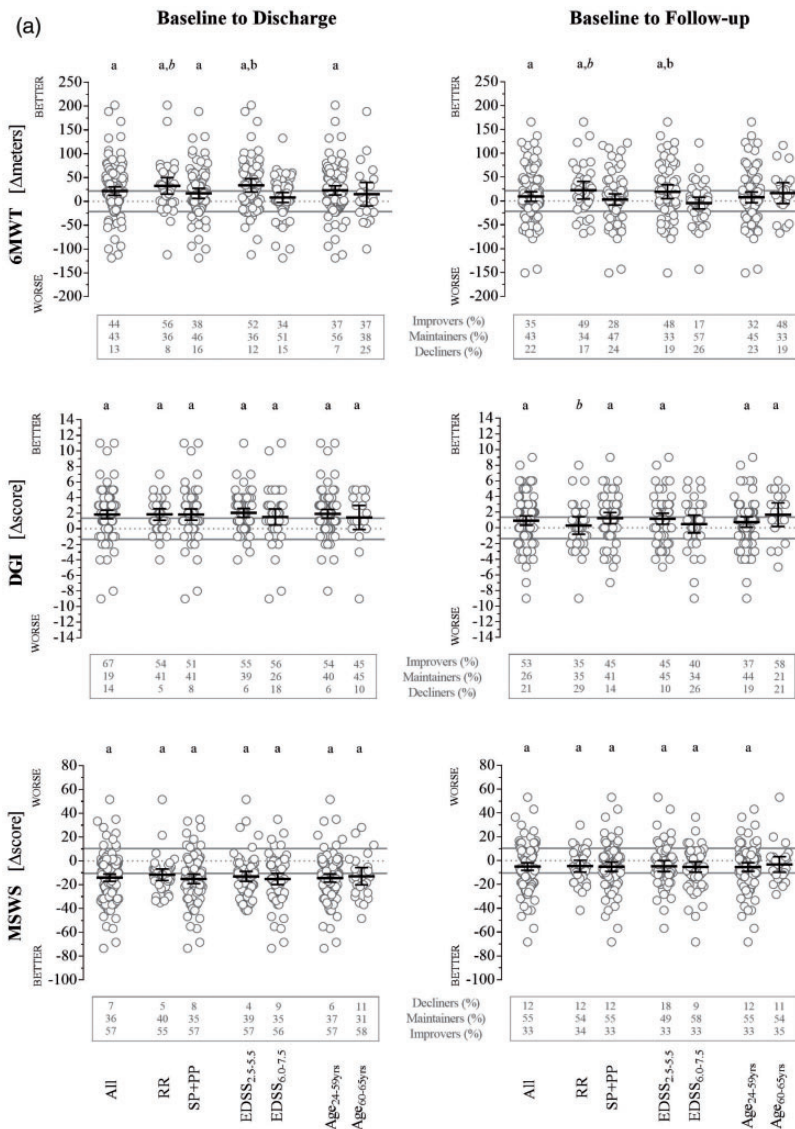


Figure 1. (a) Effects of four-week personalized inpatient MDR from baseline to discharge (left graphs) and from baseline to six months follow-up (right graphs) on 6MWT (change in meters), DGI (change in score) and MSWS (change in score). Data are shown for all MS patients and for the different subgroups and are displayed as individual values along with mean \pm 95% CI. Grey horizontal lines denote established clinical cut points (6MWT \pm 21.6 m, DGI \pm 1.36 points, MSWS \pm 10.4 points), i.e. whether the personalized MDR elicited clinically relevant improvements. Based on these established cut points, the proportion of improvers (positive changes at or beyond cut point values), maintainers (changes not reaching cut point values) and decliners (negative changes at or beyond cut point values) are also displayed. For exact values at baseline, discharge and follow-up, see Table 3. The level of statistical significance was set at $p < 0.05$; a: different from baseline ($p < 0.05$), b: Baseline-to-Discharge or Baseline-to-Follow-up change different from the other subgroup (i.e. SP+PP vs. RR, EDSS_{6.0-7.5} vs. EDSS_{2.5-5.5}, Age_{60-65yrs} vs. Age₂₄₋₅₉). MS: multiple sclerosis, RR: relapsing-remitting, SP: secondary progressive, PP: primary progressive, EDSS: expanded disability status scale. 6MWT: six-minute walk test, DGI: dynamic gait index, MSWS: 12-item MS walking scale. (b) Effects of four-week personalized inpatient MDR from baseline to discharge (left graphs) and from baseline to six months follow-up (right graphs) on SSST (change in seconds), 5STS (change in seconds) and NHPT (relative change in percentage). Data are shown for all MS patients and the different subgroups and are displayed as individual values along with median \pm IQR. Grey horizontal lines denote established clinical cut points (SSST \pm 1.4 s, 5STS \pm -2.03 s, NHPT \pm 24%), i.e. whether the personalized MDR elicited clinically relevant improvements. Based on these established cut points, the proportion of improvers (positive changes at or beyond cut point values), maintainers (changes not reaching cut point values) and decliners (negative changes at or beyond cut point values) are also displayed. For exact values at baseline, discharge and follow-up, see Table 3. The level of statistical significance was set at $p < 0.05$; a: different from baseline ($p < 0.05$), b: Baseline-to-Discharge or Baseline-to-Follow-up change different from the other subgroup (i.e. SP + PP vs. RR, EDSS_{6.0-7.5} vs. EDSS_{2.5-5.5}, Age₆₀₋₆₅ vs. Age₂₄₋₅₉). MS: multiple sclerosis, RR: relapsing-remitting, SP: secondary progressive, PP: primary progressive, EDSS: expanded disability status scale. SSST: six-spot step test, 5STS: five times sit to stand, NHPT: nine-hole peg test.

reaching cut point values) or decliners (negative changes at or beyond cut point values).

Results

A total of n = 142 MS patients participated in the study and completed baseline testing, n = 137 completed discharge testing (n = 5 dropped out or failed to participate in the assessment of physical function at discharge) and n = 126 completed testing at six months follow-up (n = 11 dropped out or failed to participate in the assessment of physical function at follow-up). The number of days they received personalised inpatient MDR was 18.9 [18.5:19.3] (mean [95%CI]) days. The demographic characteristics of the participants are shown in Table 1.

Almost any combinations of overlap were observed between MS patients belonging to the different subgroups (MS phenotype, disease severity, age) (Table 2), although those being RR were rarely also EDSS_{6.0-7.5} (for both Age₂₄₋₅₉ and Age₆₀₋₆₅) or rarely also EDSS_{2.5-5.5} and Age₆₀₋₆₅.

Adaptations in physical function

All data (absolute values) at baseline, discharge and six months follow-up are presented in Table 3, with the data on the changes from Baseline-to-Discharge and from Baseline-to-Follow-up presented in Figure 1. Within-group improvements (p < 0.05) were observed for all outcomes in the entire study population at discharge and at six months follow-up. Weak to moderate associations were observed

Table 1. MS patients’ characteristics.

	Age (years) Mean [95%CI]	MS type (RR/SP/PP) Numbers [%]	EDSS (score 0–10) Median [IQR]	Diagnosis (years) Mean [95%CI]	DMT (yes/no) Numbers [%]
All n = 142, 66% females	52.0 [60.6:53.4]	41/76/25 [29/54/18]	6.0 [4.0:6.5]	12.1 [10.6:13.5]	66/76 [46/54]
RR n = 41, 73% females	46.8 [43.8:49.7]	41 [100]	4.5 [4.0:6.0]	8.2 [6.3:10.1]	34/7 [83/17]
SP+PP n = 101, 63% females	54.2 [52.8:55.6]	c 76/25 [75/25]	c 6.0 [4.0:6.5]	c 13.6 [11.8:15.5]	c 32/69 [32/68]
EDSS _{2.5-5.5} n = 70, 63% females	51.4 [49.3:53.6]	29/31/10 [42/44/14]	4.0 [3.5:5.0]	11.5 [9.1:13.9]	34/36 [49/51]
EDSS _{6.0-7.5} n = 72, 69% females	52.6 [50.7:54.5]	12/45/15 [17/62/21]	c 6.5 [6.0:6.5]	c 12.6 [10.8:14.4]	32/40 [44/56]
Age ₂₄₋₅₉ n = 115, 67% females	49.7 [48.3:51.1]	40/62/13 [35/54/11]	5.5 [4.0:6.5]	11.3 [9.8:12.8]	62/53 [54/46]
Age ₆₀₋₆₅ n = 27, 63% females	62.0 [61.4:62.5]	c 1/14/12 [4/52/44]	c 6.0 [5.0:6.5]	15.3 [10.8:19.8]	c 4/23 [15/85]

Level of statistical significance set at p < 0.05; c: different from the other subgroups (i.e. SP+PP vs. RR, EDSS_{6.0-7.5} vs. EDSS_{2.5-5.5}, Age₆₀₋₆₅ vs. Age₂₄₋₅₉).

MS: multiple sclerosis, RR: relapsing–remitting, SP: secondary progressive, PP: primary progressive, EDSS: expanded disability status scale. DMT: disease-modifying drug treatment.

Table 2. Combinations of subgroups overlap.

Overlapping MS patient subgroups	RR EDSS _{2.5-5.5} Age ₂₄₋₅₉	RR EDSS _{6.0-7.5} Age ₂₄₋₅₉	RR EDSS _{2.5-5.5} Age ₆₀₋₆₅	RR EDSS _{6.0-7.5} Age ₆₀₋₆₅	SP + PP EDSS _{2.5-5.5} Age ₂₄₋₅₉	SP + PP EDSS _{6.0-7.5} Age ₂₄₋₅₉	SP + PP EDSS _{2.5-5.5} Age ₆₀₋₆₅	SP + PP EDSS _{6.0-7.5} Age ₆₀₋₆₅
Numbers	n = 22	n = 11	n = 7	n = 1	n = 20	n = 30	n = 21	n = 30
[% of total sample n = 142]	[15.5%]	[7.7%]	[4.9%]	[0.7%]	[14.1%]	[21.1%]	[14.8%]	[21.1%]

Table 3. Effects of personalized MDR on physical function.

	6MWT (m)		DGI (score 0-24)		MSWS (score 0-100)		SSST (s)		5STS (s)		9HPT (s)	
	Mean	[95%CI]	Mean	[95%CI]	Mean	[95%CI]	Median	[IQR]	Median	[IQR]	Median	[IQR]
All	n = 142	247 [220:273]	14.9 [14.2:15.7]	74.6 [71.5:77.7]	14.9 [10.6:24.5]	14.8 [11.8:20.6]	28.8 [24.0:36.8]					
	n = 137	260 [231:290]	a 16.8 [16.0:17.6]	a 60.4 [57.1:63.4]	a 13.7 [9.5:23.2]	a 13.0 [9.7:17.5]	a 26.5 [21.4:33.8]					
	n = 126	258 [226:290]	a 15.9 [15.0:16.8]	a 68.2 [64.3:72.0]	a 14.8 [10.1:22.3]	a 13.3 [10.0:18.0]	a 26.7 [22.3:34.3]					
RR	n = 41	296 [244:348]	16.3 [15.1:17.5]	69.7 [63.4:76.0]	12.0 [8.1:20.6]	13.8 [11.8:17.9]	25.8 [23.2:30.8]					
	n = 41	322 [264:381]	a,b 18.2 [16.8:19.5]	a 58.3 [52.0:64.8]	a 11.3 [6.6:18.2]	a 12.9 [8.6:15.4]	a 23.6 [20.6:28.1]					
	n = 37	324 [260:388]	a,b 16.4 [14.6:18.2]	b 61.8 [54.9:68.6]	a 10.7 [6.9:20.7]	a 11.7 [8.8:14.5]	a 22.7 [20.3:27.1]					
SP + PP	n = 101	224 [193:255]	c 14.3 [13.4:15.2]	c 76.5 [73.0:80.0]	c 15.8 [11.3:27.2]	c 15.6 [12.0:22.6]	c 30.8 [24.6:39.6]					
	n = 96	234 [202:267]	a 16.2 [15.2:17.1]	a 61.3 [57.3:65.3]	a 14.3 [9.9:25.8]	a 13.2 [9.9:18.4]	a 28.3 [22.5:35.5]					
	n = 89	229 [193:266]	a 15.6 [14.5:16.7]	a 70.8 [66.2:75.3]	a 16.2 [10.9:25.6]	a 14.0 [10.6:19.9]	a 30.0 [23.6:35.7]					
EDSS _{2.5-5.5}	n = 70	359 [330:388]	16.9 [16.1:17.6]	65.1 [60.8:69.5]	c 11.2 [8.4:13.9]	12.4 [10.3:14.8]	25.3 [21.5:30.3]					
	n = 69	390 [358:421]	a,b 18.9 [18.1:19.8]	a 52.5 [48.3:56.7]	a 9.8 [7.1:12.5]	a 9.9 [8.5:12.4]	a 22.8 [20.2:27.8]					
	n = 64	382 [348:416]	a,b 18.2 [17.2:19.2]	a 58.8 [54.1:63.6]	a 10.5 [7.7:12.6]	a 10.3 [8.4:12.5]	a,b 22.8 [20.7:26.6]					
EDSS _{6.0-7.5}	n = 72	121 [102:141]	c 12.1 [11.2:13.0]	c 83.6 [80.4:86.8]	c 24.5 [18.6:34.8]	c 20.2 [14.7:28.0]	c 32.8 [27.2:47.1]					
	n = 68	127 [107:146]	a 13.7 [12.8:14.5]	a 68.5 [63.9:73.1]	a 24.6 [17.3:32.8]	a 16.9 [13.4:22.1]	a 30.5 [26.2:40.0]					
	n = 62	111 [89:133]	12.2 [11.1:13.3]	78.0 [72.9:83.1]	a 25.7 [19.1:46.7]	17.5 [13.7:24.4]	33.3 [27.1:46.1]					
Age ₂₄₋₅₉	n = 115	246 [216:276]	14.9 [14.1:15.7]	75.0 [71.6:78.3]	14.5 [10.4:24.3]	14.8 [11.6:21.0]	29.6 [24.4:38.4]					
	n = 111	261 [228:293]	a 16.9 [16.0:17.8]	a 60.7 [56.8:64.6]	a 13.7 [9.4:22.2]	a,b 13.1 [9.9:17.2]	a 26.8 [21.3:34.7]					
	n = 100	258 [221:295]	15.7 [14.6:16.7]	a 67.9 [63.6:72.3]	a 14.4 [10.0:22.8]	13.3 [10.0:17.9]	a 26.7 [22.0:34.5]					
Age ₆₀₋₆₅	n = 27	248 [182:314]	15.1 [13.2:17.0]	73.0 [64.8:81.1]	15.3 [10.8:27.2]	14.5 [12.0:20.5]	26.6 [22.3:34.0]					
	n = 26	259 [189:329]	16.4 [14.4:18.4]	a 59.4 [52.8:66.1]	a 14.2 [9.9:27.9]	a 11.4 [8.7:18.1]	a 24.8 [21.6:31.0]					
	n = 26	259 [188:330]	16.6 [14.7:18.4]	a 69.0 [60.3:77.8]	14.9 [10.7:19.6]	a 13.3 [10.1:18.9]	a 26.2 [22.6:33.8]					

Data that were not normally distributed were transformed prior to statistical analysis (SSST: log, STSS: log, NHPT: inverse) and presented as median±IQR. Normally distributed data (6MWT, DGI and MSWS) were presented as mean ± 95%CI. Statistical significance was set at p < 0.05; a: different from baseline (p < 0.05), b: Baseline-to-Discharge or Baseline-to-Follow-up change different from the other group (i.e. SP+PP vs. RR, EDSS_{6.0-7.5} vs. EDSS_{2.5-5.5}, Age₆₀₋₆₅ vs. Age₂₄₋₅₉), c: different from the other subgroup at baseline (i.e. SP + PP vs. RR, EDSS_{6.0-7.5} vs. EDSS_{2.5-5.5}, Age₆₀₋₆₅ vs. Age₂₄₋₅₉).

MS: multiple sclerosis, RR: relapsing-remitting, SP: secondary progressive, PP: primary progressive, EDSS: expanded disability status scale, 6MWT: six-minute walk test, SSST: six-spot step test, 5STS: five times sit to stand test, NHPT: nine-hole peg test, DGI: dynamic gait index, MSWS: 12-item MS walking scale.

between changes in *pure* walking capacity outcomes (i.e. 6MWT, DGI, MSWS and SSST) from Baseline-to-Discharge (range of numerical $r=0.20-0.34$, $p<0.05$; except for SSST and MSWS along with DGI and MSWS) and from Baseline-to-Follow-up (range of numerical $r=0.21-0.41$, $p<0.05$). When separated into subgroups of MS phenotype, disease severity and age, within-subgroup improvements ($p<0.05$) were also observed at discharge (except for 6MWT in EDSS_{6.0-7.5} and Age₆₀₋₆₅, which did not change) and at six months follow-up (with the most exceptions in EDSS_{6.0-7.5} and Age₆₀₋₆₅, which did not change). Some between-subgroup differences ($p<0.05$) were observed, most evident for 6MWT in RR vs. SP + PP and in EDSS_{2.5-5.5} vs. EDSS_{6.0-7.5} from Baseline-to-Follow-up) (Table 3, Figure 1).

In the entire study population, clinically relevant improvements from Baseline-to-Discharge were observed for 6MWT = 21.6 [12.5:30.7] m (mean [CI 95%]), DGI = 1.83 [1.30:2.36] (mean [CI 95%]), MSWS = -14.0 [-17.1:-10.9] (mean [CI95%]), SSST = -1.9 [-4.5:-0.2] and 5STS = -2.30 [-0.55:-30.60] s (median [IQR]) (Figure 1 (a) and (b), left graphs). For DGI, MSWS, SSST and 5STS, clinically relevant improvements were observed in all subgroups (i.e. RR and SP + PP, EDSS_{2.5-5.5} and EDSS_{6.0-7.5}, Age₂₄₋₅₉ and Age₆₀₋₆₅), but for 6MWT, they were observed only in the least affected subgroups (i.e. RR, EDSS_{2.5-5.5}, Age₂₄₋₅₉). This was accompanied by high proportions of improvers across all MS patients (ranging from 44% to 67%), least affected MS patients (i.e. RR, EDSS_{2.5-5.5}, Age₂₄₋₅₉; ranging from 37% to 64%) and most affected MS patients (i.e. SP + PP, EDSS_{6.0-7.5}, Age₆₀₋₆₅; ranging from 34% to 82%) for 6MWT, DGI, MSWS, SSST and 5STS (see Figure 1(a) and (b), left graphs), along with small proportions of decliners across all MS patients (ranging from 7% to 14%), least affected MS patients (ranging from 4% to 12%) and most affected MS patients (ranging from 4% to 25%) for 6MWT, DGI, MSWS, SSST and 5STS (see Figure 1(a) and (b), left graphs). Few clinically relevant improvements were observed from Baseline-to-Follow-up (see Figure 1(a) and (b), right graphs).

Dose-response between minutes of physical training and adaptations in physical function

Overall, the participants received 86 [80:91] minutes per day (mean [CI95%]) of supervised planned/structured physical training, and 130 [118:141] minutes per day of supervised planned/structured

physical training plus non-supervised self-training. Despite minor numerical differences, comparable minutes of physical training were observed between RR and SP + PP, EDSS_{2.5-5.5} and EDSS_{6.0-7.5}, as well as Age₂₄₋₅₉ and Age₆₀₋₆₅ (data not shown). More importantly, no associations (i.e. dose-response) were found between minutes of physical training and adaptations in physical function (range of $r=0.01-0.204$, non-significant).

Discussion

In a pragmatic real-world setting, four weeks of personalised inpatient MDR specifically targeting physical function in $n=142$ MS patients resulted in significant improvements in objective (6MWT, SSST, 5STS and NHPT) and subjective (DGI and MSWS) measures of physical function beyond the established clinical cut points (except for NHPT). These improvements were still significant at six months follow-up but were no longer beyond the established clinical cut points. In subgroups based on MS phenotype, disease severity and age, somewhat similar findings were observed. The main exceptions were subgroups EDSS_{6.0-7.5} and Age₆₀₋₆₅, which failed to improve in 6MWT during the four weeks of personalised inpatient MDR and generally failed to maintain MDR-induced improvements at follow-up.

The finding of the present study that four weeks of inpatient MDR improves MS patients' physical function are in overall agreement with the findings of previous studies. Specifically, in small explorative trials emphasising intensive physiotherapy, 6MWT outcomes have been shown to improve by 61.2m after three weeks of inpatient MDR,¹² and DGI has been shown to improve by 2.4 points after four weeks of inpatient MDR that focused on either strength training or dual task walking.¹¹ Our observation of a somewhat attenuated adaptation in NHPT following MDR (at least in comparison to the lower extremity physical function outcomes) is also supported by previous study findings, as both no improvements in NHPT¹² and minor improvements in NHPT (one hand only)²⁶ have been reported after three to four weeks of inpatient MDR.

A direct comparison of MDR-induced effects on physical function in the present study with the findings of the above-mentioned studies is, however, challenging because of methodological differences. First, the studies that examined the effect of MDR on physical function were likely not performed under identical settings as the present one. Second, the

studies most often included a small heterogeneous sample of MS patients, thereby limiting external validity. This also restricts the direct comparison of results and limits their applicability to specific subgroups of MS patients.^{11,12,26} Third, some studies were inconsistent in testing at discharge, with testing being performed days to weeks after the inpatient MDR stay. The results may therefore not reflect the effects of MDR directly, thus limiting comparability to the present study.^{12,26} Fourth, only one study carried out a follow-up assessment,²⁷ which limits our knowledge of the sustained effect of MDR. Moreover, those studies that did carry out a follow-up did so in a short period, which leaves the long-term effect (six \geq months) of MDR largely unknown.

As the associations observed between the changes (mostly improvements) in *pure* walking capacity outcomes (i.e. 6MWT, DGI, MSWS and SSST) were only weak to moderate, they support the notion that the different outcomes capture different aspects of walking impairments and limitations. It therefore seems advisable to use a battery of both objective and subjective (therapist reported + patient reported) walking capacity outcomes in clinical research studies, just as the present study did.

We also evaluated whether the MDR-induced effects on physical function differed between subgroups of MS phenotype, disease severity and age, with a specific interest in the more vulnerable patients (i.e. SP + PP, EDSS_{6.0-7.5} and Age₆₀₋₆₅). These three subgroups have reduced physical reserve capacity,^{5,28,29} which is likely driven by an advanced course of disability progression attributed to MS, along with low levels of physical activity.³⁰⁻³² We assumed that this could attenuate an (exercise- or) MDR-induced response. However, all subgroups appeared to achieve comparable MDR-induced effects on physical function, which is aligned with the fact that all received comparable volumes (i.e. minutes) of MDR without/with self-training. The only exception was 6MWT, revealing an attenuated adaptation in these vulnerable subgroups. Previous studies have shown that long-distance walk tests, such as 6MWT, in addition to capturing walking capacity alone, capture motor fatigability in patients with MS.^{29,33} Future studies should help elucidate whether vulnerable MS patient subgroups require specific exercise or MDR strategies to achieve improvements in 6MWT. One solution could involve adapted exercise training (e.g. body-weight-supported treadmill training), with a number of studies involving mobility-

limited pwMS reporting improvements in 6MWT.³⁴ Another explanation is that 6MWT may be a particularly sensitive outcome that is more closely related to the progression of MS capacity than the other outcomes, as previously indicated.^{5,28,29} Hence, these vulnerable subgroups may have experienced positive MDR-induced effects on 6MWT (partly indicated by the improved MSWS score along with the numerically greater proportion of improvers vs. decliners (37% and 25%, respectively)), i.e. seen as a 6MWT preservation versus a 6MWT reduction if no MDR had been provided. This interpretation is nevertheless not possible to verify, as there was no control group in the present study. Moreover, whilst reduction in walking capacity occurs over time (years) in pwMS and preferentially in vulnerable subgroups,^{35,36} it rarely becomes detectable within a time span of three to six months.³⁷ Future longitudinal (ranging from months to years) studies should help establish the trajectory of walking capacity across MS patient subgroups.

The statistically significant MDR-induced improvements in physical function observed in the present study and in previous ones are clearly important. However, increasingly more focus has been directed towards interventions that elicit clinically relevant improvements rather than purely statistically significant changes. Only a few studies have previously attempted to determine the clinical relevance of their findings. Salhofer-Polanyi and colleagues compared changes in 6MWT to clinically relevant deterioration and found an improvement of 61.2 m to be of clinical relevance.¹² Craig and colleagues evaluated the 36-item Short Form Survey questionnaire with regard to clinical cut points from a pilot study and found improvements in six subdomains to be of clinical relevance.¹³ Jonsdottir and colleagues used a somewhat arbitrary 15% improvement clinical cut point for 2MWT, showing that dual task training was more effective than strength training in eliciting clinically relevant improvements.¹¹ Taken together, all three studies reported some clinically relevant improvements amongst MS patients, although the basis of this was not well founded and therefore questionable. By contrast, the present study included clinically relevant improvement (change) cut points that were specific to each individual outcome; and whilst we did observe clinically relevant improvements for all outcomes (except for NHPT) following four weeks of inpatient MDR (alongside statistical significance and a very high proportion of improvers), this was no longer present at six months follow-up (except for some subgroups).

The latter is nevertheless contrasted by the numerically greater proportion of improvers vs. decliners observed in the entire study population and in all subgroups, corresponding to as much as a two- to fourfold increase. The divergence between the former and latter findings are obviously a challenge yet may stimulate further research into the optimisation of the long-term maintenance of MDR effects.

The choice of cut points to be used for investigating clinically relevant effects stems from three studies with different numbers of participants and expressions of clinically relevant improvements. In the studies by Baert and colleagues, this was based on 191²⁴ and 290 MS patients,²³ respectively, whereas Hervault and colleagues used a sample of 69 MS patients.²⁵ The non-published SSST data used a sample of 118 MS patients. This obviously raises the question of how large a sample should be, when clinically relevant improvements are being determined. Whilst much more research is needed to address such statistical issues, the studies by Baert and colleagues^{23,24} are so far the most robust and thus preferable with regard to generalisability and precision. Furthermore, no consensus exists on the calculation of clinically relevant improvements (the identified studies use minimal important changes and minimal detectable changes), and the expressions of clinically relevant improvements can be presented as relative or absolute changes. Both aspects affect the perception and interpretation of the results.³⁸ The use of relative vs. absolute changes appears particularly relevant in highly disabled MS patients, in which small absolute changes correspond to large relative (percentage) changes. In the present study, NHPT was the only outcome that used relative Baseline-to-Discharge changes to indicate clinically relevant improvements. Here, 90% of the patients did not reach the threshold of clinically relevant improvements in their performance, despite approximately 50% of the patients reaching the threshold of clinically relevant improvements in all other outcomes. We can only speculate whether this NHPT cut point is erroneous or whether the MDR of the present study was inefficient in eliciting changes in NHPT (either attributed to the few MS patients choosing this as a specific focus or the upper extremity function being overlooked).

This study has some limitations. First, no control group was included to enable comparisons with the MDR-induced effects on physical function. This is contrary to the study of Boesen and colleagues, which evaluated MDR-induced effects on quality

of life.¹⁵ This limits the study in excluding any learning effects and variations in test performance from having an influence on the results. Second, a highly detailed description of the intervention regarding the specific exercise/activity type and its intensity was not registered and reported in the present study, thereby limiting the identification of the true cause of the improvements observed. However, such a specific description of the intervention is difficult because of the personalised inpatient MDR approach. Third, there was a lack of blinding of the assessors, as they were all recruited from among the physical therapist staff employed at the Danish MS hospitals where the interventions were carried out. Fourth, nearly half of the involved MS patients received DMTs comprising a plethora of different drugs. Although this may have influenced the effects of the personalised MDR, we did not observe any interactions between the effects of the MDR and receiving vs. not receiving DMTs (data not shown).

In conclusion, the present study provides novel evidence supporting that personalised inpatient MDR targeting physical function elicits significant and clinically relevant improvements in numerous physical domains in patients with multiple sclerosis. This also applies to the most affected and vulnerable MS patients (i.e. those having progressive MS, high EDSS scores and an advanced age). Future randomised controlled trials with large sample sizes and a comprehensive test battery to assess physical function (along with other outcomes of interest) are needed to further our understanding of the effects of personalised MDR.

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Authors' contributions

M.N., A.G.S. and F.B. initiated, designed and conducted the study with support from P.V.R. and T.P.; M.K.S. and A.G.S. cleaned the data; L.G.H., T.G. and U.D. designed and undertook the statistical analysis; L.G.H., T.G. and A.G.S. wrote the manuscript; All the authors contributed to critically revising it.




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