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Response heterogeneity in fitness, mobility and cognition with exercise-training in MS

Brian M. Sandroff | **Jessica F. Baird** | **Stephanie L. Silveira** | **Robert W. Motl**

Department of Physical Therapy, University of Alabama at Birmingham, Birmingham, Alabama

Correspondence
Brian M. Sandroff, Department of Physical Therapy, University of Alabama at Birmingham, Birmingham, AL.
Email: sandroff@uab.edu

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Background: Exercise-training is a beneficial approach for improving function in persons with multiple sclerosis (MS). However, it is unlikely that every participant who engages in an exercise-training intervention will demonstrate similar benefits. Identifying factors that may influence the accrual of specific exercise-training benefits can aid in the development of optimized rehabilitation interventions for improving specific outcomes in MS.

Objective: This study described possible response heterogeneity in physical fitness, mobility and cognitive outcomes with exercise-training and identified baseline performance, compliance and demographic/clinical outcomes as possible predictors of exercise-related changes in those outcomes.

Methods: Thirty-two persons with MS-related mobility disability completed 6-months of multimodal exercise-training. Physical fitness, mobility and cognitive processing speed (CPS) were measured before and after the 6 months.

Results: There was response heterogeneity in fitness, mobility and cognitive outcomes with multimodal exercise-training. Low baseline aerobic fitness, slow walking speed and slow CPS were associated with greater exercise-related improvements in those respective outcomes.

Conclusions: Those with MS-related mobility disability who have the lowest aerobic fitness, walking speed and CPS might benefit the most from multimodal exercise-training. This provides critical evidence for informing the development of a precision medicine framework for improving targeted outcomes with exercise-training in MS.

KEYWORDS
cognitive processing speed, exercise, mobility, multiple sclerosis, physical fitness, response heterogeneity

1 | INTRODUCTION

Exercise-training can improve a range of outcomes among persons with multiple sclerosis (MS),[1] including aerobic and muscular fitness, mobility, depression, fatigue and quality of life.[2,3] This has resulted in exercise-training being recognized as one of the best approaches for restoring function in MS[7] and has yielded evidence-based, MS-specific guidelines for the prescription of exercise-training.[8]

The provision of guidelines for prescribing exercise-training in MS has an underlying assumption that persons will accrue consistent and similar benefits with the same efficacious exercise-training stimulus (ie, homogeneity of exercise-training outcomes). This assumption might not be correct, particularly considering response heterogeneity with mobility outcomes in randomized controlled trials (RCTs) of dalfampridine in MS.[9] There is further response heterogeneity in physiological and functional adaptations with supervised exercise-training in the general population.[10,11] Although there is evidence of response heterogeneity in physical activity with an Internet-delivered behavioural intervention in MS,[15] we are unaware of direct examinations of response heterogeneity with supervised exercise-training in this population.[1]

The study of response heterogeneity with exercise-training is important for precision medicine. The identification of response heterogeneity and factors that influence the effects of exercise-training on physiological and functional outcomes at the individual level has direct relevance for developing tailored and optimized exercise-training interventions in MS. Individual responses to exercise-training may differ based on baseline levels of physiological and functional outcomes, the actual amount of exercise completed (ie, compliance), or demographic/clinical characteristics. Such an examination could provide critical information on the development of targeted exercise-training interventions for optimally improving selective outcomes among MS subgroups.

This study involved a secondary analysis of data from a multisite, multimodal exercise-training intervention among persons with substantial MS-related mobility disability.[16,17] That Phase-II RCT reported that persons with MS who completed the intervention demonstrated statistically significant improvements in physical fitness, mobility and cognitive processing speed (CPS) compared with an active control condition using both intent-to-treat and per-protocol analyses.[17] The aims of the current paper were twofold: (a) describe response heterogeneity in physical fitness, mobility and CPS outcomes in response to exercise-training (ie, constructs that significantly improved relative to the control condition in the overall RCT[17]); and (b) identify possible baseline performance, compliance and demographic/clinical (ie, body mass index [BMI], assistive-device use) variables as predictors of exercise-related changes (or lack thereof) in physical fitness, mobility and CPS.

2 | METHODS

2.1 | Participants

Details on participant recruitment are reported elsewhere.[17] Inclusion criteria involved being 18-64 years of age with a definite MS diagnosis, insufficiently physically active (ie, participating in <2 days of ≥30 minutes of aerobic or resistance exercise/wk), relapse-free over the past 30 days and low risk for contraindications for exercise testing. All participants had a neurologist's verification of Expanded Disability Status Scale (EDSS) score between 4.0 and 6.0 for confirmation of the onset of substantial MS-related mobility disability[18]; this was not a study outcome. This resulted in 83 persons who enrolled in the study, completed baseline testing and were subsequently randomly assigned to either multimodal exercise-training (N = 43) or an active control condition (N = 40).[17] We primarily focus on those who were randomly assigned into the exercise-training condition, but report control data for accounting for practice effects as a threat towards conclusions involving heterogeneity. After accounting for dropouts, the final analysed samples included 32 persons with MS who completed 6-months of multimodal exercise-training and 30 persons who completed the control condition.

2.2 | Outcomes

Complete details on the physical fitness, mobility and CPS outcomes are reported elsewhere.[17] We note that all outcome measures were collected using the same procedures and equipment across sites.

2.2.1 | Physical fitness

Cardiorespiratory fitness, operationalized as VO_{2peak} (mL/kg/min) and peak power output (PPO; W), was measured using a maximal, incremental exercise test on an electronically braked, computer-driven cycle ergometer (Lode BV, Groningen, the Netherlands) and a calibrated open-circuit spirometry system (TrueOne, Parvo Medics, Sandy, UT, USA) for analysing respiratory gases. The standardized protocol has been validated in MS.[19]

Bilateral isometric knee extensor (KE) and flexor (KF) peak torque were measured using an isokinetic dynamometer (Biodex System 3 Dynamometer, Shirley, NY, USA). The specific testing protocol is reported elsewhere.[17] The highest recorded peak torque for the stronger leg provided a measure of KE and KF isometric strength (N·m).

2.2.2 | Mobility

The timed 25-foot walk (T25FW) was administered as a measure of walking speed (ie, feet/s)[9,20] per standardized procedures.[21] The 6-minute walk (6MW) was administered as a measure of walking endurance (feet) per standardized procedures for MS.[22]

2.2.3 | CPS

Cognitive processing speed was measured using the Symbol Digit Modalities Test (SDMT)[23] and 3′ Paced Auditory Serial Addition Test (PASAT).[24] The primary SDMT outcome was the total number of correct responses that were verbally provided in 90 seconds (ie, raw score). The primary 3′ PASAT outcome was the raw score (ie, total number of correct responses out of a possible 60).

2.2.4 | Compliance

Compliance was expressed based on the number of exercise sessions attended out of a possible 72 sessions, as the intervention took place three times/wk over a 24-week period (see below).

2.2.5 | Demographic/Clinical characteristics

All participants provided information on age and sex. BMI (kg/m^2) was measured using a scale stadiometer (Detecto Inc, Webb City, MO, USA). Participants provided information on assistive-device use (ie, no assistance, unilateral assistance, or bilateral assistance). Disability status was assessed using the Patient-Determined Disease

TABLE 1 Baseline demographic and clinical characteristics of 32 persons with MS-related mobility disability

Variables	N = 32
Age (y)	49.8 (9.4)
Sex (n, % female)	25/32 (78.1%)
BMI (kg/m^2)	29.1 (10.9)
PDDS (median, IQR)	4.0 (2.0)
Assistive-device use	
None (n, %)	16/32 (50.0%)
Unilateral (n, %)	7/32 (21.9%)
Bilateral (n, %)	9/32 (28.1%)

All data presented as mean (SD) unless otherwise noted.
BMI, body mass index; MS, multiple sclerosis; PDDS, patient-determined disease steps.

Steps (PDDS) scale.[25] The PDDS is strongly correlated with EDSS scores and validated in MS.[26] The PDDS involves a single item for measuring MS-related neurological disability on ordinal scale ranging from 0 (normal) through 8 (bedridden).

2.3 | Multimodal exercise-training intervention

The intervention condition involved 6 months (ie, 24-weeks) of supervised, progressive (ie, intensity and duration) multimodal exercise-training (ie, aerobic, resistance, and balance exercise). Exercise-training sessions were led by trained exercise leaders and occurred three times/wk over 24 weeks. The actual sessions initially lasted between 30 and 60 minutes over the intervention period; all exercise-training procedures were standardized across sites. The exercise prescription involved approximately equal durations of aerobic, lower-extremity resistance and balance training. Aerobic exercise-training involved self-selected modalities of leg cycle ergometry, treadmill walking and recumbent stepping exercise. Lower-limb resistance exercise-training involved leg press, knee extension/flexion and ankle dorsiflexion/plantarflexion exercise. Balance training consisted of heel-to-toe (ie, tandem) walks, tandem stance, single-leg stands and single-leg calf raises. Complete details on intensity/progression of the multimodal exercise-training intervention are reported elsewhere.[16,17] We further note that information on the active control condition is reported elsewhere.[16,17]

2.4 | Procedure

Study procedures were approved by University institutional review boards, and all participants provided written informed consent. Participants initially provided demographic/clinical information and underwent physical fitness, mobility and CPS assessments. After baseline testing, participants were randomly assigned into the intervention or active control conditions. All participants were asked to not undertake additional exercise over the study. Participants completed the same assessments in the laboratory immediately following the 6-month study period (ie, follow-up).

2.5 | Data analysis

All analyses were performed using SPSS Statistics 24 (IBM, Inc, Armonk, NY, USA). Baseline descriptive characteristics are reported as mean (SD) or as a frequency (ie, percentage). Mean changes in physical fitness, mobility and CPS outcomes for those who completed the intervention were expressed using paired-samples t tests with Bonferroni corrections for multiple comparisons within each category (ie, physical fitness, mobility, CPS). Regarding possible response heterogeneity, absolute changes in physical fitness, mobility and CPS were calculated as follow-up minus baseline. Relative (ie, percent) changes in those outcomes were calculated as ((absolute change/baseline) × 100). Heterogeneity of absolute and relative changes for outcomes that significantly changed in response to the intervention is depicted using bar graphs and boxplots. We report mean changes in the outcomes for those who completed the control condition as prescribed for comparison purposes, as reported elsewhere.[17] We further performed Spearman rank-order correlations (ρ) or chi-square (χ^2) difference tests to determine whether baseline outcome measures, compliance or demographic/clinical outcomes were associated with absolute or relative changes in physical fitness, mobility and CPS outcomes that significantly changed for those who completed the intervention.

3 | RESULTS

3.1 | Participants

Baseline characteristics are provided in Table 1. Overall, the sample was primarily female with substantial MS-related mobility disability based on a median PDDS score of 4.0 (ie, early cane). On average, the sample was overweight (mean BMI of 29.1 kg/m^2). Fifty percent of the sample was independently ambulatory; the other 50% used an assistive-device.

3.2 | Mean responses to the intervention

Baseline and follow-up scores on the physical fitness, mobility and CPS measures for those who completed the intervention are presented in Table 2. We note that these constructs all significantly improved for the intervention compared with the control condition in the overall RCT.[17] Paired-samples t tests indicated that the multimodal exercise-training intervention yielded mean improvements in physical fitness based on statistically significant changes in PPO ($t = -6.48$, $P < 0.01$; ~46% improvement) and KF peak torque ($t = -2.97$, $P = 0.01$; ~17% improvement). There were improvements in mobility based on statistically significant changes in T25FW speed ($t = -3.12$, $P < 0.01$; ~17% improvement) and 6MW

TABLE 2 Baseline and follow-up scores expressed as absolute and relative changes in 32 persons with MS who underwent multimodal exercise-training

Variables	Baseline	Follow-up	*P*-value	Absolute change	Relative change (%)
Physical fitness					
VO_{2peak} (mL/kg/min)	17.3 (6.7)	18.0 (5.9)	0.25	0.8 (3.7)	7.9 (19.8)
Peak power (W)	82.6 (40.6)	103.2 (39.2)	<0.01[a]	22.4 (19.3)	46.1 (65.7)
KE Peak Torque (Nm)	124.6 (42.9)	136.5 (53.8)	0.05	11.9 (30.9)	9.8 (26.7)
KF Peak torque (Nm)	51.6 (18.6)	61.7 (31.2)	0.01[a]	10.1 (19.2)	16.9 (29.7)
Mobility					
T25FW (feet/s)	3.6 (1.9)	4.0 (2.1)	<0.01[a]	0.4 (0.7)	16.7 (30.1)
6MW (feet)	1055.3 (551.6)	1193.4 (626.3)	<0.01[a]	138.1 (191.5)	14.6 (25.3)
Cognitive processing speed					
SDMT (raw score)	45.8 (11.3)	48.8 (9.1)	0.01[a]	2.9 (5.3)	10.3 (23.7)
3′ PASAT (raw score)	43.0 (11.2)	47.5 (8.8)	0.01[a]	4.5 (8.6)	18.4 (49.4)

All data presented as mean (SD).
KE, knee extensor; KF, knee flexor; MS, multiple sclerosis; PASAT, paced auditory serial addition test; SDMT, symbol digit modalities test; T25FW, timed 25-foot walk; VO_{2peak}, peak oxygen consumption; 6MW, six-minute walk.
[a]Denotes statistical significance based on paired-samples *t* test with Bonferroni corrections for multiple comparisons within each category.

performance ($t = -4.08$, $P < 0.01$; ~15% improvement). The intervention resulted in improvements in CPS based on statistically significant changes in SDMT raw score ($t = -3.12$, $P < 0.01$; ~10% improvement) and 3′ PASAT raw score ($t = -2.93$, $P = 0.01$; ~18% improvement). We note that the mean change of the control group was minimal and non-significant for those outcomes (Figure 1).[17]

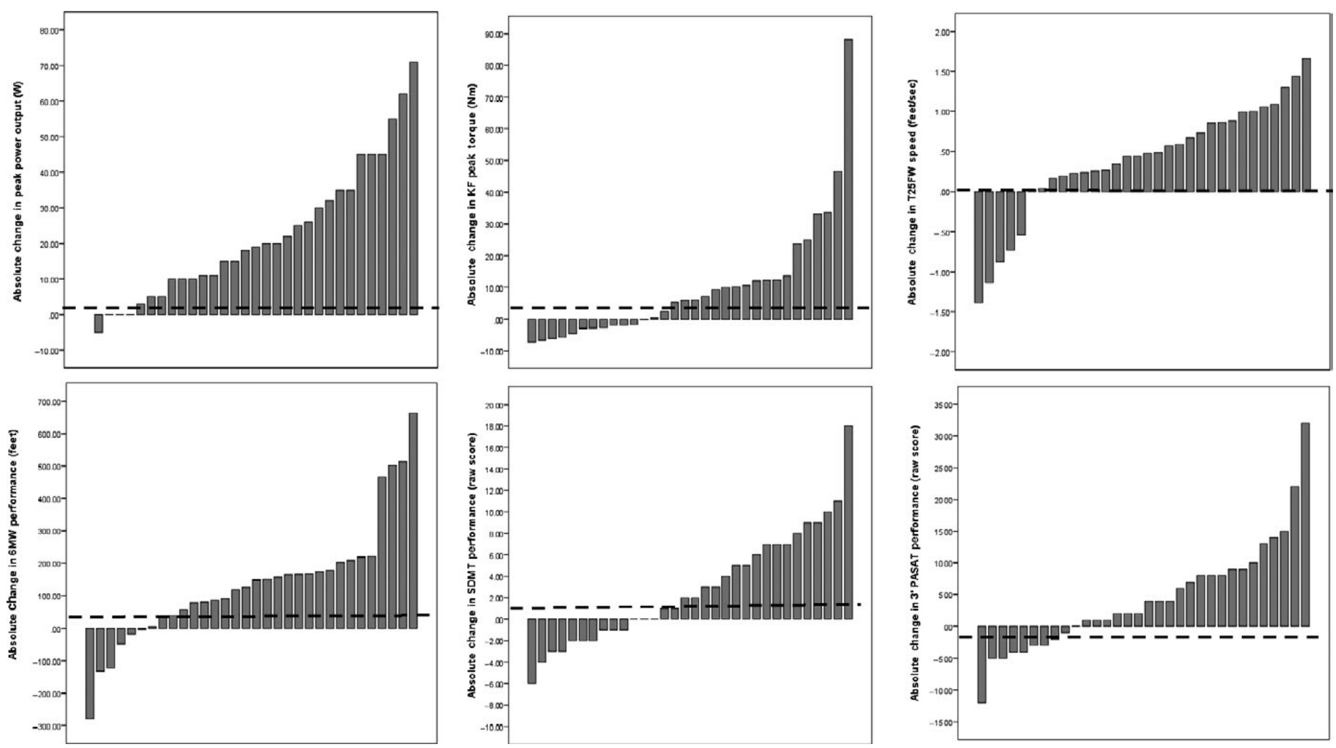

FIGURE 1 Individual absolute changes in peak power output, KF peak torque, T25FW speed, 6MW performance, SDMT performance and 3′ PASAT performance in 32 persons with MS. Dashed lines represent mean absolute changes in the outcomes for the control group reported in ref [[17]]. Mean absolute change for the control group in peak power output = 1.2 W; KF peak torque = 2.1 Nm; T25FW speed = 0.0 feet/s; 6MW performance = 25.8 feet; SDMT = 1.0 points; 3′ PASAT = −1.5 points. KF, knee flexor; MS, multiple sclerosis; PASAT, paced auditory serial addition test; SDMT, symbol digit modalities test; T25FW, timed 25-foot walk; 6MW, six-minute walk

3.3 | Compliance

On average, participants attended 59 (SD = 9.6) of the 72 possible exercise-training sessions (ie, 81.9%). All participants who completed the intervention attended at least 54% of sessions; 4/32 participants attended all 72 sessions.

3.4 | Response heterogeneity

Response heterogeneity of absolute and relative (ie, percentage) changes in PPO, KF peak torque, T25FW speed, 6MW distance and SDMT and 3′ PASAT performance at the individual level are presented as bar graphs in Figures 1 and 2, respectively. Absolute changes relative to the mean change of the control group for each outcome[17] are depicted in Figure 1. Relative changes at the individual level in those outcomes are presented as boxplots in Figure 3. Based on visual inspection of the graphs and plots, the response to the intervention on each of the aforementioned outcomes was heterogeneous, whereby despite mean intervention-related improvements on each outcome, some participants demonstrated worsening or no change (ie, performance at or below the level of mean control group change), compared with others who demonstrated large, clinically meaningful changes.

3.5 | Factors influencing response heterogeneity

3.5.1 | Baseline outcomes

Figure 4 depicts the scatter plots of the associations between baseline performance and absolute/relative changes in the outcomes. Importantly, Spearman correlations indicated that absolute and relative changes were strongly and significantly correlated with one another for each outcome (ie, all ρ = 0.77-0.99, $P < 0.01$). Regarding PPO, baseline performance was significantly associated with relative (ρ = −0.47, P = 0.01), but not absolute change in that outcome. Regarding KF peak torque, baseline performance was not significantly associated with absolute or relative change in that outcome in response to the intervention. Regarding T25FW speed, baseline performance was significantly associated with relative (ρ = −0.48, P = 0.01), but not absolute change in that outcome. For the 6MW, baseline performance was not significantly associated with absolute or relative change in distance walked. Regarding both the SDMT and 3′ PASAT, baseline performance was significantly associated with both absolute (SDMT: ρ = −0.46, P = 0.01; 3′ PASAT: ρ = −0.54, $P < 0.01$) and relative (SDMT: ρ = −0.52, $P < 0.01$; 3′ PASAT: ρ = −0.56, $P < 0.01$) changes in those outcomes.

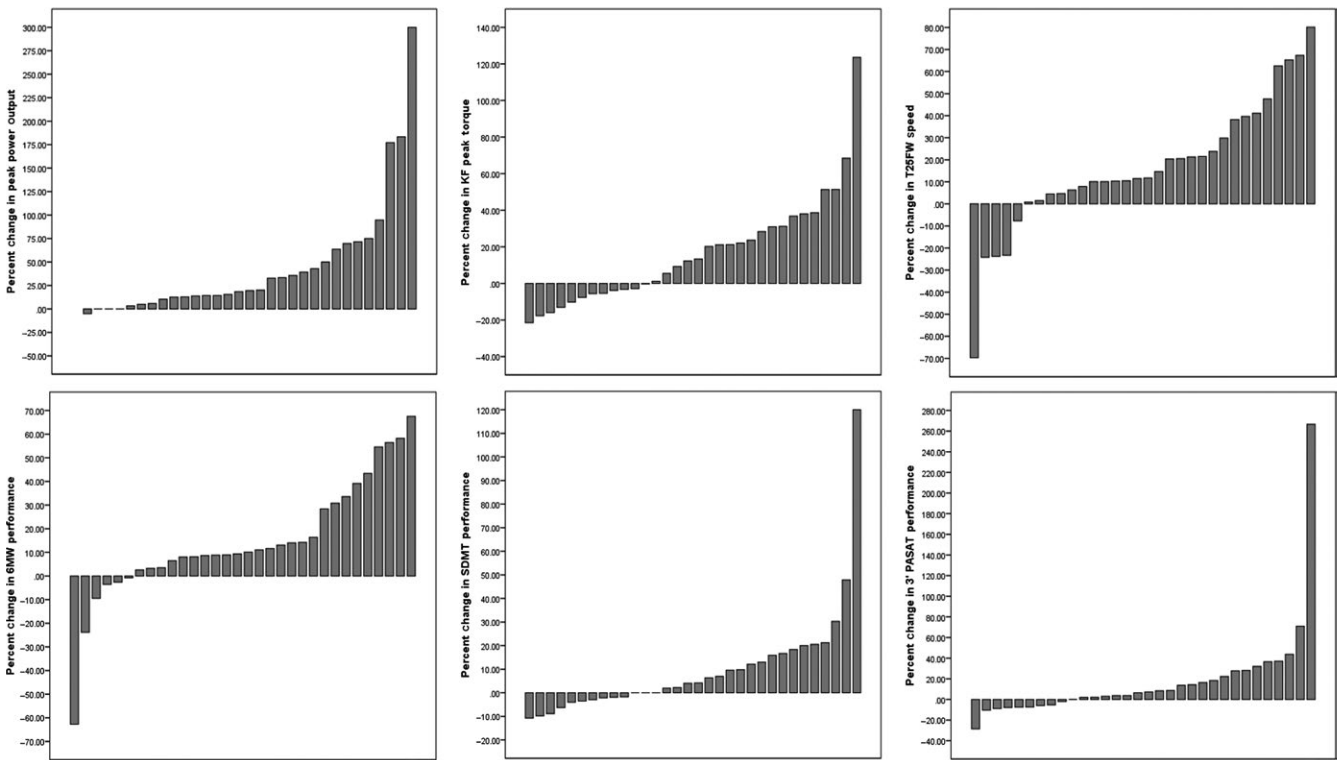

FIGURE 2 Individual relative (percent) changes in peak power output, KF peak torque, T25FW speed, 6MW performance, SDMT performance and 3′ PASAT performance in 32 persons with MS. KF, knee flexor; MS, multiple sclerosis; PASAT, paced auditory serial addition test; SDMT, symbol digit modalities test; T25FW, timed 25-foot walk; 6MW, six-minute walk

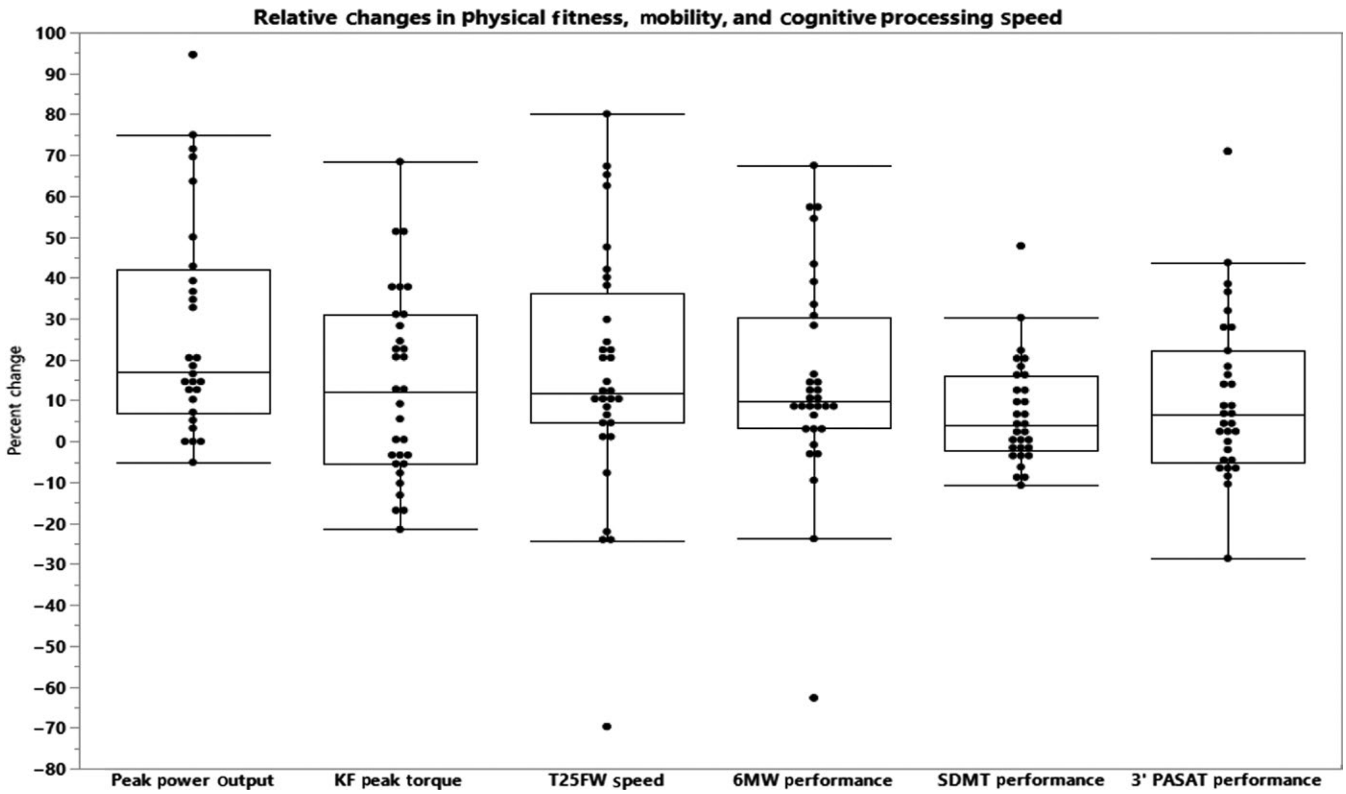

FIGURE 3 Boxplots depicting relative (percent) changes in peak power output, KF peak torque, T25FW speed, 6MW performance, SDMT performance and 3′ PASAT performance in 32 persons with MS. Outliers greater than +100% change have been removed from the figure for scaling purposes. This occurred three times for peak power output, one time for KF peak torque, zero times for T25FW speed, zero times for 6MW performance, one time for SDMT performance and one time for 3′ PASAT performance. The full range of relative changes on the physical fitness, mobility and cognitive processing speed outcomes is presented in Figure 2. KF, knee flexor; MS, multiple sclerosis; PASAT, paced auditory serial addition test; SDMT, symbol digit modalities test; T25FW, timed 25-foot walk; 6MW, six-minute walk

3.5.2 | Compliance

Spearman correlations indicated that the number of exercise sessions attended was not significantly associated with absolute ($|\rho| < 0.19$, $P > 0.34$) or relative ($|\rho| < 0.19$, $P > 0.35$) changes in any physical fitness, mobility or CPS outcome.

3.5.3 | Demographic/Clinical characteristics

Body mass index did not predict absolute or relative changes in any physical fitness, mobility or CPS outcome (ie, all $\rho < 0.28$, $P > 0.12$). Assistive-device use did not influence the magnitude of absolute or relative exercise-related changes in the physical fitness, mobility or CPS outcomes based on χ^2 difference tests (all $P > 0.11$).

4 | DISCUSSION

Exercise-training results in substantial response heterogeneity in physiological and functional outcomes among adults of the general population,[10,11] and there is no single exercise-training intervention that universally results in reliable benefits for all participants. However, published guidelines for exercise participation among adults with MS[8] have made this assumption (based, in part, on most exercise-training studies in MS only reporting exercise-related changes as group means).[1] To that end, identifying factors that may influence the accrual of specific exercise-training benefits can aid in the development of stepped-care models and decision trees for improving targeted outcomes among those who need such exercise interventions the most. This approach is particularly important among persons with MS who demonstrate disease-related physiological and functional impairments, namely mobility disability. Several published studies have indirectly reported response heterogeneity with supervised exercise-training among persons with MS (ie, individual responses to the exercise stimulus without this being an a priori study aim),[27,28] but there is no systematic effort to identify and describe the variability associated with physiological and functional outcomes in response to supervised exercise-training and factors that may influence such response heterogeneity in this population.[1] The present study represents an initial effort for describing a pattern of response heterogeneity in physical fitness, mobility and CPS outcomes with a 6-month, multimodal exercise-training intervention among 32 mobility-impaired persons with MS and identifying

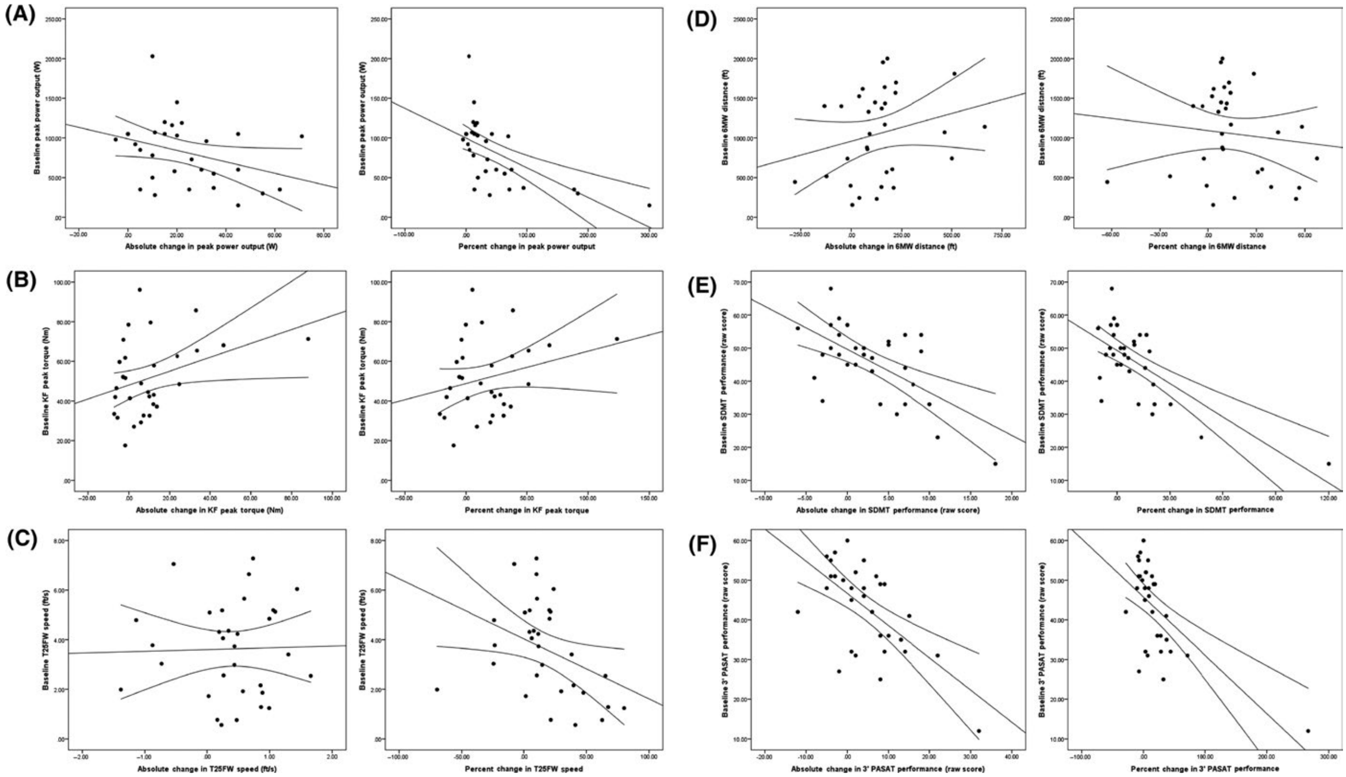

FIGURE 4 Scatter plots of the associations between baseline performance and absolute change and relative change, respectively, in (A) peak power output, (B) KF peak torque, (C) T25FW speed, (D) 6MW performance, (E) SDMT performance and (F) 3′ PASAT performance along with lines of best fit and 95% confidence intervals. KF, knee flexor; PASAT, paced auditory serial addition test; SDMT, symbol digit modalities test; T25FW, timed 25-foot walk; 6MW, six-minute walk

baseline performance as a factor that influences such response heterogeneity.

The intervention resulted in statistically significant mean improvements in aerobic fitness (ie, PPO), lower-limb muscular strength (ie, KF peak torque), walking speed (ie, T25FW speed) and endurance (ie, 6MW performance), and CPS (ie, SDMT and 3′ PASAT performance). Of note, those changes were significantly greater than in the active control condition using intent-to-treat and per-protocol analyses (reported elsewhere),[17] thereby arguing against practice effects. However, the effects of the intervention were not homogeneous. Some participants demonstrated large, clinically meaningful improvements in physical fitness, mobility and/or CPS, whereas other participants demonstrated minimal improvements or worsening in those outcomes (ie, at a level below the mean absolute change of the control group; Figure 1). Of note, 75% of the sample demonstrated clinically meaningful improvements in PPO (ie, >10% improvement)[30], 25% of the sample demonstrated clinically meaningful improvements in T25FW speed (ie, >36% improvement)[31], 28% of the sample demonstrated clinically meaningful improvements in 6MW performance (ie, >20% improvement)[31], and 41% of the sample demonstrated clinically meaningful improvements on the SDMT (ie, >4-point improvement)[32] based on published benchmarks for MS. We are unaware of benchmarks for clinical meaningfulness for KF peak torque and 3′ PASAT outcomes in MS.

The present study further examined baseline performance measures, exercise compliance and demographic/clinical characteristics as factors that may have influenced the heterogeneous effects of the intervention. The primary pattern of results indicated that lower baseline aerobic fitness (ie, PPO), slower baseline walking speed (ie, T25FW speed) and slower CPS (ie, SDMT and 3′ PASAT performance), respectively, were significantly associated with greater percent changes in those outcomes in response to the intervention. By comparison, only worse baseline SDMT and 3′ PASAT performance were significantly associated with larger absolute exercise-related improvements in CPS. Exercise compliance, BMI, and assistive-device use did not seemingly influence the absolute or relative effects of the intervention on fitness, mobility or CPS outcomes. This pattern of results suggests that among ambulatory persons with substantial MS-related mobility disability, those who have the lowest aerobic fitness and slowest walking and processing speed have the potential to gain the most in those outcomes by engaging in multimodal exercise-training. This further is supported by significant correlations between baseline performance and *relative* (ie, percent) changes on physical fitness, mobility and CPS outcomes with exercise-training, as relative change takes into account baseline performance (eg, Figure 4). We do not believe this represents regression to the mean, given that changes in fitness, mobility and CPS were significantly larger for those who underwent the intervention compared with the active control condition.[17] Collectively, this provides a foundational step for developing targeted, optimized exercise rehabilitation interventions for improving physical fitness, mobility and CPS among persons with substantial MS-related mobility disability.

Identifying factors that might influence the inter-individual variability of exercise effects on physiological and functional outcomes in MS is consistent with a precision medicine framework.[33] This involves tailoring-specific exercise prescriptions for improving certain outcomes among persons with MS who present with specific deficits. The present results suggest that among persons with substantial MS-related mobility disability, multimodal exercise-training might improve aerobic fitness, walking speed and CPS the most in those with low aerobic fitness, slow walking speed and slow CPS, respectively. There were several noteworthy cases whereby persons with initially poor fitness and CPS demonstrated improvements of upwards of 100% in those outcomes. Future research efforts might consider targeting those persons in tailored exercise-training interventions for optimizing the aforementioned outcomes and/or delineating potential mechanisms that could contribute towards a super-response.[9] There are a myriad of factors that could influence the magnitude of response in those outcomes with multimodal exercise-training. Perhaps there are neural factors that might influence the effects of multimodal exercise-training on fitness, mobility and CPS in MS.[34] There may be genetic or epigenetic factors[35] as well as exercise stimulus-specific factors that warrant exploration as possible predictors of exercise-training response heterogeneity in MS.

There are several study limitations. We did not collect data on MS phenotype, duration, disease-modifying therapy use, fatigue or depression; these factors may have influenced the effects of the intervention on physical fitness, mobility and/or CPS. We further did not perform neurological examinations for generating EDSS scores as a study outcome. The study involved a relatively small sample of persons who completed the intervention. Future research efforts might consider replicating the study in a larger cohort and increase the generalizability. This study did not involve a long-term follow-up period for examining potential sources of variability that influenced the sustainability of exercise effects on physical fitness, mobility and CPS.

5 | CONCLUSIONS

The present study provides novel evidence for response heterogeneity in fitness, mobility and cognitive outcomes associated with multimodal exercise-training among mobility-impaired persons with MS. This study further identified that those persons with MS-related mobility disability who have the lowest aerobic fitness, walk the slowest, and have the slowest CPS might benefit the most in each respective domain from such an intervention. This is critical for informing the development of optimized, tailored exercise rehabilitation interventions for improving physiological and functional outcomes among persons with MS.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

ORCID

Brian M. Sandroff http://orcid.org/0000-0002-2013-7632

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