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Heterogeneity of aerobic fitness changes with exercise training in progressive multiple sclerosis: Secondary, exploratory analysis of data from the CogEx trial

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Abstract

Background: There is heterogeneity of aerobic fitness (VO_{2peak}) changes with a standardized exercise training stimulus in the general population (i.e. some participants demonstrate improvements, others no change, and some a reduction in VO_{2peak}).

Objectives: This secondary, exploratory analysis of data examined the heterogeneity of VO_{2peak} responses and possible correlates among persons with progressive multiple sclerosis (PMS) from the CogEx trial.

Methods: CogEx was a multi-site, multi-arm, randomized, double-blinded, and sham-controlled trial undertaken by 11 sites in six different countries. Participants were randomized into one of four conditions with different combinations of exercise training and cognitive rehabilitation including respective sham conditions. The analysis focuses primarily on VO_{2peak} change for the pooled exercise training intervention conditions compared with the pooled sham exercise control conditions.

Results: Waterfall plots for change in VO_{2peak} suggested greater heterogeneity with exercise training than sham, and the proportions of difference in VO_{2peak} change (i.e. improvement/worsening) were significantly different between exercise training and sham conditions($p < 0.05$). The multivariable analysis indicated that lower baseline VO_{2peak} ($p < 0.001$) was the only statistically significant correlate of increases in VO_{2peak} with exercise training.

Conclusion: Our results highlight the heterogeneity of change in VO_{2peak} with exercise training that is correlated with initial aerobic capacity in PMS, and such results may inform hypothesis testing in future clinical trials of exercise training.

Keywords: Exercise, progressive MS, heterogeneity

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Introduction

Randomized controlled trials (RCTs) indicate that exercise training (ET) yields benefits for a variety of outcomes, notably aerobic fitness, in people with multiple sclerosis (MS).[1–3] For example, meta-analyses of RCTs examining ET effects on aerobic fitness in people with MS have reported a ½ standard deviation improvement in peak oxygen consumption (VO_{2peak}).[4,5] Such evidence supported the development of prescriptive guidelines for yielding ET effects on aerobic fitness and other outcomes in MS.[1,6] The underlying assumption of the prescriptive

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guidelines is that people with MS will on average accrue similar benefits with a standardized ET stimulus(i.e. homogeneity of responses with exercise training).

Importantly, there is increasing recognition of within-study heterogeneity of changes in outcomes, including aerobic fitness, with ET in the general population[7–9] and people with MS.[10] This indicates some participants will demonstrate improvements in aerobic fitness, others no change in aerobic fitness, and some a reduction in aerobic fitness with a standardized aerobic ET stimulus. The pattern of variation in responses with ET, including an apparent detraining with aerobic ET, has been characterized as not solely representing measurement error based on an NIA NIH Workshop summary.[9] Of note, the re-analysis of published data from an RCT of 8–10 weeks of ET in 42 people with progressive MS (PMS)[10] indicated interindividual variability of changes in VO_{2peak} based on waterfall plots and chi-square tests across three, standardized aerobic ET programs.[11]

The heterogeneity of aerobic fitness change with ET in MS may be explainable by a set of core factors.[9] The core factors may include central nervous system damage, disease burden, and sample demographic/clinical characteristics[10] as well as physiological function, adherence/compliance, and physical activity.[12] For example, one secondary analysis of data from an RCT of a 24-week period of multimodal ET in 54 people with moderate MS-disability reported that there was response heterogeneity for change in peak work rate (W_{peak}; performance-based metric of aerobic fitness) that was associated with baseline fitness.[12] We note that the NIA NIH Workshop summary did not identify a single, analytic approach as optimal for examining heterogeneity of change and its correlates within RCTs of ET.[8]

The premise and evidence for heterogeneity of aerobic fitness changes that is explainable by other factors opens the door for the application of precision medicine in MS. The premise of precision medicine focuses on identifying factors that explain heterogeneity of change in an outcome for a given treatment, and then using that information for delivering an individually-centered treatment stimulus.[13] Such an approach should optimize the benefits of ET and minimize the variability in treatment response. Within the context of ET, this often starts with aerobic fitness, as outcomes of ET often depend on adaptations in physiological systems that can translate into secondary benefits.[9,14]

This paper involved a secondary, exploratory analysis of data from the CogEx trial.[15,16] We have published results regarding group-level changes in outcomes, notably aerobic fitness based on VO_{2peak} and W_{peak} from a maximal, incremental exercise test.[16] The current paper focuses on (a) examining the heterogeneity of individual-level changes in VO_{2peak} (primary outcome) and W_{peak} (secondary outcome) within the ET intervention condition compared with the sham, exercise control condition, and (b) exploring bivariate and multivariable correlates of aerobic fitness changes within the ET condition based on a published model[10] and other research[7–9,12]; we then examine the bivariate results from the ET condition in the sham condition.

Methods

Trial description

The CogEx trial was a multi-site, multi-arm, randomized, double-blinded, and sham-controlled clinical trial undertaken by 11 sites across six countries: Canada (one site), the USA (two sites), the United Kingdom (two sites), Denmark (one site), Belgium (one site), and Italy (four sites).[15,16] Participants with PMS were randomized into one of four conditions with different combinations of ET and cognitive rehabilitation including respective sham conditions. This paper focuses on aerobic fitness changes for the pooled ET intervention conditions compared with the pooled sham exercise control conditions (i.e. ET versus sham exercise conditions collapsed across cognitive rehabilitation and sham cognitive rehabilitation conditions); this was reasonable as there were no differences for changes in outcomes between the cognitive rehabilitation conditions.[16]

Participants

The inclusion/exclusion criteria for participants are provided in Table 1.[15] Of note, the diagnosis of primary or secondary PMS was confirmed by a neurologist, and impaired cognition was defined as a Symbol Digit Modalities Test (SDMT) score of at least 1.282 standard deviations below published normative data (10th percentile), and physical inactivity was based on a Godin Leisure-Time Exercise Questionnaire Health Contribution Scale score of < 24.

Exercise training program

The ET intervention condition was fully described in the protocol[15] and outcomes[16] papers, and involved a standardized program of supervised aerobic ET on a recumbent arm-leg stepper (Nustep T5XR, Nustep Inc, Ann Arbor, MI). The ET protocol was designed based on several important features. The first is that

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Table 1. Inclusion and exclusion criteria for the CogEx trial as reported in our protocol and primary outcomes papers.

Inclusion criteria	
MS type	Primary or secondary progressive MS (confirmed by neurologist)
Age	25–65 years of age
Cognition	Failure on the SDMT defined by a performance of at least 1.282 SD below published normative data (10th percentile) specific for each Country
Visual acuity	Corrected near vision of at least 20/70 and absence of severe nystagmus.
Disease activity	Exacerbation free for the past 3 months.
Language comprehension	To ensure that participants could understand the test instructions, participants had to demonstrate at least a low average performance on the Token Test.
Exclusion criteria	
Ambulation	EDSS $\geq$ 7.0
Neurological History	A history of central nervous system disease other than PMS. Disease exacerbations in the past 3 months.
Medications	Steroids used within the past 3 months.
Current exercise activity	Regular aerobic training at an estimated intensity of > 60% of the maximal Heart rate reserve, for more than 1 day per week lasting more than 30 minutes per session for the past 3 months. Assessment of exercise habits based on the Godin Leisure-Time Exercise Questionnaire score > 23.
Medical contraindications	Failure on 2 or more statements on the American College of Sports Medicine and American Heart Association (AHA/ACSM) Health/Fitness Facility pre-participation screening questionnaire, required physician approval.
Psychiatric contraindications	History of substance abuse and severe (psychotic) mental illness, including severe depression ($\geq$ 29 on the Beck Depression Inventory).
MRI	Claustrophobia, metal implants, pacemakers.

the program is largely consistent with evidence-based guidelines for physical activity in MS. The second is that the combination of continuous, moderate-intensity ET and high-intensity interval ET on separate days of the week includes two modalities of aerobic ET that illicit acute and chronic adaptations in MS. The third is that an international team of experts designed the ET program based on both research and personal experiences with ET in MS. Briefly, the aerobic ET consisted of bouts of continuous, moderate-intensity exercise along with high-intensity interval training (HIIT) performed on alternating days, 2 times per week for 12 weeks. The continuous bouts progressed from 10 minutes of exercise at a work rate associated with 50%–60% VO_{2peak} in Week 1 towards 30 minutes of exercise at a work rate associated with 70%–80% VO_{2peak} in Week 12. The HIIT bouts progressed from 5, 1-minute intervals at a work rate associated with 80%–90% VO_{2peak} interspersed with 1-minute rest periods(i.e. lightly exercising at 15 W) in Week 1 towards 10, 2-minute intervals at a work rate associated with 90% VO_{2peak} interspersed with 2-minute rest periods in Week 12. The sham, exercise condition consisted of supervised stretching and balance that were performed 2 times per week, and this too has been described in the protocol[15] and primary outcomes[16] papers.

Procedure

Study procedures were approved by site-specific, institutional review boards, and participants provided written informed consent. Participants initially completed baseline assessments in the laboratory, and then were randomized into one of the four study conditions; 50% of participants were randomly assigned to the ET intervention conditions and 50% of participants were randomly assigned to the sham exercise control conditions. Participants completed the follow-up assessments in the laboratory following the 12-week study period.

Outcomes

The details of the outcomes included in this secondary analysis are reported in the protocol paper.[15] We note that all outcomes were collected using the same procedures with similar equipment across sites.

Aerobic fitness. Aerobic fitness, operationalized as VO_{2peak} and W_{peak}, was recorded using a maximal, incremental cardiopulmonary exercise test (CPET) on a recumbent arm-leg stepper (Nustep T5XR, Nustep Inc, Ann Arbor, MI) with respiratory gases analyzed using calibrated, open-circuit spirometry. The standardized protocol and criteria for an interpretable test result have been described and validated for MS.[17] Briefly, the CPET protocol involved a 1-minute warm-up at 15 W. The initial work rate was 15 W and gradually increased until the participant reached volitional fatigue. The work rate increased by 10 W/min or 5 W/min for participants with mild to moderate disability (i.e. EDSS of 4.0–5.5) or severe disability (i.e. EDSS of >6.0), respectively. Participants maintained a stepping rate of 60–100 steps per minute throughout the test depending on the work rate. Heart rate (Polar FT1 Heart Rate Monitor, Polar Electro Inc., Bethpage, NY, USA) and Ratings of Perceived Exertion (RPE) via the Borg Rating of Perceived Exertion Scale were recorded every minute. The highest recorded 20-second rate of oxygen consumption (VO_2) was recorded as peak oxygen consumption (VO_{2peak}), expressed in mL/kg/min, optimally when two or more of the following criteria were satisfied: (1) respiratory exchange ratio (RER) of 1.10 or greater; (2) peak heart rate within 10 beats per minute of age-predicted maximum (i.e. 220-age); or (3) RPE of 17 or greater. The highest recorded power achieved during a 20-s period was recorded as peak power output in watts (W_{peak}). The primary outcome of analysis for this article was a change in aerobic fitness between baseline and follow-up (follow-up minus baseline with a positive change indicating improvement) for both VO_{2peak} and W_{peak}.

Correlates. The correlates were selected based on a published model for MS[10] and other research.[7–9,12] Baseline VO_{2peak} and W_{peak} were considered as correlates in the analysis.[8,9,12]

Mobility. The 6-minute walk test (6MWT) characterized walking performance based on walking endurance.[18] The 6MWT has strong psychometric properties and was administered using standard instructions for MS.[18] The participant walked as far and as fast as possible, with a walking aid as necessary, and permitted rests as needed, but while remaining upright.[18] The tester recorded the total distance walked over the 6-minute period in meters.

Cognition. Cognitive performance was assessed using the Brief International Cognitive Assessment for MS (BICAMS).[19] The BICAMS battery includes the SDMT, the first five learning trials of the California Verbal Learning Test-II (CVLT-II), and the first three learning trials of the Brief Visuospatial Memory Test-Revised (BVMT-R) for measuring information processing speed, verbal learning and memory, and visuospatial learning and memory, respectively.[19] The outcomes were total scores per BICAMS test.

Adherence/compliance. Adherence was defined as attending and undertaking the exercise sessions,[20] and expressed as a percentage of the 24 total ET sessions. Compliance was defined as undertaking and completing the exercise sessions consistent with the prescription,[20] and expressed as a percentage of the 24 total ET sessions. The failure to attend a session was recorded as non-adherent/non-compliant for that session. If all sessions were missing for a participant, the participant was excluded from the analyses.

Demographic/clinical characteristics. The demographic characteristics included age, sex, marital status, primary language, years of schooling, highest education level, and current employment. The clinical characteristics included disease duration and type of PMS.

Disability status. The EDSS[21] was provided by the participant's treating neurologist.

Moderate-to-vigorous physical activity (MVPA). The ActiGraph model GT3X + accelerometer (Actigraph Corporation, FL) worn during a seven-day period provided a measure of free-living physical activity as average minutes/day of MVPA. The ActiGraph accelerometer was placed on an elastic belt worn snuggly around the waist over the non-dominant hip during the waking hours of a seven-day period. Only data from valid days (wear time ≥ 600 minutes) were processed in ActiLife (Actigraph Corporation, FL) using MS cut-points.[22]

Patient-reported outcome measures (PROMs). PROMs of fatigue (Modified Fatigue Impact Scale, MFIS),[23] subjective cognitive deficits (20-item Perceived Deficits Questionnaire),[24] walking impairment (12-item Multiple Sclerosis Walking Scale),[25] and global function (Functional Assessment of Multiple Sclerosis)[26] were included using total scores per measure.

Data analysis

The analyses included participants who were randomized, began the intervention, and had adherence/

compliance data for the exercise interventions. Waterfall plots were created to visualize the shape of the data distributions. Levene's statistic tested the homogeneity of variances between the treatment and sham conditions. Additionally, we categorized VO_{2peak} change into improved (10% or more increase over baseline value), worsened (10% or more decrease below baseline value), or no change (i.e. $< 10\%$ increase or decrease) using the guideline for interpreting VO_{2peak} change in MS.[27] The difference in VO_{2peak} change (improvement/worsening) proportions were compared between the ET and sham conditions based on chi-square test. We evaluated associations between correlates and change in VO_{2peak} and W_{peak} for the ET and sham control conditions using bivariate and multivariable methods. The bivariate correlations involved Pearson product-moment correlations (r) for continuous variables, point-biserial correlations (r_{pb}) for dichotomous variables (e.g. sex), and Spearman rank-order correlations (ρ) for multi-level categorical variables between baseline variables and change in VO_{2peak} and W_{peak}. Cohen's guidelines of 0.1, 0.3, and 0.5 indicated small, moderate, and strong correlations, respectively.[28] The multivariable analysis involved linear regression with direct entry of variables that demonstrated univariate associations ($p < 0.2$) with the outcome variables, and this was followed by a sensitivity analysis removing the respective baseline factor (e.g. baseline VO_{2peak} for VO_{2peak} change). All statistical analyses were conducted in SAS (Version 9.4, Cary, NC, USA).

Results

Sample characteristics and group-level change in fitness outcomes

The characteristics for the overall sample ($n = 304$) and the subsamples who completed the ET ($n = 152$) and sham exercise control conditions ($n = 152$), irrespective of cognitive training, are provided in Table 2a and b. There were no baseline differences between the ET and sham conditions for all included variables except adherence and compliance ($p < 0.001$) that were both lower for ET than sham. The adherence data in this study for ET were strong when compared with a recent review,[29] but compliance was weaker and might suggest some issues with delivering the ET program, notably the HIIT program. Both VO_{2peak} and W_{peak} change scores were significantly different between conditions ($p = 0.003$, $p < 0.001$, respectively), as shown in Table 2c, with higher mean change for ET.

Response heterogeneity for individual-level change in exercise training and sham conditions

The waterfall plots for change in VO_{2peak} and W_{peak} with the 12-week ET and sham conditions are provided in Figures 1 and 2, respectively. Levene's test did not identify statistically significant differences in the variances of changes in VO_{2peak} and W_{peak} between conditions, but inspection of the waterfall plots suggested greater heterogeneity (i.e. variability of the changes) with ET than sham. Among those in the ET condition, 43.7% (n = 59) demonstrated improvement in VO_{2peak} (i.e. $\geq 10\%$ increase in mL/kg/min), 34.1% (n = 46) demonstrated no change, and 22.2% (n = 30) demonstrated worsening in VO_{2peak} (i.e. $\geq 10\%$ decrease in mL/kg/min). Among those in the sham condition, 29.2% (n = 40) demonstrated improvement in VO_{2peak} (i.e. $\geq 10\%$ increase in mL/kg/min), 38.0% (n = 52) demonstrated no change, and 32.8% (n = 45) demonstrated worsening in VO_{2peak} (i.e. $\geq 10\%$ decrease in mL/kg/min). The difference in VO_{2peak} change (improvement/worsening) proportions was statistically significantly different between the ET and sham conditions ($p = 0.03$).

Bivariate correlates of response heterogeneity for exercise training

The bivariate analysis is provided in Table 3a, and only lists variables associated with either change in VO_{2peak} or W_{peak} in the ET condition. Baseline VO_{2peak} (r=–0.21, $p = 0.02$), average minutes/day of MVPA ($r = 0.16$, $p = 0.07$), average compliance($r = 0.15$, $p = 0.07$), 6MWT distance($r = 0.15$, $p = 0.09$), SDMT number correct ($r = 0.14$, $p = 0.10$), and baseline W_{peak} ($r = 0.14, p = 0.11$) were correlates of VO_{2peak} change for the ET condition. EDSS (r=–0.16, $p = 0.06$), average adherence ($r = 0.16$, $p = 0.07$), years of school ($r = 0.14$, $p = 0.10$), FAMS total ($r = 0.15$, $p = 0.10$), and 6MWT distance ($r = 0.11$, $p = 0.19$) were correlates of W_{peak} change for the ET condition. We further report the correlation between the same variables identified for the ET condition with change in VO_{2peak} or W_{peak} for the sham control condition in Table 3b, and notably baseline VO_{2peak} was significantly and inversely correlated with change in VO_{2peak}.

Multivariable correlates of response heterogeneity for exercise training

The multivariable analysis is provided in Table 4. Regarding VO_{2peak}, we included baseline VO_{2peak}, baseline W_{peak}, average compliance, SDMT number correct, 6MWT distance, and average minutes/day in MVPA as factors, and baseline VO_{2peak} (–0.37, $p < 0.001$) was the only correlate of VO_{2peak} change that was statistically significant. Regarding W_{peak},

Table 2a. Demographic characteristics of the samples in exercise training and sham conditions regardless of cognitive training group assignment.

	Overall sample ($n = 304$)	Exercise training condition ($n = 152$)	Sham condition ($n = 152$)
Age, mean (SD)	52.5 (7.12)	52.0 (7.38)	53.0 (6.84)
Sex*, n (%)			
Female	188 (61.8%)	99 (65.1%)	89 (58.6%)
Male	116 (38.2%)	53 (34.9%)	63 (41.4%)
School, mean (SD) years	13.9 (3.34)	13.9 (3.32)	14.0 (3.36)
Highest level of education completed, *n* (%)			
Primary	24 (7.9%)	12 (7.9%)	12 (7.9%)
Secondary (high school)	144 (47.4%)	71 (46.7%)	73 (48.0%)
College/university	136 (44.7%)	69 (45.4%)	67 (44.1%)
EDSS, median [25th, 75th]	6.0 [4.5, 6.5]	5.5 [4.0, 6.0]	6.0 [4.5, 6.5]
Type of MS, *n* (%)			
Primary progressive	82 (27.0%)	43 (28.3%)	39 (25.7%)
Secondary progressive	222 (73.0%)	109 (71.7%)	113 (74.3%)
Duration of MS, mean (SD) years	14.5 (9.63)	14.1 (9.44)	15.0 (9.82)
Primary language, *n* (%)**			
English	112 (37.0%)	55 (36.2%)	57 (37.7%)
Italian	150 (49.5%)	74 (48.7%)	76 (50.3%)
Dutch	18 (5.9%)	10 (6.6%)	8 (5.3%)
Danish	17 (5.6%)	9 (5.9%)	8 (5.3%)
French	1 (0.3%)	1 (0.7%)	0 (0.0%)
Other	5 (1.7%)	3 (2.0%)	2 (1.3%)
Marital status, dichotomized, n (%)			
Single	103 (33.9%)	48 (31.6%)	55 (36.2%)
Partnered	201 (66.1%)	104 (68.4%)	97 (63.8%)
Currently working, *n* (%)***	112 (37.1%)	62 (40.8%)	50 (33.3%)

EDSS: Expanded Disability Status Scale; School: total years of schooling; * Self-identified sex. ** $n = 303$. *** $n = 302$.

we included average adherence, FAMS total, EDSS score, years of school, and 6MWT distance as factors, and the analysis identified none of the factors as statistically significant correlates of W_{peak} change. Sensitivity analysis for the removal of baseline VO_{2peak} from the VO_{2peak} change regression is displayed in Table 5, yielding no statistically significant predictors of VO_{2peak} change.

Discussion

This article involved a secondary, exploratory analysis of data from the CogEx trial[15,16] and examined response heterogeneity in aerobic fitness with ET and its possible correlates in persons with PMS. We observed group-level mean changes in VO_{2peak} and W_{peak} as markers of aerobic fitness favoring the ET condition, and there was individual-level variability of the changes within the ET condition. The change in VO_{2peak} was primarily correlated with baseline aerobic fitness levels in the multivariable analyses—those with the lowest levels of aerobic fitness demonstrated the largest improvement in aerobic fitness with ET. Our results collectively highlight the presence of response heterogeneity in aerobic fitness with ET in PMS, and that this is correlated with initial levels of aerobic fitness. These analyses and results might directly inform hypothesis generation and testing in future clinical trials of response heterogeneity with ET in MS.

The ET condition resulted in statistically significant improvements in both VO_{2peak} and W_{peak} compared with no change in the sham control exercise condition, and this result argues for fitness adaptations with ET rather than practice effects with the assessment of aerobic fitness. The results further indicated heterogeneity of changes in VO_{2peak} and W_{peak} for the ET condition. The presence of this heterogeneity indicated that with the standardized aerobic ET

Table 2b. Clinical characteristics of the samples in exercise training and sham conditions regardless of cognitive training group assignment.

	Overall sample ($n = 304$)	Exercise training condition ($n = 152$)	Sham condition ($n = 152$)
SDMT number correct, mean (SD)	33.3 (8.18)	33.6 (8.47)	33.3 (8.18)
CVLT total, mean (SD)	44.8 (11.82)	45.2 (12.38)	44.8 (11.82)
BVMT-R total, mean (SD)	20.7 (7.46)	20.8 (7.24)	20.7 (7.46)
FAMS total, mean (SD)	103.5 (28.78)	105.7 (27.93)	103.5 (28.78)
MSWS total, mean (SD)	63.5 (26.60)	63.5 (27.47)	63.5 (26.60)
PDQ total, mean (SD)	28.4 (17.29)	28.4 (18.43)	28.4 (17.29)
MFIS total, mean (SD)	44.2 (17.27)	43.5 (17.79)	44.2 (17.27)
Average minutes/day MVPA, mean (SD)	13.1 (18.10)	14.7 (19.24)	13.1 (18.10)
6MWT total distance (m), mean (SD)	265.6 (140.59)	273.4 (141.49)	265.6 (140.59)
Average adherence (%), mean (SD)*	96.7 (8.17)	93.5 (10.60)	99.9 (0.95)
Average compliance (%), mean (SD)*	75.3 (27.10)	65.5 (28.79)	85.1 (21.26)
Baseline VO_{2peak}, (mL/kg/min) mean (SD)	17.5 (6.36)	17.5 (6.27)	17.5 (6.36)
Baseline W_{peak}, (W) mean (SD)	81.4 (33.72)	82.0 (34.27)	81.4 (33.72)

SDMT: symbol digit modalities test; CVLT: California Verbal Learning Test-II; BVMT-R: Brief Visuospatial Memory Test-Revised; FAMS: functional assessment of multiple sclerosis; 6MWT: 6-minute walk test; MSWS: 12-item MS walking scale; PDQ: Parkinson's disease questionnaire; MFIS: Modified Fatigue Impact Scale.
* $p < 0.001$, two-sample t-test.

Table 2c. Outcomes of the samples in exercise training and sham conditions regardless of cognitive training group assignment.

	Exercise training condition (n = 152)	Sham condition (n = 152)	p-value*
VO_{2peak} (mL/kg/min) change, mean (SD)**	1.5 (5.63)	−0.2 (4.17)	**0.003**
W_{peak} change, (W) mean (SD)***	12.3 (18.56)	−0.8 (17.36)	**< 0.001**

*Two-sample t-test. **$n = 272$. ***$n = 271$.

stimulus included in the CogEx trial, some participants demonstrated improvements in aerobic fitness, others no change, and some exhibited reductions in aerobic fitness. This is consistent with the results of a secondary analysis of data from an RCT of a 24-week period of multimodal ET in 54 people with moderate MS disability that documented response heterogeneity for change in W_{peak}.[12] The re-analysis of published data from an RCT of 8–10 weeks of ET in 42 people with PMS[11] further indicated interindividual variability of changes in VO_{2peak} based on waterfall plots and chi-square tests across three, standardized aerobic ET programs.[10] This convergence of results supports the presence of heterogeneity of changes in VO_{2peak} and W_{peak} with standardized ET conditions in persons with MS, and extends such data for the first time into PMS.

This study further examined bivariate and multivariable correlates of heterogeneity of change in VO_{2peak} and W_{peak} with the standardized ET condition. The variables were selected based on a published model for MS[10] and other research.[7–9,12] The correlation analysis identified baseline VO_{2peak}, average minutes/day of MVPA, average compliance, 6MWT distance, SDMT number correct, and baseline W_{peak} as small/weak, bivariate correlates of VO_{2peak} change for the ET condition; baseline VO_{2peak} had a significant and marginally larger correlation with change in VO_{2peak} for the sham control than ET condition. EDSS score, average adherence, years of school, FAMS total, and 6MWT were small/weak, bivariate correlates of W_{peak} change for the ET condition. The multivariable regression analysis indicated that only baseline VO_{2peak} correlated with change in

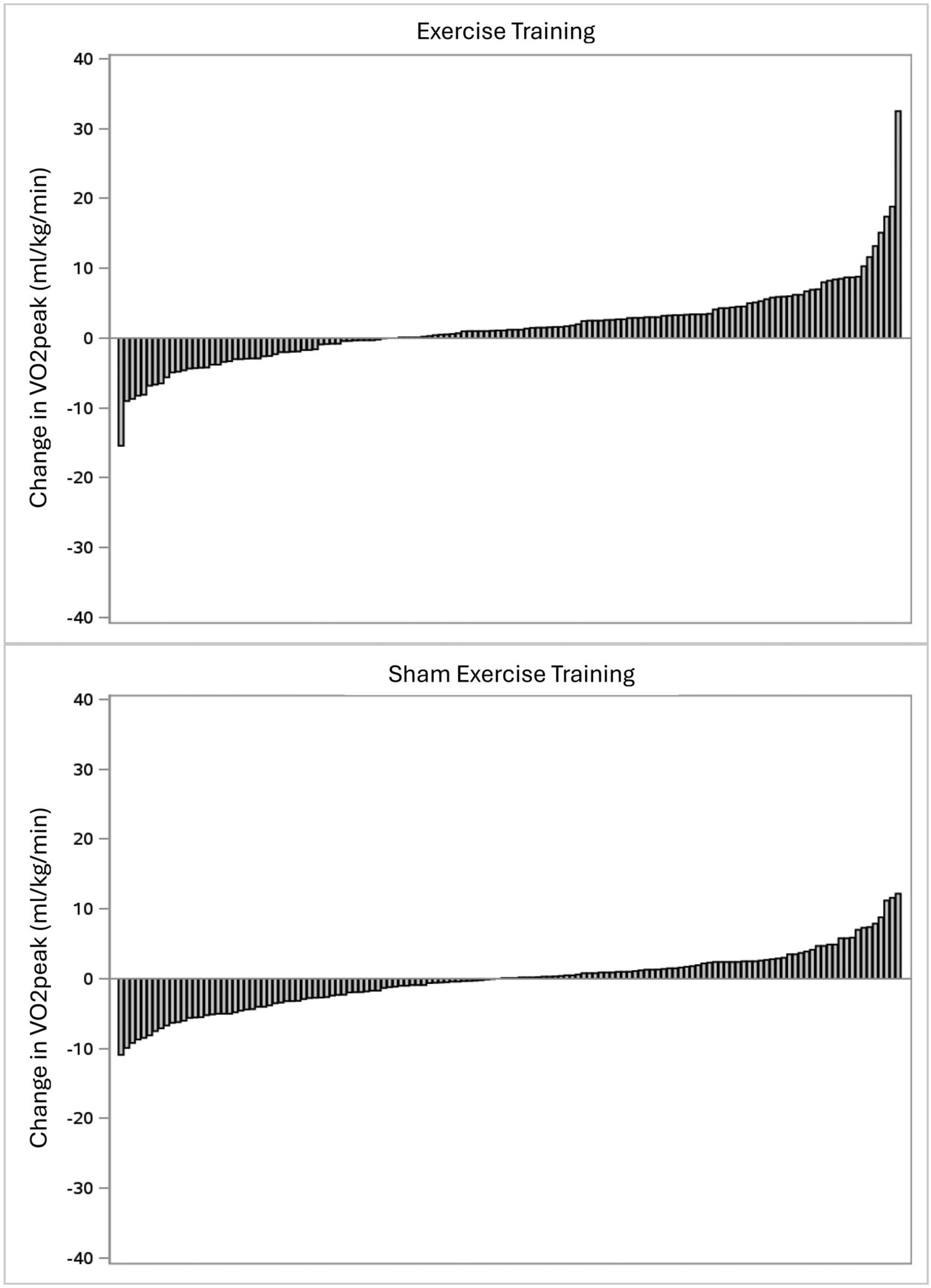

Figure 1. Waterfall plots for change in peak aerobic power based on peak oxygen consumption (VO_{2peak}; mL/kg/min) in the exercise training (Panel A) and sham exercise training (Panel B) conditions.

VO_{2peak}, and no variables correlated with change in W_{peak}. Those with lower baseline VO_{2peak} had larger changes in the respective outcome than those who had higher baseline levels, and this result was comparable with those seen for non-MS samples[8]; this may indicate that factors influencing oxidative metabolism with ET might not be influenced by MS-disease processes per se. We do not believe this represents a regression to the mean, as those in the ET intervention condition had larger changes in

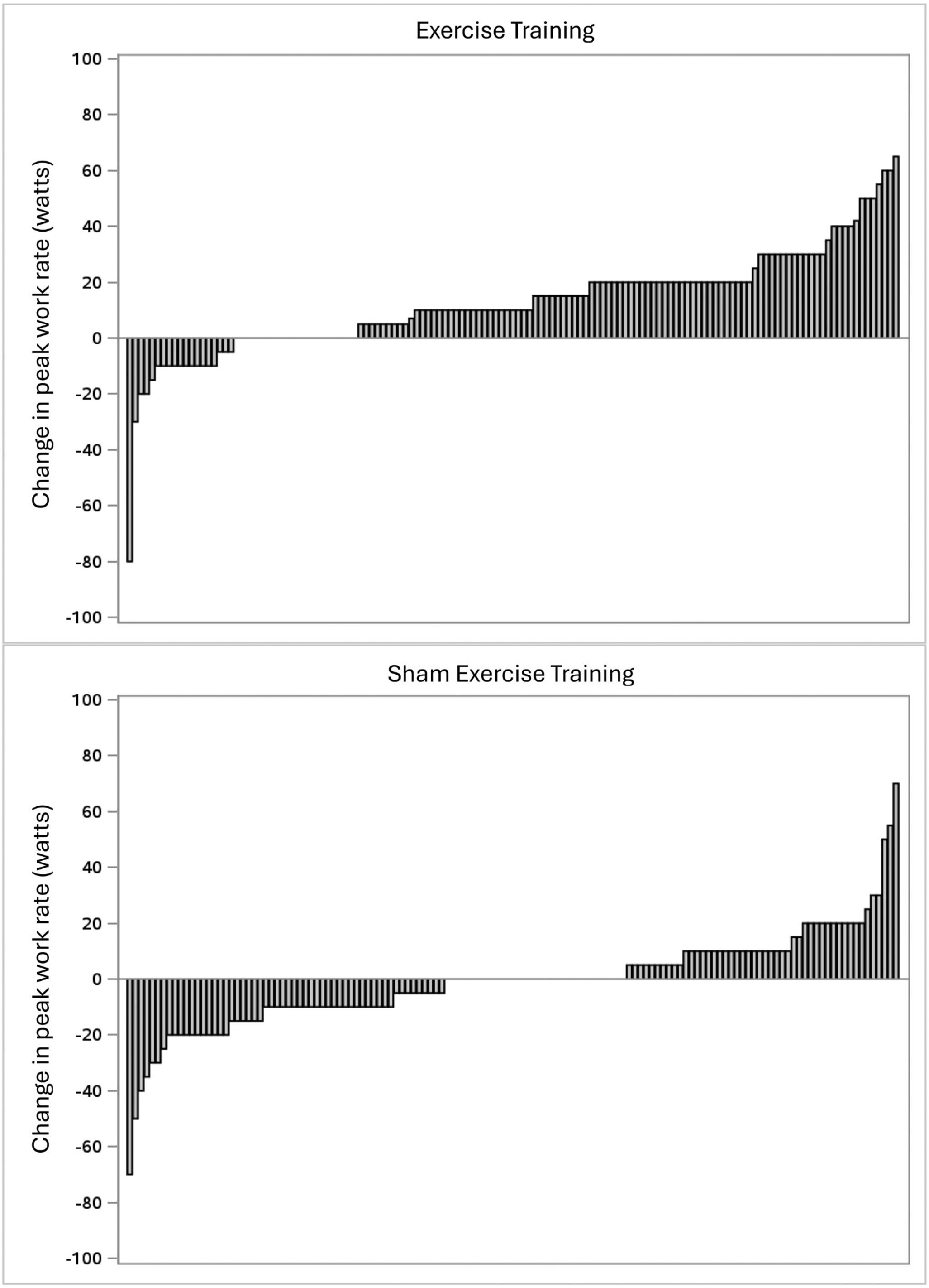

Figure 2. Waterfall plots for change in peak aerobic power based on peak work rate (W_{peak}; watts) in the exercise training (Panel A) and sham exercise training (Panel B) conditions.

VO_{2peak} and W_{peak} than those in the sham control condition. We further note that this result might reflect an artifact of the analyses that involved examining baseline aerobic fitness as a correlate of change in aerobic fitness, notably as we observed a significant correlation between baseline VO_{2peak} and change in VO_{2peak} for both the sham control and ET conditions, although there is no agreed-upon approach for studying response heterogeneity.[9] Our results suggest, in principle, that baseline aerobic fitness levels might

Table 3a. Correlation analysis of significant factors ($p < 0.2$) associated with VO_{2peak} and W_{peak} change in the exercise training condition.

	VO_{2peak} change		W_{peak} change	
	Correlation (r)	p-value	Correlation (r)	p-value
EDSS score			−0.161	0.063
Average adherence			0.157	0.069
Years of school			0.144	0.095
FAMS total			0.151	0.098
Baseline VO_{2peak}	−0.207	0.016		
Average minutes/day MVPA	0.160	0.067		
Average compliance	0.154	0.074		
6MWT total distance	0.146	0.091	0.113	0.190
SDMT number correct	0.142	0.100		
Baseline W_{peak}	0.139	0.108		

EDSS: Expanded Disability Status Scale; FAMS: functional assessment of multiple sclerosis; MVPA: moderate-to-vigorous physical activity; 6MWT: 6-minute walk test; SDMT: symbol digit modalities test.

Table 4a. Regression results for VO_{2peak} change as outcome in the exercise training condition.

Predictor	Estimate	Standard Error	p-value
Baseline VO_{2peak}	−0.37	0.10	< 0.001
Baseline W_{peak}	0.04	0.02	0.053
Average compliance	0.03	0.02	0.069
SDMT correct	0.09	0.06	0.120
6MWT total distance	0.01	0.01	0.276
Average minutes/day in MVPA	0.01	0.03	0.837

SDMT: symbol digit modalities test; MVPA: moderate-to-vigorous physical activity; 6MWT: 6-minute walk test.

Table 4b. Regression results for W_{peak} change as outcome in the exercise training condition.

Predictor	Estimate	Standard Error	p-value
Average adherence	0.32	0.22	0.154
FAMS total	0.07	0.06	0.237
EDSS score	−2.02	1.75	0.251
Total years of schooling	0.51	0.50	0.317
6MWT total distance	−0.01	0.02	0.763

FAMS: functional assessment of multiple sclerosis; EDSS: Expanded Disability Status Scale; 6MWT: 6-minute walk test.

Table 5. Regression results for VO_{2peak} change as outcome, baseline VO_{2peak} excluded as sensitivity analysis.

Predictor	Estimate	Standard Error	p-value
Average compliance	0.03	0.02	0.068
SDMT correct	0.11	0.06	0.089
Average minutes/day in MVPA	0.03	0.03	0.307
6MWT total distance	0.01	0.01	0.834
Baseline W_{peak}	0.01	0.02	0.851

SDMT: symbol digit modalities test; MVPA: moderate-to-vigorous physical activity; 6MWT: 6-minute walk test.

be an important consideration as a biomarker for precision trials of aerobic ET in PMS, particularly given that lower levels of aerobic fitness have been associated with worse outcomes in MS.[27] This implies that future research might target those with lower aerobic fitness levels, rather than physical inactivity, for inclusion in aerobic ET interventions that target beneficial outcomes in MS.

There are important limitations of this article. The CogEx trial itself was not designed for examining response heterogeneity with ET in PMS, and hence our results are largely data-driven and hypothesis-generating rather than confirmatory. The sample inclusion criteria resulted in a homogeneous sample,

Table 3b. Correlation analysis of significant factors ($p < 0.2$) associated with VO_{2peak} and W_{peak} change identified in the exercise condition that were examined in the sham condition.

	VO_{2peak} change		W_{peak} change	
	Correlation (*r*)	*p*-value	Correlation (*r*)	*p*-value
EDSS score			0.098	0.254
Average adherence			−0.059	0.495
Years of school			0.183	**0.033**
FAMS total			−0.119	0.178
Baseline VO_{2peak}	−0.331	**< 0.001**		
Average total minutes/day MVPA	0.077	0.398		
Average compliance	0.038	0.658		
6MWT total distance	−0.150	0.081	−0.053	0.542
SDMT number correct	−0.159	0.064		
Baseline W_{peak}	−0.110	0.203		

EDSS: Expanded Disability Status Scale; FAMS: functional assessment of multiple sclerosis; MVPA: moderate-to-vigorous physical activity; 6MWT: 6-minute walk test; SDMT: symbol digit modalities test.

particularly regarding processing speed impairment and physical inactivity, and the results might not be generalizable beyond the study sample. The sample size further might be too small, as we did not power the original study for this purpose.[9] The examination of correlates of heterogeneity was largely data-driven and restricted to the variables included in CogEx; other unmeasured factors might explain the variability of changes. The data analysis was exploratory and data-driven involving correlation analysis and multiple regression, and might have capitalized on chance features of the data set. We lastly analyzed the VO_{2peak} and W_{peak} changes between conditions differently than the main article,[16] although we do not believe this misrepresented the results. The sample size was based on a power analysis for the primary outcome, but not examining response heterogeneity, and future researchers might apply the results from the current article when guiding sample size calculations in confirmatory research involving predictors of heterogeneity. We did not collect data on smoking behavior, and this might have been a key influence on aerobic fitness adaptations and heterogeneity.

Overall, we observed group-level mean change in aerobic fitness favoring the ET condition, and there was heterogeneity of the change within the ET condition. The change in aerobic fitness was primarily correlated with baseline fitness levels in the multivariable analyses, such that those with the lowest levels of VO_{2peak} had the largest change in VO_{2peak}. The expanding evidence of heterogeneity of outcomes with ET interventions supports future hypothesis-driven research in this area, particularly if the field is interested in the design and testing of precision medicine approaches for optimizing outcomes with ET in MS.

Data availability

To promote data transparency, anonymized data will be available 1 year after the publication of this article, upon reasonable request. Please make the request to the corresponding author, RWM. The request will be reviewed for approval by a CogEx committee, and a data-sharing agreement will be put in place before any data are shared.

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