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Adherence and compliance with exercise training in progressive multiple sclerosis: Rates and correlates from the CogEx trial

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A R T I C L E I N F O

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A B S T R A C T

Background: There is limited understanding of adherence and compliance rates for exercise training(ET) in people with progressive multiple sclerosis(PMS).

Objectives: This secondary, exploratory data analysis examined rates of adherence and compliance for continuous, moderate intensity training and high-intensity interval training(HIIT) and possible correlates among people with 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(N = 311) were randomized into one of four conditions with different combinations of ET and cognitive rehabilitation, including respective sham conditions, delivered twice weekly over 12 weeks. The analysis focused on adherence and compliance rates and correlates for participants in the pooled ET intervention conditions who received and attempted the ET intervention(n = 152).

Results: The rates of adherence and compliance overall(combined for both training stimuli) were 94 % and 66 %, respectively. The rates of adherence and compliance for continuous, moderate-intensity exercise were 95 % and 73 %, respectively, and for HIIT were 92 % and 58 %, respectively. The multivariable regression indicated that better 6MWT performance predicted higher compliance(particularly with HITT), whereas better CVLT-II performance predicted higher adherence and compliance with continuous training in PMS.

Conclusion: Our results highlight worse compliance than adherence with ET, particularly for HIIT, in PMS. We further highlight cognitive and physical function as correlates of adherence and compliance for consideration in future clinical trials of ET in PMS.

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1. Introduction

There is increasing evidence for the benefits, safety, and prescription of exercise training in people with multiple sclerosis(MS). Meta-analyses of randomized controlled trials(RCTs) have reported beneficial effects of exercise training on cellular, functional, symptomatic, and participatory outcomes (Motl and Pilutti, 2024), and further reported on the safety of exercise training based on adverse and serious adverse events (Learmonth et al., 2023). That evidence guided the formation of prescriptive guidelines for exercise training in people with MS (Kalb et al., 2020).

The benefits of exercise seemingly depend on adherence and compliance with the training stimulus, yet the rates of those parameters are infrequently quantified and reported in RCTs of MS, perhaps based on lack of standardized definitions and metrics (Dalgas et al., 2020,Motl et al., 2023). The MoXFo initiative provided a major roadmap for advancing research on exercise training in MS (Dalgas et al., 2020), and one particular focus involved definitions and metrics of adherence and compliance with exercise training (Motl et al., 2023). Adherence was defined as completing sessions of exercise training, regardless of whether the sessions are performed as prescribed, and can be reported as the number/percentage of completed exercise sessions within an intervention(e.g., 36 of 48 or 75 % of prescribed exercise training sessions) (Motl et al., 2023). Compliance was defined as completing the sessions of exercise training as prescribed, and can be reported as the number/percent of completed exercise sessions that follow the prescription within an intervention(e.g., 36 of 48 or 75 % of prescribed exercise training sessions completed as prescribed based on intensity and duration) (Motl et al., 2023). The reporting of both adherence and compliance is important for clearly articulating the behavioral parameters underlying the validity and interpretation of exercise training and its outcomes in RCTs.

One recent paper documented the reporting and rates of adherence and compliance from 40 RCTs of exercise training in MS (Motl et al., 2024). That paper adopted definitions and metrics of adherence and compliance provided by the MoXFo adherence group (Motl et al., 2023). Adherence and compliance data were reported in approximately 50 % and 10 % of the RCTs, respectively. The rates of adherence and compliance approximated 80 % and 70 %, respectively (Motl et al., 2024). Such data are limited in scope by the few RCTs that reported on rates of adherence *and* compliance with exercise training overall and notably in people with PMS. Importantly, the results of RCTs involving relapsing-remitting MS might not generalize into PMS wherein there is markedly worse symptomology and increased prevalence and severity of cognitive and physical dysfunction that could undermine exercise adherence and compliance. There further is limited understanding of (a) adherence and compliance with different modalities of exercise training and (b) variables that might correlate with those outcomes.

The study of rates and correlates of adherence and compliance with exercise training in RCTs is important for several reasons. Such an analysis is important for characterizing the current state of the science and informing future RCTs on expected levels of adherence/compliance when planning for research (Motl et al., 2023). Such an analysis might further identify variables associated with exercise training adherence/compliance for understanding participation rates, optimizing outcomes, and reducing heterogeneity of this health-promoting behavior (Baird and Motl, 2019) for its inclusion in the clinical care of MS (Motl et al., 2017).

The current paper involved an analysis of adherence and compliance data for the exercise training conditions from the CogEx trial that enrolled people with PMS (Feinstein et al., 2020; Feinstein et al., 2023). The analysis was guided by the MoXFo initiative (Motl et al., 2023) and recent MS research (Motl et al., 2024) and focused on (a) establishing the rates of adherence and compliance overall (combined for both training stimuli) and between the two stimuli of exercise training (continuous, moderate-intensity exercise and high-intensity interval training, HIIT), and (b) exploring bivariate and multivariable correlates of adherence and compliance overall and per stimulus.

2. Methods

2.1. Trial description

The CogEx trial was a multi-site, multi-arm, randomized, double-blind, and sham-controlled clinical trial undertaken by 11 sites across six countries: Canada(1 site), USA(2 sites), United Kingdom(2 sites), Denmark(1 site), Belgium(1 site), and Italy(4 sites) (Feinstein et al., 2020; Feinstein et al., 2023). Participants with PMS(N = 311) were randomized into one of four conditions with different combinations of exercise training and cognitive rehabilitation including respective sham conditions. This analysis focuses on adherence, compliance, and associated correlates among participants from the pooled exercise training intervention conditions who received and attempted the intervention(n = 152; see Consort in Fig. 1).

2.2. Participants

The full inclusion/exclusion criteria for participants are provided in Table 1 (Feinstein et al., 2020). The diagnosis of primary or secondary PMS was confirmed by a neurologist. 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). Physical inactivity was based on a Godin Leisure-Time Exercise Questionnaire Health Contribution Scale score of less than 24. There was no inclusion/exclusion criterion for fampridine.

2.3. Exercise training program

The exercise training intervention condition was fully described in the protocol (Feinstein et al., 2020) and primary outcome (Feinstein et al., 2023) papers, and involved a standardized program of supervised aerobic exercise training on a recumbent arm-leg stepper(Nustep T5XR, Nustep Inc, Ann Arbor, MI). The exercise training protocol was designed based on several important features. The first is that the program is largely consistent with evidence-based guidelines recommending 2 days of 30-min of aerobic physical activity per week in MS (Kalb et al., 2020). The second is that the combination of continuous, moderate intensity training and HIIT on separate days of the week includes 2 stimuli of aerobic exercise training that elicit different acute and chronic adaptations in MS. The third is that an international team of experts designed the exercise training program based on both research and clinical experiences in MS. The aerobic exercise training consisted of bouts of continuous, moderate-intensity exercise and HIIT performed on alternating days, two times per week for 12 weeks. The continuous bouts progressed from 10 min of exercise at a work rate associated with 50–60 % VO_{2peak} in Week 1 towards 30 min of exercise at a work rate associated with 70–80 % VO_{2peak} in Week 12. The HIIT bouts progressed from 5, 1-min intervals at a work rate associated with 80–90 % VO_{2peak} interspersed with 1-min rest periods (i.e., lightly exercising at 15 W) in Week 1 towards 10, 2-min intervals at a work rate associated with 90 % VO_{2peak} interspersed with 2-min rest periods in Week 12. Of note, the prescribed work rates corresponding with percentages of VO_{2peak} were determined based on values from the cardiopulmonary exercise test.

2.4. Procedure

The study procedure was approved by site-specific, institutional review boards, and participants provided written informed consent. Participants initially completed baseline assessments in the laboratory, and were randomized into one of the four study conditions; 50 % of participants were randomly assigned into the exercise training condition with either cognitive rehabilitation or sham. The participants completed the

12-week study period, and we carefully monitored adherence and compliance with the exercise training condition.

2.5. Measures

Adherence/Compliance. The definitions of adherence and compliance were consistent with recent recommendations from MoXFo (Motl et al., 2023; Motl et al., 2024). Adherence was defined as attending and undertaking the exercise training sessions (Motl et al., 2023; Motl et al., 2024), and expressed as a percentage of the total sessions. Compliance was defined as undertaking and completing the exercise training sessions consistent with 90 percent of the prescription (Motl et al., 2023; Motl et al., 2024), and expressed as a percentage of the total exercise training sessions. Compliance was operationalized based on exercising within ±5 W of the prescribed work rate for 90 % of the continuous bout of exercise, and exercising within ±5 W of the prescribed work rate for n – 1 of the HIIT bouts of exercise. For example, if a participant completed the prescribed HIIT work rate for 4 of 5 intervals in week 1, the session was deemed compliant, but if a participant completed the prescribed HIIT work rate for 4 of 6 intervals in week 2, the session was deemed noncompliant. We recognize this is a rather stringent criterion for compliance, but there is no agreed up definition for a threshold available in the published literature (5–7) and we sought for a strong standard in the current study based on the expectation that compliance was critical for adaptations with exercise training (7). The failure to attend a session (i.e., missing data for a session that was not undertaken) was recorded as non-adherent/non-compliant for that session.

Demographic/Clinical Characteristics. The demographic characteristics included age, sex, marital status, years of schooling, and current employment. We did not collect data on race/ethnicity. The clinical characteristic included disease duration, and all participants had PMS.

Table 1
Inclusion and exclusion criteria for the CogEx trial as reported in our protocol (Feinstein et al., 2020) and primary outcomes (Feinstein et al., 2023) 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 past three 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 ≥ 7.0
Neurological History	A history of central nervous system disease other than PMS. Disease exacerbations in the past three months.
Medications	Steroids use within the past three months
Current exercise activity	Regular aerobic training at an estimated intensity of >60 % of the maximal heart rate reserve, for more than one day per week lasting more than 30 min per session for the past 3 months. Assessment of exercise habits based on the Godin Leisure-Time Exercise Questionnaire health contribution 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 (≥ 29 on the Beck Depression Inventory.
MRI (substudy)	Claustrophobia, metal implants, pacemakers.

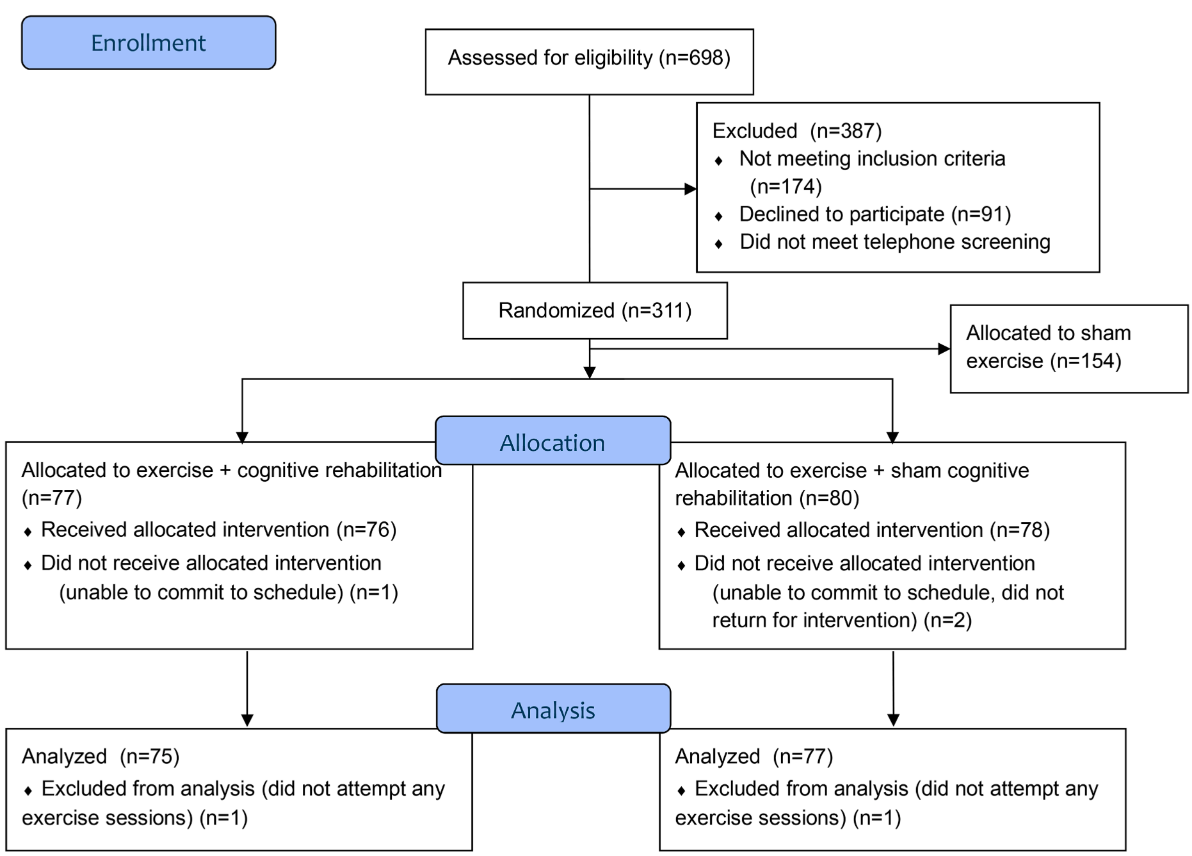

Fig. 1. Consort flow diagram (adherence/compliance).

Disability Status. The Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) score was provided by the participant's treating neurologist.

Mobility. The 6-Min Walk Test(6MWT) characterized walking performance based on walking endurance (Goldman et al., 2008). The 6MWT has strong psychometric properties and was administered using standard instructions for MS (Goldman et al., 2008). 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 (Goldman et al., 2008). The tester recorded total distance walked over the 6-min period in meters.

Cognition. Cognitive performance was assessed using the Brief International Cognitive Assessment for MS(BICAMS) (Langdon et al., 2012). The BICAMS battery includes the SDMT, first five learning trials of the California Verbal Learning Test-II(CVLT-II), and 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 (Langdon et al., 2012). The BICAMS was administered using standardized procedures across sites using validated language-specific forms. The outcomes were total(raw) scores per BICAMS test.

Cardiopulmonary Exercise Test(CPET). Aerobic fitness, operationalized as VO_{2peak} and W_{peak}, was recorded using a maximal, incremental 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 (Pilutti et al., 2015). Briefly, the CPET protocol involved a 1-min warm-up at 15 watts. The initial work rate was 15 watts and gradually increased until the participant reached volitional fatigue. The work rate increased by 10 watts per min or 5 watts per minute 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-s 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 (Langeskov-Christensen et al., 2014). The highest recorded power achieved during a 20-s period was recorded as peak power output in watts(W_{peak}).

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 min) were processed in ActiLife (Actigraph Corporation, FL) using MS-specific cut-points (Sasaki et al., 2017).

Patient Reported Outcome Measures(PROMs). The PROMs included fatigue(Modified Fatigue Impact Scale, MFIS) (Ritvo et al., 1997), subjective cognitive deficits(20-item Perceived Deficits Questionnaire, PDQ) (Sullivan et al., 1990), walking impairment(12-item Multiple Sclerosis Walking Scale, MSWS-12) (Hobart et al., 2003), global function(Functional Assessment of Multiple Sclerosis, FAMS) (Cella et al., 1996), and physical and mental health status(Multiple Sclerosis Impact Scale-29, MSIS-29) (Hobart et al., 2001).

2.6. Data analysis

The analyses included participants who were randomized, began the intervention, and had adherence/compliance data for the exercise training conditions, per the CONSORT in Fig. 1. We provide descriptive statistics as mean(SD), median(IQR), and range for the adherence and compliance data combined and between exercise training stimuli(i.e., continuous, moderate intensity training and HIIT). We evaluated associations between correlates and rates of adherence and compliance combined and per exercise training stimulus. The bivariate correlations involved point-biserial correlations(r_{pb}) for dichotomous variables(e.g., sex) and Spearman rank-order correlations(ρ) for multi-level categorical and continuous variables in association with adherence and compliance. Cohen's guidelines of 0.1, 0.3, and 0.5 indicated small, moderate, and strong correlations, respectively (Cohen, 1988). We included variables with a $p < 0.2$ from the correlation analysis into negative-binomial multivariable regression; this regression model was selected considering the highly skewed outcome variable distributions and over-dispersion. Stepwise selection was performed with a significance threshold of $p < 0.15$ for variable inclusion and Akaike Information Criterion with correction(AICc) for final model selection. The negative-binomial multivariable regression was performed on adherence and compliance data overall and per exercise training stimulus. All statistical analyses were conducted in SAS(version 9.4, Cary, NC, USA).

3. Results

3.1. Sample characteristics

The demographic and clinical characteristics for the sample who received the exercise training intervention conditions($n = 152$) are provided in Table 2a and 2b, respectively.

3.2. Adherence and compliance rates

The adherence and compliance data are provided in Table 3. The mean(SD) rates of adherence with exercise training were 93.5(10.6), 94.9(9.4), and 92.0(13.5) percent for combined, continuous, moderate intensity training, and HIIT, respectively. The mean(SD) rates of compliance with exercise training were 65.5(28.8), 73.0(29.7), and 57.9

Table 2a
Demographic characteristics of the sample in the exercise training condition regardless of cognitive training group assignment.

	Exercise Training Condition ($n = 152$)
Age, mean (SD)	52.0 (7.38)
Sex*, n (%)	
Female	99 (65.1 %)
Male	53 (34.9 %)
School, mean (SD) years	13.9 (3.32)
Highest level of education completed, n (%)	
Primary	12 (7.9 %)
Secondary (high school)	71 (46.7 %)
College / University	69 (45.4 %)
EDSS, median [25th, 75th]	5.5 [4.0, 6.0]
Type of MS, n (%)	
Primary progressive	43 (28.3 %)
Secondary progressive	109 (71.7 %)
Duration of MS, mean (SD) years	14.1 (9.44)
Primary language, n (%)	
English	55 (36.2 %)
Italian	74 (48.7 %)
Dutch	10 (6.6 %)
Danish	9 (5.9 %)
French	1 (0.7 %)
Other	3 (2.0%)
Marital status, dichotomized, n (%)	
Single	48 (31.6 %)
Partnered	104 (68.4 %)
Currently working, n (%)	62 (40.8 %)

EDSS=Expanded Disability Status Scale; School=total years of schooling;.
* Self-identified sex.

Table 2b
Clinical characteristics of the sample in exercise training condition regardless of cognitive training group assignment.

	Exercise Training Condition (n = 152)
SDMT number correct	33.6 (8.5)
CVLT-II total	45.2 (12.4)
BVMT-R total	20.8 (7.2)
FAMS total	105.7 (27.9)
MSIS-29 physical	58.0 (18.3)
MSIS-29 mental	22.4 (8.6)
MSWS-12 total	63.5 (27.5)
PDQ total	28.4 (18.4)
MFIS total	43.5 (17.8)
Average minutes/day MVPA	14.7 (19.2)
6MWT total distance (m)	273.4 (141.5)
VO_{2peak} (ml/kg/min)	17.5 (6.3)
W_{peak} (watts)	82.0 (34.3)

Note. Values reported as mean (standard deviation). SDMT=Symbol Digit Modalities Test; CVLT-II=California Verbal Learning Test-II; BVMT-*R*=Brief Visuospatial Memory Test-Revised; FAMS=Functional Assessment of Multiple Sclerosis; MSIS-29=Multiple Sclerosis Impact Scale-29; MSWS-12=Multiple Sclerosis Walking Scale-12; PDQ=Perceived Deficits Questionnaire; MFIS=Modified Fatigue Impact Scale; MVPA=moderate-to-vigorous physical activity; 6MWT=6-Min Walk Test; VO_{2peak}=peak oxygen consumption; W_{peak}=peak power output.

Table 3
Adherence and compliance rates for the exercise training condition overall and separately by the moderate, intensity continuous training and high intensity interval training components of the exercise training intervention.

Exercise Training Modality	Descriptive Statistic	Adherence (%)	Compliance (%)
Overall Exercise Training			
	Mean (SD)	93.5 (10.6)	65.5 (28.8)
	Median (IQR)	100.0 (91.7, 100.0)	75.0 (41.7, 91.7)
	Range	33.3, 100.0	0.0, 100.0
Moderate Intensity, Continuous Training			
	Mean (SD)	94.9 (9.4)	73.0 (29.7)
	Median (IQR)	100.0 (91.7, 100.0)	83.3 (58.3, 100.0)
	Range	41.7, 100.0	0.0, 100.0
High Intensity Interval Training			
	Mean (SD)	92.0 (13.5)	57.9 (34.9)
	Median (IQR)	100.0 (87.5, 100.0)	66.7 (25.0, 91.7)
	Range	0.0, 100.0	0.0, 100.0

Note. SD=standard deviation; IQR=interquartile range.

(34.9) percent for combined, continuous, moderate intensity training, and HIIT, respectively. Adherence was higher than compliance combined and between both stimuli of exercise training, and compliance was higher for continuous, moderate intensity training than HIIT. The histograms for adherence and compliance rates are provided in Fig. 2, and illustrate greater variation in compliance than adherence overall and notably for HIIT compared with continuous, moderate intensity training.

3.3. Bivariate correlates of adherence and compliance rates

The bivariate correlation analyses are provided in Table 4a and Table 4b for adherence and compliance, respectively. There were few variables associated with adherence. Only CVLT-II scores and marital status were associated with combined adherence; CVLT-II scores, 6MWT, and marital status were associated with HIIT adherence; and CVLT-II scores were associated with continuous, moderate intensity training adherence.

By comparison, there were more variables associated with compliance outcomes. Marital status, work status, disease duration, CVLT-II scores, 6MWT, FAMS, MSIS-29 physical and mental, MSWS-12, HADS depression, PDQ, and MVPA were associated with combined compliance; marital status, work status, disease duration, 6MWT, VO_{2peak}, W_{peak}, FAMS, MSIS-29 physical, MSWS-12, HADS depression, and MVPA were associated with HIIT compliance; and age, marital status, EDSS, CVLT-II scores, W_{peak}, PDQ, and HADS depression were associated with continuous, moderate intensity training compliance.

3.4. Multivariable correlates of adherence and compliance rates

The results for the multivariable analysis for adherence and compliance are provided in Table 5a and 5b, respectively, and we note that the generally small coefficients from the models likely have limited clinical interpretability. Regarding adherence combined, the variables included in the model were marital status and CVLT-II scores, and the final regression model included only CVLT-II scores. For every one-point increase in baseline CVLT-II scores, the expected combined adherence rate increased by a factor of 1.0015, or 0.15 %. Regarding adherence for HIIT, the model included marital status, 6MWT, and CVLT-II scores, and the final regression model included marital status and 6MWT. Married participants had a 4.87 % increase in the expected HIIT adherence rate compared to those that were single, while holding the 6MWT constant. For every ten-meter increase in 6MWT a participant could walk at baseline was associated with a 0.16 % increase in the expected HIIT adherence rate, while adjusting for marital status. Although both of the relationships were not statistically significant, the results still suggest a positive association between both variables and HIIT adherence. Regarding adherence for continuous, the model only included CVLT-II scores. For every one-point increase in baseline CVLT-II scores, the expected continuous adherence rate increased by a factor of 1.0016, or 0.16 %.

Regarding compliance combined, the variables included in the model were marital status, work status, disease duration, 6MWT, CVLT-II scores, FAMS total, MSIS-29(physical), MSIS-29(mental), MSWS-12, PDQ total, HADS depression, and MVPA. The final regression model included only 6MWT. For every ten-meter increase in 6MWT, the expected combined compliance rate increased by a factor of 1.0072, or 0.72 %. Regarding compliance for HIIT, the variables included in the model were marital status, work status, disease duration, 6MWT, VO_{2peak}, W_{peak}, FAMS total, MSIS-29(physical), MSWS-12, PDQ total, HADS depression, and MVPA. The final regression model included only 6MWT. For every ten-meter increase in 6MWT, the expected HIIT compliance rate increased by a factor of 1.0131, or 1.31 %. Regarding compliance for continuous, the variables included in the model were age, marital status, EDSS score, CVLT-II scores, W_{peak}, PDQ total, and HADS depression. The final regression model included only CVLT-II scores. For every one-point increase in CVLT-II scores, the expected continuous compliance rate increased by a factor of 1.0052, or 0.52 %. Although the relationship was not significant, it still suggests a positive association between baseline CVLT-II scores and continuous compliance.

4. Discussion

This paper established the rates of adherence and compliance overall (combined for both training stimuli) and between the two stimuli of aerobic exercise training(continuous, moderate-intensity exercise and HIIT), and explored bivariate and multivariable correlates of adherence and compliance in people with PMS. Such an analysis is important for characterizing the current state of the science and informing future RCTs on expected levels of adherence/compliance when planning for research on exercise training in PMS (Motl et al., 2023). The focus on PMS is important as there is markedly worse symptomology and increased prevalence and severity of cognitive and physical dysfunction that could undermine adherence and compliance with exercise training. Such an analysis might further identify variables associated with

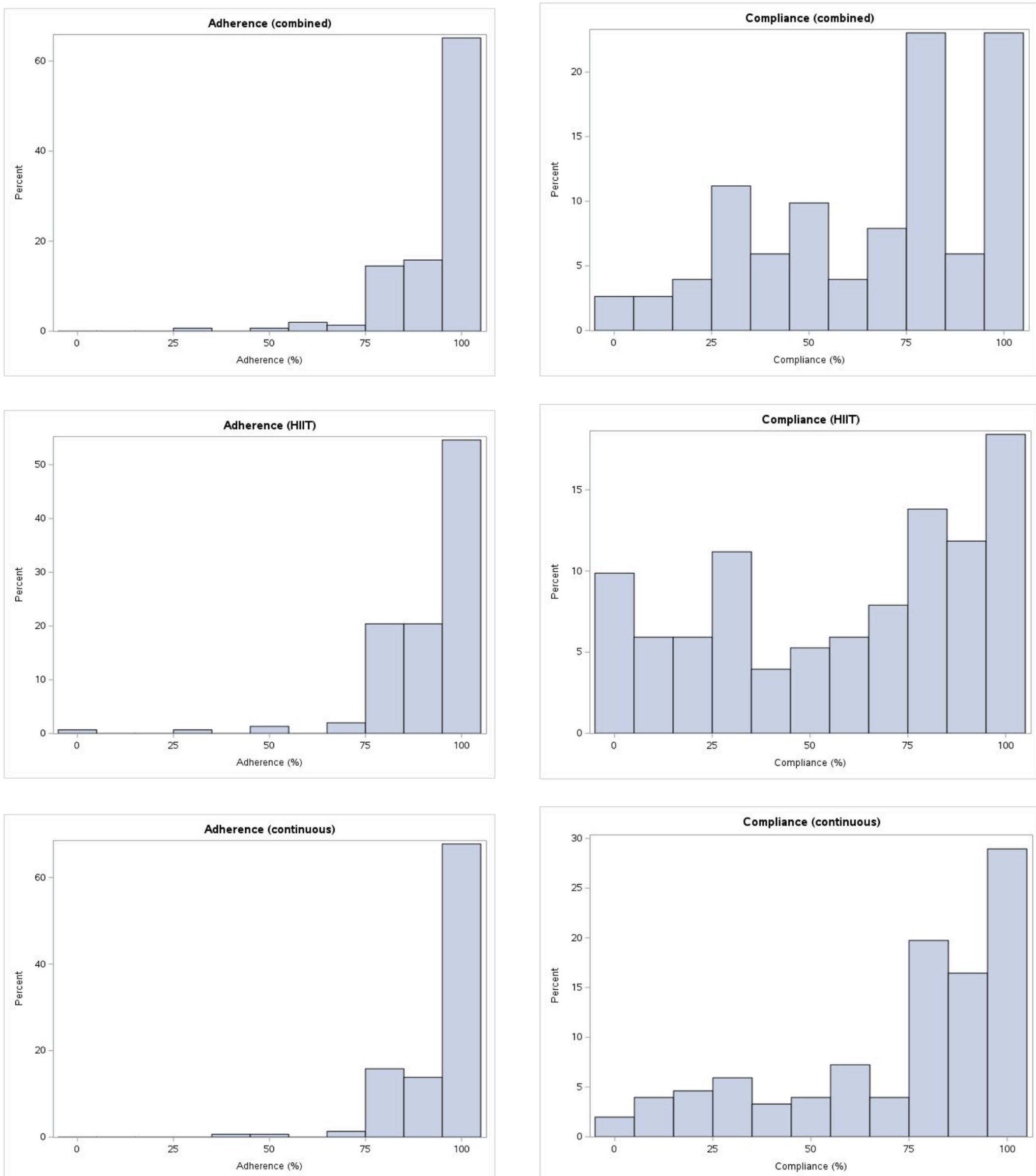

Fig. 2. Histograms of adherence and compliance rates for the exercise training conditions combined and by modality of exercise training (HITT and Continuous) delivered in the CogEx trial.

adherence/compliance for understanding participation rates, optimizing outcomes, and reducing heterogeneity of this health-promoting behavior for persons with PMS (Baird and Motl, 2019). We note that this analysis focused on adherence and compliance with supervised, center-based exercise training, and the results might have limited generalizability for exercise in home-based, unsupervised, or community settings.

The overall mean adherence rate was 94 %, and adherence did not differ between continuous, moderate intensity training and HIIT. The rate of adherence in this study was higher than reported in review papers (Motl et al., 2024; Dennett et al., 2020). One review paper reported an adherence rate of 80 % across 40 RCTs of exercise training in MS (Motl et al., 2024), and another reported an adherence rate of 87 % across 41 RCTs (Dennett et al., 2020). We further observed limited variation for adherence in the current study(COV = 11.3 %), whereas others have reported substantial variability across RCTs (Dennett et al., 2020). One potential reason for the higher adherence rate in this study might involve organization and payment for transportation when attending the exercise training sessions, as our definition of adherence based on MoXFo involved attending and undertaking the session itself.

The overall mean compliance rate was 66 %, and compliance seemingly differed between continuous, moderate intensity training and HIIT. The overall rate of compliance in this study was consistent with that reported in a recent review paper in MS (Motl et al., 2024). That review paper reported a compliance rate of 70 % across 40 RCTs of exercise training in MS. We further observed large variation for compliance in the current study(COV = 44.0 %). The reasons for the lower rate of compliance combined with larger variability for HIIT than continuous, moderate intensity training might have involved the level of exertion (Dishman and Buckworth, 1996). Indeed, participants attended and undertook the HIIT sessions, but could not complete them as prescribed based on the strenuous nature of the stimulus itself(e.g., 10, 2-min intervals @ 90 % VO_{2peak} with 2 min rest). This reflects the real challenge of the HIIT sessions for a more disabled PMS population when maintaining a strict exercise prescription. Perhaps future research might consider other parameters for the HIIT prescription such as a 1-min

Table 4a
Correlation analysis of significant variables ($p < 0.2$) associated with adherence overall and moderate intensity continuous exercise and high intensity interval training.

	Correlation with combined adherence	p-value	Correlation with HIIT adherence	p-value	Correlation with continuous adherence	p-value
Age	0.017	0.833	0.004	0.955	0.035	0.666
Gender (ref: male)*	−0.027	0.733	−0.013	0.865	−0.042	0.600
Marital status (ref: single)*	**0.115**	**0.155**	**0.150**	**0.064**	0.044	0.582
Total years of school	−0.011	0.886	0.005	0.942	−0.017	0.826
Work status (ref: no work)*	−0.041	0.615	−0.014	0.856	−0.071	0.383
Disease duration	0.039	0.629	0.029	0.719	0.065	0.424
EDSS score	−0.035	0.666	−0.068	0.405	0.023	0.773
6MWT	0.087	0.283	**0.137**	**0.090**	0.004	0.955
SDMT	0.064	0.427	0.059	0.467	0.092	0.254
CVLT-II	**0.128**	**0.114**	**0.136**	**0.092**	**0.137**	**0.090**
BVMT-R	−0.015	0.852	−0.003	0.961	−0.007	0.929
VO_{2peak}	0.066	0.414	0.081	0.319	0.024	0.768
W_{peak}	0.067	0.406	0.090	0.267	0.008	0.916
FAMS total	−0.066	0.442	−0.048	0.577	−0.055	0.522
MSIS-29 physical	0.055	0.498	0.039	0.628	0.048	0.556
MSIS-29 mental	0.067	0.406	0.067	0.409	0.046	0.568
MSWS-12 total	−0.027	0.739	−0.055	0.497	−0.014	0.863
PDQ total	0.004	0.957	−0.002	0.973	0.009	0.907
MFIS total	0.008	0.913	0.008	0.914	−0.008	0.922
HADS anxiety	0.081	0.320	0.078	0.340	0.038	0.635
HADS depression	0.082	0.311	0.077	0.346	0.027	0.740
Avg MVPA	0.031	0.706	0.069	0.410	−0.035	0.676

* Point-biserial correlation.
Bolded if $p < 0.2$, used as candidate variable for multivariable model stepwise selection.
SDMT=Symbol Digit Modalities Test; CVLT-II=California Verbal Learning Test-II; BVMT-*R*=Brief Visuospatial Memory Test-Revised; FAMS=Functional Assessment of Multiple Sclerosis; MSIS-29=Multiple Sclerosis Impact Scale-29; MSWS-12=Multiple Sclerosis Walking Scale-12; PDQ=Perceived Deficits Questionnaire; MFIS=Modified Fatigue Impact Scale; MVPA=moderate-to-vigorous physical activity; 6MWT=6-Min Walk Test; VO_{2peak}=peak oxygen consumption; W_{peak}=peak power output.

Table 4b
Correlation analysis of significant variables ($p < 0.2$) associated with compliance overall and moderate intensity continuous exercise and high intensity interval training.

	Correlation with combined compliance	p-value	Correlation with HIIT compliance	p-value	Correlation with continuous compliance	p-value
Age	0.103	0.206	0.055	0.495	**0.137**	**0.092**
Gender (ref: male)*	−0.044	0.586	−0.077	0.342	0.004	0.951
Marital status (ref: single)*	**0.132**	**0.104**	**0.118**	**0.147**	**0.117**	**0.149**
Total years of school	−0.071	0.384	−0.067	0.409	−0.084	0.301
Work status (ref: no work)*	**0.154**	**0.058**	**0.179**	**0.027**	0.088	0.280
Disease duration	**−0.123**	**0.131**	**−0.139**	**0.088**	−0.045	0.583
EDSS score	−0.014	0.861	−0.096	0.236	**0.105**	**0.196**
6MWT	**0.207**	**0.010**	**0.279**	**0.001**	0.028	0.728
SDMT	−0.075	0.357	−0.029	0.713	−0.081	0.318
CVLT-II	**0.118**	**0.144**	0.065	0.423	**0.183**	**0.023**
BVMT-R	0.075	0.354	0.090	0.270	0.017	0.830
VO_{2peak}	0.067	0.407	**0.132**	**0.104**	−0.040	0.616
W_{peak}	0.082	0.312	**0.199**	**0.013**	**−0.110**	**0.175**
FAMS total	**0.156**	**0.069**	**0.158**	**0.064**	0.078	0.362
MSIS-29 physical	**−0.126**	**0.119**	**−0.116**	**0.154**	−0.086	0.288
MSIS-29 mental	**−0.109**	**0.179**	−0.101	0.213	−0.072	0.375
MSWS-12 total	**−0.184**	**0.023**	**−0.199**	**0.014**	−0.089	0.276
PDQ total	**−0.120**	**0.142**	−0.043	0.595	**−0.177**	**0.029**
MFIS total	−0.084	0.306	−0.071	0.382	−0.079	0.332
HADS anxiety	−0.068	0.406	−0.031	0.701	−0.082	0.312
HADS depression	**−0.145**	**0.074**	**−0.121**	**0.137**	**−0.114**	**0.161**
Avg MVPA	**0.115**	**0.169**	**0.193**	**0.020**	−0.022	0.788

* Point-biserial correlation.
Bolded if $p < 0.2$, used as candidate variable for multivariable model stepwise selection.
SDMT=Symbol Digit Modalities Test; CVLT-II=California Verbal Learning Test-II; BVMT-*R*=Brief Visuospatial Memory Test-Revised; FAMS=Functional Assessment of Multiple Sclerosis; MSIS-29=Multiple Sclerosis Impact Scale-29; MSWS-12=Multiple Sclerosis Walking Scale-12; PDQ=Perceived Deficits Questionnaire; MFIS=Modified Fatigue Impact Scale; MVPA=moderate-to-vigorous physical activity; 6MWT=6-Min Walk Test; VO_{2peak}=peak oxygen consumption; W_{peak}=peak power output.

intervals at 90 % VO_{2peak} with 1 min rest(1:1 ratio) as this has been demonstrated as feasible within acute and chronic exercise involving people with MS who have EDSS 4–6.5 (Hubbard et al., 2019; Silveira et al., 2024).

The analysis of bivariate correlates indicated a larger set of variables associated with compliance(7–12 variables) than adherence(1–3 variables) overall and per exercise training stimulus. The overlapping correlates of compliance and adherence were marital status, CVLT-II scores,

Table 5
Multivariable negative binomial regression with adherence and compliance (combined, HIIT, continuous).

Exercise Stimulus	Predictor*	Rate ratio	95 % CI	p-value
Adherence				
Combined[1]	CVLT-II total	1.0015	1.0000, 1.0030	**0.045**
HIIT[2]	Marital status (ref: single)	1.0487	0.9899, 1.1110	0.106
	6MWT (10 m)	1.0016	0.9997, 1.0035	0.098
Continuous[3]	CVLT-II total	1.0016	1.0003, 1.0029	**0.016**
Compliance				
Combined[4]	6MWT (10 m)	1.0072	1.0006, 1.0139	**0.033**
HIIT[5]	6MWT (10 m)	1.0131	1.0017, 1.0245	**0.023**
Continuous[6]	CVLT-II total	1.0052	0.9976, 1.0128	0.182

* Stepwise selection was performed with candidate variables from correlation analysis ($p < 0.2$) for each respective outcome.
[1] Stepwise candidate variables: Marital status, 6MWT, CVLT total.
[2] Stepwise candidate variables: Marital status, 6MWT, CVLT total.
[3] Stepwise candidate variables: CVLT total.
[4] Stepwise candidate variables: Marital status, Work status, Disease duration, 6MWT, CVLT total, FAMS total, MSIS-29 (physical), MSIS-29 (mental), MSWS-12, PDQ total, HADS depression, Average MVPA.
[5] Stepwise candidate variables: Marital status, Work status, Disease duration, 6MWT, VO_{2peak}, W_{peak}, FAMS total, MSIS-29 (physical), MSWS-12, PDQ total, HADS depression, Average MVPA.
[6] Stepwise candidate variables: Age, Marital status, EDSS score, CVLT total, W_{peak}, PDQ total, HADS depression.

and 6MW, whereas work status, disease duration, FAMS, MSIS-29 physical and mental, MSWS-12, HADS depression, PDQ, and MVPA were associated with compliance, but not adherence. This difference might be explained by the smaller variation in adherence than compliance resulting in a truncated distribution of scores and few correlations, or ceiling effects wherein there were generally high adherence values (median = 100 %) with limited room for identifying correlations.

The multivariable analysis of correlates identified 6MWT and CVLT-II performance as the primary correlates of adherence and compliance overall and per stimulus of training. The CVLT-II was the primary correlate of adherence combined, and 6MWT was the primary correlate of HIIT combined. We further note that CLVT-II scores were primarily correlated with adherence and compliance for continuous, moderate intensity training, whereas 6MWT was primarily correlated with HIIT adherence and compliance. This suggests that those with higher cognitive status regarding verbal learning and memory had better adherence (i.e., attendance) notably for continuous, moderate intensity training, whereas those with higher physical status had better compliance (i.e., completion) notably for HIIT. This might suggest that those with better cognitive and physical function are better positioned for undertaking and completing a combined recumbent stepping exercise training approach as adopted in CogEx, and these variables might further be targets of intervention for promoting exercise adherence and compliance in those with lower levels of cognitive and physical function. Researchers might explore whether CVLT-II and 6MWT performance can serve as practical screening tools that identify participants needing additional support for maintaining adherence and compliance and reducing sample heterogeneity. We do note, importantly, that the 6MWT and CVLT-II were generally weakly correlated with adherence and compliance in the bivariate and multivariable analyses, and this might suggest limited clinical interpretability.

The primary limitation of this secondary data analysis involves the lack of theory-based variables(i.e., self-efficacy) that could be targets of behavioral change interventions for improving adherence and compliance with exercise training in PMS. This is largely the product of the secondary analysis of existing data from a trial that was not a priori designed for identifying modifiable variables for explaining exercise adherence and compliance. To that end, future researchers might consider applying theory-based approaches for identifying correlates of adherence and compliance with exercise training in PMS. This could then serve as a springboard for RCTs testing the effects of behavioral approaches targeting theory-based variables for optimizing adherence and compliance with exercise training for improving outcomes in PMS. The assessment of predictors of adherence and compliance should be emphasized in future trials to clarify variability and enable the planning of targeted supportive strategies dependent on participant characteristics. Such an endeavor might further support inquiry of optimizing outcomes and reducing heterogeneity with exercise training in people with PMS.

There are other noteworthy limitations of the study. We did not collect data on race/ethnicity, and therefore cannot provide an indication of the possible roles in adherence and compliance with exercise in PMS. There are other limitations involving selection bias, constraints of secondary data analysis, and reliance on supervised exercise training in a clinical/research setting, and those limit extension of results into home-based, unsupervised, or community settings. We lastly did not exclude participants on fampridine, and this might have influence adherence and compliance with the exercise training program (Jones et al., 2025).

Overall, we report on rates of adherence and compliance overall (combined for both training stimuli of 94 % and 66 %, respectively) and between continuous, moderate-intensity exercise(95 % and 73 %, respectively) and HIIT(92 % and 58 %, respectively) in PMS. We further report that 6MWT and CVLT-II performance were the primary correlates of adherence and compliance overall and per stimulus in PMS. Such research might (a) inform expected estimates of adherence and compliance when planning future research in PMS; (b) clarify whether baseline 6MWT and CVLT-II can function as indicators for anticipating adherence and compliance challenges for exercise training interventions in PMS; and (c) motivate future research that identifies and targets variables for optimizing adherence and compliance with exercise training in PMS.

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Data availability

To promote data transparency, anonymized data will be available 1 year after the publication of this paper, 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.

5. Role of funder

The funder had no role in the generation of the current paper.

CRediT authorship contribution statement

Robert W. Motl: Writing – original draft, Methodology, Conceptualization. **Andrew Argie:** Writing – review & editing, Conceptualization. **Roberto S. Hernandez:** Writing – review & editing, Formal analysis. **Brian M. Sandroff:** Writing – review & editing, Conceptualization. **Maria Pia Amato:** Writing – review & editing, Methodology. **Giampaolo Brichetto:** Writing – review & editing, Methodology. **Jeremy Chataway:** Writing – review & editing, Methodology. **Nancy D. Chiaravalloti:** Writing – review & editing, Methodology. **Gary Cutter:**

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Declaration of competing interest

The authors report no conflicts of interest in the publication of this paper.

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