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Cognitive Rehabilitation and Aerobic Exercise for cognitive impairment in people with Progressive Multiple Sclerosis (CogEx): A Multi-Arm, Randomized, Blinded, Sham-Controlled Trial

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Summary

Background: Cognitive dysfunction in people with relapsing-remitting MS can improve with cognitive rehabilitation or exercise. Similar effects have not been clearly shown in people with progressive MS. We aimed to investigate whether cognitive rehabilitation plus exercise would be more beneficial for processing speed than cognitive rehabilitation plus sham exercise, exercise plus sham cognitive rehabilitation, and sham exercise plus sham cognitive rehabilitation.

Methods: CogEx was a multi-arm, randomized, blinded, sham-controlled trial completed in 11 centres (hospital clinics, university/ rehabilitation centres) in Canada, USA, UK, Italy, Belgium, and Denmark. Participants were between 26 to 65 years of age with a median EDSS of 6. All had impaired processing speed defined as a performance of ≥ 1.282 SD below normative data on the Symbol Digit modalities Tests (SDMT). failure of the SDMT Participants were randomized (1:1:1:1) using an interactive web-response system accessed online from each centre. The study statistician created the randomisation sequence, which was stratified by cent. Participants, outcome assessors, and investigators were blinded to group membership. The study statistician was masked to treatment during analysis only. Interventions were conducted twice weekly for 12 weeks: cognitive rehabilitation utilized an individualized RehaCom program, a computer based incremental approach to improve processing speed.; sham cognitive rehabilitation consisted of internet training provided individually, onsite by Research Assistants; the exercise intervention involved individualized aerobic training using a recumbent arm-leg stepper; and the sham exercise involved stretching and balance tasks without inducing cardiovascular strain. The primary outcome measure was processing speed measured by Symbol Digit Modalities Test (SDMT) at 12 weeks; least squares mean differences were compared between groups using linear mixed model in all participants who had a 12-week assessment. The trial is registered with ClinicalTrials.gov (NCT03679468) and is completed.

Findings: Between December 14, 2018 and April 2, 2022, 311 people with progressive MS were enrolled and 284 (91%) completed the 12 week assessment (39% male, 61% female). Least squares mean [95%CI] group differences in SDMT at 12-weeks compared with the sham cognitive rehabilitation and sham exercise group (n=67): cognitive rehabilitation plus exercise (n=70), -1·3 [-3·75, 1·16]; sham cognitive rehabilitation plus exercise (n=71), -2·8 [-5·23,-0·33]; and cognitive rehabilitation plus sham exercise (n=76), - 0·7 [-3·11, 1·70]. Eleven adverse events possibly related to the interventions occurred, six in the exercise plus sham cognitive rehabilitation group (pain, dizziness falls), two in the cognitive rehabilitation plus sham exercise group (headache, pain), two in the cognitive rehabilitation and exercise group (increased fatigue, pain) and one in the dual sham group (fall).

Interpretation: Combined cognitive rehabilitation plus exercise is not more effective than either intervention alone in improving processing speed in people with progressive MS.

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Research in context

Evidence before the study

Cognitive dysfunction affects up to 80% of people with progressive MS and can have profound effects on maintaining employment, sustaining relationships and completing basic activities of daily living. The most common cognitive deficit is slowed processing speed. A National Library of Medicine database search spanning January 1, 1990 – December 31, 2017 with keywords multiple sclerosis, cognitive rehabilitation, exercise and cognition, exercise and cognitive rehabilitation was completed and the findings critically reviewed by the CogEx investigators in preparing the study protocol. The findings revealed that treating impaired cognition in people with MS has proved challenging with most studies heavily weighted towards people with relapsing-remitting disease (RRMS). Cognitive benefits in RRMS have been reported with cognitive rehabilitation using a miscellany of interventions, including computerised programs such as RehaCom. The findings with respect to exercise for cognitive deficits in people with relapsing-remitting multiple sclerosis are equivocal. The very few interventional studies for processing speed deficits utilizing cognitive rehabilitation or exercise that have focused on progressive MS have significant methodological problems such as cognition as a secondary outcome and small sample size. It is therefore not known whether cognition and processing speed in particular in progressive MS can improve in response to cognitive rehabilitation, exercise, or a combination of the two interventions.

Added value of this study

Our study (CogEx) focuses exclusively on people with progressive MS. In doing so it addresses one of the top research priorities of the Progressive MS Alliance, a global collaboration of 19 MS organisations, that has highlighted the dearth of adequate treatment data for cognitively impaired people with progressive MS. CogEx overcomes many of the methodological limitations that hinder interpreting the few available studies in the area, for example by assessing cognition (processing speed deficits) as the primary outcome measure, enrolling only people who had impaired processing speed, including a large enough sample size (n=311) to ensure adequate statistical power, being a multinational study, with the potential to demonstrate the wide applicability of our conclusions; using a four-arm approach, and including a 6-month post intervention assessment to determine whether the benefits of interventions endure.

Implications of the available evidence

In CogEx, cognitive rehabilitation in combination with aerobic exercise offered no additional benefits in processing speed over either intervention alone in people with progressive MS A post-hoc analysis revealed that approximately two thirds of our participants showed a clinically

significant improvement in processing speed after 12 weeks of therapy compared with baseline, with this percentage remaining at almost 50% by six months post interventions. While these improvements, seen across all four treatment arms, suggest that cognitive rehabilitation and exercise alone might be effective in addressing processing speed deficits, confirmation is needed by comparing results to a non-intervention group. The potential benefits of enhancing cognitive reserve through intellectual, physical, and social activities might also play a role. While CogEx did not demonstrate the superiority of combined cognitive rehabilitation and exercise, our findings suggest that improvements in processing speed might be attainable in people with progressive MS.

Introduction

Cognitive dysfunction affects 40-80% of people with multiple sclerosis (MS) with the highest rates in people with primary and secondary progressive MS. It is associated with widespread functional limitations.[1]

The most common cognitive difficulty across all disease types is slower information processing speed, which occurs in around half of all people with MS. Other common deficits are in learning and memory, executive function and visual-spatial abilities.[2] Treating these deficits has proved challenging, with most existing studies heavily weighted towards people with relapsing-remitting MS irrespective of treatment modality.[3] Cognitive benefits have been reported with cognitive rehabilitation using various interventions, including computerised programs such as RehaCom.[4] In other clinical populations e.g. mild cognitive impairment,[5] exercise has shown short-term cognitive benefits, although findings in MS are less clear.[6]

Few interventional studies have evaluated the cognitive benefits of cognitive rehabilitation,[7] exercise,[8] and disease modifying treatment[9] in people with progressive MS, and they have methodological problems, including small sample sizes, single-centre involvement, inclusion of participants without cognitive impairment**,** the absence of additional longitudinal assessment after interventions have completed, and cognition being a secondary outcome rather than primary measure. Furthermore, only one previous study, included people with RRMS and to progressive MS, explored the putative synergistic effects of cognitive rehabilitation and aerobic exercise on cognition. In this pilot study with a small sample size, greater cognitive benefits were reported in the combined intervention compared with aerobic exercise alone.[10]

The dearth of adequate treatment data for cognitively impaired people with progressive MS has been identified by the Progressive MS Alliance, a global collaboration of 19 MS organisations, as one of their top research priorities.[11] Whether cognitive dysfunction can improve in the more advanced stages of a degenerative condition like progressive MS is unknown, and it is also unclear what are the best putative treatment modalities with which to try to answer this question. To that end, an international group of interdisciplinary researchers came together with the aim of

determining whether cognitive rehabilitation and exercise are efficacious treatments for cognitive deficits in people with progressive MS, and to assess whether cognitive rehabilitation and exercise in combination have synergistic effects in the treatment of these deficits.

Method

Study design

The methodology of our multi-arm, randomized, rater-blinded, sham-controlled trial (CogEx, NCT03679468) has been described previously.[12] Participants were screened for eligibility, followed by an in-person baseline examination, and then randomization (1:1:1:1) into one of four treatment arms: cognitive rehabilitation plus exercise, cognitive rehabilitation plus sham exercise, exercise plus sham cognitive rehabilitation, and sham cognitive rehabilitation plus sham exercise. Following randomization, participants attended 12 weeks of their assigned intervention. Assessments were conducted immediately following the 12-week intervention (primary endpoint) and at 6 months post-intervention. A multidisciplinary team (with expertise in neurology, neuropsychology, neuropsychiatry, neurophysiotherapy, kinesiology, physiatry, exercise physiology, and statistics) from 11 hospital clinics and university and rehabilitation centres in six countries (Canada, USA, Italy, England, Denmark, Belgium) completed the assessments.. Ethics approval was obtained at each of the 11 study centres.

Participants

Key eligibility criteria were a neurologist-confirmed diagnosis of primary or secondary MS, ages 25-65 years, an EDSS < 7.0 and failure on a test of processing speed, the Symbol Digit Modalities Test (SDMT), defined as a score of ≥1·282 SD below published normative data (10th percentile) specific for each country taking part. The full list of eligibility criteria appear in the supplementary file, see page 1. Written informed consent was obtained from participants at enrollment.

Randomization and masking

The 1:1:1:1 randomization utilized a computerized random number generator created using SAS v9.4 (SAS Institute, Cary, NC) statistical software and was prepared by the study statistician (AS), who had no contact with participants. Randomization parameters consisted of a block design stratified by site with block sizes of 8. Each site had at least one blinded and unblinded research assistant. A blinded research assistant conducted the baseline and follow-up evaluations and a different, unblinded research assistant randomized the participant and did the intervention sessions. Participants were blinded to assigned interventions.

Procedures

Cognitive rehabilitation was provided by the computerized RehaCom program (Hasomed, Germany: www.hasomed.de), which was available in all the study's languages**.** To assess processing speed, we administered five RehaCom modules that appear under "divided attention 1

& 2", "attention and concentration," "vigilance 2," and "sustained attention." Details of the cognitive rehabilitation intervention can be found in the supplementary file, see page 2.

Sham cognitive rehabilitation consisted of internet training, based closely on the internet control group in a previous computer-mediated cognitive rehabilitation study.[13] Each session was designed match the cognitive rehabilitation group on the time spent in contact with study personal and using a computer. These training procedures have been shown not to impact processing speed in a normal aging sample with an age range of 62 to 94 years.[13] See Supplementary file page 2.

The exercise intervention involved an aerobic mode of training performed on a recumbent arm-leg stepper (NuStep T5XR, Ann Arbor, MI, USA). The intervention consisted of two sessions each week, one involving continuous exercise, and the other high-intensity interval training (HIIT). The continuous session progressed from 10 minutes of exercise at a work rate associated with 50-60% of VO2peak in week one towards 30 minutes of exercise at a work rate associated with 70-80% of VO2peak in week 12. The HIIT session progressed from 5, 1-minute intervals at a work rate associated with 80-90%VO2peak, with 1 minute rest between intervals in week one towards 10, 2-minute intervals at a work rate associated with 90% of VO2peak, with 2 minutes rest between intervals, in week 12. This ensured variation in the training stimulus and its parameters between the two weekly sessions for minimizing boredom as well as providing a greater volume of high intensity exercise during HIIT than would be possible if continuous training only was performed. The HITT further allowed for a stronger stimulus that approached VO_2 peak for yielding adaptations over the 12-week period. The full exercise protocol is found in the supplementary file, see pages 3 to 4.

The sham exercise intervention was adapted from Barrett et al.[14] It was designed so that there was no strain on the cardiovascular system and focused on balance and stretching. It intentionally did not contain cognitive-motor dual tasking (to avoid potentially providing cognitive training) or complex exercises requiring substantial working memory or vigilance. We minimised progression of the exercises, so that there was a restriction on the number of repetitions that could be increased per session. We needed to ensure that exercises were kept at a low heart rate. Therefore, if heart rate increased by greater than 40% at the end of each exercise, participants were asked to rest until it lowered to within 20% of resting heart rate. We also constantly monitored perceived exertion throughout the sham intervention, ensuring that the person only worked at a light level. The duration matched the exercise sessions. See the supplementary file pages 5 to 6.

All participants had the cognitive rehabilitation, exercise, and sham treatments in a set order twice weekly, onsite under individual supervision for 12 weeks. There was at least one day rest between sessions.

Outcomes

There were three data points: baseline, 12 weeks and six months post interventions. The primary outcome measure was the 12-week SDMT oral version with the number of correct responses compared between the four groups. Additionally, prespecified sensitivity analyses for the primary outcome included adjusting for site, using z-scores based on the country-specific norms, and dichotomizing change in the SDMT according to improvement of ≥ 4 points, which is considered clinically relevant for group data, and 8 points, which is considered clinically relevant for individual data.[15,16] Serial versions of the SDMT were used.

The numerous secondary endpoints are summarized in the supplementary file page 7 and are divided as follows:

1. Cognition: Verbal and visual memory measured by the California Verbal Learning Test-II (CVLT) and the Brief Visuospatial Memory Test (BVMT-R). All tests were available in the languages represented within our study sample: English, Italian, French, Dutch, and Danish. Serial versions of tests were used.
2. Physical: The IET (synonymous with CPET (cardiopulmonary exercise test) generates V02peak, heart rate (HR) and peak watts), 6 minute walk test (6MWT), and accelerometer (synonymous with actigraph) data. We also measured cognitive-motor interference (CMI) with the dual task cost (DTC).
3. Neurobehavioral measures: A number of patient reported outcome measures were completed for anxiety and depression (Hospital Anxiety and Depression Scale), fatigue (Modified Fatigue Impact Scale (MFIS), quality of life (EQ-5D-5L), subjective cognitive deficits (Perceived Deficits Questionnaire-20), subjective impact of walking (Multiple Sclerosis Walking Scale (MSWS-12), Impact of Multiple Sclerosis (Multiple Sclerosis Impact Scale (MSIS-29-V2) and the Assessment of Global Function (Functional Assessment of MS(FAMS)).
4. Magnetic Resonance Imaging (the structural and functional MRI data are still to be analyzed and will be reported later).

Adverse events were recorded at each intervention session using a standardized list of potential adverse events derived by consensus amongst the investigators when designing the study. A data and safety monitoring board comprising three individuals not affiliated with CogEx (two physicians, one statistician) met every six months to monitor the occurrence of adverse events**.**

Protocol deviations were recorded throughout the study. They were classified into the following types: consent procedures, eligibility criteria, study procedures, adverse device effects, visit schedule, and other.

The first COVID lockdown from February to September 2020 interrupted recruitment and the interventions in 36 participants for an average of 82·9 (24·3) days. When it came to restarting the interventions, a consensus agreement amongst the principal investigators was for participants to resume two sessions back from where they had left off. If these two sessions did not return participants to the cognitive and physical metrics achieved prior to interruption, additional sessions were provided to reach that point. Sensitivity analyses were pre-planned and excluding these 36 participants showed results consistent with the primary analyses.

Statistical analysis

We estimated our sample size using a one-factor analysis of variance approach with a Type I error set at 5%. We computed the sample size necessary to achieve 80% power for such a design to identify conservative changes among the four groups. For simplicity we used 4 points on the SDMT for the combined treatments (cognitive rehabilitation and exercise), to demonstrate a clinically meaningful difference on average and that the two interventions are additive. Additionally, we assumed a change of 2 points for each of the single intervention groups (cognitive rehabilitation plus sham exercise and exercise plus sham cognitive rehabilitation plus) and 0 for the double sham group. The sample size required to detect these differences (4,2,2,0) with 80% power was 90 participants per intervention group assuming an 8 point standard deviation of the change and the overall Type I error of 0·05. See protocol paper for more detail.[12]

Descriptive statistics were used to summarize the demographic and clinical characteristics among the four intervention groups. Means (standard deviation [SD]) and median (interquartile range [IQR]) were used for continuous variables and frequency (percentage) were used for categorical variables. The analysis population includes participants with an outcome measure at 12 weeks or 6 months. According to intention-to-treat principles, participants were included in the analysis according to their randomized treatment allocation. Statistical analyses were conducted in SAS v9·4 (Cary, NC).

Differences in SDMT number correct at 12-weeks (primary outcome) and 6-months between the interventions were evaluated using a linear mixed model to include all possible data in analyses. The model included SDMT number correct as the outcome and independent variables included the baseline SDMT number correct, randomized intervention group assigned (4 levels), time (12-weeks, 6-months) and an intervention by time interaction. Pairwise contrasts to evaluate hypotheses were conducted if the overall test for interventions achieved statistical significance. Pairwise comparisons evaluated absolute differences in least squares means and Dunnett's test was used to preserve the Type I error rate (control=double sham). Model assumptions were verified visually using residual plots and other regression diagnostics. The absolute difference in least squares mean at 12-weeks and 6-months and their standard errors (SE) for the intervention comparisons are reported. The significance level was set at 0·05. Secondary outcomes were analyzed similarly. However, as the primary outcome did not reach statistical significance, the

secondary outcomes report all pairwise comparisons as post-hoc comparisons with no multiple comparison correction (Dunnett's) as indicated in the protocol.
Sensitivity analyses were performed using the same model described above including site as a covariate, using SDMT z-scores (based on the country-specific regression-based normative values) and logistic regression for the dichotomous change threshold models to evaluate differences between the interventions controlling for site. Additionally, a factorial design analysis was conducted as a sensitivity analysis where the outcome for each main effect, cognitive rehabilitation and exercise, was compared in all participants who received cognitive rehabilitation (n=156) vs sham cognitive rehabilitation (n=155) regardless of the exercise assigned and in all participants receiving the exercise intervention EX (n=157) vs sham exercise (n=154) regardless of the cognitive rehabilitation assigned. The interaction between the main effects was tested and if non-significant, the main effects were evaluated using the similar ANCOVA model described above. Multiple imputation analyses were not conducted given the primary analyses results.

Role of the Funding Source

The study was funded by the MS Society of Canada with ancillary support from the Consortium of MS Centres, Danish MS Society and US National MS Society. The funders had no role in design of the study, data collection, data analysis, data interpretation, writing of the manuscript and decision to submit.

Results

Between December 14, 2018 and April 2, 2022, 698 people with progressive MS were screened in-person, of whom 311 met the inclusion criteria (figure 1). The trial closed recruitment at 86% of its pre-planned sample size due to COVID-19-related enforced delays and closures at all the study centres. CogEx was meant to run for four years, but the pandemic-related site closures meant we had to extend it for another year to try and reach the predetermined sample size. This extension was approved by the study's main funder without any additional budget. At the end of the one year extension, the budget was exhausted and the study closed. The sample breakdown according to countries was as follows: Canada (45), USA (25), Italy (154), United Kingdom (48), Denmark (19), Belgium (20). Of the 311 randomized participants, 77 were randomly assigned to cognitive rehabilitation plus exercise, 79 to cognitive rehabilitation plus sham exercise, 80 to exercise plus sham cognitive rehabilitation, and 75 to both sham interventions. Five participants did not begin the intervention and 22 withdrew from the study during the 12 weeks of interventions (cognitive rehabilitation plus exercise, n=6; cognitive rehabilitation plus sham exercise, n=3; exercise plus sham cognitive rehabilitation, n=7; both sham interventions, n=6). A further 26 participants were lost by six months (CR+EX, n=5; CR+EX-S, n=8; CR-S+EX, n=6; CR-S and EX-S, n=7). Data for this analysis included the intent-to-treat population collected between December 14, 2018 and February 3, 2023.

The demographic and disease-related characteristics in the four groups are provided in Table 1. The mean (SD) baseline SDMT z-score was -2·1 (0·75).

Participants reaching the end of interventions had an average attendance of 91% to 93% for the cognitive rehabilitation and sham cognitive rehabilitation sessions and 88% to 91% for the exercise and sham exercise sessions, see supplementary file page 8. For cognitive rehabilitation, the mean duration of the sessions was 41.4 to 42.0 minutes for all groups, see supplementary file page 8. For the exercise plus sham cognitive rehabilitation and exercise plus cognitive rehabilitation groups, 92% and 89% of HIIT sessions and 85% and 83% of continuous sessions were completed, respectively. Actual work rate during both the continuous and HIIT sessions corresponded well with the target work rate, see supplementary figures, pages 9 and 10.

There were a total of 76 protocol deviations (defined as an event that varied from the study protocol) reported with 1 (1%) for consent procedures, 2 (3%) related to eligibility criteria, 52 (68%) study procedures, 3 (4%) adverse device effect, 12 (16%) visit schedule/interval, and 6 (8%) other. The exercise plus sham cognitive rehabilitation group had the highest number of protocol deviations 25 (33%), the cognitive rehabilitation and sham exercise group had 21 (28%), the cognitive rehabilitation plus exercise had 19 (25%), and the group with both sham interventions had 11 (15%).

The mean differences in the number correct on the SDMT were not different between the four groups at 12-weeks (primary outcome, p=0·85; Table 2). The absolute differences in the least squares mean [95%CI] for the SDMT at 12-weeks compared with the sham cognitive rehabilitation and sham exercise group (n=67) were: cognitive rehabilitation and exercise group (n=70) -1·3 [-3·75, 1·16]; exercise plus sham cognitive rehabilitation group (n=71) -2·8 [-5·23 ,-0·33]; cognitive rehabilitation and sham exercise group (n=76) - 0·7 [-3·11, 1·70]). Sensitivity analysis demonstrated similar results when adjusting for site and using SDMT z-scores. The absolute differences in the least squares mean [95%CI] for the SDMT at 6-months between groups compared with the sham cognitive rehabilitation and sham exercise group (n=60) were: cognitive rehabilitation and sham exercise group (n=65) -0·8 [-3·38, 1·76]; compared exercise and sham cognitive rehabilitation group (n=65) -1·8 [-4·40, 0·75]; versus cognitive rehabilitation and sham exercise group (n=68): -1·2 [-3·76, 1·33]).

The sensitivity factorial analysis comparing the cognitive rehabilitation and sham cognitive rehabilitation groups revealed no differences in SDMT number correct at 12-weeks (-0·37 [0·86]; p=0·66) and 6-months (0·15 [0·90]; p =0·87) and no differences between the exercise and sham exercise groups (12-weeks: 1·48 [0·86], p=0·09; 6-months: 0·51 [0·90], p=0·57). In a post-hoc analysis, of the 284 participants with both baseline and 12-week SDMT scores, overall 171 (60%) individuals demonstrated SDMT improvements ≥4 points and 106 (37%) individuals demonstrated improvement ≥ 8-points compared to baseline. For the 6-month SDMT data, 119 (46%) participants showed a ≥4 points improvement and 68 (26%) participants a ≥ 8-points improvement.

In further post-hoc analysis**,** among the 119 individuals with a greater than 4-point SDMT improvement at 6- months, 100 met the same threshold at 12-weeks. The remaining 19 people showed a delayed improvement. Of the 68 individuals with a greater than 8-point improvement at 6-months, 52 met that threshold at 12-weeks and 16 had a delayed response.

There were no between-group differences in the CVLT-II and BVMT-R (Table 2).

Overall, there were some differences between groups among physical measures for the peak heart rate and watts (Table 2). At 12 weeks, the cognitive rehabilitation plus exercise group had a higher peak heart rate compared to the cognitive rehabilitation plus sham exercise group (mean difference [SE]: 4.7[2.3], p=0.038). the exercise plus sham cognitive rehabilitation group had a higher peak heart rate compared to the sham cognitive rehabilitation plus sham exercise group (mean difference [SE]: 7.0 [2.3], p=0.003) and the cognitive rehabilitation plus and sham exercise group (8.0 [2.2], p=0.0004). These differences were lost by 6 months. A sensitivity analysis showed a higher peak heart rate in the exercise versus sham exercise groups: -5.8 [1.2], p=0.0004 which attenuated by 6 months (0.7 [1.8], p=0.71). At 12 weeks the cognitive rehabilitation plus exercise group had a higher peak watts during the IET compared to the sham cognitive rehabilitation plus sham exercise group (mean difference [SE]: 14.2[3.2], p=0.0001) and cognitive rehabilitation and sham exercise group (12.7 [3.1], p=0.0001). The CR-S+EX group had a higher peak watts compared to CR-S+EX-S (15.1[3.1], p=0.0001) and CR+EX-S (13.6[3.1], p = 0.0001). A sensitivity analysis showed higher peak watts in the EX versus EX-S groups at 12-weeks (-13.9[2.2], p =0.0001) and 6-months (-4.7[2.5], p=0.0525). There were no group differences in the 6MWT, CMI and accelerometer results at 12-weeks and 6 months (Table 2).

A post-hoc analysis of the physical measures related specifically to the exercise intervention was undertaken to examine differences between groups. At 12-weeks, the cognitive rehabilitation plus exercise group had higher VO_{2}-peak improvement compared to the cognitive rehabilitation plus sham exercise group (mean difference [SE]: 1·84 [0·67], p=0·007) and the sham cognitive rehabilitation plus sham exercise group (1·67 [0·70], p=0·02) which was lost by 6-months. A sensitivity analysis using a factorial design showed a mean improvement [SE] of 1·48 [0·49] ml/kg/min (p=0·003) for the exercise compared to the sham exercise groups which was attenuated at 6-months (-0·73 [0·55], p=0·19). For the heart rate in the exercise and sham exercise groups recorded over 12 weeks, see supplementary figures, pages 11 to 13

The 12-week and 6 month data for the HADS-D, HADS-A, and MFIS revealed no between-group differences. At 12-weeks, participants in the cognitive rehabilitation plus exercise group had worse scores on the physical and mental subscales of the MSIS-29 compared to some of the other groups as follows: For the physical subscale, the cognitive rehabilitation plus exercise group was 7·9 [2·6] points higher than the exercise plus sham cognitive rehabilitation group (p=0·003) and 5·2 [2·6] points higher than the cognitive rehabilitation plus sham exercise group

(p=0·04) groups. For the mental subscale, the cognitive rehabilitation plus exercise group was 7·5 [2·8] points higher than the exercise plus sham cognitive rehabilitation group (p=0·009), and 7·5 [2·9] points higher than the sham cognitive rehabilitation plus sham exercise group (p=0·009) groups. These differences were lost at 6-months.

There were 11 minor adverse events reported, six in the exercise plus sham cognitive rehabilitation group (pain, dizziness falls), two in the cognitive rehabilitation plus sham exercise group (headache, pain), two in the cognitive rehabilitation and exercise group (increased fatigue, pain) and one in the dual sham group (fall). Five serious adverse events, unrelated to CogEx, occurred, three in the cognitive rehabilitation plus sham exercise group (symptom exacerbation, surgery for knee prosthesis, fall at home) and one each in the cognitive rehabilitation plus exercise group (syncope and panic) and dual sham group (urinary tract infection).All participants required hospitalization. Further details on the adverse events appear in supplementary file, page 14.

Discussion

In this multi-arm, randomized, blinded, sham-controlled trial of cognitive rehabilitation and and aerobic exercise in 311 people with progressive MS from six countries, our hypothesis was not upheld, that cognitive rehabilitation combined with exercise would act synergistically to bring about significant change in our primary outcome measure, processing speed. Similarly, neither cognitive rehabilitation nor aerobic exercise alone proved more effective than the combined sham interventions in improving processing speed at six months post interventions.

To our knowledge, no previous study has assessed the efficacy of cognitive rehabilitation, exercise, or both combined in treating cognitive dysfunction as the primary outcome measure in people with progressive MS. In CogEx we: a) used cognition as the primary outcome measure; b) enrolled only participants with impaired processing speed who did not engage in physical training; c) administered the study in multiple centres to ensure the general applicability of our findings.

Our findings add to a small, but growing literature, much of it published after CogEx began addressing the potential synergistic effects of cognitive rehabilitation and exercise on cognition in differing samples. Benefits from combined interventions versus single treatment modalities have been suggested for people with concussion[17] and stroke (in relation to executive function)[18]. The findings with respect to older adults with and without mild cognitive impairment is mixed, with negative findings[19, 20] and one positive result.[21] A systematic review concluded that the combined intervention was no better than cognitive training alone, even when cognitive training and exercise were given simultaneously, considered the most effective mode of administration. [22] Exercise in conjunction with cognitive training was nevertheless supported to maintain cognition and physical health in later life.[22] With respect to individuals with MS, an update literature

search revealed three reports in small samples predominantly of people with relapsing-remitting MS. One study compared three interventions; cognitive training alone versus cognitive and motor training versus motor training alone. The first group showed cognitive improvement, the last group showed motor improvement while the dual intervention group showed cognitive and motor improvement. The dual intervention did not, however, lead to greater cognitive benefits than cognitive intervention alone.[23] In a second MS study, greater cognitive benefits accrued from exercise plus cognitive training compared with exercise and sham cognitive training.[24] The third study is a more complete report of the pilot study referenced in the introduction.[10] The sample size was boosted but the result remained unchanged: cognitive rehabilitation plus exercise was more effective than exercise alone in improving cognition.[25] CogEx now adds to these findings by showing that in a much larger sample of people with more advanced progressive MS, a combined intervention is not more effective than either intervention alone in improving cognition, in particular processing speed.

A closer look at the duration and intensities of our interventions is warranted in light of our findings. We administered RehaCom for two 45 minute sessions per week over 12 weeks for a total of 24 sessions. Two recent reviews of computerized cognitive training in predominantly relapsing-remitting MS show that RehaCom is the most frequently used program. Lampit et al cite[4] six studies, two of which exceeded the number and total duration of sessions administered in CogEx. Brochet[26] cites four studies all of which provided fewer sessions that CogEx. This suggests that, relative to others, CogEx provided a robust RehaCom intervention. Of note is that the reported effect size from 20 studies using RehaCom and other programs targeting attention and processing speed was 0·32,[4] lower than our a-priori estimate of 0.5 which is commensurate with a 4-point SDMT improvement from baseline. Our fealty to a 4-point SDMT change was driven by the recommendations of the Multiple Sclerosis Outcome Assessment Consortium to the Food and Drug Administration emphasizing the ecological validity of this change, an important consideration in linking laboratory findings to real world consequences of change.[27] In following this, however, we may have overestimated the effectiveness of our cognitive rehabilitation.

The peak watts, peak heart rate, and VO_2 peak data at 12-weeks suggest a performance based improvement in the exercise compared to the sham exercise groups. The 10% VO_2 improvement at 12-weeks in the exercise group, while modest, is considered a reliable, but not necessarily meaningful, change in the MS literature.[28] We designed our sham exercise protocol to keep participants blinded to group membership while simultaneously avoiding interventions that would boost aerobic activity. Yet despite our strict adherence to this regime, the absence of between group differences in our primary outcome measure suggests our sham remained active in improving processing speed. As a systematic review of control group improvements in intervention trials reveals, factors other than the sham regime itself, such as pre-existing health status and the exclusion of active participants, both relevant to CogEx, may account for this.[29]

Having the same research assistant provide the different interventions might also have inadvertently benefitted the sham participants because of parameter drift. All of which might explain the improvement in 6MWT despite there being no specific gait or walking task in our sham exercise protocol. This in turn could have boosted processing speed.[30] The changes we found in walking endurance in the 6MWT were commensurate with 6MWT change scores in PwMS.[31]

Our findings were also notable for showing improvements across all four treatment groups in the SDMT that often exceeded 4 and 8 points, which are considered clinically significant in group and individual data, respectively.[15–16] A 4-point improvement, present in 60% of our sample at the primary endpoint of 12 weeks was consistent across 11 centres in six counties and in multiple languages. The magnitude of these changes could not fully be accounted for by regression to the mean or practice effects. The importance of the latter has been addressed in a longitudinal study of 219 healthy individuals who completed the SDMT at baseline, 6 months, and one year: group scores improved from 58·83 to 60·88 to 62·05 and were attributed to practice.[16] These changes are considerably less than those seen in our study. One important conclusion from this normative dataset was that a change of 8 points was considered meaningful at an individual level with an 80% confidence interval.[16] This threshold was reached by 46% of our sample at the primary endpoint of 12 weeks.

The most parsimonious explanation to account for the 4 and 8-point change in SDMT performance seen in so many participants is that both interventions are effective. To this may be added another possible reason. By the end of the study, anecdotal accounts from some participants informed us that the 3-month intervention period provided more physical, intellectual, and social activity (an enriched lifestyle) than they had experienced in the previous few years. This in turn may have boosted processing speed. This explanation is supported by a study of 248 people with MS (predominantly relapsing-remitting MS) that revealed an association between what the authors called a "positive lifestyle" (exercise, social/intellectual engagement, healthy nutritional choices) and processing speed.[32] The *moderating* effects of an enriched environment on cognitive decline in progressive MS were described in 2012.[33] Our data suggest that enhancing enrichment in multiple ways may offer additional *remedial* benefits, specific to processing speed in people with progressive MS. Our findings also reveal that pushing people with progressive MS too hard with taxing personalised interventions might have a temporary downside, reflected in worse scores on the MSIS-29, a self-report measure of the impact of MS.

Our study has limitations. Given that our sham exercise was not inactive, incorporating a waitlist control would have controlled for the passage of time and practice effects on the outcome measures. The COVID-19 pandemic also hindered recruitment,[34] but this is unlikely to explain the fact that our results did not support our hypothesis. SDMT outcome scores between our four

treatment arms were so similar that adding approximately 10 more participants to each arm would be unlikely to change the results. As for the SAGER guidelines, we had no prior data or rationale to suggest sex-specific treatment effects might be present, hence no such analyses were performed. Finally, our results cannot be extrapolated to include all people with progressive MS, but instead should be viewed as applicable to people with advanced disability just short of needing a wheelchair.

In conclusion, our main hypothesis regarding the superiority of cognitive rehabilitation plus exercise in improving processing speed in people with progressive MS was not supported. Our sham exercise proved active and the improvements in processing speed in a proportion of participants might be attributed to either intervention alone with no significant benefits from combining them. The fact that processing speed can indeed improve in people with progressive MS, something we did not know before CogEx, emphasizes the importance of keeping individuals with advanced disability active across multiple domains.

Contributors

All authors had access to the data. Amber Salter, Anthony Feinstein and Cecilia Meza verified the underlying data. All authors were responsible for submitting the manuscript including the revised versions.

Author contributions AF: design and conceptualized study; major role in the acquisition of funding; acquisition of data; interpreted the data; literature search; drafted and revised the manuscript for intellectual content. MPA: design and conceptualized study; acquisition of data; interpreted the data; drafted and revised the manuscript for intellectual content. GB: design and conceptualized study; acquisition of data; interpreted the data; drafted and revised the manuscript for intellectual content. JC: design and conceptualized study; major role in the acquisition of funding; acquisition of data; interpreted the data; drafted and revised the manuscript for intellectual content. NDC: design and conceptualized study; literature search; acquisition of data; interpreted the data; drafted and revised the manuscript for intellectual content. GC: design and conceptualized study; major role in the acquisition of funding; acquisition of data; interpreted the data; drafted and revised the manuscript for intellectual content. UD: design and conceptualized study; major role in the acquisition of funding; acquisition of data; interpreted the data; drafted and revised the manuscript for intellectual content. JD: design and conceptualized study; major role in the acquisition of funding; acquisition of data; literature search; interpreted the data; drafted and revised the manuscript for intellectual content. RF: design and conceptualized study; acquisition of data; interpreted the data; drafted and revised the manuscript for intellectual content. PF: design and conceptualized study; acquisition of data; interpreted the data; drafted and revised the manuscript for intellectual content. MF: design and conceptualized study; acquisition of data; interpreted the data; drafted and revised the manuscript for intellectual content. JF: design and conceptualized study; acquisition of data; interpreted the data; drafted and revised the manuscript for intellectual content. MI: design and conceptualized study; acquisition of data; interpreted the data; drafted and revised the manuscript for intellectual content. CM: overall study coordinator; acquisition of data; literature search; interpreted the data; drafted and revised the manuscript for intellectual content. RM: design and conceptualized study; acquisition of data; interpreted the data; drafted and revised the manuscript for intellectual content. MAR: design and conceptualized study; major role in the acquisition of funding; acquisition of data; interpreted the data; drafted and revised the manuscript for intellectual content. BMS: design and conceptualized study; acquisition of data; literature search; interpreted the data; drafted and revised the manuscript for intellectual content AS: design and conceptualized study; major role, performed statistical analysis; acquisition of data; interpreted the data; drafted and revised the manuscript for intellectual content.

Declaration of interests

Anthony Feinstein reports grants from the MS Society of Canada, book royalties from Johns Hopkins University Press, Cambridge University Press, Amadeus Press and Glitterati Editions, and speaker's honoraria from Novartis.

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Nancy D. Chiaravalloti is on an Advisory Board for Akili Interactive and is a member of the Editorial Boards of Multiple Sclerosis Journal and Frontiers in NeuroTrauma.

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Cecilia Meza has no disclosures to report.

Peter Feys is editorial board member of NNR and MSJ, provides consultancy to NeuroCompass and was board of advisory board meetings for BIOGEN.

Massimo Filippi is Editor-in-Chief of the Journal of Neurology and Associate Editor of Human Brain Mapping, Neurological Sciences, and Radiology, received compensation for consulting services and/or speaking activities from Alexion, Almirall, Bayer, Biogen, Celgene, Eli Lilly, Genzyme, Merck-Serono, Novartis, Roche, Sanofi, Takeda, and Teva Pharmaceutical Industries, and receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Teva Pharmaceutical Industries, the Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA).

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Gary Cutter is a member of Data and Safety Monitoring Boards for Astra-Zeneca, Avexis Pharmaceuticals, Biolinerx, Brainstorm Cell Therapeutics, Bristol Meyers Squibb/Celgene, CSL Behring, Galmed Pharmaceuticals, Horizon Pharmaceuticals,Hisun Pharmaceuticals, Mapi Pharmaceuticals LTD, Merck, Merck/Pfizer, Opko Biologics, OncoImmune, Neurim, Novartis, Ophazyme, Sanofi-Aventis, Reata Pharmaceuticals, Teva pharmaceuticals, VielaBio Inc, Vivus, NHLBI (Protocol Review Committee), NICHD (OPRU oversight committee). He is on Consulting or Advisory Boards for Biodelivery Sciences International, Biogen, Click Therapeutics, Genzyme, Genentech, GW Pharmaceuticals, Klein-Buendel Incorporated, Medimmune, Medday, Neurogenesis LTD, Novartis, Osmotica Pharmaceuticals, Perception Neurosciences, Recursion/Cerexis Pharmaceuticals, Roche, TG Therapeutics. Dr. Cutter is employed by the

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Amber Salter receives research funding from Multiple Sclerosis Society of Canada, National Multiple Sclerosis Society, CMSC and the Department of Defense Congressionally Directed Medical Research Program and is a member of editorial board for Neurology. She serves as a consultant for Gryphon Bio, LLC. She is a member of the Data and Safety Monitoring Board for Premature Infants Receiving Milking or Delayed Cord Clamping (PREMOD2), Central Vein Sign: A Diagnostic Biomarker in Multiple Sclerosis (CAVS-MS), and Ocrelizumab for Preventing Clinical Multiple Sclerosis in Individuals With Radiologically Isolated Disease (CELLO). She holds the Kenney Marie Dixon-Pickens Distinguished Professorship in Multiple Sclerosis Research.

Data Sharing Statement

To promote data transparency, anonymized data will be available one year after the publication of the primary paper, upon reasonable request. Please make the request to the corresponding author, AF. A CogEx Committee will then review the request for approval. A data sharing agreement will be put in place before any data are shared.

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Supplementary Information – web appendix

Eligibility criteria

Inclusion criteria	
MS type	Primary and Secondary Progressive MS (confirmed by attending neurologist)
Age	25-65 years
Cognition	Failure on the SDMT defined by a performance of at least 1.282 SD below published normative data (10th percentile) specific for each center taking part[1,2,3,4,5,6]
Visual acuity	Corrected near vision of at least 20/70 and absence of severe nystagmus.
Disease activity	Exacerbation free for three months.
Language comprehension	To ensure that participants could understand the test instructions, they 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 30min 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 (≥ 29 on the Beck Depression Inventory.
MRI	Claustrophobia, metal implants, pacemakers.

Cognitive Rehabilitation (CR) protocol:

CR was provided by the computerized RehaCom program. RehaCom is available in over 20 languages including all the languages needed for our trial. The language selection is built into the computer program and accessed via a simple drop down menu. This is a major asset of the RehaCom software as few cognitive rehabilitation programs are available in multiple languages. To address processing speed (PS), the single most common cognitive deficits observed in persons with MS[7] we administered the RehaCom module shown to be effective in targeting this aspect of cognition.[8] In particular, there are five RehaCom training modules, "divided attention 1," "divided attention 2" "attention and concentration," "vigilance 2" and "sustained attention" that are integral to processing speed. For example, in the divided attention 1 module, the person is required to simulate a train conductor, carefully observing the control panel of the train and the countryside. Several distractions, such as animals, railway signals and train speed must be taken into account, with increasing levels of difficulty. In the divided attention 2 module, the person is required to simulate driving a car, carefully observing the control panels and the road. Several distractors, such as billboard signs, speed limit signs, radio noise, and remembering to signal right or left turns must be taken into account, with increasing levels of difficulties. In the attention and concentration module, an individual picture (target) is presented and then compared with a matrix of pictures. The person has to recognize the target picture (coded as symbols, items, animals, or abstract figures) and select it from the matrix. The abilities to differentiate and to concentrate are trained simultaneously. The level of difficulty rises as the number and complexity of pictures to recognize increases. During the vigilance 2 task, the person is trained to sustain his or her attention for a prolonged period by providing response times limited to the various items. The task is to control a conveyor belt and to select the objects that differ from a target sample in one or more details. Finally, in the sustained attention module, is similar to the vigilance task, except the speed of the conveyor belt has increased. Participants began at level 1 on each RehaCom module and advanced through the program as dictated by their performance, under the guidance of the RA. Progression was thus individualized, based on the success on each task. Each session comprised of two out of the five modules randomized each session, each module programmed to last 20 minutes, making the duration of each cognitive session 40 minutes, as has been accomplished successfully in previous RehaCom research in persons with MS.[9,10]

Sham Cognitive Rehabilitation (CR-S) protocol: The CR-S condition consisted of internet training, based closely on the internet control group utilized in previous computer-mediated cognitive rehabilitation studies in the literature.[11] The control condition began with more basic tasks such as learning to use a computer and the internet to search for information, including locating information regarding medications, gardening, getting directions, etc. Participants began at the most appropriate level, completing the 24 sessions that followed to match the frequency of the CR treatment group interventions. The control sessions were designed to equate the two CR groups (active and sham) on social and computer contact. This approach has been demonstrated to be effective in controlling for these factors in previous research.[11]

Exercise protocol: In accordance with the MS literature, the exercise intervention of choice was aerobic and performed by recumbent stepper.[12,13] It consisted of one weekly session of continuous exercise alternating with one weekly session of interval training. This ensured variation as well as a greater volume of high intensity exercise during the interval training, thus allowing more exercise time at intensities approaching the VO_{2peak}. The exercise intervention complied with the basic principle of progressive overload. This meant that there was an inherent progression built into the program involving changes in both exercise time (volume) and intensity.

Type: Aerobic training was performed on an arm-leg recumbent stepper with all centres using the same equipment (NuStep T5XR, https://www.nustep.com/international/products/t5xr/) that allowed individual adjustment of stepper settings as well as providing a valid measure of the applied resistance expressed as wattage or kp.

Frequency: Twice weekly with each session separated by one day of rest.

Supervision: Full supervision of all exercise sessions by the trained RA to match that provided during the cognitive rehabilitation sessions.

Format/duration: (Tables A and B)

One session involved continuous exercise initially commencing at 10 minutes and progressing towards 30min/session, with 5 minutes of warm up and 5 minutes of cool down.

Table A: Continuous exercise schedule

Week	Duration	Target intensity zone (% of HR-reserve*)
1	10 minutes	50-60% of HR-reserve
2	15 minutes	50-60% of HR-reserve
3	20 minutes	50-60% of HR-reserve
4	25 minutes	50-60% of HR-reserve
5	30 minutes	50-60% of HR-reserve
6	30 minutes	50-60% of HR-reserve
7	30 minutes	60-70% of HR-reserve
8	30 minutes	60-70% of HR-reserve
9	30 minutes	65-75% of HR-reserve
10	30 minutes	65-75% of HR-reserve
11	30 minutes	70-80% of HR-reserve
12	30 minutes	70-80% of HR-reserve

* Peak HR was determined by formal cardiopulmonary exercise testing. Resting HR was also determined at baseline.

One session involved interval training (5 x 1 min progressing towards 10 x 2min) in line with the schedule in Table 1b.

Table B: Interval Training Schedule

Week	Number of intervals	Duration	Rest	Target intensity zone (% of HR-reserve*)
1	5	1min	1min	80-90% of HR-reserve
2	5	1.5min	1.5min	80-90% of HR-reserve
3	5	2min	2min	80-90% of HR-reserve
4	6	2min	2min	80-90% of HR-reserve
5	7	2min	2min	80-90% of HR-reserve
6	8	2min	2min	80-90% of HR-reserve
7	9	2min	2min	80-90% of HR-reserve
8	10	2min	2min	80-90% of HR-reserve
9	10	2min	2min	90% of HR-reserve
10	10	2min	2min	90% of HR-reserve
11	10	2min	2min	90% of HR-reserve
12	10	2min	2min	90% of HR-reserve

* Peak HR was determined by formal cardiopulmonary exercise testing. Resting HR was also determined at baseline.

Sham exercise protocol: (adapted from Barrett et al.[14])

Generally, this one hour, twice weekly sham exercise intervention did not put any strain on the cardiovascular system, focusing on balance and stretching. Further, it intentionally did not contain any cognitive-motor dual tasking to avoid potentially providing any cognitive training. Also, it did not include complex exercises where patients needed substantial working memory or (sustained) attention. The duration was one hour. Six types of exercises were identified as being appropriate for inclusion: stretches, exercises in crook lying, unilateral exercises in side lying, exercises in prone, exercises in unsupported sitting and exercises in standing.

Type 1: Stretches Hamstrings Quadriceps Hip flexors Hip abductors Ankle plantar-flexors	**Type 2: Exercises in crook lying** Bridging (two legs/single leg) Trunk rotation Pelvic tilt Unilateral hip abduction Bilateral hip abduction Hip and knee flexion/extension	**Type 3: Exercises in side lying** Unilateral hip abduction Unilateral hip lateral rotation Unilateral hip abduction/lateral rotation Unilateral knee flexion/extension
Type 4: Exercises in prone Unilateral hip extension Unilateral/bilateral knee flexion Bilateral isometric gluteal contraction Unilateral/bilateral hip rotation	**Type 5: Exercises in unsupported sitting** Anterior/posterior pelvic tilt Trunk rotation Forward trunk flexion Unilateral trunk extension (reach out of base of support) Unilateral knee extension/flexion Unilateral hip abduction Bilateral hip abduction	**Type 6: Exercises in standing** Squats (two legs/single leg) Step-ups onto low step. Balancing on one leg (single-leg stance) Sideways stepping Backwards stepping Balancing in step-stance Lateral reaching out of base of support

Format/duration: A standardized (minimal) progression of exercises was undertaken over the 12 weeks to reduce the possible cognitive demand that might be required for dealing with exercise variation. To ensure the exercises were at low HR, they were undertaken with rest periods at a 2:1 ratio to avoid a potential aerobic effect of the sham intervention. Further, the number of consecutive repetitions were low. In line with the EX intervention, the sham session initially commenced at 15-30 min. and ultimately progressed towards 60 min/sessions. The program was further designed to avoid improvements of lower limb muscular strength, as this has been associated with faster processing speed.[15,16]

Table C. Summary of sham exercise intervention characteristics.

Week	Duration (in minutes)	Stretching and balance exercises
1	15-20 min	**Type 1, 2 , 3 , 4 , 5 , 6**
2	20-30min	**Type 1, 2 , 3 , 4 , 5 , 6**
3	25-35min	**Type 1, 2 , 3 , 4 , 5 , 6**
4	25-35min	**Type 1, 2 , 3 , 4 , 5 , 6**
5	25-40min	**Type 1, 2 , 3 , 4 , 5 , 6**
6	25-40min	**Type 1, 2 , 3 , 4 , 5 , 6**
7	30-45min	**Type 1, 2 , 3 , 4 , 5 , 6**
8	30-45min	**Type 1, 2 , 3 , 4 , 5 , 6**
9	35-50min	**Type 1, 2 , 3 , 4 , 5 , 6**
10	40-55min	**Type 1, 2 , 3 , 4 , 5 , 6**
11	45-60min	**Type 1, 2 , 3 , 4 , 5 , 6**
12	45-60min	**Type 1, 2 , 3 , 4 , 5 , 6**

CogEx study endpoints.

Outcome	Measurement(s)	Primary/secondary

Cognitive		
SDMT[17]	Information processing speed	*Primary
CVLT[18]	Verbal memory	**Secondary
BVMT-R[19]	Visual memory	**Secondary
Physical		
Accelerometer[20] (derived from ActiGraph wearable device)	Average % of wear time in MVPA	**Secondary
IET[21] (synonymous with CPET)	VO_2 peak (mL/kg/min); Peak Watts, Peak Heart Rate	**Secondary
CMI[22]	DT cost (motor); DT cost (cognitive)	**Secondary
6MWT[23]	Total distance walked in meters in the 6-minute period	**Secondary
Patient reported outcomes (PROs)		
HADS[24]	Anxiety and depression	**Secondary
FAMS[25]	Assessment of Global Function	**Secondary
EQ-5D-5L[26]	Quality of Life (generic)	**Secondary
MSIS-29-V2[27]	Impact of Multiple Sclerosis	**Secondary
MSWS-12[28]	Subjective impact of walking	**Secondary
PDQ-20[29]	Subjective cognitive difficulties	**Secondary
MFIS[30]	Fatigue	**Secondary
⚕ MRI		
Functional (Go/No-Go[31] task and resting state)	Task activation along with reaction times, omission errors, commission errors, and correct responses. RS functional connectivity	**Secondary
Structual	Brain T2-hyperintense and T1-hypointense lesion volume, WMV, GMV, Hipp v, Thal V.	**Secondary

SDMT=Symbol digit modalities test; CVLT=California verbal learning test; Brief visuospatial memory test – revised; MVPA=free-living moderate-to-vigorous physical activity; $V0_2$ peak=peak oxygen uptake; IET=Incremental exercise test; CPET=Cardiopulmonary Exercise Test; HR=heart rate; CMI=Cognitive motor interference; DT=dual task; nr=number; 6MWT=six minute walk test; HADS=Hospital Anxiety and Depression Scale; FAMS= Functional Assessment of Multiple Sclerosis; EQ5D-5=European Quality of Life-5 Dimensions; MSIS-29-V2=Multiple Sclerosis Impact Scale; MSWS-12=Multiple Sclerosis Walking Scale-12; PDQ=Perceived Deficits Questionnaire; MFIS= Modified Fatigue Impact Scale; RS=resting state; WMV=white matter volume; GMV=Gray matter volume; Hipp v=Hippocampus volume; Thal V=Thalamus volume.

* The primary outcome of the study is the change in processing speed at immediate post -12 weeks, assessed with the SDMT.

**All secondary outcomes will be assessed during the in-person interview or baseline assessment, at the post 12-week assessment and at the 6 month follow-up assessment (apart from accelerometer data at 6 month).

⚕ MRI data, not included in this report.

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Attendance rates

	Cognitive Sessions Attended	Exercise Sessions Attended

Treatment Group	Study Status	N	Mean*	Std Dev	Mean*	Std Dev
EX-S + CR-S	Reached End of Study	65	92.2	11.6	91.2	11.6
	Early Termination	10	55.0	40.7	51.2	36.6
EX + CR-S	Reached End of Study	67	92.7	9.4	90.7	12.8
	Early Termination	13	53.5	41.5	50.7	40.3
EX-S + CR	Reached End of Study	73	91.2	14.1	87.6	19.9
	Early Termination	6	59.7	33.9	57.6	32.1
EX + CR	Reached End of Study	67	91.2	9.9	90.3	10.1
	Early Termination	10	44.2	37.3	43.3	37.0

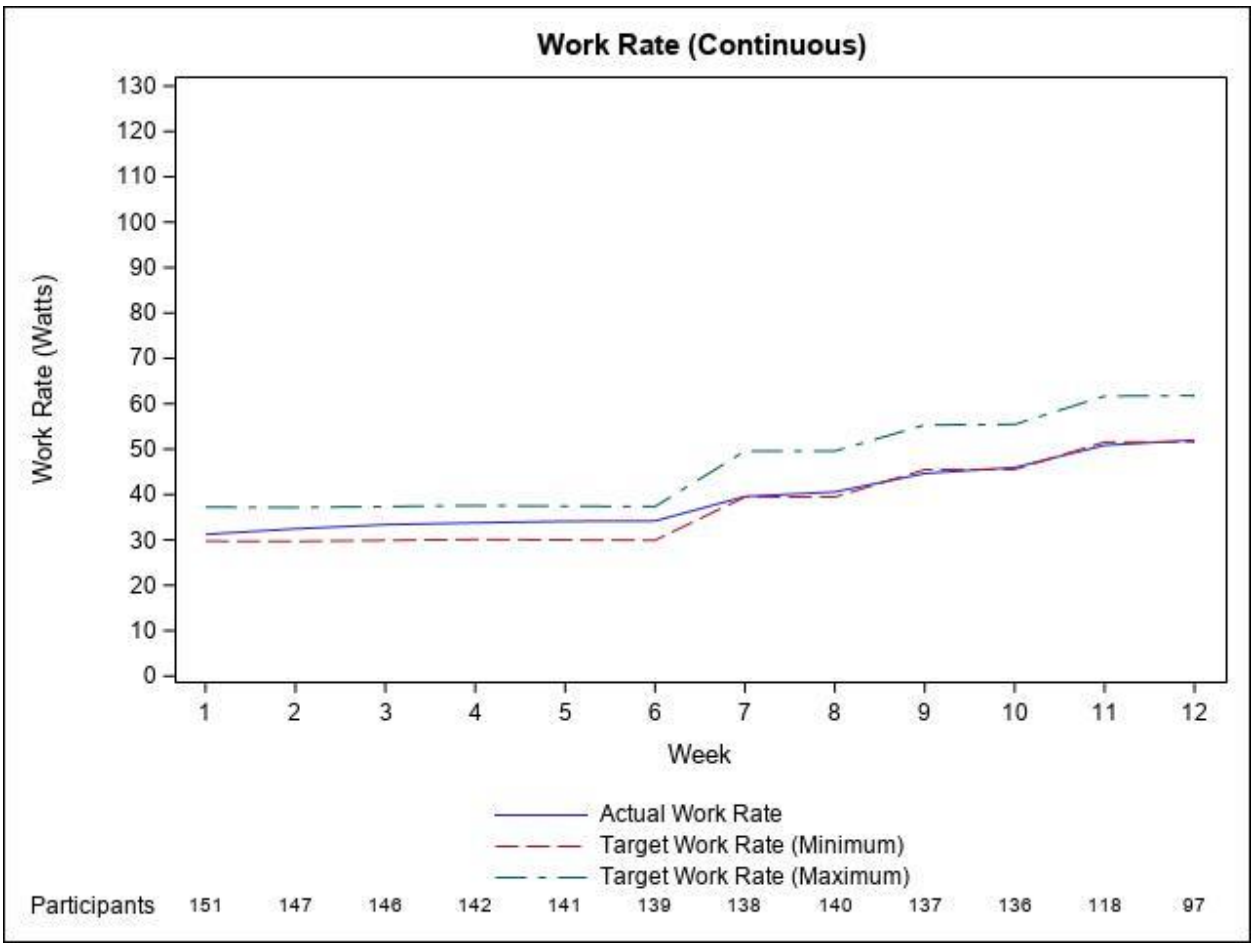
EX=exercise; CR=cognitive rehabilitation; CR-s=sham cognitive rehabilitation; EX-S=sham exercise.

Average Duration of Cognitive sessions

Treatment Group	Study Status	N	Mean*	Std Dev
EX-S + CR-S	Reached End of Intervention	65	41.4	3.0
	Early Termination	10	43.3	4.1
EX + CR-S	Reached End of Intervention	67	41.9	3.1
	Early Termination	13	40.3	1.6
EX-S + CR	Reached End of Intervention	73	42.0	2.9
	Early Termination	6	41.2	4.6
EX + CR	Reached End of Intervention	67	41.8	3.7
	Early Termination	10	41.7	2.5

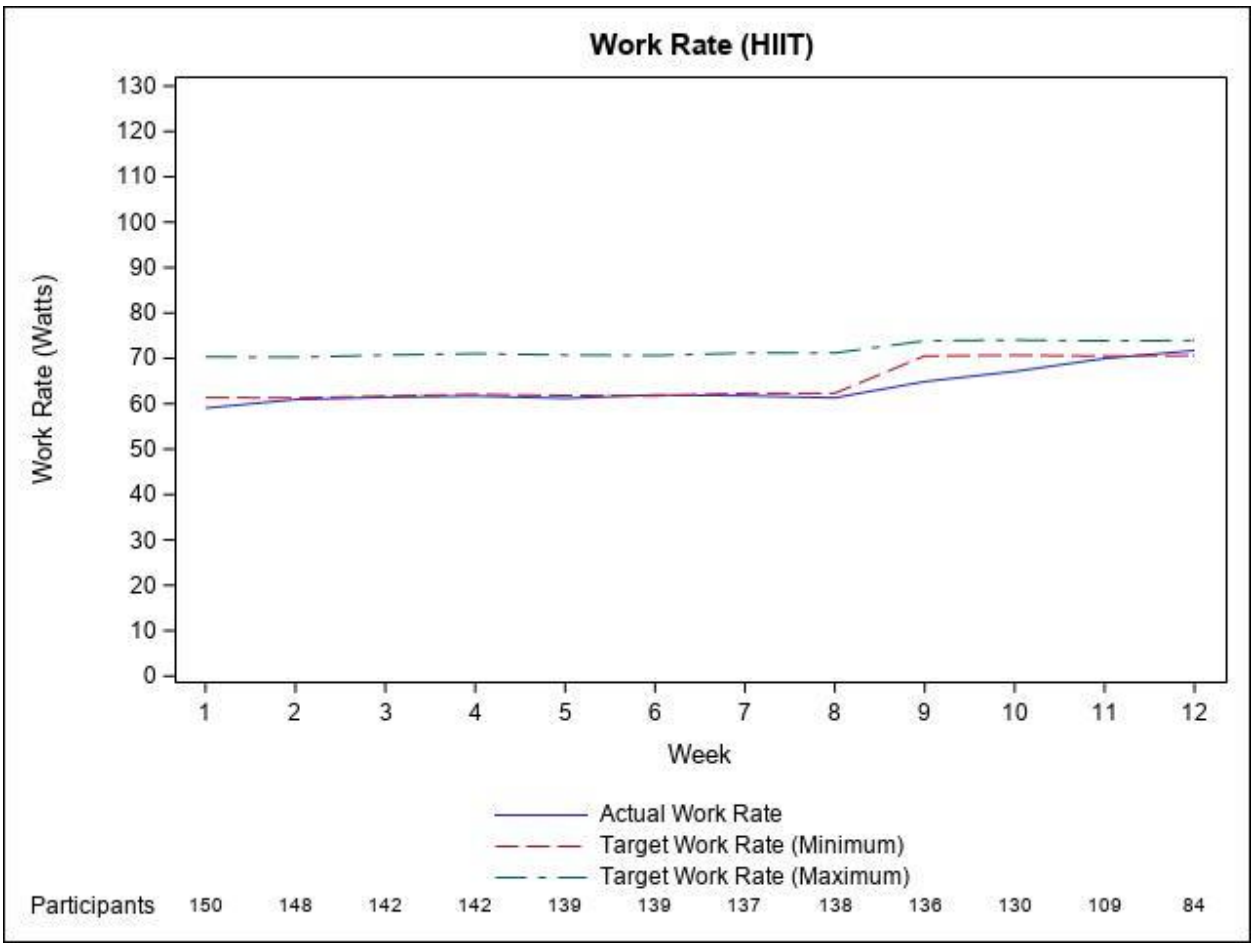
EX=exercise; CR=cognitive rehabilitation; CR-s=sham cognitive rehabilitation; EX-S=sham exercise.

Work rate for continuous exercise, recorded over 12 weeks



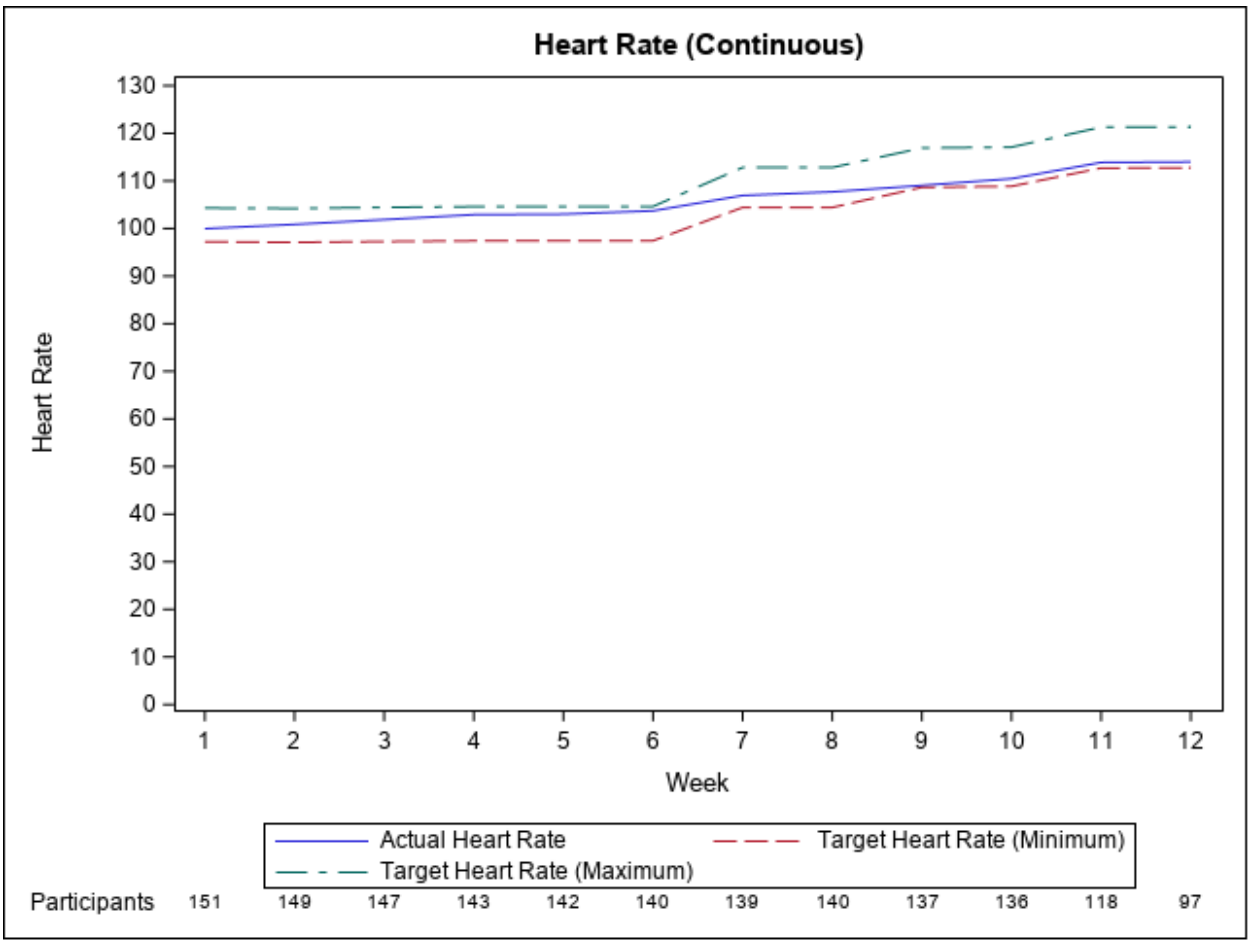
The figure depicts the work rate target zone (red line: lower limit target work rate; green line: upper limit target work rate) and the actual work rate (blue line) during continuous exercise for the pooled exercise groups.

Work rate for high intensity interval training (HIIT) exercise, recorded over 12 weeks

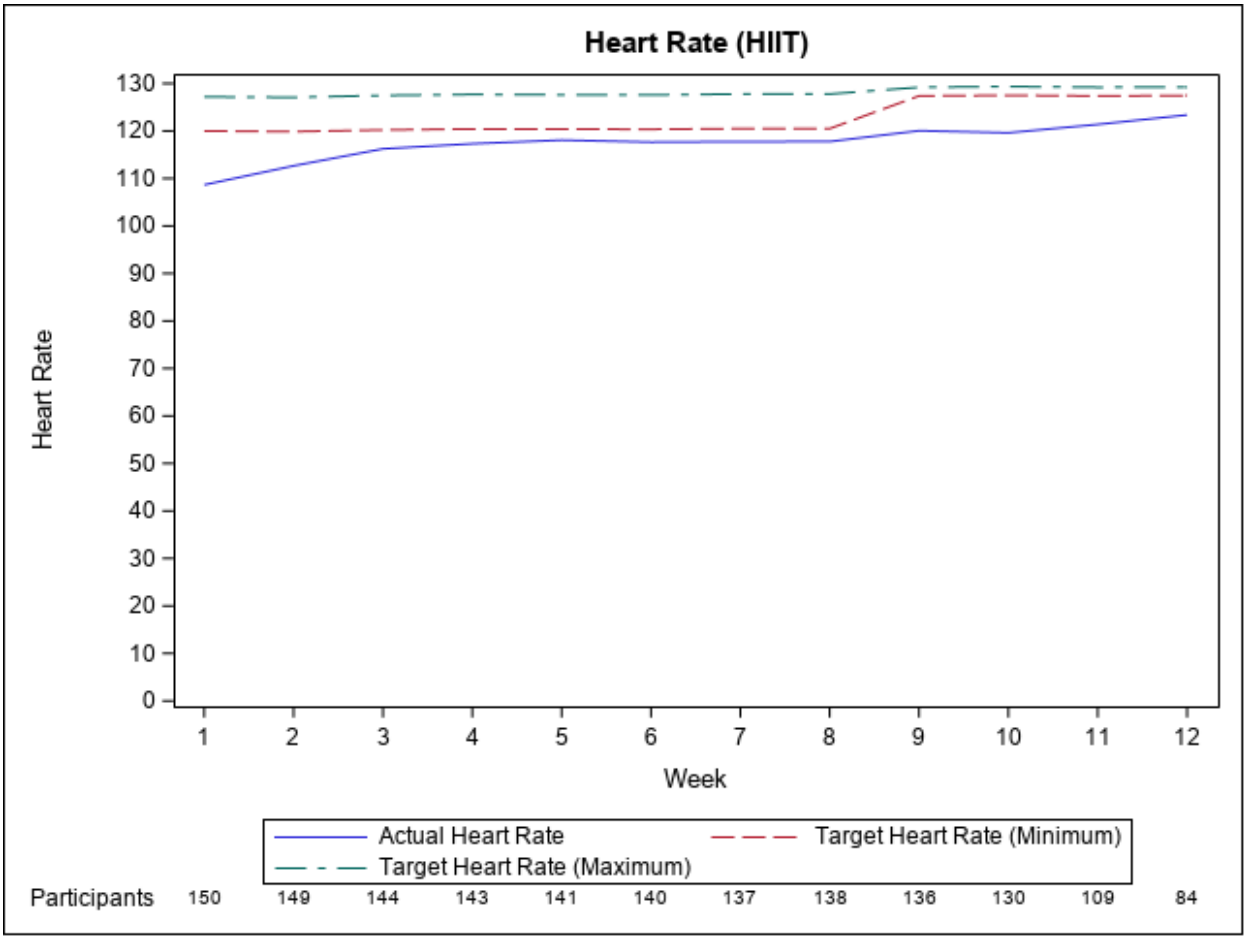


The figure depicts the work rate target zone (red line: lower limit target work rate; green line: upper limit target work rate) and the actual work rate (blue line) during HIIT exercise for the pooled exercise groups.

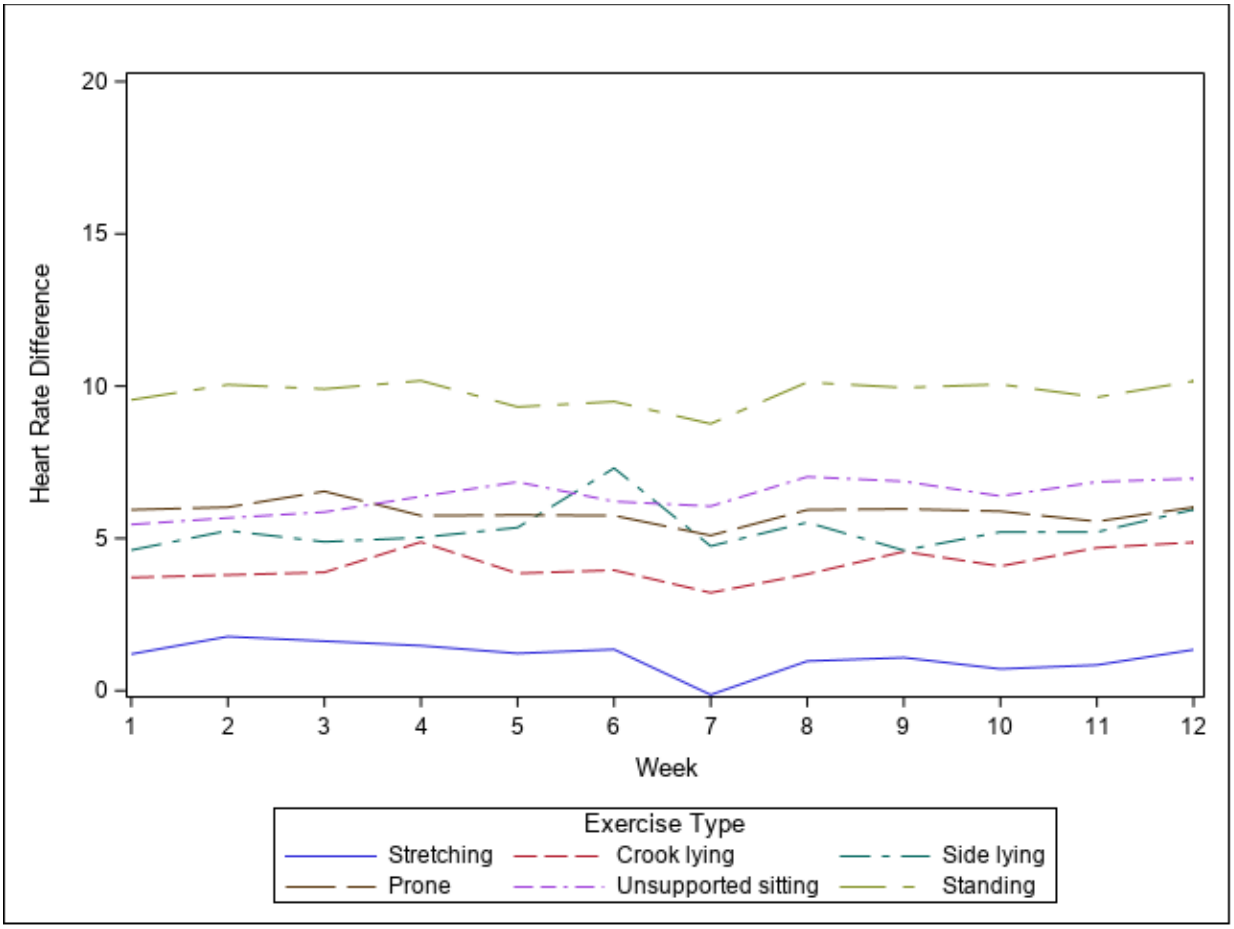
Heart Rate for continuous exercise, recorded over 12 weeks



Heart Rate for high intensity interval training



Exercise sham average heart rate (HR) differences (peak HR – resting HR), recorded over 12 weeks



Adverse events			
Group	**Description**	**Relationship to intervention**	**Outcome**
EX-S + CR-S	Fell during sham exercise. Not hurt.	Probably related	Resolved.
EX + CR-S	Transient, mild back pain that worsened after exercise session.	Probably related	Condition worsening
EX + CR-S	Transient left knee pain.	Probably related	Resolved
EX + CR	Fatigue and a flare in fibromyalgia following baseline IET.	Probably related	Recovered with minor ongoing pain
EX-S + CR	Transiet headache after RehaCom session brough on my image disortion on the computer screen.	Probably related	Resolved
EX-S + CR	Painful, swollen and hot knee.	Possibly related	Ongoing/Continuing treatment
EX + CR-S	Trip and fall with no injury sustained.	Possibly related	Resolved
EX + CR-S	Low back pain	Possibly related	Unknown
EX + CR	Transient thight pain during the continuous exercise session.	Possibly related	Resolved
EX + CR-S	Dizziness, loss of balance and a fall after completing an exercise session. Unhurt.	Possibly related	Resolved
EX + CR-S	Transient pain in both legs during an exercise session.	Probably related	Resolved
EX-S + CR-S=Exercise-sham plus Cognitive rehabitation-sham; EX + CR-S=Exercise plus cognitive rehabilitation-sham; EX + CR=Exercise plus cogitive rehabiliation; EX-S + CR=Exercise-sham plus cognitive rehabiliation.			

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Serious adverse events			
EX-S + CR	Surgery for knee prosthesis	Unrelated	Hospitalization/Surgery
EX-S + CR	Exacerbation in symptoms possibly caused by humid and hot weather.	Unrelated	Hospitalization.
EX-S + CR-S	Urinary tract infecrtion	Unrelated	Hospitalization/antibiotic medication
EX-S + CR	Fall at home home causing lumber spine fractures.	Unrelated	Hospitalization/ Behavioral/lifestyle
EX + CR	Syncope with loss of consciousness. Further frequent panic attacks	Unrelated	Hospitalization/Medication change
EX-S + CR	Surgery for knee prosthesis	Unrelated	Hospitalization/Surgery
EX-S + CR-S=Exercise-sham plus Cognitive rehabitation-sham; EX + CR-S=Exercise plus cognitive rehabilitation-sham; EX + CR=Exercise plus cogitive rehabiliation; EX-S + CR=Exercise-sham plus cognitive rehabiliation.			

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1 Tables

Table 1: Demographic and disease related data

	Total (n=311)	**CR + EX (n=77)**	**CR + EX-S (n=79)**	**CR-S + EX (n=80)**	**CR-S+EX-S (n=75)**
Age, mean (SD)	52.6 (7.2)	52.6 (8.0)	52.9 (6.7)	51.6 (6.9)	53.4 (7.1)
Sex*, n (%)					
Female	194 (62 %)	49 (64 %)	46 (58 %)	54 (68 %)	45 (60 %)
Male	117 (38 %)	28 (36 %)	33 (42 %)	26 (32 %)	30 (40 %)
School, mean (SD) years	13.9 (3.3)	13.7 (3.6)	14.1 (3.2)	14.2 (3.1)	13.8 (3.5)
Highest level of education completed, n (%)					
Primary	25 (8.0)	9 (11.7)	2 (2.5)	4 (5.0)	10 (13.3)
Secondary (high school)	146 (46.9)	36 (46.8)	42 (53.2)	36 (45.0)	32 (42.7)
College / University	140 (45.0)	32 (41.6)	35 (44.3)	40 (50.0)	33 (44.0)
EDSS, median [25th, 75th]	6.0 [4.5, 6.5]	6.0 [4.5,6.5]	6.0 [4.5,6.5]	5.5 [4.0,6.0]	6.0 [4.0,6.5]
Type of MS, n (%)					
Primary progressive	84 (27 %)	24 (31 %)	22 (28 %)	20 (25 %)	18 (24 %)
Secondary progressive	227 (73 %)	53 (69 %)	57 (72 %)	60 (75 %)	57 (76 %)
Duration of MS (in years)	14.5 (9.6)	14.2 (10.0)	14.1 (9.2)	13.9 (8.7)	15.9 (10.6)
Medications					
Stimulants, n (%)	47 (15 %)	11 (14 %)	12 (15 %)	11 (14 %)	13 (17 %)
Anxiolytics/Hypnotics, n (%)	23 (7 %)	6 (8 %)	4 (5 %)	5 (6 %)	8 (11 %)
Antidepressants/mood stabilizers, n (%)	96 (31 %)	26 (34 %)	22 (28 %)	25 (31 %)	23 (31 %)
Analgesics, n (%)	64 (21 %)	16 (21 %)	22 (28 %)	13 (16 %)	13 (17 %)
DMTs, n (%)	134 (43 %)	31 (40 %)	38 (48 %)	37 (46 %)	28 (37 %)

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

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Table 2: Group comparison of outcomes at 12 weeks and 6 months							
		Total	**CR + EX**	**CR + EX-S**	**CR-S + EX**	**CR-S+EX-S**	**p value***
N	Baseline	311	77	79	80	75	-
	12-week	284	70	76	71	67	
	6 month	258	65	68	65	60	
Cognitive outcomes							
SDMT[↓]	Baseline	33.4 (8.2)	32.2 (8.6)	33.0 (7.4)	35.1 (8.1)	33.3 (8.4)	0.85
	12-week	39.3 (11.5)	38.0 (11.9)	39.1 (10.3)	39.9 (11.1)	40.2 (12.8)	
	6 month	36.8 (11.6)	35.8 (11.1)	35.9 (12.5)	37.9 (10.3)	37.8 (12.4)	
Difference in SDMT[†]	Baseline to 12-week	5.9 (7.5)	5.7 (7.2)	6.3 (6.6)	4.5 (7.5)	7.1 (8.6)	0.23
	4 points or greater, n (%)[‡]	171 (60.2)	45 (64.3)	50 (65.8)	36 (50.7)	40 (59.7)	0.24
	8 points or greater, n (%)[§]	106 (37.3)	26 (37.1)	31 (40.8)	24 (33.8)	25 (37.3)	0.86
	Baseline to 6 month	3.5 (7.3)	3.5 (6.8)	3.1 (8.2)	2.8 (6.7)	4.4 (7.2)	0.63
	4 points or greater, n (%)[‡]	119 (46.1)	30 (46.2)	34 (50.0)	29 (44.6)	26 (43.3)	0.88
	8 points or greater, n (%)[§]	68 (26.4)	17 (26.2)	17 (25.0)	15 (23.1)	19 (31.7)	0.73
CVLT⁕	Baseline	45.1 (11.9)	44.9 (12.2)	44.2 (10.9)	46.3 (12.7)	45.1 (11.9)	0.95
	12-week	46.2 (11.4)	46.6 (11.7)	45.6 (10.8)	47.5 (11.8)	45.1 (11.3)	
	6 month	48.7 (12.5)	48.7 (12.3)	47.9 (12.6)	50.6 (12.7)	47.7 (12.4)	
BVMT-R⁕	Baseline	20.8 (7.5)	20.6 (7.2)	21.1 (7.4)	21.2 (7.2)	20.2 (8.1)	0.93
	12-week	20.1 (7.8)	19.7 (7.7)	19.6 (7.6)	20.9 (7.7)	20.4 (8.2)	
	6 month	19.5 (7.8)	19.3 (8.3)	18.8 (8.0)	19.8 (7.1)	20.1 (8.1)	
Physical outcomes							
IET - VO_2 Peak⁕	Baseline	17.5 (6.3)	16.4 (5.3)	17.3 (5.8)	18.5 (6.7)	17.6 (7.2)	0.22
	12-week	18.2 (6.9)	17.9 (6.7)	17.2 (6.6)	20.0 (7.4)	17.6 (6.6)	
	6 month	17.6 (6.0)	17.8 (5.6)	17.4 (5.9)	18.4 (6.5)	16.6 (6.0)	
IET – Peak Watts⁕	Baseline	81.0 (33.6)	76.8 (32.3)	77.1 (28.8)	86.1 (35.6)	83.9 (36.9)	0.004
	12-week	87.7 (38.0)	89.7 (33.8)	78.2 (32.4)	100.4 (39.7)	83.0 (43.0)	
	6 month	81.2 (34.6)	81.3 (33.8)	78.3 (33.4)	83.3 (36.4)	82.2 (35.8)	
IET –Peak HR⁕	Baseline	132.8 (21.3)	130.9 (22.2)	132.0 (20.4)	137.0 (21.6)	131.0 (20.8)	0.04
	12-week	133.9 (22.5)	133.3 (21.3)	130.0 (23.4)	142.5 (21.7)	129.7 (21.2)	
	6 month	131.3 (20.9)	129.6 (20.1)	132.6 (19.3)	134.0 (23.0)	128.4 (21.1)	
CMI Dual Task Cost (DTC) Cognition⁕	Baseline	0.39 (43.6)	-7.9 (68.6)	0.73 (36.8)	3.8 (26.9)	5.0 (27.8)	0.92
	12-week	3.7 (29.9)	-4.4 (43.1)	2.2 (22.6)	9.0 (23.0)	8.4 (25.1)	
	6 month	4.1 (39.4)	-2.4 (48.6)	5.7 (39.2)	5.2 (29.7)	8.0 (38.1)	
CMI Dual Task Cost (DTC) Motor⁕	Baseline	15.9 (14.4)	14.4 (16.5)	17.5 (12.9)	15.6 (15.3)	16.1 (12.7)	0.92
	12-week	15.7 (15.0)	13.4 (13.4)	17.0 (14.3)	16.2 (15.9)	16.1 (16.4)	
	6 month	14.6 (16.0)	11.4(18.4)	15.7(16.0)	16.6(15.6)	14.7(13.5)	
6MWT, total distance⁕	Baseline	265.5 (141.0)	258.5 (143.1)	241.7 (136.2)	286.8 (142.7)	275.3 (140.4)	0.40
	12-week	281.0 (141.5)	273.6 (138.0)	259.5 (150.6)	299.8 (135.3)	293.2 (140.0)	
	6 month	273.3 (138.0)	277.2 (137.6)	258.2 (151.6)	272.0 (128.0)	287.6 (135.7)	
Accelerometer Average % MVPA⁕	Baseline	1.7 (2.3)	1.7 (2.4)	1.5 (2.7)	2.1 (2.5)	1.4 (1.6)	0.95
	12-week	1.7 (2.3)	1.8 (2.8)	1.5 (1.8)	1.8 (2.3)	1.5 (2.0)	

Patient reported outcomes							
HADS-D⁕	Baseline	6.2 (4.0)	6.2 (4.0)	6.7 (4.5)	5.6 (3.7)	6.2 (3.7)	0.51
	12-week	5.7 (3.6)	6.4 (3.9)	5.5 (3.8)	5.0 (3.3)	5.9 (3.3)	
	6 month	6.3 (4.1)	6.5 (4.0)	6.4 (4.4)	6.2 (4.4)	6.3 (3.8)	
HADS-A⁕	Baseline	6.5 (4.5)	6.8 (5.0)	6.5 (4.6)	6.2 (3.9)	6.7 (4.5)	0.87
	12-week	6.0 (4.1)	6.7 (4.7)	5.7 (3.9)	5.4 (3.8)	6.1 (4.0)	
	6 month	6.4 (4.2)	7.1 (4.7)	5.8 (3.9)	6.3 (4.2)	6.4 (3.8)	
FAMS Total⁕	Baseline	103.4 (28.7)	100.6 (29.4)	98.9 (29.5)	110.3 (25.5)	103.6 (29.5)	0.88
	12-week	106.2 (29.5)	100.5 (30.7)	105.6 (30.0)	111.0 (28.3)	107.9 (28.6)	
	6 month	100.9 (29.5)	98.7 (29.3)	100.3 (29.2)	104.4 (30.0)	99.9 (29.9)	
EQ-5D-5L VAS⁕	Baseline	59.7 (20.7)	59.3 (23.3)	56.8 (20.9)	61.9 (20.4)	60.7 (18.1)	0.93
	12-week	64.5 (18.8)	63.5 (20.9)	64.1 (20.0)	65.5 (17.7)	64.9 (16.4)	
	6 month	62.3 (19.5)	63.1 (19.3)	62.8 (21.2)	62.1 (18.8)	61.1 (18.9)	
MSIS-29, Physical⁕	Baseline	47.0 (22.9)	51.3 (22.7)	49.2 (23.4)	43.6 (22.2)	43.7 (22.7)	0.85
	12-week	42.8 (23.1)	49.3 (24.3)	42.7 (23.1)	37.6 (21.6)	41.7 (22.0)	
	6 month	48.5 (23.0)	53.2 (22.6)	47.4 (23.6)	44.8 (21.8)	48.7 (23.6)	
MSIS-29, Mental⁕	Baseline	37.2 (24.1)	40.5 (24.5)	37.3 (24.6)	34.4 (22.5)	36.8 (24.9)	0.07
	12-week	34.4 (23.6)	41.5 (25.5)	34.1 (23.7)	30.6 (22.0)	31.4 (22.0)	
	6 month	39.4 (24.9)	40.9 (25.6)	38.3 (23.3)	37.8 (24.0)	40.8 (27.1)	
MSWS-12⁕	Baseline	63.3 (26.6)	67.1 (26.5)	64.6 (25.5)	60.0 (28.0)	61.7 (26.0)	0.74
	12-week	59.3 (26.6)	61.7(25.5)	60.7(27.6)	57.3(27.1)	57.5 (26.4)	
	6 month	63.9 (26.9)	65.4 (25.4)	62.4 (28.9)	63.3 (28.3)	64.9 (24.9)	
PDQ Total⁕	Baseline	28.5 (17.2)	30.7 (18.9)	28.9 (16.2)	26.6 (17.5)	27.8 (16.1)	0.80
	12-week	26.4 (16.6)	29.9 (17.3)	25.1 (15.0)	23.2 (17.1)	27.4 (16.7)	
	6 month	29.4 (16.6)	31.6(16.7)	27.7(14.7)	27.4(17.8)	31.3(17.2)	
MFIS⁕	Baseline	44.1 (17.1)	46.4 (17.9)	45.8 (16.3)	40.9 (16.8)	43.6 (17.1)	0.84
	12-week	40.1 (17.3)	43.1 (17.7)	40.7 (18.0)	36.2 (16.3)	40.2 (16.7)	
	6 month	44.7 (16.7)	46.7 (16.3)	44.7 (17.5)	42.9 (16.6)	44.5 (16.5)	

SDMT=Symbol Digit Modalities Test; CVLT=California Verbal Learning Test; BVMT=Brief Visual Memory Test – revised
IET=incremental exercise test; VO_2 =V stands for volume and O_2 stands for oxygen; HR=Heart Rate; CMI=Cognitive-motor interference; 6MWT=6 minute walk test; MVPA=Moderate to vigorous physical activities *p-value is based on the longitudinal model adjusting for baseline and site; HADS-D=Hospital Anxiety and Depression Scale-Depression; HADS-A=Hospital Anxiety and Depression Scale-Anxiety; FAMS=Functional Assessment of Multiple Sclerosis; EQ-5D-5L=European Quality of Life 5 Dimensions 5 Level; VAS=Visual Analog Scale; MSIS-29=Multiple Sclerosis Impact Scale-29; MSWS-12=12-Item MS Walking Scale; MFIS=Modified Fatigue Impact Scale.
*p-value is based on the longitudinal model adjusting for baseline and site. *†=Difference in raw SDMT score between baseline and 12-week follow-up; ‡ 4 points or greater change on the SDMT at 12-weeks; § 8 points or greater change on the SDMT at 12-weeks.
⭳Primary analysis ⁕Secondary analysis ⭱Sensitivity analysis

No multiple comparison correction was performed for secondary outcomes.