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# Cognitive rehabilitation and aerobic exercise for cognitive impairment in people with progressive multiple sclerosis (CogEx): a randomised, blinded, sham-controlled trial

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4 **Cognitive Rehabilitation and Aerobic Exercise for cognitive impairment in people with**  
5 **Progressive Multiple Sclerosis (CogEx): A Multi-Arm, Randomized, Blinded, Sham-**  
6 **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  $\geq 1.282$  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).

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

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124 Funding: MS Society of Canada.

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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

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

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210

## 211 **Introduction**

212 Cognitive dysfunction affects 40-80% of people with multiple sclerosis (MS) with the highest  
213 rates in people with primary and secondary progressive MS. It is associated with widespread  
214 functional limitations.<sup>1</sup>

215

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

224

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

234

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

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

## 244 **Method**

### 245 *Study design*

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

258

### 259 *Participants*

260 Key eligibility criteria were a neurologist-confirmed diagnosis of primary or secondary MS, ages  
261 25-65 years, an EDSS < 7.0 and failure on a test of processing speed, the Symbol Digit  
262 Modalities Test (SDMT), defined as a score of  $\geq 1.282$  SD below published normative data (10<sup>th</sup>  
263 percentile) specific for each country taking part. The full list of eligibility criteria appear in the  
264 supplementary file, see page 1. Written informed consent was obtained from participants at  
265 enrollment.

266

### 267 *Randomization and masking*

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

275

### 276 *Procedures*

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



280 & 2”, “attention and concentration,” “vigilance 2,” and “sustained attention.” Details of the  
281 cognitive rehabilitation intervention can be found in the supplementary file, see page 2.

282

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

289

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

304

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

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

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*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  $\geq 4$  points, which is considered clinically relevant for group data, and 8 points, which is considered clinically relevant for individual data.<sup>15,16</sup> 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 (BVM-T-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.

360 The first COVID lockdown from February to September 2020 interrupted recruitment and the  
361 interventions in 36 participants for an average of 82.9 (24.3) days. When it came to restarting the  
362 interventions, a consensus agreement amongst the principal investigators was for participants to  
363 resume two sessions back from where they had left off. If these two sessions did not return  
364 participants to the cognitive and physical metrics achieved prior to interruption, additional  
365 sessions were provided to reach that point. Sensitivity analyses were pre-planned and excluding  
366 these 36 participants showed results consistent with the primary analyses.

367

### 368 *Statistical analysis*

369 We estimated our sample size using a one-factor analysis of variance approach with a Type I  
370 error set at 5%. We computed the sample size necessary to achieve 80% power for such a design  
371 to identify conservative changes among the four groups. For simplicity we used 4 points on the  
372 SDMT for the combined treatments (cognitive rehabilitation and exercise), to demonstrate a  
373 clinically meaningful difference on average and that the two interventions are additive.  
374 Additionally, we assumed a change of 2 points for each of the single intervention groups  
375 (cognitive rehabilitation plus sham exercise and exercise plus sham cognitive rehabilitation plus)  
376 and 0 for the double sham group. The sample size required to detect these differences (4,2,2,0)  
377 with 80% power was 90 participants per intervention group assuming an 8 point standard  
378 deviation of the change and the overall Type I error of 0.05. See protocol paper for more detail.<sup>12</sup>

379

380 Descriptive statistics were used to summarize the demographic and clinical characteristics  
381 among the four intervention groups. Means (standard deviation [SD]) and median (interquartile  
382 range [IQR]) were used for continuous variables and frequency (percentage) were used for  
383 categorical variables. The analysis population includes participants with an outcome measure at  
384 12 weeks or 6 months. According to intention-to-treat principles, participants were included in  
385 the analysis according to their randomized treatment allocation. Statistical analyses were  
386 conducted in SAS v9.4 (Cary, NC).

387

388 Differences in SDMT number correct at 12-weeks (primary outcome) and 6-months between the  
389 interventions were evaluated using a linear mixed model to include all possible data in analyses.  
390 The model included SDMT number correct as the outcome and independent variables included  
391 the baseline SDMT number correct, randomized intervention group assigned (4 levels), time (12-  
392 weeks, 6-months) and an intervention by time interaction. Pairwise contrasts to evaluate  
393 hypotheses were conducted if the overall test for interventions achieved statistical significance.  
394 Pairwise comparisons evaluated absolute differences in least squares means and Dunnett's test  
395 was used to preserve the Type I error rate (control=double sham). Model assumptions were  
396 verified visually using residual plots and other regression diagnostics. The absolute difference in  
397 least squares mean at 12-weeks and 6-months and their standard errors (SE) for the intervention  
398 comparisons are reported. The significance level was set at 0.05. Secondary outcomes were  
399 analyzed similarly. However, as the primary outcome did not reach statistical significance, the

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

414

#### 415 *Role of the Funding Source*

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

420

#### 421 **Results**

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

439

440 The demographic and disease-related characteristics in the four groups are provided in Table 1.  
441 The mean (SD) baseline SDMT z-score was -2.1 (0.75).  
442 Participants reaching the end of interventions had an average attendance of 91% to 93% for the  
443 cognitive rehabilitation and sham cognitive rehabilitation sessions and 88% to 91% for the  
444 exercise and sham exercise sessions, see supplementary file page 8. For cognitive rehabilitation,  
445 the mean duration of the sessions was 41.4 to 42.0 minutes for all groups, see supplementary file  
446 page 8. For the exercise plus sham cognitive rehabilitation and exercise plus cognitive  
447 rehabilitation groups, 92% and 89% of HIIT sessions and 85% and 83% of continuous sessions  
448 were completed, respectively. Actual work rate during both the continuous and HIIT sessions  
449 corresponded well with the target work rate, see supplementary figures, pages 9 and 10.  
450  
451 There were a total of 76 protocol deviations (defined as an event that varied from the study  
452 protocol) reported with 1 (1%) for consent procedures, 2 (3%) related to eligibility criteria, 52  
453 (68%) study procedures, 3 (4%) adverse device effect, 12 (16%) visit schedule/interval, and 6  
454 (8%) other. The exercise plus sham cognitive rehabilitation group had the highest number of  
455 protocol deviations 25 (33%), the cognitive rehabilitation and sham exercise group had 21  
456 (28%), the cognitive rehabilitation plus exercise had 19 (25%), and the group with both sham  
457 interventions had 11 (15%).  
458  
459 The mean differences in the number correct on the SDMT were not different between the four  
460 groups at 12-weeks (primary outcome,  $p=0.85$ ; Table 2). The absolute differences in the least  
461 squares mean [95%CI] for the SDMT at 12-weeks compared with the sham cognitive  
462 rehabilitation and sham exercise group ( $n=67$ ) were: cognitive rehabilitation and exercise group  
463 ( $n=70$ ) -1.3 [-3.75, 1.16]; exercise plus sham cognitive rehabilitation group ( $n=71$ ) -2.8 [-5.23 ,  
464 0.33]; cognitive rehabilitation and sham exercise group ( $n=76$ ) - 0.7 [-3.11, 1.70]. Sensitivity  
465 analysis demonstrated similar results when adjusting for site and using SDMT z-scores. The  
466 absolute differences in the least squares mean [95%CI] for the SDMT at 6-months between  
467 groups compared with the sham cognitive rehabilitation and sham exercise group ( $n=60$ ) were:  
468 cognitive rehabilitation and sham exercise group ( $n=65$ ) -0.8 [-3.38, 1.76]; compared exercise  
469 and sham cognitive rehabilitation group ( $n=65$ ) -1.8 [-4.40, 0.75]; versus cognitive rehabilitation  
470 and sham exercise group ( $n=68$ ): -1.2 [-3.76, 1.33]).  
471  
472 The sensitivity factorial analysis comparing the cognitive rehabilitation and sham cognitive  
473 rehabilitation groups revealed no differences in SDMT number correct at 12-weeks (-0.37 [0.86];  
474  $p=0.66$ ) and 6-months (0.15 [0.90];  $p=0.87$ ) and no differences between the exercise and sham  
475 exercise groups (12-weeks: 1.48 [0.86],  $p=0.09$ ; 6-months: 0.51 [0.90],  $p=0.57$ ). In a post-hoc  
476 analysis, of the 284 participants with both baseline and 12-week SDMT scores, overall 171 (60%)  
477 individuals demonstrated SDMT improvements  $\geq 4$  points and 106 (37%) individuals demonstrated  
478 improvement  $\geq 8$ -points compared to baseline. For the 6-month SDMT data, 119 (46%)  
479 participants showed a  $\geq 4$  points improvement and 68 (26%) participants a  $\geq 8$ -points improvement.

480 In further post-hoc analysis, among the 119 individuals with a greater than 4-point SDMT  
481 improvement at 6- months, 100 met the same threshold at 12-weeks. The remaining 19 people  
482 showed a delayed improvement. Of the 68 individuals with a greater than 8-point improvement at  
483 6-months, 52 met that threshold at 12-weeks and 16 had a delayed response.

484

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

486

487 Overall, there were some differences between groups among physical measures for the peak heart  
488 rate and watts (Table 2). At 12 weeks, the cognitive rehabilitation plus exercise group had a higher  
489 peak heart rate compared to the cognitive rehabilitation plus sham exercise group (mean difference  
490 [SE]: 4.7[2.3],  $p=0.038$ ). the exercise plus sham cognitive rehabilitation group had a higher peak  
491 heart rate compared to the sham cognitive rehabilitation plus sham exercise group (mean difference  
492 [SE]: 7.0 [2.3],  $p=0.003$ ) and the cognitive rehabilitation plus and sham exercise group (8.0 [2.2],  
493  $p=0.0004$ ). These differences were lost by 6 months. A sensitivity analysis showed a higher peak  
494 heart rate in the exercise versus sham exercise groups: -5.8 [1.2],  $p=0.0004$  which attenuated by 6  
495 months (0.7 [1.8],  $p=0.71$ ). At 12 weeks the cognitive rehabilitation plus exercise group had a  
496 higher peak watts during the IET compared to the sham cognitive rehabilitation plus sham exercise  
497 group (mean difference [SE]: 14.2[3.2],  $p=0.0001$ ) and cognitive rehabilitation and sham exercise  
498 group (12.7 [3.1],  $p=0.0001$ ). The CR-S+EX group had a higher peak watts compared to CR-  
499 S+EX-S (15.1[3.1],  $p=0.0001$ ) and CR+EX-S (13.6[3.1],  $p = 0.0001$ ). A sensitivity analysis  
500 showed higher peak watts in the EX versus EX-S groups at 12-weeks (-13.9[2.2],  $p = 0.0001$ ) and  
501 6-months (-4.7[2.5],  $p=0.0525$ ). There were no group differences in the 6MWT, CMI and  
502 accelerometer results at 12-weeks and 6 months (Table 2).

503

504 A post-hoc analysis of the physical measures related specifically to the exercise intervention was  
505 undertaken to examine differences between groups. At 12-weeks, the cognitive rehabilitation plus  
506 exercise group had higher  $VO_2$ -peak improvement compared to the cognitive rehabilitation plus  
507 sham exercise group (mean difference [SE]: 1.84 [0.67],  $p=0.007$ ) and the sham cognitive  
508 rehabilitation plus sham exercise group (1.67 [0.70],  $p=0.02$ ) which was lost by 6-months. A  
509 sensitivity analysis using a factorial design showed a mean improvement [SE] of 1.48 [0.49]  
510 ml/kg/min ( $p=0.003$ ) for the exercise compared to the sham exercise groups which was attenuated  
511 at 6-months (-0.73 [0.55],  $p=0.19$ ). For the heart rate in the exercise and sham exercise groups  
512 recorded over 12 weeks, see supplementary figures, pages 11 to 13

513

514 The 12-week and 6 month data for the HADS-D, HADS-A, and MFIS revealed no between-  
515 group differences. At 12-weeks, participants in the cognitive rehabilitation plus exercise group  
516 had worse scores on the physical and mental subscales of the MSIS-29 compared to some of the  
517 other groups as follows: For the physical subscale, the cognitive rehabilitation plus exercise  
518 group was 7.9 [2.6] points higher than the exercise plus sham cognitive rehabilitation group  
519 ( $p=0.003$ ) and 5.2 [2.6] points higher than the cognitive rehabilitation plus sham exercise group

520 (p=0.04) groups. For the mental subscale, the cognitive rehabilitation plus exercise group was  
521 7.5 [2.8] points higher than the exercise plus sham cognitive rehabilitation group (p=0.009), and  
522 7.5 [2.9] points higher than the sham cognitive rehabilitation plus sham exercise group  
523 (p=0.009) groups. These differences were lost at 6-months.

524  
525 There were 11 minor adverse events reported, six in the exercise plus sham cognitive  
526 rehabilitation group (pain, dizziness falls), two in the cognitive rehabilitation plus sham exercise  
527 group (headache, pain), two in the cognitive rehabilitation and exercise group (increased fatigue,  
528 pain) and one in the dual sham group (fall). Five serious adverse events, unrelated to CogEx,  
529 occurred, three in the cognitive rehabilitation plus sham exercise group (symptom exacerbation,  
530 surgery for knee prosthesis, fall at home) and one each in the cognitive rehabilitation plus  
531 exercise group (syncope and panic) and dual sham group (urinary tract infection). All participants  
532 required hospitalization. Further details on the adverse events appear in supplementary file, page  
533 14.

534

## 535 **Discussion**

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

542

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

549

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

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

573  
574 A closer look at the duration and intensities of our interventions is warranted in light of our  
575 findings. We administered RehaCom for two 45 minute sessions per week over 12 weeks for a  
576 total of 24 sessions. Two recent reviews of computerized cognitive training in predominantly  
577 relapsing-remitting MS show that RehaCom is the most frequently used program. Lampit et al  
578 cite<sup>4</sup> six studies, two of which exceeded the number and total duration of sessions administered  
579 in CogEx. Brochet<sup>26</sup> cites four studies all of which provided fewer sessions than CogEx. This  
580 suggests that, relative to others, CogEx provided a robust RehaCom intervention. Of note is that  
581 the reported effect size from 20 studies using RehaCom and other programs targeting attention  
582 and processing speed was 0.32,<sup>4</sup> lower than our a-priori estimate of 0.5 which is commensurate  
583 with a 4-point SDMT improvement from baseline. Our fealty to a 4-point SDMT change was  
584 driven by the recommendations of the Multiple Sclerosis Outcome Assessment Consortium to  
585 the Food and Drug Administration emphasizing the ecological validity of this change, an  
586 important consideration in linking laboratory findings to real world consequences of change.<sup>27</sup> In  
587 following this, however, we may have overestimated the effectiveness of our cognitive  
588 rehabilitation.

589  
590 The peak watts, peak heart rate, and VO<sub>2</sub> peak data at 12-weeks suggest a performance based  
591 improvement in the exercise compared to the sham exercise groups. The 10% VO<sub>2</sub> improvement  
592 at 12-weeks in the exercise group, while modest, is considered a reliable, but not necessarily  
593 meaningful, change in the MS literature.<sup>28</sup> We designed our sham exercise protocol to keep  
594 participants blinded to group membership while simultaneously avoiding interventions that  
595 would boost aerobic activity. Yet despite our strict adherence to this regime, the absence of  
596 between group differences in our primary outcome measure suggests our sham remained active  
597 in improving processing speed. As a systematic review of control group improvements in  
598 intervention trials reveals, factors other than the sham regime itself, such as pre-existing health  
599 status and the exclusion of active participants, both relevant to CogEx, may account for this.<sup>29</sup>



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

606  
607 Our findings were also notable for showing improvements across all four treatment groups in the  
608 SDMT that often exceeded 4 and 8 points, which are considered clinically significant in group  
609 and individual data, respectively.<sup>15-16</sup> A 4-point improvement, present in 60% of our sample at  
610 the primary endpoint of 12 weeks was consistent across 11 centres in six counties and in multiple  
611 languages. The magnitude of these changes could not fully be accounted for by regression to the  
612 mean or practice effects. The importance of the latter has been addressed in a longitudinal study  
613 of 219 healthy individuals who completed the SDMT at baseline, 6 months, and one year: group  
614 scores improved from 58.83 to 60.88 to 62.05 and were attributed to practice.<sup>16</sup> These changes  
615 are considerably less than those seen in our study. One important conclusion from this normative  
616 dataset was that a change of 8 points was considered meaningful at an individual level with an  
617 80% confidence interval.<sup>16</sup> This threshold was reached by 46% of our sample at the primary  
618 endpoint of 12 weeks.

619  
620 The most parsimonious explanation to account for the 4 and 8-point change in SDMT  
621 performance seen in so many participants is that both interventions are effective. To this may be  
622 added another possible reason. By the end of the study, anecdotal accounts from some  
623 participants informed us that the 3-month intervention period provided more physical,  
624 intellectual, and social activity (an enriched lifestyle) than they had experienced in the previous  
625 few years. This in turn may have boosted processing speed. This explanation is supported by a  
626 study of 248 people with MS (predominantly relapsing-remitting MS) that revealed an  
627 association between what the authors called a “positive lifestyle” (exercise, social/intellectual  
628 engagement, healthy nutritional choices) and processing speed.<sup>32</sup> The *moderating* effects of an  
629 enriched environment on cognitive decline in progressive MS were described in 2012.<sup>33</sup> Our data  
630 suggest that enhancing enrichment in multiple ways may offer additional *remedial* benefits,  
631 specific to processing speed in people with progressive MS. Our findings also reveal that  
632 pushing people with progressive MS too hard with taxing personalised interventions might have  
633 a temporary downside, reflected in worse scores on the MSIS-29, a self-report measure of the  
634 impact of MS.

635  
636 Our study has limitations. Given that our sham exercise was not inactive, incorporating a waitlist  
637 control would have controlled for the passage of time and practice effects on the outcome  
638 measures. The COVID-19 pandemic also hindered recruitment,<sup>34</sup> but this is unlikely to explain the  
639 fact that our results did not support our hypothesis. SDMT outcome scores between our four

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

646

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

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## **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.

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811

### 812 **Data Sharing Statement**

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

817

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## Supplementary Information – web appendix

### Eligibility criteria

<b>Inclusion criteria</b>	
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 (10 <sup>th</sup> percentile) specific for each center taking part <sup>1,2,3,4,5,6</sup>
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.
<b>Exclusion criteria</b>	
Ambulation	EDSS $\geq$ 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 ( $\geq$ 29 on the Beck Depression Inventory).
MRI	Claustrophobia, metal implants, pacemakers.

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997 Cognitive Rehabilitation (CR) protocol:  
998 CR was provided by the computerized RehaCom program. RehaCom is available in over 20  
999 languages including all the languages needed for our trial. The language selection is built into  
1000 the computer program and accessed via a simple drop down menu. This is a major asset of the  
1001 RehaCom software as few cognitive rehabilitation programs are available in multiple languages.  
1002 To address processing speed (PS), the single most common cognitive deficits observed in  
1003 persons with MS<sup>7</sup> we administered the RehaCom module shown to be effective in targeting this  
1004 aspect of cognition.<sup>8</sup> In particular, there are five RehaCom training modules, “divided attention  
1005 1,” “divided attention 2” “attention and concentration,” “vigilance 2” and “sustained attention”  
1006 that are integral to processing speed. For example, in the divided attention 1 module, the  
1007 person is required to simulate a train conductor, carefully observing the control panel of the  
1008 train and the countryside. Several distractions, such as animals, railway signals and train speed  
1009 must be taken into account, with increasing levels of difficulty. In the divided attention 2  
1010 module, the person is required to simulate driving a car, carefully observing the control panels  
1011 and the road. Several distractors, such as billboard signs, speed limit signs, radio noise, and  
1012 remembering to signal right or left turns must be taken into account, with increasing levels of  
1013 difficulties. In the attention and concentration module, an individual picture (target) is  
1014 presented and then compared with a matrix of pictures. The person has to recognize the target  
1015 picture (coded as symbols, items, animals, or abstract figures) and select it from the matrix. The  
1016 abilities to differentiate and to concentrate are trained simultaneously. The level of difficulty  
1017 rises as the number and complexity of pictures to recognize increases. During the vigilance 2  
1018 task, the person is trained to sustain his or her attention for a prolonged period by providing  
1019 response times limited to the various items. The task is to control a conveyor belt and to select  
1020 the objects that differ from a target sample in one or more details. Finally, in the sustained  
1021 attention module, is similar to the vigilance task, except the speed of the conveyor belt has  
1022 increased. Participants began at level 1 on each RehaCom module and advanced through the  
1023 program as dictated by their performance, under the guidance of the RA. Progression was thus  
1024 individualized, based on the success on each task. Each session comprised of two out of the five  
1025 modules randomized each session, each module programmed to last 20 minutes, making the  
1026 duration of each cognitive session 40 minutes, as has been accomplished successfully in  
1027 previous RehaCom research in persons with MS.<sup>9,10</sup>

1028  
1029 Sham Cognitive Rehabilitation (CR-S) protocol: The CR-S condition consisted of internet training,  
1030 based closely on the internet control group utilized in previous computer-mediated cognitive  
1031 rehabilitation studies in the literature.<sup>11</sup> The control condition began with more basic tasks such  
1032 as learning to use a computer and the internet to search for information, including locating  
1033 information regarding medications, gardening, getting directions, etc. Participants began at the  
1034 most appropriate level, completing the 24 sessions that followed to match the frequency of the  
1035 CR treatment group interventions. The control sessions were designed to equate the two CR  
1036 groups (active and sham) on social and computer contact. This approach has been  
1037 demonstrated to be effective in controlling for these factors in previous research.<sup>11</sup>

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1039 Exercise protocol: In accordance with the MS literature, the exercise intervention of choice was  
1040 aerobic and performed by recumbent stepper.<sup>12,13</sup> It consisted of one weekly session of  
1041 continuous exercise alternating with one weekly session of interval training. This ensured  
1042 variation as well as a greater volume of high intensity exercise during the interval training, thus  
1043 allowing more exercise time at intensities approaching the VO<sub>2peak</sub>. The exercise intervention  
1044 complied with the basic principle of progressive overload. This meant that there was an  
1045 inherent progression built into the program involving changes in both exercise time (volume)  
1046 and intensity.

1047  
1048 Type: Aerobic training was performed on an arm-leg recumbent stepper with all centres using  
1049 the same equipment (NuStep T5XR, <https://www.nustep.com/international/products/t5xr/>)  
1050 that allowed individual adjustment of stepper settings as well as providing a valid measure of  
1051 the applied resistance expressed as wattage or kp.

1052

1053 Frequency: Twice weekly with each session separated by one day of rest.

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1055 Supervision: Full supervision of all exercise sessions by the trained RA to match that provided  
1056 during the cognitive rehabilitation sessions.

1057

1058 Format/duration: (Tables A and B)

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1060 One session involved continuous exercise initially commencing at 10 minutes and progressing  
1061 towards 30min/session, with 5 minutes of warm up and 5 minutes of cool down.

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1063 **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

1064 \* Peak HR was determined by formal cardiopulmonary exercise testing. Resting HR was also  
1065 determined at baseline.

1066

1067 One session involved interval training (5 x 1 min progressing towards 10 x 2min) in line with the  
1068 schedule in Table 1b.

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1070 **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

1071 \* Peak HR was determined by formal cardiopulmonary exercise testing. Resting HR was also  
1072 determined at baseline.

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1093 Sham exercise protocol: (adapted from Barrett et al.<sup>14</sup>)

1094 Generally, this one hour, twice weekly sham exercise intervention did not put any strain on the  
 1095 cardiovascular system, focusing on balance and stretching. Further, it intentionally did not  
 1096 contain any cognitive-motor dual tasking to avoid potentially providing any cognitive training.  
 1097 Also, it did not include complex exercises where patients needed substantial working memory  
 1098 or (sustained) attention. The duration was one hour. Six types of exercises were identified as  
 1099 being appropriate for inclusion: stretches, exercises in crook lying, unilateral exercises in side  
 1100 lying, exercises in prone, exercises in unsupported sitting and exercises in standing.  
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<b>Type 1: Stretches</b> Hamstrings Quadriceps Hip flexors Hip abductors Ankle plantar-flexors	<b>Type 2: Exercises in crook lying</b> Bridging (two legs/single leg) Trunk rotation Pelvic tilt Unilateral hip abduction Bilateral hip abduction Hip and knee flexion/extension	<b>Type 3: Exercises in side lying</b> Unilateral hip abduction Unilateral hip lateral rotation Unilateral hip abduction/lateral rotation Unilateral knee flexion/extension
<b>Type 4: Exercises in prone</b> Unilateral hip extension Unilateral/bilateral knee flexion Bilateral isometric gluteal contraction Unilateral/bilateral hip rotation	<b>Type 5: Exercises in unsupported sitting</b> 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	<b>Type 6: Exercises in standing</b> 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

1102  
 1103 Format/duration: A standardized (minimal) progression of exercises was undertaken over the  
 1104 12 weeks to reduce the possible cognitive demand that might be required for dealing with  
 1105 exercise variation. To ensure the exercises were at low HR, they were undertaken with rest  
 1106 periods at a 2:1 ratio to avoid a potential aerobic effect of the sham intervention. Further, the  
 1107 number of consecutive repetitions were low. In line with the EX intervention, the sham session  
 1108 initially commenced at 15-30 min. and ultimately progressed towards 60 min/sessions. The  
 1109 program was further designed to avoid improvements of lower limb muscular strength, as this  
 1110 has been associated with faster processing speed.<sup>15,16</sup>

1111 **Table C. Summary of sham exercise intervention characteristics.**

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

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**CogEx study endpoints.**

<b>Outcome</b>	<b>Measurement(s)</b>	<b>Primary/secondary</b>
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<b>Cognitive</b>		
SDMT <sup>17</sup>	Information processing speed	*Primary
CVLT <sup>18</sup>	Verbal memory	**Secondary
BVMT-R <sup>19</sup>	Visual memory	**Secondary
<b>Physical</b>		
Accelerometer <sup>20</sup> (derived from ActiGraph wearable device)	Average % of wear time in MVPA	**Secondary
IET <sup>21</sup> (synonymous with CPET)	VO <sub>2</sub> peak (mL/kg/min); Peak Watts, Peak Heart Rate	**Secondary
CMI <sup>22</sup>	DT cost (motor); DT cost (cognitive)	**Secondary
6MWT <sup>23</sup>	Total distance walked in meters in the 6-minute period	**Secondary
<b>Patient reported outcomes (PROs)</b>		
HADS <sup>24</sup>	Anxiety and depression	**Secondary
FAMS <sup>25</sup>	Assessment of Global Function	**Secondary
EQ-5D-5L <sup>26</sup>	Quality of Life (generic)	**Secondary
MSIS-29-V2 <sup>27</sup>	Impact of Multiple Sclerosis	**Secondary
MSWS-12 <sup>28</sup>	Subjective impact of walking	**Secondary
PDQ-20 <sup>29</sup>	Subjective cognitive difficulties	**Secondary
MFIS <sup>30</sup>	Fatigue	**Secondary
<b>‡ MRI</b>		
Functional (Go/No-Go <sup>31</sup> task and resting state)	Task activation along with reaction times, omission errors, commission errors, and correct responses. RS functional connectivity	**Secondary
Structural	Brain T2-hyperintense and T1-hypointense lesion volume, WMV, GMV, Hipp v, Thal V.	**Secondary
<p>SDMT=Symbol digit modalities test; CVLT=California verbal learning test; Brief visuospatial memory test – revised; MVPA=free-living moderate-to-vigorous physical activity; VO<sub>2</sub> 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.</p> <p>* The primary outcome of the study is the change in processing speed at immediate post -12 weeks, assessed with the SDMT.</p> <p>**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).</p> <p>‡ MRI data, not included in this report.</p>		

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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.

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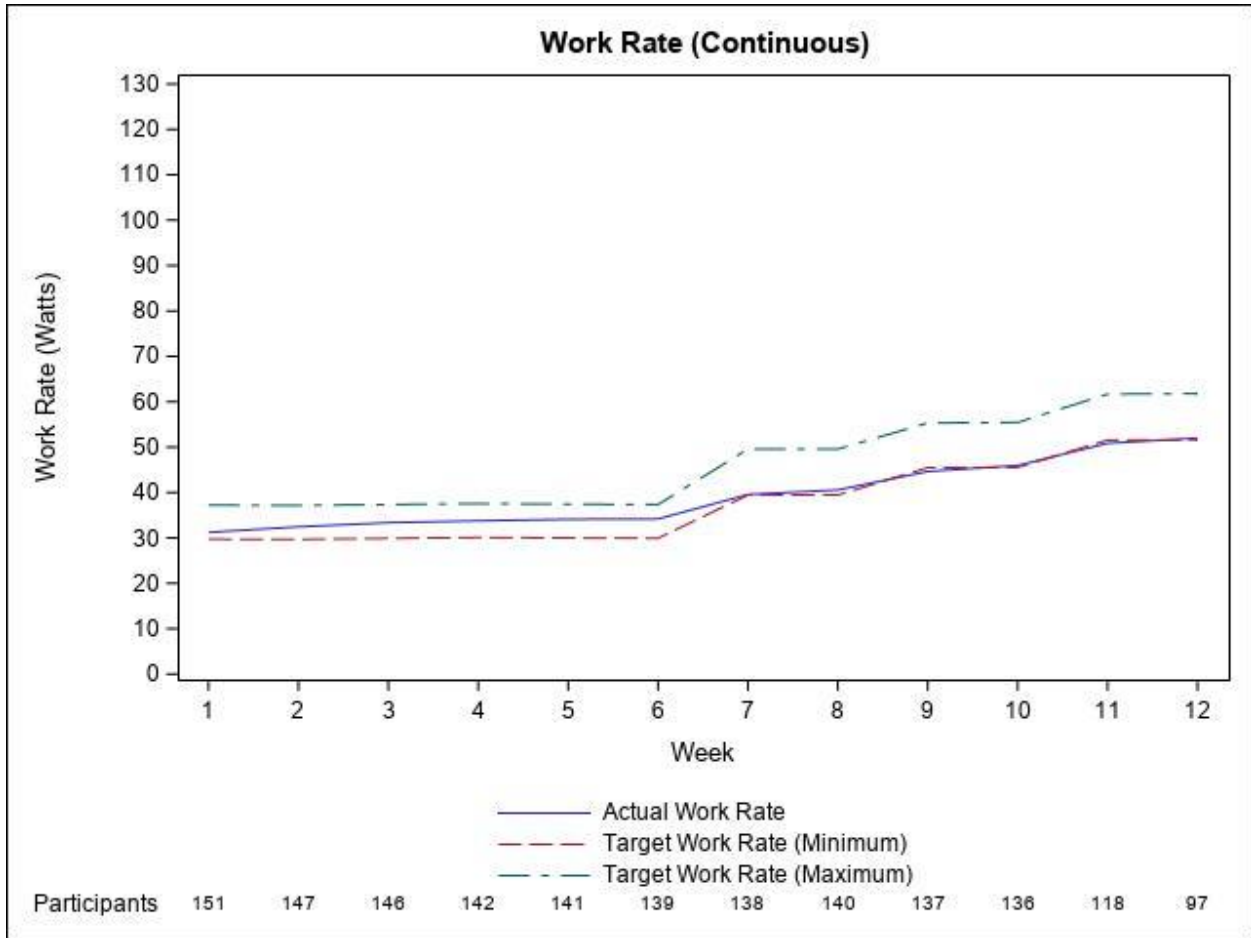
**Average Duration of Cognitive sessions**

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.

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1147 Work rate for continuous exercise, recorded over 12 weeks



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1149 The figure depicts the work rate target zone (red line: lower limit target work rate; green line: upper limit target  
1150 work rate) and the actual work rate (blue line) during continuous exercise for the pooled exercise groups.

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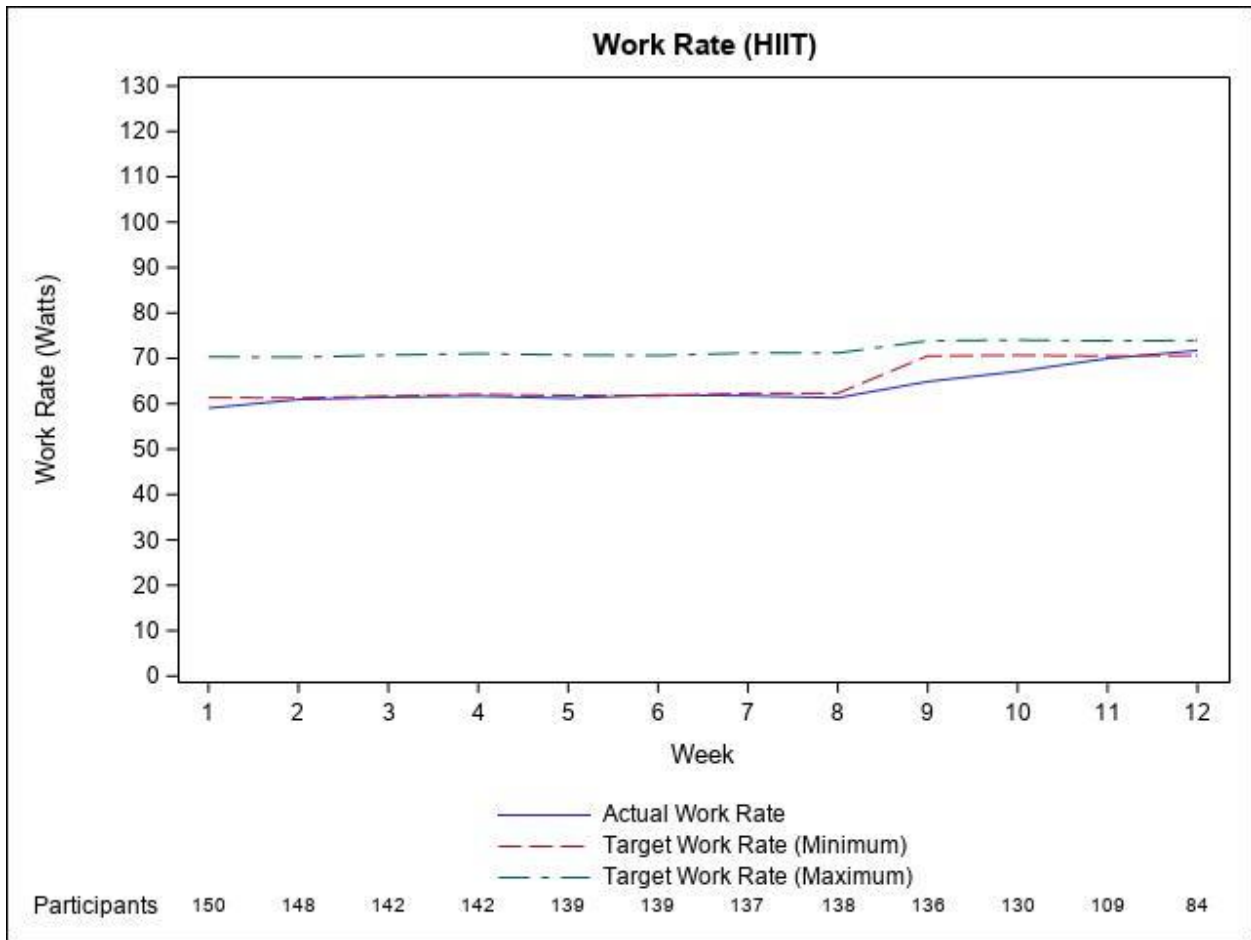
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1162 Work rate for high intensity interval training (HIIT) exercise, recorded over 12 weeks



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1164 The figure depicts the work rate target zone (red line: lower limit target work rate; green line: upper limit target  
1165 work rate) and the actual work rate (blue line) during HIIT exercise for the pooled exercise groups.

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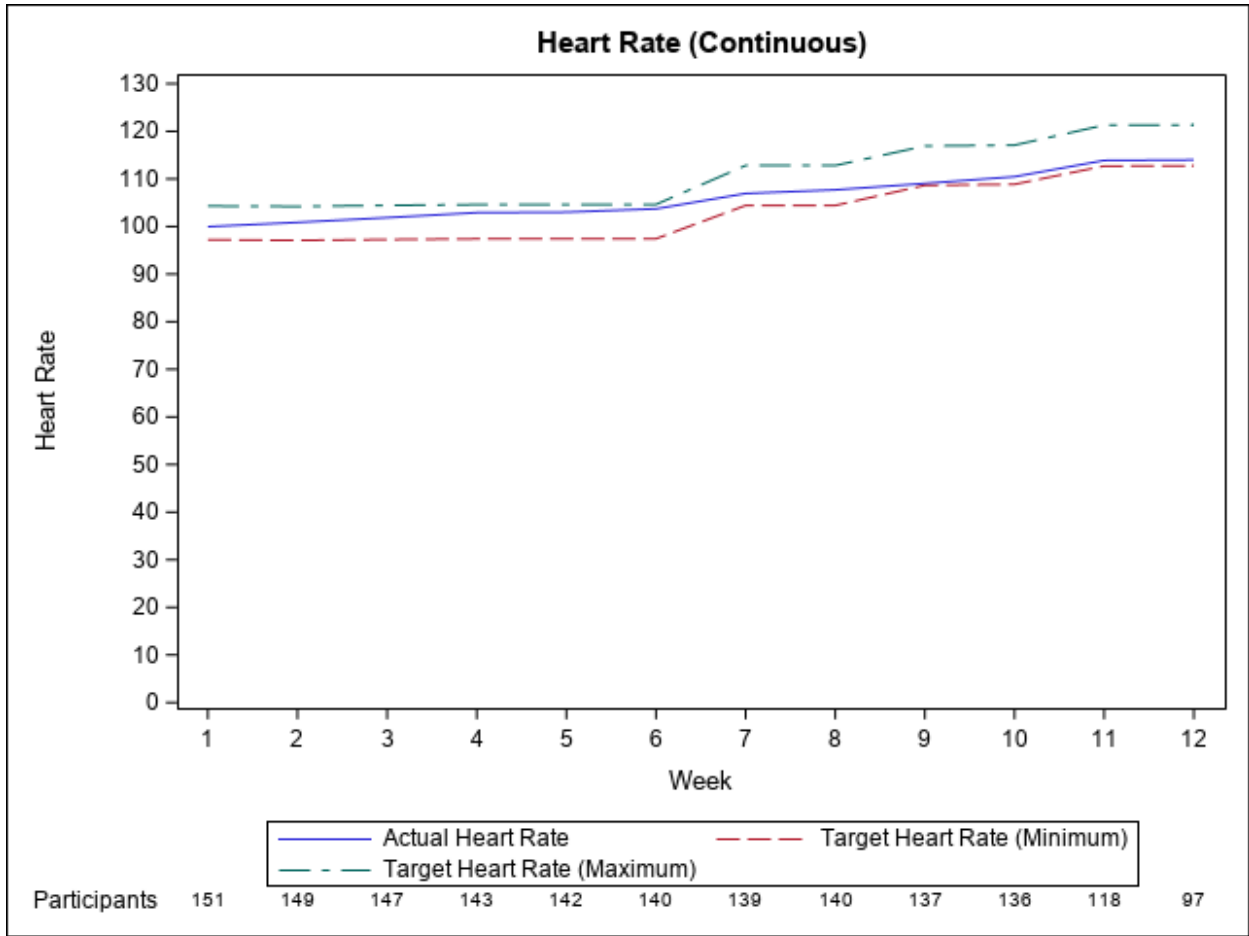
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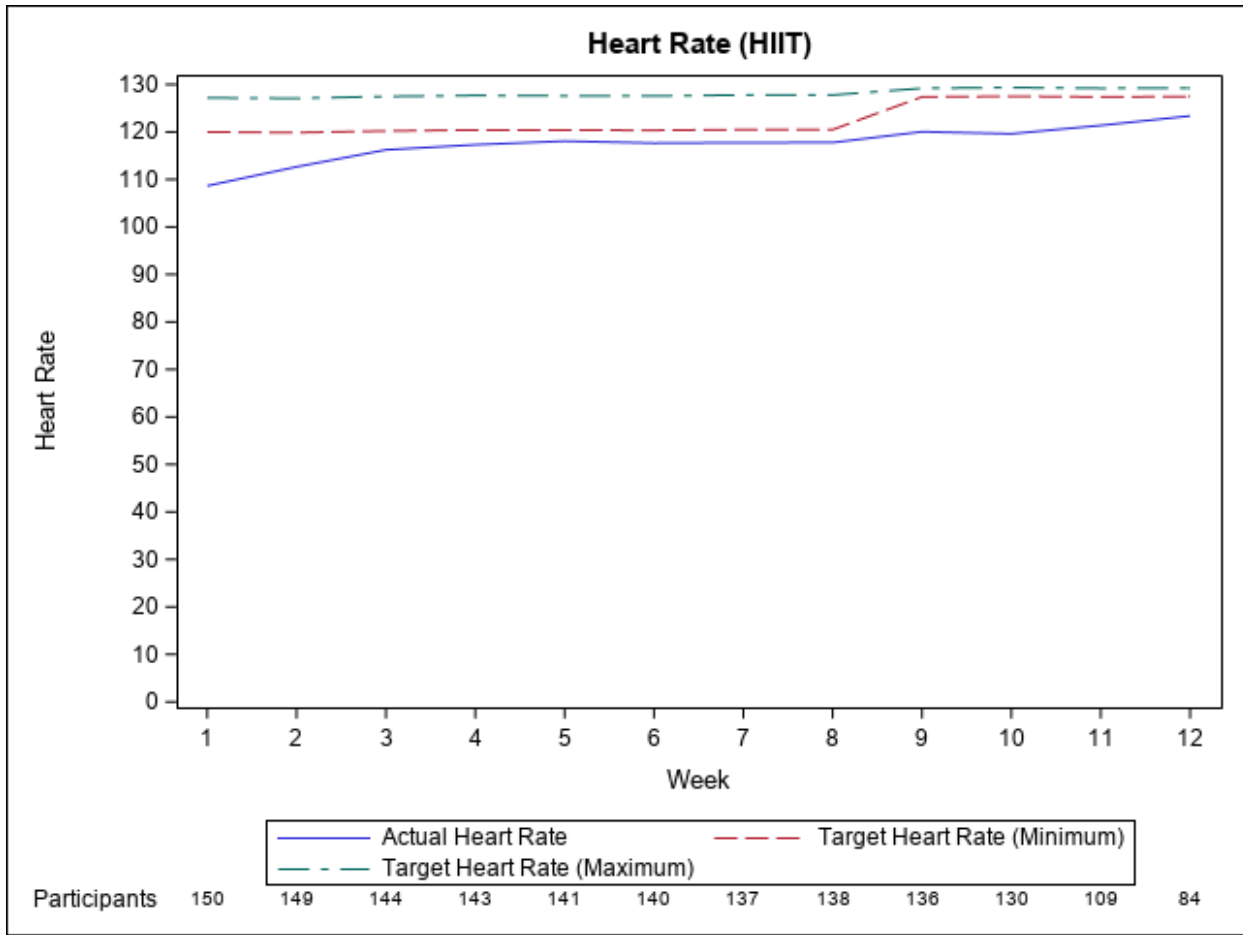
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1177 Heart Rate for continuous exercise, recorded over 12 weeks



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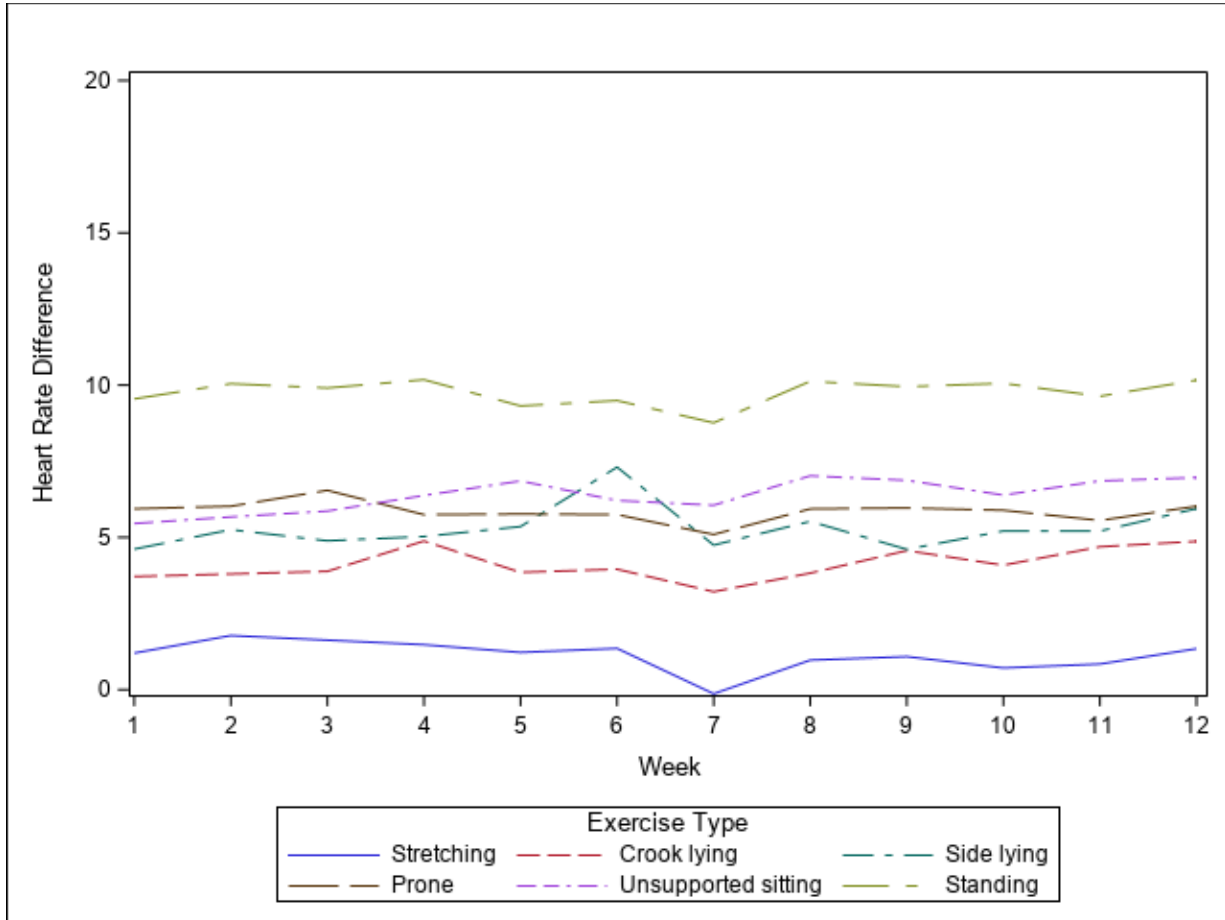
1202 Heart Rate for high intensity interval training  
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Exercise sham average heart rate (HR) differences (peak HR – resting HR), recorded over 12 weeks



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<b>Adverse events</b>			
<b>Group</b>	<b>Description</b>	<b>Relationship to intervention</b>	<b>Outcome</b>
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	Transient headache after RehaCom session brought on by image distortion 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 thigh 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 rehabilitation-sham; EX + CR-S=Exercise plus cognitive rehabilitation-sham; EX + CR=Exercise plus cognitive rehabilitation; EX-S + CR=Exercise-sham plus cognitive rehabilitation.			

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<b>Serious adverse events</b>			
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 infection	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 rehabilitation-sham; EX + CR-S=Exercise plus cognitive rehabilitation-sham; EX + CR=Exercise plus cognitive rehabilitation; EX-S + CR=Exercise-sham plus cognitive rehabilitation.			

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## 1 Tables

2 **Table 1: Demographic and disease related data**

	<b>Total (n=311)</b>	<b>CR + EX (n=77)</b>	<b>CR + EX-S (n=79)</b>	<b>CR-S + EX (n=80)</b>	<b>CR-S+EX-S (n=75)</b>
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 [25 <sup>th</sup> , 75 <sup>th</sup> ]	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 %)

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



<b>Table 2: Group comparison of outcomes at 12 weeks and 6 months</b>							
		<b>Total</b>	<b>CR + EX</b>	<b>CR + EX-S</b>	<b>CR-S + EX</b>	<b>CR-S+EX-S</b>	<b>p value*</b>
N	Baseline	311	77	79	80	75	-
	12-week	284	70	76	71	67	
	6 month	258	65	68	65	60	
<b>Cognitive outcomes</b>							
SDMT <sup>†</sup>	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 <sup>†</sup>	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 (%) <sup>‡</sup>	171 (60.2)	45 (64.3)	50 (65.8)	36 (50.7)	40 (59.7)	0.24
	8 points or greater, n (%) <sup>§</sup>	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 (%) <sup>‡</sup>	119 (46.1)	30 (46.2)	34 (50.0)	29 (44.6)	26 (43.3)	0.88
	8 points or greater, n (%) <sup>§</sup>	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)	
<b>Physical outcomes</b>							
IET - VO <sub>2</sub> 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)	

<b>Patient reported outcomes</b>							
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 <sub>2</sub> =V stands for volume and O <sub>2</sub> 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. * <sup>†</sup> p-value is based on the longitudinal model adjusting for baseline and site. * <sup>‡</sup> =Difference in raw SDMT score between baseline and 12-week follow-up; <sup>§</sup> 4 points or greater change on the SDMT at 12-weeks; <sup>§</sup> 8 points or greater change on the SDMT at 12-weeks. <sup>‡</sup> Primary analysis *Secondary analysis <sup>†</sup> Sensitivity analysis No multiple comparison correction was performed for secondary outcomes.							