Sandroff BM, Motl RW, Amato MP, Brichetto G, Chataway J, Chiaravalloti ND, Cutter GR, Dalgas U, DeLuca J, Farrell R, Feys P, Filippi M, Freeman J, Inglese M, Meza C, Rocca MA, Salter A, Feinstein A.
Cardiorespiratory fitness and free-living physical activity are not associated with cognition in persons with progressive multiple sclerosis: Baseline analyses from the CogEx study.

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Abstract

Background: Aerobic exercise training (physical activity for improving cardiorespiratory fitness) represents a promising approach for managing cognitive impairment in multiple sclerosis (MS). However, there is limited evidence that **levels of** physical activity and fitness are associated with cognition in progressive MS.

Objective: We examined associations among cardiorespiratory fitness, **moderate-to-vigorous** physical activity (MVPA), and cognitive performance in a large, international progressive MS sample.

Methods: 240 European and North American persons with progressive MS **underwent** cardiorespiratory fitness **measurement** on a recumbent stepper, wore an ActiGraph GT3X+ accelerometer for 7-days for measuring MVPA, **and underwent the Brief International Cognitive Assessment in MS**.

Results: Cardiorespiratory fitness was not significantly correlated with Symbol Digit Modalities Test (SDMT; r=−.01;r=−.04), California Verbal Learning Test-II (CVLT-II; r=.05;r=.05), or Brief Visuospatial Memory Test-Revised (BVMT-R; r=−.14;r=−.14) z-scores controlling for age, sex, and education. MVPA and SDMT (r=.05), CVLT-II (r=−.07), and BVMT-R (r=.01) z-scores **were not significantly correlated**.

Conclusion: Cardiorespiratory fitness and MVPA were not associated with cognition in this large progressive MS sample, yet these outcomes represent critical manipulation checks for documenting the success of the CogEx trial. This highlights the importance of examining other exercise-related mechanisms-of-action for improving cognition in progressive MS.

Keywords: *fitness; physical activity; cognition; multiple sclerosis; progressive*

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Introduction

Multiple sclerosis (MS) is a neurological disease that affects upwards of 2.5 million people worldwide.[1] **Progressive forms of the disease are** typified by neurodegeneration and axonal transection, resulting in profound brain damage.[2,3] Cognitive impairment, in particular, represents a hallmark consequence of **progressive** MS. Recent epidemiological data suggest that approximately 75% of **progressive** MS patients demonstrate impaired cognition based on objective neuropsychological tests of cognitive processing speed (CPS), learning and memory, and executive functioning.[4] **Progressive** MS-related cognitive impairment is associated with unemployment, social isolation, and reduced quality of life, and is unmitigated by pharmacotherapies.[3] This highlights the importance of considering other approaches for managing cognitive dysfunction **in progressive MS**.[3]

Aerobic exercise training, defined as chronic physical activity for improving **or maintaining** cardiorespiratory fitness,[5] represents a promising approach for managing cognitive impairment in **progressive** MS.[3,6,7] This is based, in part, on evidence reporting on AET-related cognitive improvements in persons with **relapsing-remitting MS**[6] and **older** adults who often have progressive brain atrophy and associated loss of function over time.[8] By comparison, we are aware of only one study reporting on **aerobic exercise training**-related cognitive benefits in **progressive MS**. That pilot randomized controlled trial (RCT) reported that 8-10 weeks of aerobic cycle ergometer exercise training was associated with improvements in cardiorespiratory fitness, verbal memory, and alertness in a small sample of persons with **progressive MS**.[9]

One approach for informing the development of future **aerobic exercise training** interventions for improving cognition involves examining associations among cardiorespiratory fitness, **physical activity** (as cross-sectional surrogates for components of **aerobic exercise**), and cognition in this population. There is evidence describing significant associations between cardiorespiratory fitness and cognition,[10-12] and **physical activity** and cognition,[13] respectively, in non-**progressive** MS samples. Several recent studies have reported particularly strong correlations in cognitively-impaired MS samples;[11,13] that early-stage evidence has directly informed the development of ongoing RCTs.[6] Such results support the possibility of strong associations among cardiorespiratory fitness, **physical activity**, and cognition in **progressive** MS cohorts, and further might allow for head-to-head comparisons of cardiorespiratory fitness and **physical activity** as correlates of cognitive performance in this population. Indeed, the possibility of differential associations between cardiorespiratory fitness and **physical activity** with cognition would provide important information on the potential foci (i.e., improving fitness and/or enhancing **physical activity** behavior) of subsequent **aerobic exercise training** interventions in **progressive** MS.

The current study involved a **cross-sectional analysis of associations** among measures of cardiorespiratory fitness, free-living moderate-to-vigorous **physical activity** (MVPA), and cognitive performance in a large, international sample of persons with **progressive MS** who presented with objective CPS impairment **from the multi-site CogEx RCT**[14]. Based on previous evidence of particularly strong associations among cardiorespiratory fitness, **free-living physical activity**, and cognitive performance in cognitively-impaired persons with MS,[11,13] the overall hypothesis was that higher cardiorespiratory fitness and levels of free-living MVPA would similarly be associated with better cognitive performance.

Materials and Methods

The current study represents analyses of currently accrued baseline data from a multi-arm, randomized, blinded, sham-controlled trial of cognitive rehabilitation and **aerobic exercise training** on cognition and neuroimaging outcomes in persons with **progressive MS** and CPS impairment across 11 sites in North America and Europe (i.e., CogEx). The complete study protocol is described elsewhere.[14] Of note, all procedures described below were standardized across sites via comprehensive in-person and remote training, along with quality control on a case-by-case basis.

Participants

Participants were recruited via inpatient and outpatient MS clinics, databases of previous research participants, and via media advertising in the community. Prospective participants underwent an initial telephone screen for demographic and clinical inclusion/exclusion criteria, followed by an in-person screen. All participants (a) had a clinically-definite **progressive** MS diagnosis; (b) were between 25-65 years of age; (c) were ambulatory with or without assistance; (d) were relapse-free without acute steroid use for 90 days; (e) had no history of neurological disorders besides MS; (f) did not have severe psychiatric illness; (g) did not use drugs that could affect cognition (excluding cannabis); (h) demonstrated low risk for contraindications for **physical activity**; and (i) were insufficiently active based on a Health Contribution Score of the Godin Leisure-Time Exercise Questionnaire <23 units.[15] To pass the in-person screen, participants (a) demonstrated corrected visual acuity better than 20/80; (b) were not severely depressed based on Beck Depression Inventory-II scores <29;[16] (c) demonstrated intact language comprehension based on Token Test scores <28;[17] and (d) demonstrated impaired CPS based on Symbol Digit Modalities Test (SDMT) scores ≥1.282 SD-units below the age-, sex-, and education- adjusted normative score (i.e., ≤10th percentile). As the CogEx study is an international, multi-site trial, the normative SDMT scores that were used were specific for each country wherein data were collected (i.e., Belgium, Canada, Denmark, Italy, United Kingdom, United States).[18-22]

Outcomes

Cardiorespiratory Fitness. Cardiorespiratory fitness was measured as peak oxygen consumption (VO_{2peak}; ml/kg/min) and peak work rate (WR_{peak}; W) using an incremental exercise test on a recumbent stepper (Nustep T5XR, Nustep Inc, Ann Arbor, MI) and an open-circuit spirometry system for analyzing expired gases. We included WR_{peak}, as this might represent an integrative fitness measure in persons with MS.[23] Participants were appropriately positioned in the stepper, fit with a mouthpiece and/or mask for collecting expired gases, and were read scripted, standardized procedures for the **incremental exercise test** and reporting of rating of perceived exertion (RPE). After an initial 1-minute rest period on the stepper, participants performed a 1-minute warm-up at 15 W, stepping at a cadence of 60 steps/minute. The initial WR for the **incremental exercise test** was 15 W, and the WR continuously increased at a rate of 5-10 W/minute; participants stepped at prescribed cadence rates with metronomic assistance to correspond with increasing WR.[24] Participants stepped until reaching volitional fatigue or when cadence fell ≥15 **steps/minute** below the prescribed value for 30 seconds. During the IET, the open-circuit spirometry system continuously measured VO_2, respiratory exchange ratio (RER), and heart rate (HR) using a HR monitor or electrocardiogram; those outcomes were expressed as 20-second averages. WR, RPE, and **steps/minute** were recorded each minute during the test. VO_{2peak} was based on highest recorded 20-second VO_2 value when two of four criteria were satisfied: (1) VO_2 plateau with increasing WR; (2) RER ≥1.10; (3) peak HR within 10 beats per minute of age-predicted maximum (i.e., 220-age); or (4) peak RPE ≥17. WR_{peak} was based on the recorded WR at test termination.

Free-Living MVPA. Free-living MVPA was measured using waist-worn ActiGraph model GT3x+ accelerometers (Actigraph, Inc., Pensacola, FL) over a seven-day period. Participants wore the accelerometer on an elastic belt around the waist over the non-dominant hip during the waking hours of a seven-day period, and further recorded wear-time in a log for compliance. The raw accelerometer data were downloaded and processed using the low frequency extension into 60-second epochs using ActiLife (Actigraph Corporation, FL) software. The data were then scored for wear-time and minutes/day of MVPA using MS-specific cut-points.[25] Days consisting of ≥10 hours of wear time (≥600 minutes) were considered valid and cases demonstrating ≥1 valid day were included in the analyses.[26] This was confirmed using the aforementioned compliance log. **Free-living MVPA was expressed in minutes/day and percent of total wear-time (i.e., percent MVPA)**, and the primary accelerometer outcomes **were average minutes/day of MVPA and** percent MVPA across valid days.

Cognitive Performance. Cognitive performance was measured using the Brief International Cognitive Assessment for MS (BICAMS) neuropsychological battery. The BICAMS includes the SDMT as a test of CPS, the California Verbal Learning Test-II (CVLT-II) as a test of verbal **learning and memory**, and the Brief Visuospatial Memory Test-Revised (BVMT-R) as a test of visuospatial **learning and memory**.[22] BICAMS scores have been validated in Danish,[20] Dutch,[18] Italian,[21] and English[22] (i.e., the languages spoken at the CogEx study sites). The SDMT, CVLT-II, and BVMT-R were administered and scored according to standardized procedures.[22] Raw SDMT, CVLT-II, and BVMT-R scores, respectively, were converted to country-specific *z*-scores that adjusted for age-, sex-, and education;[18-22] those *z*-scores represented the primary cognitive outcomes.

Ambulatory Disability Status. Ambulatory disability status was measured using the Expanded Disability Status Scale (EDSS).[27] Along with confirming a clinically-definite **progressive** MS diagnosis, the participant's neurologist provided the most recent EDSS score at the time of the telephone screen. As this was not tightly standardized across sites, we further administered the six-minute walk (6MW) test[28] as a measure of walking endurance for better characterizing ambulatory disability status. The 6MW was administered using standardized procedures for persons with MS,[28] and the primary outcome was total distance walked (m) in the six-minute period.

Procedures

The study was approved by each site's research ethics board or institutional review board, and all participants provided written informed consent. After satisfying the in-person screen, participants underwent the BICAMS neuropsychological battery, 6MW, and completed questionnaires assessing demographic and clinical characteristics; participants subsequently underwent the **incremental exercise test**. We note that there was at least 15-minutes of rest in between administration of the 6MW and **incremental exercise test**, and that the order of outcome assessments was standardized across sites. Following **incremental exercise test** administration, participants were provided with the accelerometer, elastic waist band, log book, along with instructions for wearing the device for seven days. Upon completion of the seven-day period, participants returned the accelerometer materials to the investigators.

Data Analyses

Across the 11 CogEx study sites, data were entered using REDCap®. The data were analyzed by the study biostatistician (AS) using SAS v9.4 software (SAS Inc., Cary, NC), and are reported in text and tables as mean (SD) unless otherwise noted. The primary analyses involved bivariate Pearson product-moment correlations (r) among measures of cardiorespiratory fitness (i.e., VO_{2peak}, WR_{peak}), free-living MVPA (i.e., **minutes/day of MVPA**, percent MVPA), and cognitive performance (i.e., SDMT z-score, CVLT-II z-score, BVMT-R z-score), respectively. We performed additional bivariate Pearson correlations among the cardiorespiratory fitness, free-living MVPA, and 6MW data to examine possible specificity/generality, given well-established correlations among fitness, **physical activity**, and walking endurance in persons with MS across the disability spectrum.[29] For the bivariate correlations, we applied a Benjamini-Hochberg false discovery rate correction for multiple comparisons at a rate of 5%;

this resulted in a final adjusted value of .015 for statistical significance. Values for correlation coefficients of .1, .3, and .5 were interpreted as small, moderate, and large, respectively.[30]

Results

Participant Characteristics

240 North American and European persons with **progressive** MS satisfied inclusion/exclusion criteria and provided baseline (trial) data on the outcomes; the baseline data were analyzed as of 14 June 2021. Demographic and clinical characteristics of the full sample are reported in Table 1. Overall, the sample was predominantly female (61%), married (60%), well-educated (45% College educated), but unemployed (66%). Approximately 73% of participants presented with a secondary **progressive** MS clinical course, and demonstrated relatively severe ambulatory disability based on a median EDSS score of 6.0 and frequent assistive device use (65%). On average, the sample demonstrated low cardiorespiratory fitness and engaged in **low levels of free-living MVPA**, consistent with other samples of persons with substantial MS disability.[31,32] **Regarding physiological criteria for determining maximal effort during the incremental exercise test, 66% of participants demonstrated RER values of 1.10 or greater, and 98% of participants had a HR_{peak} within 10 beats/min of age-predicted maximum; such proportions are consistent with those from other cardiopulmonary exercise test protocols in MS.[31]** The sample demonstrated substantial CPS impairment, as well as impaired verbal **learning and memory** based on mean age-, sex-, and education-adjusted *z*-scores of −2.2 and −1.1 SD-units, respectively, on the SDMT and CVLT-II. By comparison, the sample demonstrated a lesser degree of visuospatial **learning and memory** impairment based on a mean BVMT-R *z*-score of −0.8 SD-units. The pattern of cognitive performance further was comparable with other **progressive** MS samples.[4]

Correlations

Correlations among cardiorespiratory fitness, free-living MVPA, and BICAMS outcomes are presented in Table 2 and depicted in Figures 1-3. When correcting for multiple comparisons, there were no statistically significant correlations between VO_{2peak} or WR_{peak} and SDMT (r=−.01,p=.83; r=−.04,p=.49), CVLT-II (r=.05,p=.41; r=.05,p=.44), or BVMT-R (r=−.14,p=.03; r=−.13,p=.03) z-scores, respectively. There further were **no statistically significant** correlations between **minutes/day of MVPA or** percent MVPA and SDMT (***r*=.06,*p*=.40**; r=.05,p=.49), CVLT-II (***r*=−.05,*p*=.44**; r=−.07,p=.31), and BVMT-R (***r*=.01,*p*=.88**; r=.01,p=.87) z-scores, respectively. The correlations further were **not statistically significant** when adjusting for country. Of note, VO_{2peak} (r=.51), WR_{peak} (r=.66), **minutes/day of MVPA (*r*=.59),** and percent MVPA (r=.60) were significantly and strongly correlated with 6MW performance, whereby higher cardiorespiratory fitness and levels of MVPA were associated with better walking endurance.

Discussion

The current analysis of baseline data from the CogEx trial examined cardiorespiratory fitness and free-living MVPA as correlates of cognitive performance in a large, international sample of cognitively-impaired persons with **progressive** MS. The primary novel results indicated that baseline measures of cardiorespiratory fitness and **free-living MVPA**, as cross-sectional components of **aerobic exercise training**, were not associated with cognitive performance in persons with **progressive MS, given the minimal magnitude of correlation coefficients**. The overall lack of observed associations suggests that cardiorespiratory fitness and free-living MVPA **might not represent primary mechanisms-of-action for aerobic exercise training effects on cognition in this population.** As the null results derive from cross-sectional analyses of baseline data, the forthcoming RCT results will better permit inferences of causation for **aerobic exercise training**-related changes in cardiorespiratory fitness and free-living MVPA as possible mechanisms for cognitive improvements. This is critical as there is a truncated range of scores in the baseline cognitive assessment based on screening criteria (i.e., SDMT scores ≤10th percentile), which would reduce the observed correlations.

The observed lack of associations among cardiorespiratory fitness, free-living MVPA, and cognitive performance did not support our primary hypothesis. That hypothesis was based on previous evidence reporting stronger associations among cardiorespiratory fitness, **physical activity**, and cognition in cognitively-impaired compared with non-cognitively impaired persons with predominantly **relapsing-remitting MS** and mild-to-moderate disability.[11,13] The current pattern of results was consistent with other research describing disability status as a moderator of the cardiorespiratory fitness/cognition relationship in MS, whereby the relationship was **not statistically significant** in persons with moderate-to-severe MS disability (EDSS ≥4.0).[10] This suggests that perhaps ambulatory disability status has a stronger influence on the fitness/cognition relationship than cognitive status in this population. Indeed, the current sample involved persons with definitive **progressive** MS and relatively severe ambulatory disability (i.e., 55% with EDSS ≥6.0), and it is possible that the progression of the MS disease process has overwhelmed the capacity for cardiorespiratory fitness and free-living MVPA to influence cognitive performance.[10]

Another possible explanation for the overall pattern of correlations **that were not statistically significant** involves a restricted range of **cardiorespiratory fitness, free-living MVPA, and cognitive performance** scores. Indeed, there is evidence that persons with **progressive** MS and severe ambulatory disability have particularly poor cardiorespiratory fitness, engage in less free-living MVPA, and demonstrate impaired cognition relative to persons with **relapsing-remitting MS** and mild-to-moderate ambulatory disability.[4,24,32] As expected, the current sample presented with such characteristics, as the CogEx trial aims to evaluate the comparative and combined effects of cognitive rehabilitation and **aerobic exercise training** on cognition in CPS-impaired persons with **progressive** MS. Although screening for **progressive** MS, physical inactivity, and low SDMT scores is advantageous for the design of the CogEx

RCT[7,14] (i.e., pre-screening participants for the problem being studied), this effectively restricted the range of scores on the baseline outcomes, increasing the likelihood of smaller, cross-sectional correlations.[33] By extension, given previous reports of **statistically** significant correlations among cardiorespiratory fitness, **physical activity**, and cognition in primarily **relapsing-remitting** MS samples,[10-13] perhaps larger baseline correlations may have been observed if physical inactivity and CPS impairment were not inclusion criteria.

The inclusion of cardiorespiratory fitness and MVPA outcomes as manipulation checks in the forthcoming RCT analyses is critical for documenting the success of the CogEx trial (and for aerobic exercise training interventions in general). As the definition of aerobic exercise training involves health-enhancing physical activity for improving or maintaining aerobic fitness,[5] documenting changes in physical activity and aerobic fitness over time in a RCT is appropriate for interpreting the extent to which an intervention condition (i.e., independent variable) was manipulated relative to a control condition. That is, the observation of between-group differences in changes in cardiorespiratory fitness and MVPA should confirm the separation between the intervention and control conditions in a RCT of aerobic exercise training. By extension, within the context of the forthcoming RCT results from the CogEx trial, we expect that the conditions involving aerobic exercise training will be associated with improved or maintained cardiorespiratory fitness and MVPA relative to the conditions involving sham (non-aerobic) exercise, regardless of whether or not changes in those outcomes are associated with cognitive improvements (i.e., primary mechanisms-of-action). We further note that the inclusion of those outcomes will represent an important addition to the evidence base on aerobic exercise effects on cardiorespiratory fitness and free-living MVPA in persons with progressive MS.

Although baseline cardiorespiratory fitness and free-living MVPA were not associated with cognitive performance, the current cross-sectional results have important implications for the consideration of **aerobic exercise training** as an approach for managing **progressive** MS-related cognitive impairment. The overall pattern of null correlations suggests that perhaps cardiorespiratory fitness and free-living MVPA might not represent primary mechanisms-of-action for **aerobic exercise training** effects on cognition in persons with **progressive** MS, and other mechanisms might explain potential **aerobic exercise training**-related changes in cognitive performance in this population. For example, one conceptual framework and model posits that the processing and integration of multisensory input for the physiological regulation of exercise represents the driving force behind exercise-related adaptations in brain-systems and function (i.e., cognition) in persons with MS.[34] As the CogEx trial involves neuroimaging outcomes,[14] the RCT analyses will allow for testing such a hypothesis, in addition to better clarifying the role of **aerobic exercise training**-related changes in cardiorespiratory fitness and free-living MVPA for explaining possible cognitive improvements in persons with **progressive** MS.

Interestingly, there were **statistically** significant and strong associations among cardiorespiratory fitness, free-living MVPA, and walking endurance. This is consistent with previously reported correlations among those outcomes across the MS disability spectrum.[29] Such a pattern of results seemingly suggests against a generalized effect whereby cardiorespiratory fitness and free-living MVPA would correlate with multiple domains of functioning (i.e., cognitive-motor coupling)[35] in **progressive** MS. By comparison, perhaps the concept of cognitive-motor coupling and associated prediction by **cardiorespiratory fitness and free-living MVPA** better applies in **relapsing-remitting** MS.

Study strengths include the large, international **progressive** MS sample and the rigorous standardization of outcome assessment methodologies across sites. There are several limitations. Of note, this study represents an analysis of baseline data from a parent RCT (i.e., the CogEx trial),[14] and was not designed to specifically address cross-sectional correlations among cardiorespiratory fitness, free-living MVPA, and cognitive performance. As described above, although a strength of the parent RCT involved the pre-screening of physically inactive and CPS-impaired persons with **progressive** MS, this may have restricted the ranges of the outcome measure scores, thereby downwardly biasing the correlations in this analysis. Furthermore, the current analyses were cross-sectional and do not allow for inferences of causation; however, the RCT analyses should provide such an opportunity. Finally, MRI data were not available for the present analysis as an additional outcome measure. This would have afforded the opportunity to evaluate neural substrates underlying cardiorespiratory fitness, free-living MVPA, walking endurance, and cognition in the present sample. We note that such outcomes will be available for the primary RCT analyses in a subsample of patients.

Conclusions

Cardiorespiratory fitness and free-living MVPA were not associated with cognitive performance in this large, international sample of CPS-impaired persons with **progressive** MS. Nevertheless, cardiorespiratory fitness and free-living MVPA still represent critical manipulation checks for documenting the success of RCTs evaluating the effects of **aerobic exercise training** on cognition in **progressive** MS (i.e., the CogEx trial). This highlights the importance of examining other exercise-related mechanisms-of-action for improving cognition and brain health in RCTs in this population.

Declaration of Conflicting Interest

The authors declare that there is no conflict of interest for the current manuscript.

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