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The Effect of Aerobic Exercise on Concussion Recovery: A Pilot Clinical Trial

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Abstract

Objective: The purpose of this study was to pilot safety and tolerability of a 1-week aerobic exercise program during the post-acute phase of concussion (14–25 days post-injury) by examining adherence, symptom response, and key functional outcomes (e.g., cognition, mood, sleep, postural stability, and neurocognitive performance) in young adults.

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CONFLICTS OF INTEREST

None.

SUPPLEMENTARY MATERIAL

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Method: A randomized, non-blinded pilot clinical trial was performed to compare the effects of aerobic versus non-aerobic exercise (placebo) in concussion patients. The study enrolled three groups: 1) patients with concussion/mild traumatic brain injury (mTBI) randomized to an aerobic exercise intervention performed daily for 1-week, 2) patients with concussion/mTBI randomized to a non-aerobic (stretching and calisthenics) exercise program performed daily for 1-week, and 3) non-injured, no intervention reference group.

Results: Mixed-model analysis of variance results indicated a significant decrease in symptom severity scores from pre- to post-intervention (mean difference = −7.44, 95% *CI* [−12.37, −2.20]) for both concussion groups. However, the pre- to post-change was not different between groups. Secondary outcomes all showed improvements by post-intervention, but no differences in trajectory between the groups. By three months post-injury, all outcomes in the concussion groups were within ranges of the non-injured reference group.

Conclusions: Results from this study indicate that the feasibility and tolerability of administering aerobic exercise via stationary cycling in the post-acute time frame following post-concussion (14–25 days) period are tentatively favorable. Aerobic exercise does not appear to negatively impact recovery trajectories of neurobehavioral outcomes; however, tolerability may be poorer for patients with high symptom burden.

Keywords

Neuropsychology; Return to Sport; Brain Injuries; Sports; Feasibility Studies; Public Health

INTRODUCTION

Concussion or mild traumatic brain injury (mTBI) is a major source of worldwide disability and accounts for substantial psychological, healthcare, and financial burden to patients and families (Borg et al., 2004; Hilz et al., 2011; Rockhill et al., 2010; Voss et al., 2015). Pathophysiological recovery from concussion occurs with the self-limited resolution of parallel and dynamic processes including normalization of cerebral blood flow, reduction of inflammation, balancing of neurochemical homeostasis, and stabilization of metabolic functioning (Giza & Hovda, 2014; Kamins et al., 2017). However, the resolution of pathophysiology is not closely coupled to the resolution of clinical post-injury signs and symptoms, and a substantial proportion of concussion patients go on to experience persistent post-concussion symptoms (PPCS), lasting for longer than 2–3 months (Bigler, 2007; Kamins et al., 2017; Polinder et al., 2018). Clinicians have few empirically based tools with which to manage or treat concussion, except for some burgeoning promise in physiotherapy and multimodal collaborative care to address specific symptoms.

Exercise is known to have distributed and broadly beneficial effects on neurologic systems, even after brain injury (Devine & Zafonte, 2009; Fogelman & Zafonte, 2012; Vanderbeken & Kerckhofs, 2017; Zafonte et al., 2018). Preclinical and clinical studies have demonstrated that the timing and type of post-injury physical activity can affect concussion outcomes and alter recovery trajectories (Asken et al., 2016, 2018; Charek et al., 2019; Grace S. Griesbach, 2011; Thomas et al., 2015; Yoon & Kim, 2018). Preclinical animal models show that voluntary aerobic exercise initiated within 7–14 days after mTBI best enhances the

production of endogenous concentrations of brain-derived neurotrophic factor (BDNF), a growth factor that promotes neurorestoration (Griesbach, Hovda, Molteni, Wu, & Gomez-Pinilla, 2004; Griesbach, Hovda, & Gomez-Pinilla, 2009). However, exercise initiated too soon, performed too intensely, or implemented under forced conditions can reverse these beneficial effects in animals, perhaps due to additive strain on neurometabolism in an already compromised system (Griesbach, Tio, Vincelli, McArthur, & Taylor, 2012; Kreber & Griesbach, 2016; Yoon & Kim, 2018).

Results from clinical studies support these preclinical findings. In the acute post-injury time frame, a period of 24–48 hours of rest is recommended for most concussion patients (McCrory et al., 2017; Silverberg & Iverson, 2013), and there appear to be recovery costs for athletes who are not immediately removed from play (Asken et al., 2016; Charek et al., 2019). Strict rest extended for longer than 24–48 hours may stall recovery by exacerbating emotional symptoms (Thomas, Apps, Hoffmann, McCrea, & Hammeke, 2015). Introducing exercise within the first 1–2 weeks post-injury can also reduce the likelihood of developing persistent symptoms (Grool et al., 2016; Howell et al., 2020; Lawrence et al., 2018; Leddy et al., 2019). A retrospective study of college student athletes demonstrated better neurocognitive performance and symptom reporting for individuals who were moderately active after injury compared to those who were minimally active. In comparison, participation in high-intensity physical activity after concussion was associated with poorer neurocognitive performance (Majerske et al., 2008). In the chronic time frame (greater than 2 months post-injury), exercise has been called “medicine for concussion” and seems to be a highly effective tool for treating PPCS (Leddy et al., 2018).

Taken together, preclinical and clinical findings underscore the need for empirical evidence to support the safety and tolerability of post-concussion exercise that is initiated in the subacute time frame in order to ensure optimal recovery and to avoid exacerbating symptoms and/or pathophysiology. Leddy et al. (2019) examined subsymptom threshold aerobic exercise in youths initiated within 10 days of a sports-related concussion. They found that it contributed to quicker recovery and reduced incidence of delayed recovery compared to a “placebo-like” (stretching) group. Besides Leddy et al., few studies have examined the benefits or risks of exercise initiated in the post-acute period (2 to 3 weeks) after concussion, when the capacity for neurorestoration might be at its greatest (Giza & Hovda, 2014). Even less is known about the tolerability of more vigorous (above symptom threshold) aerobic exercise in this time period and its effect on outcomes other than self-reported symptoms. More simply put, does exercising while potentially still symptomatic after concussion cause problems for recovery?

The purpose of this study was to pilot the safety and tolerability of implementing a brief, 1-week aerobic exercise program during the post-acute time frame of concussion recovery (14–25 days post-injury) by examining adherence, symptom response, and key functional outcomes (e.g., cognition, mood, sleep, and postural stability). The longer-term impact of the aerobic exercise intervention was also assessed at 3 months post-injury. A demographically matched, non-injured participant group underwent pre-intervention and post-intervention assessment at corresponding time frames as well as a single aerobic exercise session to provide reference values for within-session symptom response.

METHOD

Design

A randomized, non-blinded pilot clinical trial was performed to compare the effects of aerobic versus non-aerobic exercise placebo in concussion patients within 14–25 days post-injury. The study enrolled three groups: 1) patients with concussion/mTBI randomized to a daily, 1-week aerobic exercise intervention, 2) patients with concussion/mTBI randomized to a daily, 1-week non-aerobic exercise program, and 3) non-injured, no intervention reference group. See Figure 1 for study design. Block randomization was used to equally allocate concussion participants to the aerobic vs non-aerobic groups. The random allocation sequence was created by a random number generator for blocks of 4 that were also stratified by sex. Approval was secured from the University of Florida Institutional Review Board (IRB-01), informed consent was obtained from all participants, and the trial was registered with ClinicalTrials.gov (NCT02276079). Research was completed in accordance with ethical standards set forth in the Helsinki Declaration.

Participants

Clinical pathways were utilized to identify individuals who presented to either the community Neurotrauma Emergency Department or the Sports Concussion Center at the University of Florida for concussion care between February 2014 and December 2016. Study inclusion criteria for concussion participants were as follows: between the ages of 18 and 40, diagnosed with concussion by a physician according to criteria for mTBI/concussion set forth by the American Congress of Rehabilitation Medicine (Kay et al., 1993), and availability to begin an exercise protocol within 14–25 days post-injury.

After being identified for the study by the research staff, prospective participants underwent a telephone screening procedure to ensure eligibility. Patients were medically cleared to participate by their attending or primary care physician prior to initiating exercise. Exclusionary criteria included abnormal structural findings on at least one post-injury CT scan, comorbid orthopedic injury inhibiting movement, prior history of serious psychiatric disturbance with hospitalization, current or prior history of alcohol or substance use disorder, diabetes diagnosis, previous history of moderate or severe head injury, current or past diagnosis of neurological disorder unrelated to TBI, and non-English speakers. Non-injured participants were recruited from the university and local community and were demographically matched by age and sex to the concussion participants in the aerobic group. Exclusionary criteria were the same as the concussion group. Participants in the concussion group were instructed to avoid engaging in outside physical activity such as going to the gym or sports practices during the seven-day intervention period. All participants were compensated for their participation at a rate of $12/hour.

For the purposes of randomization, 87 individuals were assessed for eligibility. Only four failed to meet eligibility criteria, and of the 83 eligible participants, 55 either declined to participate due to stated scheduling conflicts or failure to respond to scheduling requests. There were 28 who were randomized to the exercise groups and completed a baseline assessment. However, two participants in the aerobic exercise group did not receive

their allocated intervention. One reported a scheduling conflict and the other failed to respond to follow-up contacts for scheduling and was withdrawn. A total of 26 concussion participants received an intervention. For the non-injured reference group, 21 were assessed for eligibility, 11 declined to participate, and 10 participants completed the study protocol (i.e., pre-assessment, 1-day of aerobic exercise, and post-assessment procedures) (See Figure 2).

Interventions

The aerobic exercise program consisted of 7 consecutive, daily in-person exercise sessions, administered by research staff with a single rest day taken after 3 to 6 days of the exercise intervention were completed. Participants rode a Lode Corival (Groningen, The Netherlands) stationary exercise bicycle at moderate intensity for two consecutive 20-minute periods with a 5-minute break in between. Brief warm-up and cool-down periods were included (5-minutes each). Moderate intensity was defined as maintaining 65–75% of estimated maximum heart rate during the exercise period, calculated using the Tanaka, Monahan, and Seals (2001) equation (HRmax = 208 – 0.7 × age). Heart rate was monitored continuously by the research staff using a finger pulse oximeter to ensure a moderate intensity was maintained. Feedback was provided as needed to help participants stay within the target heart rate range. This exercise program was chosen because moderate aerobic exercise for this duration has been shown to consistently upregulate BDNF in healthy humans and promote plasticity in the hippocampus (Coelho et al., 2013; Ferreira et al., 2011).

A non-aerobic stretching and callisthenic movements program was used as an “exercise placebo.” Previous studies have found that this approach best ensures “clinically meaningful treatment” for aerobic exercise by accounting for participant expectation and social contact variables (Dunn et al., 2005; Leddy et al., 2019). The protocol is available as supplemental material. Participants engaged in two consecutive 20-minute periods of non-aerobic exercise with a 5-minute break in between led by trained research staff. To ensure that participants remained within the non-aerobic heart rate range (50% or less of maximum heart rate), heart rate was monitored continuously using a pulse oximeter. Exercise characteristics were adjusted as needed to lower heart rate (i.e., participants were asked to slow their movements or complete fewer sets). Participants in this group exercised daily for a period of 7 days with a single rest day, mirroring the aerobic group.

Assessment

At pre-intervention, informed consent was first obtained followed by the collection of demographic and medical history information. History of physical activity was also assessed at pre-intervention using a modified version of the physical activity questionnaire from the Framingham Heart Study (Albanes et al., 1990; Kannel & Sorlie, 1979), which requires participants to provide estimates of hours spent engaged in different levels of physical activity (i.e., sedentary, at work, and during extracurricular activities). The YMCA’s three-minute step-test was used to measure aerobic fitness at pre-intervention (Golding, 2000). This test is used to provide an approximate estimate of cardiovascular fitness by measuring how quickly heart rate returns to baseline after a brief period of exercise. Participants stepped up and down at a rate of 24 cycles (up-up-down-down) per minute (metronome

setting of 96) for 3 minutes on a 12-inch step or bench. Immediately after 3 minutes of stepping, the 60-second pulse rate was measured within 5 seconds.

Outcomes

The impact of exercise was measured through several outcomes spanning cognitive, emotional, and physiological domains designed to produce a robust picture of biopsychosocial functioning post-concussion. The significance of each of these outcomes in post-injury recovery has been well established in the literature (Iverson et al., 2017). The primary outcome was change in self-reported symptoms from pre- to post-intervention. A web-based electronic data capture system (REDCap) was used to collect all data with the exception of neurocognitive outcomes, which were administered via paper and pencil testing methods (Harris et al., 2009). Prior to intervention, neurocognitive, and mood assessments were collected and then repeated at intervention conclusion. Mood assessments were conducted again at the 3-month follow-up.

Symptom report—Symptom severity scores from the post-concussion symptom checklist on the Sport Concussion Assessment Tool (SCAT3) was used as the primary outcome in this study. This list contains 22 symptoms associated with concussion (e.g. headache, nausea/dizziness, neck pain, etc. (McCrory et al., 2013). The symptom checklist was used to assess pre- to post-intervention symptom change and to monitor symptom exacerbation and adverse events during the study. For this checklist, participants were asked to rate the severity of symptoms encompassing somatic, mood, and physical experience on a Likert scale of 0 (none) to 6 (severe) with a maximum of 132 points available. This checklist was completed at pre-intervention, daily (both before- and immediately following exercise) during the intervention, and at 3-month follow-up. At pre-intervention, participants were also asked to retrospectively evaluate the symptoms they experienced within the first 24 hours after their concussion. Symptom score (the number of symptoms rated as higher than 0) was also examined on the first day of exercise.

Sleep—The medical outcome scale (MOS), a 12-item, self-reported measure of sleep quality, was used to evaluate participants' subjective sleep experience as it demonstrates good reliability and responsiveness to change in clinical trials (Allen et al., 2009; Hays et al., 2005; Katz & McHorney, 2002). The Sleep Problems Index II from the MOS was chosen as the outcome variable because it provides a summary score from 9 items tapping into the following constructs: time to fall asleep, sleep restlessness, sufficient sleep, awakening with shortness of breath or headache, feeling drowsy, trouble falling asleep, awakening during sleep, trouble staying awake, and amount of sleep needed. Higher values indicate greater sleep difficulties.

Mood—The Beck Depression Inventory (BDI-II) (Beck et al., 1996) and State Trait Anxiety Inventory (STAI) (Spielberger et al., 1970) are frequently used in both clinical and research settings for assessing depression and anxiety, and the BDI-II is responsive to exercise following TBI (Wise et al., 2012). The STAI includes a form for situational (i.e., State, how participants feel at the time of testing) and general (i.e., Trait, how participants generally feel) levels of anxiety symptoms. Instructions for the BDI-II were

modified to assess depressive symptoms for the previous week only. Mood questionnaires were administered at pre-intervention, post-intervention, and 3-month post-injury follow up.

Postural stability—The Balance Error Scoring System (BESS) is sensitive to deficits in balance following mild head injury (Riemann & Guskiewicz, 2000). Participants were asked to close their eyes and remain stable for 20 seconds in three different postural stances: double leg, single leg, and tandem stance (heel to toe). The number of times they lost their balance in each stance was counted as an error (range, 0 to 10 for each stance), and a total error score was computed for all errors. The modified version of the BESS (mBESS) was used, which utilizes the hard floor surface only (McCrory et al., 2009). Research staff underwent 2 hours of mBESS training procedures. Intraclass correlation (ICC) for double, single, and tandem stance measurements among raters was examined based on a mean-rating (k = 3), absolute-agreement, and 2-way random-effects model (Koo & Li, 2016). Interrater reliability ranged from moderate (single leg stance; ICC = .72, 95% CI [.26, .99]) to good (double stance; ICC = .95, 95% CI [.75, .99]), consistent with previous research (Finnoff et al., 2009).

Neurocognition—To measure performance on neurocognitive domains most vulnerable to decline following concussion (Moser et al., 2007), a 2-hour battery of standardized neuropsychological tests was administered at pre- and post-intervention by trained research staff. For tests with alternate forms (i.e., WMS-III Logical Memory, CVLT-II, COWA), administration order was determined by using a random number generator. The neurocognitive battery was designed to provide an objective assessment of performance in attention, processing speed, memory, and executive functioning. All normed scores from individual measures were converted to z-scores, then index scores were computed as the average z-score across component measures (see Table 1). Practice effects were expected and accounted for by using linear mixed-effects modeling to examine the visit by group interaction (Beglinger et al., 2005; Calamia et al., 2012).

Safety monitoring and adverse events

Participants were monitored for adverse events throughout the exercise intervention. During the intervention period, a moderate adverse event was defined by exacerbation of symptom severity scores above individual baseline scores by one standard deviation or more according to existing normative data on the post-concussion symptom checklist (Lovell et al., 2006). Moderate adverse events were grounds for participant discontinuation if the criterion was met for two days in a row during the intervention and deemed to be related to the intervention by a medical safety monitor (board-certified neurologist). The medical safety monitor received cumulative symptom reports for each concussion participant by intervention day 4 or sooner if any significant symptom exacerbation occurred.

Study procedures took place at a clinical research facility where nurses were present in the event of an emergency. A data and safety monitoring plan was in place during data collection. Three independent clinical faculty members with scientific training served as evaluators of all study and data integrity procedures. Reports were submitted twice to these senior scientists for evaluation and corrective feedback. Results from their reviews

indicated no concerns for trial conduct or participant safety. Data quality was ensured through secondary review and verification of all initial data entry by research staff.

Analysis

Sample size was based on recommendations from the literature to include at least 12 participants per intervention arm for a pilot study (Julious, 2005; van Belle, 2011). Summary data were presented using descriptive statistics, and inferential t-tests and chi-square analyses were used to compare the groups at pre-intervention baseline.

Primary and secondary analyses were carried out via linear mixed-effects analysis of variance for repeated measures using a heterogeneous first-order autoregressive covariance structure (after examining covariance structures for optimal model fit) and fit using Maximum Likelihood (ML) estimation. This approach was chosen because the covariance structure from pre- to post-assessment can be specified to better account for the nonindependence in observations and improve accuracy (Boisgontier & Cheval, 2016). The models' random effect was individual subject and fixed effects included within-subjects time (visit), between-subjects group (aerobic, non-aerobic), and visit by group interaction. Additional models included the non-injured group as a fixed factor. There were no missing data for the primary outcome analyses. Post-exercise symptom ratings on the first day of intervention were unavailable for two participants in the non-aerobic group. Two participants suffered a second concussion in the period between post-intervention and follow-up, so their three-month follow-up data were excluded.

Post hoc analyses corrected for multiple comparisons were conducted using Sidak corrections. Pearson's chi-square analysis was used to examine the proportion of symptom response by group on the first day of exercise. All statistical analyses were completed using SPSS statistical software (IBM Corp., 2016) and GraphPad Prism version 8.00 for MacOSX, GraphPad Software, La Jolla California USA, www.graphpad.com.

RESULTS

Participants

At baseline, participant demographic characteristics were well matched across groups. See Table 2 for demographic and injury characteristics for the participant groups. No significant differences across groups were found regarding sex, age, years of education, or previous history of mood disorder. The age range of the participants was 18 to 32 years. Most participants were highly educated and had completed at least 2 years of college study. Regarding baseline levels of aerobic fitness (3-minute step test), groups did not statistically differ, and performance was in the average range or better for all groups based on age and sex norms (Golding, 2000). Members of the concussion groups almost all reported a positive history of prior (diagnosed) concussion and no one in the control group reported any medically confirmed prior concussive injury. One participant in the aerobic group experienced an adverse event and did not complete the intervention.

Pre-post analyses

Results of the mixed-model analysis with the primary outcome, symptom severity, as the dependent variable indicated that there was a main effect of visit, $F(1, 25) = 8.69$, $p = .007$, 95% CI [−2.37, −2.20] which showed a significant mean reduction in symptom severity of 7.28 points from pre- to post-intervention for both concussion groups. However, the visit by group interaction was not significant ($p = 0.78$), indicating that the pre- to post-change was not statistically different between groups. Despite high between-subjects variability, all concussion participants demonstrated reductions in symptom severity from pre- to post-intervention. Parameter estimates are provided in Table 3 where the fixed effect of group is composed of the aerobic compared to non-aerobic participants. The outcome means at pre- to post-intervention visits are provided in Table 4.

At pre-intervention, the symptom severity ratings did not statistically differ between groups; however, Bartlett's test of homogeneity of variances demonstrated significant differences in variation ($p < .001$) between the concussion groups and non-injured participants in their ratings. By the three-month follow-up, symptom severity ratings for both concussion groups were commensurate with those reported by non-injured controls at pre-intervention (aerobic: $M = 0.30$, $SD = 0.95$; non-aerobic: $M = 0.92$, $SD = 1.61$) (See Figure 3). All concussion participants' symptom severity ratings were within 1 SD or below the pre-intervention control mean besides one ($z = 2.12$, $p = .02$), suggesting full symptom resolution and recovery for almost all concussed participants by three months. Taken together, exercise type did not alter the trajectory of post-concussion symptom recovery in this sample. Sex was added in a separate model given the well-documented relationship of higher post-concussion symptom burden in females (Brown et al., 2015; Covassin et al., 2012), but no significant main or interaction effects were observed.

For secondary outcomes, a significant main effect of visit was demonstrated for STAI trait anxiety, $F(1, 25) = 27.3$, $p < .001$, 95% CI [−4.52, −1.96] suggesting continued reduction in general anxiety score from pre- to postintervention for both concussion groups, but there were no significant exercise group by visit interactions for any of the secondary outcome variables. Even though there was not a main effect of visit for scores on the STAI State ($p = .13$), BDI-II ($p = .21$), MOS ($p = .09$), or mBESS ($p = .14$), there was a general trend across outcomes showing broad improvement in scores from pre- to post-intervention (see Table 3). Neurocognitive index scores all significantly improved over time as predicted. When the concussion groups were examined alongside the non-injured reference group in the mixed model, none of the change trajectories for secondary outcomes were significantly different from pre- to post-intervention (i.e., no group by visit interactions). By three-month follow-up, there were no significant differences between the two concussion groups on any of the neurobehavioral outcomes.

Single session exercise

The intrasession response to exercise was evaluated on the first day of intervention where all participant groups participated in an exercise session (non-injured participants completed the same aerobic protocol as the aerobic exercise group). Symptom response to exercise was similar across all groups using Pearson Chi-Square analyses (see Table 5).

Intervention days

The pre-exercise symptom ratings were analyzed across the seven days of intervention (see Figure 4). Visual inspection shows a downward trend of symptoms over the intervention days, but there were no significant differences in either the fixed effect of visit ($p = .65$) or the group by day interaction ($p = .97$) in the mixed-effects model comparing exercise type, again suggesting similar symptom ratings across the seven-day intervention period.

Adverse events

One participant in the aerobic exercise group was withdrawn per study protocol after experiencing a moderate adverse event. On the first intervention day, the participant experienced decreased symptoms after exercise, but on the second intervention day, the participant reported acutely elevated symptoms (e.g., dizziness, tunnel vision, and feeling faint) during exercise. Research staff immediately discontinued exercise and the participant received a medical examination that was unremarkable aside from nystagmus in both eyes. A psychotherapist (Master's level psychology staff member), who was part of the research staff, administered deep breathing and relaxation techniques that resulted in participant stabilization and the resolution of all symptoms except for dizziness and headache. A neurological consultation was conducted by the research study medical safety monitor. The examination concluded no neurological deficits but noted evidence of soft tissue injury from whiplash. Compared to all other concussion participants in the study, this individual had the highest 24-hour retrospective symptom recall for any participant ($z = 2.33$) along with other known premorbid medical and psychiatric risk factors for PPCS.

DISCUSSION

Results from this pilot study indicate that the feasibility and tolerability of administering aerobic exercise via stationary cycling in the post-acute time frame following concussion (14–25 days after injury) are tentatively favorable. The cumulative effect of 7 days of consecutive exercise resulted in similar changes in symptom report across aerobic and non-aerobic exercise groups. For both exercise groups, symptom severity decreased over time, likely reflecting continued recovery. For secondary outcomes, trait (not state) anxiety significantly improved over the intervention period for both groups. Positive changes were also observed for depression, state anxiety, sleep, and postural stability, although these changes were not statistically significant. Compared to normative values for concussion symptom reporting over time (Chin et al., 2016) and the reference values provided by the non-injured group at pre-intervention, the concussion participants' 3-month symptom ratings seem to indicate full recovery, regardless of exercise group assignment.

Adherence to the study protocol was good for both the aerobic and non-aerobic groups. Attrition rates for the exercise groups (7.7% [n = 1] for aerobic and 0% for non-aerobic) were commensurate with or better than typically acceptable rates in clinical trials, which range from 5% to 20% (Sackett et al., 2000). Qualitatively, feedback from participants was broadly positive in that they enjoyed the opportunity for structured exercise after injury. We found that proper stationary bicycle fitting was critical to participant comfort, so we recommend that future exercise protocols using stationary bicycles emphasize optimal seat

to pedal height as well as flexibility in upright seated positioning through modifiable seat-to-handlebar distance.

As anticipated, this study found that exercise can provoke mild increases in nonspecific symptoms (i.e., headache and dizziness) to a similar extent in both non-injured and concussion participants, similar to previous studies. The number and severity of symptoms experienced immediately before and after the first day of exercise were comparable between concussion participants who completed aerobic and non-aerobic exercise. When compared to non-injured participants who completed one session of aerobic exercise, both concussion exercise groups had a similar proportion of individuals who experienced a mild exacerbation in symptom severity. In the concussion group, the most frequently reported exercise-induced symptoms during the exercise intervention were fatigue/low energy (8 participants, 32%) and headache (8 participants, 32%) and the elevations after exercise were less than 2 points on average.

Exercise-induced headaches (also known as primary exertional headache) occur in non-injured individuals, and as high as 20–30% of athletes and non-athletes alike experience some type of exercise-induced headache, most commonly connected to effort or exertion (Halker & Vargas, 2013; Sandoe & Kingston, 2018). However, the injury experience may interact with concussion patients' interpretation of what is "normal" after injury. Several studies have demonstrated a "good old days" bias in concussion patients, which minimizes premorbid symptom experience (Ferguson et al., 1999; Iverson et al., 2010; Mittenberg et al., 1992) and could be particularly relevant to postmorbid expectations for exercise. Given the findings in this study, it may be helpful to explore the effect of pre-exercise instructions that help frame patients' beliefs about post-injury exercise and normative rates of exercise-induced symptoms with the hope that it minimizes expectation bias or overinterpretation of normal exercise experience as pathological.

Although the present study did not detect statistically significant changes in neurobehavioral outcomes, the fact that they were not worsened by moderate-intensity aerobic exercise is an important finding. This result supports emerging literature demonstrating that exercising at a moderate intensity while still symptomatic is not inherently hazardous for concussion patients. Exercise programs generally require several weeks of regular training to exert lasting, beneficial effects on outcomes such as cognition, mood, and sleep (Chennaoui et al., 2015; Kelly et al., 2014), although shorter-term improvements have also been documented (Chan et al., 2019). In the context of brain injury, even brief exercise programs initiated closer to injury may have the ability to positively influence recovery due to a boost from injury-induced neuroplasticity (Grace S. Griesbach, 2011). Leddy et al. (2019) found that sub-symptom threshold exercise initiated within the first 10 days after injury (but not earlier than 48 hours) reduced the chance of delayed recovery compared to a placebo-like stretching group in youth. Besides limitations from sample size, the duration of the exercise in the present study was likely too short to effectively improve neurobehavioral function, and it may have also been started too late to maximally impact recovery. Optimizing exercise program type and timing for neurobehavioral improvement after concussion remains an important thrust for future research efforts.

For one participant, the aerobic exercise session provoked a significant increase in physical and psychiatric symptoms on the second day of the intervention. Neurological examination showed that this participant had findings of whiplash, which can be comorbid with concussion and presents with similar or overlapping symptoms (i.e., dizziness and unsteadiness). Whiplash injuries typically feature strain or sprain to cervical muscles and ligaments, and this injury is thought to impact the vestibular system in different ways than those impairments typically associated with concussion (Elliott et al., 2008; Treleaven et al., 2005). The participant who experienced the adverse event had several other risk factors for PPCS such as clinically elevated post-injury depression, anxiety, and sleep disturbances. Besides whiplash, patients with predominately headache/migraine, vestibular, and/or ocular-motor symptom clusters could also be at higher risk for exercise-provoked symptoms (Langdon et al., 2020). This study favored younger, physically fit participants, which raises questions about the effect of aerobic exercise after concussion in older individuals or those with lower physical conditioning which should be further explored in future studies.

Taken together, caution is warranted in generalizing results across the range of concussion patients. Moreover, the occurrence of this adverse event raises the possibility that a certain subset of concussion patients may have unfavorable reactions to exercise beyond typical, effort-induced headaches and with a different etiology than exacerbated concussion-related pathophysiology. Individual vulnerability to exercise-induced symptom exacerbation may overlap with known risk factors for PPCS. Additionally, the breadth and number of symptoms should be considered in clinical decision making and monitoring for post-concussion exercise programs, particularly if the patient is reporting a high number of symptoms across domains. Patients who remain highly symptomatic, for example, may benefit from reduced exercise intensity (e.g., subsymptom threshold programs; Leddy et al., 2018).

The current study is one of many needed to establish empirically based protocols for exercise in the post-acute time frame after concussion. Exercise timing, intensity, and type should be evaluated in the future to better understand tolerability as this study is limited by a conservative post-injury time frame in which most patients are considered “safe” to return to exercise. The study participants were predominately young, college students and were supervised in a research lab, which ensured compliance but also reduces ecological validity. A more representative participant population should be examined in the future with consideration for diversity in age, education, race, and other socioeconomic variables. There is also risk for participant selection bias in laboratory studies that require high levels of in-person contact like this one. Future efforts should collect basic demographic information on those who decline to participate in order to better address this risk.

Another notable limitation is that this pilot study was not powered to detect main effects or interactions in predefined outcomes. Interactions between sex and exercise assignment are likely to be important given the role of sex differences in symptom experience (Broshek et al., 2005; Covassin et al., 2012). Nonetheless, these results can be used to more appropriately provide power estimates for larger and more comprehensive clinical trials. The fact that this pilot study was not designed to address the efficacy of aerobic exercise for improving recovery after concussion/mTBI deserves emphasis. Future studies that examine

the efficacy of post-concussion exercise for improving neurorecovery should consider much longer-term interventions that last for several weeks at a minimum.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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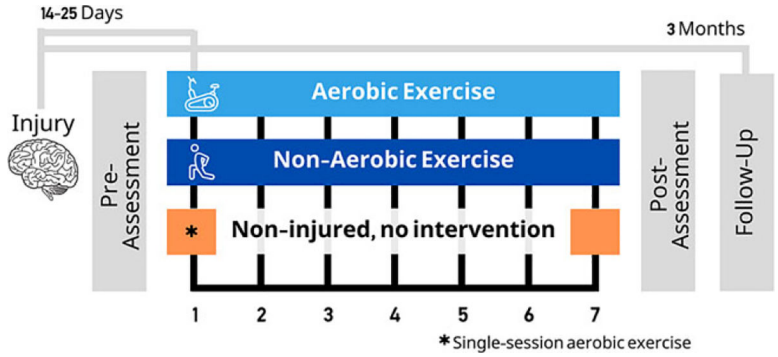

Figure 1.
Study overview.

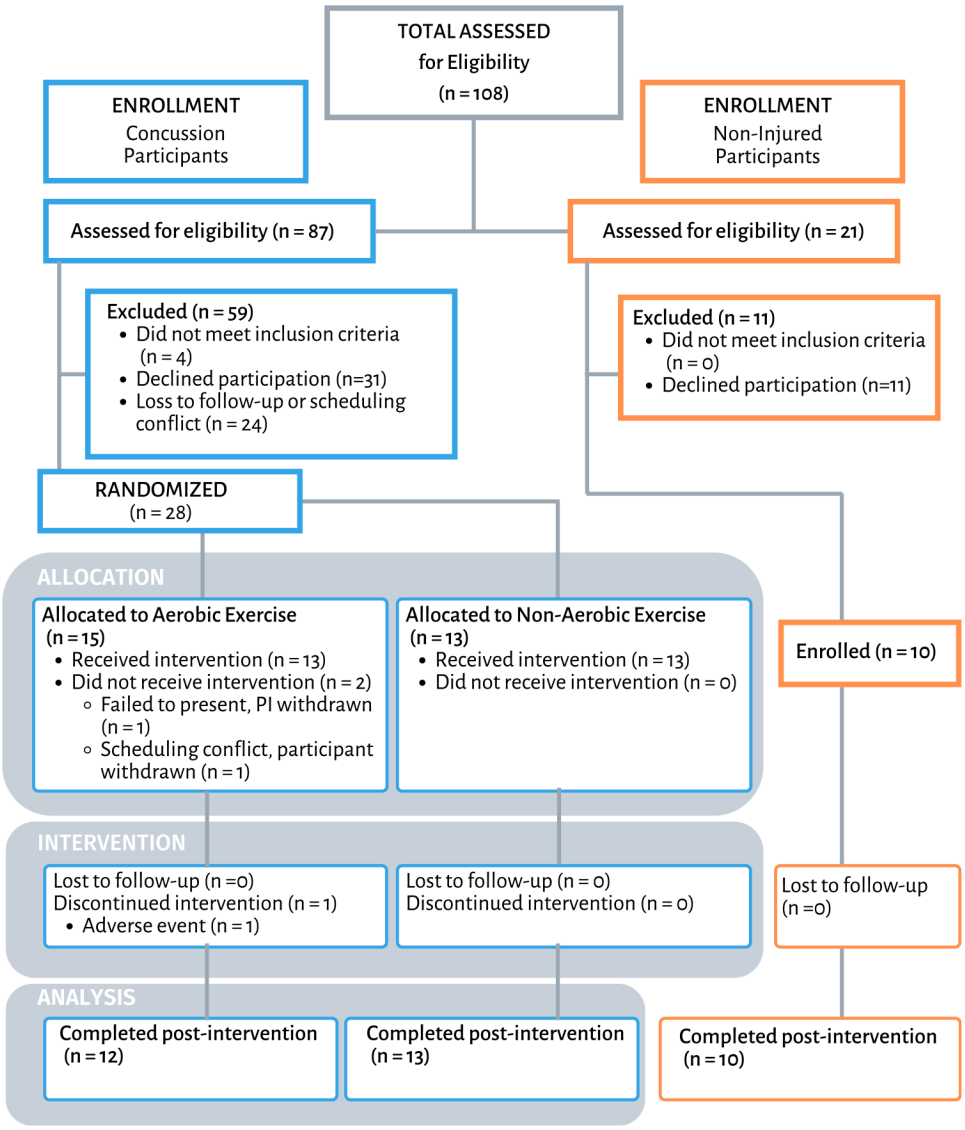

Figure 2.
CONSORT enrollment and allocation flow diagram.

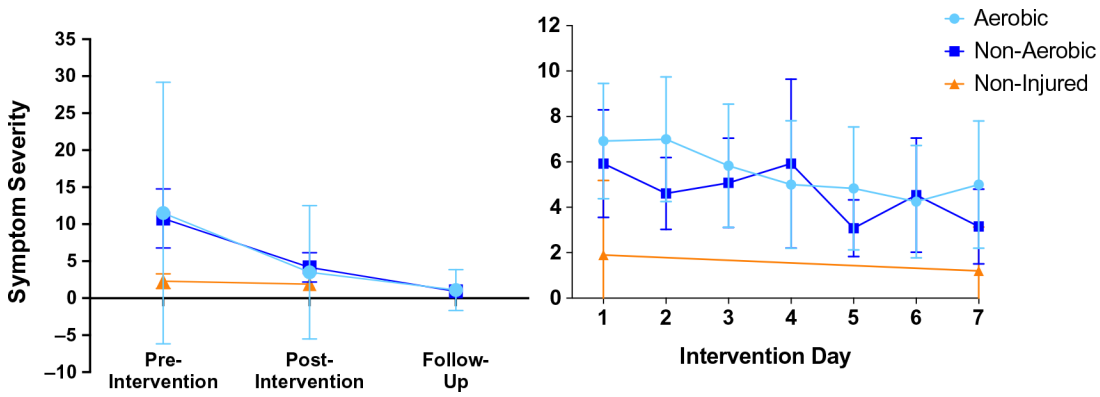

Figure 3.

Symptom severity ratings by group across study visits and the seven-day intervention.

Note. Error bars represent standard error of the mean

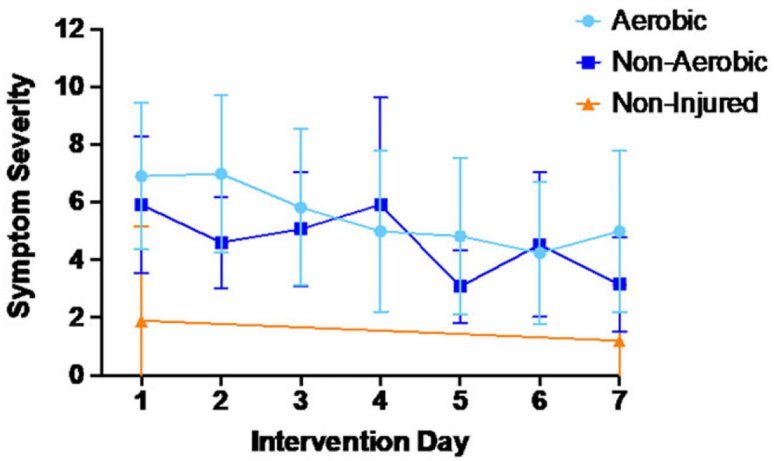

Figure 4.

Pre-exercise symptoms severity ratings across the 7-day intervention period by groups.

Note. Error bars represent standard error of the mean

Table 1.

Components of neuropsychological indices

Index	Test and reference	Description	Outcome
Attention	Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III), Digit Span (We9chsler, 1997a)	Attention span for remembering digit strings.	Total correct score.
	Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977)	Remember and sum digits presented auditorily	Total number of correct responses
	Ruff 2 & 7 (Ruff et al., 1992)	Selective attention test that requires “canceling” all instances of 2 and 7.	Total accuracy score
Processing Speed	DKEFS Trail Making Test, Condition 2, number sequencing (Dean C. Delis et al., 2004)	Speeded number sequencing	Total time to completion
	Ruff 2 & 7 (Ruff et al., 1992)	Selective attention test that requires “canceling” all instances of 2 and 7.	Total speed
	Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III), Digit Symbol (Wechsler, 1997a)	Speeded transcription of symbols paired with digits	Total correct score
Memory	California Verbal Learning Test–2nd Edition (CVLT-II) (Delis, Kramer, Kaplan, & Ober, 2000)	Verbal memory test that assesses learning strategy, immediate and delayed recall, recognition, interference, and errors.	Delayed free recall (total words recalled)
	Wechsler Memory Scale-III, Logical Memory II (Wechsler, 1997b)	Measure of contextual verbal memory	Score for delayed recall of stories
	Wechsler Memory Scale-III, Visual Reproduction II (Wechsler, 1997b)	Measure of figure/nonverbal memory	Score for delayed recall of figures
Executive Functioning	DKEFS Trail Making Test, Condition 4, Letter-number sequencing (Delis et al., 2004)	Speeded switching between letter-number sequencing	Total time to completion
	Wisconsin Card Sorting Test (Heaton, 1981)	Card sorting task according to principle. Measure of mental flexibility and problem solving.	Total errors (perseverative and non-perseverative)
	Controlled Oral Word Association (COWA) (Benton, 1969)	Verbal fluency to alphabet letter (e.g., C,F,L).	Total correct exemplars

Note. Outcomes scores were demographically corrected for age where available.

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Table 2.

Demographic information and injury characteristics by participant group

Demographics	Aerobic exercise (n = 12)	Non-aerobic exercise (n = 13)	a p-value	Effect size	Non-injured (n = 10)	b p-value	Effect size
Sex (n)							
Male	7	6	.54	.12	6	.67	.07
Female	5	7			4		
Age (yr)	22.2 (3.7)	20.5 (2.8)	.23	.52	20.4 (2.0)	.42	.34
Race/Ethnicity (n)							
White/Caucasian	7	10	–	–	6	–	–
Black/African American	2	0	–	–	0	–	–
Hispanic/Latino	2	3	–	–	2	–	–
Asian/Pacific	1	0	–	–	1	–	–
Mixed Race	0	0	–	–	1	–	–
Years of Education	14.9 (2.0)	14.2 (2.2)	.37	.33	14.4 (1.5)	.87	.07
Baseline Aerobic Fitness							
3-minute step test	88.5 (9.7)	98.1 (18.7)	.12	.68	102.6 (30.0)	.38	.40
Average hours of non-sedentary activity (PAS)	6.6 (2.2)	6.7 (2.9)	.98	.04	6.4 (2.1)	.75	.12
Mood Disorder y (n)	1 (11)	2 (11)	.58	.11	2 (8)	.54	.10
Previously Diagnosed Concussion y (n)	12 (0)	12 (1)	.33	.20	0 (10)	<.01	.93
Injury Characteristics							
Sports-related injury (y)	5	4	.57	.11			
Days since injury at intervention day 1	20.1 (3.9)	18.1 (3.3)	.15	.56	–	–	
Positive LOC (y)	4	5	.79	.05	–	–	
24 hr injury symptom score	12.8 (5.1)	14.5 (5.3)	.42	.33	–	–	
24 hr injury symptom severity	37.7 (29.4)	44 (26.2)	.58	.23	–	–	

Note: Values are presented in mean (SD) form unless noted otherwise.

[a] Comparison of aerobic versus non-aerobic groups.

[b] Comparison of concussion versus non-injured groups.

[+]Cramer's *V*, all other effect sizes are Cohen's *d*. LOC, loss of consciousness

Table 3.

Parameter estimates for the mixed-effects model group by time interaction

Outcome	Estimate	SE	*p*-value	CI		Cohen's *d*	
				Lower	Upper		
Symptom Severity							
Intercept	4.21	2.14	0.06	−0.21	8.62	–	
Group	0.76	3.08	0.81	−5.58	7.11	0.00	
Visit	−7.28	2.47	<0.01	−12.37	−2.20	−0.58	
Group × Visit	−1.38	4.94	0.78	−11.55	8.78	−1.00[a]	−0.52[b]
MOS Sleep Problems Index 2							
Intercept	30.23	3.63	<0.01	22.79	37.68	–	
Group	12.29	5.06	0.02	1.87	22.71	−0.85	
Visit	−4.25	2.41	0.09	−9.21	0.70	−0.23	
Group × Visit	−0.13	4.82	0.98	−10.05	9.79	−0.31[a]	−0.43[b]
STAI - State							
Intercept	46.56	2.63	<0.01	41.16	51.96	–	
Group	3.58	3.67	0.34	−3.97	11.14	−0.35	
Visit	−2.60	1.67	0.13	−6.03	0.83	−0.26	
Group × Visit	0.51	3.34	0.88	−6.36	7.38	−0.32[a]	−0.30[b]
STAI - Trait							
Intercept	48.68	2.83	<0.01	42.87	54.50	–	
Group	5.17	3.98	0.21	−3.02	13.36	−0.50	
Visit	−3.24	0.62	<0.01	−4.52	−1.96	−0.66	
Group × Visit	−0.18	1.24	0.89	−2.73	2.38	−1.22[a]	−0.99[b]
BDI-II Raw							
Intercept	5.87	2.34	0.02	1.06	10.69	–	
Group	−3.01	3.34	0.38	−9.90	3.87	0.40	
Visit	−1.88	1.44	0.21	−4.85	1.09	−0.35	
Group × Visit	−2.47	2.85	0.39	−8.33	3.39	−0.55[a]	−0.22[b]

				CI		Cohen's *d*	
Outcome	**Estimate**	**SE**	***p*-value**	**Lower**	**Upper**		
mBESS Total							
Intercept	2.63	0.58	<0.01	1.43	3.83	–	
Group	0.56	0.84	0.51	−1.16	2.28	−0.40	
Visit	−0.52	0.34	0.14	−1.22	0.18	−0.43	
Group × Visit	1.16	0.64	0.08	−0.16	2.48	0.06[a]	−0.61[b]
Neurocognition							
Attention Index Intercept	0.65	0.13	<0.01	0.38	0.92	–	
Group	0.14	0.19	0.48	−0.25	0.52	−0.16	
Visit	0.45	0.07	<0.01	0.32	0.59	1.50	
Group × Visit	−0.13	0.13	0.33	−0.40	0.14	1.24[a]	1.47[b]
Processing Speed Index							
Intercept	1.10	0.16	<0.01	0.77	1.43	–	
Group	−0.09	0.23	0.70	−0.56	0.38	0.19	
Visit	0.47	0.08	<0.01	0.30	0.63	1.41	
Group × Visit	−0.17	0.15	0.27	−0.49	0.15	0.81[a]	1.59[b]
Memory Index							
Intercept	1.05	0.14	<0.01	0.76	1.35	–	
Group	0.33	0.20	0.11	−0.08	0.73	−0.43	
Visit	0.44	0.13	<0.01	0.17	0.71	0.60	
Group × Visit	−0.35	0.25	0.18	−0.89	0.17	0.33[a]	1.23[b]
Executive Functioning Index							
Intercept	0.77	0.10	<0.01	0.57	0.96	–	
Group	0.10	0.13	0.50	−0.18	0.36	−0.25	
Visit	0.50	0.09	<0.01	0.32	0.67	1.11	
Group × Visit	0.20	0.17	0.24	−0.14	0.55	1.23[a]	1.36[b]

Note: Values provided are for parameter estimates of the aerobic group at posttreatment compared to pretreatment and the non-aerobic group. The group effects are composed of the aerobic compared to non-aerobic groups only. SE = standard error; CI = 95% confidence Intervals of the estimate.

[a]Aerobic group

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[b] Non-aerobic group.

Table 4.

Pre- and post-intervention outcomes by participant group

Outcomes	Aerobic (n = 12)		Non-aerobic (n = 13)			Non-injured (n = 10)		
	Pre	Post	Pre	Post	*p*-value	Pre	Post	*p*-value
Symptom Severity	11.50 (17.68)	3.50 (9.02)	10.77 (14.37)	4.15 (7.14)	0.49	2.30 (3.16)	1.90 (2.82)	0.24
MOS Sleep Problems Index 2	22.24 (16.02)	17.92 (10.90)	34.44 (14.52)	30.25 (16.40)	0.74	18.36 (7.92)	20.17 (7.21)	0.29
STAI - State[a]	45.42 (12.70)	43.08 (10.25)	49.31 (8.87)	46.46 (10.10)	0.93	44.1 (5.55)	42.1 (9.00)	0.98
STAI - Trait[a]	46.75 (11.39)	43.42 (10.95)	51.92 (9.32)	48.77 (10.79)	0.89	46.9 (5.38)	42.2 (8.56)	0.8
BDI-II Raw	11.75 (14.17)	8.58 (10.48)	6.85 (4.76)	6.15 (7.09)	0.18	6.5 (5.36)	3.25 (4.74)	0.61
mBESS Total	2.08 (2.35)	1.82 (1.54)	3.62 (2.79)	2.5 (2.54)	0.14	4.3 (4.06)	2.3 (1.89)	0.19
Neurocognition								
Attention Index[b]	0.39 (.68)	0.51 (.59)	0.35 (.49)	0.65 (.38)	0.55	0.45 (.64)	0.67(.58)	0.59
Digit Span Total	18.58 (4.44)	18.42 (4.38)	18.92 (3.25)	21.15 (3.76)	–	19.00 (3.59)	20.10 (3.93)	–
PASAT Total Correct	140.92 (29.17)	162.50 (23.46)	139.31 (28.63)	158.00 (25.85)	–	146.80 (28.13)	173.30 (15.48)	–
Ruff 2 & 7 Accuracy	96.67 (12.04)	105.42 (8.20)	100.15 (12.07)	106.77 (8.36)	–	92.60 (18.48)	102.90 (17.91)	–
Processing Speed Index[b]	1.07 (0.70)	1.16 (0.61)	0.74 (.62)	1.12 (.61)	0.37	0.94 (.64)	1.19 (.53)	0.32
DKEFS Trail Making Test, Number sequencing	19.42 (5.10)	17.41 (5.30)	25.35 (6.28)	18.95 (4.22)	–	27.02 (7.91)	20.60 (6.66)	–
Ruff 2 & 7 Total Speed	109.92 (21.40)	115.67 (21.88)	105.69 (21.34)	117.23 (19.97)	–	105.90 (20.15)	116.90 (20.14)	–
WAIS-III Digit Symbol Coding	90.82 (15.54)	98.75 (13.37)	91.38 (10.16)	98.92 (13.97)	–	92.60 (9.97)	103.60 (9.64)	–
Memory Index[b]	0.68 (.73)	0.66 (.55)	0.65 (.62)	1.11 (.57)	0.21	0.6 (.56)	0.74(.58)	0.46
CVLT-II Delayed Free Recall	11.50 (2.32)	11.50 (2.94)	13.00 (2.24)	13.00 (3.46)	–	12.60 (2.12)	12.70 (2.87)	–
WMS-III Logical Memory II	29.58 (5.18)	30.83 (6.46)	29.85 (5.30)	32.08 (6.08)	–	27.30 (6.38)	29.30 (5.64)	–
WMS-II Visual Reproductions II	82.42 (16.36)	92.83 (9.60)	83.00 (13.15)	98.23 (2.52)	–	83.00 (11.94)	97.80 (2.62)	–
Executive Functioning Index[b]	0.33 (.45)	0.71 (.51)	0.59(.49)	0.73 (.20)	0.15	0.55 (.69)	0.86 (.63)	0.55
DKEFS Trail Making Test, Letter-number sequencing	46.44 (12.04)	38.78 (9.65)	55.35 (13.30)	45.39 (13.86)	–	52.08 (8.57)	43.43 (7.30)	–
Wisconsin Card Sorting Test	31.50 (23.37)	17.82 (18.75)	17.69 (13.39)	8.42 (3.09)	–	25.70 (19.79)	12.90 (14.96)	–
Controlled Oral Word Association	40.92 (9.76)	47.42 (11.57)	40.83 (6.58)	42.31 (5.86)	–	45.91 (12.64)	49.90 (11.83)	–

Note: Values are presented in mean (SD) form unless noted otherwise. *p*-values were derived from the mixed-effect model for study visit by group interaction. The parameter estimates from the analyses associated with the first column of p-values are presented in Table 2.

[a] Data presented as T-scores.

[b] Data presented as z-scores

* n = 10, 2 participants were excluded from this group due to re-injury.

Table 5.

Cross-tabulation of symptom change from pre- to post-exercise on intervention day 1

Outcome	Group	Decrease or no change	Increase	*p*-value	Cramer's *V*
Symptom score	Aerobic	10	3	0.87	0.09
	Non-aerobic exercise	8	2		
	Non-injured	7	3		
Symptom severity	Aerobic exercise	11	2	0.37	0.25
	Non-aerobic exercise	8	2		
	Non-injured	6	4		

Note. p-values presented for Pearson Chi-Square analyses.

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