THE EFFECT OF EXERCISE ON NEURORECOVERY FOLLOWING MILD TRAUMATIC BRAIN INJURY: A PILOT STUDY

By

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To my family and my mentors
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Mild traumatic brain injury (mTBI), also known as concussion, is a costly and common public health “epidemic.” Pre-clinical research has identified aerobic exercise as a promising intervention after mTBI due in part to its enhancement of endogenous neureparative processes and its enhancement of anti-inflammatory pathways, but these findings have not yet been translated to humans. The purpose of this project was to assess the safety, tolerability, and feasibility of a 1-week aerobic exercise program administered in the post-acute period (14-25 days post-injury). A secondary goal was to examine the characteristics of circulating BDNF concentration after mTBI and in response to acute exercise.

This study was a non-blind randomized controlled-trial that enrolled three groups: 1) mTBI patients randomized to a daily, 1-week aerobic exercise intervention (n = 13), 2) mTBI patients randomized to a daily, 1-week non-aerobic exercise program (n = 13), and 3) non-injured, no intervention reference group (n = 12). 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-mTBI.
Adherence to the study protocol was good for both the aerobic and non-aerobic groups. Based on the results from this pilot study, the feasibility of administering aerobic exercise via stationary cycling in the post-acute period is tentatively favorable with some caveats. The aerobic exercise program did not provoke more symptom exacerbation in mTBI patients than would be expected for normal, non-injured population with the exception of one adverse event. There were no meaningful trends in differences between the aerobic and non-aerobic group on functional outcomes after the intervention. Resting BNDF concentration was associated with sleep problems and with symptom severity at pre-intervention. BDNF increase in response to exercise was detected in platelet-poor plasma only. Recommendations for future safety and efficacy studies are provided.
CHAPTER 1
INTRODUCTION

Background

According to the World Health Organization (WHO), rates of traumatic brain injury (TBI) continue to increase over time and are expected to become one of the leading causes of mortality and disability worldwide by 2020 (Cassidy et al., 2004). Of all TBIs, an estimated 75% of reported cases are considered to be mild (mTBI), an umbrella term that includes, but is also used synonymously with, concussion (Wright, Kellermann, McGuire, Chen, & Popovic, 2013). A generally accepted definition of TBI is, “an alteration in brain function, or other evidence of brain pathology, caused by an external force (Menon et al., 2010),” and the qualifier of “mild” is typically dependent on the presence of altered brain function (i.e., disorientation, confusion, other transient neurological abnormalities, etc.) in the absence of detectable structural injury on clinical brain scans as well as a limited duration of post-traumatic amnesia (PTA) and/or loss of consciousness (LOC) (Ruff et al., 2009).

Best estimates of mTBI incidence place the true-population base rates at around 600 per 100,000, with elderly individuals and older teenagers typically at highest risk for incurring mTBI (Cassidy et al., 2004; Faul, Xu, Wald, Coronado, & Dellinger, 2010). The most frequent causes of mTBI are sports-related concussion, motor vehicle collisions, combat-related injuries (blast), and falls (Cassidy et al., 2004; Faul, Xu, & Sasser, 2016). The economic burden associated with mTBI includes increased healthcare costs (Rockhill, Fann, Fan, Hollingworth, & Katon, 2010) and loss of work productivity (Boake et al., 2005). Research also links mTBI to increased risk for neurodegenerative disease in later life, particularly for complicated presentations and individuals who sustain
multiple injuries (Gavett, Stern, Cantu, Nowinski, & McKee, 2010; Graves et al., 1990; Lee et al., 2013)

Pathophysiology of mTBI

mTBI is a complex injury with a temporally-dynamic course of evolving pathophysiology. The initial stage of injury results from an external force (e.g. concussive impact) that transfers energy to brain parenchyma causing biomechanical injury, which subsequently triggers acute neurochemical and cellular cascades within neural tissue (Barkhoudarian, Hovda, & Giza, 2016; Blennow, Hardy, & Zetterberg, 2012). Focal brain damage is possible in mTBI, but usually occurs with more severe brain injuries (e.g., penetrating head injuries) (Andriessen, Jacobs, & Vos, 2010). In contrast, mTBI neuropathology is normally characterized by diffuse injury caused by the rapid acceleration and deceleration forces, which differentially injure axons by stretching and shearing vulnerable white matter tracts necessary for neurotransmission (Andriessen et al., 2010; V. E. Johnson, Stewart, & Smith, 2013). Once the viscoelastic thresholds of cell membranes are exceeded, ionic flux is triggered, which further depolarizes cell membranes resulting in the release of excess excitatory neurotransmitters into extracellular spaces (Barkhoudarian et al., 2016).

The feedback loop of neurotransmitter release and subsequent ionic flux causes brain cells to operate at maximum capacity in order to restore homeostasis. This causes an “energy crisis” within the brain as a result of increased energy demands in the context of diminished resources to supply needed energy that arise from disrupted cerebral blood flow, mitochondrial dysfunction, and altered neurotransmission (Blennow et al., 2012; MacFarlane & Glenn, 2015). Diffuse axonal injury is also associated with punctate ischemic damage and micro hemorrhages throughout the brain, most
commonly in cortical and subcortical regions and at gray-white matter junctions
(Shenton et al., 2012; Wong, 2015).

Brain regions that are most vulnerable damage from mTBI include the prefrontal
cortex, subcortical white matter, medial temporal lobes (including the hippocampi),
brainstem, and cerebellum (Eierud et al., 2014; Umile, Sandel, Alavi, Terry, & Plotkin,
2002; Zhang, Yang, & King, 2004; Viano, Casson, Pellman, Zhang, King, & Yang,
2005), and damage to these areas has the potential to produce a wide range of
neurobehavioral dysfunction. White matter tracts in the brain stem including thalamic
projections, corticospinal tracts, and the pontine tegmentum are especially susceptible
to the effects traumatic axonal injury in mTBI and underlie physical, vestibular, and
autonomic mTBI sequelae (Bigler, 2013; Delano-Wood et al., 2015). The degree to
which brain areas are damaged often corresponds to the severity of symptoms and
cognitive deficits.

Clinical Presentation

The clinical presentation of mTBI spans symptoms from multiple domains of
functioning including mood, postural stability, oculomotion, sleep, and cognition
(Bazarian et al., 1999; Ciuffreda et al., 2007; Riemann & Guskiewicz, 2000; Stulemeijer
et al., 2006). In many cases, the severity of clinical symptoms in the acute period can be
linked to the severity of the pathophysiological burden (Giza & Hovda, 2014). For
example, increased fractional anisotropy detected via diffusion tensor imaging and/or
the presence of microbleeds measured via susceptibility-weighted imaging are
correlated with greater cognitive impairment post-mTBI (Bigler & Maxwell, 2012; Wada,
Asano, & Shinoda, 2012). Neuropsychological deficits are also linked to post-mTBI
neurotransmission changes in cholinergic, glutamatergic, and noradrenergic systems that broadly regulate arousal and cognition (Khurana & Kaye, 2012).

According to the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury, the most common self-reported symptoms of mTBI are headache, fatigue, dizziness, sleep problems, vision changes, and cognitive problems (Cassidy et al., 2004). With regards to symptom experience, females typically report greater symptoms following mTBI. Although this trend remains largely unexplained, several factors have been proposed that may underlie sex differences in symptom reporting including neurobiological differences in hormones and cerebral blood flow, as well as psychosocial factors (Bazarian, Blyth, Mookerjee, He, & McDermott, 2010; Covassin, Elbin, Harris, Parker, & Kontos, 2012). As noted above, significant neuropathological heterogeneity exists in mTBI and this is echoed in the clinical manifestation of the injury as well. Although there are typical symptoms, the experience of one individual with mTBI is often vastly different from the next.

Mood and affective dysregulation immediately following mTBI is common, but it is one of the most poorly understood consequences. Emotional sequelae can arise from specific damage to emotional control networks in the brain, but they are also strongly related to pre-injury characteristics such as genetic, social, and psychiatric risk factors (Jorge & Arcinieagas, 2014). In the acute period, affective disturbance frequently presents as emotional instability or lability, and may be mistaken for a purely psychological reaction to the injury. However, Borgaro, Prigatano, Kwasnica, and Rexer (2003) demonstrated that subtler aspects of the affective system can be compromised and are related to injury severity. They found that spontaneous generation of affect was
impaired in both acute complicated and uncomplicated mTBI whereas cued expression of affect was associated with more severe injuries.

Depression and anxiety are the most frequently co-morbid mood disorders in mTBI. Acute mood symptoms are often present in the days to weeks immediately following the injury, but mTBI patients remain more vulnerable to both new-onset and re-occurrence of psychiatric diagnoses up to a year after the injury (Ruff, Camenzuli, & Mueller, 1996). A prospective study of 80 patients showed that mTBI was significantly related to new-onset depression and anxiety and that a high-rate of dissociative experiences was noted in those patients who experienced protracted recoveries (Mooney & Speed, 2001). Animal studies have documented injury-induced alterations in limbic functioning that lead to increased anxiety and fear conditioning (Meyer, Davies, Barr, Manzerra, & Forster, 2012). Notably, patients with pre-existing psychiatric conditions appear to be especially vulnerable to the emotional effects of TBI, and a previous anxiety or depressive disorder is a risk factor for post-injury psychiatric difficulties as well for future injuries (Mooney & Speed, 1997; Ruff et al., 1996).

Deficits in postural stability are another prominent clinical feature of mTBI, since high-level sensory-integration necessary for vestibular function is easily affected by brain injury. Maintaining balance is a body- and brain-intensive task that requires intact peripheral sensory and motor systems as well as uninterrupted functioning in the higher-cortical association areas, cerebellum and brain stem (Guskiewicz, 2001). The vestibular consequences of mTBI consist of a constellation of symptoms including dizziness, vertigo, and balance problems, the more severe of which may require
vestibular rehabilitation (e.g., benign positional vertigo) (Hoffer, Gottshall, & Viirre, 2012).

Oculomotor disturbances in mTBI are usually characterized by prolonged saccadic latencies, convergence insufficiency, decreased spatial accuracy in smooth pursuits, and increased eye position errors, which have been documented in the acute and post-acute periods after mTBI (Ciuffreda et al., 2007; Heitger et al., 2004; Suh, Kolster, et al., 2006). Related patient complaints include blurred vision, difficulty reading, and concentration problems. Oculomotor deficits can arise from damage to cranial nerves, which control basic motor movements of the eye, or to cerebellar-cortical white matter connections, which are involved in higher cortical control of predictive eye movements, tracking, and sensory integration (Coello, Canals, Gonzalez, & Martin, 2010; Kheradmand & Zee, 2011). Neurocognitive dysfunction may accompany oculomotor impairments due to the overlap between cortical and subcortical regions important for attention, working memory, and executive functioning (i.e. cortical-cerebellar tracts and pre-frontal cortex), but oculomotor deficits can also occur independently in mTBI (Heitger et al., 2004; Suh, Basu, et al., 2006).

The importance of sleep dysfunction following mTBI has only recently been emphasized for its role in mediating other symptom domains and injury recovery (Chaput, Giguere, Chauny, Denis, & Lavigne, 2009; Wickwire et al., 2016). The majority of mTBI patients will experience some degree of sleep abnormality, which can arise from the primary injury (e.g., axonal injury affecting midline brain structures, locus coeruleus, and/or pontine connections) or from secondary effects (e.g., neurometabolic cascades and increased energy demand) (Jaffee, Winter, Jones, & Ling, 2015).
Findings from a national working group on sleep and mild traumatic brain injury classify associated sleep disturbances into four categories: 1) insufficient sleep duration or continuity, 2) alterations in sleep stages, 3) sleep pathologies, and 4) timing abnormalities (Wickwire et al., 2016). Insomnia and excessive daytime somnolence are the most commonly reported complaints, and they are linked to documented dysfunction in sleep onset and sleep maintenance post-mTBI (Verma, Anand, & Verma, 2007). The biological timing and rhythm of sleep are also disrupted due to dynamic alteration of hormone secretion (e.g., melatonin) that impacts circadian control resulting in delayed sleep phases. Changes in sleep phases may also be interpreted by individuals with mTBI as insomnia (Jaffee et al., 2015; Shekleton et al., 2010). The consequences of post-injury sleep disturbances are far-reaching. Sleep restriction can negatively impact normal physiologic operations of metabolic, cardiovascular, immune, and endocrine functioning (Banks & Dinges, 2007; Van Dongen, Maislin, Mullington, & Dinges, 2003), as well as cognitive performance in attention, learning and memory, executive functioning, and processing speed (Dean & Sterr, 2013; Fulda & Schulz, 2001; Maquet, 2001). Pain experience following mTBI has also been associated with the need for more or better quality sleep (Suzuki et al., 2017).

Neuropsychological deficits linked to mTBI include attention, processing speed, memory, and executive functioning, but individual presentation is highly heterogeneous within and across these areas (Karr, Areshenkoff, & Garcia-Barrera, 2014; Rabinowitz & Levin, 2014). Belanger, Curtiss, Demery, Lebowitz, and Vanderploeg (2005) noted that deficits in delayed memory and fluency are the most prominent neuropsychological problems within the acute post-injury period. However, executive functioning appears to
be the most susceptible to decline after multiple injuries (Karr et al., 2014). Overall, the severity of neuropsychological deficits in the acute- and sub-acute timeframe likely relates to the level of neuropathological disruption via primary and secondary injury effects, which can be loosely predicted by injury characteristics such as loss of consciousness and post-traumatic amnesia (Iverson, 2006; McCrea, Kelly, Randolph, Cisler, & Berger, 2002). Symptomatic mTBI patients are more likely to demonstrate cognitive impairments in attention and motor speed than those who are asymptomatic at 11 days post-injury (Collie, Makdissi, Maruff, Bennell, & McCrory, 2006), but the utility of symptom severity as a predictor of longer-term outcomes is disputed (Spencer, Drag, Walker, & Bieliauskas, 2010; Stulemeijer, Vos, Bleijenberg, & van der Werf, 2007). Additional patient factors such as depression, personality, and possibly education may contribute to subjective cognitive difficulties after mTBI, especially after the first few weeks of recovery (Chamelian & Feinstein, 2006). Importantly, for serial testing after injury, neuropsychological impairment presents as an “attenuation of practice effects” rather than an overt decline in performance (Collie, Darby, & Maruff, 2001; Collie et al., 2006).

Recovery

Pathophysiological recovery from mTBI occurs with the resolution of parallel and dynamic physiologic processes including normalization of cerebral blood flow, reduction of inflammation, balancing of neurotransmission, and stabilization metabolic functioning (Giza & Difiori, 2011). The inflammatory response acts as a double edged sword in brain injury, since excessive inflammation is neurotoxic. Attenuating the acute inflammatory response by administering pharmaceutical therapeutics can be beneficial; however, full suppression of the inflammatory response results in poorer post-injury
outcomes (Galea, Heneka, Dello Russo, & Feinstein, 2003; Kumar & Loane, 2012). In fact, brain inflammation and neural damage serve as triggers for increased neurotrophin production, which enable and support neuroreparative processes.

Neurotrophins such as brain-derived neurotrophic factor (BDNF), insulin growth factor (IGF), and endothelial growth factor (EGF) promote synaptic plasticity, neurogenesis, and angiogenesis, which are directly related to improved cognitive and mood outcomes following injury (Griesbach, Hovda, Molteni, & Gomez-Pinilla, 2002). Of these, BDNF appears to be the most influential in facilitating neurorecovery and injury-induced plasticity (Coughlan, Gibson, & Murphy, 2009; Kaplan, Vasterling, & Vedak, 2010). Under normal circumstances, BDNF underlies long-term potentiation by supporting neurogenesis and synaptic plasticity critical for learning and memory. In the context of brain injury, not only is BDNF an important component of neurorepair, but it also has value as a diagnostic indicator. Lower day-of-injury concentration of BDNF in circulating serum correlates with more severe injuries in humans, and it is also associated with prognostic usefulness such that lower day-of serum values predict individuals who will have longer recoveries at 6-months (Korley et al., 2016).

A large, cross-sectional review concluded that prognosis is good for children and adults to experience full recovery from mTBI within 3 to 12 months (Carroll et al., 2004). The majority of patients with mTBI typically recover to baseline levels on clinical measures of neurological, cognitive, and physical symptoms within approximately 7 to 14 days after injury (Lovell et al., 2003; McCrea et al., 2003). However, considerable heterogeneity for “normative” recovery exists in the literature. Many estimates are based on athletes, which may skew the expected timeline towards the one to two week
window since athletes generally have neuroprotective baseline characteristics (e.g., better aerobic fitness) that may predispose them towards more efficient mTBI recovery. For healthy adults, a prospective longitudinal study conducted by Losoi et al. (2016) showed that 62% of mTBI patients were no longer experiencing moderate post-concussion symptoms at 1 month and that over 80% had resolved by 6 months.

A growing body of evidence exists that demonstrates a link between extended recoveries after mTBI and markers of prolonged pathophysiological disruption such as decreased mitochondrial metabolism and abnormal electrical connectivity. Neuroimaging and electrophysiological studies show that biomarkers of dysfunction can outlast clinical symptom resolution. Cerebral metabolic functioning and blood flow are generally restored by 1 month after injury, (Vagnozzi et al., 2010; Vagnozzi et al., 2008), but lower values of cerebral blood flow are also associated with poorer outcomes at 1 month (Meier et al., 2015; Vagnozzi et al., 2010). Alterations in brain connectivity detected by functional magnetic resonance imaging (fMRI) have been found in mTBI participants that are most prominent in the first few months after injury (B. Johnson et al., 2012), but there is also evidence for longer-term abnormalities in functioning lasting up to one year (Bigler & Maxwell, 2012). Further proof for a period of prolonged brain vulnerability that outlasts clinical symptoms is presented in studies showing compounding effects of secondary injuries that are sustained within two weeks of the initial injury as well as cumulative clinical effects associated with repeated injuries at longer intervals (Guskiewicz et al., 2003; McCrea et al., 2009; Vagnozzi et al., 2008).

At least 10% to 15% of all individuals with documented mTBIs experience persistent post-concussion syndrome (PPCS), with symptoms lasting for three months
or longer (Bigler, 2008; McInnes, Friesen, MacKenzie, Westwood, & Boe, 2017; Ryan & Warden, 2003). In some patients, such symptoms extend even further into the chronic period and are a source of continuing distress and disability for a year or longer (Carroll et al., 2004; Iverson, 2005). The etiology of persistent post-concussion syndrome is hotly debated, but the consensus opinion among researchers is that a biopsychosocial model best explains those at risk for PPCS in which the neurobiological and psychological elements of pre-morbid characteristics, injury factors, and post-injury adaptation are considered (Silverberg & Iverson, 2011). For instance, current litigation was one of the strongest predictors for persistent cognitive sequelae after 3-months (Belanger et al., 2005). However, other factors such as sleep dysfunction and psychological factors (e.g., depression and anxiety) have also been implicated in the development of PPCS (Clarke, Genat, & Anderson, 2012; Schreiber et al., 2008).

**Clinical Intervention**

Clinicians have few empirically-based tools with which to manage or treat acute mTBI, and, except for intensive multimodal rehabilitation, no empirically validated clinical interventions currently exist that consistently prevent or reduce the acute or subacute pathophysiological effects of injury (Hadanny & Efrati, 2016; Maas, Marmarou, Murray, & Steyerberg, 2004; Maas, Roozenbeek, & Manley, 2010). Individual therapies such as vestibular rehabilitation and cognitive behavioral therapy are available to target specific problematic symptoms (Gurley, Hujsak, & Kelly, 2013; Scheenen et al., 2017; Wickwire et al., 2016). Pharmacological treatments may also be helpful for some mTBI patients, particularly for those with psychiatric co-morbidities, but none of these therapies are integrative nor do they promote broad improvement in recovery across physiological and neurobehavioral domains.
In clinical practice, healthcare providers’ approaches to treating patients with mTBI in the acute and chronic periods are varied, and empirically-based guidelines for care have only recently emerged in the past 15 years. Consensus guidelines have been developed for gradual return-to-activity for sports-related concussion patients, but routine application of these guidelines in clinical practice has not yet occurred (Covassin, Elbin, & Stiller-Ostrowski, 2009; McCrory et al., 2017; Zonfrillo et al., 2012). Return-to-activity guidelines have yet to develop strong support in the literature, since few research trials have systematically examined the effects of their implementation (Burke, Fralick, Nejatbakhsh, Tartaglia, & Tator, 2015). However, the nature and timing of re-introducing physical activity after injury is worth the research effort, because pre-clinical studies have demonstrated that they can significantly impact injury severity and alter recovery trajectories (Silverberg & Iverson, 2013).

**Literature Review**

**Exercise After mTBI**

Preclinical research has identified aerobic exercise as a promising target for human translation due its multidimensional role in supporting brain function and health after brain injury (Griesbach, Hovda, Molteni, Wu, & Gomez-Pinilla, 2004). These studies in animal models have shown interventions that directly or indirectly enhance the regulation of BDNF produce better immediate and long-term neurological and functional outcomes regardless of injury severity (Gomez-Pinilla, Ying, Roy, Molteni, & Edgerton, 2002; Griesbach, Hovda, & Gomez-Pinilla, 2009). In experimental models, aerobic exercise upregulates BDNF, which facilitates neuroplastic changes that support neurorestoration of damaged neurological systems through mechanisms of neurogenesis, angiogenesis and synaptogenesis (Griesbach et al., 2009). Research
into exercise as a potential treatment for brain injury or as a preventative intervention for PPCS has been mostly limited to preclinical animal models thus far, but these studies show that voluntary aerobic exercise initiated within a post-acute time frame after injury (7-14 days for mTBI), best enhances concentrations of BDNF production in the brain, which ameliorates anxiety behaviors and improves memory and balance (Griesbach et al., 2007; Griesbach et al., 2009). However, exercising animals too soon and too intensely (within a few days after injury), or under forced conditions results in the reversal of these beneficial effects likely due to additive strain on neurometabolism and increased inflammation (Kreber & Griesbach, 2016).

**Human Translation**

Clinical trials for brain injury therapeutics have echoed preclinical findings, although in less direct ways, by showing that pharmaceutical or other interventions must always have an enhancing effect on mechanisms that upregulate neuroplasticity to yield improved outcomes (Kumar & Loane, 2012; Maas et al., 2010; Xiong, Mahmood, & Chopp, 2009). Exercise has been shown to increase BDNF concentrations in healthy and human medical populations without brain injuries (e.g. multiple sclerosis, Parkinson’s disease, and diabetes), and the associated BDNF upregulation is related to subsequent improvements in cognitive functioning and mood (Cotman, Berchtold, & Christie, 2007; Dishman et al., 2006).

An increasing body of literature is collecting that parallels some of the pre-clinical findings discussed above by examining the impact of rest, exercise and return-to-activity timing in humans. Most of these studies are aimed at assessing the effects of clinical recommendations for rest after injury. In general, a period of 24 to 48 hours of rest after injury is recommended for most mTBI patients (Schneider et al., 2017). For children and
young adults, Thomas, Apps, Hoffmann, McCrea, and Hammeke (2015) found that strict rest lasting for 5 days resulted in greater post-concussion symptoms and slower resolution of those symptoms compared to a normal care group who progressed to stepwise return-to-activity after 1 to 2 days of rest. A large, prospective study noted that a similar population who returned to physical activity within 7 days following mTBI had reduced rates of PPCS at approximately one month follow up (Grool et al., 2016). Although an excellent addition to the literature, this latter study was not a randomized clinical trial and used self-report measures that did not capture duration or validate exercise intensity. In an older cohort of patients, strict bed rest for 6 days after mTBI had no effect on general health status at intervals up to 6 months (de Kruijk, Leffers, Meerhoff, Rutten, & Twijnstra, 2002). One proposed mechanism of harm from extended or strict rest practices is the “nocebo” effect, whereby the continuation or exacerbation of symptoms is caused by the patient’s inhabitation of the sick role rather than the injury itself (DiFazio, Silverberg, Kirkwood, Bernier, & Iverson, 2016; Whittaker, Kemp, & House, 2007).

Conversely, Asken et al. (2016) showed that average recovery timelines were pushed back for college athletes who were not immediately removed from game or practice play following a concussion, which appears to corroborate the findings of deleterious early exercise in pre-clinical studies. However, the nature and timing of post-injury exercise in humans remains uncertain. A retrospective study of college student athletes demonstrated differential effects of post-injury intensity on outcomes such that high intensity activity after concussion was associated with poorer neurocognitive performance, but the best post-injury outcomes for both neurocognitive and symptom
report were for individuals who met criteria for a moderate level of post-concussion activity (Majerske et al., 2008). This research further underscores the need for prospective studies that investigate the type and amount of post-injury exercise in order to balance outcome optimization while avoiding exacerbation of mTBI neuropathology.

A few studies have examined exercise in the peripheral period after mTBI as an intervention for PPCS, with seemingly consistent benefits in cognitive and emotional improvement (J. Leddy, Hinds, Sirica, & Willer, 2016). J. J. Leddy et al. (2010) implemented a treadmill exercise paradigm aimed at reducing PPCS several months after injury and found that it succeeded in decreasing post-concussion symptoms. Similarly, Gagnon, Galli, Friedman, Grilli, and Iverson (2009) showed that an active rehabilitation program, consisting of aerobic exercise and tailored coordination exercises helped children who experienced prolonged recoveries after 1 month post-injury. No studies thus far have examined the benefits or risks of exercise initiated in the immediate post-acute period (2 to 3 weeks) after mTBI, when the capacity for neurorestoration is presumably at its greatest (Giza & Hovda, 2014). Additionally, the role of BDNF, which is a critical mediator in activity-enhanced recovery, has not been examined in any of the human studies.

**Significance and Implications**

Exercise is a behavior that unmistakably impacts physical health, but now science is focusing on how exercise can also impact “brain health”, manifested in cognitive and emotional outcomes. This study combines assessments of both physical and mental health into one research question that also addresses clinical translation, a distinct research priority for the National Institute of Mental Health. Exercise as a clinical intervention has the unique advantage of being generalizable and widely accessible to
many populations, but a thorough understanding of its effects during the post-acute time frame after mTBI is needed before proceeding to examine its efficacy as a clinical treatment option. This study will deliver comprehensive pilot data for follow-up studies designed to investigate the efficacy of implementing aerobic exercise.

Specific Aims

The overall goal of this study was to conduct a pilot study of a daily aerobic exercise program lasting for one week during the post-acute phase of mTBI in humans (defined as 14-25 days post injury), which conservatively parallels the time frame set forth in Griesbach et al. (2007) pre-clinical exercise research. Several neurobehavioral markers of recovery were examined in two participant groups with mTBI who were randomized to a 1-week aerobic exercise group or a 1-week non-aerobic exercise (stretching and passive movement) group. The following specific aims were investigated:

Specific Aim 1

The primary aim was to assess the safety, feasibility, and tolerability of implementing a brief, 1-week aerobic exercise program during the post-acute phase of mTBI. Towards this end, changes in key functional outcomes derived from the biopsychosocial model of mTBI were examined following the exercise interventions and compared between groups (McCrea et al., 2009). These outcomes included cognition, symptom report, mood, sleep, and postural stability. The longer-term impact of the aerobic exercise intervention was also compared to the non-aerobic intervention at 3 months post-mTBI on select outcomes. This time point was chosen as it corresponds to the typical time frame in which patients with continuing post-mTBI symptoms would be classified as having PPCS. Ideally, these data will also be used as the foundation from
which to design efficacy studies as the next phase in researching exercise effects after mTBI. 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 normal, reference values for change in functional outcomes.

- Prediction 1a. The aerobic exercise intervention will be well-tolerated by mTBI participants in terms of study adherence and completion rates. Self-reported symptoms after aerobic exercise will not be increased beyond the non-aerobic group or that which is demonstrated in a non-injured population.

- Prediction 1b. Performance on functional outcomes after the intervention week is predicted to be similar for the aerobic group compared to the theoretically inert 1-week non-aerobic exercise control group and the non-injured participant group.

- Prediction 1c. The aerobic exercise group will perform equivalently to the non-aerobic exercise group on functional outcomes at 3-months post-injury.

**Specific Aim 2**

The purpose of specific aim 2 was to describe the characteristics of circulating BDNF concentration in serum and platelet-poor plasma during the post-acute recovery period after mTBI as well as its dynamic response to a single session of aerobic exercise. Basal (resting) BDNF concentration was compared to normal, non-injured participants at baseline, before the mTBI groups began their assigned intervention. The acute post-exercise response of BDNF concentration was measured in the aerobic and non-aerobic exercise groups on the first day of the exercise intervention and compared
to the non-injured participants who underwent a single, parallel session of aerobic exercise.

- Prediction 2. The mTBI and non-injured aerobic exercise groups will experience an increase in serum and platelet-free plasma BDNF concentration relative to the non-aerobic exercise group, consistent with previous research in humans showing this effect (Gilder, Ramsbottom, Currie, Sheridan, & Nevill, 2014; Griffin et al., 2011)
CHAPTER 2
METHOD

Overview and Trial Design

The trial design for this study was a non-blind randomized controlled-trial with an equal allocation ratio. Block randomization was used to allocate mTBI participants to the aerobic or non-aerobic groups. The random allocation sequence was created by the random number generator in Microsoft Excel for blocks of 4 that were stratified by sex. Assignment was kept concealed by blackened cells in the Microsoft Excel document until informed consent was completed.

Existing University of Florida (UF) TBI clinical pathways were utilized to identify individuals who presented to either the UF Neurotrauma Emergency Department (ED) or the UF Sports Concussion Center (SPCC) for mTBI care. The study enrolled three groups: 1) mTBI patients randomized to a daily, 1-week aerobic exercise intervention, 2) mTBI patients randomized to a daily, 1-week non-aerobic exercise program, and 3) non-injured, no intervention reference group. Study procedures took place at the UF Clinical and Translational Science Institute’s (CTSI) Clinical Research Center. Approval was secured from the Institutional Review Board (IRB-01) at UF and informed consent was obtained from all participants. Compensation was in the form of pre-loaded gift cards at a rate of $12/hr.

Initially, a single symptom assessment was administered prior to exercise on each exercise intervention day. However, within the first few days of trial commencement, it became apparent that self-reported symptoms should be measured both before and after each intervention day to fully capture the participant’s acute response to the intervention rather than basal response only. Therefore, a second, post-
exercise symptom evaluation was added to the protocol in order to capture acute symptom response to exercise. This change was implemented midway through the intervention for the second and third participants and was standardized for all subsequent participants.

**Participant Characteristics and Recruitment Strategy**

**mTBI participants**

Participants (n = 26) between the ages of 18-40 who were diagnosed with mTBI according to criteria set forth by the American Congress of Rehabilitation Medicine (Kay, Harrington, Adams, Anderson, et al., 1993) were included in the study. These criteria included:

- any period of loss of consciousness;
- any loss of memory for events immediately before or after the accident;
- any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); and/or
- focal neurological deficit(s) that may or may not be transient;

but where severity of the injury does not exceed the following:

- loss of consciousness of approximately 30 minutes or less;
- after 30 minutes, an initial Glasgow Coma Scale (GCS) of 13–15; and
- posttraumatic amnesia (PTA) not greater than 24 hours.

After being identified for the study by 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 their assigned exercise intervention. Exclusionary criteria included abnormal
structural findings on post-injury CT neuroimaging, comorbid orthopaedic injury inhibiting movement, prior history of serious psychiatric disturbance with hospitalization, prior history of neurologic disease, current or prior history of alcohol or substance abuse disorder, diabetes diagnosis, previous history of moderate or severe head injury, or neurological disorder unrelated to TBI, and non-English speakers. Participants began the first day of their assigned exercise intervention within 14-25 days post-injury.

Non-injured participants

Participants (n = 10) between the ages of 18-40 were recruited to provide a normal reference group for relevant outcome measures (i.e. symptom change due to a single session of exercise, neuropsychological performance, mood, and circulating BDNF). These participants were demographically-matched to the mTBI participants in the aerobic group and recruited from UF and the Gainesville community. Exclusionary criteria were the same as the mTBI group. Non-injured participants completed the same pre-intervention procedures and assessments as the mTBI group with the exception of questionnaires related to injury characteristics. They participated in a single day of aerobic exercise followed by another study visit 7 days later to provide symptom, postural stability, and BDNF reference values. Non-injured participants also completed the same post-intervention assessments as the mTBI participants.

Intervention

Daily Aerobic Exercise

Aerobic exercise consisted of riding a Lode Corival 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 \(HR_{max} = 208 - 0.7 \times \text{age}\). Heart rate was monitored every 5 minutes by research staff using a finger pulse oximeter. Feedback was provided to the participant as needed to help participants stay within the target range. This exercise program was chosen, because moderate, aerobic exercise for this duration has been shown to consistently upregulate BDNF in humans and promote plasticity in the hippocampus (Coelho et al., 2013; Ferreira, Real, Rodrigues, Alves, & Britto, 2011). A stationary bicycle was chosen, because it provided a stable exercise platform for safety purposes. All exercise sessions were conducted with equipment and facilities provided by the UF Clinical Research Center (CRC). Participants in this group exercised daily for a period of one week. A single rest day was taken on the weekend, after the participant had completed 3 to 6 days of the exercise intervention in a row.

**Daily Non-Aerobic Exercise**

Non-aerobic exercises was used as an “exercise placebo,” since previous studies have found that using a similar approach best ensures “clinically-meaningful treatment” for aerobic exercise by accounting for participant expectation and social contact variables that would differ in no-contact or other types of inert control groups (Dunn, Trivedi, Kampert, Clark, & Chambliss, 2002). The non-aerobic intervention arm featured a series of very low-intensity static stretching and callisthenic movements. 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 at 10-minute intervals 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 one week. A single rest day was taken on the weekend after the participant had completed 3 to 6 days of the exercise intervention in a row. The non-aerobic intervention protocol summary is included in Appendix B.

**Clinical Assessment and Outcome Measures**

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-mTBI. The significance of each of these outcomes in post-injury recovery has been well established in the literature (Iverson, 2005). A web-based electronic data capture system (REDCap) was used to collect all demographic, injury, and outcome data with the exception of neurosychological 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. Blood draws, postural stability measures, symptom report, and behavioral assessments were measured according to the study design outlined in Figure 1. All participants received a digital fitness monitor to be worn during the 7-day intervention period for the purpose of measuring sleep.

**Self-Reported Symptoms**

The post-concussion symptom checklist from the Sport Concussion Assessment Tool (SCAT3) contains 22 symptoms associated with mTBI (e.g. headache, nausea/dizziness, and neck pain) (McCrory et al., 2013). This checklist was used to assess symptom change as an outcome, but also as part of an objective system for monitoring post-concussion symptom exacerbation and adverse events during the study. For this checklist, participants were asked to rate the severity of different
symptoms encompassing somatic, mood, and physical experience on a Likert scale of 0 (none) to 6 (severe). This checklist was completed at pre-intervention, daily (both pre- and post-exercise) during the 7-day intervention period, and then again at the 3-month post-injury follow-up.

**Baseline Aerobic Fitness**

History of physical activity was assessed at pre-intervention using a modified version of the physical activity questionnaire from the Framingham Heart Study (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 is measured within 5 seconds. Scores were compared to normative values stratified by sex and age that are provided by the YMCA (Golding, 2000).

**Cognition**

To measure neuropsychological performance on cognitive domains vulnerable to decline following mTBI (Moser et al., 2007), a 2-hour battery was administered to participants at pre- and post-intervention by trained research staff. 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 2-1). Reliable change metrics were computed according to methods set forth in (Iverson, Lovell, & Collins, 2003) to account for practice effects from pre- to post-intervention. Test-retest statistics were derived from the non-injured group rather than normative reference data, because the non-injured group provided an optimally matched fit in terms of test-retest timeline and demographics of the intervention groups.

**Mood**

mTBI is associated with increased incidence of post-injury depression and anxiety disorders as well as difficulty regulating emotion. The Beck Depression Inventory (BDI-II) (Beck, Steer, & Brown, 1996) and State Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1968) are frequently used in both clinical and research settings for assessing depression and anxiety, respectively. The instructions for the BDI-II were modified to assess depressive symptoms for the previous week instead of the customary two-week window used in the standard instruction set. Mood questionnaires were administered at pre-intervention, post-intervention, and 3-month post-injury follow up.

**Sleep**

Sleep disturbances after mTBI are common and typically present as insomnia, apnea, and/or fatigue. The medical outcome scale (MOS), a 12-item, self-reported measure of sleep quality, was used to evaluate participants’ subjective sleep experience (Hays, Martin, Sesti, & Spritzer, 2005). The sleep problems index 2 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.

Objective sleep quantity and quality was measured during the intervention period using digital fitness monitors. All participants were instructed to wear a digital fitness monitor on their wrists for 24 hours per day during the 7-day duration of the exercise intervention. For mTBI participants, the monitors were removed at the beginning of each exercise visit to be charged and synced then returned to the participant at visit completion. Data collection via the digital fitness monitors proved to be problematic during this study for several reasons. Originally, Misfit Shine™ fitness monitors were used, but the construction and design of the monitor rendered them vulnerable to the sensor becoming separated from the wrist band. All original Misfit Shine™ monitors were lost by participants despite several prophylactic efforts including super-glue and pre-emptive instructions to the participants. They were replaced with Fitbit Flex™ wrist monitors chosen for their similarity to the Shines on technology levels and measurement characteristics, as well as their improved wearability. Only one Fitbit Flex was lost by a participant during the intervention phase. However, the data uploading process resulted in corrupted, deleted, or incomplete data. Therefore, self-reported bedtime and wake times were collected from participants midway through the study. These reports were collected every day during the 7-day intervention period. The available sleep monitor data and daily reports were combined into an average nightly sleep score for the intervention week.

Postural Stability

Postural control is impaired after mTBI due to interrupted sensory-motor integration. The Balance Error Scoring System (BESS) is commonly used to measure
post-injury impairment that is sensitive to deficits in balance following mild head injury (Riemann & Guskiewicz, 2000). Participants are asked to close their eyes and remain stable in three different postural stances: double leg, single leg, and tandem stance. The number of times they lose their balance in each stance is counted as an error (range, 0 to 10 for each stance) and a total error score is available for errors committed across all stances. Each are tested for a period of 20” each, during which time participants are asked to close their eyes and maintain their balance with their hands on their hips. For the single-leg stance, participants stood on their non-dominant foot and for the tandem stance; the non-dominant foot was placed in the rear. Leg dominance was defined as the leg with which the participant would normally use to kick a ball.

Errors were defined as an occurrence of any of the following during the 20” test period:

- Lifting hands off the iliac crests,
- Opening the eyes,
- Stepping, stumbling, or falling
- Moving the hip into more than 30° of flexion or abduction
- Lifting the forefoot or heel

If the participant was unable to maintain his or her balance for more than 5”, the trial was discontinued and maximum points were awarded. The modified version of the BESS (mBESS) was used in this study, which utilizes the hard floor surface only (McCrory et al., 2013). Research staff was administered two hours of mBESS training procedures which included viewing standardized videos, scoring practice, administration observation, and feedback by an expert administrator prior to clearance for assessing study participants. Intraclass correlation (ICC) for double, single, and tandem stance
measurements among raters after completing mBESS training procedures was examined based on a mean-rating (k = 3), absolute-agreement, 2-way random-effects model (Koo & Li, 2016). For double leg stance, ICC = .95 with 95% confidence interval = .75 - .99. For single leg stance, absolute agreement, ICC = .72 with 95% confidence interval = .26 - .99. For tandem stance, ICC = .91 with 95% confidence interval = .65 - .99. Overall, interrater reliability ranged from moderate (single leg stance) to good (double and tandem stance), consistent with previous research (Finnoff, Peterson, Hollman, & Smith, 2009).

**BDNF**

Blood sampling was accomplished via a 17-mL withdrawal that was collected by research nurses at the UF CRC from the antecubital forearm vein while the participant was in a seated position. Initial sample processing was completed at the CRC. For serum, samples were collected in a serum separator tube and allowed to clot for 30 minutes prior to centrifugation for 15 minutes at 1000 x g. For platelet-poor plasma: samples were collected in EDTA tubes and stored on ice prior to centrifugation at 2-8°C for 15 minutes at 1000 x rcf (within 30 minutes of collection). Plasma was then separated in Eppendorf tubes and underwent an additional centrifugation step at 10,000 x rcf for 10 minutes, which produced a small "pellet" in the bottom of the tube (representing the remaining platelet granules). The platelet-poor plasma was then aliquoted into new Eppendorf tubes, snap frozen in liquid nitrogen, and stored at -80°C until all samples were collected. In order to adjust for plasma volume change after acute exercise according to recommendations by (Dill & Costill, 1974), hemoglobin measurements were taken before and after exercise on intervention day 1. Hematocrit
was calculated indirectly from hemoglobin measurement (Hematocrit = 2.94 x Hemoglobin (g/dL)).

Serum and platelet-poor BDNF were assayed using an enzyme-linked immunosorbent assay (ELISA, R&D Systems, Minneapolis, MN) kit. The reported sensitivity for minimal detectable dose in the ELISA kit manual is typically <20 pg/mL. The average intra-assay coefficient of variations (CV) ranged from 2.1% - 6.9%, which is well within the recommendations of the ELISA kit. Inter-assay CV was assessed from 9 samples and 3 controls on two separate plates, which indicated 8.1% inter-assay CV (samples) and <3.5% inter-assay CV (controls), both of which also within expected values.

Data Quality and Safety Monitoring

Safety Monitoring

Study procedures took place at the UF CRC, a clinical research facility where nurses were on hand in the event of an emergency. For mTBI participants, a qualified medical safety monitor received safety reports on day 4 of the intervention period or earlier that contained symptom reporting data for review and monitoring of symptom exacerbation. The medical safety monitor also conducted a follow-up neurological examination for one participant due to an adverse event discussed below. A data and safety monitoring plan was also in place during data collection. Three independent clinical faculty members with scientific training served as evaluators of all study and data integrity procedures. Reports detailing study procedures, participant accrual, participant demographics in each group, and participant compliance were submitted twice to these senior scientists for evaluation and corrective feedback. Results from data safety and monitoring board’s 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.

**Adverse Events**

Participants were monitored for the following adverse events (AE):

- Exacerbation of post-concussion symptoms defined as elevation of symptom score or symptom severity as measured by the post-concussion checklist.
- Increase in frequency or intensity of pre-existing medical conditions reported by the participant.
- Medical condition detected or diagnosed after the intervention.

The grading scale for evaluating adverse event seriousness was classified as: mild (easily tolerated, causing minimal discomfort), moderate (sufficiently discomforting to interfere with every day activities), and severe (prevents normal every day activities). The relationship of adverse events to study interventions was defined as follows: a) unrelated (there is no association between the study intervention and the reported event), b) related (a definite causal relationship exists between the event and the study, and other conditions (concurrent illness, progression of disease or concomitant medication use do not appear to explain the event), or c) cannot be ruled out (the event might be related to the intervention, but could also have been produced by other factors).

Exacerbation of post-concussion symptoms during the intervention period above individual baseline scores by one standard deviation or more was considered a moderate adverse event and 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 the medical study monitor. Standard deviations were obtained from existing normative data on the post-concussion symptom checklist (Lovell et al., 2006)

**Statistical Approach**

Sample size was based on recommendations from the literature to include at least 12 participants per intervention arm for a pilot study (Burrell, 2004; Julious, 2005; Van Belle, 2011). In order to account for participant attrition, intended enrollment was 15 per exercise group. No interim analyses were completed. Data were analyzed under the intent-to-treat principle. Although the purpose for specific aims 1 and 2 are largely descriptive in nature, inferential statistics were performed to identify potential patterns and associations in subgroups and outcomes that may be relevant to larger studies. The significance of change from pre- to post-intervention was examined via analysis of covariance (ANCOVA), which controls for baseline (pre-intervention) performance in a given outcome and is considered superior to repeated measures analyses which do not appropriately address covariance structure in serial measurement (Pocock, Assmann, Enos, & Kasten, 2002). Covariates were limited to 2 per model, and sex was frequently included since this variable was used in group stratification. Because the sample size does not provide sufficient power to detect significant differences for most outcomes, effect sizes are also interpreted. Adjustments for multiple comparisons were made using Sidak correction (Benjamini & Hochberg, 1995). All statistical analyses were completed using SPSS statistical software (Corp, 2016)
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<th>Description</th>
<th>Outcome</th>
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<td>Attention span for remembering digit strings.</td>
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<td>(D. Wechsler, 1997)</td>
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<td>Paced Auditory Serial Addition Test (PASAT) (Gronwall &amp; Sampson, 1974)</td>
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<td>Processing speed</td>
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<td>Speeded number sequencing</td>
<td>Total time to completion</td>
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<td>Measure of contextual verbal memory</td>
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<td>Total errors (perseverative and non-perseverative)</td>
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<td>Controlled Oral Word Association (COWA) (Benton, 1969)</td>
<td>Verbal fluency to alphabet letter (e.g., C,F,L).</td>
<td>Total correct exemplars</td>
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Figure 2-1. Study overview with outcomes and measurement time points.
CHAPTER 3
RESULTS

Recruitment and Adherence

Study recruitment began in February 2014 and lasted until accrual goals were met in September 2016. Data collection concluded in December 2016. Participants’ time in the study is presented in Table 3-1. Attrition rates for participants who began the intervention were 7.7% for the aerobic exercise group and 0% for the non-aerobic exercise and non-injured groups. Attrition for the aerobic group was due to a single participant who experienced an adverse event, which is detailed further in the adverse events section below.

Participant Characteristics

At baseline, participant demographic characteristics were relatively evenly matched across groups. See Table 3-2 for demographic and injury characteristics for the participant groups. No distribution differences across groups were found regarding sex, $\chi^2(2, N = 36) = 0.44, p = .80$, or age $F(2, 33) = 1.81, p = .18$. The racial/ethnic makeup of the sample was predominately white (64%), and minorities were represented in all groups. The large majority of participants was highly educated and had completed at least 2 years of college study. No significant differences in educational attainment were present, $F(2, 33) = .54, p = .59$. Regarding baseline levels of aerobic fitness (3-minute step test), groups did not differ, $F(2, 18.27) = .84, p = .45$, and performance was in the average range or better for all groups based on age and sex.

Self-reported hours of non-sedentary activity, $F(2, 32) = .13, p = .88$ was also similar across groups. Average self-reported alcohol use was commensurate across the groups with the large majority of participants in each group reporting typical weekly
alcohol usage in the 0 to 2 drink range. The self-reported average hours of sleep per night was consistent across groups, $F(2, 33) = .22, p = .80$ and fell within the recommended range (7 to 9 hours) for young adults by the National Sleep Foundation (Hirshkowitz, 2015). For the MOS sleep problems index 2, there was no significant main effect of group, $F(2, 26.08) = 26.08$, $p = .05$, but the significance level was borderline. Further examination of Sidak-adjusted post-hocs showed that the non-aerobic group reported more sleep problems compared to non-injured controls at pre-intervention ($p = .06$). Parameter estimates demonstrated that the non-aerobic group scored 16 points higher (worse) on average than the non-injured group ($p = .02$) and the aerobic group scored approximately 8 points higher ($p = .26$) than the non-injured group. Few participants reported a positive history of psychiatric diagnosis (including depression, anxiety, or other psychiatric disorder), and participants who did were evenly distributed across groups, (Fisher’s exact test) $p = .84$.

When comparing the mTBI participant groups on injury characteristics at pre-intervention, no significant differences were detected between the aerobic and non-aerobic groups for the following outcomes: days elapsed since injury on intervention day 1, $t(24) = 1.46$, $p = .16$, number of participants who sustained LOC, (Fisher’s exact test) $p = .21$, duration of LOC, $t(18) = -.40, p = .70$, and estimated symptom score, $t(24) = .73, p = .47$ or symptom severity, $t(24) = .58, p = .57$, within 24 hours after injury.

**Missing Data**

Two participants suffered a second concussion in the period between post-intervention and follow-up. The first occurred in the context of playing recreation-league rugby and the second was from a low-speed bicycle collision with a motor vehicle.
Therefore, their three-month follow up data is excluded due to interference from the second injury. For the BDNF analyses, a total of three extreme outliers defined as >4 standard deviations above the mean (one each from the aerobic, non-aerobic, and non-injured groups) were identified and removed from the analyses. Their abnormally high values in reference to the rest of the sample suggest that platelet-removal procedures were likely sub-optimal in these samples. Other missing data were present in some outcomes, but at low frequency (less than two data points per variable), so systematic missingness was not examined. As a result, missing data were treated as missing at random.

**Outcomes and Estimation**

**Symptom Report**

Symptom score and symptom severity were compared by groups prior to entering the study (pre-intervention). A one-way non-parametric ANOVA (Kruskal-Wallis) test was used to examine group differences. For symptom score and severity, group means were not significantly different, $H(2) = 3.64, p = .16$ (symptom score), $H(2) = 3.89, p = .14$, nor were group medians using the Jonckheere-Terpstra test, $H(2) = 151.50, p = .06$ (symptom score), $H(2) = 153.50, p = .07$. Although group comparisons were not significant, this study was not powered to detect statistically meaningful changes. The variation in the aerobic (symptom score, $M = 6.3, SD = 6.8$; symptom severity, $M = 11.5, SD = 17.7$) and non-aerobic (symptom score, $M = 5.5, SD = 6.1$; symptom severity, $M = 10.8, SD = 14.4$) groups was greater than non-injured participants and their means fell more than a standard deviation higher than the non-injured group (symptom score, $M = 5.5, SD = 6.1$; symptom severity, $M = 2.3, SD = 3.2$), suggesting the mTBI participants did report more symptoms at baseline than non-injured participants. No differences in
sex were present for symptom reporting at pre-intervention (symptom score, \( p = .33 \); symptom severity \( p = .31 \)). When comparing the current sample to normative data from Chin, Nelson, Barr, McCrory, and McCrea (2016), mTBI participants in this study reported higher symptom severity than concussed athletes at 8 days (\( M = 7.44, SD = 14.32 \)) and 15 days (\( M = 3.16, SD = 6.95 \)) post-injury.

**Symptom Response to Single Session Exercise**

A two-way ANCOVA was conducted on log-transformed outcomes (due to positive skew) with participant group and sex as predictors and covarying for pre-exercise symptom ratings to determine meaningful change in symptom score and symptom severity after a single session of exercise on intervention day 1. For symptom score, there was no significant main effect of group on symptom score \( F(2, 28) = .12, p = .89, \eta^2 = .002 \) or symptom severity, \( F(2, 28) = .05, p = .95, \eta^2 = <.001 \), and the effect sizes were negligible. There was no significant main effect of sex or an interaction for either outcomes. Since outcome variables remained fairly skewed despite transformations, symptom response to exercise was dichotomized and examined through Fisher’s exact test to account for small sample size. Symptom ratings were coded as either an increase (1) or decrease (0) from pre to post-exercise session. Results are presented in Table 3-3 and showed no significant differences between groups for either symptom score, \( p = 1.0 \), or symptom severity, \( p = .47 \).

**Pre-Post Analyses**

A two-way ANCOVA was conducted to determine change in reported symptom score and severity from pre- to post-intervention, covarying for pre-intervention symptom ratings. Additional covariates were explored including aerobic fitness (3-minute step test), average hours of sleep for the week before post-intervention, and
seconds of LOC in a stepwise manner, but none were significant and thus not included in the final models. Sex was also included as a main effect. Analyses were performed on Blom-transformed outcomes. For both symptom score and severity, the homogeneity of regression assumption was met. There was no main effect of group on post-intervention symptom score, $F(2, 28) = 1.54, p = .23, \eta^2 = .04$, or symptom severity, $F(2, 28) = 1.61, p = .22, \eta^2 = .04$, indicating no meaningful change in symptoms for either the aerobic or non-aerobic groups, even when compared to the non-injured participants. There was a significant, moderate main effect of sex for both symptom score, $F(1, 28) = 13.19, p = .001, \eta^2 = .19$, and symptom severity, $F(2, 28) = 12.08, p = .002, \eta^2 = .16$, such that females experience a greater relative decline in symptom experience from pre- to post-intervention (see Figure 3-2). This effect appears especially true for the mTBI participants, although the sex by group interaction was not significant in the model nor did it have a meaningful effect size.

The number of participants who experienced an increase in post-intervention symptom score relative to their pre-intervention symptom score was also examined (see Table 3-4). For the three mTBI participants who experienced an increase in symptom score from pre- to post-intervention, the average increase was 3.67 (SD = 4.62). Fisher’s exact test revealed no significant differences between groups in the number of participants who had greater symptom scores at post-intervention than at pre-intervention, $p = .58$.

At the 3-month follow-up, no significant differences were found between the aerobic ($Mdn = 0$) and non-aerobic ($Mdn = .92$) intervention groups in symptom score, $U = .33, p = .57$ or symptom severity $U = .33, p = .57$. Nor were there any significant
differences between sex on either measure, \( p = .73 \) and \( p = .61 \) respectively. Symptoms reported by the mTBI groups at 3-month follow up (symptom score, \( M = 0.88, SD = 1.73 \); symptom severity, \( M = 1.00, SD = 2.17 \)) were similar to the baseline symptom experience in the non-injured participants at pre-intervention (symptom score, \( M = 2.20, SD = 2.90 \); symptom severity, \( M = 2.30, SD = 3.16 \)), indicating that both groups of mTBI participants experienced full resolution of symptoms by 3 months after their injury.

**Mood**

At pre-intervention, MANOVA was used to examine the differences between groups on BDI-II raw score and STAI State anxiety. Outcomes were Blom-transformed due to non-normality. Sex was included as an additional predictor. MANOVA results using Pillai’s trace, indicated no significant differences between groups or sex on depression or anxiety score at pre-intervention, \( V = .13, F(4, 60) = 1.02, p = .41 \).

Average depression score (BDI-II) for the aerobic group (\( M = 13.69, SD = 15.27 \)) fell above the clinical cut-off for mild depression (9) and was twice as high as either the non-aerobic (\( M = 6.85, SD = 4.76 \)) or non-injured groups (\( M = 6.50, SD = 5.26 \)). Approximately 2 points of the aerobic group mean could be attributed to a single participant. Without this outlier, the aerobic group mean was 11.75 (\( SD = 14.17 \)). State anxiety scores were relatively uniform across the aerobic (\( M = 47.77, SD = 11.51 \)), non-aerobic (\( M = 51.92, SD = 9.32 \)), and non-injured (\( M = 46.90, SD = 5.38 \)) groups at pre-intervention and fell within expected clinical ranges.

Separate two-way ANCOVAs were conducted on the transformed outcomes (post-intervention depression and anxiety) to determine change in mood ratings from pre- to post-intervention, covarying for pre-intervention ratings. For depression, ANCOVA results showed no main effect of group, \( F (2, 26) = 1.73, p = .20, \eta^2 = .06 \), and
the effect size was small, suggesting that the group assignment had little impact on depression change. Sex was examined as a covariate but neither its main effect nor its interaction with group was significant. Overall, depression scores decreased from pre- to post-intervention, but the rate of change did not significantly differ by group (see Figure 3-3). Graphical analysis shows that males in the non-aerobic group were the only ones who experienced an increase in depressive symptoms at post-intervention. For anxiety, ANCOVA results showed no significant main effect of group on state anxiety change from pre- to post-intervention, $F(2, 28) = .25, p = .76, \eta^2 = .02$, and the effect size was small. There was no significant main effect of sex in the model.

At 3-month follow-up, two separate non-parametric t-tests were used to compare the mTBI groups on mood ratings. For state anxiety, the group means for aerobic exercise ($M = 40.00, SD = 9.38$) and non-aerobic exercise ($M = 41.46, SD = 7.61$) were not significantly different from each other, $U = 1.33, p = .25$. For depression results also showed no significant differences between the aerobic exercise ($M = 3.2, SD = 3.71$) or the non-aerobic ($M = 4.23, SD = 6.22$) groups, $U = .01, p = .95$. When compared to non-injured participants’ mood ratings at baseline, the mTBI participants’ ratings for depression and anxiety at follow-up fell well within the non-injured range.

**Sleep**

Pre-intervention sleep quality as measured by the MOS is reported in table 3-2 above and described in participant characteristics. At pre-intervention, there was a moderate effect of group, $F(2, 30) = 2.78, p = .08, \eta^2 = .14$, such that mTBI groups (aerobic, $M = 25.95, SD = 20.37$; non-aerobic, $M = 34.44, SD = 14.52$) scored higher than the non-injured groups ($M = 18.36, SD = 7.92$) on the sleep problems index. Over
the intervention week, participants in the aerobic ($M = 6.90$, $Mdn = 7.30$, $SD = 1.29$), non-aerobic ($M = 7.24$, $Mdn = 7.14$, $SD = .84$), and non-injured groups ($M = 7.56$, $Mdn = 7.96$, $SD = 1.24$) reported or were monitored as sleeping a similar average number of hours, $F(2, 29) = 1.03$, $p = .37$, $\eta^2 = .001$.

Pre- to post-intervention change in sleep problems (MOS Sleep Problems Index 2) was examined via ANCOVA on Blom-transformed outcomes, controlling for pre-intervention sleep problems and hours of average sleep during the intervention. Sex was also included as a main effect along with a sex by group interaction. Results indicated a small effect of group $F(2, 26) = .85$, $p = .44$ (group), $\eta^2 = .03$, and a smaller effect of sex $\eta^2 = .01$ on pre- to post-intervention change in sleep problems, neither main effect reached the level of significance. Graphical analysis (see Figure 3-4), and parameter estimates (see Table 3-6) show a 5.25 point greater decrease in relative pre-to post-intervention change in the aerobic group compared to the non-injured group and less than a 1 point greater decrease in the non-aerobic group compared to the non-injured group, suggesting possible sleep benefits for aerobic exercise versus non-aerobic exercise. This appears especially true for females in the non-aerobic group, although this finding did not approach significance in the model.

At 3-month follow-up, an ANCOVA was conducted controlling for post-intervention sleep problems which revealed no significant differences for either group, $F(1, 17) = .33$, $p = .57$, $\eta^2 = .01$, or sex, $F(1, 17) = .90$, $p = .36$, $\eta^2 = .04$. The effect size of sex slightly increased from the pre- to post-intervention analysis; however, the effect size of group declined indicating the impact of group as a predictor of change from post-intervention to 3-month follow up was even less than for pre- to post-intervention.
Participants in the mTBI groups (aerobic, $M = 15.31$, $SD = 9.08$; non-aerobic, $M = 16.96$, $SD = 11.12$) all scored within close range of the non-injured group at pre-intervention ($M = 18.36$, $SD = 7.92$), indicating a full return to typical sleep functioning by 3 months post-injury.

**Postural Stability**

A two-way ANOVA was conducted on total mBESS and single stance scores at pre-intervention using Blom-transformed outcomes. For mBESS total score at pre-intervention, the main effects of group $F(2, 30) = 1.21$, $p = .31$, $\eta^2 = .06$, and sex were not significant; however, there was a group by sex interaction with a moderate effect size that approached significance, $F(2, 30) = 2.94$, $p = .07$, $\eta^2 = .15$. Sidak-adjusted post-hoc follow-ups showed that males in the aerobic group ($M = 1.0$, $SD = 1.0$) performed better than females ($M = 4.33$, $SD = 3.20$), $p = .04$ at pre-intervention, but females’ total mBESS performance was comparable to the other groups at pre-intervention (see Figure 3-5).

Two-way ANCOVAs were conducted to assess for pre to post-intervention change in postural stability measures controlling for pre-intervention performance and sex. Results showed no significant group difference in total errors committed, $F(2, 28) = 1.33$, $p = .28$, $\eta^2 = .05$, and the effect size was small, but larger than that of sex ($\eta^2 = .003$), which was also not significant. Regarding the individual stances, only one participant in any group committed an error on the double leg stance (at pre-intervention), so data were not analyzed. For the single leg stance, group remained non-significant, $F(2, 28) = .67$, $p = .52$, $\eta^2 = .03$, and the effect size was small, comparable to that of sex ($\eta^2 = .02$). For the tandem stance, group was not significant, $F(2, 28) = .67$, $p = .52$, but sex approached significance, $F(2, 28) = 3.11$, $p = .09$ and the
small to medium effect size for sex ($\eta^2 = .07$) was larger than that of group ($\eta^2 = .03$). The sex by group interaction was not significant, indicating that the approximate main effect of sex is independent of group assignment. In general, females appeared to make slightly more errors than males on the tandem stance.

At 3-month follow up, group differences remained non-significant for total errors when controlling for post-intervention performance, $F(1, 19) = .05, p = .82, \eta^2 = .002$. For the single leg stance, group differences remained non-significant, $F(1, 20) = .45, p = .51$. The relative effect size of group ($\eta^2 = .02$) compared to sex ($\eta^2 = .05$) appeared to decrease at follow-up, suggesting that group had an even smaller effect on single leg stance performance at post-intervention to 3-month follow up than from pre- to post-intervention. For the tandem leg stance, group remained non-significant $F(1, 20) = 1.95, p = .18$. Group had a small to moderate effect size on tandem stance performance ($\eta^2 = .08$) and sex had a very small effect size ($\eta^2 = .01$), meaning group assignment was more important for predicting tandem stance performance at 3-month follow up than sex. The aerobic group improved more on the tandem stance relative to the non-injured group from post-intervention to 3-month follow up.

**Cognition**

Group differences in neurocognitive performance at pre-intervention were investigated by MANOVA using Blom transformed neuropsychological index scores. There was no significant effect of group on neurocognitive performance (Pillai’s Trace), $V = .14, F(8, 62) = .59, p = .78$. Separate univariate ANOVAs on the outcome variables demonstrated non-significant group effects on attention, $F(2, 33) = .32, p = .73, \eta^2 = .02$, processing speed, $F(2, 33) = .07, p = .07, \eta^2 = .004$, memory $F(2, 33) = .24, p = .79, \eta^2$.
= .01, or executive functioning $F(2, 33) = 2.08, p = .14, \eta^2 = .11$. However, the effect size for executive functioning was moderate, and parameter estimates indicated that the mTBI participants performed worse on this index compared to the non-injured participants (aerobic exercise, $B = -.78$, non-aerobic exercise, $B = -.24$).

Pre- to post-intervention differences in neurocognitive performance were analyzed via two-way ANCOVAs controlling for pre-intervention neurocognitive performance. Sex was also included as an additional predictor. For attention, group was not a significant predictor for pre- to post-intervention change, $F(2, 28) = 1.19, p = .32$, $\eta^2 = .02$, and the effect size was small. For processing speed, the main effect of group remained non-significant, $F(2, 28) = .70, p = .50, \eta^2 = .02$ with a similar effect size. For memory, group differences were non-significant, $F(2, 27) = 2.15, p = .13, \eta^2 = .09$, but the effect size was medium. Parameter estimates show that both the mTBI groups had more improvement in memory performance from pre- to post-intervention than the non-injured groups did, likely reflecting continued resolution of mild residual memory weakness from their mTBIs, although the degree of improvement in memory for the aerobic group appeared somewhat attenuated compared to the non-aerobic group.

Baseline aerobic conditioning (3-minute step test) was added as a covariate to the model and bordered on significant with a moderate effect on memory change, $F(1, 27) = 3.64, p = .07, \eta^2 = .09$, such that better baseline aerobic fitness at pre-intervention predicted more improvement in memory performance. Notably, baseline aerobic fitness was not a significant covariate for any of the other neurocognitive composites, although it approached significance for attention ($p = .08$) and accounted for an equivalent amount of variance in the model as group.
For executive functioning, group differences were not significant and the overall effect size was small to medium, $F(2, 28) = 1.85, p = .18, \eta^2 = .07$. The main effect of sex was significant, $F(2, 28) = 5.31, p = .03, \eta^2 = .10$ with a moderate effect size. Parameter estimates showed that the non-aerobic exercise group had lower relative change in executive functioning performance from pre- to post-intervention and that females across groups had decreased trajectory of improvement from pre- to post-intervention.

Reliable change analyses for neurocognitive composite scores and individual measures are summarized in Table 3-7. Neither the aerobic nor non-aerobic groups demonstrated reliable change in test re-test performance based on the 95% confidence intervals predicted from the non-injured group, consistent with ANCOVA results.

**BDNF**

Basal circulating levels of BDNF in serum and platelet-free plasma were examined at intervention day 1 (before exercise). An exploratory two-way ANCOVA was run with injury status and sex as predictors and multiple covariates (mood, memory, symptom severity, and baseline aerobic fitness) theoretically chosen based on previous literature demonstrating relationships with BDNF (Griffin et al., 2011; Martinowich & Lu, 2008; Yamada, Mizuno, & Nabeshima, 2002). The sleep problems index 2 was retained as a covariate in the final model due to the high amount of variance explained. Results from the two-way ANCOVA (with injury status and sex as predictors) showed no significant main effect of injury status, $F(1, 31) = .003, p = 0.10, \eta^2 = <.001$ or sex $F(1, 31) = .65, p = 0.43, \eta^2 = .02$ on resting concentration of BDNF in serum. However, sleep problems was a significant covariate and showed a moderate to large effect such that
higher scores (poorer sleep) at pre-intervention predicted lower circulating BDNF concentration in serum, $F(1, 31) = .6.73, p = .01, \eta^2 = .17$, (see Figure 3-7). This correlation remained significant when examining separate regressions lines for mTBI ($p = .04$) and non-injured groups ($p = .01$).

BDNF concentration in platelet-free plasma at intervention day 1 was also examined via two-way ANCOVA. There was a sex by injury status interaction that approached significance, $F(1, 31) = 2.91, p = 0.01, \eta^2 = .08$ and had a small to medium effect. Females in the non-injured group demonstrated lower basal concentration of BDNF in platelet-free plasma than females in the mTBI group (See Figure 3-8). Sleep problems explained very little variance in the outcome, and was not retained in the model. However, symptom severity rating at pre-intervention was included as a covariate and was significantly related to BDNF concentration in platelet-poor plasma at intervention day 1 (regardless of injury status), $F(1, 31) = 6.34, p = 0.02, \eta^2 = .16$. The covariate had a moderate effect size such that greater symptom severity at pre-intervention was related to lower basal BDNF concentration in platelet-free plasma. The sex by injury status interaction neared significance ($p = .11$) and had a small to moderate effect size ($\eta^2 = .07$). Figure 3-8 shows that females with mTBI ($M = 372.37, SD = 407.30$) appeared to have higher basal concentration of BDNF in platelet-free plasma than males with mTBI ($M =198.48, SD = 192.57$) and non-injured participants without mTBI (total, $M = 236.13, SD = 235.04$).

Acute BDNF response to exercise on intervention day 1 in both serum and platelet-free plasma was investigated through ANCOVA, covarying for pre-exercise concentration. For serum, there was no effect of exercise type, $F (1, 31) = .30, p = .59,$
\( \eta^2 = .008 \), or sex \( F(1, 31) = .12, p = .73, \eta^2 = .003 \), on post-exercise serum BDNF concentration, and the effect size was very small. A separate ANCOVA examining injury status independent of exercise type showed a small to medium interaction effect for sex by injury status that approached significance, \( F(1, 29) = 3.49, p = .07, \eta^2 = .08 \).

Graphical analysis (see figured 3-8) demonstrated that this trend was likely due to a notable decrease in serum BDNF for non-injured females relative to the other groups.

For BDNF platelet-poor plasma change in response to exercise, the type of exercise (aerobic vs. non-aerobic) had a larger effect size than for serum change (\( \eta^2 = .07 \)), but it still remained non-significant in the model, \( F(1, 24.045) = 1.98, p = .17 \). The aerobic exercise groups experienced an increase of 45% in platelet-free plasma BDNF concentration compared to a 44% decrease in the non-aerobic group, and this effect would likely reach significance in a larger sample size. Notably, males in the non-injured group did not experience an increase in platelet-poor plasma BDNF, but there was no significant sex by injury status interaction, and the effect size was extremely small.

**Adverse Events**

One participant in the aerobic exercise group was withdrawn from the study due to meeting criteria for a moderate adverse event during intervention day 2, which was classified as expected and possibly related to the intervention. On intervention day 1, the participant experienced a 5% increase in symptom score (+1) after exercise and a 12% decrease symptom severity (-9) of symptoms from pre- to post-exercise. On intervention day 2, the participant completed the first 20 minutes of the aerobic exercise session with some complaints of discomfort, but stated that she would like to continue after the standard 5-minute break. Within the first 5 minutes of the second exercise
period, she reported that she felt like she was “blacking out.” Research staff immediately discontinued exercise and initiated medical examination procedures conducted by the CRC nurses. Results showed normal blood pressure and heart rate. Pupils were normal, but nystagmus was detected in both eyes.

The participant continued to develop symptoms including head pain, inability to speak or walk, and dizziness. A cognitive-behavioral trained therapist, who was part of the research staff, administered deep breathing and relaxation techniques, which resulted in participant stabilization and the resolution of all symptoms except for dizziness and headache. A neurological consultation was conducted the following day by the research study medical safety monitor. The examination concluded no neurological deficits and “…soft tissue damage to back of neck, consistent with soft tissue injury from whiplash. Believe that headaches are from muscle spasms from trauma, cervicalgia, leading to migraine. Believe that visual difficulty are due to migraine.” Inspection of MRI scan by neurologist was read as normal with the exception of increased sulcation for age. Although participant indicated the desire to continue with the research study despite her reaction, she was withdrawn per study protocol for exacerbated symptoms and provided with appropriate referrals for medical follow up and mental health providers.

This participant sustained her mTBI during an occupational incident in which she was struck in the back of the head. Participant reported that she did not lose consciousness and underwent neuroimaging following her injury (CT), which was normal. Her recall of symptom severity within the first 24 hours after injury was the highest for any participant ($z = 2.33, p = .02$). Medical history assessed at pre-
intervention was positive for migraines. Sleep problems ($z = 3.01, p < .001$), depression ($z = 3.07, p < .001$), and state anxiety, ($z = 2.74, p < .01$) were all significantly elevated compared to the rest of the study population. Basal BDNF concentration was within normal limits for serum ($z = -.27, p = .79$) and platelet-poor plasma ($z = -.74, p = .46$).

One additional minor adverse event occurred during the study. A blood draw was discontinued due to the participant’s discomfort with needles. This was classified as unrelated to the intervention. Table 3-8 shows the number of participants in each group who experienced an increase in symptom severity from pre- to post-exercise along with statistical comparisons using Fisher’s exact test. The most frequently exacerbated symptoms were fatigue or low energy, dizziness, headache, blurred vision, and pressure in the head.
Figure 3-1. Enrollment and allocation flow diagram. The numbers of participants for each group who were randomly assigned (mTBI group only), received intended treatment, and analyzed for pre- to post-intervention change are presented per CONSORT reporting (Schulz, Altman, Moher, & Group, 2010)
Table 3-1. Time in study for mTBI participants

<table>
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<th>Time in study</th>
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Table 3-2. Demographic information and injury characteristics by participant group

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<td>Hispanic/Latino</td>
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<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Mixed Race</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Asian/Pacific</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Years of Education</td>
<td></td>
<td>14.5 (1.9)</td>
<td>14.9 (1.9)</td>
<td>14.2 (2.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14.4 (1.5)</td>
</tr>
<tr>
<td>Baseline Aerobic Fitness</td>
<td>3-minute step test</td>
<td>96.7 (20.7)</td>
<td>90.8 (12.6)</td>
<td>98.1 (18.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>102.6 (30.0)</td>
</tr>
<tr>
<td>Average hours of non-sedentary activity (PAS)</td>
<td>6.7 (2.3)</td>
<td>6.9 (2.3)</td>
<td>6.7 (2.9)</td>
<td>6.4 (2.1)</td>
</tr>
<tr>
<td>Alcohol Consumption</td>
<td>0-2 Drinks/Week</td>
<td>27</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>3-9 Drinks/Week</td>
<td>6</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt;9 Drink/Week</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sleep</td>
<td>Average hours of sleep per night (PAS)</td>
<td>7.5 (0.9)</td>
<td>7.6 (1.0)</td>
<td>7.6 (0.9)</td>
</tr>
<tr>
<td></td>
<td>Sleep Problems Index 2 (MOS)</td>
<td>26.9 (16.5)</td>
<td>26.0 (20.4)</td>
<td>34.4 (14.5)</td>
</tr>
<tr>
<td></td>
<td>Psychiatric history</td>
<td>5 (13.9)</td>
<td>1 (7.7)</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td></td>
<td>(n)(%)</td>
<td></td>
<td></td>
<td>2 (20)</td>
</tr>
<tr>
<td>mTBI Characteristics</td>
<td>Days since injury at intervention day 1</td>
<td>19.1 (3.7)</td>
<td>20.2 (3.9)</td>
<td>18.1 (3.3)</td>
</tr>
<tr>
<td></td>
<td>Positive LOC (n) (%)</td>
<td>9 (34.6)</td>
<td>4 (30.8)</td>
<td>5 (38.5)</td>
</tr>
<tr>
<td></td>
<td>Total seconds of LOC</td>
<td>22.8 (57.9)</td>
<td>17 (39.3)</td>
<td>27.5 (71.2)</td>
</tr>
<tr>
<td></td>
<td>24 hr injury symptom score</td>
<td>14.0 (5.3)</td>
<td>13.5 (5.5)</td>
<td>14.5 (5.3)</td>
</tr>
<tr>
<td></td>
<td>24 hr injury symptom severity</td>
<td>43.4 (30.0)</td>
<td>42.9 (33.8)</td>
<td>44 (26.2)</td>
</tr>
</tbody>
</table>

Note: Values are presented in mean (SD) form unless noted otherwise. Alcohol consumption represents reported average weekly drinks consumed per week. LOC, Loss of Consciousness
Table 3-3. Cross-tabulation of symptom change from pre- to post-exercise on intervention day 1 by group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group</th>
<th>Decrease or no change</th>
<th>Increase</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom score</td>
<td>Aerobic exercise</td>
<td>10</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Non-aerobic exercise</td>
<td>8</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Non-injured</td>
<td>7</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Symptom severity</td>
<td>Aerobic exercise</td>
<td>11</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Non-aerobic exercise</td>
<td>8</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Non-injured</td>
<td>6</td>
<td>4</td>
<td>10</td>
</tr>
</tbody>
</table>
Figure 3-2: Graph of sex differences by group for symptom severity changes from pre- to post-intervention.
Table 3-4. Cross-tabulation of participants who experienced symptom score increase from pre- to post-intervention by group

<table>
<thead>
<tr>
<th>Group</th>
<th>Decrease or no change</th>
<th>Increase</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic exercise</td>
<td>10</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Non-aerobic exercise</td>
<td>12</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Non-injured</td>
<td>7</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>
Figure 3-3. Change in depression and anxiety ratings by group and sex.
Table 3-5. Mood changes from post-intervention to 3 month follow up

<table>
<thead>
<tr>
<th>Mood outcome</th>
<th>Aerobic exercise</th>
<th>Non-aerobic exercise</th>
<th>Total</th>
<th>Fisher's exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI-II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease or no change</td>
<td>8</td>
<td>11</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>1.00</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>13</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>STAI State</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease or no change</td>
<td>5</td>
<td>11</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>.17</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>13</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>
Figure 3-4. Change in sleep ratings by group and sex.
Figure 3-5. Group performance on postural stability. Bars represent average total errors committed broken down by single and tandem stances. Errors bars represent bootstrapped 95% confidence intervals of the mean.
<table>
<thead>
<tr>
<th>Outcome</th>
<th></th>
<th>Pre- to post-intervention</th>
<th></th>
<th>Post-intervention to follow up</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aerobic</td>
<td>Non-aerobic</td>
<td>Group</td>
<td>Aerobic</td>
<td>Group</td>
</tr>
<tr>
<td></td>
<td>exercise</td>
<td>exercise</td>
<td>effect size</td>
<td>exercise</td>
<td>effect size</td>
</tr>
<tr>
<td></td>
<td>B&lt;sup&gt;a&lt;/sup&gt;</td>
<td>95% Cl&lt;sup&gt;c&lt;/sup&gt;</td>
<td>η&lt;sup&gt;2&lt;/sup&gt;</td>
<td>B&lt;sup&gt;b&lt;/sup&gt;</td>
<td>95% Cl&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Symptom score</td>
<td>-2.25</td>
<td>(-6.9, 2.38)</td>
<td>-0.68</td>
<td>(-4.9, 3.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Symptom severity</td>
<td>-3.47</td>
<td>(-12.82, 51)</td>
<td>2.16</td>
<td>(-15.06, 2.85)</td>
<td>0.04</td>
</tr>
<tr>
<td>BDI-II</td>
<td>1.55</td>
<td>(-2.92, 5.79)</td>
<td>1.14</td>
<td>(-4.57, 5.94)</td>
<td>0.06</td>
</tr>
<tr>
<td>STAI State</td>
<td>1.09</td>
<td>(-4.14, 6.76)</td>
<td>3.39</td>
<td>(-1.75, 9.46)</td>
<td>0.02</td>
</tr>
<tr>
<td>MOS Sleep Problems</td>
<td>-5.93</td>
<td>(-20.59, 7.66)</td>
<td>-1.47</td>
<td>(-15.24, 12.30)</td>
<td>0.03</td>
</tr>
<tr>
<td>Index 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mBESS Single Stance</td>
<td>.91</td>
<td>(-1.91, 1.99)</td>
<td>1.23</td>
<td>(-1.2, 2.59)</td>
<td>0.03</td>
</tr>
<tr>
<td>mBESS Tandem Stance</td>
<td>.27</td>
<td>(-2.44, 2.45)</td>
<td>-.41</td>
<td>(-2.79, .85)</td>
<td>0.03</td>
</tr>
<tr>
<td>mBESS Total</td>
<td>1.27</td>
<td>(-1.78, 3.78)</td>
<td>.86</td>
<td>(-2.43, 3.42)</td>
<td>0.05</td>
</tr>
<tr>
<td>Attention index</td>
<td>-.04</td>
<td>(-.38, .32)</td>
<td>.29</td>
<td>(.05, .70)</td>
<td>0.02</td>
</tr>
<tr>
<td>Processing speed index</td>
<td>-.07</td>
<td>(-.63, .48)</td>
<td>-.15</td>
<td>(-.47, .23)</td>
<td>0.02</td>
</tr>
<tr>
<td>Memory Index</td>
<td>.46</td>
<td>(-.24, 1.71)</td>
<td>.61</td>
<td>(-.21, 1.76)</td>
<td>0.09</td>
</tr>
<tr>
<td>Executive functioning</td>
<td>.25</td>
<td>(-.29, 1.00)</td>
<td>-.10</td>
<td>(-.54, .55)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Note. <sup>a</sup>Parameter estimates derived from ANCOVAs conducted on non-transformed variables and use the non-injured group as the referent. <sup>b</sup>Non-aerobic exercise group is the referent. <sup>c</sup>Bootstrapped 95% confidence interval. <sup>d</sup>Eta squared derived from transformed ANCOVA analyses discussed above.
Figure 3-6. Pre- and post-intervention z-scores for neurocognitive composites.
Table 3-7. Test-retest, post-intervention scores, and reliable change confidence intervals for mTBI groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>Test-retest&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Actual score (M, SD)</th>
<th>z-score&lt;sub&gt;diff&lt;/sub&gt;</th>
<th>Predicted score 95% confidence interval</th>
<th>Actual score (M, SD)</th>
<th>z-score&lt;sub&gt;diff&lt;/sub&gt;</th>
<th>Predicted score 95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M (SD)</td>
<td></td>
<td></td>
<td>M (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention index</td>
<td>.86</td>
<td>.51 (.59)</td>
<td>-.31</td>
<td>-.02 – 1.24</td>
<td>.65 (.38)</td>
<td>.06</td>
<td>0 – 1.26</td>
</tr>
<tr>
<td>Digit Span</td>
<td>.68</td>
<td>.33 (1.10)</td>
<td>-.44</td>
<td>-.75 – 2.03</td>
<td>.90 (.98)</td>
<td>.38</td>
<td>-.76 - 2.02</td>
</tr>
<tr>
<td>PASAT</td>
<td>.91</td>
<td>.85 (.63)</td>
<td>-.29</td>
<td>.26 - 1.64</td>
<td>.78 (.63)</td>
<td>-.14</td>
<td>.14 – 1.52</td>
</tr>
<tr>
<td>Ruff 2 &amp; 7, Accuracy</td>
<td>.83</td>
<td>.33 (.41)</td>
<td>.12</td>
<td>-.75 - 1.29</td>
<td>.33 (.43)</td>
<td>-.17</td>
<td>-.60 - 1.44</td>
</tr>
<tr>
<td>Processing speed index</td>
<td>.92</td>
<td>1.16 (.61)</td>
<td>-1.00</td>
<td>.95 – 1.81</td>
<td>1.12 (.61)</td>
<td>-.23</td>
<td>.74 – 1.6</td>
</tr>
<tr>
<td>DKEFS, Number Sequencing</td>
<td>.81</td>
<td>1.22 (.52)</td>
<td>-.87</td>
<td>.73 - 2.49</td>
<td>1.00 (.36)</td>
<td>-.18</td>
<td>.20 – 1.96</td>
</tr>
<tr>
<td>Ruff 2 &amp; 7, Speed</td>
<td>.83</td>
<td>.97 (1.11)</td>
<td>-.25</td>
<td>-.04 - 2.28</td>
<td>1.09 (1.05)</td>
<td>.29</td>
<td>-.24 - 2.08</td>
</tr>
<tr>
<td>Digit Symbol Coding</td>
<td>.83</td>
<td>1.21 (.78)</td>
<td>-.69</td>
<td>.76 - 2.14</td>
<td>1.28 (.90)</td>
<td>-.69</td>
<td>.83 - 2.21</td>
</tr>
<tr>
<td>Memory index</td>
<td>.87</td>
<td>.66 (.55)</td>
<td>-.41</td>
<td>.21 – 1.35</td>
<td>1.11 (.57)</td>
<td>.79</td>
<td>.31 – 1.45</td>
</tr>
<tr>
<td>CVLT</td>
<td>.85</td>
<td>-.46 (1.16)</td>
<td>.35</td>
<td>-2.24 - .78</td>
<td>.23 (1.35)</td>
<td>.77</td>
<td>-1.87 – 1.15</td>
</tr>
<tr>
<td>Logical Memory II Visual</td>
<td>.69</td>
<td>.72 (.75)</td>
<td>-.46</td>
<td>-.25 - 1.99</td>
<td>.90 (.82)</td>
<td>.14</td>
<td>-.30 - 1.94</td>
</tr>
<tr>
<td>Reproductions II</td>
<td>.54</td>
<td>1.72 (.78)</td>
<td>-.72</td>
<td>.93 - 3.43</td>
<td>2.21 (.35)</td>
<td>.08</td>
<td>.91 - 3.41</td>
</tr>
<tr>
<td>Executive functioning index</td>
<td>.71</td>
<td>.71 (.51)</td>
<td>.16</td>
<td>-.35 – 1.61</td>
<td>.73 (.20)</td>
<td>-.24</td>
<td>-.13 – 1.83</td>
</tr>
<tr>
<td>DKEFS, Letter-Number Sequencing</td>
<td>.78</td>
<td>1.06 (.31)</td>
<td>-.37</td>
<td>.68 - 1.62</td>
<td>.84 (.50)</td>
<td>.12</td>
<td>.34 – 1.28</td>
</tr>
<tr>
<td>WCST, Errors</td>
<td>.72</td>
<td>.45 (1.21)</td>
<td>-.80</td>
<td>-.43 – 2.55</td>
<td>1.11 (.60)</td>
<td>-1.33</td>
<td>.63 – 3.61</td>
</tr>
<tr>
<td>Letter Fluency</td>
<td>.59</td>
<td>.61 (.86)</td>
<td>.29</td>
<td>-1.48 - 2.16</td>
<td>.23 (.46)</td>
<td>-.11</td>
<td>-1.49 - 2.15</td>
</tr>
</tbody>
</table>

Note: <sup>a</sup> derived from non-injured group; z-score<sub>diff</sub>: computed from the difference in actual post-intervention score relative to predicted value and 95% confidence intervals.
Figure 3-7. Relationship between resting BDNF serum concentration and sleep problems at pre-intervention.
Figure 3-8. Change in BDNF serum and platelet-free plasma concentrations before and exercise on intervention day 1. Error bars represent standard deviation.
Table 3-8. Frequency and descriptives of symptom severity increase after exercise

<table>
<thead>
<tr>
<th>Intervention day</th>
<th>Aerobic</th>
<th>Non-aerobic</th>
<th>Non-injured</th>
<th>(p)-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>M(SD)</td>
<td>n</td>
<td>M (SD)</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>2.50 (.71)</td>
<td>2</td>
<td>2.00 (1.41)</td>
</tr>
<tr>
<td>2*</td>
<td>3</td>
<td>9.00 (12.17)</td>
<td>2</td>
<td>2.00 (1.41)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>2.00 (2.00)</td>
<td>3</td>
<td>1.00 (.00)</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>1.80 (.84)</td>
<td>1</td>
<td>1.00 (.0)</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>1.00 (.00)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>3.33 (2.52)</td>
<td>1</td>
<td>1.00 (.0)</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>1.00 (.00)</td>
<td>3</td>
<td>2.00 (2.24)</td>
</tr>
</tbody>
</table>

*Adverse event took place on this day that affected a participant in the aerobic exercise group.

Note. \(a\)Fisher’s exact test.
CHAPTER 4
DISCUSSION

Specific Aim 1

Based on the results from this pilot study, the feasibility of administering aerobic exercise via stationary cycling in the post-acute (14-25 days post-injury) period is tentatively favorable with some caveats. Adherence to the study protocol was good for both the aerobic and non-aerobic groups. Attrition rates for the exercise groups were commensurate with or better than typical acceptable rates in clinical trials, which range from 5% to 20%. This was likely due in part to the convenient co-location of the clinical research center with the university campus coupled with the high proportion of participants who were college students.

Feedback from the participants was overwhelmingly positive in that they enjoyed the opportunity for structured exercise. 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. The actual timeline for participant recruitment (20 months) was much longer than the original estimate (12 months). Recruiting from a student health care clinic proved to be successful, but accrual significantly slows in the summer months for this population due to summer breaks. When planning future studies, a multicenter research network should be considered to ensure continual enrollment and improved generalizability. With regard to randomization, stratification based on sex is also recommended due to the noted interaction of sex and several outcome variables including symptom reporting, mood, postural stability, and cognition.
The number and severity of symptoms experienced after the first day of exercise were comparable between mTBI participants who completed aerobic and non-aerobic exercise, and group assignment accounted for very little variance in pre- to post-exercise symptom reporting. When compared to non-injured participants who completed one session of aerobic exercise, the mTBI aerobic exercise group had a similar proportion of individuals who experienced a mild exacerbation in symptom score and severity. The most frequently reported exercise-induced symptoms were headache, blurred vision, and dizziness. Exercise-induced headaches are not uncommon in non-injured individuals, and as many as 1/3 of college students experience some type of exercise-induced headache, most commonly connected to effort or exertion (Williams & Nukada, 1994a, 1994b). Therefore, the aerobic exercise program did not provoke more symptom exacerbation in mTBI patients than would be expected for normal, non-injured population.

The cumulative effect of 7 days of aerobic and non-aerobic exercise resulted in similar pre- to post-intervention changes in symptom report. For both groups, symptom severity decreased over time, probably reflecting continued injury resolution. Exercise assignment did not appear to alter the trajectory of this decrease. However, when examining the interactive effect of sex, females with mTBI (regardless of exercise type) experienced steeper symptom resolution trajectories than males, but the effect size of this potential interaction was negligible in the analysis. Compared to non-injured participants, males with mTBI remained slightly higher in symptom severity after the intervention period, but females with mTBI resolved to severity levels almost identical to the non-injured participants. At 3-month follow-up, there was no appreciable difference
in symptom ratings between the aerobic and non-aerobic groups. Compared to normative values for mTBI symptom reporting over time (Chin et al., 2016), the mTBI participants’ symptom ratings at 3-months indicated full recovery. At the group level, this study did not find any indication that aerobic exercise acutely provoked group-level post-concussion symptoms or that it prolonged expected recovery trajectories after the intervention and at 3-months post-injury.

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 co-morbid with mTBI and presents with similar symptoms (i.e., dizziness and unsteadiness). Whiplash injuries typically feature sprain or strain to cervical musculoligaments, and this injury is thought to impact the vestibular system in different ways than those impairments typically associated with mTBI as a result of disrupted afferent input from cervical receptors and/or chronic cervical pain (Elliott, Jull, Noteboom, & Galloway, 2008; Treleaven, Jull, & Lowchoy, 2005). Treleaven et al. (2005) noted that balance disturbances in the persistent whiplash population occur independently of other relevant factors such as medication, anxiety, and compensation status, unlike in PPCS.

The participant who experienced the adverse event had several other risk factors for PPCS such as clinically elevated post-injury depression, anxiety, sleep disturbances. She also possessed pre-morbid risk factors that may have further complicated post-injury symptom experience included a history of migraines and panic attacks. Taken together, the occurrence of this adverse event raises the possibility that a certain subset
of mTBI patients may have unfavorable reactions to exercise beyond normal, effort-induced headaches. Individual vulnerability to exercise-induced symptom exacerbation may overlap with known risk factors for PPCS. Furthermore, the presence of whiplash injury should be considered in clinical decision-making and monitoring in post-mTBI exercise, because the presence of this type of co-morbidity could complicate etiology and contribute to exercise-induced symptoms.

The effect of exercise group on pre- to post-intervention change in functional outcomes in this study was minimal. For mood, the aerobic exercise group had mildly improved resolution in depression symptoms from pre- to post-intervention compared to the aerobic group, although this trend appeared to be isolated to differences between males in the aerobic group compared to males in the non-aerobic group. Anxiety scores remained relatively steady over time, and there was virtually no effect of group assignment on pre- to post-intervention outcome. Similarly, postural stability was not meaningfully affected by exercise assignment, although there was some indication that the aerobic exercise group may have differentially improved on the tandem stance. Aerobic exercise appeared to mildly enhance the resolution trajectory of sleep problems, and this effect was more prominent for females than for males. This type of exercise has well-documented benefits for sleep and depression (Dunn et al., 2002; Sengul, Ozalevli, Oztura, Itil, & Baklan, 2011), so it is possible that the slight trend in improved sleep and depression noted in this study are attributed to the exercise, but these positive effects are usually observed after several weeks or months of aerobic training.
Comparison of reliable change indices from pre- to post-intervention on attention, processing speed, memory, and executive functioning showed that all groups performed within normal limits when accounting for expected practice effects. Overall, there was some mild evidence for suppression of the practice-effect in the aerobic group compared to the non-aerobic group on all cognitive domains except for executive functioning. This finding may be incidental owing to the small sample size, but it is one of the only areas that indicate any degree of poorer outcome for the aerobic versus non-aerobic groups. Inferential statistics showed that group assignment had minimal value for predicting pre- to post-intervention change in cognition on all domains except for memory. Group assignment had a small to medium effect such that the non-aerobic group showed better change in pre- to post-intervention performance than the aerobic or non-injured groups. However, baseline aerobic fitness level proved more important than group assignment and was significantly predictive in the model.

Participants with better aerobic conditioning at baseline on the 3-minute step test had better improvement in memory performance from pre- to post-intervention. This effect was equally important across groups, and lends indirect support to the theory that exercise-induced plasticity in the brain differentially affects hippocampal functioning (van Praag, Shubert, Zhao, & Gage, 2005), since no other cognitive domains were related to baseline aerobic fitness. Moreover, higher levels of fitness are suspected to have “prehabilitation” advantages for athletes such that individuals with better physical conditioning may recover from mTBI more quickly.

At 3-months post-injury, both the aerobic and non-aerobic exercise groups returned to normal ranges as defined by the non-injured group at pre-intervention on
reported symptoms, anxiety, postural stability, and sleep. For depression, males in the non-aerobic group remained at the same level of severity as their post-intervention measurements, which bordered on the clinical cut off for mild depression, in comparison to the aerobic group, whose depressive symptom further declined to the sub-clinical level. Overall, the timeline of mTBI recovery in this study supports previous research showing resolution of symptoms and normalization of functional performance by 3-4 weeks post-injury and full recovery by 3-months. In this sample, symptom report normalized by the end of the intervention (post-intervention), but depression and sleep problems demonstrated further resolution into the 3-month follow up period. Sleep problems and depression demonstrated the most relative improvement during the intervention and in the interim between post-intervention and 3-months post-injury.

**Specific Aim 2**

The secondary aim of this study was to explore the dynamics of circulating BDNF and its response to exercise in an mTBI population. In general, BDNF concentrations in serum and platelet-poor plasma were not directly associated with injury status. The most profound finding was that poor sleep at pre-intervention predicted lower basal BDNF concentration in serum. This correlation was significant for both non-injured participants and those who had sustained an mTBI. However, for BDNF in platelet-poor plasma, concentration was not related to sleep quality, but rather to symptom severity at pre-intervention. Those participants who endorsed a higher severity of symptoms had lower basal BDNF in platelet-poor plasma, and mTBI participants were more likely to have higher symptom severity levels than non-injured participants. The relationship of basal BDNF concentration in platelet-poor plasma to symptom severity in this study supports the findings of Korley et al. (2016), who reported that acute circulating BDNF is
predictive of TBI severity. Our results suggest that circulating BDNF is related to increased mTBI symptom severity and therefore may be a marker of injury severity in the post-acute period as well.

BDNF concentrations in serum and platelet-poor plasma have been linked to slightly different sources in the body. While both have a direct relationship with brain levels, serum concentration is more highly correlated with BDNF from the central nervous system than plasma (Rasmussen et al., 2009). In this context, serum BDNF appears to be more strongly affected by sleep, which is known to have important effects in the hippocampus, a primary source of BDNF production in the brain. Therefore, the decreased BDNF in serum can reasonably be hypothesized to be due to decreased release from the brain associated with poor sleep (Karege et al., 2005), but the converse may also be true. Faraguna, Vyazovskiy, Nelson, Tononi, and Cirelli (2008) proposed that BDNF may play a causative role in sleep quality such that greater expression of BDNF during wakeful states promotes increased regulation of slow wave activity during sleep. Results from the current study further underscore the importance of sleep after mTBI and connects sleep quality to neurophysiological effects via circulating BDNF. Importantly, both sleep and BDNF have been theorized to play a mediating role in long-term risk for neurodegeneration (Di Meco, Joshi, & Pratico, 2014).

The relationship between BDNF concentration in serum and aerobic exercise is relatively well established (Knaepen, Goekint, Heyman, & Meeusen, 2010), but the expected increase in serum BDNF after acute exercise was not demonstrated in this study for any of the participant groups, including the non-injured participants who completed a single session of aerobic exercise. A number of biological variables such
as diet, time of blood sampling, and menstruation cycle can affect normal individual variation in serum BDNF (Bus et al., 2011; Bus et al., 2012; Lommatzsch et al., 2005), and none of these confounds were controlled for in the current study, which may have obscured the predicted effect. On the other hand, BDNF concentration in platelet-poor plasma showed a 45% average increase from pre- to post-exercise in the aerobic groups (non-injured and mTBI) whereas the non-aerobic group demonstrated decreased pre- to post-exercise BDNF plasma concentration. Notably, injury status did not have a meaningful impact on plasma BDNF dynamics with aerobic exercise. Following from the discussion above, the increase in plasma BDNF with aerobic exercise may reflect proportionally higher BDNF release from tissue other than the central nervous system (Fujimura et al., 2002), but it may also reflect greater-brain based release, since contributions from the hippocampus and cortex to circulating plasma BDNF concentration become more pronounced during exercise (Rasmussen et al., 2009). Much more research is needed to understand the underlying sources of circulating BDNF in humans after mTBI, and scientific exploration of the meaning and nature of BDNF in humans is still in its infancy.

**General Discussion**

Some argue that the use of inferential statistics in pilot studies is inappropriate due to inadequate sample size (Leon, Davis, & Kraemer, 2011), but we would argue that the data presented in this study provide important preliminary safety, feasibility, and tolerability information regarding physical activity after mTBI. Current clinical guidelines from the sports concussion world already recommend that athletes return to aerobic exercise by the time frame investigated in this study, and this recommendation appears to be appropriate based on our findings. However, we note that special considerations
may be needed when implementing exercise prescription, particularly for individuals with whiplash injury and biopsychosocial risk factors such as pre-morbid psychiatric problems and post-injury elevations in depression, anxiety, and sleep dysfunction. From a biological perspective, the BDNF data presented in this study emphasizes the importance of sleep in neurorecovery, but the dynamics of this relationship need much more attention in translational research models in order to understand the mechanisms.

When discussing post-mTBI exercise with patients in a clinical setting, it is critical to address the patient’s interpretation of increased symptoms after exercise. We found that exercise can provoke mild increases in nonspecific symptoms (i.e., headache and dizziness) to an equal extent in both non-injured and mTBI participants. However, the injury experience may interact with mTBI patients’ interpretation of what is “normal” after injury as well as their expectations for symptom-free recovery. Indeed, studies have been conducted in this regard that demonstrate a “good old days” bias in mTBI patients, which minimizes pre-morbid symptom experience (Ferguson, Mittenberg, Barone, & Schneider, 1999; Iverson, Lange, Brooks, & Rennison, 2010; Mittenberg, Digiulio, Perrin, & Bass, 1992), and is particularly relevant to post-morbid expectations for exercise. Therefore, administering pre-exercise instructions that help frame patients’ beliefs about post-injury exercise and normative rates of exercise-induced symptoms may be helpful in minimizing expectation bias or over-interpretation of normal exercise experience.

The current study is the first of many needed to establish post-mTBI exercise safety. Timing, intensity, and exercise types should be tested 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. A maximum-tolerated dose design could be used for this purpose whereby the “dose” would be defined as time after injury. A standardized aerobic session could be introduced at decreasing time intervals after injury to determine the optimal timing for post-injury return to exercise. Another notable limitation is the very small sample size used in the study, and the fact that it was not powered to detect main effects or interactions in pre-defined outcomes. In studies with small sample sizes, the results are more likely to be highly skewed; so all presented results should be interpreted conservatively with this in mind. The study participants were also predominately young, college students, which limits the generalizability of findings. A more representative participant population should be examined in the future with consideration for diversity in age, education, race, and other socioeconomic variables.

Future studies that examine the efficacy of post-mTBI exercise for improving neurorecovery should consider much longer-term interventions that last for several weeks at a minimum. Sleep quality proved to have one of the more significant effects on functional and biological outcomes in this study and should also be considered for randomized controlled trials in the future either in combination with exercise programs or independently. Lastly, the utility of BDNF as a biomarker in recovery is uncertain, but the demonstrated relationship of certain circulating parameters and relevant outcomes like sleep and symptoms in this study warrants continued exploration.
APPENDIX A
FUNDING ACKNOWLEDGMENT AND CLINICAL TRIALS REGISTRATION

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APPENDIX B
NON-AEROBIC EXERCISE PROTOCOL

Part I (Sequence x 2)
Stretches (hold for 30-count)
  - Toe Touch (:.30)
  - Single Quadricep (1:30)
Standing March (1-minute) (2:30)
Standing Reverse March (1-minute) (3:30)
Stretches (hold for 30-count)
  - Toe Touch (4:00)
  - Single Quad (5:00)
  - Runner’s Lunge (6:00)
Wall Sit (30-second hold, then rest) (6:30)
Stretch
  - Calf (7:30)
Wall Sit (30-second hold, then rest) (8:00)
Stretch
  - Calf (9:00)

*Take Heart Rate*

Part 2 (Sequence x 2)
Arm Circles (30-count)
  - Both Forward (.30)
  - Both Backwards (1:00)
  - Single Forward (1:30)
  - Single Backward (2:00)
Stretches (hold for 30-count)
  - Single Arm Across (3:00)
  - Single Arm Tricep (4:00)
Bicep Curls (1-minute) (5:00)
Forward Raises (1-minute) (6:00)
Stretches (hold for 30-count)
  - Single Arm Across (7:00)
  - Single Arm Tricep (8:00)
Lateral Raises (1-minute) (9:00)
Tricep Presses (1-minute) (10:00)

*Take Heart Rate*
LIST OF REFERENCES


BIOGRAPHICAL SKETCH

Aliyah Snyder received her doctoral degree in the neuropsychology track of the clinical and health psychology program at the University of Florida in the fall of 2017. While at UF, Dr. Snyder completed a predoctoral training fellowship in clinical and translational science (CTSI TL1) and founded Athlete Brain, a student-run organization dedicated to promoting concussion safety and awareness in the community. Her predoctoral clinical internship was completed at the Emory University School of Medicine in the adult and pediatric neuropsychology track, specializing in rehabilitation neuropsychology. Her research interests include translational models of post-injury neuroplasticity, biobehavioral interventions to enhance recovery from concussion, and prevention of persistent post-concussion syndrome.