ABSTRACT

The Effects of Including Aerobic Exercise in the Treatment Protocol of Concussions: A Systemic Review and Meta-Analysis

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More research studies are being completed advocating for the use of exercise as an intervention and form of treatment for concussions. However, exercise can include many forms of physical activity, intensities, and durations. This systemic review and meta-analysis focused on the use of aerobic exercise, such as cycling or walking, as an intervention and form of treatment for children and young adults suffering from a concussion. The purpose of this systematic review and meta-analysis was to determine if the addition of aerobic exercise to an individual concussion treatment makes a significant difference when compared to treatments using flexibility as a form of physical activity or traditional methods of treatment following guidelines from the 2016 Berlin Consensus Statement on Concussion in Sport. The search conducted for articles generated 472 studies. Out of these, 5 studies were selected based from the inclusion criteria. Aerobic exercise was shown to significantly decrease the absolute risk difference for the development of prolonged post-concussion symptoms in children and adolescents with concussions when compared to those who reported no physical activity. The mean risk

difference for the independent variable (IV) was -0.12 with a 95% confidence interval was reported to be -0.17 to -0.07 and an effect size of $Z = 4.94$ ($P < 0.00001$). Aerobic exercise was also shown to have an effect on the change in post-concussion symptom scale scores. The mean IV difference was 8.7 with a 95% confidence interval of 2.05 to 14.35 and an effect size of $Z=3.02$ ($p=0.003$). In conclusion, while there is evidence that aerobic exercise is beneficial for children and adolescents with a concussion, more studies need to be completed focusing on this age group and the effects of aerobic exercise on concussion recovery.

The Effects of Including Aerobic Exercise in the Treatment Protocol of Concussions: A Systematic Review and Meta-Analysis

by

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A Thesis

Approved by the Department of Health, Human Performance and Recreation

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Submitted to the Graduate Faculty of
Baylor University in Partial Fulfillment of the
Requirements for the Degree
of

Master of Science

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SCAT – Sport Concussion Assessment Tool

ImPACT – Immediate post-concussion assessment and cognitive testing

mTBI – Mild Traumatic Brain Injury

PCSS – Post Concussion Symptom Scale Score

PCSI – Post Concussion Symptom Inventory

PPCS – Prolonged Post Concucssion Symptoms

TBI – Traumatic Brain Injury

ACKNOWLEDGMENTS

This thesis would not have been possible without God, the help and guidance of a lot of people including but not limited to my thesis chair, Dr. Darryn Willoughby, and my thesis committee members, Dr. Tracey Sulak and Dr. Yunsuk Koh.

CHAPTER ONE

Introduction

Concussions are considered to be a form of traumatic brain injury that is classified as mild (1). They are the result of a force that has impacted the brain. In the case of sports-related concussions, this force is a biomechanically-acquired and can either be directly or indirectly applied to the head (1).

Once a sports-related concussion is suspected, medical practitioners and researchers highly recommend that the individual is removed from play immediately (1, 2). Once diagnosed, the individual undergoes a return to play protocol that historically is advised to begin once the athlete is asymptomatic (2, 3). The theory behind this is to allow the brain to rest, and allow the brain to return to normal neurologic and metabolic function (4).

However, rest alone may not the best course of action for concussion treatments. A meta-analysis published in 2017 included data supporting the notion that exercise might be helpful to treat concussions, including those that are sports related (5). The authors discussed the impact of exercise at various intensities on lowering Post-Concussion Symptom Scale (PCSS) score (5).

Currently, there are no universally-established guidelines for prescribing exercise and aerobic exercise intensities, especially aerobic exercise intensities, for concussed individuals (6, 7). Likewise, standardized methods for identifying an appropriate exercise intensity in a concussion treatment protocol do not exist (6, 7). There is, however, a treadmill protocol for an exercise test to determine a sub-symptom threshold for exercise in concussed individuals (8). It is important to note, however, that unless the concussed individual has access to a treadmill and an medical professional trained in executing and evaluating the exercise test, the concussed individual would not be able to use the treadmill protocol to determine a sub-symptom threshold with which to exercise.

With the lack of universally-established guidelines for prescribing exercise for concussed individuals, investigators researching exercise intensities, exercise protocols, and physical activity protocols for concussions are inconsistent with what is included in the treatment for concussed individuals. In addition to these inconsistencies within the exercise programs, there are also inconsistencies with results reported by investigators analyzing the recovery times with different exercise intensities (5).While the intensity of exercise is a variable that can affect one's recovery from a concussion, another variable that could account for the varied recovery times is the modality of the exercise used as treatment. Exercise can be used through either an exercise protocol using modes of aerobic exercise such as cycling, running, walking, or as rehabilitation exercises that are part of a rehabilitation program.

With respect to aerobic exercise programs, such as those including walking, cycling, and running, there is evidence suggesting that these activities have a positive effect on brain function and health. Researchers have determined that aerobic exercise has the ability to decrease the severity of cognitive impairment and lower one's risk of developing dementia (9). One way that researchers have shown this is through completing both rodent and human studies. Results from these studies have lead researchers to determine that aerobic exercise can increase factors involved in neuron growth and repair (9). Further studies completed that analyzed the effects of aerobic exercise on a concussed brain have shown that aerobic exercise will lead to the up-regulation of a neurotrophic factor, brain-derived neurotrophic factor (BDNF), responsible for having a neuroplastic effect on the brain when the exercise is completed voluntarily (9). It is important to note that, in animal studies where exercise is forced, this upregulation is not present (9).

While various treatment methods using physical activity and exercise are available for individuals with concussions, children and adolescents might not have the resources available to undergo various rehabilitation programs that could be effective in their recovery. Furthermore, if the individual is a student-athlete, the school might not be equipped with the proper materials or personnel to set up a rehabilitation protocol that the student can complete with the athletic trainers. Also, the knowledge and guidelines that the health professionals working with students have regarding concussion treatment could have an effect on the treatment that an individual might receive.

Allowing a concussed individual, especially one who is a student-athlete, to continue aerobic exercise while completing a concussion treatment program has strong benefits for the students, their coaches, and the sports-medicine practitioners with whom they work. The individual would possibly recover more quickly from a concussion, be allowed to return to normal activities sooner, and, if an athlete, not have his or her in-season physical condition deteriorate severely (5). Regardless of whether or not the individual was an athlete, participating in aerobic exercise while completing a concussion program would prevent deconditioning and prevent significant decreases in one's aerobic fitness levels.

This systematic review and meta-analysis will compare the effects of aerobic exercise to control groups undergoing either a flexibility-based protocol or the standard of care, which includes rest and abstaining from unnecessary physical activity, on symptomatic concussed athletes' residual symptoms.

Purpose of the Study

The purpose of this systematic review and meta-analysis is to determine if the addition of aerobic exercise to an individual concussion treatment makes a significant difference when compared to treatments using flexibility as a form of physical activity or traditional methods of treatment following the 2016 Berlin Consensus Statement on Concussion in Sport.

Significance of Study

This study is significant because it will help determine the effectiveness of incorporating aerobic exercise as a part of concussion treatment for children and adolescents. Being able to establish that aerobic exercise can help concussion recovery in children and adolescents can lead to medical practitioners and athletic trainers further developing recovery protocols that allow for improved recovery times and allow for further research to be done on exercise prescription for concussed patients.

Hypotheses

H_0: Concussed individuals who participate in aerobic exercise while concussed will have the same changes in symptom duration and severity as those who follow the standard of care or use a flexibility protocol.

H_a: Concussed individuals who participate in aerobic exercise while concussed will have decreases in symptom duration and severity differently than those who follow the standard of care or use a flexibility protocol.

Delimitations

1. With the keywords used, there might be studies that meet the inclusion criteria that did not show up when the search was completed
2. There might be studies that meet the inclusion criteria that did not show up when the search was completed because they were published in journals not indexed in the databases utilized.
3. There might be unpublished studies that meet the inclusion criteria or are not finished and therefore the results are not complete.

Limitations

1. Limited studies were found on specifically sports-related concussion so the inclusion criteria had to be modified to include all concussions.
2. Limited studies were found on specifically high school students so the inclusion criteria had to account for a larger age group.
3. Limited studies were found using a strict rest protocol as a control group so the inclusion criteria had to account for the control group not participating in aerobic exercise.

CHAPTER TWO

Review of Literature

Introduction

Every year thousands of high school students across the United States sign up to be a part of their high school's athletic programs. In 2016 alone, data collected from a concussion questionnaire added to the 2016 Monitoring The Future (MTF) Survey found that among 13,088 8th, 10th, and 12th grade U.S. students surveyed, approximately 76.7% participated in some form of athletic activity (10). With the participation of sports, there is also an increased risk for an individual to acquire a sports related injury (11). For most of the possible injuries that these athletes can acquire, the injuries are related to the musculoskeletal system (12). Whether it be forms of contusions, fractures, a sprained or torn ligament, strained muscle, or just mild lacerations, all of these injuries, in some form or fashion, can be visibly observed.

Concussion is an injury that impacts the brain and the body's nervous system. It is one injury in which children and adolescents, regardless of their level of participation in a sport, are subjected to. A concussion injury is not necessarily as visible as other injuries; therefore, the standard methods for treatment relies on symptoms present as well as what resources are available and the concussion management knowledge of the athletic trainers, team physicians, or other medical professionals that are available to treat the individual (13).

When dealing with a concussion, specifically one that is sports related, the goal is the same as with any other injured individual, which is to return the individual back to competition as soon and as safely as possible. Because of the risks associated with returning a concussed individual back to competition too soon, concussion treatment has often been very conservative (1, 2). Within the past 3 years, this conservative method of treatment has been questioned as researchers are finding that maybe rest is not the best course of action (1).

The purpose of this systemic review will be to describe what is presently known about the effects of exercise in post-concussion treatment protocols. The systemic review will explore exercise programs that have been introduced, potential risks, benefits, and any existing evidence for including exercise in return-to-play protocols. Concussions will also be defined and will be discussed throughout the review as a form of traumatic brain injury (TBI). In the review, there be a discussion about concussion pathophysiology, concussion management, and the possible benefits of exercise for individuals suffering from a concussion.

Concussions

Defining Concussions as Traumatic Brain Injuries

In 2013, the Centers for Disease Control and Prevention (CDC) estimated that, of all of the TBIs acquired, 85% of these were mild traumatic brain injuries (mTBIs) (14). Concussion is a form of mild TBIs (14), and concussions can be defined as "representing the immediate and transient symptoms of traumatic brain injury (1)." One of the first things to understand is exactly what is a TBI. It characterized by two partially overlapping phases referred to as primary and secondary injuries (15). The primary injury is defined as the moment that a mechanical force disrupts the structure of the brain (15). These mechanical forces can be either the direct or indirect result from an impact (16). These forces can act in a linear direction or as rotational forces (16). Regardless of if they are a direct or indirect result from an impact, these forces lead to inertia acting on the brain (16). This inertia, despite the direction that it acts on the brain, causes the brain to collide with the inside of the skull (17). Because of the brain's physiological structure, immediate damage to the gray and white matter can result (16). The secondary injury is considered to be the result of this primary injury on a biochemical and cellular level (15). The onset of this second injury can be delayed depending on the nature of the impact that resulted in the primary injury (17). It is characterized by widespread damage of neurons, unlike the primary injury (16). The reason for dividing a TBI into these two phases is that the resulting secondary injury does not always occur simultaneously with the primary injury; however, many times they overlap (18, 19).

Traumatic Brain injury severity is determined through using a Glasgow coma scale (GCS) (18). The GCS allows for a score range for 3 to 15 points with lower scores being most severe. However, there is some debate about this assessment for an out of clinical setting (20). Despite this debate, the scoring system is still in place and the debate will not be discussed in this review. Based off of the GCS, a TBI can be classified as either mild, moderate, or severe depending on the range in which patients' score falls (18). The mTBIs fall into a range of 13 to 15, moderate TBIs fall into the range of 9 to 13, and severe TBIs fall into the score of 3 to 8 (18).

Since concussions are considered to be mTBIs (1, 14, 21), using GCS they can be defined as a traumatic brain injury where there is likely a full neurological recovery despite some short-term memory and concentration deficits being expected (18). However, not all mTBIs are a concussion and not all concussions are sports-related. In an attempt to clarify the definition of a sports-related concussion, the 2016 Consensus Statement on Concussions defined a sports-related concussion as a TBI that is the result of a biomechanical force (1). More specifically, this biomechanical force is not limited to solely being a direct impact to the head. The concussion inducing force can be the result of any biomechanical force that is applied to the body and travels to the head (1).

Pathophysiology of Concussions

Traumatic Brain Injuries can be the result of a wide range of incidents including falls, combat-related events, and sports-related events (22). These events can cause the primary injury phase associated with TBIs (18, 22). This phase can be characterized by mechanical-focal damage along with diffuse axonal injury (22). Focal damage is primarily caused by forces acting in a linear direction and result in damage to the gray matter of the brain (16, 17). It can include cortical contusions and both extradural and intradural hematomas (17). The disruption of deep white matter caused primarily by rotational forces acting on the brain during the primary injury is referred to as diffuse axonal injury (16). Diffuse axonal injury does not always show up on a macroscopic level (23). However, on a microscopic level damaged axons can appear to be swollen or disconnected from the cell body (23). The primary injury phase has various degrees of severity. The severity can be classified as either subclinical, mild, moderate, or severe (22). A TBI, if severe enough, or the result of an accumulation of mild events, can lead to damage to the structure and integrity of the blood brain barrier (BBB) (22), which is a key physiological element that helps regulate the brain's environment (25) . This damage is the result of the production of bradykinin, an inflammatory mediator, that signals for astrocytes to release interleukin-6. The result of releasing interleukin-6 is the separation of the tight junctions that hold the BBB together (24). The brain's environment is highly-regulated to maintain homeostasis (25). The BBB's function is to strictly control the influx and efflux of glucose, amino acids, ions, and proteins from the circulatory system into brain tissue (25). In regards to ion concentrations, the brain interstitial fluid has a potassium concentration of approximately 2.5-2.9 mM (25). The brain interstitial fluid also has specific calcium ion concentrations that are regulated by the BBB (24). Any damage to the BBB will have a negative effect on the brain (26).

The secondary injury that results from the primary injury induces biochemical changes that affect the homeostatic levels within the brain. This includes ion imbalances, excessive neurotransmitter release, mitochondrial dysfunction, and cell membrane degradation (19, 22). These biochemical changes can also impact the BBB by producing pro-inflammatory molecules that include prostaglandins, chemokines, and cytokines. The production of these pro-inflammatory molecules leads to lipid peroxidation and BBB disruption (19). The 3 stages of a TBI are outlined in Figure 1.

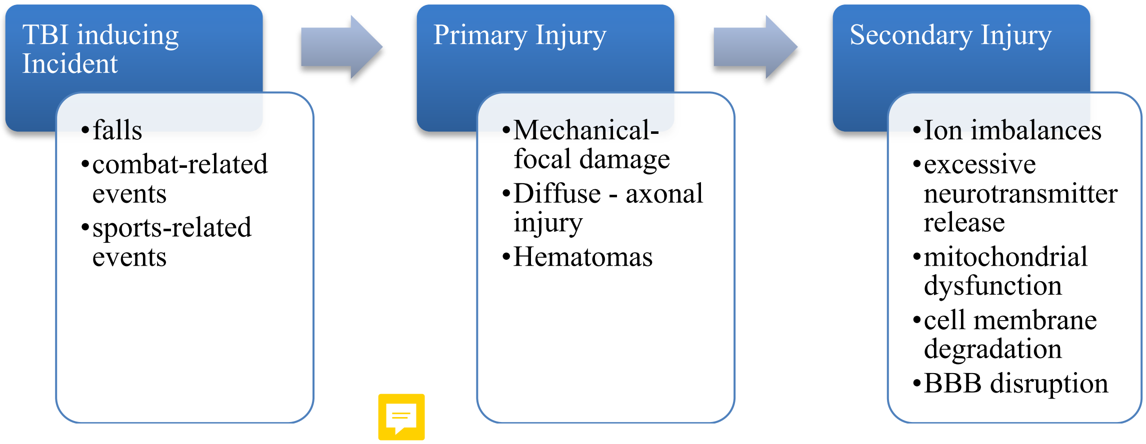


Figure 1. Stages of TBI

Despite being classified as a mTBI, concussions are not excluded from resulting in damage to metabolic and physiological systems within the brain despite there being no significant structural brain damage (27). When a biomechanical force produces a brain injury, the force acts by causing the brain to rapidly move in a linear direction, either accelerating and decelerating the brain and causing it to collide with the interior sides of the skull (16, 17, 28). The biomechanical force can also lead to rotational forces that the brain is normally not exposed to, thereby acting on the brain (16, 17, 28). These combined forces result in the stretching and injuring of neuronal and glial cells and blood vessels (28, 29). They also result in altering membrane permeability (30).

The events following the application of the concussion-inducing biomechanical force are referred to as the neurometabolic cascade (31). These events are initially characterized by changes in the neuronal cell's ion concentrations. Potassium efflux along with sodium and calcium influx occur due to damage caused by the biomechanical force damaging the integrity of cell membranes (30). These changes in ion concentrations can then further result in the activation of both ligand and/or voltage gated ion channels (30).

As a result of the ion concentration levels deviating away from homeostatic values, energy dependent ion pumps are activated in order to return the cells and their environment back to homeostasis. However, because of the amount of pumps activated and the extent of the energy demand that they impose on the cells, hyperglyocolysis occurs (30, 32). This hyperglycolysis is characterized by a high intracellular energy demand in the presence of a low energy supply (30).

In attempt to restore intracellular calcium levels, some of the calcium is absorbed through the mitochondria. However, this can lead to mitochondrial dysfunction and further the inability of the cells to match the energy demand of the ion pumps (30). This is especially important to note because an estimated 94.74% of the brain's energy comes from reactions within the mitochondria (33).

An important aspect of the hyperglycolysis period for dealing with sports related concussions is the generation of free radicals and the metabolic state of the brain. These two can lead to individuals having concussion symptoms lasting longer and the individuals becoming more susceptible to a repeated injury (30). After hyperglycolysis, the brain enters a state of impaired glucose metabolism that is referred to as the hypometabolic period that, in animal studies, has been shown to last between 7 to 10 days (30). This hypometabolic period has also been shown to be present in individuals with post-concussion syndrome as a result from blast exposure-induced mTBI (34).

The changes in metabolism due to the injury are also thought to be affected by changes in gene expression along with enzymatic and cell transporting regulation (30). A study published in 2016 analyzing TBIs in rats found that the changes in the brain's ability to metabolize glucose are not only related to the damage to the glycolytic pathways, but are also related to overexpression of glycolytic enzyme genes (33). The researchers found that, unlike with severe TBI, mTBIs show alterations in gene expression starting within 120 hours from the initial injury (33). The rats that had a mTBI were observed to have no changes in gene expression after 24 hours; however, between a time range of 48 to 120 hours there was a 3- to 5-fold increase in the expression of the glycolytic genes, ALDOC, GAPDH, and ENO2 (33). These glycolytic genes are important because they play a role in decreasing gap between ATP supply and demand resulting from the hyperglycolysis period of a mTBI (33).

Symptoms of a Concussion

As a result of the cellular damage, concussions can lead to an array of various symptoms that fall into different clinical domains. These clinical domains are listed in the 2016 Berlin Consensus Statement as somatic, physical signs, balance impairment, forms of behavioral changes, forms of cognitive impairment, and sleep disturbances (1). Specific examples of symptoms include, but are not limited to, dizziness, gait unsteadiness, and blurred vision (1).

Symptoms including impaired balance, vertigo, dizziness, nausea, and unstable vision are evidence that a concussion results in damage of the vestibular system (35). These symptoms could be the result of the primary injury inducing biomechanical force damaging some of the structures and organs that are part of the vestibular system, damage to the vestibular nerve, or even damage to visual and motor pathways. These symptoms could also be the result of secondary vestibular issues that can result from a concussion such as post-traumatic Meniere’s disease or post-traumatic migraines (36).

Cognitive symptoms, such as decreased memory, are correlated to damage to white brain matter (37). There is also evidence from analyzing retired NFL athletes' brains through diffuse tenor imaging of a correlation between white matter damage and depression, another possible symptom of a concussion and post-concussion syndrome (38). However, it is important to note that while an athlete might present themselves as asymptomatic, there could still be damage to the white matter (39).

Diagnosing Concussions

The methods used for diagnosing concussions has changed as more information about the injury has been discovered. One of the first methods for determining if a concussion was sustained involves determining if a loss of consciousness occurred (40). However, this is no longer a valid and accurate method for diagnosing a concussion because loss of consciousness is not a requirement for a concussion (1, 40).

Assessment of sports-related concussions normally begins with a sideline evaluation, if an athlete has sustained a head impact severe enough to warrant concern of a concussion or the athlete has a clear presence of symptoms and is thus removed from play. According to the most recent Sports Related Consensus statement, a SCAT5 test and the Standardized Assessment of Concussion (SAC) can be used for sideline evaluations (1). It is important to note that these sideline evaluations only screen for a suspected sports-related concussion and do not definitively diagnose that the athlete has sustained a concussion (1). Once removed from play due to being suspected of receiving a concussion, the athlete should not return to play the same day even if the sideline evaluation does not suggest a concussion (1). If the SCAT or SAC test provide significant enough evidence to suggest that a concussion has been sustained, the athlete should be taken to an environment free of distractions for more evaluations to be completed (1).

Additional Evaluations and Monitoring Recovery

Follow-up evaluations after an initial sideline evaluation should include the athlete's concussion history, a neurological exam, determining if the athlete's condition has improved or worsened since the initial time of injury, and determining if there is a possibility for the occurrence of a moderate or severe TBI instead of a mild one (1).

There is evidence that suggests there is damage to the vestibular system following a concussion. This conclusion is based off of many of the symptoms that are present when an individual is concussed. These symptoms include impaired balance, vertigo, dizziness, nausea, and unstable vision (35). Testing the vestibular system can be conducted through a vestibular ocular motor screening assessment (VOMS) (35). The VOMS is responsible for assessing vestibular and oculomotor control in five different areas: 1) smooth pursuit, 2) saccades, a type of eye movement involving simultaneous movement of both eyes, 3) near point convergence (NPC), 4) horizontal vestibular ocular reflex, and 5) visual motion sensitivity (VMS) (35).

For monitoring recovery, the symptom checklist for the SCAT test has been shown to be effective (1). Since it was first published in 2004, the SCAT test has evolved to also include a Balance Error Scoring System (BESS) (40). Most recently the 2016 Concussion in Sport Conference consensus statement released what the most recent version of the SCAT test, the SCAT5 (1). The SCAT test should only be performed by a trained sports medicine practitioner. This can either be a certified athletic trainer, a team physician, or a physician's assistant for the team. It consists of an immediate on-field assessment test and an off-field assessment (1). The immediate assessment consists of identifying signs of a sustained concussion, completing a memory assessment, determining a Glasgow coma scale, and completing a cervical spine assessment (1). The off-field assessment consists of determining the athlete's concussion background, completing a brief medical history questionnaire, completing a symptom evaluation, and completing a series of cognitive and neurological screenings (1).

It is important to note that while a concussed athlete's symptoms might have cleared, the athlete might not be fully cognitively recovered (1). One of the tests that can be used to identify any impairments to an individual's neurocognitive function as a result of a concussion is the computerized test battery called the ImPACT (41). The ImPACT test has been used to assess the neurocognitive effects on an athlete that has sustained a concussion (42). Researchers have found, when comparing ImPACT results from concussed individuals to healthy control subjects, that the test is a good way to assess whether or not an individual is concussed based off of performance on various neuropsychological and neurocognitive tests (41). A complete table of different assessment and evaluation tools for concussion can be found in Table 4 of the appendix.

Concussion Protocols and Treatment

The methods to treating a concussion have undergone multiple changes as the understanding of concussions have developed. One of the risks involved with treating a concussion is declaring an individual clear to return to play before the concussion has healed (1, 43). Having an athlete return to play too early can lead to the athlete being more susceptible to a secondary concussion, post-concussion syndrome, and, more significantly, damaging injuries such as second impact syndrome (1).

Previous researchers have made recommendations that an athlete should be completely asymptomatic before starting a gradual return to activity protocol (4). This protocol would be for both physical and cognitive activities (4). The concept behind waiting until asymptomatic ties in with the metabolic changes that occur during the primary and secondary injuries of any form of TBI (4). Increases in neurometabolic activity could result in a longer recovery period if the activity levels reached a level above a threshold that leads to an increase or prolongation of symptoms (4). Since exercise can increase the metabolic demands of the brain, waiting until the athlete is asymptomatic to begin physical and cognitive activity would, in theory, prevent symptom exacerbation (4).

Recent research, however, is shedding light that physical rest might not the best approach to treating concussions (5). There is already evidence that exercise is beneficial to brain health in non-concussed individuals. In older populations, exercise has shown to improve learning, memory, and help prevent brain tissue atrophy associated with age (44). Exercise has also shown to be beneficial in lowering the risks of Alzheimer's. These benefits are thought to be the result of neuronal circuits involving various growth factors that are activated through exercise (45).

Exercise and Concussions

Benefits of Exercise for Concussed Individuals

Evidence is accumulating that demonstrates exercise is beneficial for symptomatic concussed individuals (5). One study analyzed concussions in rodents and focused on changes in the expression of five genes and their corresponding molecules located in the prefrontal cortex and the hippocampus (46). These genes included BDNF, DNMT1, IGF1, PGC1-α, and TERT. In addition to focusing on these molecules and their genes, the study also focused on the effect of various time intervals of returning to exercise on telomere length (46). This study found that while a concussion has a tendency to cause deregulation of the five genes researchers studied, a return to exercise showed up-regulation of the 5 genes. This is important because these genes each play an important role in cellular metabolism, cellular repair, overall neurological health, and neurological functions (46).

Exercising Concussion Patients

Determining when a concussed individual should return to physical activity is still a debated topic. While studies using animals can control homogeneity in the concussions, clinical research cannot control this due to the various possible mechanisms of injury and being unable to control the individual's physiological characteristics (45).

Investigators studying return to physical activity in rats following a concussion found that a return to physical activity for rats between 1 to 3 days post-injury had the earliest demonstration of significant improvements in motor and cognitive function (46). A second group demonstrated significant improvements when the group that was restricted from physical activity by 3 days. The researchers found that another group which was restricted by 7 days had the longest time with no significant improvements. The researchers found that their results matched up with the 2012 Consensus Statement on Sport Concussion guidelines in that 5 to 7 days of clinical rest were recommended post-concussion (46). However, it is important to note that these researchers were testing concussed rats and not concussed humans.

A systematic review published in 2017 analyzed the recommended period of rest for concussed athletes. Researchers concluded that, unlike the 5 to 7 day recommended clinical rest, 24-48 hours should be sufficient. However, they did note that this would also be subjective based on the severity of the concussion and other factors that can vary from individual to individual, such as concussion history (47).

While the debate is still ongoing for how long an individual should wait before being allowed to return to physical activity following a concussion, research has provided sufficient evidence to suggest that an exercise program of some sort should be maintained by individuals who suffer from any TBI, not limited to or excluding concussions. The continuation of exercise has been shown to decrease depression, increase overall health status, and decrease symptoms in individuals suffering from a traumatic brain injury (48).

Exercise Modality

Exercise and physical activity can cover a variety of forms of activity and has been proven to have a positive effect on brain health and function (49). Aerobic exercise specifically has been linked to improvements in individuals suffering from forms of cognitive impairment and memory deficits related to Alzheimer's and dementia (9). It is believed that exercise helps improve cognitive function and memory through the release of BDNF (49). This is noteworthy since BDNF is responsible for multiple neuroplastic processes including, but not limited to, the growth and function of neurons and synapses (50). However, the mechanisms behind the up-regulation and function of BDNF fall out of the scope and purpose for this review. Because of the impact of aerobic exercise on brain health and function, it is reasonable to suggest that aerobic exercise could have a positive impact on concussion recovery. Leddy et. al. completed a literature review in which the topic of aerobic exercise and concussion was discussed (9). The review pointed out that there is evidence in animal models that aerobic exercise does up-regulate neuroplasticity in rodents suffering from a simulated concussion or brain injury, and that there is enough evidence to support the conclusion that aerobic exercise could be used as a treatment for concussion symptoms (9). Incidentally, forms of aerobic exercise that have been used throughout protocols in studies include cycling and walking (51).

Exercise Intensity and Quantity

Another debate concerning concussions and physical activity is what duration and intensity should be prescribed for these individuals. In respect to both mTBIs and moderate TBIs, one study used a sample of individuals who had their most recent TBI approximately 4 years prior to volunteering for the study (52). The individuals had been sedentary before the study and had no contraindications that suggested they could not participate in exercise (52). The individuals completed 30 minutes of supervised vigorous intensity aerobic exercise on a treadmill 3 times a week for 12 weeks (52). The researchers used the percent heart rate reserve range of 70%-80% to define vigorous intensity (52). The individuals showed improvements in overall cardiovascular health in addition to improvements in cognitive function (52). However, it is important to note in regards to this study that the individuals had a significant time between their last injury and the start of the study (52).

In a pilot study involving concussed college student-athletes, the athletes were assigned a mild to moderate intensity aerobic exercise protocol using a cycle ergometer (53). The researchers defined mild-to-moderate intensity by the range of 0-6 on the modified Borg Rate of Perceived Exertion (RPE) scale (53). The individuals cycled for

20 minutes and concussion symptoms increased initially following exercising; however, the increase was temporary and did not result in a prolonged recovery period. Individuals who reported a modified Borg RPE scale rating higher than 6 after exercising showed an overall greater temporary increase in symptoms and had a significant increase in the time it took to recover (53). The average recovery time for the individuals who exercised at a mild-to-moderate intensity did not seem to be affected (53). It is important to note that, since this was a pilot study, the sample might not be a proper representation of a population of concussed college student-athletes. Because of the use of a Borg RPE scale to measure exercise intensity, the perceived exertion rating could be subjective to each athlete and incorrectly reported by the athletes (53).

Research has suggested that optimal improvements in concussion recovery is found when the individuals complete moderate intensity exercise (5). However, intensity is not the only factor when prescribing exercise. When prescribing exercises for concussed individuals, it is important to keep in mind that an excess amount of exercise can have negative effects instead of positive effects on individuals (54). This can occur in the form of overtraining (54). In respect to duration, a study found that 90 minutes of exercise a week was sufficient for individuals with a traumatic brain injury (48). This correlates with the previously-mentioned study of individuals who had a history of TBIs exercising at a vigorous intensity three times a week for 90 minutes (52). Both studies, however, did not have individuals performing controlled exercise programs until at least 6 months following the last acquired TBI.

Conclusion

There has been evidence throughout the literature to suggest that exercise, primarily aerobic exercise, provides benefits on a molecular level that translates into improvements in recovery time. On a microscopic level, these benefits include upregulation in genes that signal for an upregulation in mitochondria biogenesis along with glycolytic enzymes that can help the brain meet the energy demand placed on it by the primary and secondary injuries. While more studies should be completed to identify proper exercise prescription parameters for concussed individuals, the conclusion can also be drawn that aerobic exercise is beneficial to concussed individuals.

CHAPTER THREE

Methods

EBSCO Host was used to search, the databases Medline, Pysch Info, and Sport Discus using the key words: "sports related concussion or concussion” AND "aerobic exercise or aerobic training or physical activity or exercise or physical exercise” AND "exercise therapy or exercise intervention”. The databases SCOPUS, Pubmed, and the Cochrane central register of controlled trials were then searched with the same key words. The date range for articles included all dates up until the day the search was completed, January 24, 2019. The PRISM method was used to select the articles for the systematic review and meta-analysis (appendix A2).

472 articles were found after the search was completed. Once duplicates were removed, there were 399 articles remaining. An initial selection was done by one reviewer based off of the title and abstract to see which articles concerned aerobic exercise and concussion recovery, and 62 articles were selected. Out of the 62, 8 articles were removed for being control trials that were unfinished but were found during the search of the Cochrane central register of controlled trials. As a result, 54 articles remained after the removal of the unfished control trials and were reviewed by both the principal investigator and a second reviewer to see which ones met the inclusion criteria. Out of the 54 articles, 5 articles were determined to meet all the inclusion criteria.

Risk of Bias Assessment and Data Extraction

Using the Cochrane Review Manager 5.3, the randomized control studies were assessed for any possible risk of bias. To determine if there was a possibility that the study was biased, 6 areas that could lead to the study being biased were reviewed. These 6 areas included randomization, allocation concealment, participant blinding, outcome assessments, attrition bias due to any outcome data being incomplete, and whether or not the authors of the studies selectively reported their results.

The data extracted from the studies was performed for the measures that applied to the purpose of this systemic review and meta-analysis. Data extracted included PCSS, PCSI, and ImPACT scores and days until medical clearance for children and adolescents. The data was uploaded into the Review Manager 5.3 to be analyzed.

Experimental Approach

Inclusion and Exclusion Criteria

Inclusion criteria for articles included participants suffering from a concussion ages 18 and younger. The control group not participating in aerobic exercise as a form of treatment and the experimental group following a treatment protocol including aerobic exercise. Outcomes measured by the articles had to include concussion symptom duration and symptom severity.

Exclusion criteria for articles included participants suffering from a moderate, severe, or mTBI, a treatment intervention not clearly defined, participants older than 19, and the study failing to have a control group. Articles were also excluded if the results gave no information about concussion symptom duration and symptom severity.

Variables and Statistical Analysis

Variables

The IV for this study was the protocol used for treatment of concussions. The experimental groups in the studies used a form of aerobic exercise as part of their intervention while the control groups underwent either a flexibility or standard method of treatment.

The dependent variables for this study were the concussion symptom duration and severity. These were measured using the PCSS, PCSI, and ImPACT test. One study was included that reported absolute risk difference but had gathered results using PCSS.

Statistical Analysis

Meta Analysis: The meta-analysis was completed for all of the articles included in the study using Cochrane Collaboration software, Review Manager 5.3. The control consisted of concussed children and adolescents who underwent either the standard method of treatment outlined by the 2016 consensus statement on sport concussions or underwent a treatment protocol that included rest and flexibility exercises, but no aerobic exercise.

For continuous data, the means and mean differences were used with a 95% confidence interval. For dichotomous variables, the IV risk ratios were calculated and a 95% confidence interval used as well.

Grade Assessment: The outcomes from the studies were assessed using the GRADE process. The software GRADEpro was used and, based off of the components by required by the software, the total outcomes were determined to be either high, moderate, low, or very low quality. The required components for GRADEpro to perform the analysis included risk of bias, inconsistency (heterogeneity), indirectness, imprecision, publication bias, large effect size, plausible confounding, and dose-response relationship. A complete table of the GRADE assessment can be found in the appendix (Table 1A).

CHAPTER FOUR

Results

The initial search conducted resulted in a total of 472 articles being identified as possible sources for this systematic review and meta-analysis. After the selection process, 5 articles were determined to have met all of the inclusion criteria (55–59).

Study Characteristics

Five studies were selected by the principle investigator and by a secondary reviewer. All studies were full text articles (55–59). Out of the 5 studies selected there were 2 randomized control trials, 1 randomized control study, 1 multicenter prospective quasi-experimental control group design, and 1 prospective, multicenter cohort study (55–59). One study used a flexibility program as the control. Three of studies used either treatment as usual or usual/standard care as the control. One study used no physical activity as the control.

The researchers in Chan et. al.'s 2018 study used an active rehabilitation program that included aerobic exercise as the intervention for their experimental group and treatment as usual (TAU) as their intervention for the control group (55). The active rehabilitation program was led by a physiotherapist and consisted of submaximal aerobic training, light coordination and sport-specific exercises, visualization and imagery techniques, and an at-home exercise program. The TAU included an education session by an occupational therapist which covered information concerning symptom management and returning to play, a school consultation with a teacher that was hospital-affiliated and who facilitated the individual's return to school, and a physiatrist consultation (55).

The researchers in Gauvin-Lepage's 2018 study defined their experimental group's intervention as an active rehabilitation intervention (ARI). The intervention consists of 5 components that include aerobic activity, coordination/sport-specific activity, mental imagery, education, and a home program. The aerobic activity component takes place until the individual is free of any symptoms both while at rest and while performing physical activity. The aerobic exercise intensity is determined by a maximum heart rate value of 50-60% or by using a Pictorial Children's Effort Rating Table (PCERT) and having the individual stay at either a level 2 or 3. The exercise duration would be 15 minutes and could be a fast-paced walk on a treadmill, a jog on a treadmill, or cycling on a stationary bike (57). They defined their control group as undergoing standard care. This was defined as having the individuals either rest or only do light symptom-limited activities, general education concerning concussions, and academic adaptations as well as a gradual return to school. The standard care also consisted of the participants not being allowed to participate in vigorous activities or sports until the participants symptoms had completely ceased (57). It is the same standard care procedure that is advised through the 2016 Berlin Consensus Statement.

For the study published by Grool et. al in 2018, the subgroup for light intensity aerobic exercise was characterized by having participants either walking, swimming, or stationary cycling (56). However, no exercise intensity or duration was described (56). The control group consisted of individuals who did not perform any physical activity (56). The authors of the study did mention that because this was a study in which individuals self-reported their activities and their activity levels, there is a risk of bias (56).

The researchers in Kurowski et. al.'s 2017 study used cycling on a stationary bike as the mode of aerobic exercise for the participants in the experimental group (58). The participants assigned to the experimental group were asked to complete a sub-symptom aerobic exercise test in order to determine the exercise intensity for their at-home exercise program that would be done 5-6 times a week on a stationary bike that was provided by the researchers (58). The stationary bike was the same kind as the one that was used for the sub-symptom aerobic exercise test. For the control group, an at-home full body flexibility program was used. The exact stretches were not reported in the study (58). Once an individual in either group had returned to baseline and was able to perform the assigned protocol without symptom exacerbation, they would be moved to the study's post-intervention period (58).

The researchers in Micay et. al.'s 2018 study used a stepwise aerobic exercise intervention for the individuals in the experimental group (59). The participants completed 8 exercise sessions that increased in duration and intensity. The mode of exercise was cycling on a Velotron Racermate Pro stationary cycle ergometer. A heart rate monitor digitally connected to the cycle ergometer was used to monitor the exercise intensity. Intensity for the individuals was determined by the individual's age-predicted maximal heart rate (HR_{max}). Exercise intensity for the first session was 50% HR_{max}. The target prescribed exercise intensity increased by 5% for each session until the individual had reached an exercise intensity of 70% HR_{max}. Exercise sessions following the session where the target percent HR_{max} was 70% continued to have the target exercise intensity be 70% HR_{max}. Duration for the first exercise session was 10 minutes. All following exercise sessions were 20 minutes in duration (59). The control group used a usual care group that followed the same guidelines as recommended by the 2016 consensus statement on sport and concussion (59).

A complete table of all of the characteristics of the studies' interventions and outcome measures can be found in Table 1. Of all of the included articles, 1 reported absolute risk difference, 2 reported results of an ImPACT test, 2 reported the results of an adolescent PCSI test, 1 reported changes in PCSS, 1 reported PCSS scores, and 1 reported days until medical clearance (55–59). All 5 articles combined involved a total of 1,599 participants. The included studies saw a range of the number of participants 15-1,531 (55–59). It is important to note that while Kurowski et. al's 2017 study had completed and reported the data as if all 30 individuals had completed the study, participants had dropped out during the study and the experimental group only saw 12 of the 15 participants complete the study and the control group only saw 14 of the original 15 participants that were assigned to the group complete the study (58).

Excluding Grool et. al's 2016 study, there was an estimated number of 65 males and 48 females who took part in all 5 studies (55–59). In Kurowski 2017, 5 of the original 15 members of the experimental group were males and 8 of the 15 members of the control group were males (58). In Chan et. al's 2018 study, 4 of the 10 individuals in the experimental group were males and 1 of the 9 individuals in the control group were males (55). All of the 15 participants in Micay et. al's 2018 study were males (59). In Gauvin-Lepage's study, the control group had 8 out of 13 participants that were males and the experimental group had 15 out of 36 participants that were males (57).

Table 1: *Characteristics of studies' outcome's measures and descriptions of both experimental and control groups.*

Study	Outcome's Measures	Experimental Group Intervention Descriptions	Control Group Description
Chan 2018	PCSS, Pediatric Quality of Life Multi-Dimensional Fatigue Scale, PROMIS scales, Beck Depression Inventory, Balance Error Scoring System, ImPACT	Active Rehabilitation Program	Treatment as usual (TAU)
Grool 2016	Acute concussion evaluation inventory, Absolute Risk, Absolute Risk Difference	Light intensity aerobic exercise	No physical activity
Gauvin - Lepage	PCSI,	Active Rehabilitation Program	Standard Care
Kurowski 2017	Adolescent PCSI, parent PCSI	Cycling using a stationary bike	Flexibility Protocol
Micay 2018	PCSS, days until medical clearance	Cycling using a stationary bike	Usual Care Group

A complete table of the characteristics of the study methods and participants are found in Table 2. The age range of the participants fell within 5 to 18 years of age (55–59). It is important to note that while the age range of participants was 5 to 18 years, studies had various mean ages for their participants. Chan 2018 reported an age range of 12-18 years. The mean (±SD) age for all 19 participants was 15.5 (+/-1.47) (55). The experimental group had a mean (±SD) age of 15.9 (+/-1.66) (55). The control group had a mean (±SD) age of 15.2 (+/-1.15) (55). Grool 2018 reported an age range of 5-18 (56). However, because we only analyzed the data for a subgroup of individuals and the mean ages were not reported per subgroup, we were unable to determine the mean age of the subgroup for the Grool 2018 study (56). Gauvin 2018 reported an age range of 8-17 for their inclusion criteria for their study (57). The mean (±SD) age for n=13 participants in the control group was 13.2 (+/-2.6) years (57). The mean (±SD) age for n=36 participants in the experimental group was 14.0 (+/-1.9) years (57). Kurowski 2017 saw their experimental group having a mean (±SD) age of 15.22 years (+/- 1.37) and their control group having a mean (±SD) age of 15.50 years (+/-1.80) (58). Micay 2018 reported an age range of 14-18 (59). The mean (±SD) age for the experimental group was 15.8 (+/-1.2) years, and for the control group was 15.6 (+/-1.0) (59).

The number of prior concussions for participants reported in Chan et. al's 2018 study averaged to be 1.8 +/-1.15 (55). Researchers for Gauvin – Lepage et. al.'s 2018 study reported that their control group saw 10 individuals with no prior concussions, 2 individuals had a range of 1-2 concussions and 1 individual had 3 or more concussions (57). In the experimental group, researchers for Gauvin – Lepage et. al's 2018 study reported 21 individuals with no prior concussions, 13 individuals with 1-2 prior concussions, and 2 individuals with 3 or more concussions (57). Because the researchers for Grool et. al's 2018 study did not report characteristics of participants by subgroup of intervention, we were unable to determine the number individuals with prior concussions or the number of prior concussions those individuals had (56). Researchers working on Kurowski et. al's 2017 study reported the number of participants who had a history of 2 or more concussions including the injury related to the injury (58). The exercise group was reported to have 10 out of 15 participants with a history of 2 or more concussions and the control group was reported to have 6 out of 10 participants having a history of 2 or more concussions (58). The researchers working on Micay et. al's 2018 study reported an average of the number of prior concussions for the individuals in each group. The experimental group and the control group had an average of 0 prior concussions and a range of 0-2 prior concussions (59).

Aerobic Exercise and Absolute Risk Difference for Developing PPCS

The Grool et. al reported in their study 249 out of 795 individuals in the light-intensity aerobic exercise group for children and adolescents developed prolonged post-concussion symptoms. The control group, which participated in no physical activity for children and adolescents, was reported to have 320 out of 736 individuals who developed prolonged post-concussion symptoms. The mean IV risk difference was reported to be -0.12 with a 95% confidence interval of -0.17 to -0.07, and an effect size of $Z = 4.94$ ($P<0.00001$). Because of the large effect size, we can be very confident that the difference in occurrence of prolonged post-concussion symptoms is due a distinct difference between the two groups and did not occur by chance. Results from the meta analysis can be seen in figure 2.

Table 2: *characteristics of studies' methods and participants*

Study	Method	Number of Participants			Age of Participants Range	Sex
		total	Control group	Experimental		
Chan 2018	Single-site, parallel, open-label, randomized controlled trial	19	9	10	12-18	14 males
Grool 2016	Prospective, multicenter cohort study	1531	736	795	5-18	NR*
Gauvin - Lepage 2018	multicenter prospective quasi-experimental control group design	49	13	36	8-17	23 males
Kurowski 2017	Randomized clinical trial	30	14	12	12-17	13 males
Micay 2018	Randomized Controlled Study	15	7	8	14-18	15 males

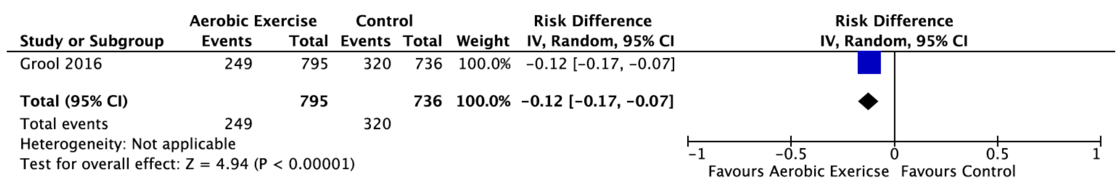


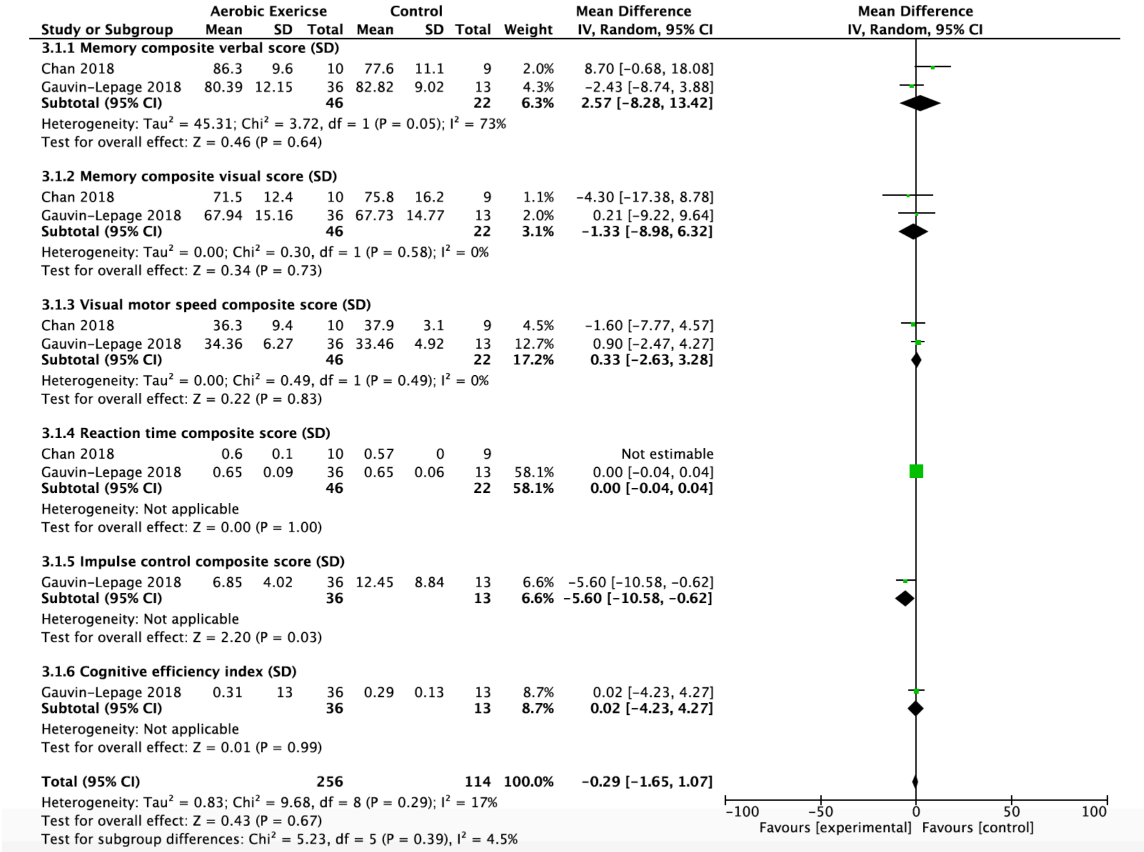
Figure 2. Aerobic exercise and absolute risk difference for developing prolonged post-concussion symptoms.

Aerobic Exercise's Effects on ImPACT Results

The results of a meta-analysis of Gauvin-Lepage et. al.'s 2018 study and Chan et. al's 2018 study are shown in Figure 3. The effect sizes showed that the differences between the aerobic exercise group and the control group were not significant for the memory composite verbal score ($Z = 0.46$, $P=0.64$), memory composite visual score ($Z=0.34$, $P = 0.73$), Visual Motor Speed Composite Score ($Z=0.22$, $P = 0.83$), Reaction Time Composite Score ($Z = 0.00$, $P = 1.00$), and Cognitive efficiency index ($Z = 0.01$, $P = 0.99$). The effect size for the impulse control composite score; however, was significant ($Z = 2.20$, $P = 0.03$) and suggests that the difference in scores could be due to the type of intervention used. The results of the meta analysis can be seen in figure 3.

Aerobic Exercise's Effect on PCSI Scores

A meta-analysis was completed on Kurowski et. al's 2017 study and Gauvin-Lepage et. al's 2018 study. Both studies reported an overall PCSI score; however, only the researchers working on Gauvin-Lepage et. al's study reported scores for individual clusters of the PCSI test. Because of the effect size for the overall PCSI score ($Z=1.63$, $P=0.10$), we can conclude that it is possible that the differences in scores was not because of the intervention used. When looking at the sub-groups or clusters of scores reported by researchers working on Gauvin – Lepage et. al's 2018 study, we can also conclude that the difference between the aerobic exercise group and the control group are not likely to be due to the intervention for the physical cluster ($Z=1.31$, $P = 0.1$), the fatigue cluster ($Z=1.51$, $P = 0.13$), the emotional cluster ($Z = 0.12$, $P = 0.90$), and the cognitive cluster ($Z = 0.18$, $P = 0.86$). Results of the meta-analysis can be seen in figure 4.



Study or Subgroup	Aerobic Exericse Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.1.1 Memory composite verbal score (SD)								
Chan 2018	86.3	9.6	10	77.6	11.1	9	2.0%	8.70 [−0.68, 18.08]
Gauvin–Lepage 2018	80.39	12.15	36	82.82	9.02	13	4.3%	−2.43 [−8.74, 3.88]
Subtotal (95% CI)			**46**			**22**	**6.3%**	**2.57 [−8.28, 13.42]**
Heterogeneity: $Tau^2 = 45.31$; $Chi^2 = 3.72$, df = 1 (P = 0.05); $I^2 = 73\%$								
Test for overall effect: Z = 0.46 (P = 0.64)								
3.1.2 Memory composite visual score (SD)								
Chan 2018	71.5	12.4	10	75.8	16.2	9	1.1%	−4.30 [−17.38, 8.78]
Gauvin–Lepage 2018	67.94	15.16	36	67.73	14.77	13	2.0%	0.21 [−9.22, 9.64]
Subtotal (95% CI)			**46**			**22**	**3.1%**	**−1.33 [−8.98, 6.32]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.30$, df = 1 (P = 0.58); $I^2 = 0\%$								
Test for overall effect: Z = 0.34 (P = 0.73)								
3.1.3 Visual motor speed composite score (SD)								
Chan 2018	36.3	9.4	10	37.9	3.1	9	4.5%	−1.60 [−7.77, 4.57]
Gauvin–Lepage 2018	34.36	6.27	36	33.46	4.92	13	12.7%	0.90 [−2.47, 4.27]
Subtotal (95% CI)			**46**			**22**	**17.2%**	**0.33 [−2.63, 3.28]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.49$, df = 1 (P = 0.49); $I^2 = 0\%$								
Test for overall effect: Z = 0.22 (P = 0.83)								
3.1.4 Reaction time composite score (SD)								
Chan 2018	0.6	0.1	10	0.57	0	9		Not estimable
Gauvin–Lepage 2018	0.65	0.09	36	0.65	0.06	13	58.1%	0.00 [−0.04, 0.04]
Subtotal (95% CI)			**46**			**22**	**58.1%**	**0.00 [−0.04, 0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
3.1.5 Impulse control composite score (SD)								
Gauvin–Lepage 2018	6.85	4.02	36	12.45	8.84	13	6.6%	−5.60 [−10.58, −0.62]
Subtotal (95% CI)			**36**			**13**	**6.6%**	**−5.60 [−10.58, −0.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.20 (P = 0.03)								
3.1.6 Cognitive efficiency index (SD)								
Gauvin–Lepage 2018	0.31	13	36	0.29	0.13	13	8.7%	0.02 [−4.23, 4.27]
Subtotal (95% CI)			**36**			**13**	**8.7%**	**0.02 [−4.23, 4.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.01 (P = 0.99)								
Total (95% CI)			**256**			**114**	**100.0%**	**−0.29 [−1.65, 1.07]**
Heterogeneity: $Tau^2 = 0.83$; $Chi^2 = 9.68$, df = 8 (P = 0.29); $I^2 = 17\%$								
Test for overall effect: Z = 0.43 (P = 0.67)								
Test for subgroup differences: $Chi^2 = 5.23$, df = 5 (P = 0.39), $I^2 = 4.5\%$								

Figure 3: Effect of aerobic exercise on ImPACT results

Aerobic Exercise's Effects on Days Until Medical Clearance

Researchers working on Micay et. al's 2018 study reported days until medical clearance and determined days until medical clearance through the use of electronic medical records to see when return to play decisions were made. Based off of the effect size (Z = 0.17, P = 0.87), we can conclude that it is not likely that the difference in days until medical clearance was not significant between the aerobic exercise group and the control group. Results of the meta-analysis can be seen in figure 5.

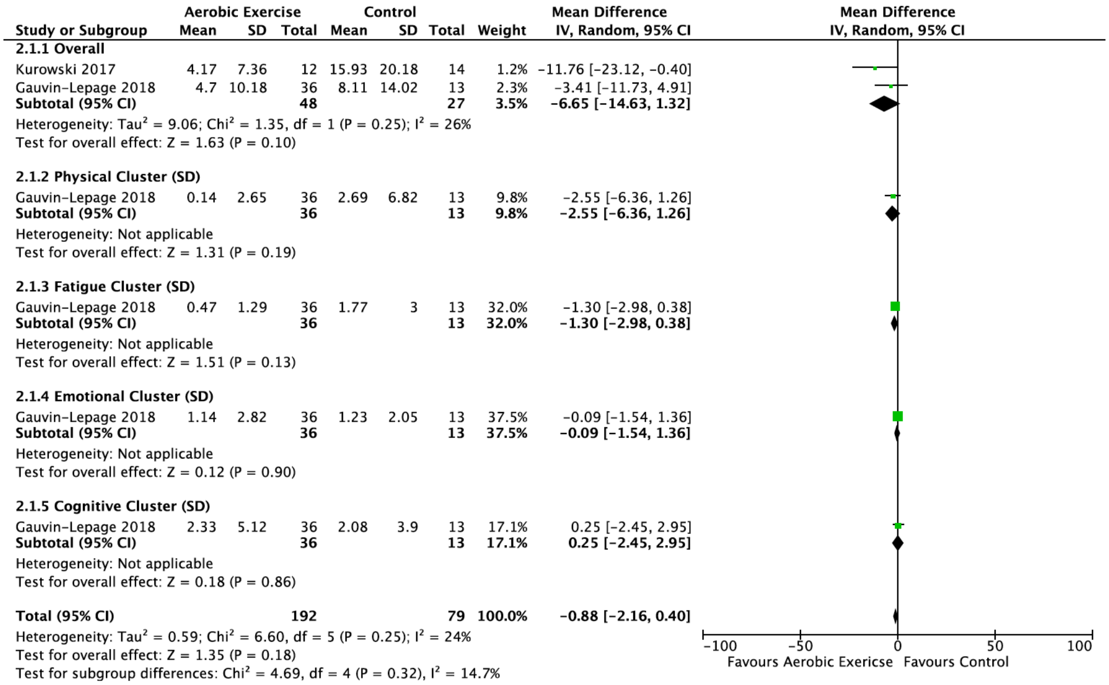


Figure 4. Effect of aerobic exercise on the PCSI score.

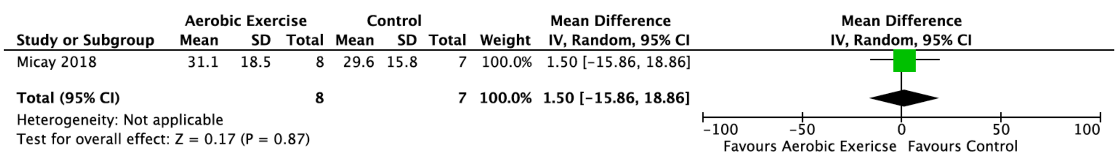


Figure 5. Aerobic Exercise's effects on days until medical clearance

Aerobic Exercise's Effects on PCSS Scores

The Post-Concussion Scale Score (PCSS) consists of 22 symptoms that can be rated on a scale of 0-6. We can conclude, based off the effect size (Z=0.87, P=0.38), that it is not likely that the differences between the group's PCSS scores is due to the intervention alone. The results of the meta-analysis can be seen in figure 6.

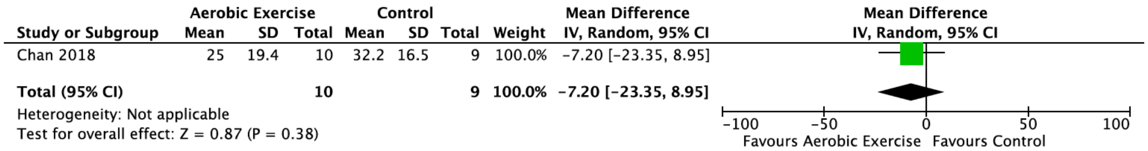


Figure 6. *Aerobic Exercise's effects on PCSS scores*

Aerobic Exercise's Effects on Changes in PCSS Scores

The Post-Concussion Scale Score (PCSS) consists of 22 symptoms that can be rated on a scale of 0-6. The scale used by the researchers working on Micay et. al's 2018 study was from the SCAT3 test. Based off of the effect size, we can conclude that it is possible that the difference in the changes seen in PCSS scores between the aerobic exercise group and the control group could be due to the intervention used (Z=3.02, P=0.003). The results of the meta-analysis can be seen in figure 7.

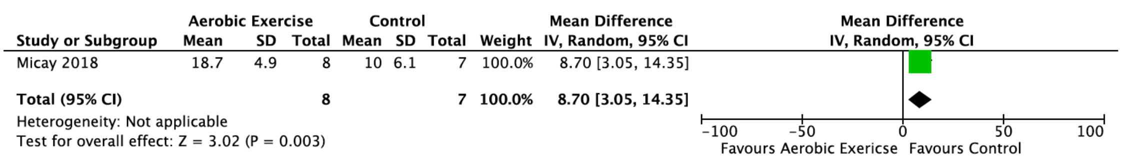


Figure 7. Aerobic Exercise's effects on changes in PCSS scores

CHAPTER FIVE

Discussion

The purpose of this systemic review and meta-analysis was to determine if the addition of aerobic exercise to an individual concussion treatment makes a significant difference in concussion symptom duration and symptom severity when compared to treatments using flexibility as a form of physical activity or traditional methods of treatment following the 2016 Berlin Consensus Statement on Concussion in Sport. Specifically, the population we were interested in was children and adolescents with a concussion.

Our null hypothesis was that concussed individuals who participate in aerobic exercise while concussed would have the same changes in symptom duration and severity as those who followed the standard of care or used a flexibility protocol. Meanwhile our alternative hypothesis was that concussed individuals who participate in aerobic exercise while concussed would have decreases in symptom duration and severity differently than those who followed the standard of care or used a flexibility protocol. Based off of the analysis of various outcomes used to measure concussion recovery that focused on either physical symptoms, cognitive symptoms, or both it can be determined that aerobic exercise is beneficial for adolescents with a concussion. It should be noted that, because of the median age of the participants of the studies, we cannot confidently apply our results so children. It should also be noted that the extent to which aerobic exercise is beneficial cannot be clearly determined by this meta-analysis because of conflicting evidence.

In regards to post concussion symptoms in adolescents, there is significant evidence that aerobic exercise can help prevent the onset of prolonged post-concussion symptoms. This conclusion is based off of the large effect size for the results of Grool et. al's 2016 study ($Z = 4.94$ ($P<0.00001$)). With this large effect size, we can be confident that there are distinct differences between the two groups. If assuming that the only difference between the two groups was the intervention, we can be confident that this difference is the light aerobic exercise that was completed by the experimental group. However, there were issues with this study and the outcome. The authors of the study did report limitations and possible rooms for error because the physical activity was self-reported by the patients and their parents (56). The researchers also suggested that a well-designed and powered randomized clinical trial should be completed in order to further establish the benefits of early return to physical activity. This is because if the individuals reported doing physical activity or exercise, they might have been exercising because they felt better but could still have had lingering symptoms. In respect to the control group, those individuals might have done more cognitively demanding tasks that could have subsequently led them to be more symptomatic (56). Another issue with this study what would have to be addressed in a well-designed randomized clinical trial would be the treatment prescribed by the physicians. The authors of this study noted that the rest and activity recommendations provided by the medical staff at the different sites could have varied between both locations and medical staff. These results help support the alternative hypothesis that aerobic exercise will decrease symptom duration and severity in adolescents. However, the lack of studies reporting absolute risk difference and the quality of the Grool et. al's study does give this outcome a GRADE rating of low and limits our ability to confidently say that this effect size could be repeated if more studies reported this outcome or Grool et. al's study had fewer issues and limitations.

Aerobic exercise does not seem to have an overall significant effect on the ImPACT scores of adolescents. There were no statistically significant differences based off of the effect sizes in memory composite verbal score (Z = 0.46, P=0.64), memory composite visual score (Z=0.34, P = 0.73), Visual Motor Speed Composite Score (Z-0.22, P = 0.83), Reaction Time Composite Score (Z = 0.00, P = 1.00), and Cognitive efficiency index (Z = 0.01, P = 0.99). Two possible reasons for the small effect sizes throughout different aspects of the ImPACT test could be the small amount of studies and the smaller sample sizes we had that reported ImPACT test scores. Having more studies and larger sample sizes that reported ImPACT test results, would have allowed for a possible greater effect size. It should be noted that there was an I^2 value of 26% when comparing the Memory composite verbal score between Chan et .al's study and Gauvin – Lepage's study. This heterogeneity could be explained by the difference in sample size. Because of the small effect size that resulted from the meta-analysis for these areas of the ImPACT test, these outcomes do not support the alternative hypothesis but do support the null hypothesis. We also cannot be confident, because of the size of the effect sizes, that any difference between the results of the groups was solely due to the presence or absence of aerobic exercise. However, all but one of the ImPACT test related outcomes were given a GRADE assessment of moderate. This was because there was a lack in the number of studies that reported ImPACT scores and scores on different portions of the

ImPACT test. It is also due to the fact that, when combining the sample sizes of both studies, there are 46 participants in the experimental group but only 22 participants in the control group. Because of the moderate GRADE assessment, we cannot be very confident that the effect sizes would be the same if more studies were done that reported these outcomes. Looking specifically at the ImPACT Reaction time composite score, this outcome received a GRADE assessment of low because of the lack of studies reporting this outcome, the difference in number of participants between the experimental and control groups, and because we know from looking at the impulse control composite scores reported, there is a possibility that errors were made while individuals were taking the test that cannot be accounted for because of a concussion.

One area of the ImPACT test that did see a statistically significant effect size was the impulse control composite score ($Z = 2.20$, $P = 0.03$). This score is representative of errors made during the reaction time tests and can be used to determine if there was confusion with testing instructions or if maximal effort was done by the athlete (60). With the statistically significant effect size for the impulse control composite score, the conclusion can be drawn that while throughout the different aspects of the ImPACT test there were no significant differences between the aerobic exercise group and the control group, the difference in the amount of errors made throughout the test between the aerobic exercise group and the control group were significant. These results suggest that while there are statistically insignificant differences between different portions of the ImPACT test, the cumulative amount of errors made by the aerobic exercise group versus the control group is significant enough to determine there is a distinct difference between the two groups. Based off of the GRADE assessment given to this outcome, moderate, we can be fairly confident that if more studies reported this outcome, similar effect sizes would be reproduced. If we assume that the only difference is the presence or absence of aerobic activity, then these results support the alternative hypothesis.

A similar situation to that in the meta-analysis of ImPACT tests occurred for the results of the meta-analysis conducted on articles reporting PCSI scores. We were able to conclude that the difference between the aerobic exercise group and the control group are not likely to be due to the intervention for the physical cluster (Z=1.31, P = 0.1), the fatigue cluster (Z=1.51, P = 0.13), the emotional cluster (Z = 0.12, P = 0.90), and the cognitive cluster (Z = 0.18, P = 0.86) of the PCSI scores. An increase in the number of studies done and then included in this meta-analysis and systemic review that used PCSI scores would result in possibly a larger effect size. There was also an I^2 value of 73% for heterogeneity between Gauvin-Lepage et. al's results and Chan et. al's results when comparing overall PCSI scores. This difference could be explained by the difference in sample sizes for each of the studies. Researchers working on Gauvin – Lepage et. al's study reported a sample size of 49 while researchers working on Chan et. al's study reported a sample size of 19. Based off of the moderate GRADE assessment for these outcomes due to the lack of studies reporting this outcome, we can be fairly confident that the effect size reported would be similar to that if more studies reported the same outcome. The results support the null hypothesis that there would be no statistically significant difference in symptom duration and severity between the aerobic exercise group and the control group assuming that the only difference between the groups was the presence or absence of aerobic exercise.

While the results reported by Micay et. al did not show a significant effect size for a difference in the days until medical clearance ((Z = 0.17, P = 0.87), it is important to note that researchers collected this data through electronic medical records that stated when a return to play decision was made. Because a medical professional is responsible for making the return to play decision, it is possible that an individual in either group could have been ready to return to play but the decision was delayed because of the individual not being able to meet with the medical professional on a earlier date or time (59). Also, as with other outcomes measured in this systematic review and meta-analysis, an increase in the number of participants and number of studies that reported days until medical clearance would allow for a greater effect size. A GRADE Assessment of moderate was given to this outcome because there was only one study that reported this outcome which results in the analysis of the outcome being biased towards Micay et. al's study. Based off of the results, the outcome "days until medical clearance" did not support our alternative hypothesis and we cannot determine that any differences in the results was due solely due to the presence or absence of aerobic exercise. Instead it supported our null hypothesis that there would be no statistically significant difference in symptom duration and severity between the aerobic exercise group and the control group.

The difference in PCSS scores between the aerobic exercise group and the control group was determined to not be significant based off of the effect size (Z=0.87, P=0.38). The same is true for the differences in the changes in the PCSS score between the aerobic exercise group and the control group based off of the effect size (Z=3.02, P=0.003). It is possible if more participants or more studies were done using these same outcomes that the effect size for these two outcomes would increase. Because there was no statistically significant difference in PCSS scores, these results support the null hypothesis and we cannot assume that any differences between the results of the two groups is solely due to the presence or absence of aerobic exercise. The GRADE assessment of this outcome due to the lack of studies reporting this outcome was moderate. This results in us being able to say that we can be fairly confident that if more studies were done, a similar effect size would be reproduced.

Based off of the results of this systemic review and meta-analysis, there does not appear to be an overall significant effect on concussion recovery when aerobic exercise is used as a treatment intervention instead of the traditional treatment recommended by the 2016 Berlin Consensus Statement on Concussion in Sport. This supports our null hypothesis because the effect sizes are not large enough for us to assume that any differences in the results are solely because of the presence or absence of aerobic exericse. However, there does appear to be a significant risk of developing prolonged post-concussion symptoms if an individual does not engage in physical activity while suffering from a concussion in comparison to if the individual participated in light intensity aerobic activity. This evidence, along with the statistically significant difference in the impulse score support our alternative hypothesis that, if we assume aerobic exercise is the only difference between the experimental group and the control group there is a difference in concussion symptoms.

This systemic review and meta-analysis had several limitations. Because of the inclusion and exclusion criteria that was determined in order to answer our research questions, only 5 articles were selected. A larger selection of articles would have allowed for a more accurate analysis of the effect of aerobic exercise on concussion recovery.

Limitations resulting from the studies could have an impact on the results of the meta-analysis. Because physical activity has only recently been advocated as a form of concussion treatment and as an intervention for concussion rehabilitation, the body of literature is scarce and still growing. In addition to the body of literature being relatively new, studies involving children and adolescents also contain larger risks when it comes to maintaining a good study quality. It also involves study designs that could result in various errors. Another limitation with using children and adolescents is the ages of individuals who are recruited and will participate. While the studies we included had an age range that included both children and adolescents, the average age of the participants from the included studies was not low enough to apply the results to both children and adolescents. Because of the average age of the participants, our results are only limited to being applicable to adolescents.

Limitations were also present because of the outcomes that were measured. Because children and adolescents are school-aged, it can be assumed that there is a possibility an athletic trainer could be overseeing the individual's recovery until the individual is assessed by a physician or other medical professional to return to play or normal activities. The outcomes we included were those that are used by athletic trainers in a school setting if an individual has a sports-related concussion. Outcomes selected to be analyzed also were related to what emergency room physicians might use while evaluating an individual. This was done because we did not limit ourselves to just sports-related concussions and it is possible if a child or adolescent acquires a concussion the individual could be evaluated by an emergency room physician. Another limitation to the outcomes included is that those that measure the presence of concussion symptoms and concussion symptom severity are prone to measurement error because what one individual might describe as severe, another individual might describe as mild or moderate. With the specific outcome days until medical clearance, published by Micay 2018, there is a limitation. The outcome, days until medical clearance, is not synonymous with days until asymptomatic. There was no reported evidence that an individual was medically cleared the same day that the individual was free of symptoms. Therefore, we cannot use days until medical clearance as a clear way to determine how long symptoms lasted.

It is important to note that the sample sizes for the outcomes could be considered a limitation. All but one of the outcomes had a very small sample size in comparison to Grool et. al's 2016 study. Increasing the sample sizes for the studies for the other outcomes and having more high quality studies completed could lead to changes in the effect sizes for various outcomes. If the effect sizes for outcomes such as PCSS, change in PCSS, PCSI, days until medical clearance, and the ImPACT clusters were to change and become statistically significant, we would be more confident in being able to reject the null hypothesis and declaring that the difference in results between the groups is a result of the presence or absence of aerobic exercise. However, because not all of the concussion outcome measures supported the null hypothesis and one of the outcomes showed a very significant effect size, we cannot be confident in rejecting the alternative hypothesis.

This systematic review and meta-analysis was conducted in order to further determine if aerobic exercise could be beneficial to children and adolescents who are diagnosed with a concussion. The PRISMA guidelines for conducting the systematic review and meta-analysis were followed. Based off of the results, while it cannot be determined that the difference in treatment with aerobic exercise versus either a flexibility program of traditional methods of treatment, it can be concluded that there is also not a significant negative effect on adolescents who undergo a treatment or intervention using aerobic exercise. This being said, there is a significant decrease in risk of developing prolonged post-concussion symptoms for adolescents who participate in light intensity aerobic exercise while concussed.

This systemic review and meta-analysis does demonstrate a need for further research to be done on the effects of aerobic exercise in children and adolescents with concussions. The lack of high GRADE assessments for the outcomes and the reasons for the assessment rating given to the outcomes provides evidence that more high quality studies should be attempted and completed. However, there are issues with this that are supported by the limitations encountered in this systemic review and meta-analysis.

In the 2016 Berlin Consensus statement on sport and concussion, the authors mentioned that there is a lack of understanding and clear definitions throughout concussion research (1). Based off of the limitations encountered through this systemic review and meta-analysis, we can support this conclusion. We can also suggest that further research studies should take into account that there is a possibility that there are discrepancies in the methods of treatment of a concussion, the recommendations for patients following a concussion, and the methods of how to test and monitor symptoms of a concussion. Researchers should also take into consideration that as treatment evolves, ethical considerations will have to be made when determining how to design a study comparing interventions and treatment methods. Researchers and physicians should also take into consideration having a universally acceptable way, or gold standard, for measuring concussion symptoms and severity in both a research and clinical setting. This would provide for better comparisons to be made between various studies and interventions used.

Aerobic exercise does not appear to show a significantly detectable detrimental effect to concussion recovery. Instead, it does show to be beneficial in long term concussion recovery by decreasing the risk of an adolescent developing prolonged post-concussion symptoms. This is important because the symptoms of a concussion can impact not only an adolescent's physical activity levels, but can impact an adolescent's attendance and performance in school. It can be concluded that, while more and better research still needs to be done to determine the extent to which aerobic exercise is beneficial, aerobic exercise could possibly be used as an intervention for adolescents with a concussion in order to decrease the risk of developing prolonged post-concussion symptoms.

APPENDIX

APPENDIX A

Supplemental figures

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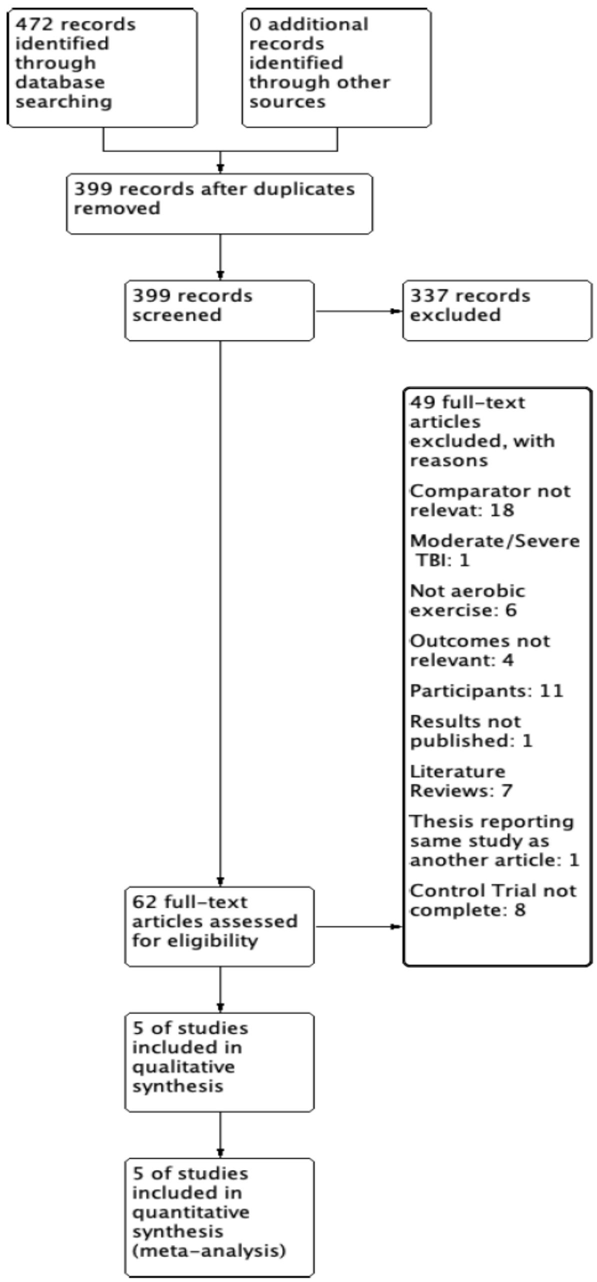

Figure A.1. PRISM (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram

Table A.1. GRADE assessment and summary of findings table

Aerobic Exercise compared to Control for Concussions in Children and Adolescents

Patient or population: Concussions in Children and Adolescents
Intervention: Aerobic Exercise
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	Risk with Aerobic Exercise				
Absolute Risk Difference assessed with: Risk of developing PPCS (prolonged post concussion symptoms)	435 per 1,000	**0 per 1,000** (0 to 0)	not estimable	1531 (1 observational study)	⨁⨁◯◯ LOW [a,b]	
PCSI - Overall	The mean PCSI - Overall was **12.16 (15.94)**	The mean PCSI - Overall in the intervention group was 6.65 lower (14.63 lower to 1.32 higher)	-	75 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]	
PCSI - Physical Cluster (SD)	The mean PCSI - Physical Cluster (SD) was **2.69 (6.82)**	The mean PCSI - Physical Cluster (SD) in the intervention group was 2.55 lower (6.36 lower to 1.26 higher)	-	49 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	
PCSI - Fatigue Cluster (SD)	The mean PCSI - Fatigue Cluster (SD) was **1.77 (3)**	The mean PCSI - Fatigue Cluster (SD) in the intervention group was 1.3 lower (2.98 lower to 0.38 higher)	-	49 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	

Aerobic Exercise compared to Control for Concussions in Children and Adolescents

Patient or population: Concussions in Children and Adolescents
Intervention: Aerobic Exercise
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	**Risk with Aerobic Exercise**				
PCSI - Emotional Cluster (SD)	The mean PCSI - Emotional Cluster (SD) was **1.23 (2.05)**	The mean PCSI - Emotional Cluster (SD) in the intervention group was 0.09 lower (1.54 lower to 1.36 higher)	-	49 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	
PCSI - Cognitive Cluster (SD)	The mean PCSI - Cognitive Cluster (SD) was **2.08 (3.9)**	The mean PCSI - Cognitive Cluster (SD) in the intervention group was 0.25 higher (2.45 lower to 2.95 higher)	-	49 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	
Change in PCSS	The mean change in PCSS was **10 (6.1)**	The mean change in PCSS in the intervention group was 8.7 higher (3.05 higher to 14.35 higher)	-	15 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	
Days Until Medical Clearance assessed with: Days	The mean days Until Medical Clearance was **29.6 (15.8)** days	The mean days Until Medical Clearance in the intervention group was 1.5 days higher (15.86 lower to 18.86 higher)	-	15 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	
PCSS	The mean PCSS was **32.2 (16.5)**	The mean PCSS in the intervention group was 7.2 lower (23.35 lower to 8.95 higher)	-	19 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	

Aerobic Exercise compared to Control for Concussions in Children and Adolescents

Patient or population: Concussions in Children and Adolescents
Intervention: Aerobic Exercise
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	Risk with Aerobic Exercise				
ImPACT - Memory composite verbal score (SD)	The mean imPACT - Memory composite verbal score (SD) was **36.95 (8.96)**	The mean imPACT - Memory composite verbal score (SD) in the intervention group was 2.57 higher (8.28 lower to 13.42 higher)	-	68 (2 RCTs)	⨁⨁◯◯ LOW [a]	
ImPACT - Memory composite visual score (SD)	The mean imPACT - Memory composite visual score (SD) was **71.03 (13.95)**	The mean imPACT - Memory composite visual score (SD) in the intervention group was 1.33 lower (8.98 lower to 6.32 higher)	-	68 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]	
ImPACT - Impulse control composite score (SD)	The mean imPACT - Impulse control composite score (SD) was **12.45 (8.84)**	The mean imPACT - Impulse control composite score (SD) in the intervention group was 5.6 lower (10.58 lower to 0.62 lower)	-	49 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	
ImPACT - Cognitive efficiency index (SD)	The mean imPACT - Cognitive efficiency index (SD) was **.29(.13)**	The mean imPACT - Cognitive efficiency index (SD) in the intervention group was 0.02 higher (4.23 lower to 4.27 higher)	-	49 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	

Aerobic Exercise compared to Control for Concussions in Children and Adolescents

Patient or population: Concussions in Children and Adolescents
Intervention: Aerobic Exercise
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	**Risk with Aerobic Exercise**				
ImPACT - Visual motor speed composite score (SD)	The mean imPACT - Visual motor speed composite score (SD) was **35.28 (3.8)**	The mean imPACT - Visual motor speed composite score (SD) in the intervention group was 0.33 higher (2.63 lower to 3.28 higher)	-	68 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]	
ImPACT - Reaction time composite score (SD)	The mean imPACT - Reaction time composite score (SD) was **0.617 (0.03)** seconds	The mean imPACT - Reaction time composite score (SD) in the intervention group was 0 seconds (0.04 lower to 0.04 higher)	-	68 (2 RCTs)	⨁⨁◯◯ LOW [a]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. 3 or less studies for this outcome
b. poor quality study

Table A.2. Assessment and description of various concussion assessments.

Assessment	Description
Balance Error Scoring System (BESS)	A test designed to measure static posture stability. An individual completes a series of stances including a double leg stance, single leg stance, and a tandem stance. Each stance is held for 20 seconds on a firm surface and then also on a foam surface. An individual can make a total number of 10 errors maximum for each condition. The errors are defined by certain movements leading to changes in the stance being held by the individual. A modified version of this test is part of the SCAT5. (61)
Immediate post-concussion assessment and cognitive testing (ImPACT)	A computerized test that uses various neuropsychological tests and screenings to assess a sports related concussion. (60)
Post-Concussion Symptom Scale Score (PCSS)	A total of 22 symptoms that can be rated on a 0-6 scale. This can also be part of the SCAT3 or SCAT5 test (55).
SCAT3/SCAT5	A collection of neuropsychological tests that can be administered on a sideline of a sporting event. It consists of a modified BESS, Maddocks' questions, and the Standardized Assessment of Concussion. It also consists of an immediate or on-field assessment, an office or off-field assessment, cognitive screening, neurological screening, and tests assessing delayed recall (62).
Maddock's questions	A series of questions that assess memory and are part of the SCAT5 test (1)
VOMS	responsible for assessing vestibular and oculomotor control in five different areas: 1) smooth pursuit 2) saccades 3) near point convergence (NPC) 4) horizontal vestibular ocular reflex 5) visual motion sensitivity (VMS) (35)

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