Exercise for Sport-Related Concussion and Persistent Postconcussive Symptoms

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Context: Emerging research supports the use of mild to moderate aerobic exercise for treating sport-related concussion (SRC) and persistent postconcussive symptoms (PPCS), yet the current standard of care remains to be strict rest. The purpose of this review is to summarize the existing literature on physical activity and prescribed exercise for SRC and PPCS.

Evidence Acquisition: PubMed and Embase were searched in April of 2019 for studies assessing rest or prescribed exercise for SRC and PPCS. No specific search syntax was used.

Study Design: Clinical review.

Level of Evidence: Level 4.

Results: A majority of studies show that spontaneous physical activity is safe after SRC and that subsymptom threshold aerobic exercise safely speeds up recovery after SRC and reduces symptoms in those with PPCS. Exercise tolerance can safely be assessed using graded exertion test protocols within days of injury, and the degree of early exercise tolerance has diagnostic and prognostic value.

Conclusion: Subsymptom threshold aerobic exercise is safe and effective for the treatment of SRC as well as in athletes with PPCS. Further research is warranted to establish the most effective method and dose of aerobic exercise for the active treatment of SRC and whether early exercise treatment can prevent PPCS in athletes.

Strength of Recommendation Taxonomy: 2.

Keywords: sport-related concussion; subsymptom threshold aerobic exercise; treatment; postconcussion syndrome; persistent postconcussive symptoms

Sport-related concussion (SRC) is defined by the most recent Concussion in Sport Group (CISG) consensus statement as a subset of mild traumatic brain injury, caused by a force applied directly to the head or elsewhere on the body with impulsive forces transmitted to the brain producing transient functional impairments.³⁷ SRC causes a range of somatic, cognitive, sleep, and affective symptoms,⁸ including symptom-limited exercise intolerance; that is, the inability to exercise to near age-appropriate maximum heart rate due to exacerbation of concussion-related symptoms.²¹ The exact cause of exercise intolerance is unclear, but it is suspected to be due to impairment of autonomic nervous system

regulation of cerebral blood flow (CBF), which may be due to damage to the autonomic nervous system centers and/or to uncoupling of these centers from the cardiovascular nervous system.^{23,33} In most cases of SRC, symptoms rapidly decline over the first 2 weeks, however, 10%⁵² to 30%¹⁶ of adolescents and 10% to 15%^{20,44} of adults may take longer to recover. Symptoms that persist for more than 2 weeks in adults or for more than 1 month in adolescents are now referred to as persistent postconcussive symptoms (PPCS).³⁷

Treatment of SRC and of PPCS has changed dramatically over the past 2 decades. The previous standard of care recommended complete physical and cognitive rest until all

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symptoms resolved.^{1,38} This “cocooning” model of care was supported by animal (male Sprague-Dawley rats) studies that showed excessive physical and/or cognitive activity within days to weeks after simulated concussion prolonged cognitive recovery, particularly if the activity was imposed on them.¹³ Conversely, when these animals were allowed to perform voluntary, self-limited exercise, they improved cognitive task performance in association with upregulation of brain-derived neurotrophic factor (BDNF).¹⁴ BDNF promotes neuron growth and repair and is associated with increased hippocampal volume and improved spatial memory.¹⁰ Human studies have also shown that exercise increases BDNF levels as early as 5 to 6 weeks after initiation of aerobic training, in association with enhanced brain neuroplasticity.^{15,47}

Emerging research is revealing the benefits of prescribing mild to moderate levels of physical activity after SRC, which has led to a significant change in the management of SRC and of PPCS. The most recent CISC guidelines³⁷ recommend a short period of relative rest (24–48 hours) followed by a graded return to activity while staying below symptom exacerbation thresholds. The purpose of this review is to summarize the published literature on rest versus mild to moderate levels of physical activity, either spontaneous or prescribed, on symptom improvement in SRC and PPCS.

PubMed and Embase were searched in April of 2019 for studies assessing rest, activity, or prescribed exercise for SRC and PPCS. No specific search syntax was used. Details of included studies are presented in Table 1.

PREScribed REST AFTER SRC AND PPCS

Complete physical and cognitive rest has been the standard of care for concussive head injuries for decades. A retrospective study⁴⁹ assessed 95 adolescents with acute concussion (68% SRC) and found that an immediate return to physical and cognitive activity after injury resulted in a 4.6-day delay in symptom recovery compared with those who were prescribed immediate rest. The authors not only concluded that an initial period of rest before resuming activity was beneficial but also noted that rest was only beneficial if instituted within 7 days postinjury. Another retrospective study³⁵ of 95 adolescent athletes (all with SRC) found that high levels of physical activity (ie, sports participation) were associated with more symptoms and worse neurocognitive scores than those who reported moderate levels of physical activity. A larger prospective study on 335 adolescent athletes with SRC³ also showed an association between cognitive activity in the few weeks after injury and longer recovery time. In a prospective randomized trial,³⁴ researchers assigned college athletes to rest or to 20 minutes of mild to moderate aerobic exercise in the first days after SRC. The exercise group recovered in 15 days versus 13 days for the rest group, which was not statistically different. They also reported that athletes who performed more vigorous exercise tended to take longer to recover. Nevertheless, the authors concluded that mild to moderate aerobic exercise was

safe to perform early after SRC and that transient symptom exacerbation was not harmful. A prospective, nonrandomized trial⁴ of 50 acutely concussed collegiate athletes compared a prescription for 1 day of physical and cognitive rest with no days of rest. The group that did not rest became asymptomatic significantly sooner than the group prescribed rest (3.9 vs 5.2 days), suggesting that a prescribed day of cognitive and physical rest was not effective in this cohort. A randomized controlled trial (RCT)⁵⁰ performed in the emergency department compared a recommendation of 5 days of strict rest with 2 days of strict rest immediately after concussion in 88 adolescents; the authors found no benefit, as the 5-day rest group remained symptomatic longer. A reanalysis of this sample⁴⁸ reported that patients who predominantly had *symptoms* (headache, dizziness) were more likely to remain symptomatic if prescribed rest, whereas patients with *signs* of injury (loss of consciousness, posttraumatic amnesia/confusion) benefited more from a recommendation to rest. In another reanalysis of this sample using 63 participants,⁴⁶ the authors reported that increased cognitive activity (defined as returning to school and extracurricular activities), but not physical activity, was associated with an acute increase in symptoms. This exacerbation typically resolved within 24 hours and was not associated with delayed recovery.⁴⁶

The limitations of the studies that provided evidence supporting prescribed rest were either not randomized^{3,46,49} or compared rest with an excessive form of physical activity, such as sports participation,³⁵ which is a known risk when the brain is still concussed, as it increases the likelihood of another head injury.³⁶ While the remaining studies did not provide explicit evidence supporting the use of prescribed physical activity after SRC, they concluded that mild to moderate levels of spontaneous physical activity were safe to perform^{34,46} or that rest was not beneficial.^{4,48,50} It is for these reasons the most recent CISC guidelines only recommend a short period of relative rest (24–48 hours) after SRC before beginning moderate physical activity.³⁷

PREScribed PHYSICAL ACTIVITY FOR PPCS

The first application of exercise as treatment for concussion was in adolescents with PPCS. In a 2009 prospective case-controlled study of adolescents with PPCS (>6 weeks' duration),¹¹ prescribed generic submaximal aerobic exercise (50% to 60% of estimated maximal capacity) was combined with coordination and visualization exercises. The authors found that an active intervention program, including aerobic exercise, safely improved recovery in children and adolescents who were slow to recover. In close proximity to that study, another small prospective trial³¹ systematically evaluated the level of exercise tolerance in adult athletes and nonathletes with PPCS using the Buffalo Concussion Treadmill Test (BCTT). The heart rate at symptom exacerbation was used to prescribe a progressive program of individualized subsymptom threshold aerobic exercise, which safely sped recovery when compared with a no-intervention run-in period. This study also established the

Table 1. Details of included studies

Study	Study Design	Sample Size	Mean Age	Sex
Brown et al 2014 ³	Retrospective cohort	335	15 y (range 8-23 y)	62% male
Buckley et al 2016 ⁴	Quasi-experimental	50	19.6 y	62% male
Chrisman et al 2017 ⁵	Retrospective cohort	83	14.9 ± 2.3 y	54% female
Cordingley et al 2016 ⁶	Retrospective cohort	106	15.1 y (range 11-19 y)	57% female
Dematteo et al 2015 ⁷	Prospective cohort	54	Range 8.5-18.3 y	59% male
Gagnon et al 2009 ¹¹	Prospective case series	16	14.25 y (range 8-17 y)	69% male
Gauvin-Lepage et al 2018 ¹²	Quasi-experimental	49	13.8 y (range 8-17 y)	53% female
Grool et al 2016 ¹⁶	Prospective cohort	2413	11.77 ± 3.4 y	61% male
Howell et al 2016 ¹⁸	Prospective cohort	364	15 y (range 8-27 y)	61% male
Kurowski et al 2017 ²²	RCT	30	15.4 y (range 12-17 y)	57% female
Lawrence et al 2018 ²⁴	Retrospective cohort	253	Median age 17 y	59% male
Leddy et al 2010 ³¹	Prospective case series	11	15.8 y (range 13-22 y)	64% male
Leddy et al 2013 ²⁷	Quasi-experimental	12	22 y (range 18-33 y)	64% female
Leddy et al 2019 ²⁹	Quasi-experimental	54	15.13 ± 1.4 y	All male
Leddy et al 2019 ²⁸	RCT	103	15.4 ± 1.7 y	54% male
Maerlender et al 2015 ³⁴	RCT	28	College-aged	71% female
Majerske et al 2008 ³⁵	Retrospective cohort	95	15.88 ± 1.35 y	84% male
McGeown et al 2018 ³⁹	Prospective cohort	9	16.3 y (range 14-21 y)	56% female
Micay et al 2018 ⁴⁰	RCT	15	15.7 y (range 14-18 y)	All male
Popovich et al 2018 ⁴³	Retrospective cohort	124	15.4 y	71% male
Rytter et al 2019 ⁴⁵	RCT	89	Adults (range 18-65 y)	66% female
Silverberg et al 2016 ⁴⁶	RCT	63	13.8 ± 1.8 y	65% male
Sufrinko et al 2017 ⁴⁸	RCT	93	13.87 ± 1.68 y	65% male
Taubman et al 2016 ⁴⁹	Prospective cohort	95	14.3 ± 2.0	60% male
Thomas et al 2015 ⁵⁰	RCT	88	Median age 13.7 y	64% male

RCT, randomized controlled trial.

safety of the BCTT for assessing exercise tolerance in patients with prolonged symptoms after concussion. In a subsequent study,²⁷ the same authors reported that subsymptom aerobic exercise restored local CBF regulation (on functional magnetic resonance imaging) when compared with a placebo-like stretching intervention, suggesting that aerobic exercise had a physiological effect on the cerebrovascular of the concussed brain. These small nonrandomized studies were among the first

to provide evidence that subsymptom exercise could safely improve symptoms in patients with PPCS.

Several studies performed since 2010 provide substantial evidence for the usefulness of prescribing light to moderate physical activity as treatment for PPCS. A retrospective study⁵ including 83 adolescents with PPCS, mostly after SRC, reported an exponential decrease in symptoms after initiating a prescribed subsymptom aerobic exercise program. Similarly, a

prospective intervention trial³⁹ found a significant improvement in symptom scores and, to a lesser degree, cognitive function and static balance in 9 patients with PPCS (mean duration, 3 months) after a 4-week active rehabilitation program (12 one-hour subsymptom stationary cycle workouts). The authors concluded that active treatment improved outcome more than rest-based treatments. Efficacy of exercise has also been reported in the nonsport-injured population. An exploratory randomized trial²² assigned 30 adolescents with PPCS (lasting 4-16 weeks) after nonsport-related mild traumatic brain injury to either subsymptom aerobic training or to a full-body placebo-stretching program. Despite lower adherence to the home aerobic exercise program, symptoms improved faster over 6 weeks in the aerobic training group, suggesting a physiological effect of aerobic exercise on recovery. Importantly, the authors included only those patients with demonstrated exercise intolerance and excluded those with substantial cervical injury. This may reduce the generalizability of their findings since a high percentage of individuals with concussion have concomitant sprains/strains of the cervical region.⁴¹ Last, an RCT⁴⁵ published in 2019 assessed the effectiveness of a specialized 22-week interdisciplinary rehabilitation protocol (including exercise) added to the current standard of care (cognitive and physical rest) in patients with PPCS for longer than 6 months. The intervention group had significantly improved scores in the physical, cognitive, and emotional domains; and had improved social functioning, increased levels of activity, reduced mental fatigue, and increased life satisfaction when compared with the standard of care rest group.

PRESCRIBED PHYSICAL ACTIVITY FOR SRC

Recent studies have begun to examine the effect of prescribed physical activity in the acute and subacute phases after SRC. This represents a paradigm shift in the management of SRC since the first international CISC guidelines, written less than 2 decades ago, required an athlete to rest from physical activity and to be completely asymptomatic with normal neurological and cognitive evaluations before starting any physical rehabilitation.¹ Prospective interventional studies^{19,40} prescribing subsymptom exercise within 1 week of injury in adolescents after SRC have concluded that mild to moderate exercise is safe to perform while patients are still symptomatic.

A retrospective study²⁴ examining the time of initiation of aerobic exercise with duration of clinical recovery in 253 acutely concussed adolescents found that earlier initiation of aerobic exercise was associated with earlier return to sport and/or school, while each day aerobic exercise was delayed was associated with a less favorable recovery trajectory. Another retrospective study⁴³ found that patients prescribed a structured exercise program within 16 days of injury recovered and returned to sport faster than those who were not prescribed any structured exercise (mean 26.5 vs 35.1 days). A prospective study⁶ prescribed an individualized submaximal aerobic exercise program based on performance on the BCTT to adolescents

after SRC. Of those who had complete follow-ups, 90% improved clinically and 81% returned to sporting activities. Those who did not respond included 7 patients with migraines and 1 with a psychiatric disorder. The authors concluded that prescribed exercise based on a systematic evaluation of exercise tolerance was safe in the management of pediatric SRC. A large prospective observational study¹⁶ followed 2413 concussed children for a month after they presented to the emergency department. Patients reporting return to some form of physical activity within 7 days of injury had a significantly lower risk of PPCS at 4 weeks (24.6% vs 43.5%) compared to those reporting rest.

The strongest evidence supporting the use of prescribed physical activity is from 2 randomized and nonrandomized clinical trials. In a nonrandomized trial,²⁹ adolescent males were prescribed either 20 minutes of daily subsymptom aerobic exercise or strict rest within the first week of injury (mean 5 days). The aerobic exercise group recovered faster (mean days to recovery since start of intervention, 8.3 vs 23.9), and most symptom types (eg, cognitive, physical) improved in a similar manner and rate regardless of whether there was spontaneous improvement (ie, during rest) or improvement aided by exercise. A quasi-experimental trial¹² that compared active rehabilitation (aerobic exercise and other nonpharmacological interventions) with standard of care found that it significantly improved symptom recovery, quality of life, and anger level. In the largest RCT to date,²⁸ adolescents within 10 days of SRC (mean 5 days) were assigned to a recommendation of either 20 minutes of daily subsymptom threshold aerobic exercise (calculated as 80% of the heart rate achieved on the BCTT at symptom exacerbation) or to a placebo-like stretching program that would not elevate heart rate. The aerobic exercise group became asymptomatic in a significantly shorter number of days than the group prescribed stretching (median of 13 vs 17 days), even after controlling for sex and initial symptom severity. These data were reanalyzed and compared with a historic cohort of age- and sex-matched adolescents who had been prescribed relative rest.⁵¹ The group that was prescribed aerobic exercise early after SRC recovered significantly faster than those prescribed relative rest or the placebo-stretching program. Interestingly, this study found that female patients prescribed relative rest had an increase in symptoms the day after the recommendation for rest, which was not seen in the other groups. These 2 studies provide some of the strongest evidence yet for the efficacy and safety of early individualized aerobic exercise for the treatment of SRC.

EXERCISE TOLERANCE ASSESSMENT FOR MANAGEMENT OF SRC AND PPCS

Exercise intolerance, that is, the worsening of concussion-specific symptoms that limits physical exertion, is a physiological biomarker of SRC³⁰ and is present in some cases of PPCS.^{9,25} The degree of exercise intolerance can assist in identifying symptom generators after SRC. Early exercise intolerance (defined as symptom exacerbation at <70% of

age-appropriate maximum heart rate) is characteristic of autonomic/physiological dysfunction in SRC and PPCS,³² which is believed to reflect abnormal autonomic control of CBF during exercise. Exercise intolerance later in the test (defined as symptom exacerbation at $\geq 70\%$ of age appropriate maximum heart rate) is often associated with other causes of symptoms, for example, vestibulo-ocular and/or cervical posttraumatic disorders. These disorders can be confirmed by the presence of abnormal physical examination findings, for example, positional vertigo or cervical strain.²⁶

The safety of exercise tolerance testing after concussion has been assessed in several studies. A prospective study⁷ performed the McMaster All-Out Progressive Continuous Cycling Test on adolescents with PPCS, and although there was an increase in symptoms on the day of the test, participants improved significantly within 24 hours of performing the exercise test. The authors concluded that graded exertion testing was safe and important for the evaluation of symptoms and readiness to return to activity, particularly in those who are slow to recover. An RCT³⁰ assigned adolescents with SRC (1-10 days since injury) to perform the BCTT at the initial clinical visit or not and longitudinally tracked their symptoms. There were no significant differences in daily symptoms or recovery duration between the 2 cohorts, providing evidence that exercise testing is safe to perform in the acute period after SRC, provided the test stopping criteria are followed. This study also found a strong correlation with the heart rate at symptom exacerbation on the BCTT and duration of recovery (the lower the heart rate, ie, the worse the exercise tolerance, the longer the recovery, even after accounting for initial symptom burden). This relationship was subsequently validated in 3 separate cohorts,¹⁷ suggesting exercise tolerance within a week of SRC is a physiological biomarker for the severity of SRC.

METHODS OF PRESCRIBING SUBSYMPTOM THRESHOLD EXERCISE AFTER SRC

The methods for prescribing exercise after SRC vary in the literature. The majority of studies^{5,11,12,19,34,39,43,45} used a generic (percentage of estimated maximum heart rate) low to moderate intensity exercise prescription. Three studies^{6,28,29} assessed individualized level of exercise tolerance using the BCTT and prescribed at least 20 minutes of aerobic exercise at 80% of the heart rate achieved on the BCTT. Although individualized medicine is considered superior, there are currently no studies comparing personalized, targeted heart rate exercise with a generic exercise prescription.

If systematic exercise tolerance testing is available, a tailored subsymptom threshold aerobic exercise prescription can be provided. Patients are advised to exercise for at least 20 minutes a day at 80% to 90% of the maximum heart rate achieved on symptom exacerbation, or until symptom exacerbation occurs. Patients should typically return every 1 to 2 weeks to reassess exercise tolerance for a new exercise prescription.²⁸ If exercise

tolerance testing is not available, a more conservative approach can be utilized. Concussed patients can calculate their age-appropriate maximum heart rate using the Karvonen equation⁴² (maximum heart rate $HR_{max} = 220 - \text{age in years}$) and begin exercising at 50% of their maximum using a consumer-approved heart rate monitoring device. If patients are able to tolerate this intensity of exercise without worsening of symptoms, they can increase their target heart rate prescription by 5 to 10 beats the subsequent day. If patients begin to feel symptomatic at a specific intensity of exercise, they should perform aerobic exercise below that level until they are able to tolerate higher intensities.² It is of paramount importance to caution patients to avoid sustained exercise above the symptom threshold because it may prolong symptoms.^{34,35} Aerobic exercise is recommended over resistance exercise (eg, rowing and weight lifting) because the concussed brain cannot tolerate wide swings in blood pressure. The authors recommend stationary biking to begin with since it is safe and minimizes head motion. If that is tolerated, then the patient may advance to brisk walking or jogging, either on a treadmill or outside. Swimming is an ideal form of aerobic exercise, but patients may find it hard to actively monitor their heart rate, although water jogging with a flotation device would be acceptable. Similarly, outdoor biking is not recommended to begin with, as those with vestibular dysfunction may be at risk for high velocity falls and further trauma. Patients should be exercise tolerant, have returned to a baseline level of symptoms, and have a normal physical examination before starting a graduated return-to-play protocol.³⁷

LIMITATIONS

The primary limitation is that this is not a systematic review and does not represent the cumulative view of all of the published literature on exercise and SRC; it is, therefore, at risk of selection bias.

CONCLUSION

The most recent CISC guidelines state that there is insufficient evidence to support prescribing prolonged physical or cognitive rest after SRC. Emerging research is demonstrating the safety of mild to moderate levels of spontaneous physical activity after concussion and the efficacy of prescribed individualized subsymptom threshold aerobic exercise for improving outcome after acute SRC, which may also reduce the risk of PPCS in athletes. It is important that providers give patients specific instructions on acceptable activity levels after SRC since intense physical and cognitive activity too soon after SRC, such as very early return to school or to sports participation, have been associated with acute symptom exacerbation. Systematic evaluation of exercise tolerance is safe to perform within days of SRC, and the level of early exercise tolerance has important diagnostic and prognostic value. Further studies are encouraged to determine the optimum dose and mode of aerobic exercise

for amelioration of symptoms and for the prevention of delayed recovery after SRC, and to study appropriate methods to improve cognition after SRC.

REFERENCES

- Aubry M, Cantu R, Dvorkin J, et al; Concussion in Sport Group. Summary and agreement statement of the First International Conference on Concussion in Sport, Vienna 2001. Recommendations for the improvement of safety and health of athletes who may suffer concussive injuries. *Br J Sports Med*. 2002;36:6-10.
- Bezherano I, Haider MN, Willer BS, Leddy JJ. Practical management: prescribing subsymptom threshold aerobic exercise for sport-related concussion in the outpatient setting [published online February 13, 2020]. *Clin J Sport Med*. doi:10.1097/JSM.0000000000000809
- Brown NJ, Mannix RC, O'Brien MJ, Gostine D, Collins MW, Meehan WP. Effect of cognitive activity level on duration of post-concussion symptoms. *Pediatrics*. 2014;133:e299-e304.
- Buckley TA, Munkasy BA, Clouse BP. Acute cognitive and physical rest may not improve concussion recovery time. *J Head Trauma Rehabil*. 2016;31:233-241.
- Chrisman SP, Whitlock KB, Somers E, et al. Pilot study of the Sub-Symptom Threshold Exercise Program (SSTEP) for persistent concussion symptoms in youth. *NeuroRehabilitation*. 2017;40:493-499.
- Cordingley D, Girardin R, Reimer K, et al. Graded aerobic treadmill testing in pediatric sports-related concussion: safety, clinical use, and patient outcomes. *J Neurosurg Pediatr*. 2016;18:693-702.
- Dematteo C, Volterman KA, Breithaupt PG, Claridge EA, Adamich J, Timmons BW. Exertion testing in youth with mild traumatic brain injury/concussion. *Med Sci Sports Exerc*. 2015;47:2283-2290.
- Elbin RJ, Knox J, Kegel N, et al. Assessing symptoms in adolescents following sport-related concussion: a comparison of four different approaches. *Appl Neuropsychol Child*. 2016;5:294-302.
- Ellis MJ, Leddy JJ, Willer B. Physiological, vestibulo-ocular and cervicogenic post-concussion disorders: an evidence-based classification system with directions for treatment. *Brain Inj*. 2015;29:238-248.
- Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*. 2011;108:3017-3022.
- Gagnon I, Galli C, Friedman D, Grilli L, Iverson GL. Active rehabilitation for children who are slow to recover following sport-related concussion. *Brain Inj*. 2009;23:956-964.
- Gauvin-Lepage J, Friedman D, Grilli L, et al. Effectiveness of an exercise-based active rehabilitation intervention for youth who are slow to recover after concussion [published online August 8, 2018]. *Clin J Sport Med*. doi:10.1097/JSM.0000000000000634
- Giza CC, Hovda DA. The neurometabolic cascade of concussion. *J Athl Train*. 2001;36:228-235.
- Griesbach GS, Tio DL, Vincelli J, McArthur DL, Taylor AN. Differential effects of voluntary and forced exercise on stress responses after traumatic brain injury. *J Neurotrauma*. 2012;29:1426-1435.
- Griffin EW, Mullally S, Foley C, Warmington SA, O'Mara SM, Kelly AM. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiol Behav*. 2011;104:934-941.
- Grool AM, Aglipay M, Momoli F, et al; Pediatric Emergency Research Canada (PERC) Concussion Team. Association between early participation in physical activity following acute concussion and persistent postconcussive symptoms in children and adolescents. *JAMA*. 2016;316:2504-2514.
- Haider MN, Leddy JJ, Wilber CG, et al. The predictive capacity of the Buffalo Concussion Treadmill Test after sport-related concussion in adolescents. *Front Neurol*. 2019;10:395.
- Howell DR, Mannix RC, Quinn B, Taylor JA, Tan CO, Meehan WP 3rd. Physical activity level and symptom duration are not associated after concussion. *Am J Sports Med*. 2016;44:1040-1046.
- Howell DR, O'Brien MJ, Beasley MA, Mannix RC, Meehan WP 3rd. Initial somatic symptoms are associated with prolonged symptom duration following concussion in adolescents. *Acta Paediatr*. 2016;105:e426-e432.
- Jotwani V, Harmon KG. Postconcussion syndrome in athletes. *Curr Sports Med Rep*. 2010;9:21-26.
- Kozlowski KF, Graham J, Leddy JJ, Devinney-Boymel L, Willer BS. Exercise intolerance in individuals with postconcussion syndrome. *J Athl Train*. 2013;48:627-635.
- Kurowski BG, Hugentobler J, Quatman-Yates C, et al. Aerobic exercise for adolescents with prolonged symptoms after mild traumatic brain injury: an exploratory randomized clinical trial. *J Head Trauma Rehabil*. 2017;32:79-89.
- La Fontaine MF, Heffernan KS, Gossett JD, Bauman WA, De Meersman RE. Transient suppression of heart rate complexity in concussed athletes. *Auton Neurosci*. 2009;148:101-103.
- Lawrence DW, Richards D, Comper P, Hutchison MG. Earlier time to aerobic exercise is associated with faster recovery following acute sport concussion. *PLoS One*. 2018;13:e0196062.
- Leddy J, Baker JG, Haider MN, Hinds A, Willer B. A physiological approach to prolonged recovery from sport-related concussion. *J Athl Train*. 2017;52:299-308.
- Leddy J, Lesh K, Haider MN, et al. Derivation of a focused, brief concussion physical examination for adolescents with sport-related concussion [published online October 29, 2018]. *Clin J Sport Med*. doi:10.1097/JSM.0000000000000686
- Leddy JJ, Cox JL, Baker JG, et al. Exercise treatment for postconcussion syndrome: a pilot study of changes in functional magnetic resonance imaging activation, physiology, and symptoms. *J Head Trauma Rehabil*. 2013;28:241-249.
- Leddy JJ, Haider MN, Ellis MJ, et al. Early subthreshold aerobic exercise for sport-related concussion: a randomized clinical trial. *JAMA Pediatr*. 2019;173:319-325.
- Leddy JJ, Haider MN, Hinds AL, Darling S, Willer BS. A preliminary study of the effect of early aerobic exercise treatment for sport-related concussion in males. *Clin J Sport Med*. 2019;29:353-360.
- Leddy JJ, Hinds AL, Miecznikowski J, et al. Safety and prognostic utility of provocative exercise testing in acutely concussed adolescents: a randomized trial. *Clin J Sport Med*. 2018;28:13-20.
- Leddy JJ, Kozlowski K, Donnelly JP, Pendergast DR, Epstein LH, Willer B. A preliminary study of subsymptom threshold exercise training for refractory post-concussion syndrome. *Clin J Sport Med*. 2010;20:21-27.
- Leddy JJ, Kozlowski K, Fung M, Pendergast DR, Willer B. Regulatory and autoregulatory physiological dysfunction as a primary characteristic of post concussion syndrome: implications for treatment. *NeuroRehabilitation*. 2007;22:199-205.
- Len T, Neary J. Cerebrovascular pathophysiology following mild traumatic brain injury. *Clin Physiol Funct Imaging*. 2011;31:85-93.
- Maerlender A, Rieman W, Lichtenstein J, Condricci C. Programmed physical exertion in recovery from sports-related concussion: a randomized pilot study. *Dev Neuropsychol*. 2015;40:273-278.
- Majerske CW, Mihalik JP, Ren D, et al. Concussion in sports: postconcussive activity levels, symptoms, and neurocognitive performance. *J Athl Train*. 2008;43:265-274.
- McCreary M, Broglio S, McAllister T, et al. Return to play and risk of repeat concussion in collegiate football players: comparative analysis from the NCAA Concussion Study (1999-2001) and CARE Consortium (2014-2017). *Br J Sports Med*. 2020;54:102-109.
- McCrory P, Meeuwisse W, Dvořák J, et al. Consensus statement on concussion in sport—the 5th International Conference on Concussion in Sport held in Berlin, October 2016. *Br J Sports Med*. 2017;51:838-847.
- McCrory P, Meeuwisse W, Johnston K, et al. Consensus statement on concussion in sport: the 3rd International Conference on Concussion in Sport held in Zurich, November 2008. *Br J Sports Med*. 2009;43(suppl 1):i76-i90.
- McGeown JP, Zerpa C, Lees S, Niccoli S, Sanzo P. Implementing a structured exercise program for persistent concussion symptoms: a pilot study on the effects on salivary brain-derived neurotrophic factor, cognition, static balance, and symptom scores. *Brain Inj*. 2018;32:1556-1565.
- Micay R, Richards D, Hutchison MG. Feasibility of a postacute structured aerobic exercise intervention following sport concussion in symptomatic adolescents: a randomised controlled study. *BMJ Open Sport Exerc Med*. 2018;4:e000404.
- Morin M, Langevin P, Fait P. Cervical spine involvement in mild traumatic brain injury: a review. *J Sports Med*. 2016;2016:1590161.
- Peres G, Vandewalle H, Havette P. Heart rate, maximal heart rate and pedal rate. *J Sports Med Phys Fitness*. 1987;27:205-210.
- Popovich M, Almeida A, Freeman J, et al. Use of supervised exercise during recovery following sports-related concussion. *Neurology*. 2018;91(23 suppl 1):S15.
- Prigatano GP, Gale SD. The current status of postconcussion syndrome. *Curr Opin Psychiatry*. 2011;24:243-250.
- Rytter HM, Westenbaek K, Henriksen H, Christiansen P, Humle F. Specialized interdisciplinary rehabilitation reduces persistent post-concussive symptoms: a randomized clinical trial. *Brain Inj*. 2019;33:266-281.
- Silverberg ND, Iverson GL, McCreary M, Apps JN, Hammeke TA, Thomas DG. Activity-related symptom exacerbations after pediatric concussion. *JAMA Pediatr*. 2016;170:946-953.
- Stroth S, Hille K, Spitzer M, Reinhardt R. Aerobic endurance exercise benefits memory and affect in young adults. *Neuropsychol Rehabil*. 2009;19:223-243.

-
48. Sufrinko AM, Kontos AP, Apps JN, et al. The effectiveness of prescribed rest depends on initial presentation after concussion. *J Pediatr*. 2017;185:167-172.
 49. Taubman B, Rosen F, McHugh J, Grady MF, Elci OU. The timing of cognitive and physical rest and recovery in concussion. *J Child Neurol*. 2016;31:1555-1560.
 50. Thomas DG, Apps JN, Hoffmann RG, McCrea M, Hammeke T. Benefits of strict rest after acute concussion: a randomized controlled trial. *Pediatrics*. 2015;135:213-223.
 51. Willer BS, Haider MN, Bezherano I, et al. Comparison of rest to aerobic exercise and placebo-like treatment of acute sport-related concussion in male and female adolescents. *Arch Phys Med Rehabil*. 2019;100:2267-2275.
 52. Williams RM, Puetz TW, Giza CC, Broglio SP. Concussion recovery time among high school and collegiate athletes: a systematic review and meta-analysis. *Sports Med*. 2015;45:893-903.
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