

A Randomized Controlled Trial Investigating the Feasibility and Adherence to an Aerobic Training Program in Healthy Individuals

Elizabeth F. Teel, Stephen W. Marshall, L. Gregory Appelbaum, Claudio L. Battaglini, Kevin A. Carneiro, Kevin M. Guskiewicz, Johna K. Register-Mihalik, and Jason P. Mihalik

Context: Concussion management is moving from passive rest strategies to active interventions, including aerobic exercise therapy. Little information is available regarding the feasibility and adherence of these programs. **Objectives:** To determine whether an aerobic exercise training program intended for rehabilitation in people with concussion is feasible. Healthy, nonconcussed subjects were studied in this phase 1 trial. **Design:** Phase 1 parallel-group, randomized controlled trial in a sample of healthy (nonconcussed), recreationally active university students. **Setting:** Laboratory. **Patients:** 40 healthy university students. **Methods:** Participants were equally randomized to acute concussion therapy intervention (ACTIVE) training or nontraining groups. All participants completed maximal cardiopulmonary exercise tests on a stationary cycle ergometer at 2 test sessions approximately 14 days apart. During this 2-week study period, ACTIVE training participants completed six 30-minute cycling sessions, progressing from 60% to 80% of the participant's individualized maximal oxygen consumption. A subset of participants ($N_{ACTIVE} = 12$, $N_{nontraining} = 11$) wore physical activity monitors throughout the 2-week study period. **Main Outcomes Measures:** Study protocol and randomization effectiveness, exercise safety and adherence, and progressive intensity of the ACTIVE training procedures. **Results:** No adverse events occurred during any exercise sessions. Twelve ACTIVE training participants (60%) completed all training sessions, and every participant completed at least 4 sessions. Heart rate increased throughout the training period ($P < .001$), but symptom changes and training adherence remained stable despite the progressively increasing workload. ACTIVE training participants completed approximately 30 additional minutes of physical activity on training sessions days, although that was not statistically significant ($P = .20$). **Conclusions:** University-aged students were adherent to the ACTIVE training protocol. Future research should investigate the safety and feasibility of aerobic training programs in acutely concussed individuals to determine their appropriateness as a clinical rehabilitation strategy.

Keywords: exercise, therapeutics, brain injuries (traumatic)

Concussions are the most frequently occurring traumatic brain injury resulting from sport¹ and represent a significant public health concern. Concussions can result in recognizable signs and reported symptoms as well as cognitive and balance dysfunction.² Most individuals recover from concussion within 2 weeks,³ yet up to 500,000 people annually report persistent dysfunction for months to years postinjury.⁴ This significant minority is forcing researchers and clinicians to reconsider passive treatment strategies and progress toward active rehabilitation paradigms capable of mitigating deleterious injury consequences.

Previous clinical guidelines supported cognitive and physical rest for individuals with concussion until symptom resolution, followed by gradual return to activity.^{3,5} However, the literature about the effectiveness of prescribed rest is mixed, with many studies finding no benefit or harm.⁶⁻⁸ Current evidence suggests that complete rest should persist up to 3 days, followed by a

reintegration of activity as tolerated.⁷ These emerging recommendations have created a shift in management techniques, with more active treatment strategies considered for acute clinical use.

Concussion is known to disrupt cerebral metabolism,⁹ cerebrovascular regulation,¹⁰ and autonomic nervous system¹¹ functioning. Physical activity interventions may offer a clinical strategy designed to address the shortcomings of prescribed rest by targeting the physiologic domains affected after concussion. Literature supports exercise implementation in chronic concussion recovery stages because exercised individuals have shorter symptom durations,¹²⁻¹⁴ decreased depression scores,¹⁵ and improved mood.¹⁵ Still, clinicians remain cautious when prescribing acute exercise treatments despite no serious adverse events (AEs) related to exercise therapy reported in previous studies.¹⁶ Such caution is consistent with animal models suggesting that exercise too close to injury may be detrimental to recovery.¹⁷ To inform acute concussion exercise guidelines, interventions should first undergo a thorough evaluation of safety, feasibility, and adherence in healthy individuals before implementation in patients with concussion. To our knowledge, few studies have examined the safety and feasibility of as well as adherence to acute concussion rehabilitation programs related to exercise.¹⁸

The acute concussion therapy intervention (ACTIVE) training exercise parameters were developed with the premise of being an acute concussion rehabilitation tool. The ACTIVE training includes 3 training days per week, beginning as early as 3 days postinjury in patients with stable or declining symptoms. Concussions are known to result in acute balance deficits,¹⁹ and cycle

Teel is with the School of Physical and Occupational Therapy, McGill University, Montreal, Quebec, Canada. Marshall is with Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC. Appelbaum is with Psychiatry and Behavioral Sciences, Duke University, Durham, NC. Battaglini is with Exercise and Sport Science, University of North Carolina at Chapel Hill, Chapel Hill, NC. Carneiro is with Physical Medicine and Rehabilitation, University of North Carolina at Chapel Hill, Chapel Hill, NC. Guskiewicz and Register-Mihalik are with Exercise and Sport Science, University of North Carolina at Chapel Hill, Chapel Hill, NC. Mihalik is with the Department of Exercise and Sport Science, The University of North Carolina, Chapel Hill, NC. Teel (elizabeth.teel@mail.mcgill.ca) is corresponding author.

ergometers are used in place of treadmills to alleviate safety concerns in patients with ongoing balance and vestibular deficits. Much of the previous concussion rehabilitation work focuses on athletic populations, often with college or professional athletes, who have unique schedules and access to advanced medical personnel. Many concussions occur among children and adolescents without these luxuries, however.^{20,21} In addition, a significant concussion incidence occurs in nonathletic populations through car crashes and falls,²² with similar limitations to accessing medical providers able to prescribe or monitor rehabilitation. The 3 training days per week prescribed in the ACTIVE protocol is meant to increase the protocol's feasibility and translatability for future applications to nonathletic populations as well as youth athletes without access to athletic trainers.

The purpose of this phase 1 clinical trial was to establish the safety, feasibility, and adherence of an aerobic training program in healthy, recreationally active university students. We hypothesized that ACTIVE training would be safe and feasible in this cohort and that participants would adhere to the training schedule. Phase 1 trials examine a proposed treatment in small cohorts to evaluate study protocols, describe protocol adherence, and identify potential unintended effects of treatment. The intent of this research is to ensure that healthy university students adhere to a brief aerobic training program and to provide a foundation for future applications of active interventions in concussion management for injured subjects.

Methods

Design

A parallel-group, unblinded, randomized controlled trial assessed ACTIVE training on feasibility and adherence outcomes in healthy participants. All subjects completed a preintervention and postintervention maximal cardiopulmonary exercise test (CPET) approximately 14 days apart. Participants randomized to ACTIVE training completed six 30-minute training sessions between CPETs, while nontraining participants received no intervention.

Participants

Recreationally active individuals ($n = 40$) between 18 and 30 years of age were recruited for this study. *Recreationally active* was defined as ≥ 30 minutes of physical activity ≥ 3 days per week. Participants were excluded if they sustained a head injury within the year prior to enrollment, had any lower-extremity injury preventing stationary cycling or balancing on 1 leg, used recreational drugs, or had known cardiovascular health issues. Participants had no contraindications to exercise based on the Physical Activity Readiness Questionnaire, a general medical history, and an electrocardiogram, as determined by the study physician, who reviewed all medical documents and provided medical clearance. All participants meeting the inclusion criteria provided informed consent, which the University of North Carolina at Chapel Hill institutional review board (IRB) approved (IRB #15-2387).

Procedures

Participants were randomized to the ACTIVE training (intervention) or nontraining (no intervention) groups based on a computer-generated randomization sequence with block sizes of 4. Participants completed an orientation session and 2 CPETs in a controlled

laboratory setting. Postconcussion aerobic exercise interventions often use a progressive exercise test, gradually increasing exercise intensity until a patient's symptoms are exacerbated.^{11,12} Participants in this study were healthy, not limited by a symptom threshold, and continued the exercise test until volitional fatigue. Therefore, CPET and subsequent exercise intensity prescribed during the ACTIVE training sessions were chosen to approximate procedures already used in concussed samples, while modifying the protocol to account for the lack of symptom presence in the healthy study cohort. An orientation session familiarized participants with testing equipment and provided pretest guidelines (hydrate prior to scheduled session and avoid eating within 2 h, exercise within 12 h, alcohol within 48 h, and diuretic medication within 7 d of a CPET). For the CPET familiarization session, participants were fitted for a respiratory mask, and seat height was adjusted for proper pedaling mechanics on the cycle ergometer. Participants underwent the earliest stages of the CPET following a warm-up at no resistance to minimize any learning effect associated with subsequent CPET administrations. Test sessions were conducted roughly 14 days apart to best approximate typical duration between incident concussion and clinical recovery.¹⁹ All exercise sessions were completed on a stationary electric-brake bike (Load BV, Groningen, The Netherlands) to make this intervention more translatable to acutely concussed participants because treadmill protocols may be difficult for participants with balance deficits.²³

All participants completed a CPET at both test sessions, following standardized procedures set forth by the American College of Sports Medicine.¹⁸ A physician and a certified athletic trainer were on call at a nearby location and prepared to respond in the case of an AE. Before each CPET, the metabolic cart was calibrated by following manufacture guidelines. Participants began the maximal exercise test at 50 W, and intensity was increased by 50 W for the first 2 stages and 30 W for every stage following. Each stage lasted 2 minutes for the first 10 minutes, with 1-minute stages following until volitional exhaustion. When applying this protocol to future concussed populations, the CPET would have a milder progression and end with symptom exacerbation or reported volitional fatigue.

Ventilatory outcomes were collected using a Parvo Medics TrueOne 2400 metabolic cart (Parvo Medics, Sandy, UT). Heart rate was collected every minute, and a Borg rating of perceived exertion was collected in the last 30 seconds of every stage. Blood lactate was collected by using a lactate plus analyzer (Sports Resource Group, Hawthorne, NY) 3 minutes after CPET completion. For a CPET to be valid, athletes had to meet at least 3 of the following criteria: (1) plateau in maximal volume of oxygen values (≤ 2.1 mL/kg/min) with increases in exercise intensity, (2) respiratory exchange ratio ≥ 1.10 , (3) rating of perceived exertion ≥ 17 , (4) lactate ≥ 8.0 mmol/L, and (5) heart rate within 10 beats of age-predicted heart rate max ($220 - \text{age}$). All but 2 CPETs met this requirement.

The ACTIVE training consisted of 6 cycling sessions of progressive intensity performed over the 2-week study period to align with the recommended 3 training sessions per week that would be prescribed to patients with concussion. Participants in the ACTIVE training group were asked to continually cycle at the given exercise intensity for 30 minutes during each session, with an additional 3-minute warm-up and 3-minute cool-down performed. Using the first CPET as a baseline assessment, target training intensity progressed from 56% to 60% of maximal oxygen consumption (VO_2max), 60% to 64% of VO_2max , 64% to 68% of VO_2max , 68% to 72% of VO_2max , 72% to 76% of VO_2max , and

76% to 80% of VO_2max over the course of the 6 prescribed sessions; this progression from 60% to 80% of VO_2max aligns with the exercise prescription guidelines set forth by the American College of Sports Medicine.²⁴ To ensure that participants were training at the appropriate intensity, oxygen consumption levels were checked at the 5-, 15-, and 25-minute marks (3-min recordings) during training sessions, with adjustments occurring as needed to ensure that participants achieved target exercise intensity. The lead author, who has more than 7 years of experience with this population, supervised all training sessions, assisted by an exercise physiologist with more than 20 years of experience working in exercise prescription in clinical populations. The lead author was also responsible for generating the allocation sequence, enrolling participants, and assigning participants to intervention arms. Because this study involved healthy participants, no premature stopping guidelines were implemented.

Feasibility, adherence, and AE outcomes were recorded during all study sessions. These metrics included evaluations of the (1) study protocol and randomization procedure's effectiveness, (2) exercise safety and adherence, (3) progressive intensity of the ACTIVE training procedures, and (4) potential energy imbalance across randomization arms (evaluated using Fitbit [Fitbit, Boston, MA] charge heart rate devices). This study defined *adverse event* as any unanticipated, unfavorable medical occurrence associated with a subject's participation in research.

To examine the progressive intensity of the exercise intervention, heart rate, rate of perceived exertion, and symptom reporting were collected at the end of every exercise session. Heart rate was collected using heart rate monitors (Polar Electro Oy, Kempele, Finland). The Borg scale, a valid and reliable scale, was used to gather rate of perceived exertion.^{25,26} Participants rate their exertion on a scale from 6 (no exertion at all) to 20 (maximal exertion). The graded symptom checklist is a list of 27 common symptoms participants experienced following concussion. Participants were asked to rank each symptom on a Likert scale from 0 (symptom not present) to 6 (severe symptom presence). The graded symptom checklist is summed to create a total symptom score ranging from 0 to 162, where higher scores encompass more symptoms endorsed or the presence of more severe symptoms. This study used the total symptom score, where lower scores represent fewer concussion-like symptoms. The graded symptom checklist has previously been found to be a sensitive, valid, and reliable assessment tool.²⁷

Statistical Analyses

All statistical analyses were completed in SAS (version 9.4; SAS Institute Inc, Cary, NC), with the biostatistician blinded to group assignment. Intention-to-treat analyses were performed; groups were analyzed based on the randomization assigned upon enrollment regardless of participant adherence. Descriptive analyses were completed for all outcome variables. Chi-square and independent samples *t* tests were used to assess randomization effectiveness. Repeated 1-way analyses of variance were used to evaluate differences in physiologic and symptom outcomes across sessions, with Tukey's post hoc analyses conducted where significant main effects were determined. Mixed-design linear regressions using restricted maximum likelihood estimators were conducted to determine whether energy expenditure differed between groups. A priori alpha was set to .05. Sample size was determined using a priori power analyses conducted in G*Power (version 3.1; Düsseldorf, Germany). Thirty-six participants (18 per group)

were needed, and 40 participants were recruited to account for potential attrition.

Results

In total, 45 participants were screened during a 7-month period from August 2016 to February 2017. Of those, 41 individuals (91%) met the inclusion criteria, with 40 participants (98%) enrolled and retained (Figure 1). Participants were randomized to ACTIVE training or nontraining groups upon study enrollment. No significant group differences were observed for any demographic variable (Table 1).

A total of 77 CPETs and 110 ACTIVE training sessions were completed, with no AEs reported in conjunction with the exercise protocols. One participant (2.5%) fainted during a venipuncture associated with a larger study, a known risk of phlebotomy for which the research team was adequately prepared. Three (3.6%) CPETs were missed because of the participant fainting during the preceding venipuncture ($n = 1$) and calibration issues associated with software malfunctions of the metabolic cart computer ($n = 2$). Out of 120 training sessions, 10 (8.3%) were missed, with reasons including inclement weather ($n = 3$), illness ($n = 4$), and forgetting about the scheduled session ($n = 3$). No exercise sessions ended early.

Within the intervention arm, a significant main effect of sessions was noted for heart rate outcomes ($F_{5,101} = 4.57$, $P < .001$). Post hoc analyses revealed that heart rate in the sixth training session was significantly higher than in the first training session (mean difference = 13.11 beats per minute [bpm], $P < .05$); the fifth (mean difference = 14.29 bpm, $P < .05$) and sixth (mean difference = 16.11 bpm, $P < .05$) training sessions resulted in significantly higher heart rates compared with the second test session. The rate of perceived exertion tended to increase ($F_{5,95} = 2.11$, $P = .07$) with subsequent training sessions, but the main effect and all post hoc comparisons failed to reach statistical significance ($P > .05$). Change in symptom scores from preexercise to postexercise and workload at training termination did not significantly differ across sessions (Table 2). Participants were tolerant of the prescribed training intensity, with 13 participants (65%) able to exercise within the target intensity range at all 6 training sessions and 4 participants (20%) during 5 sessions. Three participants (15%) were unable to tolerate the exercise intensity at the final 3 training sessions ($>70\%$ of VO_2max), and the exercise prescription was modified for these participants.

Fitbit outcomes were reported in daily values and split into 3 groups: intervention participants on days with a scheduled ACTIVE training session (ACTIVE training), intervention participants on days without a scheduled ACTIVE training session (ACTIVE no training), and nontraining group participants (nontraining). More minutes of total activity (ACTIVE training: 284.8 [123.7], ACTIVE no training: 264.0 [108.9], and nontraining: 252.3 [118.3]; $P = .47$) and number of steps taken (ACTIVE training: 12,080 [4959], ACTIVE no training: 10,555 [4780], and nontraining: 10,051 [4897]; $P = .24$) were higher on days of scheduled ACTIVE training sessions, although these results did not reach statistical significance. Minutes of low-, moderate-, and high-intensity activity were not different between groups ($P > .05$).

Discussion

Active rehabilitation strategies have potential as a therapeutic intervention in concussion management. However, few programs

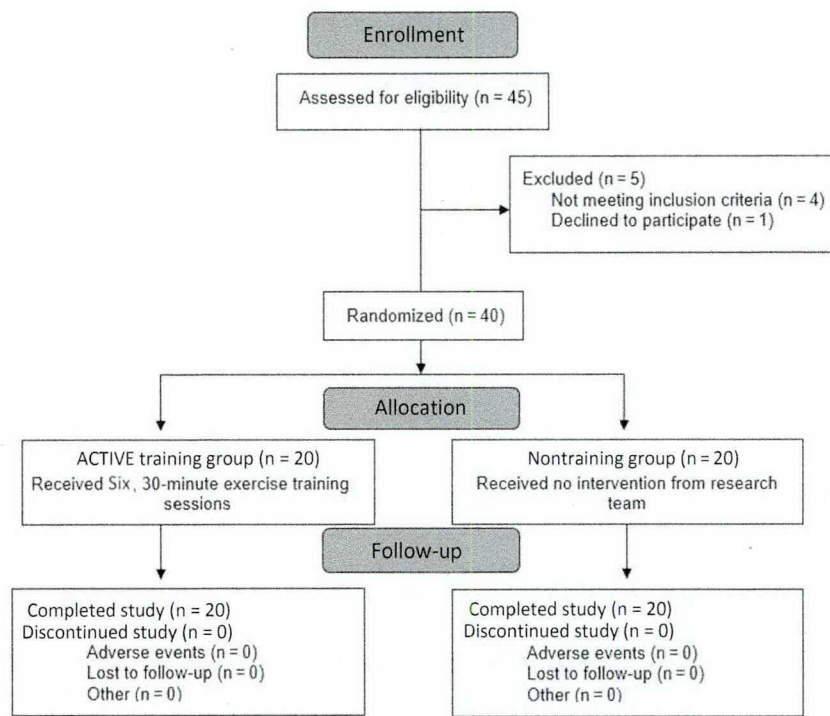


Figure 1 — Profile of the randomized controlled trial.

Table 1 Effectiveness of Randomization Procedures as Measured by Differences in Demographic Information Between Groups

	Nontraining group (n = 20)	Active training group (n = 20)	P value
Age	21.15 (2.70)	20.4 (1.14)	.25
Sex	10 males and 10 females	10 males and 10 females	>.99
Height, cm	174.3 (9.30)	173.5 (11.44)	.81
Weight, kg	71.1 (11.16)	71.2 (12.82)	.98
Days between sessions	12.68 (3.04)	14.77 (2.80)	.07
No. previous concussions	0.55 (1.10)	0.27 (0.55)	.35
Premorbid conditions			
ADHD	2	2	>.99
ADD	1	1	>.99
Learning disability	0	1	.31
Seizure	0	0	>.99
Depression	0	3	.71
Psychiatric	0	0	>.99
Anxiety	0	2	.14
Migraines	2	0	.14
Any condition	4	6	.46
Family condition	7	9	.52
Self-perceived fitness ^a	4.1 (0.55)	3.75 (0.63)	.07

Abbreviations: ADD, Attention deficit disorder; ADHD, Attention deficit hyperactivity disorder.

^aSelf-perceived fitness was rated on a scale of 1 to 5, where 1 = much less fit than your peers, 3 = just as fit as your peers, and 5 = much more fit than your peers.

have been implemented acutely. Safety and feasibility concerns, such as the frequency and duration of prescribed training, transportation to rehabilitation, cost of rehabilitation services, lack of access to a medical professional to supervise rehabilitation activities, and severity of acute concussion deficits, have precluded an

earlier and wider implementation of active concussion rehabilitation strategies, and these concerns are particularly relevant for youth or nonathletic cohorts. As such, the development of low-cost programs that are highly accessible to all concussed cohorts and have the ability to be easily translated to home-based programs

Table 2 Adherence and Tolerance of All ACTIVE Training Sessions, With Results From the First Maximal Exercise Test for Reference

	First maximal exercise test	ACTIVE training 1 (56%–60% of max)	ACTIVE training 2 (60%–64% of max)	ACTIVE training 3 (64%–68% of max)	ACTIVE training 4 (68%–72% of max)	ACTIVE training 5 (72%–76% of max)	ACTIVE training 6 (76%–80% of max)
Δ total symptom score	2.2 (5.0)	0.5 (2.2)	0.4 (1.9)	0.4 (1.9)	0.1 (2.0)	0.6 (1.5)	0.4 (1.9)
HR at termination	180.9 (9.7)	143.3 (12.6)	141.1 (12.1)	146.5 (14.7)	152.1 (11.9)	155.9 (11.2) ^b	158.2 (12.1) ^{a,b}
RPE at termination	18.2 (1.4)	12.9 (2.1)	12.6 (1.7)	13.2 (1.35)	13.6 (1.6)	13.8 (1.6)	14.2 (1.6)
Workload (W) at termination	239.7 (60.8)	105.7 (41.2)	107.1 (35.3)	117.1 (37.7)	116.6 (34.9)	125.9 (34.3)	129.8 (34.6)
Missed sessions	0 (0%)	2 (10%)	3 (15%)	2 (10%)	0 (0%)	1 (5%)	2 (10%)
Adverse events	0	0	0	0	0	0	0

Abbreviations: ACTIVE, acute concussion therapy intervention; HR, heart rate; RPE, rating of perceived exertion.

^aSignificantly higher value compared with the first ACTIVE training session. ^bSignificantly higher value compared with the second ACTIVE training session.

would be of significantly high clinical benefit. The future goal of ACTIVE training is to address these feasibility concerns.

This study represents a detailed and thorough evaluation of the program in healthy individuals as a first step in achieving those goals. Our results indicate that ACTIVE training is a safe and feasible aerobic training program in active young adults, and participants were adherent to and tolerant of the training protocol. The majority of previous work in exercise interventions postconcussion use treadmills; ACTIVE training successfully used stationary bikes, which may also be beneficial for acute care because they enhance safety for patients who have balance deficits. Outcomes presented here for healthy participants, particularly symptom and rating of perceived exertion changes recorded in response to ACTIVE training, can serve as normative data for future research in concussed populations.

Healthy university students were adherent to the ACTIVE training schedule, and no AEs occurred throughout this study. Most participants (60%) completed all 6 training sessions over the 2-week intervention interval, with every participant completing at least 4 sessions. Only 6.5% of exercise sessions were missed throughout this study, with missed sessions evenly distributed throughout the training period. Previous concussion intervention protocols show similar levels of adherence for both healthy²⁸ and concussed^{13,29} populations. In addition, the high recruitment and low dropout rates in this study meet levels reported previously.²⁹ This information suggests that the adherence to ACTIVE training may be similar in concussed populations; however, most concussion rehabilitation interventions fail to report information about protocol feasibility or adherence.^{15,30,31} Concussed people may be experiencing symptoms as well as cognitive, balance, and visual deficits that may interfere with performing prescribed rehabilitation exercises such as physical activity interventions. In addition, young or nonathletic cohorts may struggle with the transportation to or cost of accessing medical providers to prescribe and monitor rehabilitation. These barriers to care have been largely unaddressed in the current concussion rehabilitation literature and limit our ability to discuss the translation of ACTIVE training to concussed populations with greater certainty.

Participants were tolerant of ACTIVE training intensity. The significant increases in heart rate throughout the training period, combined with a trend toward higher perceived exertion and training workload, support our hypothesis that the progressively increasing intensity of the training program was appropriately met.

Changes in symptoms score preexercise to postexercise and missed sessions did not significantly differ throughout the training period, showcasing no evidence of overtraining or burnout. This study consisted of young, healthy adults who volunteered for participation; clinical populations, such as concussed individuals, may display depressed tolerance to training intensity, requiring further evaluation. Other studies report that a small portion of concussed individuals cannot tolerate aerobic exercise at moderate intensities because of symptom exacerbation, but lowering the exercise workload can eliminate this negative response without further issue.^{14,29}

Fitbit outcomes failed to reach statistical significance. Minutes of total activity and step counts trended toward higher levels for intervention participants on scheduled training days, with approximately 20 (compared with days for ACTIVE participants with no scheduled training sessions) and 32 (compared with the nontraining group) more minutes of activity completed. This additional activity on scheduled ACTIVE days suggests that training was completed in addition to, not in place of, normal physical activity for intervention participants. Minutes of moderate and vigorous activity were not significantly different between groups; however, training sessions were completed on a stationary cycle ergometer, and Fitbit monitors are known to significantly underestimate energy expenditure during cycling activities.^{32,33} The exercise intensity recorded during training sessions may have been incorrectly classified, which may explain why total minutes of activity but not moderate or vigorous activity minutes were higher on days of scheduled training sessions. The Fitbit was prone to missing data, even on days when research team members verified that the device was appropriately worn and charged, highlighting potential limitations of using Fitbit devices as research tools.

Aerobic exercise influences the physiologic domains affected postconcussion and may be a mechanistic approach to facilitating recovery, providing additional benefits to patients with concussion above those shown in healthy cohorts. This study using healthy participants showed that moderate-intensity ACTIVE training workouts could alter symptom ratings, ranging from a 5-point decrease to a 6-point increase in symptom scores after exercise. Importantly, no participants reported symptom changes exceeding previously published reliable change indices,²⁷ further highlighting the safety of the protocol, and a small symptom increase following exercise in patients with concussion may not be of medical concern. Reliable change scores and clinical judgment from a

supervising medical professional may represent better methods of determining clinically meaningful symptom increases. Other studies in concussed cohorts found that symptom exacerbation following exercise can easily be managed by reducing intensity,¹⁴ and no serious AEs have been reported following exercise in patients with concussion.^{14,18,29} ACTIVE training used a training schedule of 3 sessions per week, which was feasible in this cohort. Rehabilitation schedules in other settings are often completed between 3 and 5 days per week, and previous studies evaluating home-based exercise training programs in chronically concussed cohorts target 6 days of exercise per week,¹³ supporting the idea that ACTIVE training could be feasible in injured populations. This study provides support that aerobic exercise programs are safe and feasible in healthy populations and serves as a starting point for evaluating similar exercise interventions in acutely concussed populations.

Limitations

The ACTIVE training is a safe and feasible intervention in healthy young adults, but patients with concussion may have a different response to exercise because of ongoing clinical and physiologic deficits. Patients with concussion are often prevented from physical activity during their recovery, and aerobic exercise rehabilitation interventions would likely represent the only form of exercise concussed patients are engaging in. Because this study consisted of healthy, recreationally active participants, we were unable to prevent participants from engaging in physical activity outside the study intervention. A subset of participants wore Fitbit activity monitors to observe all their physical activity, including ACTIVE training sessions and any additional outside activity. However, the Fitbit devices had their own limitations, failing to capture data or misclassifying exercise intensity. ACTIVE training and other cycling-based interventions would benefit from activity monitors that track cadence as opposed to steps. Although impractical for continual, daily use, heart rate monitors represent another option to track intensity during an exercise session. A target heart rate zone below symptom threshold is commonly used to prescribe intensity for rehabilitation interventions in concussed cohorts, so accurate heart rate outcomes are critical for clinical concussion care. There is hope that acute aerobic exercise programs can eventually be translated into home-based rehabilitation protocols, but the current recommendation is for close monitoring of acutely concussed patients during training bouts by a medical professional.

There is no guarantee that the results of this study are translatable to other populations. Children and adolescents have unique educational and social demands, are still undergoing brain maturation, and are often reliant on parents and guardians to afford and transport them to care, all of which may cause differing safety, feasibility, and adherence outcomes. Acutely concussed individuals may have more severe concussion symptoms and deficits, which may cause different responses to aerobic exercise than currently reported in this study or the postconcussion exercise literature for chronic recovery stages.

Conclusions

Aerobic exercise may directly target the underlying physiologic deficits experienced after concussion and has several potential benefits specific to patients with concussion, including expedited symptom resolution, improved mental health outcomes, and reduced effects of detraining throughout the recovery period.

Thorough evaluations of safety, feasibility, and adherence are necessary to ensure that the potential benefits outweigh any risk of harm. ACTIVE training is a safe and feasible program for healthy, recreationally active university students, who were adherent to the designed exercise protocols. This study has potential implications for trials of concussion management protocols aimed at stimulating exercise training as a clinical intervention. The results of this study suggest that acute aerobic exercise is a safe and feasible intervention, and this study serves as a starting point for future acute concussion exercise rehabilitation interventions.

Acknowledgments

This trial was registered on ClinicalTrials.gov (Trial Registration Number: NCT02872480), a service of the US National Institutes of Health. We would like to thank Dr Shabbar Ranapurwala (biostatistics) and research assistants Grant Cabell, Madison Harper, Erin Leasure, and Austin White for their contributions to this project. Funding was provided in part by grants from the American College of Sports Medicine's Clinical Sports Medicine Endowment (Indianapolis, IN), the National Athletic Trainers' Association Research & Education Foundation Doctoral Research Grant (Carrollton, TX), and the graduate school at the University of North Carolina at Chapel Hill. The authors have no other conflicts of interest to report.

References

1. Guskiewicz KM, Weaver NL, Padua DA, Garrett WE. Epidemiology of concussion in collegiate and high school football players. *Am J Sports Med.* 2000;28(5):643–650. PubMed ID: 11032218 doi:10.1177/03635465000280050401
2. Broglio SP, Puetz TW. The effect of sport concussion on neurocognitive function, self-report symptoms and postural control. *Sports Med.* 2008;38(1):53–67. PubMed ID: 18081367 doi:10.2165/00007256-200838010-00005
3. McCrory P, Meeuwisse WH, Aubry M, et al. Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. *Br J Sports Med.* 2013;47(5):250–258. PubMed ID: 23479479 doi:10.1136/bjsports-2013-092313
4. Bazarian JJ, Atabaki S. Predicting postconcussion syndrome after minor traumatic brain injury. *Acad Emerg Med.* 2001;8(8):788–795. PubMed ID: 11483453 doi:10.1111/j.1553-2712.2001.tb00208.x
5. Broglio SP, Cantu RC, Gioia GA, et al. National Athletic Trainers' Association position statement: management of sport concussion. *J Athl Train.* 2014;49(2):245–265. PubMed ID: 24601910 doi:10.4085/1062-6050-49.1.07
6. Buckley TA, Munkasy BA, Clouse BP. Acute cognitive and physical rest may not improve concussion recovery time. *J Head Trauma Rehabil.* 2016;31(4):233–241. PubMed ID: 26394292 doi:10.1097/HTR.000000000000165
7. Silverberg ND, Iverson GL. Is rest after concussion “the best medicine?”: recommendations for activity resumption following concussion in athletes, civilians, and military service members. *J Head Trauma Rehabil.* 2013;28(4):250–259. PubMed ID: 22688215 doi:10.1097/HTR.0b013e31825ad658
8. Schneider KJ, Iverson GL, Emery CA, McCrory P, Herring SA, Meeuwisse WH. The effects of rest and treatment following sport-related concussion: a systematic review of the literature. *Br J Sports*

- Med.* 2013;47(5):304–307. PubMed ID: 23479489 doi:10.1136/bjsports-2013-092190
9. Giza CC, Hovda DA. The new neurometabolic cascade of concussion. *Neurosurgery.* 2014;75(suppl 4):S24–S33. PubMed ID: 25232881 doi:10.1227/NEU.0000000000000505
 10. Tan CO, Meehan WP 3rd, Iverson GL, Taylor JA. Cerebrovascular regulation, exercise, and mild traumatic brain injury. *Neurology.* 2014;83(18):1665–1672. PubMed ID: 25274845 doi:10.1212/WNL.0000000000000944
 11. 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(3):199–205. PubMed ID: 17917170
 12. 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(1):21–27. PubMed ID: 20051730 doi:10.1097/JSM.0b013e3181c6c22c
 13. 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(2):79–89. PubMed ID: 27120294 doi:10.1097/HTR.0000000000000238.
 14. Grabowski P, Wilson J, Walker A, Enz D, Wang S. Multimodal impairment-based physical therapy for the treatment of patients with post-concussion syndrome: a retrospective analysis on safety and feasibility. *Phys Ther Sport.* 2017;23:22–30. PubMed ID: 27665247 doi:10.1016/j.ptsp.2016.06.001
 15. Gagnon I, Grilli L, Friedman D, Iverson GL. A pilot study of active rehabilitation for adolescents who are slow to recover from sport-related concussion. *Scand J Med Sci Sports.* 2016;26(3):299–306. PubMed ID: 25735821 doi:10.1111/sms.12441
 16. Giza CC, Hovda DA. The neurometabolic cascade of concussion. *J Athl Train.* 2001;36(3):228. PubMed ID: 12937489
 17. Griesbach GS, Hovda DA, Molteni R, Wu A, Gomez-Pinilla F. Voluntary exercise following traumatic brain injury: brain-derived neurotrophic factor upregulation and recovery of function. *Neuroscience.* 2004;125(1):129–139. PubMed ID: 15051152 doi:10.1016/j.neuroscience.2004.01.030
 18. 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(6):693–702 PubMed ID: 27620871 doi:10.3171/2016.5.PEDS16139
 19. McCrea M, Guskiewicz KM, Marshall SW, et al. Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *JAMA.* 2003;290(19):2556–2563. PubMed ID: 14625332 doi:10.1001/jama.290.19.2556
 20. Dompier TP, Kerr ZY, Marshall SW, et al. Incidence of concussion during practice and games in youth, high school, and collegiate American football players. *JAMA Pediatr.* 2015;169(7):659–665. PubMed ID: 25938704 doi:10.1001/jamapediatrics.2015.0210
 21. Lincoln AE, Caswell SV, Almquist JL, Dunn RE, Norris JB, Hinton RY. Trends in concussion incidence in high school sports: a prospective 11-year study. *Am J Sports Med.* 2011;39(5):958–963. PubMed ID: 21278427 doi:10.1177/0363546510392326
 22. Summers CR, Ivins B, Schwab KA. Traumatic brain injury in the United States: an epidemiologic overview. *Mt Sinai J Med.* 2009;76(2):105–110. PubMed ID: 19306375 doi:10.1002/msj.20100
 23. Lee CW, Cho GH. Effect of stationary cycle exercise on gait and balance of elderly women. *J Phys Ther Sci.* 2014;26(3):431–433. PubMed ID: 24707100 doi:10.1589/jpts.26.431
 24. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription.* Philadelphia, PA: Lippincott Williams & Wilkins; 2013.
 25. Borg E, Kaijser L. A comparison between three rating scales for perceived exertion and two different work tests. *Scand J Med Sci Sports.* 2006;16(1):57–69. PubMed ID: 16430682 doi:10.1111/j.1600-0838.2005.00448.x
 26. Pfeiffer KA, Pivarnik JM, Womack CJ, Reeves MJ, Malina RM. Reliability and validity of the Borg and OMNI rating of perceived exertion scales in adolescent girls. *Med Sci Sports Exerc.* 2002;34(12):2057–2061. PubMed ID: 12471316 doi:10.1249/01.MSS.0000039302.54267.BF
 27. Register-Mihalik JK, Guskiewicz KM, Mihalik JP, Schmidt JD, Kerr ZY, McCrea MA. Reliable change, sensitivity, and specificity of a multidimensional concussion assessment battery: implications for caution in clinical practice. *J Head Trauma Rehabil.* 2013;28(4):274–283. PubMed ID: 22691965 doi:10.1097/HTR.0b013e3182585d37
 28. DeBusk RF, Stenestrand U, Sheehan M, Haskell WL. Training effects of long versus short bouts of exercise in healthy subjects. *Am J Cardiol.* 1990;65(15):1010–1013. PubMed ID: 2327335 doi:10.1016/0002-9149(90)91005-Q
 29. Maerlender A, Rieman W, Lichtenstein J, Condiracci C. Programmed physical exertion in recovery from sports-related concussion: a randomized pilot study. *Dev Neuropsychol.* 2015;40(5):273–278. PubMed ID: 26230745 doi:10.1080/87565641.2015.1067706
 30. Schneider KJ, Meeuwisse WH, Nettel-Aguirre A, et al. Cervicovestibular rehabilitation in sport-related concussion: a randomised controlled trial. *Br J Sports Med.* 2014;48(17):1294–1298. PubMed ID: 24855132 doi:10.1136/bjsports-2013-093267
 31. Baker JG, Freitas MS, Leddy JJ, Kozlowski KF, Willer BS. Return to full functioning after graded exercise assessment and progressive exercise treatment of postconcussion syndrome. *Rehabil Res Pract.* 2012;2012:705309. PubMed ID: 22292122 doi:10.1155/2012/705309
 32. Sasaki JE, Hickey A, Mavilia M, et al. Validation of the Fitbit wireless activity tracker for prediction of energy expenditure. *J Phys Act Health.* 2015;12(2):149–154. PubMed ID: 24770438 doi:10.1123/jpah.2012-0495
 33. Nelson MB, Kaminsky LA, Dickin DC, et al. Validity of consumer-based physical activity monitors for specific activity types. *Med Sci Sports Exerc.* 2016;48(8):1619–1629. PubMed ID: 27015387 doi:10.1249/MSS.0000000000000933