Dynamic Exertion Testing (EXiT): An Assessment to Inform Return to Play/Activity following Sport-related Concussion

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DYNAMIC EXERTION TESTING (EXIT): AN ASSESSMENT TO INFORM RETURN TO PLAY/ACTIVITY FOLLOWING SPORT-RELATED CONCUSSION

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BACKGROUND: Recently developed dynamic exertion testing (EXiT) incorporates a combination of treadmill running, functional movements, and agility tasks to inform return to play and activity (RTP/A) decision making following sport-related concussion. The identification of an assessment's stability on repeated assessments, inter-rater agreement, minimal detectable change (MDC), and examination of age, sex, body mass index (BMI), and sport-type are necessary to interpret EXiT. Additionally, previously injured athletes upon medical clearance to RTP/A should have similar physiological, performance, and clinical outcomes on EXiT as healthy athletes, including heart rate variability (HRV) responses to EXiT as a proxy of autonomic nervous system functioning.

PURPOSE: The aims of the current investigation included the following:

Aim 1) Establish intra-rater, test-retest and inter-rater reliability for EXiT physiological (age estimated percentage of maximum heart rate (HR $_{\%max}$)) and blood pressure (BP)), performance (agility task completion time and errors), and clinical (endorsed symptoms and rating of perceived exertion (RPE)) outcomes.

Aim 2) Compare age, sex, BMI, and sport-type subgroups across EXiT physiological, performance, and clinical outcomes among a heterogeneous physically active sample.

Aim 3) Determine concurrent validity of EXiT by comparing physiological, performance, and clinical EXiT outcomes and ultrashort heart rate variability responses to EXiT between athletes at medical clearance to RTP/A from SRC with healthy controls.

METHODS: Aim 1) From a total sample of 92 healthy physically active adolescents and adults, 79 (F:34, 43%) completed a demographic questionnaire, weight and height measurements for BMI ([BMI]= weight [kg]/height[m]^2), and the EXiT across 2 visits (8.7±4.7 days apart). EXiT included an aerobic component: 12- min treadmill run; and dynamic component: dynamic circuit, ball toss, box-drill shuffle and carioca, zig zag, pro agility, and arrow agility tasks. A 2nd rater separately assessed agility task completion time and errors for 15 healthy participants and 15 athletes upon medical clearance to RTP/A. Two-way, mixed, intra-class correlation coefficients were used to evaluate agility task completion time between consecutive trials (intra-rater reliability), fastest trial across visits (test-retest reliability), and agreement between raters (inter-rater reliability). Paired samples t-tests were used for HR $_{\%max}$ and agility task completion time, and Wilcoxon tests were used for endorsed symptoms, RPE, and errors. Internal consistency of symptoms at each visit was determined with Cronbach's alpha, and MDC of EXiT outcomes were calculated using the equation: MDC= standard deviation x $\sqrt{(1 - ICC)} \bullet 1.96 \bullet \sqrt{2}$.

Aim 2) 87 (F= 55, 37.4%; 19.5 ± 4.4 years) participants (from aim 1) were categorized in adolescent (14- 17 years) or adult (≥18 years), male or female (self-report), LO-BMI (BMI < 50th percentile) or HI-BMI (BMI ≥50th percentile), and collision, contact, or non-contact sport-types. Independent samples t-tests were conducted for HR $_{\%max}$, BP, and agility task completion time, and Mann-Whitney U tests for RPE, endorsed symptoms, and errors between age, sex, and BMI groups across aerobic and dynamic components. A series of 1-way ANOVAs were conducted to

compare HR $_{\%max}$, BP, and agility task completion time, and Kruskal Wallis- H tests to compare RPE, symptoms, and committed errors between collision, contact, and non-contact sport-types.
Aim 3) A sample of 46 healthy athletes including 23 (F= 10, 43.5%) healthy control (from aim 1; CONTROL) and age-, sex-, and sport- matched to patients completing EXiT at medical clearance to RTP/A (CONCUSS) completed a 5-minute seated rest period prior to and following EXiT. The final 3-min were used to calculate ultrashort HRV outcomes, including the root-mean-square of successive differences (RMSSD) and standard deviation of successive heart beats (SDNN). Independent samples t-tests were conducted to compare CONTROL and CONCUSS groups for HR $_{\%max}$, BP, and agility task completion time, and Mann-Whitney U tests were utilized for endorsed symptoms, RPE, committed errors. A series of 2X2 (GROUP X TIME) mixed model ANOVAs were conducted to compare CONCUSS and CONTROL groups on RMSSD and SDNN outcomes across time points (pre- and post-EXiT rest periods).
RESULTS: Aim 1) Pre- and post-EXiT resting HR $_{\%max}$ and BP, and HR $_{\%max}$ were reliable throughout aerobic and dynamic components (ICC=.696-.838). Symptoms and RPE were similar across visits but less errors were committed at the 2nd visit. Agility task completion time (MDC range=0.75-8.70 seconds) had good to excellent test-retest (ICC=.703-.948) and inter-rater reliability (ICC=.932-.965), but ratings of committed errors have acceptable agreement for committed errors for only the ball toss and pro agility tasks. Endorsed symptoms had a high internal consistency at both visits (α =.805-.894) and were reliable across visits during aerobic (ICC=.765) and dynamic components (ICC .519) were reliable across visits.
Aim 2) Adolescents were faster than adults on arrow agility (p=.01); males were faster than females on box drill carioca (p=.01), zig zag (p<.001, pro agility (p=.02), and arrow agility (p=.04) tasks; and the LO-BMI group was faster than the HI-BMI group on arrow agility(p<.001). Males also reported greater RPE than females after the box drill shuffle, box drill carioca, and arrow agility tasks (p<.03), but statistical differences were within established minimal detectable change scores. HR $_{\%max}$, errors, and endorsed symptoms were equivocal throughout and following aerobic and dynamic components across age, sex, BMI, and sport-type groups (p>.05).
Aim 3) The CONCUSS group had group had lower (faster) completion time during zig zag p=0.048 and pro agility p=0.018) tasks and had lower (less variable) SDNN (F=4.569, p=.047, η_p^2=. 212) and RMSSD (F=4.517, p=.049, η_p^2=.=.209) than CONTROL group. CONCUSS and CONTROL groups had similar HR $_{\%max}$, total endorsed symptoms, and RPE (p>.05).
CONCLUSION: EXiT physiological, performance, and clinical outcomes are reliable, and generalizable to physically active population of varied age, sex, BMI, and sport-type factors. The multiple objective outcomes of EXiT present a new evidence-based approach to inform clinical recovery from SRC and RTP/A decision making.

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PREFACE

This work is to be submitted for the degree of Doctor of Philosophy in Rehabilitation Science at the University of Pittsburgh is a culmination of work that would not be possible without the support I received from my colleagues, advisors, friends, and family. Firstly, the development of EXiT and its components were the result of an invaluable collaboration with the clinicians at UPMC Sports Medicine Concussion Program. Dr. Kochick, thank you for willingly extending your knowledge and becoming an invaluable part of the conceptualization of EXiT as a clinically viable assessment for the healthcare providers. Your effectiveness as a clinician and shared vision of EXiT and its impact to the larger medical community were critical to the success of this project. I look forward to sharing new research articles and discussing potential ways to improve the implementation of structured exertion as part of the active, comprehensive evaluation and treatment for concussion. The faculty neuropsychologists Dr. Michael "Mickey" Collins, Dr. Alicia Trbovich, Dr. Natalie Sherry, Dr. Jonathan French, and Dr. Nathan Kegel, in addition to the numerous post-doctoral neuropsychology fellows, you were very generous and willing to accommodate the conduct of the current investigation-even at times when the recruitment and enrollment of some participants were an inconvenience to the clinic schedule. More importantly, our conversations over the previous 4 years have changed my conceptualization of SRC and has inspired alternative ways to consider the individualized impairments of the injury which will surely play a role in the development of future research questions. Similarly, Cyndi Holland's advice and feedback were critical to the completion of this project and feedback from the research assistants from the Concussion Research Laboratory, Hannah Bitzer, Adam Colorito, and Nick Blaney, were

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1.0 INTRODUCTION

Sport-related concussion (SRC) is a mild traumatic brain injury with heterogenous signs, symptoms, and functional impairments [1], and is a major health concern for scientific and medical communities alike [2]. A gold-standard assessment for SRC is unavailable and unlikely because of the heterogeneity of the injury, and management decisions surrounding the diagnosis and treatment of functional impairments have been based on expert consensus and evolving clinical evidence [1, 3]. A critical domain of SRC clinical management with limited empirical evidence that remains a significant challenge for healthcare providers is the medical clearance decision to return to play/activity (RTP/A). The appropriate determination to RTP/A is of clinical significance as emerging evidence suggests premature RTP/A may place athletes at an increased risk for subsequent concussion [7, 8] and musculoskeletal injury [9-11]. Currently, medical clearance decisions to RTP/A involve a multifaceted evaluation of inter-related neurocognitive, vestibular, and ocular assessments. In addition, athletes must complete a staged return to sport progression comprised of increasing exercise rigor and sport specificity across 24-hour stages despite no empirical evidence[3, 5]. Recently, structured exertion has been used by clinicians to improve SRC diagnosis and treatment decisions, but to date has yet to result in a truly objective set of criteria to inform RTP/A decision making.

1.1 Structured Exertion in the Clinical Management for Concussion

Clinical management for adolescents and adults sustaining SRC has evolved from a homogenous ‘one size fits all’ to an individualized approach that requires a comprehensive,

multifaceted evaluation of signs, symptoms, and impairments [1, 4]. Since 2008, the determination of safe RTP/A after SRC has been predicated on cognitive and physical rest until symptom resolution before initiating a staged return to sport progression. This recommendation was based on early rodent models suggesting that the brain undergoes a brief period of vulnerability following a neurometabolic cascade and secondary inflammatory response to injury[21]. Surprisingly, since the widespread adoption of physical and cognitive rest until symptoms have abated, several meta-analyses have confirmed that structured exertion, even among symptomatic patients, is effective at reducing the likelihood for prolonged recovery[22-24]. The traditional approach to increase physical activity has been shown to be outdated as clinical experts have recently advocated a more active approach to treat post-concussion impairments [3]. Importantly, structured exertion has been suggested by both Clinical Profile and Pathophysiological models as a clinically viable domain to developing areas of SRC management [6, 25], including injury diagnosis [26-28], intervention recommendations [29, 30], and medical clearance decisions [31, 32].

Following the adoption of a more individualized clinical management approach and implementation of the staged return to sport progression in 2008, the medical clearance decision to RTP/A has become a significant challenge to healthcare providers. The return to sport progression is comprised structured exertion of increasing exercise intensity, duration, and sport specificity separated by 24-hour stages without symptom provocation [21, 33] (Table 1). Thus, protocol progression, and subsequent clearance is predicated on subjective symptom reporting and ambiguous exercise prescriptions at each stage. Due to these limitations, the return to sport progression is subject to inconsistent administrations between healthcare providers and there is currently sparse evidence to support this approach [34, 35]. This presents a critical gap for healthcare providers in need of evidence-based assessments to inform RTP/A decision making.

Table 1 Staged Return to Sport Progression Currently Recommended by Concussion in Sport Group

Stage	Aim	Activity/Goal
0	Physical and Cognitive Rest	Reduce risk of repeat injury and minimize brain energy demands
1	Symptom-Limited Activity	Daily activities without symptom provocation and reintroduction to academic/work activities
2	Light Aerobic Exercise	Walking or stationary cycling at a medium pace to increase heart rate
3	Sport-Specific Exercise	Running or skating drills to add movement
4	Non-contact training drills	More vigorous training drills to increase exercise intensity and coordination
5	Full Contact Practice	Following medical clearance to participate in normal training activities and assess functional skills
6	Return to Sport	Unrestricted sport participation

Adapted from 5th Concussion in Sport Consensus Statement[33]

More recently, structured exertion has been suggested to provide an objective evaluation to inform medical clearance decisions to RTP/A, and address a missing domain of a comprehensive multifaceted evaluation for SRC [31] (EXiT #1). [36]To address this need, the new Dynamic Exertion Testing (EXiT) was developed to provide a clinically intuitive and objective evaluation of the inter-related autonomic, vestibular, and ocular systems to inform RTP/A decision making (EXiT #1). EXiT provides a brief (~20 min) comprehensive evaluation of structured aerobic exertion, functional movements, and hand-timed agility tasks. In addition, the medical provider can interpret EXiT physiological (heart rate and blood pressure), performance (agility task completion time and errors), and clinical (rating of perceived exertion and endorsed symptoms) outcomes that can better inform RTP/A decision making following SRC. However, the available evidence to support the EXiT as a clinical assessment toward this purpose is sparse. There is a need for empirical evidence to establish the reliability of EXiT outcomes across repeated administrations, generalizability of EXiT components among a diverse physically active population, and validation evidence of these outcomes between athletes completing EXiT upon

medical clearance from SRC with healthy athletes. An investigation to address these shortcomings will provide preliminary support for the EXiT as an objective structured exertion test to inform RTP/A decision making.

1.2 Definition of the Problem

The medical clearance decision to resume sport and physical activity is a significant challenge to healthcare providers overseeing patient care. Concussion treatment and management has evolved to a more active, targeted approach to treat clinical subtypes and healthcare providers require evidence-based assessments as part of the multifaceted evaluation for SRC. EXiT is a clinically intuitive approach to inform RTP/A decision making but evidence to support the efficacy of EXiT is lacking and presents a current need to investigate EXiT to inform medical clearance from SRC. Thus, the purpose of the current investigation was to provide preliminary evidence of the reliability and efficacy of EXiT as a structured exertion test to inform RTP/A decision making.

1.3 Specific Aims and Hypotheses

1.3.1 Specific Aim 1:

Determine 1) intra- and test- retest reliability and minimal detectable change of EXiT outcomes, including physiological (pre- and post-EXiT resting heart rate and blood pressure, and heart rate following each EXiT task), performance (agility task completion time and committed errors), and clinical (concussion symptoms and perceived effort) outcomes; and 2) assess inter-rater agreement between independent observers recording agility task completion time and committed errors.

Hypothesis 1a: Completion time will be reliable and within minimal detectable change thresholds across consecutive agility task trials at each visit (intra-rater reliability), and physiological, performance, and clinical outcomes will be stable across visits (test-retest reliability).

Hypothesis 1b: EXiT performance outcomes (agility task completion time and errors) will have high level of agreement between independent raters (inter-rater reliability).

1.3.2 Specific Aim 2:

Compare age, sex, BMI, and sport-types across EXiT physiological— pre- and post-EXiT resting heart rate and blood pressure, and heart rate following each task, performance— agility task completion time and errors, and clinical— symptoms and perceived exertion, outcomes among healthy adolescents and adults.

Hypothesis: Adults will have lower (faster) agility task completion time than adolescents and males will have lower completion time compared to females, but physiological and clinical outcomes between age and sex would be similar. We also hypothesized that physiological— $HR_{\%max}$ and BP, performance— agility task completion time and errors, and clinical— symptoms and RPE outcomes would be similar across BMI, and sport-types.

1.3.3 Specific Aim 3

Compare physiological—pre- and post-EXiT resting heart rate and blood pressure, and heart rate following each task, performance— agility task completion time and errors, and clinical— symptoms and perceived exertion, EXiT outcomes in addition to heart rate variability outcomes between athletes completing EXiT at medical clearance to RTP/A with age-, sex-, and sport-type- matched healthy athletes.

Hypothesis: Athletes upon medical clearance to RTP/A would have similar EXiT physiological, performance, and clinical outcomes as healthy athletes.

1.4 Study Significance

The medical clearance decision for athletes to RTP/A following SRC recovery is a significant challenge for healthcare providers, and the scientific and medical communities need a structured exertion assessment to determine RTP/A readiness as part of a comprehensive clinical evaluation. EXiT may be able to address a missing component of the comprehensive evaluation and improve the standardization of clinical recovery from SRC. Additionally, a more objective RTP/A evaluation can enhance future research examining the effects of targeted interventions to improve clinical outcomes from SRC for the millions of concussions sustained each year [37]

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2.0 REVIEW OF THE LITERATURE

2.1 Sport-Related Concussion Epidemiology and Pathophysiology

The most recent Concussion in Sport Group consensus statement defines concussion as a traumatic brain injury caused by biomechanical forces applied directly to the head, or indirectly to the body with unattenuated forces transmitted to the head, leading to a rapid onset of neurological dysfunction that can present with clinical signs (e.g., unconsciousness), symptoms (e.g., headache), or impairments (e.g., convergence insufficiency) [1]. Early estimates of traumatic brain injury occurrence, including concussion and more severe brain injuries sustained in sport participation and other causes (e.g., falls and motor vehicle accidents) were between 1.2-3.8 million annually in the United States [38]. However, this statistic is suggested to be an underestimation of the true occurrence due to a substantial number of unreported cases [39, 40]. A recent report accounting for undocumented injuries estimated an annual SRC occurrence between 1.1 and 1.9 million cases among children (<18 years of age) in the United States [37]. Of these, an estimated 500,000 to 1.2 million of these injuries are not evaluated or treated by health care providers[37]. Numerous factors may place one at more risk of SRC, including older age[41, 42], previous history of concussions [43-46] and female sex when compared for equivalent sport-types[47-50].

Many of the clinical management considerations for SRC are derived from rodent models and have not been empirically established in vivo among humans [51-53]. Percussive injuries imposed to mice provide evidence of a 'Neurometabolic Cascade' characterized by immediate cellular responses and persistent blood flow alterations that spontaneously resolve after injury [52]. Biomechanical forces cause neuronal cell stretching and consequently, alter cell permeability and

disrupt cell homeostasis [51]. An immediate indiscriminate release of glutamate and other excitatory neurotransmitters increase neuronal cell activation, and a rapid efflux of potassium ions and influx of sodium and calcium ions result in axonal swelling and alter neuronal cell functioning[51, 54]. Adenosine triphosphate (ATP)-derived pumps increase activity to re-establish ionic balance and as a result, the cell undergoes hyperglycolysis to provide additional ATP resources. Intracellular Calcium ions also sequester mitochondria and disrupt ATP synthesis [55]. A final step of the neurometabolic cascade is a reduction in cerebral blood flow, leading to impaired delivery of oxygen and nutrient resources that are vital to normal cerebral functioning [52, 56]. Due to the metabolic alterations, and not structural disturbances observed with SRC, the injury is believed to be a functional injury that disrupts critical brain functioning areas [53]. Moreover, the brain is considered in a 'vulnerable' state during the subsequent recovery period while reestablishing homeostatic function. Thus, early management of SRC was predicated on strict rest and avoidance of activities to reduce risk of sustaining additional head impacts [51, 52] and minimize cognitive and physical activities that may increase cognitive resources [57, 58]. The cascading series of events and altered cerebral function in mice observations typically resolve 7-10 days following injury. There is general agreement that prolonged (>14 days in adults, > 30 days in children) non-specific symptoms reflect disruptions to brain functional pathways [20, 59] and do not indicate continued physiological dysfunction [1]. However, the exact underlying etiology of many clinical signs, symptoms, and impairments for both acute and chronic patients stemming from the pathophysiology of SRC has not been elucidated.

A difficult challenge for clinicians overseeing medical clearance decisions to RTP/A rely on interpretation evidence-based clinical assessments of inter-related brain functioning systems (e.g., vestibular, ocular. Etc.). To date, our current understanding of the pathophysiological

responses to SRC can be identified through structured exertion testing. However, heterogeneity of post-concussion impairments that influence physiological, responses to exertion can potentially alter performance outcomes of structured exertion testing. Thus, prior to embarking on a prospective investigation to determine the efficacy of EXiT we should consider the physiological responses to SRC and the previous findings of patient responses to exertion.

2.2 Autonomic Nervous System Dysfunction After Concussion

Based on cerebral blood flow reductions observed in animal model studies [52] and from human case series and cross-sectional studies among patients with persistent symptoms (>4 weeks) [20, 60], clinicians and researchers have suggested that underlying impairments to the ANS may contribute to the clinical presentation of SRC [12]. The ANS comprises of the sympathetic-'fight or flight', and parasympathetic- 'rest and digest' nervous systems (SNS and PNS, respectively) to synergistically modulate heart rate and blood vessel diameter to supply oxygen and other nutrients to the brain and other body regions in response to postural changes or physiological stressors [61-65]. Within SRC literature, ANS function is predominately examined via heart rate variability (HRV), the beat to beat interval and suggested to be proxy of ANS functioning [66]. According to the Neurovisceral Integration Model, pre-frontal cortical regions communicate with the Vagus nerve to modulate PNS and overall HR [67]. Greater activation between these regions will increase PNS input to reduce mean HR [65]. ANS phenomena following SRC are suggested to occur from decoupling of pre-frontal cortical regions and Vagus nerve communication [68], in turn suppressing PNS and increasing SNS drive (reduced HRV). Preliminary evidence of cerebral blood flow reductions in frontal and subcortical regions have been reported among children and

adolescents following TBI [69, 70], but more evidence is warranted as reductions in vagal-prefrontal pathways is also correlated with greater SNS response (lower HRV) among healthy adults in response to pain [64], psychological arousal [71]and physical deconditioning [61, 72]. Interestingly, global cerebral blood flow among 35 athletes within 7 days of SRC were not different from healthy controls (p=.46) but concussed athletes with cognitive-based symptoms exhibited lower cerebral blood flow in the frontal and subcortical regions compared to athletes with primarily somatic symptoms [70]. These findings are in alignment with previous recommendations of potential concussion clinical subtypes to injury and that phenotypic blood flow disruptions may also apply to injury subgroups and should not applied to all clinical cases [70].

A variety of HRV outcomes have been established and should be collectively reported across studies to improve the available evidence of potential ANS dysfunction after SRC[73-76]. The time domain variables include the mean (RRm) and standard deviation (SDNN) of the RR interval, the root-mean-square of squared differences between successive R-R intervals (RMSSD), and a percent of R-R intervals greater than 50 milliseconds (pRR50); and frequency domain reflects the energy signal within very low (VLF, <0.04 Hz), low (LF, 0.04-0.15 Hz) and high (HF, 0.15-0.4 Hz) frequency bands. Additionally, normalized units for LF (LFnu) and HF (HFnu) signals are calculated by dividing LF and HF with the difference between total power and VLF, and the ratio of LF to HF power (LF: HF) are suggested to reflect sympathovagal balance[62, 76, 77]. Ultrashort term recordings (<5 minutes) have recently been examined and indicate that the RMSSD is more robust to alterations in respiration rate[78] and has a high agreement (ICC>.90) with shorter epochs (e.g., 30- and 60- seconds) as 5-minute sampling among athletes prior to and following maximal exertion [79-82]. Interestingly, two separate systematic reviews examining HRV outcomes following concluded that HRV immediately following structured exertion

differed between healthy and asymptomatic post-SRC athletes [62, 83]. From these findings, potential disruptions in the functional pathways to regulate the ANS following concussion may be evident following exertion, but not resting conditions. However, more research is necessary to examine these outcomes among concussed athletes upon medical clearance to RTP/A to characterize the restoration of ANS dysfunction following concussion.

2.3 Structured Exertion Utilization in SRC Management

The Institute of Medicine and expert consensus recently called for well-controlled investigations to compare effects of exertion among concussed and comparable healthy controls to improve clinical practice [1, 2, 84], and several systematic reviews recommend a comprehensive set of physiological and clinical variables to elucidate effective strategies to implement structured exertion into concussion management [1, 85]. To improve the generalizability structured exertion as part of the clinical management for SRC, exertion-based assessments should abide by evidence-based exertion prescription recommendations acknowledged by the American College of Sports Medicine (ACSM). Metabolic Equivalents and age-estimated percentage of maximum heart rate ($HR_{\%max}$) are evidence-based measures to prescribe structured exertion as part of concussion clinical management[86]. Metabolic equivalents are a normalized estimation for physical activity, defined as 3.5 mlO_2/kg/min whereby 1 MET is equivalent to energy expenditure during sedentary (e.g., sitting) activities, whereas $HR_{\%max\ is}$ determined by age-based calculations (e.g., 220-age)[87]. Future research can utilize this framework for categorizing moderate intensity (3.0-6.0 METs; 50-75% HR_{max}) and vigorous (77-95% HR_{max}) exertion intensities to inform therapeutic exertion recommendations following SRC. Thus, structured exertion assessments aligned with

ACSM prescription components (e.g., exertion frequency, intensity, time, and type) [88-91] will address critical limitations posed by solely relying on perceived effort or subjective symptoms. Moreover, transparently reporting clinical effects of structured exertion within these guidelines will align within ACSM's mission statement to integrate scientific research with sports medicine and exertion science applications to enhance health and quality of life[92].

Concussion treatment and return to play/activity decisions are based on a multifaceted clinical evaluation to detect impairments to inter-related functional subsystems [3, 93]. As a result of the inherent ANS dysfunction observed among some patients post-SRC, the recent emergence of structured exertion testing as a component of the clinical assessment is proposed to screen individuals for physiological disturbances and recovery [20, 94, 95]. After an initial rest period post-SRC, provocative exertion can safely be conducted [19] and may have prognostic utility in potentially identifying patients at risk of protracted recovery[20, 95]. However, most evidence to support exertion assessments have been exclusively implemented during the subacute stages of recovery, and not during the medical clearance to RTP/A

To date, structured exertion following SRC has been primarily administered with a treadmill or cycle ergometer in a progressive, staged assessment until symptoms worsen or volitional exhaustion occurs [19, 20, 94, 95]. The Buffalo Concussion Treadmill Test (BCTT), adapted from the Baalke treadmill assessment for determining maximal oxygen consumption among sedentary individuals, is an incremental aerobic assessment suggested to identify exertional intolerance because of injury. The maximum heart rate attained at symptom provocation is deemed the 'symptom threshold' and is subsequently referred to during exertion therapy recommendations following SRC [20, 96]. Among recent systematic reviews, the BCTT is the most widely used

clinical exertion assessment following SRC [83, 85] and has been administered in both subacute and chronic stages of SRC recovery [19, 20, 94, 95].

In one study, 91 patients that completed the BCTT before the staged return to sport progression and returned to unrestricted sport participation were contacted to complete a telephone survey and reported instances of symptom worsening or difficulties with injury [97]. The authors reported 100% of patients were successful in returning to sport without symptom worsening during the staged return to sport progression, and concluded that the combined use of the BCTT and staged progression was a successful approach to inform RTP/A decision making [97]. However, the conclusions from this study are limited since the implementation of the staged progression was individualized to each patient and based on the criteria for return to sport, each stage was tailored to the patient's medical and sport background and exertion sequence was not controlled.

2.3.1 Role of Dynamic Exertion for Sport-Related Concussion

Exertion assessments for SRC should comprehensively evaluate the involved physiological systems that play a significant role during sport participation. Interestingly, treadmill and cycle ergometer assessments do not replicate concomitant cardiovascular alterations [98] or head-body movements [99-101] commonly performed in sport participation and may be unable to systematically evaluate the interrelated systems imposed during sport participation. Preliminary evidence among concussed and healthy athletes indicates the vestibular system has a critical role in symptom provocation during exertion [102-104]. Vestibular system dysfunction is observed in approximately half of patients observed within 2 weeks of injury [105-107] and is clinically identified by conducting brief balance and vestibular-ocular screenings[108]. Underlying impairments to this system can be provoked during dynamic head movements [13]. Dynamic

exertion, which incorporates synchronized head-body movements to spatially navigate in one's environment, is commonly performed during sport participation. Healthcare providers should consider exertion with challenges to the vestibular system to potentially identify underlying impairments that may be undetected during aerobic exertion with minimal head-body movements[36, 108]. For example, a recent retrospective chart review of adolescent athletes completing supervised exertion within 30 days of concussion reported differential clinical responses to aerobic and dynamic exertion challenges [36]The aerobic exertion challenge was intended to progressively increase to achieve a peak HR of at least 80% of age-estimated maximum heart rate; and the dynamic exertion challenges included medicine ball exertions that involved head-body repositioning, and agility drills that involved head-body movements and speed and directional changes. Of 65 patients, 45 (69.2%) experienced symptom provocation and over half (25/45, 55.6%) of these patients tolerated aerobic but not dynamic exertion; and 17 (37.0%) of patients that were symptom provoked during exertion did not endorse any symptoms beforehand[36]. All patients completed low to moderate intensity exertion on a stationary cycle, treadmill, or cycle ergometer before initiating dynamic exertion challenges and it is unknown if symptom provocation was caused by aerobic or dynamic exertion challenges. Only patients with unprovoked symptoms (3 or less points on a 10-point Likert scale) were permitted to initiate the dynamic exertion challenge. The aerobic and dynamic exertion tasks were not standardized and it is difficult to make meaningful inferences of the clinical responses to structured exertion as the type, intensity, and duration of the exercises were not standardized, which have been notable limitations of prior studies [86]. Lastly, the assessment ranged between 20 and 40 minutes (10-20 minutes for each the aerobic and dynamic exertion-types and were prone to differing administrations between clinicians. This difference in administration time can affect rest/activity

patterns between each task that influence the potential development of symptom provocation. Nevertheless, this was the first investigation to date that described symptom provocation patterns during supervised exertion bouts consisting of both aerobic and dynamic exercises and concluded that these findings improve utility of structured exertion to inform RTP/A decision making [36, 103].

Based on recent review of the vestibular profile, clinicians may implement structured exertion with more dynamic movements that involve the head or eyes [108], Various exertion modes may increase symptoms and particularly exertion that integrates vestibular, ocular, and autonomic nervous systems can provide additional benefit for patient subtypes. Among healthy collegiate athletes, vestibular-ocular motor screening symptoms have been shown to increase following a high-intensity circuit comprised of push-ups, sit-ups, and sprints [104], but a 20-minute bout of treadmill exertion with minimal vestibular and ocular input did not affect near point of convergence scores [109]. These findings provide preliminary evidence that inter-related vestibular, ocular, and cardiovascular system functioning commonly employed during sport participation may improve the sensitivity of exertion-based assessments for concussion [25, 110-115]. The results from these investigations among healthy athletes demonstrate the need to examine clinical outcomes from dynamic exertion to improve the interpretation of structured exertion assessments for SRC clinical decision making.

2.3.2 Co-Occurring Factors That May Influence Clinical Responses to Exertion

Despite the increased awareness and implementation of structured exertion in clinical practice [85, 116], previous studies have not accounted for inactivity and subsequent physical deconditioning which can drastically influence exertion testing outcomes. Deconditioning has

been a consideration for physically active patients during the acute SRC recovery period due to prolonged rest periods[117]. Even among healthy athletes prolonged rest is known to affect the sympathetic nervous system, and prolonged inactivity is a primary concern for athletes after concussion [12]. Among healthy, deconditioned athletes, greater perceived effort and heart rate are associated with earlier exertion termination and symptom provocation[118]. This is of clinical importance in concussion, as heart rate during exertion is the basis for aerobic exertion therapy recommendations and exertion assessment outcomes including heart rate, blood pressure, and heart rate variability outcomes may be misrepresented as a physiological effect of a concussion and not because of deconditioning. However, researchers have yet to discern if ANS dysfunction is directly caused by the effects of concussion, or indirectly by physical inactivity and co-occurring cardiovascular deconditioning.

Although standardized exertion assessments are clinically safe to determine exertion tolerance in the subacute and chronic phases following SRC [19, 97], symptom-limited exertion has several clinical considerations that may affect the interpretability of structured exertion. Symptom-limited exertion is reliant on subjective recall and prone to a response bias, and reporting behaviors differ by age [119, 120], sex [119, 121], learning disabilities [119, 122], and sport type [123, 124]. Secondly, symptoms are non-specific to concussion [1] and a substantial body of evidence suggests both recently-concussed and healthy athletes may experience symptom provocation during structured exertion [83, 125], and some investigators advocate that structured exertion cannot reliably be conducted based on symptoms alone[59].

For instance, achieved HR following high-intensity bouts on a cycle ergometer was greater among asymptomatic patients compared to healthy controls despite similar physical symptoms (headache, dizziness, and nausea) between the two groups [59]. Additionally, athletes motivated

to return to sport may under-report or hide symptoms to avoid being withheld from sport[40]. Lastly, endorsed symptoms are also affected by exertion intensity [116, 126, 127], healthy individuals endorse a greater number of concussion symptoms during high intensity exertion that persists up to 15 minutes after exertion cessation, whereas mild symptom provocation following moderate intensity exertion has resolved within 15 minutes of rest [127]. For these reasons, there is a critical need for more objective exertion assessments for SRC.

2.3.3 Exertion to Inform Return to Play/Activity Decision Making for Sport-Related Concussion

The medical clearance decision to RTP/A following SRC requires a multifaceted assessment in addition to a staged exertion progression replicative of sport participation [33], but to date there is little empirical evidence to support this progression and several reports have suggested that an exertion assessment may be an alternative approach to inform RTP/A readiness [5, 31] (EXiT #1).

The development of the Gapski-Goodman Test was an initial step in the development of standardized exertion to inform RTP/A decision making. The assessment consists of a series of aerobic (cycle ergometer) and plyometric tasks that increase intensity and duration to replicate sport-intensity and functional movements (e.g., hurdle hops, burpees, box jumps, and 180° rotation hops) to impose challenges to the vestibular and oculomotor system. Gapski-Goodman Test was administered to adolescent and adult athletes (range 13-25) that were asymptomatic for a minimum of 7 days upon completion of the staged progression to sporting activities, and eligible for medical clearance to return to sport participation [31]. Of 759 patients that ‘passed’ the BCTT and completed the staged RTP progression without symptom worsening, 111 (14.6%) reported symptom provocation during exertion. These findings demonstrate the need to consider exertion

type and intensity during the clinical evaluation. However, the rationale for selected tasks, intensity, duration, and the administration were not reported. Moreover, the Gapski-Goodman test was interpreted as a successful test (and clearance to RTP/A) was based on the successful completion of the tasks without any time or performance outcomes. Lastly, multiple raters administered the Gapski-Goodman test and the agreement between administrators is unknown. An effective assessment to inform RTP/A should be able to demonstrate high inter-rater agreement.

More recently, dynamic exertion testing (EXiT) was developed to inform medical clearance to RTP/A with evaluations of physiological, performance, and clinical outcomes. EXiT consists of moderate (64-76% of HR_{max}) and vigorous (77-95% HR_{max}) intensity treadmill running based on American College of Sports Medicine (ACSM) exertion prescription guidelines[128, 129]; and functional exercises and agility tasks commonly conducted during sport participation. Although the early findings suggest the comprehensive outcomes of EXiT are similar between athletes at medical clearance from concussion are like healthy athletes (EXiT #1), there are currently several key limitations of EXiT that prevent its widespread use. Firstly, similar to the Gapski-Goodman Test [31], the reliability of EXiT outcomes across repeated measurements and agreement between assessment administrators has not been examined. Potential factors that may influence clinical recovery from SRC and exertion performance outcomes have not been examined, and a well-controlled comparison of ANS functioning between athletes completing EXiT at medical clearance and healthy athletes has yet to be conducted. An investigation to address these potential pitfalls of EXiT will improve clinical care for the millions of adolescents and adults returning to sport and physical activity following concussion each year [37, 38].

3.0 METHODS

3.1 Experimental Design

For Aim 1 we employed a test-retest study design. For Aim 2 we employed a cross-sectional study design. For Aim 3 we employed a matched case-control study design.

3.2 Participants

All participants were obtained from a convenience of recreational and competitive athletes from a heterogeneous sport population residing in the Pittsburgh, PA community. For aims 1-3, we enrolled healthy physically active (based on ACSM guidance for weekly moderate or vigorous activity [described in more detail below]) healthy controls (CONTROL group). We also enrolled a sample of adolescent and adult patients upon medical clearance to return to play and activity following concussion recovery (CONCUSS group) at an outpatient multidisciplinary concussion clinic.

3.2.1 Inclusion Criteria

Aim 1)

CONTROL participants

a) Aged 14¬35 years
b) Fulfilled ACSM's guidelines for regular aerobic activity (30 minutes of moderate intensity exertion 5 days per week or 20 minutes of vigorous exertion 3 days per week)

CONCUSS participants

a) Aged 14¬35 years
b) Fulfilled ACSM's guidelines for regular aerobic activity (30 minutes of moderate intensity exertion 5 days per week or 20 minutes of vigorous exertion 3 days per week) prior to injury.
c) Diagnosed with an SRC within 14 days of injury.
d) Recently cleared to resume unrestricted sport participation after a trained clinician from UPMC Sports Medicine Concussion Program has interpreted neurocognitive, vestibular, and clinical interview outcomes and completed EXiT under direction of exertion physical therapist.

Aim 2)

a) Aged 14¬35 years
b) Fulfilled ACSM's guidelines for regular aerobic activity (30 minutes of moderate intensity exertion 5 days per week or 20 minutes of vigorous exertion 3 days per week) prior to injury.

Aim 3)

<u>CONTROL participants</u>

a) Aged 14¬35 years
b) Fulfilled ACSM's guidelines for regular aerobic activity (30 minutes of moderate intensity exertion 5 days per week or 20 minutes of vigorous exertion 3 days per week) prior to injury.

<u>CONCUSS participants</u>

a) Aged 14¬35 years
b) Fulfilled ACSM's guidelines for regular aerobic activity (30 minutes of moderate intensity exertion 5 days per week or 20 minutes of vigorous exertion 3 days per week) prior to injury.
c) Diagnosed with an SRC within 14 days of injury.

d) Recently cleared to resume unrestricted sport participation after a trained clinician from UPMC Sports Medicine Concussion Program has interpreted neurocognitive, vestibular, and clinical interview outcomes and completed EXiT under direction of exertion physical therapist.

3.2.2 Exclusion Criteria

Participants were excluded if self-reported any exclusionary item obtained during formal eligibility screening:

Aim 1)

CONTROL participants

a) Suffered a prior concussion within 6 months of enrollment.
b) More than 2 previously diagnosed concussions
c) History of brain surgery or TBI (based on Glasgow Coma Scale of <13)
d) History of neurological disorder (seizure disorder, epilepsy, brain tumors or malformations)
e) Current history of preexisting vestibular disorder benign paroxysmal positional vertigo (BPPV), labyrinthitis or vestibular neuritis
f) Previous diagnosis of ocular motor condition (e.g., ocular motor apraxia)
g) Currently taking anticoagulant, beta-blockers, and anticonvulsant prescription medication
h) Incapable of treadmill running at speeds up to 11.27 km/h (7.0 mph) and 13.67 km/h (8.5 mph) for females and males, respectively (based on assessment parameters)
i) Diagnosed with a cardiac, peripheral, or cerebrovascular disease (type 1 or 2 diabetes, or renal disease)
j) Pregnant

k) Experienced chest pain or shortness of breath while at rest or with mild exertion.

l) Lose balance because of dizziness (aside from concussion) or lose consciousness from exertion.

m) Diagnosed with or taking medication for a chronic medical condition.

n) Currently or recent (within 12 months) physical impairment exacerbated by physical activity, leading to the inability to complete 30 minutes of moderate to vigorous exertion.

o) Self-reported any exclusionary criteria from the Preparticipation Activity Questionnaire (PAR-Q), ACSM's formal screening to safely conduct submaximal exertion:

- Previous diagnosis of a heart condition or high blood pressure
- Pain in chest of shortness of breath at rest or activities of daily living
- Currently have a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be worsened by exertion.
- Been told by a doctor to only conduct physical activity under medical supervision.

<u>CONCUSS participants</u>

a) Suffered a prior concussion within 6 months (excluding current injury)

b) More than 2 previously diagnosed concussions (excluding current injury)

c) History of brain surgery or TBI (based on Glasgow Coma Scale of <13)

d) History of neurological disorder (seizure disorder, epilepsy, brain tumors or malformations)

e) Current history of preexisting vestibular disorder benign paroxysmal positional vertigo (BPPV), labyrinthitis or vestibular neuritis

f) Previous diagnosis of ocular motor condition (e.g., ocular motor apraxia)

g) Currently taking anticoagulant, beta-blockers, and anticonvulsant prescription medication

h) Incapable of treadmill running at speeds up to 11.27 km/h (7.0 mph) and 13.67 km/h (8.5 mph) for females and males, respectively (based on assessment parameters)

i) Diagnosed with a cardiac, peripheral, or cerebrovascular disease (type 1 or 2 diabetes, or renal disease)

j) Pregnant

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o) Self-reported any exclusionary criteria from the Preparticipation Activity Questionnaire (PAR-Q), ACSM's formal screening to safely conduct submaximal exertion:

    - Previous diagnosis of a heart condition or high blood pressure
    - Pain in chest of shortness of breath at rest or activities of daily living
    - Currently have a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be worsened by exertion.
    - Been told by a doctor to only conduct physical activity under medical supervision.

p) Diagnosed with a concussion more than 14 days after injury,

q) Concussion occurred outside recreational or sport participation (e.g., car crashes, falls, or other accidents),

r) If the injury occurred more than 90 days prior to the RTP/A evaluation as the recovery timeline for these individuals is beyond the typical course of recovery [1].

Aim 2)

a) Suffered a prior concussion within 6 months of enrollment.
b) More than 2 previously diagnosed concussions
c) History of brain surgery or TBI (based on Glasgow Coma Scale of <13)
d) History of neurological disorder (seizure disorder, epilepsy, brain tumors or malformations)
e) Current history of preexisting vestibular disorder benign paroxysmal positional vertigo (BPPV), labyrinthitis or vestibular neuritis
f) Previous diagnosis of ocular motor condition (e.g., ocular motor apraxia)
g) Currently taking anticoagulant, beta-blockers, and anticonvulsant prescription medication
h) Incapable of treadmill running at speeds up to 11.27 km/h (7.0 mph) and 13.67 km/h (8.5 mph) for females and males, respectively (based on assessment parameters)
i) Diagnosed with a cardiac, peripheral, or cerebrovascular disease (type 1 or 2 diabetes, or renal disease)
j) Pregnant
k) Experienced chest pain or shortness of breath while at rest or with mild exertion.
l) Lose balance because of dizziness (aside from concussion) or lose consciousness from exertion.
m) Diagnosed with or taking medication for a chronic medical condition.
n) Currently or recent (within 12 months) physical impairment exacerbated by physical activity, leading to the inability to complete 30 minutes of moderate to vigorous exertion.
o) Self-reported any exclusionary criteria from the Preparticipation Activity Questionnaire (PAR-Q), ACSM's formal screening to safely conduct submaximal exertion:
    - Previous diagnosis of a heart condition or high blood pressure

- Pain in chest of shortness of breath at rest or activities of daily living
- Currently have a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be worsened by exertion.
- Been told by a doctor to only conduct physical activity under medical supervision.

Aim 3)

CONTROL participants

a) Suffered a prior concussion within 6 months of enrollment.
b) More than 2 previously diagnosed concussions
c) History of brain surgery or TBI (based on Glasgow Coma Scale of <13)
d) History of neurological disorder (seizure disorder, epilepsy, brain tumors or malformations)
e) Current history of preexisting vestibular disorder benign paroxysmal positional vertigo (BPPV), labyrinthitis or vestibular neuritis
f) Previous diagnosis of ocular motor condition (e.g., ocular motor apraxia)
g) Currently taking anticoagulant, beta-blockers, and anticonvulsant prescription medication
h) Incapable of treadmill running at speeds up to 11.27 km/h (7.0 mph) and 13.67 km/h (8.5 mph) for females and males, respectively (based on assessment parameters)
i) Diagnosed with a cardiac, peripheral, or cerebrovascular disease (type 1 or 2 diabetes, or renal disease)
j) Pregnant
k) Experienced chest pain or shortness of breath while at rest or with mild exertion.
l) Lose balance because of dizziness (aside from concussion) or lose consciousness from exertion.
m) Diagnosed with or taking medication for a chronic medical condition.

n) Currently or recent (within 12 months) physical impairment exacerbated by physical activity, leading to the inability to complete 30 minutes of moderate to vigorous exertion.

o) Self-reported any exclusionary criteria from the Preparticipation Activity Questionnaire (PAR-Q), ACSM's formal screening to safely conduct submaximal exertion:

- Previous diagnosis of a heart condition or high blood pressure
- Pain in chest of shortness of breath at rest or activities of daily living
- Currently have a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be worsened by exertion.
- Been told by a doctor to only conduct physical activity under medical supervision.

<u>CONCUSS participants</u>

a) Suffered a prior concussion within 6 months (excluding current injury)

b) More than 2 previously diagnosed concussions (excluding current injury)

c) History of brain surgery or TBI (based on Glasgow Coma Scale of <13)

d) History of neurological disorder (seizure disorder, epilepsy, brain tumors or malformations)

e) Current history of preexisting vestibular disorder benign paroxysmal positional vertigo (BPPV), labyrinthitis or vestibular neuritis

f) Previous diagnosis of ocular motor condition (e.g., ocular motor apraxia)

g) Currently taking anticoagulant, beta-blockers, and anticonvulsant prescription medication

h) Incapable of treadmill running at speeds up to 11.27 km/h (7.0 mph) and 13.67 km/h (8.5 mph) for females and males, respectively (based on assessment parameters)

i) Diagnosed with a cardiac, peripheral, or cerebrovascular disease (type 1 or 2 diabetes, or renal disease)

j) Pregnant

k) Experienced chest pain or shortness of breath while at rest or with mild exertion.

l) Lose balance because of dizziness (aside from concussion) or lose consciousness from exertion.

m) Diagnosed with or taking medication for a chronic medical condition.

n) Currently or recent (within 12 months) physical impairment exacerbated by physical activity, leading to the inability to complete 30 minutes of moderate to vigorous exertion.

o) Self-reported any exclusionary criteria from the Preparticipation Activity Questionnaire (PAR-Q), ACSM's formal screening to safely conduct submaximal exertion:

- Previous diagnosis of a heart condition or high blood pressure
- Pain in chest of shortness of breath at rest or activities of daily living
- Currently have a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be worsened by exertion.
- Been told by a doctor to only conduct physical activity under medical supervision.

p) Diagnosed with a concussion more than 14 days after injury,

q) Concussion occurred outside recreational or sport participation (e.g., car crashes, falls, or other accidents),

r) If the injury occurred more than 90 days prior to the RTP/A evaluation as the recovery timeline for these individuals is beyond the typical course of recovery [1].

3.2.3 Power Analysis

All sample size calculations were conducted with G*Power 3.0.10 (Franz Faul, Universität Kiel, Germany) [130].

For aim 1, based on a previous investigation reporting completion time for a novel agility task among collegiate athletes [131], we determined that 64 participants (74 when accounting for 20% data loss and attrition) would be necessary to provide 80% power [132].

For aim 2, given 87 EXiT assessments with complete physiological, performance, and clinical data we determined that a total sample size of 80 (40 in each group) participants would require an adjustment of the alpha (0.0620) and beta (.248) level with a power of 0.752 to detect statistical significance between age, sex, BMI, and sport-type analyses [133].

For aim 3, based on previous findings that compared low and high frequency HRV variables among 11 post-SRC athletes at medical clearance with 7-sport matched controls, and a priori alpha=.05, effect size=0.5, we determined that 24 participants (12 age-, sex-, and sport-, matched controls will achieve 80% power when comparing HRV outcomes between CONCUSS and CONTROL groups.

3.3 Operational Definitions

3.3.1 Sport-related Concussion

Concussion was defined as a "complex pathophysiological process affecting the brain, induced by biomechanical forces" as specified in the most recent consensus statement on concussion in sport[33]. In the current investigation to meet criteria for SRC diagnosis, there had to be: 1) evidence of a clear mechanism of injury; and 2) at least one acute sign (e.g., LOC, amnesia, and disorientation/confusion) and/or immediate physical symptoms (e.g., headache, dizziness, and balance problems) following injury. All SRCs were diagnosed by a clinician (e.g., neuropsychologist, sports medicine primary care physician) trained in concussion care.

3.3.2 Medical Clearance

Medical clearance to resume RTP/A was determined by a multifaceted clinical evaluation utilizing cognitive, vestibular, ocular, and clinical interview results by clinicians and successful completion of EXiT administered by a physical therapist within the assessment's instructions. In accordance with international consensus[134], were required to 1) be symptom free at rest and following exertion; (2) demonstrate neurocognitive performance within normative or baseline reliable change indices (RCI); and (3) resume pre-injury levels for sleep and physical activity tolerance.

3.3.3 Sport-Type

Sport participation information was obtained from the demographic questionnaire and categorized based on the level of contact exposure: non-contact, contact (body-to-body contact allowed, but not purposeful), or collision (repeated, purposeful body-to-body contact) [135].

3.3.4 Recovery Time

Number of days from date of injury to full medical clearance to resume RTP/A per previously stated criteria.

3.4 Instrumentation

3.4.1 Physiological Monitoring and Processing Equipment

The Equivital Life Monitor (AD Instruments, Colorado Springs, CO; USA) physiological monitoring system was used to quantify HR and linear accelerations in the -X, -Y, and -Z coordinates at a 256 Hz sampling rate [136-138]. Importantly, sampling rates over 200hz is an adequate sampling rate for HRV data acquisition [75]. A recent validation report concluded that the Equivital monitoring system is an appropriate tool to sensitively quantify physiological data [136], and its tri-axial accelerometer and heart rate accuracy is similar to well-established activity trackers [137]. Movement patterns and physiological data were transmitted to a nearby laptop running Lab chart software (ADI Instruments; Sydney Australia) [138] for processing.

3.4.2 Exertion Testing Equipment and Materials

- Treadmill (WOODWAY USA, Waukesha, WI),
- 10”- Agility Cones
- Metronome: A free to download application (Metronome beats, Stonekick, London UK)
- Stopwatch
- Test Cards (N=40) printed on 5”X8” card stock
- Digital scale (Health-o-Meter, Sunbeam Products Inc; McCook, Il, USA)
- Wall-mounted stadiometer (Seca; Chino, CA, USA)
- An open gym space approximately 5X8 meters with a slip-resistant surface in an environment-controlled facility

3.5 Measures

3.5.1 Dynamic Exertion Testing (EXiT)

EXiT is a 30-minute clinical assessment with aerobic and dynamic components (Appendix C). The aerobic component is a high-intensity interval treadmill protocol that alternates between slow and fast treadmill running speeds (1:1 ratio) based on the 60% and 90% of the superior category (90th percentile) for aerobic capacity among 13-29 year old male and female sex [129]. The target intensities were then used in ACSM's running equation to determine horizontal running speed:

$$VO_2 = 0.2*S + (0.9 *S*G) + 3.5 \quad (1)$$

where, VO_2 is oxygen consumption [mL O_2/kg/min], S is the horizontal running speed (in meters per minute), and G is the percentage grade of the treadmill. Speed parameters underwent a brief pilot period and final adjustments to obtain a final protocol whereby females alternated between 7.2 km/h (4.5 mph; 3.14 METs) and 11.27 km/h (7.0 m/h, 6.36 METs), and males between 8.85 km/h (5.5 mph; 5.21 METs) and 13.67 km/h (8.5 mph, 7.5 METs). Thus, participants completed a 2-minute warm up (Male: 5.5 mph, Female: 4.5 mph), followed by 30-second intervals of fast and slow running speeds (Male: 8.5/5.5 mph; Female: 7.0/4.5 mph) for 10 minutes. Participants were instructed to use support handles as necessary to maintain safety. Following the aerobic component, participants completed the dynamic component which consists of 2 functional movement tasks (Dynamic Circuit [CIR] and Ball Toss [BT]) and 5 Agility Tasks (Box Drill Shuffle [SHUF], Box Drill Carioca [CAR], Zigzag [ZZ], Pro Agility [PA], and Arrow Agility [AA]) to maximal effort (Appendix C). The CIR is a 3-exercise circuit comprised of squat jumps, side-to-side pushups, and ball rotations completed for 3 sets of 10 repetitions in

synchronization with a metronome (25 beats/min) and a 30-second rest period between each cycle. The BT task was administered with the participant standing 2.5 meters in front of administrator. After administrator called 'left', or 'right', participant jumped and rotated 180° in the specified direction, caught a basketball tossed by the administrator, and tossed back before returning to the starting position for the next trial, and was repeated for 10 trials (5 jumps left and 5 jumps right) and after a 30-second rest, a second round was performed whereby administrator called direction (left or right) or 'Go' (no response) in a random sequence (completed 5 jumps left, 5 jumps right, and 2 distractors). Participants completed two trials of each agility task (30-sec rest between trials), which were hand-timed via stopwatch by the administrator. Valid EXiT tests, defined as completion of EXiT within the study parameters without assessment modifications, were included in the study.

3.5.1.1 EXiT Physiological Outcomes

- Resting systolic and diastolic blood pressure (measured in mmHg) were measured with the use of an automatic sphygmomanometer (Omron; Kyoto, Japan) during the pre- and post-EXiT 5-minute rest period. Heart rate, measured in beats per minute, was calculated for the percentage of age estimated (220-age) maximum HR ($HR_{\%max}$)[87].
- HR was recorded prior to (~5 min), during, and following (~5 min) exertion via a noninvasive heart rate monitor while participants were seated with arms supported and feet placed flat on the floor. During EXiT, heart rate was recorded upon the completion of each task.
- Heart rate variability, the beat-to-beat interval and suggested to be proxy of ANS functioning, is expressed in time and frequency domains. Specifically, time domain

outcomes are determined by variations in the R-R interval, and frequency domain reflects the energy signal within a frequency band (Table 2).

Table 2 Heart Rate Variability Time and Frequency Domain Outcomes

Time Domain	
RRm	Mean RR time interval (in milliseconds) between consecutive heartbeats
SDSDNN	Standard deviation of the RR interval
RMSSD	Root -mean square of differences between successive R-R intervals
pRR50	Percent of R-R intervals greater than 50 milliseconds
Frequency Domain	
Total Power	Variance of all RR intervals
VLF	Power in the very low (<0.04 Hz) frequency range
LF	Power in the low (0.04-0.15 Hz) frequency range
HF	Power in the high (0.15-0.4 Hz) frequency range
LFnu	Normalized units of LF power divided by difference between total power and VLF
HFnu	Normalized units of HF power divided by difference between total power and VLF
LF: HF	Ratio of LF power to HF power

3.5.1.2 EXiT Performance Outcomes

- Agility task completion time was measured by the EXiT administrator via a hand-timed stopwatch. The fastest trial of each agility task was calculated except for Arrow Agility task due to the secondary cognitive task, thus both trials were analyzed.
- Errors were counted by the EXiT administrator. For the aerobic component, excessive pulling on handrails for 10 or more seconds or additional rest periods for 10 or more seconds were counted as errors. During the dynamic component, CIR errors included improper form or inability to maintain pace with squats, pushups, or ball rotation exercises; and BT errors included a jump-turn in the wrong direction, inability to catch or toss ball back to administrator, or a jump committed after a ‘Go’ call were counted as errors. Errors were counted when a participant

kicked a cone off the original placement, mis-navigated a cone, or did not hand-touch a cone when instructed to do so.

3.5.1.3 EXiT Clinical Outcomes

- Headache, dizziness, and nausea concussion-symptoms were individually reported on a 0-10 Likert scale prior to EXiT and after completing the warmup (Post-warm up), the 5^{th} (Midpoint), and 10^{th} (End) intervals of the aerobic component and following the completion of each task of the dynamic component. Endorsed symptom were totaled within aerobic and dynamic components, and subsequently combined and an EXiT total symptom score.
- Rating of Perceived Exertion (RPE) was recorded on the 6-20 Borg scale, a valid measure of perceived effort (6 'no exertion at all' to 20 'maximal effort'), prior to, throughout, and following EXiT [139].

3.5.2 Anthropometrics

Bodyweight (in kg) was measured using a digital scale (Health-o-Meter) and height (in cm) with a wall-mounted stadiometer (Seca) among healthy controls, and values were identified in the electronic medical record for concussed participants. Weight and height measurements were used to calculate body mass index (BMI= weight [kg] / height $[m]^2$) [140], and the upper (HI-BMI) and lower (LO-BMI) 50th percentile groups were determined as a function of age for adolescents [141] and median split of BMI for adults.

3.5.3 Concussion Injury Information

For CONCUSS participants, ImPACT, and VOMS assessment results and the date of SRC diagnosis and medical clearance to RTP/A were extracted from the electronic medical record by a member of the research team not involved in assessment administration or medical clearance decision making process.

3.5.4 Vestibular/Ocular Motor Screening Tool

The VOMS tool is a brief (~5-7 min) clinically intuitive and valid assessment for vestibular and ocular motor symptoms and impairment after concussion [142]. Participants reported on a 0-10 Likert scale (0 'none' to 10 'severe') prior to (pretest) and following each of the 7 VOMS sub-tests: smooth pursuits, horizontal saccades, vertical saccades, near-point of convergence, horizontal vestibular-ocular reflex, vertical vestibular-ocular reflex, visual motion sensitivity; and NPC distance. Symptoms were totaled across all sub-tests (range: 0-240) whereby greater scores indicate worse symptom burden and may indicate dysfunction. Mucha et al reported that the VOMS components had high internal consistency (Cronbach $\alpha = .92$) and a multivariate logistic regression of the VMS, VOR, and convergence domains resulted in model that explained 61% of the variance of likelihood of concussion; a follow up receiver operator characteristic curve analysis demonstrated an area under the curve value of 0.89 [142] when utilizing clinical cut-off scores defined as a symptom severity score of 2 or greater for any subtest or NPC distance of 5 or more cm.

3.5.5 Immediate Post-Concussion Assessment and Cognitive Testing & Post-Concussion Symptom Scale (PCSS)

Neurocognitive performance was assessed using the ImPACT battery in a private testing area[123, 143-145]. The neurocognitive assessment comprises six neurocognitive test modules to populate verbal memory, visual memory, motor processing speed, and reaction time composite scores. Prior to the neurocognitive test, participants completed a sport, academic, and medical history questionnaire on a standardized form (Appendix C).

The PCSS is a reliable self-report survey consisting of 22 items rated on a 0-6 Likert-scale (0 ‘none’ to 6 ‘severe’), the total symptom severity score is calculated (range: 0-132) whereby greater scores indicate worse symptom burden [146].

3.6 Experimental Procedures

3.6.1 Recruitment and Consent

Recruitment for CONTROL participants was conducted through word of mouth, posted fliers, and online advertisement for controls (Pitt + Me), and if deemed eligible during in-person or phone screening, were scheduled for a study visit at the Neuromuscular Research Laboratory-Warrior Human Performance Research Center. Healthy control participants were also instructed to a) avoid ingesting food, alcohol, or caffeine or tobacco products within 2 hours of assessment; b) avoid vigorous exertion the day prior to and day of assessment; c) Wear clothing and footwear to permit athletic movements; and d) drink plenty of fluids the 24-hour period before enrollment. CONCUSS participants were directly identified at the UPMC Sports Medicine Concussion

Program outpatient concussion clinic by a treating clinician upon medical clearance to resume sport participation.

All participants received a thorough explanation of the study overview, procedures, and potential risks of participation prior to signing consent forms. Since EXiT was part of routine clinical practice to inform return to play, CONCUSS participants completed EXiT before being introduced to the study and (if enrolled) provided consent/assent to use EXiT results embedded within the electronic medical record and physiological data temporarily stored on a laptop.

3.6.2 Equipment Fitting and Physiological Measurements

Participants wore noninvasive heart rate monitor (i.e., Polar or Equivital strap) to capture heart rate, respiration rate, skin temperature, and accelerations in the X, Y, and Z directions during EXiT. Resting physiological measures (blood pressure [BP] and heart rate [HR]) were obtained with participant seated with back supported and feet placed flat on the floor. Pre-EXiT measurements were obtained after a 5-minute resting period whereas post-EXiT measures were collected upon returning to the private examination room (~1-5 min) but varied across the sample as some individuals requested additional time for hydration.

3.6.3 EXiT Administration

All participants completed clinical assessments (ImPACT, PCSS, and VOMS) prior to EXiT in a private examination area. One physical therapist administered EXiT to CONCUSS and one certified athletic trainer administered to CONTROL participants. Heart rate, agility task completion time, errors, symptoms, and effort were recorded on a standardized report sheet (Appendix C).

In aim 1, CONTROL participants in the control participants repeated assessment procedures (including instructions) at a 2nd visit (3-21 days between visits). A priori systematic approach to inter-rater sampling was conducted whereby the 11-15, 21-25, and 31-35 sequentially enrolled participants completed EXiT with 1 administrator but a 2nd rater (certified athletic trainer) independently recorded agility task completion time and errors. Additionally, 12 (of 15) CONTROL participants completed a 2nd visit with the same raters, which were included in the inter-rater reliability analyses. All study procedures were approved by the University of Pittsburgh Institutional Review Board

3.7 Data Reduction

For all aims, Body Mass Index ([BMI]= weight [kg]/height[m]^2) and the lowest (fastest) time between consecutive agility task trials were calculated, and participants were categorized in adolescent (14- 17 years) or adult (≥18 years), male or female (self-report), LO-BMI (BMI < 50th percentile) or HI-BMI (BMI ≥50th percentile), and collision, contact, or non-contact sport-type groups.

Participants with complete EXiT physiological, performance, and outcome data were analyzed (EXiT #1). A team member trained in the cleaning and processing procedures examined Equivital recordings for completeness and identified periods of movement and rest and calculated raw (HR_{raw}) and percentage of age estimated (220-age) maximum HR ($HR_{\%max}$)[87]. The fastest trial of each agility task was calculated with the exception of Arrow Agility task due to the secondary cognitive task, thus both trials were analyzed [88]. In aim 1 inter-rater agreement for agility task completion time included all trials. Across all aims, endorsed headache, dizziness, and

nausea symptoms were subtotaled within aerobic and dynamic components, and subsequently combined to populate EXiT total symptoms.

In aim 3, the final 3-minute sampling period was used for HRV outcomes. Time (RRm, SDSDNN, RMSSD, pRR50) and frequency (Power, VLF, LF, HF, LFnu, HFnu, and LF: HF) domain variables were calculated with Lab Chart software (AD Instruments). Although RMSSD and SDNN were primary HRV outcomes for the current investigation, all HRV variables were reported in accordance with expert recommendations[76]

3.8 Statistical Analyses

In aim 1, independent samples t-tests were conducted for continuous (e.g., age, BMI, etc.), and chi-squared (χ^2) with odds ratio (OR) values for nominal (e.g., sex, sport type, etc.) demographic variables to compare the inter-rater reliability subset from the entire sample. Systematic bias between consecutive trials and visits (e.g., learning effect) was examined with a series of paired samples t-tailed t-tests for agility task completion time, resting systolic and diastolic blood pressure heart rate responses during EXiT, and Wilcoxon Signed Rank tests for total symptoms, RPE, and errors due to non-normality. Cronbach's alpha were calculated to identify internal consistency of endorsed symptoms throughout aerobic and dynamic components at each visit and determine the contribution of each time point to the overall consistency, and was interpreted as unacceptable ($\alpha < 0.5$), poor ($\alpha = 0.50$ - .59), questionable ($\alpha = 0.60$ - 0.69), acceptable ($\alpha = 0.70 – 0.79$), good ($\alpha = 0.80$ - 89), and excellent ($\alpha \geq 0.90$), [147].

A series of 2-way random model (k=2) Intraclass Correlation Coefficient (ICC) estimates with absolute agreement and 95% confidence intervals (C.I.) were calculated for both agility task

completion time between consecutive trials at each visit (intra-rater), and between the HR responses and fastest trial across visits (test-retest). Additional 2-way random ICCs were conducted to determine the strength of agreement (absolute) between independent raters reporting agility task completion time and errors among CONTROL and CONCUSS groups. All ICCs were interpreted as poor (< .50), moderate (0.51-0.74), good (0.75-0.90) and excellent (>.90) [148]. Strength of agreement between raters recording errors were calculated with weighted kappa and interpreted as no agreement ($\kappa \leq 0$), none to slight (κ =.01–0.20), fair (κ =0.21–0.40), moderate (κ=0.41– 0.60), substantial (κ=0.61–0.80), and almost perfect (κ =0.81–1.00) agreement. Lastly, The SDs from the 2nd testing session and test-retest ICCs were used to determine standard error of measurement (SEM) for each agility task ($SEM = SD \bullet \sqrt{(1 - ICC}$)), and subsequently, the MDC ($MDC = SEM \bullet 1.96 \bullet \sqrt{2}$) [149, 150].

In aims 2 and 3, independent samples t-tests were conducted for HR $_{\%max}$, BP, and agility task completion time, and Mann-Whitney U tests for RPE, symptoms, and errors between age, sex, and BMI, groups across aerobic and dynamic components. Additionally, in aim 2 a series of 1-way ANOVAs were conducted to compare HR %max, BP, and agility task completion time, and Kruskal Wallis- H tests to compare RPE, symptoms, and errors between collision, contact, and non-contact sport-types. To determine the equivalence of EXiT HR $_{\%max}$, BP, and agility task completion time between groups, the MDCs (from aim 1) were used to determine upper and lower bounds for each variable and visually inspected with the 95% confidence interval surrounding mean difference. Specifically, if the 95% range of the mean difference between groups was within the -MDC and +MDC, the groups were equivalent[151].

Lastly, in aim 3, a series of 2X2 (GROUP X TIME) mixed model ANOVAs were conducted to compare RTP and CONTROL groups for time (RRm, SDNN, RMSSD, pRR50) and

frequency (Power, VLF, LF, HF, LFnu, HFnu, and LF: HF) HRV outcomes across pre- and post-EXiT timepoints. Any violations of sphericity underwent a Greenhouse-Geisser correction, and significance for all analyses were conducted with the 27th version of SPSS (IBM Statistics).

Significance for all analyses were set at p=.05 and magnitude of differences between groups was interpreted with Cohen's d as small (d=0.2), medium (d=0.5), and large (d=0.8) effect sizes[132]. All post-hoc pairwise comparisons underwent a Bonferroni statistical correction to reduce type I error likelihood, and analyses conduct with 26th version of SPSS (IBM Statistics).

4.0 MANUSCRIPT 1: TEST-RETEST, INTER-RATER RELIABILITY, AND MINIMAL DETECTABLE CHANGE OF DYNAMIC EXERTION TESTING (EXIT)

BACKGROUND: Dynamic exertion testing (EXiT) was recently developed and suggested to be a more objective approach to inform return to play/activity (RTP/A) decision making through a combination of treadmill running, functional movements, and agility tasks which collectively screen for concomitant autonomic, vestibular, and ocular system functioning. The identification of an assessment's reliability on repeated assessments, inter-rater agreement, and minimal detectable change (MDC) for EXiT is necessary to interpret EXiT performance.

PURPOSE: Determine intra-rater, test-retest, and inter-rater reliability and minimal detectable change (MDC) for dynamic exertion testing (EXIT) outcomes, including physiological— age estimated percentage of heart rate (HR $_{\%max}$) and blood pressure (BP), performance— agility task completion time and errors, and clinical— endorsed symptoms and rating of perceived exertion (RPE) outcomes.

METHODS: 79 (F:34 [43%], 19.6 ± 5.0 years) healthy athletes (CONTROL) completed the following EXiT aerobic and dynamic components across 2 visits (8.7±4.6 days apart). The 12 min treadmill run (Aerobic); dynamic circuit (CIRC), ball toss (BT), box-drill shuffle (SHUF) and carioca (CAR), zig zag (ZZ), pro agility (PA), and arrow agility (AA) tasks. Fifteen CONTROL and 15 participants completing EXiT at medical clearance (CONCUSS group) were scored by 2 raters. Two-way, mixed, intra-class correlation coefficients (ICC) were used to evaluate test-retest reliability. Paired samples t-tests were used for HR and test completion time, with Wilcoxon tests used for symptoms, RPE, and errors. Internal consistency of symptoms at each visit was determined with Cronbach's alpha, and minimal detectable change (MDC) of HR, symptoms, and task completion time using the equation: MDC= standard deviation x $\sqrt{(1 - ICC)}$ x 1.96 x $\sqrt{2}$.

RESULTS: When using newly established MDCs, (HR $_{\%max}$) was reliable following aerobic (ICC=.72-.74) and dynamic (ICC=.579-.618) components. Agility task completion time (MDC range=0.75-8.70 seconds) had good to excellent test-retest (ICC=.703-.948) and inter-rater reliability (ICC=.932-.965). Symptoms had a high internal consistency at visits 1 (α =.894) and 2 (α =.805) and were reliable across visits (ICC=.588; MDC=3). RPE was similar across visits but less errors were committed at the 2nd visit (2.96 ± 4.72 vs 1.99 ± 3.25, p=0.35).

CONCLUSION: The current investigation established test-retest and inter-rater reliability in addition to MDCs of an objective assessment to inform RTP/A decision making. Healthy adolescent and adult athletes have stable performances across repeated EXiT administrations. EXiT may be able to address a gap in current approaches to inform safer RTP/A following SRC recovery.

4.1 Introduction

Sport-related concussion (SRC) is a heterogeneous neurometabolic injury and clinically presents with varied signs, symptoms, and impairments to one or more inter-related brain functioning pathways[5, 33]. Due to the inability to discern complete neurometabolic recovery from SRC, medical clearance to return to play and activity (RTP/A) requires a comprehensive clinical evaluation of neurocognitive, vestibular, ocular, and autonomic nervous system functions[5, 33]. In addition, athletes must successfully complete a staged RTP/A protocol comprised of increasing exertion intensity and sport-specificity as recommended by the Concussion in Sport Group [6, 33]. However, the staged protocol is widely accepted but without empirical evidence to effectively inform RTP/A decision making[5]. The staged protocol has ambiguous exercise type, intensity, and duration parameters at each stage, protocol administration may vary between medical providers, and successful completion is reliant on patient-reported symptoms that can be non-disclosed by athletes motivated for early sport resumption [152]. During the previous decade, structured exertion assessments have emerged to inform clinical diagnosis and treatment decisions for SRC do not have empirical support to inform RTP/A decision making. The Buffalo Concussion Treadmill Test is intended to elicit concussion symptoms in response to graded treadmill walking and can inform exertional intolerance to facilitate exertion therapy decisions [25, 96]. However, it does not screen for potential vestibular or ocular system dysfunction that would be undetectable with treadmill walking and does not objectively evaluate an athlete's ability to complete the physical demands of sport-specific movements or tasks commonly performed in sport. More recently, the Gapski-Goodman Test was developed as a

structured exertion assessment that replicates the physical demands of sport participation to inform RTP/A decision making, and consists of stationary cycling intervals and plyometric exercises [31]. An initial report of the Gapski-Goodman Test revealed symptom provocation (and assessment failure) among 111/759 (14.6%) adolescents and adults upon completion of the staged return to play protocol [31]. Although these preliminary findings posit the potential clinical utility of an objective exercise-based protocol to inform RTP/A decision making, both the Buffalo Concussion Treadmill Test and Gapski-Goodman Test are reliant on symptom report and a 'pass' score is based on the observed ability to complete aerobic exertion without concussion symptom provocation. Moreover, the stability of repeated assessments or agreement between administrators have not been established with the consensus-recommended staged return to sport progression and Gapski-Goodman Test. Collectively, the staged return to sport progression, Buffalo Concussion Treadmill Test, and the Gapski-Goodman Test are not evidence-based approaches to determine clinical recovery from SRC and inform medical clearance decisions to RTP/A. There is a current need for a reliable and objective exertion assessment to inform RTP/A decision making for healthcare providers responsible for medical clearance decisions following SRC recovery.

The recently developed dynamic exertion testing (EXiT) protocol is an objective approach to inform RTP/A decision making through a combination of treadmill running, functional movements, and agility tasks, which collectively assess concomitant autonomic, vestibular, and ocular system functioning (EXIT #1). In contrast to previous exertion-based approaches to inform RTP/A readiness, the EXiT has clear, objective physiological (heart rate and blood pressure), performance (agility task completion time and errors) and clinical (perceived effort and endorsed symptoms) outcomes. A preliminary report observed similar EXiT outcomes between healthy adolescents and adults with patients completing EXiT upon medical clearance from SRC (EXiT

#1) and demonstrate the potential applications of structured exertion testing to facilitate RTP/A decisions. Despite the potential utility of EXiT as a brief, objective clinical assessment for SRC, the reliability across repeated administrations and health care providers has not been established and meaningful interpretation of EXiT outcomes remain substantially limited.

Any clinical test to inform decision-making should consistently measure the outcome (s) of interest across repeated administrations [153, 154]. Test-retest reliability, is a form of external reliability and reflects the overall consistency of a measure across time and should be established for EXiT physiological, performance, and clinical outcomes. Without sufficient reliability, performance and can serve as a reference for future analyses, including sensitivity and specificity of 'pass' and 'fail' performance [131, 155, 156]. In addition, determining the minimal detectable change (MDC) for EXiT outcomes would fulfill an initial step to determine the smallest change that is considered clinically important to the patient or clinician, and provide an intuitive interpretation of EXiT performance[157-160]. Lastly, inter-rater agreement should also be established for any clinical concussion assessment since expert consensus recommends a multidisciplinary approach to the evaluation, treatment, and medical clearance decisions, and more than one healthcare provider may be responsible for the interpretation of EXiT to inform RTP/A decisions. The purpose of this investigation is twofold: 1) determine intra- and test- retest reliability and MDC of EXiT outcomes, including heart rate response, agility task completion time, committed errors and reported symptoms and effort in healthy athletes, and 2) assess inter-rater reliability (IRR) across agility task completion time and committed errors recorded from dual raters observing healthy and recently concussed athletes. We hypothesized that healthy athletes would exhibit stable performance on consecutive agility task trials at each visit and the fastest time

(of 2 trials) will be stable across visits, and agility task completion time and errors will have high level of agreement between independent raters.

4.2 Methods

4.2.1 Experimental Design and Participants

We employed a cross-sectional test-retest study design comprised of participants obtained from a random, sample of recreational and competitive athletes from a heterogeneous sport population residing in the Pittsburgh, PA community. Participants were physically active (based on ACSM guidance for weekly moderate or vigorous activity [described in more detail below]) healthy controls. We also enrolled a sample of adolescent and adult patients upon medical clearance to return to play and activity following concussion recovery (CONCUSS group) at an outpatient multidisciplinary concussion clinic.

4.2.1.1 Inclusion Criteria

CONTROL participants

a) Aged 14¬35 years
b) Fulfilled ACSM's guidelines for regular aerobic activity (30 minutes of moderate intensity exertion 5 days per week or 20 minutes of vigorous exertion 3 days per week)

CONCUSS participants

a) Aged 14¬35 years

b) Fulfilled ACSM's guidelines for regular aerobic activity (30 minutes of moderate-intensity exertion 5 days per week or 20 minutes of vigorous exertion 3 days per week) prior to injury.
c) Diagnosed with an SRC within 14 days of injury.
d) Recently cleared to resume unrestricted sport participation after a trained clinician from UPMC Sports Medicine Concussion Program has interpreted neurocognitive, vestibular, and clinical interview outcomes and completed EXiT under direction of exertion physical therapist.

4.2.1.2 Exclusion Criteria

CONTROL participants

a) Suffered a prior concussion within 6 months
b) More than 2 previously diagnosed concussions
c) History of brain surgery or TBI (based on Glasgow Coma Scale of <13)
d) History of neurological disorder (seizure disorder, epilepsy, brain tumors or malformations)
e) Current history of preexisting vestibular disorder benign paroxysmal positional vertigo (BPPV), labyrinthitis or vestibular neuritis
f) Previous diagnosis of ocular motor condition (e.g., ocular motor apraxia)
g) Currently taking anticoagulant, beta-blockers, and anticonvulsant prescription medication
h) Incapable of treadmill running at speeds up to 11.27 km/h (7.0 mph) and 13.67 km/h (8.5 mph) for females and males, respectively (based on assessment parameters)
i) Diagnosed with a cardiac, peripheral, or cerebrovascular disease (type 1 or 2 diabetes, or renal disease)

j) Pregnant

k) Experienced chest pain or shortness of breath while at rest or with mild exertion.

l) Lose balance because of dizziness (aside from concussion) or lose consciousness from exertion.

m) Diagnosed with or taking medication for a chronic medical condition.

n) Currently or recent (within 12 months) physical impairment exacerbated by physical activity, leading to the inability to complete 30 minutes of moderate to vigorous exercise.

o) Self-reported any exclusionary criteria from the Preparticipation Activity Questionnaire (PAR-Q), ACSM's formal screening to safely conduct submaximal exertion:

- Previous diagnosis of a heart condition or high blood pressure
- Pain in chest of shortness of breath at rest or activities of daily living
- Currently have a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be worsened by exertion.
- Been told by a doctor to only conduct physical activity under medical supervision.

<u>CONCUSS participants</u>

a) Suffered a prior concussion within 6 months (excluding current injury)

b) More than 2 previously diagnosed concussions (excluding current injury)

c) History of brain surgery or TBI (based on Glasgow Coma Scale of <13)

d) History of neurological disorder (seizure disorder, epilepsy, brain tumors or malformations)

e) Current history of preexisting vestibular disorder benign paroxysmal positional vertigo (BPPV), labyrinthitis or vestibular neuritis

f) Previous diagnosis of ocular motor condition (e.g., ocular motor apraxia)

g) Currently taking anticoagulant, beta-blockers, and anticonvulsant prescription medication
h) Incapable of treadmill running at speeds up to 11.27 km/h (7.0 mph) and 13.67 km/h (8.5 mph) for females and males, respectively (based on assessment parameters)
i) Diagnosed with a cardiac, peripheral, or cerebrovascular disease (type 1 or 2 diabetes, or renal disease)
j) Pregnant
k) Experienced chest pain or shortness of breath while at rest or with mild exertion.
l) Lose balance because of dizziness (aside from concussion) or lose consciousness from exertion.
m) Diagnosed with or taking medication for a chronic medical condition.
n) Currently or recent (within 12 months) physical impairment exacerbated by physical activity, leading to the inability to complete 30 minutes of moderate to vigorous exertion.
o) Self-reported any exclusionary criteria from the Preparticipation Activity Questionnaire (PAR-Q), ACSM's formal screening to safely conduct submaximal exertion:
    - Previous diagnosis of a heart condition or high blood pressure
    - Pain in chest of shortness of breath at rest or activities of daily living
    - Currently have a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be worsened by exertion.
    - Been told by a doctor to only conduct physical activity under medical supervision.
p) Diagnosed with a concussion more than 14 days after injury,
q) Concussion occurred outside recreational or sport participation (e.g., car crashes, falls, or other accidents),

r) If the injury occurred more than 90 days prior to the RTP/A evaluation as the recovery timeline for these individuals is beyond the typical course of recovery [1].

4.2.1.3 Sample Size Estimation

All sample size calculations were conducted with G*Power 3.0.10 (Franz Faul, Universität Kiel, Germany) [130]. Based on a previous investigation of a novel agility task among exertion-based outcomes among collegiate athletes at medical clearance to RTP[131], we determined that 64 participants (74 when accounting for 20% data loss and attrition) would be necessary to provide 80% power [132].

4.2.2 Operational Definitions

4.2.2.1 Sport-related Concussion

Concussion was defined as a "complex pathophysiological process affecting the brain, induced by biomechanical forces" as specified in the most recent consensus statement on concussion in sport[33]. In the current investigation to meet criteria for SRC diagnosis, there had to be: 1) evidence of a clear mechanism of injury; and 2) at least one acute sign (e.g., LOC, amnesia, and disorientation/confusion) and/or immediate physical symptoms (e.g., headache, dizziness, and balance problems) following injury. All SRCs were diagnosed by a clinician (e.g., neuropsychologist, sports medicine primary care physician) trained in concussion care.

4.2.2.2 Medical Clearance

Medical clearance to resume RTP/A was determined by a multifaceted clinical evaluation utilizing cognitive, vestibular, ocular, and clinical interview results by clinicians and successful completion of EXiT administered by a physical therapist within the assessment's instructions. In

accordance with international consensus[134], were required to 1) be symptom free at rest and following exertion; (2) demonstrate neurocognitive performance within normative or baseline reliable change indices (RCI); and (3) resume pre-injury levels for sleep and physical activity tolerance.

4.2.2.3 Sport-Type

Sport participation information was obtained from the demographic questionnaire and categorized based on the level of contact exposure: non-contact, contact (body-to-body contact allowed, but not purposeful), or collision (repeated, purposeful body-to-body contact) [135].

4.2.2.4 Recovery Time

Number of days from date of injury to full medical clearance to resume RTP/A per previously stated criteria.

4.2.3 Instrumentation

4.2.3.1 Physiological Monitoring and Processing Equipment

The Equivital Life Monitor (AD Instruments, Colorado Springs, CO; USA) physiological monitoring system was used to quantify HR and linear accelerations in the -X, -Y, and -Z coordinates at a 256 Hz sampling rate [136-138]. A recent validation report concluded that the Equivital monitoring system is an appropriate tool to sensitively quantify physiological data [136], and its tri-axial accelerometer and heart rate accuracy is similar to well-established activity trackers [137]. Movement patterns and physiological data were transmitted to a nearby laptop running Lab chart software (ADI Instruments; Sydney Australia) [138] for processing.

4.2.3.2 Exertion Testing Equipment and Materials

- Treadmill (WOODWAY USA, Waukesha, WI),

- 10”- Agility Cones
- Metronome: A free to download application (Metronome beats, Stonekick, London UK)
- Stopwatch
- Test Cards (N=40) printed on 5”X8” card stock
- Digital scale (Health-o-Meter, Sunbeam Products Inc; McCook, Il, USA)
- Wall-mounted stadiometer (Seca; Chino, CA, USA)
- An open gym space approximately 5X8 meters with a slip-resistant surface in an environment-controlled facility

4.2.4 Measures

4.2.4.1 Dynamic Exertion Testing (EXiT)

EXiT is a 30-minute clinical assessment with aerobic and dynamic components (Appendix C). The aerobic component is a high-intensity interval treadmill protocol that alternates between slow and fast treadmill running speeds (1:1 ratio) based on the 60% and 90% of the superior category (90th percentile) for aerobic capacity among 13-29 year old male and female sexes [129]. The target intensities were then used in ACSM’s metabolic running equation to determine horizontal running speed:

$$VO_2 = 0.2*S + (0.9 *S*G) + 3.5 \quad (1)$$

where VO_2 is oxygen consumption [mL O_2/kg/min], S is the horizontal running speed (in meters per minute), and G is the percentage grade of the treadmill. Speed parameters underwent a brief pilot period and final adjustments to obtain a final protocol whereby females alternated between 7.2 km/h (4.5 mph; 3.14 METs) and 11.27 km/h (7.0 m/h, 6.36 METs), and males between

8.85 km/h (5.5 mph; 5.21 METs) and 13.67 km/h (8.5 mph, 7.5 METs). Thus, participants completed a 2-minute warm up (Male: 5.5 mph, Female: 4.5 mph), followed by 30-second intervals of fast and slow running speeds (Male: 8.5/5.5 mph; Female: 7.0/4.5 mph) for 10 minutes. Participants were instructed to use support handles as necessary to maintain safety. Following the aerobic component, participants completed the dynamic component which consists of 2 functional movement tasks (Dynamic Circuit [CIR] and Ball Toss [BT]) and 5 Agility Tasks (Box Drill Shuffle [SHUF], Box Drill Carioca [CAR], Zigzag [ZZ], Pro Agility [PA], and Arrow Agility [AA]) to maximal effort (Appendix C). The CIR is a 3-exercise circuit comprised of squat jumps, side-to-side pushups, and ball rotations completed for 3 sets of 10 repetitions in synchronization with a metronome (25 beats/min) and a 30-second rest period between each cycle. The BT task was administered with the participant standing 2.5 meters in front of administrator. After administrator called 'left', or 'right', participant jumped and rotated 180° in the specified direction, caught a basketball tossed by the administrator, and tossed back before returning to the starting position for the next trial, and was repeated for 10 trials (5 jumps left and 5 jumps right) and after a 30-second rest, a second round was performed whereby administrator called direction (left or right) or 'Go' (no response) in a random sequence (completed 5 jumps left, 5 jumps right, and 2 distractors). Participants completed two trials of each agility task (30-sec rest between trials), which were hand-timed via stopwatch by the administrator. Valid EXiT tests, defined as completion of EXiT within the study parameters without additional rest periods or assessment modifications, were included in the study.

EXiT Physiological Outcomes

- Resting systolic and diastolic blood pressure (measured in mmHg) were measured with the use of an automatic sphygmomanometer (Omron; Kyoto, Japan) during

the pre- and post-EXiT 5-minute rest period. Heart rate, measured in beats per minute, was calculated for the percentage of age estimated (220-age) maximum HR ($HR_{\%max}$)[87].

- Heart rate was recorded prior to (~5 min), during, and following (~5 min) exertion via a noninvasive heart rate monitor while participants were seated with arms supported and feet placed flat on the floor. During EXiT, heart rate was recorded upon the completion of each task.

EXiT Performance Outcomes

- Agility task completion time was measured by the EXiT administrator via a hand-timed stopwatch. The fastest trial of each agility task was calculated except for Arrow Agility task due to the secondary cognitive task, thus both trials were analyzed.
- Errors were counted by the EXiT administrator. For the aerobic component, excessive pulling on handrails for 10 or more seconds or additional rest periods for 10 or more seconds were counted as errors. During the dynamic component, CIR errors included improper form or inability to maintain pace with squats, pushups, or ball rotation exercises; and BT errors included a jump-turn in the wrong direction, inability to catch or toss ball back to administrator, or a jump committed after a 'Go' call were counted as errors. Errors were also counted during SHUF, CAR, ZZ, PA, and AA tasks when a participant kicked a cone off the original placement, mis-navigated a cone, or did not hand-touch a cone when instructed to do.

EXiT Clinical Outcomes

- Headache, dizziness, and nausea concussion-symptoms were individually reported on a 0-10 Likert scale prior to EXiT and after completing the warmup (Post-warm up), the 5th (Midpoint), and 10th (End) intervals of the aerobic component and following the completion of each task of the dynamic component. Endorsed symptom were totaled within aerobic and dynamic components, and subsequently combined and an EXiT total symptom score.
- Rating of Perceived Exertion (RPE) was recorded on the 6-20 Borg scale, a valid measure of perceived effort (6 'no exertion at all' to 20 'maximal effort'), prior to, throughout, and following EXiT [139].

4.2.4.2 Anthropometrics

Bodyweight (in kg) was measured using a digital scale (Health-o-Meter) and height (in cm) with a wall-mounted stadiometer (Seca) among healthy controls, and values were identified in the electronic medical record for concussed participants. Weight and height measurements were used to calculate body mass index (BMI= weight [kg] / height [m]^2) [140], and the upper (HI-BMI) and lower (LO-BMI) 50th percentile groups were determined as a function of age for adolescents [141] and median split of BMI for adults.

4.2.4.3 Concussion Injury Information

For CONCUSS participants, the date of SRC diagnosis and medical clearance to RTP/A were extracted from the electronic medical record by a member of the research team not involved in assessment administration or medical clearance decision making process.

4.2.5 Experimental Procedures

4.2.5.1 Recruitment and Consent

Recruitment was conducted through word of mouth, posted fliers, and online advertisement for controls (Pitt + Me), and if deemed eligible during in-person or phone screening, were scheduled for a study visit at the Neuromuscular Research Laboratory-Warrior Human Performance Research Center. Participants were also instructed to a) avoid ingesting food, alcohol, or caffeine or tobacco products within 2 hours of assessment; b) avoid vigorous exertion the day prior to and day of assessment; c) Wear clothing and footwear to permit athletic movements; and d) drink plenty of fluids the 24-hour period before enrollment. All participants received a thorough explanation of the study overview, procedures, and potential risks of participation prior to signing consent forms.

4.2.5.2 Equipment Fitting and Physiological Measurements

Participants wore noninvasive heart rate monitor (i.e., Polar or Equivital strap) to capture heart rate, respiration rate, skin temperature, and accelerations in the X, Y, and Z directions during EXiT. Resting physiological measures (blood pressure [BP] and heart rate [HR]) were obtained with participant seated with back supported and feet placed flat on the floor. Pre-EXiT measurements were obtained after a 5-minute resting period whereas post-EXiT measures were collected upon returning to the private examination room (~1-5 min) but varied across the sample as some individuals requested additional time for hydration.

4.2.5.3 EXiT Administration

One physical therapist administered EXiT to CONCUSS and one certified athletic trainer administered to CONTROL participants. Heart rate, agility task completion time, errors, symptoms, and effort were recorded on a standardized report sheet (Appendix C).

CONTROL participants repeated assessment procedures (including instructions) at a 2nd visit (3-21 days between visits). During dual ratings, the administrator for all CONTROL participants was a 2nd rater for CONCUSS participants, and another certified athletic trainer was the 2nd rater for the CONTROL participants. In these instances, the 2nd rater independently recorded agility task completion time and errors among participants systematically enrolled at 11-15, 21-25, and 31-35. Additionally, 12 (of 15) control participants completed a 2nd visit with the same raters, which were included in the inter-rater reliability analyses. All study procedures were approved by the University of Pittsburgh Institutional Review Board

4.2.6 Data Reduction

Body Mass Index ([BMI]= weight [kg]/height[m]^2) and the lowest (fastest) time between consecutive agility task trials were calculated with the exception of Arrow Agility task due to the secondary cognitive task, thus both trials were analyzed.

Participants with complete EXiT physiological, performance, and clinical outcome data were analyzed (EXiT #1). A team member trained in the cleaning and processing procedures examined Equivital recordings for completeness and identified periods of movement and rest and calculated raw (HR_{raw}) and percentage of age estimated (220-age) maximum HR ($HR_{\%max}$) [87, 88]. For inter-rater agreement, all agility task trials were included in analyses. Endorsed headache, dizziness, and nausea symptoms were subtotaled within aerobic and dynamic components, and subsequently combined to populate EXiT total symptoms.

4.2.7 Statistical Analyses

Independent samples t-tests were conducted for continuous (e.g., age, BMI, etc.), and chi-squared (χ^2) with odds ratio (OR) values for nominal (e.g., sex, sport type, etc.) demographic variables to compare the inter-rater reliability subset from the entire sample. Systematic bias between consecutive trials and visits (e.g., learning effect) was examined with a series of paired samples t-tests for agility task completion time, resting systolic and diastolic blood pressure heart rate responses during EXiT, and Wilcoxon Signed Rank tests for total symptoms, RPE, and errors due to non-normality. Cronbach's alpha were calculated to identify internal consistency of endorsed symptoms throughout aerobic and dynamic components at each visit and determine the contribution of each timepoint to the overall consistency, and was interpreted as unacceptable ($\alpha < 0.5$), poor ($\alpha = 0.50$ - .59), questionable ($\alpha = 0.60$ - 0.69), acceptable ($\alpha = 0.70 – 0.79$), good ($\alpha = 0.80$ - 89), and excellent ($\alpha \geq 0.90$), [147].

A series of 2-way random model (k=2) Intraclass Correlation Coefficient (ICC) estimates with absolute agreement and 95% confidence intervals (C.I.) were calculated for both agility task completion time between consecutive trials at each visit (intra-rater), and between the HR responses and fastest trial across visits (test-retest). Additional 2-way random ICCs were conducted to determine the strength of agreement (absolute) between independent raters reporting agility task completion time and errors among combined CONCUSS and CONTROL participants. All ICCs were interpreted as poor (< .50), moderate (0.51-0.74), good (0.75-0.90) and excellent (>.90) [148]. Strength of agreement between raters recording errors were calculated with weighted kappa and interpreted as no agreement ($\kappa \leq 0$), none to slight (κ =.01–0.20), fair (κ =0.21–0.40), moderate (κ=0.41– 0.60), substantial (κ=0.61–0.80), and almost perfect (κ =0.81–1.00) agreement. Lastly, The SDs from the 2nd testing session and test-retest ICCs were used to determine standard

error of measurement (SEM) for each agility task (SEM= SD • $\sqrt{(1 - ICC}$)), and subsequently, the MDC (MDC= SEM • 1.96 • $\sqrt{2}$) [149, 150]. Significance for all analyses were set at p=.05 and all analyses were conducted with 26th version of SPSS (IBM Statistics).

4.3 Results

4.3.1 Demographics

Of 92 CONTROL participants 6 (6.52%) had incomplete EXiT data and were excluded from analyses, 79 (85.8%) completed a 2nd visit (8.72 ± 4.65 days between visits) and were used for test-retest analyses. The test-retest sample was similar in height, weight, and BMI as the entire dataset (p>.05;Table 3). The sample for IRR analyses was older (19.6 ± 5.0 vs 17.9 ± 3.9 years; t_{145} = 2.177, p=.031; Mean difference 95% Confidence Interval [$MD_{95\%}$] = -1.72 $_{-3.26 - -1.58}$) and had a greater weight (75.77 ± 18.26 vs 67.67 ± 15.60 kg; t_{139} = 2.457, p=.015; $MD_{95\%}$ = -8.10 $_{-14.61 - -1.58}$) and BMI (25.22 ± 4.72 vs 22.88 ± 4.04kg/m^2; t_{139} = 2.708, p=.008; $MD_{95\%}$ = -2.34 $_{-4.25 - -0.42}$) than the full study sample, but height was similar (173.34 ± 8.75 vs 171.28 ± 9.32; p >.05). In addition, sport type distribution differed between entire sample and IRR subsample (χ^2_{16} = 26.99, p=.042). Among the IRR sample, CONCUSS participants were younger than CONTROLS (15.7 ± 1.8 vs 23.7 ± 4.22 years; t_{28} = -6.725, p<.001; $MD_{95\%}$=-7.93$_{-10.35- -5.52}$), but height (172.42 ± 8.87 vs 173.63 ± 8.86 cm) weight (74.15 ± 21.58 vs 77.75 ± 15.87 kg) and BMI (25.18 ± 5.92 vs 25.59 ± 3.82 kg/m^2) were similar (p>.05). There were no differences between subgroups for self-reported history of migraine, learning disability, or previous concussions (p>.05).

Table 3 . Frequency (Percentage) and Comparison Statistics Across Demographic Variables Between Full Sample (N=147), Test-Retest (N=79), and Inter-Rater (N=30) Reliability Subgroups

			Inter-Rater Reliability	
Demographic Variable	Full Sample	Test-Retest Reliability	CONTROL (N=15)	CONCUSS (N=15)
Female Sex	55 (37.4 %)	34 (43.0%)	3 (20.0 %)	5 (33.3%)
Sport [a]				
Soccer	45 (30.6 %)	26 (32.9%)	3 (20.0%)	4 (26.7%)
Football	22 (14.9 %)	6 (7.6%)	4 (26.7%)	7 (46.7%)
Ice Hockey	14 (9.52%)	4 (5.06 %)	-	-
Basketball	18 (12.2 %)	12 (15.2%)	4 (26.7%)	-
Lacrosse	12 (8.1%)	8 (10.1%)	1 (6.7%)	1 (6.7%)
Softball	6 (5.1%)	3 (3.8%)	-	-
Wrestling	6 (5.1%)	4 (5.1%)	1 (6.7%)	1 (6.7%)
Volleyball	6 (5.1%)	3 (3.8%)	1 (6.7%)	1 (6.7%)
Baseball	4 (3.4%)	2 (2.5 %)	-	1 (6.7%)
Gymnastics/Cheer	4 (3.4%)	3 (3.8%)	1 (6.7%)	-
Other [b]	15 (10.2%)	8 (10.1%)	-	-
Clinical Factors				
Migraine/Headache History	19 (16.2 %)	4 (5.06%)	4 (26.7%)	3 (20.0%)
Attention-Deficit/ Hyperactivity Disorder or Learning Disability	7 (6.0%)	4 (5.1%)	1 (6.7%)	-
Previously Diagnosed Concussions (1 or 2)	30 (25.6%)	14 (17.7%)	3 (33.3%)	8 (53.3%)

[a] Sport type distribution differed between sample and IRR subsample ($\chi^2_{16} = 26.9883$, p=.042)
[b] Includes crew, roller derby, rugby, swimming and diving, and track and field.

4.3.2 EXiT Physiological, Performance, and Clinical Outcomes

With exception to a greater Pre-EXiT SBP at the 1st visit (116.45 ± 9.25 vs 113.87 ± 8.59 mmHg, p=.016), pre-EXIT resting DBP and HR (HR_{raw} and $HR_{\%max}$) and post-EXiT physiological responses were similar between visits (p>.05; Table 4). Across study visits, heart rate responses during the aerobic component were reliable for both HR_{raw} (ICC=.741 [95% CI:.593-.824]) and $HR_{\%max}$(ICC=.723 [.566-.824])Within the dynamic component, there was a reduction in HR between study visits for CIR, BT, SHUF, CAR, and PA tasks, and an increase for the AA task (p<.05).

Table 4. Mean and Standard Deviation (M ± SD), Comparison Statistics, and Test-Retest Reliability of Resting Physiological Measures and Heart Rate Responses Across EXIT Tasks Between Consecutive Visits Among CONTROL (N=79) participants

Outcome		Visit 1	Visit 2	SEM 95% CI	t	sig	ICC 95% CI	sig	MDC
Pre-EXIT	Systolic BP	116.45 ± 9.25	113.87 ± 8.59	1.05 0.49-4.68	2.454	**0.016**	.619 -.403-.758	**<.001**	14.70
	Diastolic BP	73.78 ± 5.85	73.09 ± 6.15	0.82 -0.94-2.31	0.844	0.401	.451 .136-.651	**.005**	12.63
	HR_{Raw}	67.53 ± 10.88	68.92 ± 12.84	1.58 -4.55-1.76	-0.880	0.382	.473 .174-.664	**.003**	25.84
	$HR_{\% Max}$	33.66 ± 5.47	34.35 ± 6.45	0.79 -2.27-0.89	-0.873	0.261	.477 .181-.667	**.002**	12.93
Post EXIT	Systolic BP	129.63 ± 14.17	129.05 ± 16.57	1.70 -2.82-3.97	0.336	0.737	.705 .533-.814	**<.001**	24.95
	Diastolic BP	77.78 ± 9.22	76.18 ± 8.20	0.97 -0.33-3.55	1.652	0.103	.696 .519-.808	**<.001**	12.53
	HR_{Raw}	119.71 ± 16.94	116.94 ± 18.03	1.82 -0.86-6.41	1.523	0.132	.732 .580-.829	**<.001**	25.87
	$HR_{\% Max}$	59.65 ± 8.25	58.28 ± 8.86	0.91 -0.43-3.18	1.521	0.132	.721 .563-.822	**<.001**	12.97
Aerobic Component									
Pre- Standing Rest (0 min)	HR_{Raw}	82.68 ± 14.02	82.38 ± 12.26	1.89 -3.46-4.05	0.156	0.876	.335 -.049-.577	**.039**	27.71
	$HR_{\% Max}$	41.21 ± 6.98	41.07 ± 6.19	0.95 -1.76-2.04	0.142	0.888	.315 -.079-.565	.051	14.20
Post Warm Up (2 min)	HR_{Raw}	139.55 ± 18.24	138.99 ± 14.75	1.95 -3.32-4.45	0.289	0.773	.632 .422-.766	**<.001**	24.80
	$HR_{\% Max}$	69.57 ± 9.13	71.65 ± 7.42	0.99 -0.11-4.05	-2.107	**0.038**	.610 .392-.750	**<.001**	12.84
Midpoint (7 min)	HR_{Raw}	160.04 ± 20.06	163.14 ±16.19	2.14 -7.37-1.16	-1.450	0.151	.635 .273-.623	**<.001**	27.11
	$HR_{\% Max}$	79.81 ± 10.13	81.35 ± 8.06	1.07 -3.66-0.59	-1.439	0.154	.642 .439-.772	**<.001**	13.37
Finish (12 min)	HR_{Raw}	168.39 ± 16.34	165.17 ± 18.32	1.78 -0.32-6.77	1.810	0.074	.741 .593-.835	**<.001**	25.84
	$HR_{\% Max}$	83.96 ± 8.22	82.31 ± 8.99	0.91 -3.45-0.16	-1.811	0.074	.723 .566-.824	**<.001**	13.12
Dynamic Component									
Dynamic Circuit	HR_{Raw}	158.49 ± 16.24	153.41 ± 19.57	2.26 0.58-9.58	2.247	**0.028**	.558 .309-.718	**<.001**	36.06
	$HR_{\% Max}$	79.05 ± 8.35	76.52 ± 9.96	1.12 0.30-4.77	-2.259	**0.027**	.593 .362-.741	**<.001**	17.61
Ball Toss	HR_{Raw}	157.34 ± 16.24	152.69 ±19.51	1.48 1.70-7.59	3.145	**0.002**	.835 .726-.899	**<.001**	21.97
	$HR_{\% Max}$	78.47 ± 8.23	76.15 ± 9.83	0.74 -3.80 – (-0.85)	-3.144	**0.002**	.839 .731-.902	**<.001**	10.93
Box Drill Shuffle	HR_{Raw}	174.56 ± 12.95	170.84 ± 15.69	1.73 0.26-7.17	2.142	**0.035**	.601 .376-.745	**<.001**	27.47
	$HR_{\% Max}$	87.07 ± 6.89	85.20 ± 8.00	0.87 -0.14-3.60	-2.152	**0.035**	.638 .433-.769	**<.001**	13.34
Box Drill Carioca	HR_{Raw}	171.04 ± 12.54	165.91 ± 15.92	1.20 -7.51- (-2.75)	-4.292	**0.000**	.817 .652-.896	**<.001**	18.88
	$HR_{\% Max}$	85.32 ± 6.70	82.76 ± 8.32	0.60 1.37-3.75	4.287	**0.000**	.838 .689-.909	**<.001**	9.28
Zig Zag	HR_{Raw}	179.57 ± 10.80	176.82 ± 14.64	1.46 -0.16-5.67	1.881	0.064	.661 .469-.784	**<.001**	23.63
	$HR_{\% Max}$	89.56 ± 5.66	88.19 ± 7.54	0.73 -0.08-2.82	1.883	0.064	.697 .524-.807	**<.001**	11.50
Pro Agility	HR_{Raw}	174.64 ± 10.84	171.91 ± 14.50	1.20 0.34-5.12	2.275	**0.026**	.788 .664-.866	**<.001**	23.40
	$HR_{\% Max}$	87.09 ± 5.62	85.73 ± 7.41	0.59 0.17-2.54	2.282	**0.025**	.805 .690-.877	**<.001**	11.31
Arrow Agility	HR_{Raw}	182.77 ± 10.43	182.60 ± 9.67	1.21 -2.24-2.58	0.140	0.889	.618 .397-.757	**<.001**	12.34
	$HR_{\% Max}$	91.14 ± 5.32	94.19 ± 5.11	0.61 -4.26- -1.84	-5.001	**0.000**	.579 .256-.752	**<.001**	6.25

Abbreviations: BP, blood pressure;, $HR_{\% Max}$, Percentage of age-estimated maximum heart rate; HR_{Raw}, Heart rate (measured); MDC, Minimal detectable change; SEM, Standard error of the mean;

We observed a reduction (improvement) in completion time across consecutive trials for CAR and AA at both visits (p<.001), and at 1 visit for SHUF (visit 2) and ZZ (visit 1) (Table 5). All trial-to-trial times had a high level of agreement (ICC=.842-.972). As expected, the 2nd trial (incongruent condition) of the Arrow Agility task was longer at both visits (p<.001), and consecutive AA trials were separately analyzed in test-retest reliability analyses. No improvements between consecutive trials were observed for PA at both visits (p>.05).

Table 5. Agility Task Completion Time (in seconds) and Comparison and Reliability Statistics Between Consecutive Trials at Visits 1 and 2 Among Healthy Controls (N=79)

	Visit 1						Visit 2					
Agility Task	Trial 1	Trial 2	SEM $_{95\% CI}$	t	Sig	ICC [a]	Trial 1	Trial 2	SEM $_{95\% CI}$	t	Sig	ICC [a]
Box Drill Shuffle	22.26 ± 3.47	22.48 ± 3.33	0.11 $_{0.74\text{-}1.19}$	8.609	**0.000**	.956 $_{.747\text{-}.984}$	21.61 ± 2.79	21.49 ± 2.79	0.10 $_{-0.09\text{-}0.32}$	1.145	0.256	.972 $_{.956\text{-}.982}$
Box Drill Carioca	14.84 ± 2.09	14.34 ± 1.93	0.15 $_{0.19\text{-}0.80}$	3.233	**0.002**	.842 $_{.743\text{-}.900}$	14.12 ± 1.75	13.84 ± 1.67	0.09 $_{0.10\text{-}0.46}$	3.099	**0.003**	.938 $_{.894\text{-}.963}$
Zig Zag	30.90 ± 5.38	30.65 ± 5.28	0.22 $_{-0.19\text{-}0.69}$	1.141	0.257	962 $_{.941\text{-}.975}$	29.14 ± 5.81	29.96 ± 6.05	0.41 $_{-1.62\text{--}0.01}$	-2.009	**0.048**	.896 $_{.836\text{-}.934}$
Pro Agility	8.37 ± 1.14	8.32 ± 1.24	0.07 $_{-0.10\text{-}0.19}$	0.643	0.522	.917 $_{.872\text{-}.946}$	8.35 ± 1.16	8.36 ± 1.06	0.06 $_{-0.13\text{-}0.11}$	-0.232	0.817	.940 $_{.906\text{-}.962}$
Arrow Agility	40.24 ± 5.14	41.80 ± 5.04	0.24 $_{-.08\text{-}2.04}$	-6.498	**0.000**	.928 $_{.774\text{-}.968}$	39.44 ± 4.78	40.55 ± 4.60	0.19 $_{-1.48\text{--}0.74}$	-5.946	**0.000**	.955 $_{.862\text{-}.979}$

[a] All ICCs were significant at $p<.001$

Abbreviations: ICC, Intraclass Correlation Coefficient; SEM, Standard Error of the Mean, Sig, Significance;

With the exception of PA, completion time reduced (improved) across visits for agility tasks, All agility tasks had good to excellent test-retest reliability (ICC=.703-.948) and subsequent MDCs for each task ranged from 0.75 to 8.70 seconds (Table 6).

Table 6 Agility Task Completion Time (in seconds) Between Visits Among CONTROL participants (N=79)

Agility Task	Visit 1	Visit 2	SEM $_{95\%}$	t	Sig	ICC [a]	MDC
Box Drill Shuffle	22.13 ± 3.35	20.97 ± 3.56	0.36 $_{0.45\text{-}1.89}$	3.242	**0.002**	.703 $_{.519\text{-}.814}$	6.40
Box Drill Carioca	14.01 ± 1.67	13.73 ± 1.64	0.09 $_{0.10\text{-}0.47}$	3.058	**0.003**	.929 $_{.880\text{-}.957}$	4.55
Zigzag	29.86 ± 4.91	28.74 ± 5.76	0.49 $_{0.15\ 2.09}$	2.305	**0.024**	.801 $_{.685\text{-}.874}$	8.70
Pro Agility	8.12 ± 1.10	8.18 ± 1.01	0.09 $_{-0.12\text{-}0.23}$	0.647	0.520	.852 $_{.768\text{-}.906}$	0.75
Arrow Agility Trial 1	39.99 ± 5.09	39.34 ± 4.73	0.24 $_{0.18\text{-}1.13}$	2.729	**0.008**	.948 $_{.914\text{-}.968}$	5.85
Arrow Agility Trial 2	41.59 ± 5.13	40.54 ± 4.60	0.29 $_{0.46\text{-}1.63}$	3.577	**0.001**	.914 $_{.846\text{-}.949}$	4.91

[a] All ICCs significant at $p<.001$
Abbreviations: ICC, Intra-class Correlation Coefficient; SD, Standard Deviation; SEM, Standard Error of the Mean; MDC, Minimal Detectable Change

Symptoms, Perceived Effort, and Errors: No differences were observed for endorsed symptoms across visits for aerobic and dynamic components (Table 7). Cronbach's alpha indicated a moderate to high internal consistency at visits 1 (AC: α =.780, DMC: α = .942, combined: α = .894) and 2 (AC: α = .593, DMC: α = .766, combined α = .805; Table 8). Endorsed symptoms had a high level of agreement and acceptable MDCs for aerobic component (ICC=.765.$_{632\text{-}.850}$ $p<.001$; MDC= 2), dynamic component (ICC .519$_{.248\text{-}.693}$ $p<.001$; MDC= 1), and Total EXiT (ICC .588$_{.355\text{-}.737}$; $p<.001$; MDC= 3). There were no differences between visits for perceived effort for any task (Table 9). Lastly, there was a reduction in total committed errors between visits (2.96 ± 4.72 vs 1.99 ± 3.25, $p=0.035$).

Table 7 Endorsed Symptoms During EXiT Between Visits and Comparison Statistics Among CONTROL Group (N=79)

	Visit 1		Visit 2		
EXIT Outcome	Mean ± SD	Median [IQR]	Mean ± SD	Median [IQR]	Sig
Aerobic Component					
Pre-Standing Rest (0 min)	0.05 ± 0.32	0.00 [0.00]	0.05 ± 0.36	0.00 [0.00]	1.00
Post Warm up (2 min)	0.06 ± 0.33	0.00 [0.00]	0.04 ± 0.25	0.00 [0.00]	.414
Midpoint (7 min)	0.04 ± 0.25	0.00 [0.00]	0.03 ± 0.16	0.00 [0.00]	.564
Finish (12 min)	0.14 ± 0.50	0.00 [0.00]	0.10 ± 0.44	0.00 [0.00]	.429
Subtotal	0.30 ± 1.07	0.00 [0.00]	0.22 ± 0.86	0.00 [0.00]	.551
Dynamic Component					
Dynamic Circuit	0.19 ± 0.68	0.00 [0.00]	0.13 ± 0.57	0.00 [0.00]	.380
Ball Toss	0.13 ± 0.61	0.00 [0.00]	0.03 ± 0.16	0.00 [0.00]	.131
Box Drill Shuffle	0.18 ± 0.76	0.00 [0.00]	0.03 ± 0.16	0.00 [0.00]	.085
Box Drill Carioca	0.13 ± 0.56	0.00 [0.00]	0.01 ± 0.11	0.00 [0.00]	.071
Zig Zag	0.22 ± 0.81	0.00 [0.00]	0.23 ± 0.84	0.00 [0.00]	.842
Pro Agility	0.16 ± 0.76	0.00 [0.00]	0.15 ± 0.56	0.00 [0.00]	.905
Arrow Agility	0.32 ± 1.12	0.00 [0.00]	0.21 ± 0.81	0.00 [0.00]	.347
Subtotal	1.33 ± 4.77	0.00 [0.00]	0.78 ± 2.44	0.00 [0.00]	.299
Total Symptoms	1.63 ± 5.10	0.00 [0.00]	1.00 ± 3.00	0.00 [0.00]	.172

Abbreviations: EXiT, Exertion testing; IQR, Interquartile range; SD, Standard Deviation

Table 8 Internal Consistency Values forEndorsed Symptoms If An Individual Item Was Removed at Visits 1 and 2

Outcome	Visit 1	Visit 2
Aerobic Component		
Post Warm up	.909	.813
Midpoint	.905	.797
End	.900	.767
Dynamic Component		
Dynamic Circuit	.875	.770
Ball Toss	.874	.802
Box Drill Shuffle	.862	.797
Box Drill Carioca	.875	.802
Zigzag	.866	.820
Pro Agility	.866	.754
Arrow Agility	.883	.729

Table 9 Perceived Effort and Errors Between Consecutive Visits Among CONTROL Group (N=79)

	Rating of Perceived Exertion					Errors				
	Visit 1		Visit 2			Visit 1		Visit 2		
EXIT Outcome	Mean ± SD	Median [IQR]	Mean ± SD	Median [IQR]	Sig	Mean ± SD	Median [IQR]	Mean ± SD	Median [IQR]	Sig
Aerobic Component										
Pre-Standing Rest	7.82 ± 1.66	6.10 [0.00]	6.04 ± 0.25	6.00 [0.00]	1.00	-	-	-	-	-
Warm up	8.19 ± 1.66	8.00 [2.00]	7.85 ± 1.62	7.00 [2.00]	.414	-	-	-	-	-
Mid-interval	11.77 ± 2.18	12.00 [2.00]	11.49 ± 2.36	11.00 [3.00]	.564	-	-	-	-	-
End	13.56 ± 2.48	14.00 [3.00]	13.13 ± 2.44	13.00 [3.00]	.429	-	-	-	-	-
Dynamic Component										
Dynamic Circuit	13.03 ± 2.85	13.00 [4.00]	12.45 ± 2.57	13.00 [4.00]	.380	0.77 ± 3.10	0.00 [0.00]	0.62 ± 2.21	0.00 [0.00]	.813
Ball Toss	11.19 ± 2.79	11.00 [4.00]	11.08 ± 2.52	11.00 [3.25]	.131	0.15 ± 0.38	0.00 [0.00]	0.13 ± 0.41	0.00 [0.00]	.674
Box Drill Shuffle	12.43 ± 3.00	12.00 [3.00]	12.53 ± 2.38	13.00 [3.00]	.085	0.26 ± 1.24	0.00 [1.00]	0.24 ± 1.01	0.00 [0.00]	.833
Box Drill Carioca	12.16 ± 2.85	12.00 [4.00]	12.33 ± 2.46	12.00 [3.25]	.071	0.87 ± 1.75	0.00 [0.00]	0.31 ± 0.78	0.00 [0.00]	**.004** [a]
Zig Zag	13.84 ± 2.69	14.00 [4.00]	13.92 ± 2.66	14.00 [4.00]	.842	0.63 ± 1.02	0.00 [0.00]	0.56 ± 1.44	0.00 [0.00]	.154
Pro Agility	13.33 ± 2.80	14.00 [4.00]	13.24 ± 2.60	13.00 [3.00]	.905	0.05 ± 0.27	0.00 [0.00]	0.04 ± 0.19	0.00 [0.00]	.739
Arrow Agility	15.28 ± 2.61	15.00 [4.00]	15.09 ± 2.76	15.00 [3.25]	.347	0.24 ± 1.22	0.00 [0.00]	0.09 ± 0.40	0.00 [0.00]	.325
Total						2.96 ± 4.72	1.00 [4.00]	1.99 ± 3.25	1.00 [2.00]	**.035** [b]

[a] z= -2.88
[b] z= -2.11
Abbreviation: IQR, Interquartile Range: SD, Standard Deviation

Inter-rater Agreement:

Results from an independent samples t-tests revealed no differences between raters recording completion time for any agility task (p>.05), and a high level of agreement for SHUF (ICC= .965 $_{.944\text{-}.979}$, p<.001), CAR (ICC= .963 $_{.932\text{-}.980}$, p<.001), ZZ (ICC=.951$_{.921\text{-}.971}$, p<.001), PA (ICC=.949$_{.918\text{-}.970}$, p<.001), and AA (ICC=.932 $_{.890\text{-}.960}$, p<.001) tasks Similarly, results of Mann Whitney U tests indicated no differences between raters reporting committed errors (p>.05), but only had a moderate level of agreement for Ball Toss (κ =.548) and Pro Agility (κ =.545) tasks(Table 10).

Table 10 Inter-Rater Agreement (Weighted Kappa) of Observed Errors During Dynamic Component of EXIT for CONTROL and CONCUSSED Subgroups.

Outcome	CONTROL (N=27)		CONCUSSED (N=15)		TOTAL (N=42)	
	κ	Sig	κ	Sig	κ	Sig
Dynamic Circuit	.372	.001	.130	.255	.256	.001
Ball Toss	1.00	-	.348	.020	.548	<.001
Box Drill Shuffle	.516	.001	.054	.719	.328	.001
Box Drill Carioca	.550	.001	-.01	.944	.348	.001
Zigzag	.184	.075	.153	.189	.167	.048
Pro Agility	.786	.001	0.00	1.00	.545	.001
Arrow Agility	.172	.194	1.00	-	.238	.030

4.4 Discussion

The purpose of the current investigation was to determine intra- and test- retest reliability and MDC of EXiT outcomes, including heart rate and blood pressure response, agility task completion time, committed errors, endorsed symptoms, and rating of perceived exertion in healthy athletes, and 2) assess inter-rater reliability across agility task completion time and committed errors recorded from dual raters observing healthy and recently concussed athletes. Overall, the results from the current investigation support our hypotheses, which indicate using newly established MDCs that healthy athletes exhibited reliable performances for agility tasks between consecutive trials and across visits. We also determined a high internal consistency for symptoms reported during the aerobic and dynamic components. Independent raters also had a high level of agreement for agility task completion time, but only low-to-moderate agreement for observed errors during only 2 (of 7) tasks of the dynamic component.

We observed a statistical improvement in agility task completion time between consecutive trials and visits, but improvements were within the MDCs derived from the reliability (ICC) coefficients. Heart rate responses were also similar across visits and to our knowledge is the first investigation to demonstrate a reliable, 12-minute treadmill running protocol consisting of moderate (64-76% of HR_{max}) and vigorous (77-95% HR_{max}) exertion intensities in response to various treadmill running speeds [128, 129]. In comparison, maximal heart rate (~175 beats per minute) attained from the Buffalo Concussion Treadmill Test was reliable (ICC= 0.64, [0.02-0.90]) upon completing a mean 16.4 minutes, whereas the aerobic component of EXiT resulted in a more reliable (ICC= .723[.566-.824]) protocol to obtain submaximal heart rate (~168 beats per minute) During the dynamic component, we observed a systematic reduction in HR response between study visits. This finding may be due to increased task familiarity, verbal instruction and

demonstration were provided before each task in the same manner at both visits but upon the 2nd visit participants were aware of the individual tasks and more likely to complete certain tasks with less effort in anticipation for the final agility tasks which were longer in duration and involved more head-body movements. The current study enrolled a heterogeneous sport population comprised of athletes with varying levels of physical fitness participating in aerobic-based sports with intermittent sprints (e.g., soccer and basketball) and anerobic-based sports requiring frequent stop/starts in gameplay (e.g., football, baseball, and softball) which may have also played a role in our findings as athletes of different sport-types require different recovery periods between intermittent exertion bouts[161]. Nevertheless, our results indicate that EXiT performance and physiological outcomes were reliable among a diverse range of age and sport-types.

Our findings build upon the recent conclusions that supervised dynamic exertion challenges for SRC patients can improve clinical decision-making [36], and provide a standardized series of functional and agility tasks with reliable performance and clinical outcomes. Future clinical research can incorporate EXiT tasks and address the limitation of multiple medical providers administering variations of a given task. Total EXiT endorsed symptoms also had a moderate to high internal consistency at visits 1 ($\alpha = .894$) and 2 ($\alpha = .805$). this finding is similar to previous work examining commonly reported concussion symptoms following vestibular-ocular motor screening [142, 162, 163] (Eagle 2020 accepted). We also identified minimal detectable change cut-offs for endorsed symptoms aerobic and dynamic components and total EXiT symptoms. Despite recent evidence to suggest concussion-associated symptoms increase following exertion among healthy athletes [104, 164] (EXIT #1,) and prone to under-reporting behaviors from athletes motivated to return to sport [165, 166], symptoms (or the provocation thereof) are stopping criteria for exertion post-concussion and remain a critical part of the exertion

evaluation to determine RTP/A readiness after injury. The minimal detectable change scores identified in the current study can be used to further understand the prevalence of symptom provocation during EXiT in future studies.

We observed a reduction (improvement) in committed errors during the dynamic component which may be due to the novelty of the box drill carioca agility task, it was the only agility task with a reduction in errors across visits. We believe the reduction in committed errors was due to increased familiarization of EXiT tasks. During the dynamic component, each task was verbally instructed and physically demonstrated, and upon the 2nd visit participants were more aware of EXiT components and task requirements. In contrast, the remaining agility tasks had minimal errors for physically active adolescents and adults. Raters had a high level of agreement of measuring agility task completion time, but surprisingly low-to-moderate agreement when recording errors during dynamic component. Perhaps task familiarity and attentive focus to errors may have differed between raters, as rater 1 administered EXiT and recorded EXiT performance, whereas rater 2 only recorded performance. Although the current study did not document the extent of training between administrators, an improved training and monitoring approach could increase inter-rater agreement. The low level of agreement for commission errors may also be due to varying levels of clinical experience among EXiT administrators. Similarly, low inter-rater agreement for qualitative outcomes (e.g., errors between novice and expert raters have been reported for static balance [167] and physical performance testing[168]

Collectively, these findings extend from previously reported exertion testing and support the clinical utility of a brief exertion assessment to facilitate RTP/A decisions [31], and have several clinical implications for health care providers likely to determine RTP/A readiness after SRC. In the current investigation, all participants completed the aerobic component (treadmill

running) without errors, thus, EXiT performance and interpretation for 'pass' EXiT assessment entails successful completion of the aerobic component (without errors) and dynamic components according to the administration guide (EXIT #1). In addition, EXiT requires little equipment and space to administer and can potentially be a clinically feasible exertion-based assessment that can be readily administered in a variety of outpatient clinical settings. The current findings indicate most EXiT outcomes, including agility task completion time, heart rate, endorsed symptoms, perceived exertion, and errors were stable across visits and support the utility of a brief exertion-based assessment for adolescent and adult athletes returning to sport and physical activity following SRC.

Limitations

This study is not without its limitations which should be considered for the current study and future research involving the EXiT assessment. Firstly, there exists the possibility for an ordering effect, as all tasks were administered in a standardized sequence, and it was assumed that all participants completed EXiT with maximal effort. Findings from the current study are also limited to the test-retest study design and we observed a reduction in HR upon the 2nd visit for most EXiT tasks, additional administrations (e.g., 3-4 study visits) would provide a more robust approach to determine the within-subject variability of EXiT physiological, performance, and clinical outcomes. To provide a generalizable clinical assessment we enrolled a diverse population of adolescents and adults from various sport-type backgrounds and subsequently reduce some internal validity of the study. Lastly, there was 1 EXiT administrator for each group and our findings and reduce the external validity of our findings.

Conclusion

An objective and reliable exertion assessment to augment the clinical evaluation to resume unrestricted sport participation has not been empirically addressed; results from the current investigation support the clinically utility of EXiT. Statistical improvements were observed for heart rate response and agility task completion time across study visits for several EXiT tasks, these changes were within newly established MDCs and exhibited high test-retest reliability. Additionally, combined headache, dizziness, and nausea symptoms reported throughout EXiT had high internal consistency and moderate test-retest reliability. MDCs for endorsed symptoms identified as ≥1 for the aerobic component, ≥2 for the dynamic component, and 3≥ for total EXiT, can be used for future investigations examining symptom provocation during structured exertion. Thus, the current investigation established test-retest and minimal detectable change of an objective assessment to inform RTP/A and fulfill a critical domain of the multifaceted clinical evaluation to determine medical clearance after SRC.

5.0 MANUSCRIPT 2: THE ROLE OF AGE, SEX, BODY MASS INDEX, AND SPORT-TYPE ON DYNAMIC EXERTION TESTING (EXIT) PHYSIOLOGICAL, PERFORMANCE, AND CLINICAL OUTCOMES IN HEALTHY ATHLETES

BACKGROUND: Dynamic exertion testing (EXiT), which involves aerobic and dynamic exercises that evaluate vestibular, autonomic, and ocular domains, was developed to help inform return to play/activity (RTP/A) decision making following sport-related concussion (SRC). However, age, sex, body mass index (BMI), and sport-type may influence physiological, performance, and clinical outcomes of EXiT, and significantly threaten the internal validity of EXiT to inform RTP/A decision making.

PURPOSE: Compare age, sex, BMI, and sport-type subgroups on EXiT outcomes, including physiological— age estimated percentage of maximum heart rate (HR $_{\%max}$) and blood pressure (BP), performance— agility task completion time and errors, and clinical— endorsed symptoms and rating of perceived exertion (RPE) outcomes.

METHODS: A total of 87 (F= 55, 37.4%; 19.51 ± 4.36 years old) healthy physically active (per ACSM criteria) adolescents and adults completed a demographic questionnaire, weight and height measurements, and the EXiT which consists of an aerobic component: 12-minute treadmill running protocol; and dynamic component: dynamic circuit (CIRC), ball toss (BT), box-drill shuffle (SHUF) and carioca (CAR), zig zag (ZZ), pro agility (PA), and arrow agility (AA) tasks. Participants reported on a 0-10 Likert-type scale for headache, dizziness, and nausea symptoms, and RPE on a Borg scale (6-20) prior to and throughout aerobic and dynamic components of the EXiT. Body Mass Index ([BMI]= weight [kg]/height[m]^2) and the lowest (fastest) time between consecutive agility task trials were calculated, and participants were categorized as adolescent (14- 17 years) or adult (≥18 years), male or female (self-report), LO-BMI (BMI < 50th percentile) or HI-BMI (BMI ≥50th percentile), and collision, contact, or non-contact sport-types. Independent samples t-tests were conducted for HR $_{\%max}$, BP, and agility task completion time, and Mann-Whitney U tests for RPE, symptoms, and errors between age, sex, and BMI groups across aerobic and dynamic components. A series of 1-way ANOVAs were conducted to compare HR %max, BP, and agility task completion time, and Kruskal Wallis- H tests to compare RPE, symptoms, and errors between collision, contact, and non-contact sport-types.

RESULTS: Findings indicated that adolescents were faster than adults on AA (p=.01); males were faster than females on CAR (p=.01), ZZ (p<.001), PA (p=.02), and AA (p=.04); and the LO-BMI group was faster than the HI-BMI group on AA (p<.001). Males also reported greater RPE than females after the SHUF, CAR, and AA tasks (p<.03). HR, errors, and symptoms were equivocal throughout and following aerobic and dynamic components across age, sex, BMI, and sport-type groups (p>.05).

CONCLUSION: Adolescents were faster than adults on one agility task, whereas males were faster than females for most (4 of 5) agility tasks. Age, sex, BMI, and sport-type had a minimal effect on EXiT physiological, performance, and clinical outcomes among healthy physically active adolescents and adults. EXiT is a robust assessment generalizable to a heterogenous sport sample to inform RTP decision making.

5.1 Introduction

Clinical management decisions surrounding the medical clearance to return to play and activity (RTP/A) following sport-related concussion (SRC) is an individualized approach and based on expert consensus and evolving clinical evidence [3, 5, 32, 33]. There is no current, gold-standard assessment to delineate complete neurophysiological recovery from SRC [33, 169, 170], and several standardized exertion assessments to inform RTP/A decision making have been developed [31, 32, 171] (EXiT #1). More recently, dynamic exertion testing (EXiT) was created as a clinically intuitive evaluation to inform RTP/A decision making (EXiT #1) and is comprised of aerobic and dynamic components. The aerobic component is a 12-min treadmill running protocol derived from cardiorespiratory fitness normative data of males and females aged 13-29 years old and calculated with use of American College of Sports Medicine's VO_2 running equation. The dynamic exertion component consists of functional movements and hand-timed agility tasks replicative of sport-specific drills commonly conducted across collision, contact, and non-contact sport types. Both EXiT components are clinically intuitive and can be interpreted through physiological— age estimated percentage of maximum heart rate (HR $_{\%max}$) and blood pressure (BP), performance— agility task completion time and errors, and clinical— endorsed symptoms and rating of perceived exertion (RPE) outcomes. A preliminary report examining the EXiT among healthy adolescent and adults found moderate test-retest reliability and established minimal detectable change criterion for HR $_{\%max}$ responses (ICC= .723), endorsed symptoms (ICC= .588), agility task completion time (ICC=.842-.972), and post-EXiT systolic (ICC= .705) and diastolic (ICC=.696) blood pressure (BP) (Chapter 4). Although these findings are fundamental to assessment interpretation and establishing reliability, the validity of EXiT to inform RTP/A

decision making the test needs to be further established via comparative analyses between factors that may affect EXiT outcomes.

The interpretation of physiological, performance, and clinical outcomes on any physical exertion-based evaluation should consider the potential confounding effects of factors that may threaten the internal validity of an assessment [172]. In isolation, age, sex, BMI, and sport-type have previously affected physiological, performance[173-180], or clinical outcomes on exertion testing but the collective role of these factors on EXiT is uncertain. Older age was associated with faster reactive agility task performance among healthy basketball, volleyball, and handball athletes, [181], and adult (>18 years of age) athletes participating at more competitive levels have faster change in direction and running speeds than their younger counterparts [173, 177, 178]. In addition, adolescents undergo a more conservative management than adults[33, 43, 182].

Age and sex are suggested to be potentially be contributing factors of concussion symptom provocation during graded aerobic exertion testing[164, 183]. Among a sample of 55 (Female: 24, 43.6%) adolescents and adults (13-57 years of age), 22 (40.0%) reported headache provocation and a greater prevalence of males were adults 7/9 (77.8%) whereas 10/13 (76.9%) of females were adolescents[164]. Sex differences have also been observed for endorsed post-concussion symptoms [184, 185] and duration of clinical recovery [184][186]. Among collegiate athletes, female sex had similar clinical recovery (number of days from SRC onset to medical clearance) as male sex (Median [IQR] 13.5 [9.0-23.1] vs 11.8 [8.119.0]) at the division 1 level, but at combined divisions 2 and 3 recovery was longer amongst females (13.0 [9.2-22.7] vs 10.6 [8.1-13.9]). Moreover, some evidence suggests males complete change of directional tasks faster than females among healthy adolescent and adult athletes [179, 180, 187], but post-exertion heart rate and blood pressure measurements following short-duration exertion bouts are similar between sexes [188,

189]. These findings suggest that sex differences occur in performance-based measures among healthy athletes, but not heart rate and blood pressure responses to clinical exertion testing. Additionally, body mass index (BMI) is a common proxy for health [190], but its role in HR responses to aerobic exertion is mixed. Obese (high BMI level), sedentary adults have exhibited lower peak HR [191, 192] and blunted heart rate and blood pressure restoration immediately following exertion [193]. However, among non-obese adolescents BMI is a poor predictor of heart rate response following aerobic exertion [194] and suggest that BMI is not associated with physiological responses to exertion among non-obese physically active individuals. Lastly, an evaluation to inform RTP/A decision making should consider differences in management strategies for various sport-types since some sports may require additional time to re-establish skills and movements involved during participation [34]. For instance, female collegiate athletes reportedly had a longer clinical recovery than males in contact (12.7 [8.8-21.4] vs 11.0 [7.9-16.2]) but not non-contact (13.8 [9.1-22.0 vs 16.9 9.7-101.7]) sports types [195]. An examination of differing sport-types can improve the external validity of EXiT to inform RTP/A decision making across a variety of sport-types and competitive levels.

Collectively, age, sex, BMI, and sport-type affect SRC clinical management decisions and are potential confounding variables that compromise the internal validity of EXiT, and it is unknown if physiological, performance, and clinical outcomes on the EXiT are affected by these variables. Therefore, the purpose of the current investigation was to compare age, sex, BMI, and sport-types across EXiT physiological (pre- and post-EXiT resting heart rate and blood pressure, and heart rate following each EXiT task), performance (agility task completion time and committed errors), and clinical (endorsed symptoms and perceived effort) outcomes among healthy adolescents and adults to infer the generalizability of EXiT for RTP/A decision making.

We hypothesized similar HR, perceived effort, and endorsed symptoms between age and sex comparisons for the aerobic component; and lower (faster) agility task completion time among adults compared to adolescents and males compared to females, but would have similar physiological and clinical outcomes across remaining EXiT tasks. We also hypothesized that physiological, performance, and clinical outcomes across BMI, and sport-type would be similar.

5.2 Methods

5.2.1 Experimental Design and Participants

We employed a cross-sectional study design comprised of participants obtained from a random, sample of recreational and competitive athletes from a heterogeneous sport population residing in the Pittsburgh, PA community. Participants were physically active (based on ACSM guidance for weekly moderate or vigorous activity [described in more detail below]) healthy controls.

5.2.1.1 Inclusion Criteria

a) Aged 14¬35 years
b) Fulfilled ACSM's guidelines for regular aerobic activity (30 minutes of moderate intensity exertion 5 days per week or 20 minutes of vigorous exertion 3 days per week).

5.2.1.2 Exclusion Criteria

a) Suffered a prior concussion within 6 months.
b) More than 2 previously diagnosed concussions
c) History of brain surgery or TBI (based on Glasgow Coma Scale of <13)

d) History of neurological disorder (seizure disorder, epilepsy, brain tumors or malformations)
e) Current history of preexisting vestibular disorder benign paroxysmal positional vertigo (BPPV), labyrinthitis or vestibular neuritis
f) Previous diagnosis of ocular motor condition (e.g., ocular motor apraxia)
g) Currently taking anticoagulant, beta-blockers, and anticonvulsant prescription medication
h) Incapable of treadmill running at speeds up to 11.27 km/h (7.0 mph) and 13.67 km/h (8.5 mph) for females and males, respectively (based on assessment parameters)
i) Diagnosed with a cardiac, peripheral, or cerebrovascular disease (type 1 or 2 diabetes, or renal disease)
j) Pregnant
k) Experienced chest pain or shortness of breath while at rest or with mild exertion.
l) Lose balance because of dizziness (aside from concussion) or lose consciousness from exertion.
m) Diagnosed with or taking medication for a chronic medical condition.
n) Currently or recent (within 12 months) physical impairment exacerbated by physical activity, leading to the inability to complete 30 minutes of moderate to vigorous exertion.
o) Self-reported any exclusionary criteria from the Preparticipation Activity Questionnaire (PAR-Q), ACSM's formal screening to safely conduct submaximal exertion:
    - Previous diagnosis of a heart condition or high blood pressure
    - Pain in chest of shortness of breath at rest or activities of daily living
    - Currently have a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be worsened by exertion.

- Been told by a doctor to only conduct physical activity under medical supervision.

5.2.1.3 Sample Size Estimation

All sample size calculations were conducted with G*Power 3.0.10 (Franz Faul, Universität Kiel, Germany) [130]. Given 87 EXiT assessments with complete physiological, performance, and clinical data we determined that a total sample size of 80 (40 in each group) participants would require an adjustment of the alpha (0.0620) and beta (.248) level with a power of 0.752 to detect statistical significance between age, sex, BMI, and sport-type analyses [133].

5.2.2 Operational Definitions

5.2.2.1 Sport-Type

Sport participation information was obtained from the demographic questionnaire and categorized based on the level of contact exposure: non-contact, contact (body-to-body contact allowed, but not purposeful), or collision (repeated, purposeful body-to-body contact) [135].

5.2.3 Instrumentation

5.2.3.1 Physiological Monitoring and Processing Equipment

The Equivital Life Monitor (AD Instruments, Colorado Springs, CO; USA) physiological monitoring system was used to quantify HR and linear accelerations in the -X, -Y, and -Z coordinates at a 256 Hz sampling rate [136-138]. A recent validation report concluded that the Equivital monitoring system is an appropriate tool to sensitively quantify physiological data [136], and its tri-axial accelerometer and heart rate accuracy is similar to well-established activity trackers [137]. Movement patterns and physiological data were transmitted to a nearby laptop running Lab chart software (ADI Instruments; Sydney Australia) [138] for processing.

5.2.3.2 Exertion Testing Equipment and Materials

- Treadmill (WOODWAY USA, Waukesha, WI),
- 10”- Agility Cones
- Metronome: A free to download application (Metronome beats, Stonekick, London UK)
- Stopwatch
- Test Cards (N=40) printed on 5”X8” card stock
- Digital scale (Health-o-Meter, Sunbeam Products Inc; McCook, Il, USA)
- Wall-mounted stadiometer (Seca; Chino, CA, USA)
- An open gym space approximately 5X8 meters with a slip-resistant surface in an environment-controlled facility

5.2.4 Measures

5.2.4.1 Dynamic Exertion Testing (EXiT)

EXiT is a 30-minute clinical assessment with aerobic and dynamic components (Appendix C.). The aerobic component is a high-intensity interval treadmill protocol that alternates between slow and fast treadmill running speeds (1:1 ratio) based on the 60% and 90% of the superior category (90th percentile) for aerobic capacity among 13-29 year old male and female sex [129]. The target intensities were then used in ACSM’s metabolic running equation to determine horizontal running speed:

$$VO_2 = 0.2*S + (0.9 *S*G) + 3.5 \quad (1)$$

where VO_2 is oxygen consumption [mL O_2/kg/min], S is the horizontal running speed (in meters per minute), and G is the percentage grade of the treadmill. Speed parameters underwent a brief pilot period and final adjustments to obtain a final protocol whereby females alternated

between 7.2 km/h (4.5 mph; 3.14 METs) and 11.27 km/h (7.0 m/h, 6.36 METs), and males between 8.85 km/h (5.5 mph; 5.21 METs) and 13.67 km/h (8.5 mph, 7.5 METs). Thus, participants completed a 2-minute warm up (Male: 5.5 mph, Female: 4.5 mph), followed by 30-second intervals of fast and slow running speeds (Male: 8.5/5.5 mph; Female: 7.0/4.5 mph) for 10 minutes. Participants were instructed to use support handles as necessary to maintain safety. Following the aerobic component, participants completed the dynamic component which consists of 2 functional movement tasks (Dynamic Circuit [CIR] and Ball Toss [BT]) and 5 Agility Tasks (Box Drill Shuffle [SHUF], Box Drill Carioca [CAR], Zigzag [ZZ], Pro Agility [PA], and Arrow Agility [AA]) to maximal effort. The CIR is a 3-exercise circuit comprised of squat jumps, side-to-side pushups, and ball rotations completed for 3 sets of 10 repetitions in synchronization with a metronome (25 beats/min) and a 30-second rest period between each cycle. The BT task was administered with the participant standing 2.5 meters in front of administrator. After administrator called 'left', or 'right', participant jumped and rotated 180° in the specified direction, caught a basketball tossed by the administrator, and tossed back before returning to the starting position for the next trial, and was repeated for 10 trials (5 jumps left and 5 jumps right) and after a 30-second rest, a second round was performed whereby administrator called direction (left or right) or 'Go' (no response) in a random sequence (completed 5 jumps left, 5 jumps right, and 2 distractors). Participants completed two trials of each agility task (30-sec rest between trials), which were hand-timed via stopwatch by the administrator. Valid EXiT tests, defined as completion of EXiT within the study parameters without assessment modifications, were included in the study.

EXiT Physiological Outcomes

- Resting systolic and diastolic blood pressure (measured in mmHg) were measured with the use of an automatic sphygmomanometer (Omron; Kyoto, Japan) during

the pre- and post-EXiT 5-minute rest period. Heart rate, measured in beats per minute, was calculated for the percentage of age estimated (220-age) maximum HR ($HR_{\%max}$)[87].

- HR was recorded prior to (~5 min), during, and following (~5 min) exertion via a noninvasive heart rate monitor while participants were seated with arms supported and feet placed flat on the floor. During EXiT, heart rate was recorded upon the completion of each task.

EXiT Performance Outcomes

- Agility task completion time was measured by the EXiT administrator via a hand-timed stopwatch. The fastest trial of each agility task was calculated except for Arrow Agility task due to the secondary cognitive task, thus both trials were analyzed.
- Errors were counted by the EXiT administrator. For the aerobic component, excessive pulling on handrails for 10 or more seconds or additional rest periods for 10 or more seconds were counted as errors. During the dynamic component, CIR errors included improper form or inability to maintain pace with squats, pushups, or ball rotation exercises; and BT errors included a jump-turn in the wrong direction, inability to catch or toss ball back to administrator, or a jump committed after a 'Go' call were counted as errors. Errors were counted when a participant kicked a cone off the original placement, mis-navigated a cone, or did not hand-touch a cone when instructed to do.

EXiT Clinical Outcomes

- Headache, dizziness, and nausea concussion-symptoms were individually reported on a 0-10 Likert scale prior to EXiT and after completing the warmup (Post-warm up), the 5th (Midpoint), and 10th (End) intervals of the aerobic component and following the completion of each task of the dynamic component. Endorsed symptom were totaled within aerobic and dynamic components, and subsequently combined and an EXiT total symptom score.
- Rating of Perceived Exertion (RPE) was recorded on the 6-20 Borg scale, a valid measure of perceived effort (6 'no exertion at all' to 20 'maximal effort'), prior to, throughout, and following EXiT [139].

5.2.4.2 Anthropometrics

Bodyweight (in kg) was measured using a digital scale (Health-o-Meter) and height (in cm) with a wall-mounted stadiometer (Seca) among healthy controls, and values were identified in the electronic medical record for concussed participants. Weight and height measurements were used to calculate body mass index (BMI= weight [kg] / height [m]^2) [140], and the upper (HI-BMI) and lower (LO-BMI) 50th percentile determined as a function of age for adolescents [141] and median split of BMI for adults.

5.2.5 Experimental Procedures

5.2.5.1 Recruitment and Consent

Recruitment was conducted through word of mouth, posted fliers, and online advertisement (Pitt + Me), and if deemed eligible during in-person or phone screening, were scheduled for a study visit at the Neuromuscular Research Laboratory-Warrior Human Performance Research Center. Participants were also instructed to a) avoid ingesting food, alcohol, or caffeine or tobacco

products within 2 hours of assessment; b) avoid vigorous exertion the day prior to and day of assessment; c) Wear clothing and footwear to permit athletic movements; and d) drink plenty of fluids the 24-hour period before enrollment. All participants received a thorough explanation of the study overview, procedures, and potential risks of participation prior to signing consent forms.

5.2.5.2 Equipment Fitting and Physiological Measurements

Participants wore noninvasive heart rate monitor (i.e., Polar or Equivital strap) to capture heart rate, respiration rate, skin temperature, and accelerations in the X, Y, and Z directions during EXiT. Resting physiological measures (blood pressure [BP] and heart rate [HR]) were obtained with participant seated with back supported and feet placed flat on the floor. Pre-EXiT measurements were obtained after a 5-minute resting period whereas post-EXiT measures were collected upon returning to the private examination room (~1-5 min) but varied across the sample as some individuals requested additional time for hydration.

5.2.5.3 EXiT Administration

One certified athletic trainer administered to all participants. Heart rate, agility task completion time, errors, symptoms, and effort were recorded on a standardized report sheet (Appendix C). One physical therapist administered EXiT to CONCUSS participants, and one certified athletic trainer administered to CONTROL participants. Heart rate, agility task completion time, errors, symptoms, and effort were recorded on a standardized report sheet (Appendix C).

In aim 1, participants in the control participants repeated assessment procedures (including instructions) at a 2nd visit (3-21 days between visits). A priori systematic approach to inter-rater sampling was conducted whereby the 11-15, 21-25, and 31-35 sequentially enrolled participants completed EXiT with 1 administrator but a 2nd rater (certified athletic trainer) independently

recorded agility task completion time and errors. Additionally, 12 (of 15) CONTROL participants completed a 2nd visit with the same raters, which were included in the inter-rater reliability analyses. All study procedures were approved by the University of Pittsburgh Institutional Review Board

5.2.5.4 Data Reduction

Body Mass Index ([BMI]= weight [kg]/height[m]^2) and the lowest (fastest) time between consecutive agility task trials were calculated, and participants were categorized in adolescent (14-17 years) or adult (≥18 years), male or female (self-report), LO-BMI (BMI < 50th percentile) or HI-BMI (BMI ≥50th percentile), and collision, contact, or non-contact sport-types.

Participants completed EXiT physiological, performance, and outcome data were analyzed (EXiT #1). A team member trained in the cleaning and processing procedures examined Equivital recordings for completeness and identified periods of movement and rest and calculated raw (HR_{raw}) and percentage of age estimated (220-age) maximum HR ($HR_{\%max}$) [87, 88]. Endorsed headache, dizziness, and nausea symptoms were subtotaled within aerobic and dynamic components, and subsequently combined to populate EXiT total symptoms.

5.2.5.5 Statistical Analyses

Independent samples t-tests were conducted for continuous (e.g., age, BMI, etc.), and Chi-squared (χ^2) with odds ratio (OR) values for nominal (e.g., female sex, sport type, etc.) demographic variables to compare age, sex, and BMI subgroups. Independent samples t-tests were conducted for HR %max, BP, and agility task completion time, and Mann-Whitney U tests for RPE, symptoms, and errors between adolescents and adults, males and females, LO-BMI and HI-BMI across aerobic and dynamic components. Cohen's d was used to infer magnitude of

differences and was interpreted with as small (d=0.2), medium (d=0.5), and large (d=0.8) effect sizes[132]. A series of 1-way ANOVAs were conducted to compare HR $_{\%max}$, BP, and agility task completion time, and Kruskal Wallis- H tests to compare RPE, symptoms, and errors between collision, contact, and non-contact sport-types. Additional Chi-squared analyses were conducted compare group prevalence of individuals exceeding minimal detectable change scores for endorsed symptoms across aerobic and dynamic EXiT components. To determine the equivalence of EXiT HR $_{\%max}$, BP, and agility task completion time between age, sex, and BMI groups, the MDCs (from Chapter 4) were used to determine upper and lower bounds for each variable and visually inspected with the 95% confidence interval surrounding mean difference. Specifically, if the 95% range of the mean difference between groups was within the -MDC and +MDC for that variable, the groups were equivalent[151]. Significance for all analyses was set at p=.05. All post-hoc pairwise comparisons underwent a Bonferroni statistical correction to reduce type I error likelihood, and analyses were conducted with 26th version of SPSS (IBM Statistics).

5.3 Results

5.3.1 Demographics

Of 92 enrolled participants, 87 (F= 55, 37.4%; 19.51± 4.36 years old) completed EXiT and were analyzed. Expectedly, adolescents had lower weight (Mean Difference [MD]: -9.53 kg, p<.001) and BMI (MD: -2.76, p<.001) than adults, males were taller (MD: 11.88 cm, p<.001) and weighed more (MD: 13.25 kg, p<.001) than females, and LO-BMI was younger (MD: -4.13 years, p<.001), shorter (MD: -6.51, p<.001), and weighed less (MD: -21.83, p<.001) than HI-BMI participants (Table 11). Five adolescents in the LO- BMI group had a previous ADHD/Learning

disability diagnosis; thus, those without a learning disability were less likely to be in the LO-BMI group (χ^2 =4.515, p=0.034; OR, 95%CI: 0.894, 0.810-0.986). Among sport-types, more non-contact sports had a greater prevalence of females (χ^2 =14.482, p<.001_, there were no differences observed for mean age, height, weight, and BMI. between sport-types (p>.05).

Table 11 Mean and Standard Deviation (SD) and Frequency (Percentage) and Comparison Statistics Across Demographic Variables Between Age, Sex, BMI, and Sport-Type Subgroups (N=87)

		Age			Sex			Body Mass Index			Sport-Type			
Variable	Full Sample	Adolescents (N=36)	Adults (N=51)	T, sig, MD [95%]	Males (N=51)	Females (N=36)	T, sig, MD [95%]	LO-BMI (N=47)	HI-BMI (N=40)	T, sig, MD [95%]	Collision (N=20)	Contact (N=60)	Non-Contact (N=7)	ANOVA
Age	19.51 (4.36)	15.61 (1.15)	22.27 (3.62)	12.28, ***p*<0.001** 6.66 [5.57,7.74]	19.78 (4.96)	19.13 (3.36)	0.68, *p*=0.500 0.65 [-1.25, 2.54]	17.61 (3.40)	21.75 (4.34)	-4.97, ***p*<0.001** -4.13 [-5.79, -2.48]	19.4 (5.08)	19.7 (4.30)	18.28 (2.69)	F (2,84) =0.33, *p*=0.717
Height (cm)	171.56 (8.93)	170.50 (7.69)	172.31 (9.71)	0.92, *p*=0.357 1.80 [-2.06, 5.67]	176.48 (7.27)	164.60 (5.93)	8.08, ***p*<0.001** 11.89 [8.96, 14.81]	168.57 (7.48)	175.08 (9.29)	-3.62, ***p*<0.001** -6.52 [-10.09, -2.94]	174.65 (7.66)	170.8 (9.36)	169.34 (7.17)	F (2,84) =1.65, *p*=0.197
Weight (kg)	67.84 (15.02)	61.35 (14.5)	72.41 (13.75)	3.61, ***p*<0.001** 11.05 [4.96, 17.14]	73.32 (16.29)	60.07 (8.32)	4.48, ***p*<0.001** 13.25 [7.37, 19.14]	57.80 (6.69)	79.63 (13.44)	-9.805, ***p*<0.001** -21.84 [-26.26, -17.41]	73.98 (20.04)	66.07 (13.3)	65.4 (7.69)	F (2,84) =2.24, *p*=0.112
BMI	22.87 (3.74)	20.99 (3.98)	24.2 (2.94)	4.32, ***p*<0.001** 3.21 [1.73, 4.68]	23.39 (4.35)	22.14 (2.53)	1.54, *p*=0.127 1.25 [-0.36, 2.86]	20.32 (1.79)	25.87 (3.17)	-10.22, ***p*<0.001** -5.55 [-6.63, -4.47]	24.02 (5.32)	22.49 (3.13)	22.88 (3.03)	F (2,84) =1.25, *p*=0.29
BMI %	52.68 (25.19)	48.68 (25.93)	-	-	52.41 (27.60)	53.06 (21.89)	-0.08, *p*=0.931 -0.65[-15.89, 14.59]	42.16 (22.08)	77.46 (10.16)	-5.7, ***p*<.001** -35.29[-47.76, -22.82]	54.62 (31.38)	51.37 (22.61)	55.18 (27.06)	F (2, 84) =0.98, *p*=.907
Female Sex [a]	55 (37.4 %)	14 (38.9%)	22 (43.1%)	0.157, *p*=0.694 1.19 [0.50, 2.84]	-	-	-	26 (55.3%)	10 (25.0%)	8.189, ***p*=0.004** 0.27 [0.11, 0.67]	2 (10%)	28 (46.7%)	6 (85.7%)	-
Migraine Hx [a]	5 (5.75%)	4 (11.1%)	1 (2.0%)	3.262, *p*=0.075 0.16 [0.02, 1.50]	3 (5.9%)	2 (5.6%)	0.004, *p*=0.949 0.94 [0.15, 5.94]	4 (8.5%)	1 (2.5%)	1.441, *p*=0.230 0.276 [0.03, 2.57]	1 (5.0%)	4 (6.7%)	0 (0.0%)	-
ADHD/LD [a]	5 (5.75%)	4 (11.1%)	1 (2.0%)	3.262, *p*=0.072 0.16 [0.02, 1.50]	4 (7.8%)	1 (2.8%)	1.000, *p*=0.317 0.34 [0.36, 3.12]	5 (10.6%)	-	4.515, ***p*=0.034** 0.51 [0.42, 0.63]	2 (10.0%)	3 (5.0%)	0 (0.0%)	-
Concussion Hx [a]	15 (17.2%)	5 (13.9%)	10 (19.6%)	0.484, *p*=0.499 1.51 [0.47, 4.89]	9 (17.6%)	6 (16.7%)	0.14, *p*=0.905 0.93 [0.30, 2.90]	9 (19.1%)	6 (15.0%)	0.261, *p*=0.610 0.75 [0.24, 2.31]	6 (30.0%)	8 (13.3%)	1 (14.3%)	-
<u>Sport-Type</u>														-
Full Contact	71 (81.6%)	35 (76.09%)	36 (87.80%)	-	48 (94.1%)	23 (63.9%)	-	37 (78.7%)	34 (85.0%)	-	-	-	-	-
Limited	8 (9.2%)	5 (10.87%)	3 (7.32%)	-	2 (3.9%)	6 (16.7%)	-	6 (12.8%)	2 (5.0%)	-	-	-	-	-
Non-Contact	8 (9.2%)	6 (13.04%)	2 (4.88%)	-	1 (1.9%)	7 (19.4%)	-	4 (8.5%)	4 (10.0%)	-	-	-	-	-

[a] Chi-Squared value reported in contrast to t-value

Abbreviations: ADHD/LD; Attention-Deficit/ Hyperactivity Disorder or Learning Disability; BMI; Body Mass Index; BMI %, BMI normative percentile; Hx, Prior history; MD, Mean Difference; OR, Odds Ratio

5.3.1 EXiT Physiological, Performance, and Clinical Outcomes

Among the resting physiological outcomes, individuals with greater BMI had greater pre-EXiT systolic (MD: 4.24, p=.003) and diastolic (MD: 3.99, p<.001) BP than those with lower BMI, we observed a lower post-EXiT systolic BP (MD: -7.92, p=.01) by the adolescent group of medium effect post-EXiT systolic and diastolic BP and HR outcomes were similar between sex, BMI, and sport-type comparisons (p>.05). During aerobic component, both HR_{raw} and $HR_{\%max}$ physiological outcomes following the warm-up midpoint and end stages were similar between age, sex, BMI, and sport-type comparisons (p>.05). Moreover, across all subgroups the mean $HR_{\%max}$ exceeded 80% of upon completion of the aerobic component and 90% for the dynamic component (Table 12). Between age groups, we observed greater $HR_{\%max}$ following BT (MD:5.00, p<.001), SHUF (MD: 3.77, p=.02), CAR (MD: 4.49, p<.001), and PA (MD: 2.98, p=.02) among adults. Statistical differences were within previously established minimal detectable change cut-offs (Chapter 4).

Table 12 Resting Physiological Measures and Comparison Statistics Between Age, Sex, BMI and Sport-type Subgroups (N=86)

		Age				Sex				Body Mass Index				Sport-Type			
Outcome	MDC (Ch 4)	Adolescents (N=36)	Adults (N=51)	T, sig, MD [95%]	*d*	Males (N=51)	Females (N=36)	T, sig, MD [95%]	*d*	LO-BMI (N=47)	HI-BMI (N=40)	T, sig, MD [95%]	*d*	Collision (N=20)	Contact (N=60)	Non-Contact (N=7)	F, sig
Pre-EXiT Systolic BP	14.70	116.13 (9.52)	116.6 (9.08)	0.22, *p*=0.822 0.46 [-3.57,4.49]	0.050	118.96 (9.79)	112.86 (7.06)	3.18, ***p*=0.002** 6.10 [2.29, 9.91]	0.696	114.43 (8.44)	118.67 (9.65)	-2.17, ***p*=0.034** -4.24 [-8.12, -0.35]	-0.470	118.2 (8.51)	115.44 (9.24)	119.42 (10.87)	F (2,83) =1.07 *p*=0.344
Pre-EXiT Diastolic BP	12.63	72.41 (6.14)	74.2 (5.59)	1.39, *p*=0.166 1.78 [-0.75, 4.31]	0.306	74.70 (6.36)	71.72 (4.63)	2.39, ***p*=0.025** 2.98 [0.50, 5.46]	0.522	71.28 (5.71)	75.95 (5.02)	-3.99, ***p*<0.001** -4.66 [-6.99, -2.34]	-0.863	75.05 (5.23)	72.57 (6.14)	76.28 (3.14)	F (2,83) =2.28 *p*=0.108
Pre-EXiT HR_{Raw}	25.84	68.16 (10.43)	67.43 (11.04)	-0.31, *p*=0.759 -0.730 [-5.40, 3.93]	-0.068	67.01 (11.43)	68.75 (9.73)	-0.74, *p*=0.468 -1.73 [-6.39, 2.93]	-0.161	69.12 (9.67)	66.10 (11.78)	1.31, *p*=0.195 3.02 [-1.54, 7.60]	0.283	66.05 (11.08)	68.21 (11.24)	68.42 (3.1)	F (2,84) =0.31 *p*=0.729
Pre-EXiT $HR_{\%\ Max}$	12.93	33.36 (5.18)	34.11 (5.59)	0.63, *p*=0.529 0.740 [-1.60, 3.10]	0.138	33.49 (5.80)	34.23 (4.85)	-0.63, *p*=0.536 -0.74 [-3.09, 1.61]	-0.136	34.17 (4.88)	33.36 (6.01)	0.69, *p*=0.489 0.81 [-1.51, 3.13]	0.149	32.94 (5.54)	34.07 (5.67)	33.93 (1.71)	F (2,84) =0.32 *p*=0.723
Post-EXiT Systolic BP	24.95	132.8 (14.78)	124.88 (12.81)	-2.63, ***p*=0.018** -7.92 [-13.90, -1.93]	-0.580	129.61 (13.73)	126.13 (14.6)	1.12, *p*=0.272 3.47 [-2.69, 9.63]	0.246	128.86 (14.59)	127.32 (13.72)	0.49, *p*=0.617 1.54 [-4.59, 7.67]	0.109	126.8 (10.77)	127.84 (15.35)	134.42 (11.65)	F (2,82) =0.79 *p*=0.456
Post-EXiT Diastolic BP	12.53	78.37 (8.64)	76.3 (9.16)	-1.04, *p*=0.300 -2.06 [-6.00, 1.87]	-0.231	77.65 (8.18)	76.48 (10.02)	0.59, *p*=0.56 1.17 [-2.79, 5.13]	0.130	76.66 (8.35)	77.74 (9.68)	-0.54, *p*=0.588 -1.07 [-4.99, 2.83]	-0.120	78.55 (11.16)	76.7 (8.53)	77 (4.33)	F (2,81) =0.30 *p*=0.733
Post-EXiT HR_{Raw}	25.87	122.38 (16.14)	118.5 (16.34)	-1.09, *p*=0.275 -3.87 [-10.91, 3.16]	-0.239	119.39 (16.08)	121.13 (16.74)	-0.49, *p*=0.632 -1.75 [-8.83, 5.33]	-0.107	121.19 (14.42)	118.85 (18.33)	0.66, *p*=0.509 2.34 [-4.64, 9.32]	0.143	120.35 (14.16)	120 (17.52)	120.42 (12.01)	F (2,84) =0.00 *p*=0.995
Post-EXiT $HR_{\%\ Max}$	12.97	59.88 (7.95)	59.90 (7.96)	0.01, *p*=0.990 0.010 [-3.42, 3.46]	0.002	59.61 (7.83)	60.29 (8.11)	-0.39, *p*=0.705 -0.68 [-4.12, 2.77]	-0.085	59.88 (7.07)	59.91 (8.89)	-0.01, *p*=0.984 -0.02 [-3.43, 3.37]	-0.004	59.98 (6.74	59.88 (8.5)	59.75 (6.52)	F (2,84) =0.00 *p*=0.997

Abbreviations: $HR_{\%\ Max}$, Percentage of age-estimated maximum heart rate; HR_{Raw}, Heart rate (measured); MD, Mean difference; MDC, Minimal detectable change

Table 13 HR $_{\%max}$ Responses During Aerobic Componentof EXiT Between Age, Sex, and BMI Subgroups (N=86)

		Age				Sex				Body Mass Index				Sport-Type			
Outcome	MDC (Ch 4)	Adolescents (N=36)	Adults (N=51)	T, sig MD [95%]	*d*	Males (N=51)	Females (N=36)	T, sig MD [95%]	*d*	LO-BMI (N=47)	HI-BMI (N=40)	T, sig MD [95%]	*d*	Collision (N=20)	Contact (N=60)	Non-Contact (N=7)	ANOVA
Pre- Standing Rest (0 min)	14.20	41.09 (6.7)	41.53 (6.9)	0.29, *p*=0.760 0.43 [-2.51, 3.39]	0.064	40.48 (6.96)	42.57 (6.43)	-1.42, *p*=0.1687 -2.08 [-5.01, 0.84]	-0.309	42.10 (6.31)	40.46 (7.29)	1.12, *p*=0.266 1.63 [-1.26, 4.53]	0.241	40.87 (6.69)	41.07 (6.79)	45.08 (6.87)	F (2,84) =1.15 *p*=0.318
Post-Warm Up (2 min)	12.84	69.7 (8.2)	69.91 (9.84)	0.10, *p*=0.910 0.20 [-3.77, 4.19]	0.023	70.39 (9.32)	69.02 (8.96)	0.68, *p*=0.505 1.36 [-2.61, 5.33]	0.148	68.58 (9.33)	71.28 (8.82)	-1.37, *p*=0.178 -2.69 [-6.59, 1.19]	-0.296	71.79 (7.95)	69.04 (9.85)	70.88 (4.92)	F (2,84) =0.72 *p*=0.487
Midpoint (7 min)	13.37	80.03 (7.57)	80.53 (11.27)	0.23, *p*=0.819 0.50 [-3.83, 4.84]	0.051	80.04 (11.2	80.71 (7.83)	-0.31, *p*=0.764 -0.67 [-4.99, 3.65]	-0.067	79.78 (7.59)	80.95 (12.07)	-0.54, *p*=0.586 -1.17 [-5.43, 3.09]	-0.118	82.65 (7.17)	79.5 (11.03)	80.65 (4.51)	F (2,83) =0.75 *p*=0.47
Finish (12 min)	13.12	83.18 (7.87)	84.96 (8.17)	1.00, *p*=0.316 1.78 [-1.73, 5.29]	0.221	84.74 (8.09)	83.54 (8.06)	0.68, *p*=0.508 1.20 [-2.31, 4.71]	0.149	82.99 (7.88)	85.74 (8.10)	-1.58, *p*=0.117 -2.74 [-6.18, 0.68]	-0.344	84.38 (8.05)	84.11 (8.45)	84.97 (4.52)	F (2,83) =0.03 *p*=0.962

Abbreviations: HR $_{\% Max}$, Percentage of age-estimated maximum heart rate; HR $_{Raw}$, Heart Rate (measured); MD, Mean difference; MDC, Minimal detectable change

Table 14 Heart Rate (HR $_{\%max}$) Responses and Comparison Statistics During Dynamic Component of EXiT Between Age, Sex, BMI and Sport-type Subgroups (N=86)

		Age				Sex				BMI				Sport Type			
Outcome	MDC	Adolescents (N=36)	Adults (N=51)	T, sig MD [95%]	*d*	Males (N=51)	Females (N=36)	T, sig MD [95%]	*d*	LO-BMI (N=47)	H-BMI (N=40)	T, sig MD [95%]	*d*	Collision (N=20)	Contact (N=60)	Non-Contact (N=7)	ANOVA
Dynamic Circuit	17.61	76.11 (9.72)	81.32 (7.75)	1.35, *p*=0.172 5.21 [1.46, 8.96]	0.604	79.47 (8.81)	78.68 (9.26)	0.41, *p*=0.690 0.80 [-3.12, 4.71]	0.089	78.35 (9.24)	80.05 (8.65)	-0.87, *p*=0.386 -1.70 [-5.56, 2.15]	-0.190	80.28 (8.57)	78.92 (9.44)	77.75 (6.01)	F (2,83) =0.25 *p*=0.772
Ball Toss	10.93	75.57 (9.4)	80.57 (7.13)	2.82, ***p*<0.001** 5.00 [1.47, 8.53]	0.614	77.74 (8.53)	79.58 (8.37)	-0.99, *p*=0.327 -1.83 [-5.50, 1.83]	-0.216	77.77 (9.04)	79.36 (7.76)	-0.87, *p*=0.383 -1.59 [-5.22, 2.03]	-0.188	78.97 (7.95)	78.39 (8.86)	78.16 (7.36)	F (2,84) =0.04 *p*=0.96
Box Drill Shuffle	13.34	84.55 (8.67)	88.32 (6.3)	2.34, ***p*=0.024** 3.77 [0.57, 6.96]	0.511	87.48 (7.12)	85.74 (8.14)	1.06, *p*=0.293 1.74 [-1.53, 5.01]	0.230	85.64 (8.56)	88.08 (6.03)	-1.5, *p*=0.139 -2.43 [-5.64, 0.77]	-0.324	87.76 (6.42)	86.71 (8.18)	84.29 (4.61)	F (2,84) =0.54 *p*=0.583
Box Drill Carioca	9.28	82.32 (8.29)	86.82 (6.02)	2.77, ***p*<0.001** 4.49 [1.26, 7.73]	0.638	85.56 (6.67)	84.10 (8.23)	0.91, *p*=0.368 1.46 [-1.72, 4.65]	0.199	83.8 (8.17)	86.31 (6.06)	-1.6, *p*=0.119 -2.51 [-5.62, 0.60]	-0.345	85.09 (6.67)	85.2 (7.75)	82.46 (5.80)	F (2,84) =0.43 *p*=0.649
Zig Zag	11.50	87.74 (7.16)	90.08 (5.53)	1.72, *p*=0.087 2.34 [-0.36, 5.05]	0.375	89.45 (5.54)	88.63 (7.36)	0.59, *p*=0.550 0.82 [-1.93, 3.57]	0.129	88.96 (6.72)	89.29 (5.91)	-0.24, *p*=0.804 -0.33 [-3.05, 2.39]	-0.052	88.32 (6.24)	89.45 (6.6)	88.47 (4.27)	F (2,84) =0.27 *p*=0.76
Pro Agility	11.31	85.15 (6.95)	88.13 (5.18)	2.28, ***p*=0.024** 2.98 [0.38, 5.58]	0.499	86.95 (5.22)	86.79 (7.28)	0.12, *p*=0.906 0.17 [-2.51, 2.85]	0.027	86.90 (6.63)	86.86 (5.55)	0.02, *p*=0.970 0.03 [-2.62, 2.69]	0.005	86.46 (6.6)	86.94 (6.29)	87.55 (3.42)	F (2,83) =0.08 *p*=0.915
Arrow Agility	6.25	90.25 (5.61)	91.3 (5.8)	0.83, *p*=0.416 .05 [-1.43, 3.53]	0.184	91.42 (5.28)	90.08 (6.25)	1.07, *p*=0.298 1.34 [-1.14, 3.82]	0.235	91.06 (5.43)	90.63 (6.10)	0.34, *p*=0.73 0.42 [-2.04, 2.90]	0.074	91.05 (5.31)	90.71 (6.17)	91.64 (1.52)	F (2,83) =0.09 *p*=0.91

Abbreviations: HR $_{\% Max}$, Percentage of age-estimated maximum heart rate; MDC, Minimal detectable change

Adolescents had lower (faster) agility task completion time than adults for 1st (MD: -2.63 sec, p=.01) and 2nd (MD: -2.98 sec, p<.001) AA trials, but were similar among SHUF, CAR, ZZ, and PA tasks (p>.05). Males were faster than females for CAR (MD: -1.78, p=.01), Zig Zag (MD: -2.81, p<.001), PA (MD: -0.51, p=.02), and trials 1 (MD: -2.98, p<.001) and 2 (MD: -2.1, p=.04) of the AA task. Of which, the 95% CI of the mean differences exceeded the MDC threshold for only the PA task Among the BMI comparison, only the 2nd trial of the AA task was lower among LO-BMI (MD: -2.14, p<.001) but similar for remaining agility tasks (p>.05). There were no differences in agility task completion time between sport-types. Lastly, there were no differences in the total number of committed errors for adolescents and adults (2.65 ± 5.03 vs 3.47 ±4.59), males and females (3.34 ± 5.37 vs2.61 ± 3.98), and LO-BMI and Hi-BMI (3.31 ± 5.48 vs 2.69 ± 3.92) comparisons (p>.05).

Table 15 Agility Task Completion Time (in seconds) Between Age, Sex, BMI, and Sport-type Subgroups (N=86).

	Age					Sex				BMI				Sport Type			
Outcome	MDC (Chapter 4)	Adolescents (N=36)	Adults (N=51)	T, sig MD [95%]	*d*	Males (N=51)	Females (N=36)	T, sig MD [95%]	*d*	LO-BMI (N=47)	HI-BMI (N=40)	T, sig MD [95%]	*d*	Collision (N=20)	Contact (N=60)	Non-contact (N=7)	ANOVA
Box Drill Shuffle	6.40	22.62 (3.36)	21.92 (3.16)	-0.98, *p*=0.32 -7.00 [-2.10, 0.70]	0.215	21.47 (3.44)	23.25 (2.66)	-2.6, ***p*=0.01** -1.78[-3.14, -0.41]	-0.566	22.66 (2.59)	21.69 (3.85)	1.35, *p*=0.17 0.97 [-0.45, 2.40]	0.301	21.74 (2.32)	22.11 (3.48)	24.42 (2.85)	F (2,84) =1.89 *p*=0.156
Box Drill Carioca	4.55	13.98 (1.62)	14.2 (1.68)	-0.6, *p*=0.54 0.21 [-0.50, 0.93]	0.131	13.83 (1.69)	14.50 (1.53)	-1.89, *p*=0.061 -0.67[-1.37,0.03]	-0.413	14.11 (1.13)	14.11 (2.12)	-0.01, *p*=0.98 0.00 [-0.75, 0.74]	-0.004	14.04 (1.54)	14.03 (1.71)	15.03 (1.35)	F (2,84) =1.17 *p*=0.313
Zig Zag	8.70	29.85 (4.68)	30.34 (5.27)	0.44, *p*=0.65 0.48 [-1.69, 2.66]	0.097	28.98 (5.03)	31.79 (4.57)	-2.66, ***p*=0.009** -2.81[-4.9, -0.71]	-0.579	30.59 (4.26)	29.61 (5.79)	0.87, *p*=0.38 0.97 [-1.23, 3.18]	0.194	29.79 (4.56)	30.12 (5.33)	31.28 (3.61)	F (2,84) =0.22 *p*=0.799
Pro Agility	0.75	8.12 (1.00)	8.11 (1.10)	-0.03, *p*=0.97 0.00 [-0.46, 0.45]	0.007	7.90 (1.09)	8.41 (0.92)	-2.27, ***p*=0.025** -0.51[-0.95, -0.06]	-0.479	8.18 (1.00)	8.03 (1.11)	0.64, *p*=0.51 0.14 [-0.30, 0.60]	0.141	7.99 (1.01)	8.13 (1.09)	8.3 (0.92)	F (2,83) =0.23 *p*=0.793
Arrow Agility Trial 1	5.85	39.18 (3.96)	40.97 (5.75)	1.59, *p*=0.11 1.78 [-4.02, -0.44]	0.348	39.19 (5.03)	41.67 (5.00)	-2.24, ***p*=0.027** -2.48[-4.67, -0.28]	-0.351	39.82 (4.15)	40.76 (6.16)	-0.80, *p*=0.42 -0.93 [-3.27, 1.39]	-0.182	39.2 (3.39)	40.54 (5.64)	40.74 (4.92)	F (2,82) =0.64 *p*=0.528
Arrow Agility Trial 2	4.91	40.51 (4.59)	42.77 (5.14)	2.09, ***p*=0.03** 2.25 [-4.39, -0.11]	0.458	40.95 (5.25)	43.05 (4.46)	-1.94, *p*=0.054 -2.1[-4.25,0.04]	-0.458	40.85 (4.20)	43.00 (5.69)	-2.01, *p*=0.10 -2.14 [-4.27, -0.02]	-0.434	41.47 (3.41)	41.83 (5.57)	42.3 (4.09)	F (2,83) =0.04 *p*=0.956

Symptoms reported during the aerobic component were similar between males (0.35 ± 1.19) and females (0.27 ± 1.05; (p>.05), but greater among males (1.6 ± 4.84 vs 0.33 ± 1.37) during the dynamic component (t=2.12, p=0.03; MD [95%] = 2.15 [0.12-4.18]). Total EXiT symptoms were similar across age (adolescents: 1.41 ± 4.56 vs adults 2.78 ±7.32), sex (males: 2.98 ± 7.52 vs females: 0.75 ± 2.33) and BMI (LO-BMI: 1.42 ± 4.55 vs HI-BMI: 2.8 ± 7.39) comparisons (p>.05). Females were less likely to exceed EXiT total symptom cut-off scores than males (OR 95% CI= 0.19, 0.04-0.92, p=.025).

Table 16 Frequency (Percentage) of Participants Exceeding Minimal Detectable Change for Endorsed Symptoms Across EXiT Components Between Between Age, Sex, BMI, and Sport-type Subgroups (N=86).

Outcome	Age			Sex			BMI			Sport Type			
	Adolescents (N=36)	Adults (N=51)	Chi-square, sig OR [95%]	Males (N=51)	Females (N=36)	Chi-square, sig OR [95%]	LO-BMI (N=47)	HI-BMI (N=40)	Chi-square, sig OR [95%]	Collision (N=20)	Contact (N=60)	Non-contact (N=7)	Chi-square, sig
Aerobic	2 (5.6%)	5 (9.8%)	0.515, *p*= 0.473 1.85 [0.34, 10.10]	5 (9.8%)	2 (5.6%)	0.515, *p*=0.473 0.54 [0.10, 2.96]	3 (6.4%)	4 (10%)	0.382, *p*=0.536 1.63 [0.34, 7.76]	1 (5%)	6 (10%)	0 (0%)	1.173, *p*=0.556
Dynamic	10 (27.8%)	11 (21.6%)	0.444, *p*=0.505 0.72 [0.27, 1.92]	15 (29.4%)	6 (16.7%)	1.872, *p*=0.171 0.48 [0.17, 1.39]	11 (23.4%)	10 (25.0%)	0.030, *p*=0.862 1.09 [0.41, 2.92]	7 (35.0%)	12 (20.0%)	2 (28.6%)	1.925, *p*=0.382
EXiT Total Symptoms	5 (13.9%)	9 (17.6%)	0.221, *p*=0.638 1.33 [0.41, 4.36]	12 (23.5%)	2 (5.6%)	5.049, ***p*=0.025** 0.19 [0.04, 0.92]	6 (12.8%)	8 (20.0%)	0.838, *p*=0.360 1.71 [0.54, 5.42]	7 (35.0%)	7 (11.7%)	0 (0%)	7.508, ***p*=0.023**

Males reported greater RPE than females following SHUF (12.97 ± 2.49 vs 11.85 ± 2.75; 2.53, p=0.01; MD [95%]: 1.43 [0.30-2.55]), CAR (M: 11.65 ± 2.85 vs 12.55 ± 2.92; t=2.18, p=0.03; MD [95%]: 1.34 [0.11-2.58]), and AA (15.78 ± 2.36 vs 14.5 ± 2.84; t=2.27, p=0.02; 1.28 [0.16-2.39]) tasks (Table 17). Perceived exertion between adolescents and adults were similar throughout EXiT and following the aerobic (3.52 ± 2.74 vs 13.41 ± 2.38) and dynamic (14.65 ± 2.34 vs 15.92 ± 2.81) components and were equivocal between LO-BMI and HI-BMI groups following the aerobic (13.25 ± 2.49 vs 13.72 ± 2.66) and dynamic (15.64 ± 2.52 vs 14.91 ± 2.7) components (p>.05).

Table 17 Rating of Perceived Exertion, Endorsed Symptoms, and Errors Across Exertion Testing (EXiT) Components Between Age, Sex, BMI, and Sport-Types(N=86)

	Age		Sex		BMI		Sport-Type		
Outcome	Adolescents (N=36)	Adults (N=51)	Males (N=51)	Females (N=36)	LO-BMI (N=47)	H-BMI (N=40)	Collision (N=20)	Contact (N=60)	Non-Contact (N=7)
Rating of Perceived Exertion									
Aerobic Component									
Pre- Standing Rest (0 min)	6.19 (0.62)	6.04 (0.28)	6.18 (0.59)	6.00 (0.00)	6.14 (0.55)	6.05 (0.32)	6.31 (0.82)	6.03 (0.25)	6.14 (0.37)
Post- Warm up (2 min)	8.52 (1.73)	7.88 (1.53)	8.12 (1.69)	8.19 (1.58)	8.17 (1.55)	8.12 (1.76)	8.26 (2.02)	8.08 (1.52)	8.42 (1.71)
Midpoint (7 min)	12.11 (2.23)	11.34 (2.13)	11.78 (2.25)	11.5 (2.14)	11.78 (2.14)	11.51 (2.28)	11.47 (2.54)	11.71 (2.1)	11.71 (2.28)
Finish (12 min)	13.80 (2.53)	13.16 (2.55)	13.82 (2.60)	12.88 (2.41)	13.25 (2.49)	13.64 (2.64)	13.36 (2.71)	13.46 (2.59)	13.28 (2.05)
Dynamic Component									
Dynamic Circuit	12.69 (2.96)	13.24 (2.81)	13.36 (2.69)	12.52 (3.07)	12.93 (3.01)	13.1 (2.73)	13.57 (2.85)	12.8 (2.91)	13.28 (2.69)
Ball Toss	10.86 (2.96)	11.31 (2.62)	11.53 (2.90)	10.56 (2.47)	10.87 (2.89)	11.43 (2.59)	11.50 (2.63)	11.07 (2.89)	10.57 (2.07)
Box Drill Shuffle	11.72 (2.92)	12.86 (2.43)	13.00 (2.74)	11.52 (2.39)	11.85 (2.75)	13.02 (2.50)	12.89 (2.90)	12.3 (2.74)	11.71 (1.38)
Box Drill Carioca	11.38 (3.08)	12.54 (2.72)	12.62 (3.02)	11.27 (2.60)	11.65 (2.85)	12.53 (2.96)	12.63 (3.36)	12.06 (2.83)	10.42 (1.90)
Zigzag	12.80 (2.72)	14.42 (2.49)	14.16 (2.66)	13.16 (2.68)	13.34 (2.69)	14.23 (2.66)	13.89 (2.82)	13.80 (2.79)	12.85 (1.34)
Pro Agility	12.66 (2.94)	13.7 (2.58)	13.70 (2.90)	12.66 (2.50)	13.04 (2.76)	13.53 (2.79)	13.78 (2.93)	13.16 (2.82)	12.71 (1.79)
Arrow Agility	14.52 (2.53)	15.76 (2.61)	15.78 (2.36)	14.5 (2.84)	14.91 (2.70)	15.64 (2.52)	15.94 (1.98)	15.13 (2.9)	14.28 (1.11)
Endorsed Symptoms									
Aerobic Component	0.16 (0.60)	0.34 (1.23)	0.26 (1.00)	0.27 (1.05)	0.34 (1.29)	0.17 (0.55)	0.00 (0.00)	0.38 (1.20)	0.00 (0.00)
Dynamic Component	1.47 (4.99)	1.42 (4.77)	2.14 (6.14)	0.47 (1.50)	1.08 (4.30)	1.87 (5.43)	3.15 (7.32)	1.01 (4.00)	0.42 (0.78)
EXiT Total	1.63 (5.11)	1.76 (5.16)	2.40 (6.34)	0.75 (2.33)	1.42 (4.55)	2.05 (5.75)	3.15 (7.32)	1.4 (4.49)	0.42 (0.78)
Errors	3.08 (5.60)	3.00 (4.23)	3.34 (5.37)	2.61 (3.98)	3.31 (5.48)	2.69 (3.92)	2.84 (3.62)	3.23 (5.38)	1.85 (1.77)

5.4 Discussion

The primary purpose of the current study was to examine EXiT physiological—systolic and diastolic BP and HR $_{\%max,}$ performance— agility task completion time and errors, and clinical— symptoms and RPE, outcomes across age, sex, BMI, and sport-type subgroups among a sample of healthy adolescents and adults. We hypothesized that adults would have faster completion time than adolescents, and males compared to females across agility tasks, but remaining physiological, performance, and clinical outcomes would be similar between age and sex comparisons. We also hypothesized that BMI and sport-type groups would have similar physiological, performance, and clinical outcomes. Our findings failed to reject the null hypothesis for age, adults and adolescents had equivocal completion time for all agility tasks, however, adolescents had greater post-EXiT systolic BP and lower HR $_{\%max}$ following BT, SHUF, and CAR tasks than adults. Our findings rejected the null hypothesis for sex as males were faster than females across 4 (of 5) agility tasks. The results also support our hypothesis of similar physiological and clinical EXiT outcomes. Additionally, the current findings support the hypothesis that EXiT physiological, performance, and clinical outcomes would be similar across BMI and sport-types. A key finding from this study is that HR $_{\%max}$, endorsed symptoms, and perceived effort throughout and upon completing the aerobic and dynamic components are not affected by age, sex, BMI, or sport-type.

Among our findings, adolescent and adults had similar SHUF, CAR, ZZ, and PA completion time, and less time to complete consecutive AA trials. This finding is in disagreement wither earlier work suggesting older age is associated with faster agility task and functional testing performances among adolescent soccer [174, 177], football [173], and volleyball [178] athletes. Perhaps, adolescents had similar physical fitness characteristics as adults, most adolescents were routinely engaged in cardiovascular conditioning as part of sport participation whereas most adults

were recreationally active. The dynamic component had intermittent rest periods (30-60 sec), and individuals with greater aerobic capacity or physical fitness will be better able to recover during rest periods and sustain perform throughout all agility tasks. [175, 196, 197]. In addition, males were also statistically faster than females for most agility tasks, but only the PA task had a significant difference that extended beyond the minimal detectable change. This finding may be due to potential differences in neuromuscular strength [198] and power [199, 200]. However, male and female sex had equivocal heart rate responses during EXiT in addition to post-EXiT heart rate and blood pressure, and builds upon evidence to suggest that EXiT physiological outcomes are generalizable to male and female sex [188, 189]. Lastly, the current study included participants from non-contact, contact, and collision sport-types and based on our findings, sport-type did not have affect EXiT physiological, performance, or clinical outcomes.

Our findings revealed all subgroups exceeded 80% of HR $_{\%max}$ following the aerobic, and 90% HR $_{\%max}$ following the dynamic components. Certainly, attaining these exercise intensities may be detrimental acutely after SRC due to ongoing neurometabolic crisis and secondary inflammatory response to injury [116]. But following a progressive exertion regimen and recovery period it is plausible to suggest that high intensity (HR $_{\%max}$: 75-95%) exertion can cause symptom recurrence with unresolved SRC and inform clinical decision making. These findings build upon staged progressive treadmill protocols to screen for exertional intolerance post-concussion [95, 96], and support the benefits of integrating evidence-based exertion prescription recommendations into clinical research [2](EXiT 1, chapter 4) [128, 129]. In addition, the prevalence of individuals exceeding symptom cut-off scores for aerobic and dynamic components were similar for age, sex, BMI, and sport-types. For total EXiT, females and non-contact sport participants were less likely to exceed total EXiT minimal detectable change values established with the current sample

(Chapter 4), the role of EXiT endorsed symptom cut-off scores among patients at RTP/A are uncertain at this time. Future work should consider the prevalence of exceeding clinical cut-offs among uninjured and recently recovered athletes from SRC to improve the interpretation of normal and abnormal responses to structured exertion. Lastly, future studies examining aerobic and dynamic exertion post-SRC should consider potential sex-related differences in aerobic capacity [201], neuromuscular strength and power [198-200] and agility performance [176, 179-181, 202] that may influence EXiT performance outcomes.

Limitations

Firstly, physical fitness characteristics such as body fat composition, cardiorespiratory fitness, muscular strength, and flexibility were not examined, and it is unknown if potential differences between these factors contributed to our findings. Endorsed symptoms and effort after EXiT tasks may be subject to recall bias. In addition, the current study had a limited number of non-contact sport athletes and the findings might not be generalizable to all sports and activities. Although the BMI comparison was based on median (50^{th} percentile among adolescents), a vast majority of participants in the current study were predominately in healthy BMI ranges and we did not specifically examine individuals excessively under- or overweight, and our findings may not be generalizable to obese individuals. Lastly, all participants were instructed to completed EXiT components to best effort and participant motivation was not controlled for and should be considered in our findings.

Conclusion

The EXiT is a brief, objective, and clinically intuitive approach to inform RTP/A medical clearance decisions for physically active adolescents and adults following SRC recovery. Age, sex, BMI, and sport-type had minimal effect on physiological, performance, and clinical outcomes of

EXiT, and support the use of combined aerobic and dynamic structured exertion as part of a comprehensive evaluation to determine medical clearance from SRC. Medical professionals can administer EXiT without sophisticated equipment, staffing, or facilities, and apply recently established cut-off scores for endorsed symptoms across a broad clinical population to identify patients with unresolved concussion impairments.

6.0 MANUSCRIPT 3: COMPARISON OF DYNAMIC EXERTION TESTING (EXIT) OUTCOMES IN ATHLETES CLEARED FOR RETURN TO PLAY/ACTIVITY FOLLOWING SPORT-RELATED CONCUSSION AND MATCHED HEALTHY ATHLETES

BACKGROUND: Dynamic exertion testing (EXiT), which involves aerobic and dynamic exercises that evaluate vestibular, autonomic, and ocular subsystems, was developed to help inform return to play/activity (RTP/A) decision making following sport-related concussion (SRC). One of the key tenets to the success of the EXiT is to establish that objective outcomes (e.g., performance, heart rate variability [HRV]) normalize in previously injured athletes. However, researchers have yet to examine performance and ultrashort (<5 min) HRV in recently concussed athletes who have been medically cleared for RTP/A and healthy athletes.
PURPOSE: Compare EXiT physiological— age estimated percentage of heart rate (HR $_{\%max}$) and blood pressure (BP), performance— agility task completion time and errors, and clinical— endorsed symptoms and rating of perceived exertion outcomes in addition to HRV outcomes between athletes at medical clearance to RTP/A from SRC with healthy athletes.
METHODS: A sample of 46 (43.5% female) athletes including 23 recently concussed athletes medical cleared for RTP/A (CONCUSS) and 23 sex-, age-, and sport-matched healthy athletes (CONTROL) of similar height, weight, and body mass index participated in the study. Participants completed the EXiT, a ~20-min exertion assessment involving a 12 min treadmill run (Aerobic component) and DYN; dynamic circuit (CIRC), ball toss (BT), box-drill shuffle (SHUF) and carioca (CAR), zig zag (ZZ), pro agility (PA), and arrow agility (AA) tasks (Dynamic component). Participants reported on a 0-10 Likert-type scale for headache, dizziness, and nausea symptoms, and RPE on a Borg scale (6-20) prior to and throughout each components of the EXiT. The EXiT also includes a 5-min seated rest prior to and following the testing. The final 3-min of pre- and post-EXiT rest periods were used to calculate the HRV outcomes: root-mean-square of the successive differences (RMSSD) and standard deviation of successive heart beats (SDNN). Group comparisons were examined with independent samples t-tests for agility task completion time and HR, and Mann-Whitney U tests were utilized for symptoms, RPE, and errors. ANOVAs were conducted to compare CONCUSS and CONTROL groups on RMSSD and SDNN outcomes across time points (pre- and post-EXiT rest periods).
RESULTS: The CONCUSS group had faster ZZ completion time (MD [95%]: -2.72 [-5.41, -0.02], p=0.048;) and PA (-0.69 [-1.27, -0.12], p=0.018) tasks and lower symptom severity (p=.019) during DYN component; SHUF, CAR, and AA completion time, HR, total symptoms, and RPE were similar between groups p>.05). The CONCUSS group had lower HRV SDNN (F=4.569, p=.047, η_p^2=. 212) and RMSSD (F=4.517, p=.049, η_p^2=.=.209) than controls
CONCLUSION: Overall, EXiT agility task completion time, symptoms, RPE, and errors were equivocal between patients returning to sport after SRC and healthy controls. However, our preliminary findings also indicate differences in ultrashort HRV immediately following EXiT between athletes at clinical recovery from SRC and healthy controls. Future work should consider the role of ANS observation post-exertion to improve medical clearance decision making. This study contributes to the growing evidence of the clinical utility of EXiT to inform RTP/A readiness following SRC recovery.

6.1 Introduction

In response to recommendations to improve return to sport paradigms for concussion set forth by the American Medical Society for Sports Medicine [5], dynamic exertion testing (EXiT) was developed to inform return to play/activity (RTP/A) decision making (EXiT #1). The EXiT is comprised of aerobic (treadmill running), and dynamic (head-body movements and agility tasks) components that enable the collection of physiological— age-estimated heart rate (HR $_{\%max}$) and blood pressure data, performance (agility task completion time and errors), and clinical (endorsed symptoms and rating of perceived exertion (RPE)) data. An initial report of EXiT concluded that physiological, performance, and clinical outcomes were similar between athletes at medical clearance to RTP/A and healthy athletes (EXiT #1). More recently, these outcomes were shown to be reliable and generalizable to a diverse sample of varying ages, sexes, and sport-types (Chapter 4/5). Although these studies suggest EXiT as a useful clinical assessment to inform RTP/A decision making, medical clearance decisions require a comprehensive multifaceted evaluation of the subsystems commonly employed during sport participation [5, 33].

Previous research examining cerebrovascular alterations across rodent models and human case series [20, 52, 53, 60] suggest underlying impairments to the autonomic nervous system may contribute to the clinical presentation of SRC [84, 125, 171, 203-207]. The autonomic nervous system is comprised of the sympathetic, and parasympathetic nervous systems which synergistically modulate heart rate and blood vessel diameter to supply oxygen and nutrients to the brain and other body regions in response to physiological stressors [61, 63, 65, 208, 209]. Heart rate variability (HRV), a proxy of autonomic nervous system function [67, 79, 210, 211], is the variation of successive heart beats (R-R interval) and suggested to be a viable method to detect physiological impairments following traumatic brain injury [59, 62, 74, 79, 210, 212, 213].

Moreover, observing HRV in response to postural changes or structured exertion may be a more sensitive approach to evaluate autonomic nervous system functioning than resting conditions [73, 84, 125, 171, 203-206, 213-215]. For instance, HRV during a 5-minute resting period was similar between uninjured collegiate athletes with a previous concussion (n=41; 5-43 months post-concussion) and those without (n=69) [216], but athletes 25.5 days post-SRC had an altered heart rate and blood pressure response during repeated sit-to-stand maneuvers that were undetected during a 5-min seated rest period compared to 11 sport- and sex- matched controls [213]. More recently, the standard deviation of successive heart beats (SDNN) and the root-mean-square of differences between successive R-R intervals (RMSSD) from ultrashort HRV recordings (e.g., 30- and 60- seconds) have a high agreement (ICC>.90) with longer sampling periods following maximal exertion[81, 82]. Additionally, the SDNN and RMSSD are robust to alterations in respiration rate and may be a sensitive HRV outcome following concussion recovery [79-82]. Taken together, ultrashort HRV may be able to ensure autonomic nervous system functioning has resolved from SRC and facilitate RTP/A decision making [84, 215]. However, the HRV responses to EXiT at medical clearance are unknown.

To date, physiological, performance, and clinical EXiT outcomes have been shown to be reliable and generalizable to a heterogeneous population (Chapters4/5). However, no studies have determined if EXiT performance and HRV outcomes are similar between recently concussed athletes upon medical clearance to RTP/A with healthy athletes. Thus, the purpose of the current study was to compare athletes at medical clearance to RTP/A with sex, age, and sport matched healthy athletes across pre-and post-EXiT ultrashort HRV and EXiT physiological (heart rate and blood pressure), performance (agility task completion time and committed errors), and clinical (endorsed symptoms and RPE) outcomes. Since athletes being cleared to RTP/A undergo a

comprehensive evaluation including the successful completion of EXiT, we hypothesized that athletes upon medical clearance to RTP/A would have similar EXiT physiological, performance, and clinical outcomes when compared to sex, age, and sport matched healthy athletes.

6.2 Methods

6.2.1 Experimental Design and Participants

We employed a matched case-control study design comprised of participants obtained from a random, sample of recreational and competitive athletes from a heterogeneous sport population residing in the Pittsburgh, PA community. More specifically, we enrolled healthy physically active (based on ACSM guidance for weekly moderate or vigorous activity [described in more detail below]) healthy controls. We also enrolled a sample of adolescent and adult patients upon medical clearance to return to play and activity following concussion recovery (CONCUSS) at an outpatient multidisciplinary concussion clinic.

6.2.1.1 Inclusion Criteria

CONTROL participants

a) Aged 14¬35 years
b) Fulfilled ACSM's guidelines for regular aerobic activity (30 minutes of moderate-intensity exertion 5 days per week or 20 minutes of vigorous exertion 3 days per week).

CONCUSS participants

a) Aged 14¬35 years

b) Fulfilled ACSM's guidelines for regular aerobic activity (30 minutes of moderate-intensity exertion 5 days per week or 20 minutes of vigorous exertion 3 days per week) prior to injury.
c) Diagnosed with an SRC within 14 days of injury.
d) Recently cleared to resume unrestricted sport participation after a trained clinician from UPMC Sports Medicine Concussion Program has interpreted neurocognitive, vestibular, and clinical interview outcomes and completed EXiT under direction of exertion physical therapist.

6.2.1.2 Exclusion Criteria

CONTROL participants

a) Suffered a prior concussion within 6 months.
b) More than 2 previously diagnosed concussions
c) History of brain surgery or TBI (based on Glasgow Coma Scale of <13)
d) History of neurological disorder (seizure disorder, epilepsy, brain tumors or malformations)
e) Current history of preexisting vestibular disorder benign paroxysmal positional vertigo (BPPV), labyrinthitis or vestibular neuritis
f) Previous diagnosis of ocular motor condition (e.g., ocular motor apraxia)
g) Currently taking anticoagulant, beta-blockers, and anticonvulsant prescription medication
h) Incapable of treadmill running at speeds up to 11.27 km/h (7.0 mph) and 13.67 km/h (8.5 mph) for females and males, respectively (based on assessment parameters)
i) Diagnosed with a cardiac, peripheral, or cerebrovascular disease (type 1 or 2 diabetes, or renal disease)

j) Pregnant

k) Experienced chest pain or shortness of breath while at rest or with mild exertion.

l) Lose balance because of dizziness (aside from concussion) or lose consciousness from exertion.

m) Diagnosed with or taking medication for a chronic medical condition.

n) Currently or recent (within 12 months) physical impairment exacerbated by physical activity, leading to the inability to complete 30 minutes of moderate to vigorous exercise.

o) Self-reported any exclusionary criteria from the Preparticipation Activity Questionnaire (PAR-Q), ACSM's formal screening to safely conduct submaximal exertion:

- Previous diagnosis of a heart condition or high blood pressure
- Pain in chest of shortness of breath at rest or activities of daily living
- Currently have a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be worsened by exertion.
- Been told by a doctor to only conduct physical activity under medical supervision.

<u>CONCUSS participants</u>

a) Suffered a prior concussion within 6 months (excluding current injury)

b) More than 2 previously diagnosed concussions (excluding current injury)

c) History of brain surgery or TBI (based on Glasgow Coma Scale of <13)

d) History of neurological disorder (seizure disorder, epilepsy, brain tumors or malformations)

e) Current history of preexisting vestibular disorder benign paroxysmal positional vertigo (BPPV), labyrinthitis or vestibular neuritis

f) Previous diagnosis of ocular motor condition (e.g., ocular motor apraxia)

g) Currently taking anticoagulant, beta-blockers, and anticonvulsant prescription medication
h) Incapable of treadmill running at speeds up to 11.27 km/h (7.0 mph) and 13.67 km/h (8.5 mph) for females and males, respectively (based on assessment parameters)
i) Diagnosed with a cardiac, peripheral, or cerebrovascular disease (type 1 or 2 diabetes, or renal disease)
j) Pregnant
k) Experienced chest pain or shortness of breath while at rest or with mild exertion.
l) Lose balance because of dizziness (aside from concussion) or lose consciousness from exertion.
m) Diagnosed with or taking medication for a chronic medical condition.
n) Currently or recent (within 12 months) physical impairment exacerbated by physical activity, leading to the inability to complete 30 minutes of moderate to vigorous exertion.
o) Self-reported any exclusionary criteria from the Preparticipation Activity Questionnaire (PAR-Q), ACSM's formal screening to safely conduct submaximal exertion:
    - Previous diagnosis of a heart condition or high blood pressure
    - Pain in chest of shortness of breath at rest or activities of daily living
    - Currently have a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be worsened by exertion.
    - Been told by a doctor to only conduct physical activity under medical supervision.
p) Diagnosed with a concussion more than 14 days after injury,
q) Concussion occurred outside recreational or sport participation (e.g., car crashes, falls, or other accidents),

r) If the injury occurred more than 90 days prior to the RTP/A evaluation as the recovery timeline for these individuals is beyond the typical course of recovery [1].

6.2.1.3 Sample Size Estimation

All sample size calculations were conducted with G*Power 3.0.10 (Franz Faul, Universität Kiel, Germany) [130]. Based on previous findings that compared low and high frequency HRV variables among 11 post-SRC athletes at medical clearance with 7-sport matched controls, and a priori alpha=.05, effect size=0.5, we determined that 24 participants (12 age-, sex-, and sport-, matched controls will achieve 80% power when comparing HRV outcomes between CONCUSS and CONTROL groups.

6.2.2 Operational Definitions

6.2.2.1 Sport-Related Concussion

Concussion was defined as a "complex pathophysiological process affecting the brain, induced by biomechanical forces" as specified in the most recent consensus statement on concussion in sport[33]. In the current investigation to meet criteria for concussion diagnosis, there had to be: 1) evidence of a clear mechanism of injury; and 2) at least one acute sign (e.g., LOC, amnesia, and disorientation/confusion) and/or immediate physical symptom (e.g., headache, dizziness, and balance problems) following injury. All concussions were diagnosed by a neuropsychologist or sports medicine physician.

6.2.2.2 Medical Clearance

Medical clearance to resume unrestricted sport participation was determined by a multifaceted clinical evaluation utilizing cognitive, vestibular, ocular, and clinical interview results by a neuropsychologists or sports medicine physician, and successful completion of EXiT

administered by a physical therapist within the assessment's instructions. In accordance with international consensus[134], were required to 1) be symptom free at rest and following exertion; (2) neurocognitive performance within normative or baseline reliable change indices (RCI); and (3) resume pre-injury levels for sleep and physical activity tolerance.

6.2.2.3 Recovery Time

Number of days from concussion injury to medical clearance to resume unrestricted sport participation.

6.2.2.4 Sport-Type

Sport participation information was obtained from the demographic questionnaire and categorized based on the level of contact exposure: non-contact, contact (body-to-body contact allowed, but not purposeful), or collision (repeated, purposeful body-to-body contact) [135].

6.2.3 Instrumentation

6.2.3.1 Physiological Monitoring and Processing Equipment

The Equivital Life Monitor (AD Instruments, Colorado Springs, CO; USA) physiological monitoring system was used to quantify HR and linear accelerations in the -X, -Y, and -Z coordinates at a 256 Hz sampling rate [136-138]. Importantly, sampling rates over 200hz is an adequate sampling rate for HRV data acquisition [75]. A recent validation report concluded that the Equivital monitoring system is an appropriate tool to sensitively quantify physiological data [136], and its tri-axial accelerometer and heart rate accuracy is similar to well-established activity trackers [137]. Movement patterns and physiological data were transmitted to a nearby laptop running Lab chart software (ADI Instruments; Sydney Australia) [138] for processing.

6.2.3.2 Exertion Testing Equipment and Materials

- Treadmill (WOODWAY USA, Waukesha, WI),
- 10”- Agility Cones
- Metronome: A free to download application (Metronome beats, Stonekick, London UK)
- Stopwatch
- Test Cards (N=40) printed on 5”X8” card stock
- Digital scale (Health-o-Meter, Sunbeam Products Inc; McCook, Il, USA)
- Wall-mounted stadiometer (Seca; Chino, CA, USA)
- An open gym space approximately 5X8 meters with a slip-resistant surface in an environment-controlled facility

6.2.4 Measures

6.2.4.1 Dynamic Exertion Testing (EXiT)

EXiT is a 30-minute clinical assessment with aerobic and dynamic components (Appendix C.). The aerobic component is a high-intensity interval treadmill protocol that alternates between slow and fast treadmill running speeds (1:1 ratio) based on the 60% and 90% of the superior category (90th percentile) for aerobic capacity among 13-29 year old male and female sex [129]. The target intensities were then used in ACSM’s metabolic running equation to determine horizontal running speed:

$$VO_2 = 0.2*S + (0.9 *S*G) + 3.5 \quad (1)$$

where VO_2 is oxygen consumption [mL O_2/kg/min], S is the horizontal running speed (in meters per minute), and G is the percentage grade of the treadmill. Speed parameters underwent a brief pilot period and final adjustments to obtain a final protocol whereby females alternated

between 7.2 km/h (4.5 mph; 3.14 METs) and 11.27 km/h (7.0 m/h, 6.36 METs), and males' range between 8.85 km/h (5.5 mph; 5.21 METs) and 13.67 km/h (8.5 mph, 7.5 METs). Thus, participants completed a 2-minute warm up (Male: 5.5 mph, Female: 4.5 mph), followed by 30-second intervals of fast and slow running speeds (Male: 8.5/5.5 mph; Female: 7.0/4.5 mph) for 10 minutes. Participants were instructed to use support handles as necessary to maintain safety. Following the aerobic component, participants completed the dynamic component which consists of 2 functional movement tasks (Dynamic Circuit [CIR] and Ball Toss [BT]) and 5 Agility Tasks (Box Drill Shuffle [SHUF], Box Drill Carioca [CAR], Zigzag [ZZ], Pro Agility [PA], and Arrow Agility [AA]) to maximal effort (Appendix C). The CIR is a 3-exercise circuit comprised of squat jumps, side-to-side pushups, and ball rotations completed for 3 sets of 10 repetitions in synchronization with a metronome (25 beats/min) and a 30-second rest period between each cycle. The BT task was administered with the participant standing 2.5 meters in front of administrator. After administrator called 'left', or 'right', participant jumped and rotated 180° in the specified direction, caught a basketball tossed by the administrator, and tossed back before returning to the starting position for the next trial, and was repeated for 10 trials (5 jumps left and 5 jumps right) and after a 30-second rest, a second round was performed whereby administrator called direction (left or right) or 'Go' (no response) in a random sequence (completed 5 jumps left, 5 jumps right, and 2 distractors). Participants completed two trials of each agility task (30-sec rest between trials), which were hand-timed via stopwatch by the administrator. Valid EXiT tests, defined as completion of EXiT within the study parameters without assessment modifications, were included in the study.

EXiT Physiological Outcomes

- Resting systolic and diastolic blood pressure (measured in mmHg) were measured with the use of an automatic sphygmomanometer (Omron; Kyoto, Japan) during the pre- and post-EXiT 5-minute rest period. Heart rate, measured in beats per minute, was calculated for the percentage of age estimated (220-age) maximum HR ($HR_{\%max}$)[87].
- HR was recorded prior to (~5 min), during, and following (~5 min) exertion via a noninvasive heart rate monitor while participants were seated with arms supported and feet placed flat on the floor. During EXiT, heart rate was recorded upon the completion of each task.
- Heart rate variability, the beat-to-beat interval and suggested to be proxy of ANS functioning, is expressed in time and frequency domains. Specifically, time domain outcomes are determined by variations in the R-R interval, and frequency domain reflects the energy signal within a frequency band (Table 18).

Table 18 Time Domain and Frequency Domain Heart Rate Variability Outcomes

Outcome	Description
Time Domain	
RRm	Mean RR time interval (in milliseconds) between consecutive heartbeats
RRNN	Standard deviation of the RR interval
RMSSD	Sum of squared differences between successive R-R intervals
pRR50	Percent of R-R intervals greater than 50 milliseconds
Frequency Domain	
Total Power	Variance of all RR intervals
VLF	Power in the very low (<0.04 Hz) frequency range
LF	Power in the low (0.04-0.15 Hz) frequency range
HF	Power in the high (0.15-0.4 Hz) frequency range
LFnu	Normalized units of LF power divided by difference between total power and VLF
HFnu	Normalized units of HF power divided by difference between total power and VLF
LF: HF	Ratio of LF power to HF power

EXiT Performance Outcomes

- Agility task completion time was measured by the EXiT administrator via a hand-timed stopwatch. The fastest trial of each agility task was calculated except for Arrow Agility task due to the secondary cognitive task, thus both trials were analyzed.
- Errors were counted by the EXiT administrator. For the aerobic component, excessive pulling for 10 or more seconds or additional rest periods for greater than 10 seconds were counted as errors. During the dynamic component, CIR errors included improper form or inability to maintain pace with squats, pushups, or ball rotation exercises; and BT errors included a jump-turn in the wrong direction, inability to catch or toss ball back to administrator, or a jump committed after a 'Go' call were counted as errors. Errors were counted when a participant kicked a cone off the original placement, mis-navigated a cone, or did not hand-touch a cone when instructed to do.

EXiT Clinical Outcomes

- Headache, dizziness, and nausea concussion-symptoms were individually reported on a 0-10 Likert scale prior to EXiT and after completing the warmup (Post-warm up), the 5^{th} (Midpoint), and 10^{th} (End) intervals of the aerobic component and following the completion of each task of the dynamic component. Endorsed symptom were totaled within aerobic and dynamic components, and subsequently combined and an EXiT total symptom score.

- Rating of Perceived Exertion (RPE) was recorded on the 6-20 Borg scale, a valid measure of perceived effort (6 ‘no exertion at all’ to 20 ‘maximal effort’), prior to, throughout, and following EXiT [139].

6.2.4.2 Anthropometrics

Bodyweight (in kg) was measured using a digital scale (Health-o-Meter) and height (in cm) with a wall-mounted stadiometer (Seca) among healthy controls, and values were identified in the electronic medical record for concussed participants. Weight and height measurements were used to calculate body mass index (BMI= weight [kg] / height $[m]^2$) [140], and the upper (HI-BMI) and lower (LO-BMI) 50th percentile groups were determined as a function of age for adolescents [141] and median split of BMI for adults.

6.2.4.3 Concussion Injury Information

For CONCUSS participants, ImPACT, and VOMS assessment results and the date of SRC diagnosis and medical clearance to RTP/A were extracted from the electronic medical record by a member of the research team not involved in assessment administration or medical clearance decision making process.

6.2.5 Clinical Assessments and Questionnaires

6.2.5.1 Vestibular Ocular Motor Screening Tool

The Vestibular/ocular Motor Screening (VOMS) tool is a brief (~5min) clinically intuitive and valid assessment for vestibular and ocular motor impairments after concussion [142]. Participants reported on a 0-10 Likert scale (0 ‘none’ to 10 ‘severe’) prior to (pretest) and following each of the 7 VOMS sub-tests: smooth pursuits, horizontal saccades, vertical saccades, near-point of convergence, horizontal vestibular-ocular reflex, vertical vestibular-ocular reflex, visual motion

sensitivity; and NPC distance. Symptoms were totaled across all sub-tests (range: 0-240) whereby greater scores indicate worse symptom burden and may indicate dysfunction. Mucha et al reported that the VOMS components had high internal consistency (Cronbach $\alpha = .92$) and a multivariate logistic regression of the visual motion sensitivity, vestibular-ocular reflex, and convergence domains resulted in model that explained 61% of the variance of likelihood of concussion; a follow up receiver operator curve analysis demonstrated an area under the curve (AUC) value of 0.89 [142] when utilizing clinical cut-off scores defined as a symptom severity score of 2 or greater for any subtest or NPC distance of 5 or more cm.

6.2.5.2 Immediate Post-Concussion Assessment and Cognitive Testing & Post-Concussion Symptom Scale

Neurocognitive performance was assessed using the ImPACT battery in a private testing area[123, 143-145]. The neurocognitive assessment comprises six neurocognitive test modules to populate verbal memory, visual memory, motor processing speed, and reaction time composite scores. Prior to the neurocognitive test, participants completed a sport, academic, and medical history questionnaire on a standardized form (Appendix C).

The PCSS is a reliable self-report survey consisting of 22 items rated on a 0-6 Likert-scale (0 ‘none’ to 6 ‘severe’), the total symptom severity score is calculated (range: 0-132) whereby greater scores indicate worse symptom burden [146].

6.2.6 Experimental Procedures

6.2.6.1 Recruitment and Consent

For CONTROL participants, recruitment was conducted through word of mouth, posted fliers, and online advertisement (Pitt + Me), and if deemed eligible during in-person or phone screening were scheduled for a study visit at the Neuromuscular Research Laboratory-Warrior

Human Performance Research Center. CONTROL participants were also instructed to a) avoid ingesting food, alcohol, or caffeine or tobacco products within 2 hours of assessment; b) avoid vigorous exertion the day prior to and day of assessment; c) Wear clothing and footwear to permit athletic movements; and d) drink plenty of fluids the 24-hour period before enrollment. CONCUSS participants were directly identified at the UPMC Sports Medicine Concussion Program outpatient concussion clinic by a treating clinician upon medical clearance to resume sport participation.

All participants received a thorough explanation of the study overview, procedures, and potential risks of participation prior to signing consent forms. Since EXiT was part of routine clinical practice to inform return to play, CONCUSS participants completed EXiT before being introduced to the study and (if enrolled) provided consent/assent to use EXiT results embedded within the electronic medical record and physiological data temporarily stored on a laptop.

6.2.6.2 Equipment Fitting and Physiological Measurements

Participants wore noninvasive heart rate monitor (i.e., Polar or Equivital strap) to capture heart rate, respiration rate, skin temperature, and accelerations in the X, Y, and Z directions during EXiT. Resting physiological measures (blood pressure [BP] and heart rate [HR]) were obtained with participant seated with back supported and feet placed flat on the floor. Pre-EXiT measurements were obtained after a 5-minute resting period whereas post-EXiT measures were collected upon returning to the private examination room (~1-5 min) but varied across the sample as some individuals requested additional time for hydration.

6.2.6.3 EXiT Administration

All participants completed clinical assessments (ImPACT, PCSS, and VOMS) prior to EXiT in a private examination area. One physical therapist administered EXiT to CONCUSS participants, and one certified athletic trainer administered EXiT to healthy CONTROL

participants. Heart rate, agility task completion time, errors, symptoms, and effort were recorded on a standardized report sheet (Appendix C). All study procedures were approved by the University of Pittsburgh Institutional Review Board

6.2.6.4 Data Reduction

For all aims, Body Mass Index ([BMI]= weight [kg]/height[m]^2) and the lowest (fastest) time between consecutive agility task trials were calculated.

A team member trained in the cleaning and processing procedures examined Equivital recordings for completeness and identified periods of movement and rest and calculated raw (HR_{raw}) and percentage of age estimated (220-age) maximum HR ($HR_{\%max}$)[87]. The fastest trial of each agility task was calculated with the exception of Arrow Agility task due to the secondary cognitive task, thus both trials were analyzed [88]. Endorsed headache, dizziness, and nausea symptoms were subtotaled within aerobic and dynamic components, and subsequently combined to populate EXiT total symptoms.

The final 3-minute sampling period was used for HRV outcomes. Time (RRm, RRNN, RMSSD, pRR50) and frequency (Power, VLF, LF, HF, LFnu, HFnu, and LF: HF) domain variables were calculated with Lab Chart software (AD Instruments). Although RMMSD and RRNN were primary HRV outcomes for the current investigation, all HRV variables were reported in accordance with expert recommendations[76] Statistical outliers (>3 standard deviations) for HRV outcomes were excluded from analysis.

6.2.6.5 Statistical Analyses

Independent samples t-tests were conducted for continuous (e.g., age, BMI, etc.), and chi-squared (χ^2) with odds ratio (OR) values for nominal (e.g., sex, sport type, etc.) demographic variables to compare groups. Independent samples t-tests were conducted for $HR_{\%max}$, BP, and

agility task completion time, and Mann-Whitney U tests for RPE, symptoms, and errors between age, sex, and BMI, groups across aerobic and dynamic components. Significance for all analyses were set at p=.05 and magnitude of differences between groups was interpreted with Cohen's d as small (d=0.2), medium (d=0.5), and large (d=0.8) effect sizes[132]. To determine the equivalence of EXiT HR $_{\%max}$, BP, and agility task completion time between CONCUSS and CONTROL groups, the MDCs (from Chapter 4) were used to determine upper and lower bounds for each variable and visually inspected with the 95% confidence interval surrounding mean difference. Specifically, if the 95% range of the mean difference between groups was within the -MDC and +MDC for that variable, the groups were equivalent[151].

A series of 2X2 (GROUP X TIME) mixed model ANOVAs were conducted to compare CONCUSS and CONTROL groups for time (RRm, RRNN, RMSSD, pRR50) and frequency (Power, VLF, LF, HF, LFnu, HFnu, and LF: HF) HRV outcomes across pre- and post-EXiT timepoints. Any violations of sphericity underwent a Greenhouse-Geisser correction. All post-hoc pairwise comparisons underwent a Bonferroni statistical correction to reduce type I error likelihood, and all analyses were conducted with 26th version of SPSS (IBM Statistics).

6.3 Results

6.3.1 Demographics and Clinical Outcomes

From the entire study sample, 23 (25%) of 92 healthy control participants were matched by age, sex, and sport-type with 23 (37.1%) CONCUSS participants, and groups were of similar height, weight, BMI, and prevalence of individuals below 50th BMI-percentile (p>.05, Table 19). CONCUSS participants were diagnosed a mean 4.91 ± 3.25 (range: 1-14) days after SRC and

completed EXiT 18.52 ± 12.34 (range: 7-51) days after SRC. Those in the CONCUSS group were 5.35 times more likely to report a history of migraine (χ^2 (1) =6.769, p=.009, 95% CI: 1.09-58.93), but previous diagnosis of concussions or learning disabilities were equally distributed between groups (p>.05). For HRV analyses, 6 CONCUSS and 1 CONTROL participants were statistical outliers or unable to maintain a stationary 5-minute resting period prior to or following EXiT. Since HRV data acquisition was a supplementary procedure to routine clinical care, some patients were unable to fulfill an entire 5-minute stationary resting period due to clinic scheduling, data processing of these participants revealed a substantial number of irregular RR intervals captured in the 3-minute sample, and were statistical outliers (>3 SDs) from the remaining sample In these instances, both statistical outliers and their corresponding matched participant were excluded from analysis. CONCUSS and CONTROL groups were of similar height (172.21 ± 8.89 vs 172.03 ± 10.32), weight (68.77 ± 13.25 vs 61.80 ± 12.71), and BMI (22.92 ± 2.99 vs 20.89 ± 4.00), and similar prevalence of individuals with a previous diagnosis of concussion or learning disability (p>.05).

Table 19 Mean and Standard Deviation (M ± SD), Frequency (Percentage) and Comparison Statistics Across Demographic Variables Between CONCUSS (N=23) and CONTROL (N=23) Groups.

Variable	CONCUSS (N=23)	CONTROL (N=23)
Age (in years)	16.34 ± 2.26	16.34 ± 2.26
Height (cm)	170.66 ± 11.1	169.5 ± 6.92
Weight (kg)	65.57 ± 11.83	61.72 ± 14.29
BMI	22.17 ± 2.12	21.38 ± 4.30
BMI 50% -low	15 (69.6%)	16 (65.2%)
Female Sex	10 (56.5 %)	10 (56.5 %)
Sport		
Soccer	8 (34.8%)	8 (34.8%)
Ice Hockey	4 (17.5%)	4 (17.5%)
Football	3 (13.1%)	3 (13.1%)
Basketball	2 (8.7%)	2 (8.7%)
Volleyball	2 (8.7%)	2 (8.7%)
Softball	1 (4.3%)	1 (4.3%)
Wrestling	1 (4.3%)	1 (4.3%)
Gymnastics/Cheer	1 (4.3 %)	1 (4.3 %)
Swimming/Diving	1 (4.3 %)	1 (4.3 %)
Migraine/Headache History*	8 (34.8 %)	1 (4.3%)
Attention-Deficit/ Hyperactivity Disorder or Learning Disability	3 (13.0%)	1 (4.3%)
Previously Diagnosed Concussions (1 or 2)	4 (17.4%)	8 (34.8%)

* p=.009

Across ImPACT and VOMS outcomes, the CONCUSS group had worse visual memory composite score (t= -2.7, p=0.009; MD [95%]: -9.04 [-15.78, -2.31]) and lower NPC distance (t=-2.61, p=0.012; MD [95%]: -1.25 [-2.22, -0.28]) (Table 20) but verbal memory, processing speed, and reaction time composites and all symptoms outcomes of VOMS were similar between groups (p>.05).

Table 20 Mean and Standard Deviation and Median [Interquartile Range] and Comparison Statistics Across ImPACT and VOMS Outcomes Between CONCUSS (N=23) and CONTROL (N=23) Groups.

Outcome	CONCUSS	CONTROL

	Mean ± SD	Median [IQR]	Mean ± SD	Median [IQR]
Immediate Post-Concussion Assessment and Cognitive Testing				
Verbal Memory	90.00 ± 8.43	91.5.0 [13.50]	94.13 ± 6.39	96.00 [10.00]
Visual Memory [a]	77.90 ± 12.50	77.00 [19.75]	86.95 ± 9.79	90.00 [18.00]
Motor Processing Speed	40.23 ± 6.69	39.22 [11.31]	43.70 ± 5.94	42.78 [10.05]
Reaction Time	0.58 ± 0.14	0.59 [0.13]	0.59 ± 0.07	0.58 [0.11]
Impulse Control	3.63 ± 2.71	2.00 [3.25]	5.69 ± 3.88	5.00 [6.00]
PCSS Total Score	1.63 ± 2.98	0.50 [2.00]	3.17 ± 5.49	1.00 [5.00]
Vestibular-Ocular Motor Screening				
Baseline Symptoms	0.39 ± 1.30	0.00 [0.00]	0.34 ± 1.19	0.00 [0.00]
Smooth Pursuits	0.39 ± 1.30	0.00 [0.00]	0.34 ± 1.19	0.00 [0.00]
Horizontal Saccades	0.39 ± 1.30	0.00 [0.00]	0.34 ± 1.19	0.00 [0.00]
Vertical Saccades	0.39 ± 1.30	0.00 [0.00]	0.34 ± 1.19	0.00 [0.00]
Convergence	0.39 ± 1.30	0.00 [0.00]	0.47 ± 1.23	0.00 [0.00]
Horizontal VOR	0.39 ± 1.30	0.00 [0.00]	0.52 ± 1.30	0.00 [0.00]
Vertical VOR	0.39 ± 1.30	0.00 [0.00]	0.39 ± 1.19	0.00 [0.00]
VMS	0.47 ± 1.70	0.00 [0.00]	0.34 ± 1.11	0.00 [0.00]
NPC (cm) [b]	0.60 ± 1.26	0.00 [1.00]	1.86 ± 1.91	1.00 [3.67]
Total Symptoms	3.21 ± 10.83	0.00 [0.00]	3.47 ± 9.27	0.00 [1.00]

Abbreviation: NPC, Near Point of Convergence; PCSS, Post-concussion Symptom Scale; VOR, Vestibular-Ocular Reflex; VMS, Visual Motion Sensitivity
[a] p=.009, [b] p=0.012

6.3.2 EXiT Physiological, Performance, and Subjective Outcomes

Pre- and post-EXiT resting heart rate and blood pressure, in addition to HR recorded throughout aerobic and dynamic components were similar between CONCUSS and CONTROL groups (p>.05) (Table 21)

Table 21 Physiological Outcomes During EXiT Between CONCUSS (N=23) and CONTROL (N=23) Groups

Outcome		CONCUSS	CONTROL	T, sig; MD [95% CI]	MDC (Chapter 4)
Resting Physiological					
Pre-EXiT	Systolic BP	117.13 ± 17.89	115.95 ± 7.77	0.28, *p*=0.774; 1.17 [-7.02, 9.37]	14.70
	Diastolic BP	71.95 ± 11.99	72.21 ± 6.25	-0.09, *p*=0.926; -0.26 [-5.94, 5.42]	12.63
	HR_{Raw}	65.86 ± 9.12	68.39 ± 10.40	-0.87, *p*=0.386; -2.52 [-8.33, 3.29]	25.84
	$HR_{\%\ Max}$	32.34 ± 4.41	33.61 ± 5.33	-0.88, *p*=0.382; -1.27 [-4.18, 1.63]	12.93
Post-EXiT	Systolic BP	130.54 ± 19.63	132.73 ± 15.24	-0.41, *p*=0.676; -2.19 [-12.73, 8.34]	24.95
	Diastolic BP	72.59 ± 10.25	77.5 ± 10.37	-1.57, *p*=0.121; -4.9 [-11.18, 1.36]	12.53
	HR_{Raw}	121.54 ± 19.06	121.52 ± 16.19	0.00, *p*=0.996; 0.02 [-10.59, 10.64]	25.87
	$HR_{\%\ Max}$	59.66 ± 9.27	59.69 ± 8.07	-0.01, *p*=0.99; -0.03 [-5.25, 5.19]	12.97
Aerobic Component					
Pre-Standing Rest (0 min)	$HR_{\%\ Max}$	42.88 ± 7.23	41.24 ± 5.79	0.84, *p*=0.401; 1.63 [-2.25, 5.53]	14.20
Post-Warm Up (2 min)	$HR_{\%\ Max}$	69.79 ± 6.65	70.76 ± 7.68	-0.45, *p*=0.647; -0.97[-5.24, 3.29]	12.84
Midpoint (7 min)	$HR_{\%\ Max}$	82.09 ± 8.37	77.48 ± 12.02	1.5, *p*=0.138; 4.61[-1.54, 10.77]	13.37
Finish (12 min)	$HR_{\%\ Max}$	84.23 ± 8.02	83.28± 8.7	0.38, *p*=0.705; 0.94 [-4.08, 5.97]	13.12
Dynamic Component					
Dynamic Circuit	$HR_{\%\ Max}$	79.72 ± 7.86	74.39 ± 10.38	1.93, *p*=0.059; 5.33[-0.22, 10.88]	17.61
Ball Toss	$HR_{\%\ Max}$	78.08 ± 7.73	75.57 ± 9.1	1.00, *p*=0.319; 2.50 [-2.51, 7.52]	10.93
Box Drill Shuffle	$HR_{\%\ Max}$	83.41 ± 7.64	83.52 ± 8.01	-0.04, *p*=0.961; -0.11 [-4.76, 4.54]	13.34
Box Drill Carioca	$HR_{\%\ Max}$	83.3 ± 6.46	81.44 ± 8.32	0.84, *p*=0.403; 1.85 [-2.57, 6.28]	9.28
Zig Zag	$HR_{\%\ Max}$	87.9 ± 5.71	86.31 ± 7.48	0.81, *p*=0.421; 1.59 [-2.36, 5.55]	11.50
Pro Agility	$HR_{\%\ Max}$	85.55 ± 6.48	84.76 ± 6.91	0.40, *p*=0.69; 0.79 [-3.19, 4.77]	11.31
Arrow Agility	$HR_{\%\ Max}$	90.32 ± 4.63	89.61 ± 5.82	0.45, *p*=0.647; 0.71 [-2.41, 3.84]	6.25

Abbreviation: $HR_{\%\ max}$, percentage of age estimated heart rate; BP, Blood pressure; MD, Mean difference; MDC, Minimal detectable change

Mean HR during 3-minute sampling for HRV was equivocal between CONCUSS and CONTROL groups. Results of the mixed model ANOVAs revealed no significant interactions for any HRV outcome (p>.05). A main effect of TIME was observed for all HRV outcomes except for pNN50 and LF (%) Power (Table 22). We observed a main effect of GROUP and revealed greater LFnu (F=5.120, p=.037, η_p^2=.231) and HF % ($F_{2.341, 140.86}$ = 10.507 p<.001, η_p^2=.149), but lower SDNN (F=4.569, p=.047, η_p^2=.212), RMSSD (F=4.517, p=.049, η_p^2=.209), and HFnu

(F=6.782, p=.019, η_p^2=.285) than the CONTROL group. Pairwise comparisons revealed post-EXiT differences in Post-EXiT SDNN: (*t*=-2.553, *p*=.020; MD [95%]: -19.32 [-35.23, -3.422]) and RMSSD (*t*= -2.46, *p*=.042; MD [95%]: -18.54 [-36.23, -.85]), but not pre-EXiT SDNN and RMSSD). There were no differences across remaining HRV outcomes between CONCUSS and CONTROL groups.

Table 22. Heart Rate Variability Outcomes Between CONCUSS (N=13) and CONTROL (N=13) Groups And Results of Within Subjects ANOVA Prior to and Immediately Following EXiT

	Pre-EXiT			Post-EXiT			
Variable	Combined	CONCUSS	CONTROL	Combined	CONCUSS	CONTROL	F test (Time)
Mean HR	72.97 ± 9.48	72.4 ± 10.03	73.93 ± 9.12	114.27 ± 12.39	117.06 ± 9.80	109.49 ± 15.57	F=146.98, p<.001, η_p^2=.836
Included Beats	211.08 ± 37.11	208.92 ± 43.46	214.10 ± 27.84	329.37 ± 56.73	333.64 ± 60.67	323.40 ± 53.29	F=93.74, p<.001, η_p^2=.846
RRm	789.47 ± 216.39	765.04 ± 262.95	831.37 ± 102.29	532.71 ± 63.41	516.43 ± 42.83	560.61 ± 85.21	F=21.73, p<.001, η_p^2=.562
SDNN*	74.79 ± 24.58	69.67 ± 24.67	83.55 ± 23.57	23.68 ± 18.85	16.90 ± 5.75	35.30 ± 27.50	F=60.28, p<.001, η_p^2=.760
RMSSD*	58.21 ± 24.27	54.12 ± 25.77	65.23 ± 21.42	12.01 ± 15.89	5.52 ± 2.95	23.15 ± 22.65	F=48.54, p<.001, η_p^2=.740
pRR50	2.81 ± 8.09	4.34 ± 10.23	0.40 ± 0.17	0.02 ± 0.07	0.00 ± 0.00	0.05 ± 0.12	F=1.43, p=.322
Total Power (ms^2)	5564.63 ± 3512	5078.25 ± 3321.02	6398.42 ± 3936.74	273.21 ± 263.31	194.77 ± 185.31	407.67 ± 334.13	F=42.53, p<.001, η_p^2=.714
VLF (ms^2)	1580.69 ± 1378.02	1577.94 ± 1520.06	1585.41 ± 1208.59	261.89 ± 609.33	129.50 ± 122.37	488.83 ± 995.62	F=13.72, p<.002, η_p^2=.446
LF (ms^2)	2092.66 ± 1562.31	1981.46 ± 1311.28	2283.30 ± 2025.58	152.61 ± 255.66	54.07 ± 58.09	321.54 ± 370.4	F=26.73, p<.001, η_p^2=.611
HF (ms^2) *	1879.12 ± 1694.91	1497.73 ± 1340.86	2532.92 ± 2128.95	58.41 ± 22.14	69.01 ± 14.16	40.25 ± 22.20	F=18.81, p<.001, η_p^2=.525
LFnu*	55.36 ± 13.88	59.93 ± 10.9	47.51 ± 15.72	75.35 ± 19.81	80.56 ± 14.47	66.42 ± 25.43	F=57.16, p<.001, η_p^2=.771
HFnu*	44.15 ± 13.82	39.48 ± 10.97	52.15 ± 15.31	22.05 ± 17.03	16.37 ± 7.73	31.8 ± 24.18	F=28.08, p<.001, η_p^2=.623
LF: HF	1.45 ± 0.70	1.67 ± 0.63	1.07 ± 0.69	5.63 ± 4.05	6.40 ± 3.76	4.32 ± 4.48	F=16.31, p=.001, η_p^2=.490

Abbreviation: HF, high frequency; HFnu, high frequency normalized units; LF, low frequency; LFnu, low frequency normalized units; pRR50, % R-R intervals > 50 ms; RRMSSD, sum of squared differences between R-R intervals; RRm, mean RR interval; SDNN, standard deviation of RR interval; VLF, very low frequency

* Group Difference p<.05

During EXiT, the CONCUSS group also had lower (better) completion time for Zig Zag (MD -2.72, p=0.048) and Pro Agility (MD:0.69, p=0.018) tasks. The 95% CI of the mean differences for PA exceeded the MDC threshold, indicating the CONCUSS group was statistically faster and non-equivalent to the CONTROL group. Completion time for SHUF, CAR, and AA tasks were similar between groups (p>.05,Table 23)

Table 23. Agility Task Completion Time (in seconds) Between CONCUSS (N=23) and CONTROL (N=23) Groups

Outcome	CONCUSS	CONTROL	T, sig; MD [95%]	MDC (Chapter 4)
Box Drill Shuffle	21.99 ± 3.25	23.00 ± 3.43	-1.01, p=0.314; -1.00 [-2.99, 0.98]	6.40
Box Drill Carioca	14.42 ± 1.42	14.23 ± 1.58	0.44, p=0.659; 0.19 [-0.69, 1.09]	4.55
Zig Zag [a]	28.34 ± 4.78	31.06 ± 4.27	-2.03, p=0.048; -2.72 [-5.41, -0.02]	8.70
Pro Agility [b]	7.51 ± 0.84	8.21 ± 1.07	-2.45, p=0.018; -0.69 [-1.27, -0.12]	0.75
Arrow Agility Trial 1	39.77 ± 8.99	39.88 ± 4.90	-0.04, p=0.962; -0.01 [-4.40, 4.20]	5.85
Arrow Agility Trial 2	40.54 ± 4.36	41.44 ± 4.71	-0.66, p=0.506; -0.89 [-3.59, 1.80]	4.91

Abbreviation: MDC, Minimal Detectable Change
[a] p=0.048
[b] p=0.018

The CONCUSS group also reported lower symptom severity during the dynamic component (21.00 vs 26.00; U = 322.00, z = 2.338, p=.019), but aerobic symptoms and RPE during all EXiT tasks were similar between groups (p>.05; table X). The CONCUSS group was less likely to exceed dynamic component minimal detectable change scores than control group (χ^2 = 5.610; OR 95% CI: 0.44, 0.31-0.62, p=.018).

Table 24. Rating of Perceived Exertion and Endorsed Symptoms Between CONCUSS (N=23) and CONTROL (N=23) Groups

	CONCUSS		CONTROL	
Outcome	Mean ± SD	Median [IQR]	Mean ± SD	Median [IQR]
Rating of Perceived Exertion				
Pre-Standing Rest	6.00 ± 0.00	6.00 [0.00]	6.26 ± 0.75	6.00 [0.00]
Post Warm up	9.82 ± 2.60	9.00 [3.00]	8.82 ± 1.87	9.00 [3.00]
Midpoint	12.91 ± 2.95	13 [4.00]	12.39 ± 1.80	13.00 [2.00]
End	14.02 ± 3.23	15.00 [5.00]	14.26 ± 2.15	14.00 [3.00]
Dynamic Circuit	13.34 ± 2.93	14.00 [4.00]	12.95 ± 2.91	13.00 [5.00]
Ball Toss	11.26 ± 3.45	11.00 [7.00]	11.26 ± 3.00	11.00 [5.00]
Box Drill Shuffle	12.30 ± 3.32	12.00 [5.00]	12.13 ± 3.23	12.00 [5.00]
Box Drill Carioca	11.91 ± 3.13	12.00 [6.00]	11.86 ± 3.57	11.00 [7.00]
Zigzag	13.21 ± 3.32	13.00 [6.00]	13.34 ± 2.87	13.00 [5.00]
Pro Agility	12.82 ± 3.43	13.00 [5.00]	13.04 ± 3.02	13.00 [5.00]
Arrow Agility	15.04 ± 2.99	15.00 [4.00]	15.13 ± 2.43	15.00 [4.00]
Endorsed Symptoms				
Aerobic Component	0.34 ± 1.66	0.00 [0.00]	0.08 ± 0.41	0.00 [0.00]
Dynamic Component [a]	0.00 ± 0.00	0.00 [0.00]	1.91± 6.20	0.00 [0.00]
EXiT Total Symptom Severity	0.34 ± 1.66	0.00 [0.00]	2.00 ± 6.31	0.00 [0.00]

[a] p=.019
Abbreviation: IQR, Interquartile Range; SD, standard deviation;

Table 25. Frequency (Percentage) of Participants Exceeding Minimal Detectable Change Scores Across EXiT Components Across CONCUSS (N=23) and CONTROL (N=23) Groups.

Outcome	CONCUSS	CONTROL	Chi-square, sig OR [95%]
Aerobic	1 (4.3%)	1 (4.3%)	0.000, p=1.000 1.00 [0.06, 17.02]
Dynamic	0 (0%)	5 (21.7%)	5.610, ***p*=0.018** 0.44 [0.31, 0.62]
EXiT Total Symptoms	1 (4.3%)	3 (13.0%)	1.095, p=0.295 3.30 [0.32, 34.35]

6.4 Discussion

The purpose of current study was to compare physiological, performance, and clinical EXiT outcomes between athletes at medical clearance to RTP/A with sex-, age-, and sport-matched healthy athletes. Contrary to our hypothesis we observed lower SDNN and RMSSD after EXiT among athletes at medical clearance to RTP/A. However, remaining EXiT physiological— $HR_{\%max}$ and BP, performance— agility task completion time and errors, and clinical— endorsed symptoms and RPE outcomes were similar between athletes upon medical clearance to RTP/A and healthy athletes.

Growing evidence suggests that autonomic nervous system dysfunction can become elucidated following structured exertion that may be otherwise undetected under resting conditions [73, 211, 217]. In the current study, we observed similar HRV outcomes between athletes at medical clearance from SRC and healthy controls prior to exertion, but lower RMSSD, pNN50, and SDNN heart rate variability outcomes among the CONCUSS group following EXiT. Our findings are similar to reports of asymptomatic concussion patients with lower mean and SDNN,

RMSSD, and LF during a standing task [59, 63], and lower HR complexity during an isometric handgrip exercise compared to age, sport, and sex- matched healthy control athletes [214]. Although it is difficult to ascertain our findings across these investigations due to different sampling methods, duration, and type of exertion, our findings provide further evidence that physiological recovery may extend beyond the clinical recovery of SRC[59, 63, 214]. Additionally, alternative causes for our findings should be considered as greater sympathetic nervous system responses (lower HRV) have been observed among healthy adults due to residual physical deconditioning from injury [61, 72], or state arousal [77, 218] which may have occurred for patients upon completion of EXiT pending notification of medical clearance to return to sport. Additionally, the time course of parasympathetic nervous system reactivation and HR recovery post-EXiT is dependent on exertion intensity preceding the rest period with vigorous intensity associated with lower HRV for longer durations than low or moderate intensities [219]. Based on our findings, post-EXiT heart rate during HRV sampling was greater (but statistically similar) among the CONCUSS group and may have led to inconsistent HRV sampling between groups. We are unable to conclude if the differences in heart rate or HRV responses to EXiT were due to autonomic nervous system dysfunction or an artifact from between-group discrepancies in HRV sampling. Future work should consider the intensity and duration of exertion in addition to the time course post-exertion for HRV sampling. The potential effects of psychological state may have also affected our findings and should be considered in future investigations of autonomic nervous system functioning post-SRC.

Overall, athletes completing EXiT upon medical clearance to RTP/A had similar heart rate and blood pressure responses, agility task completion time, committed errors, and perceived exertion and lower total symptoms as healthy controls. In fact, CONCUSS group was statistically

faster than CONTROL group for zig zag and pro agility tasks, but had similar completion times for SHUF, CAR, and AA tasks. These findings build upon earlier work that revealed similar physiological, performance, and clinical EXiT outcomes between athletes at medical clearance with healthy athlete (EXiT #1). The current study took a superior methodological approach to assure group equivalency by matching participants between groups by age-, sex-, and sport-type, while also examining HRV prior to and following EXiT. Thus, it was not surprising that most comparisons were equivocal between groups. Although groups performed similarly on most agility tasks, we observed faster ZZ and PA tasks by the CONCUSS group, this finding can be partly explained by greater effort by the CONCUSS group. These individuals may have had greater motivation to complete EXiT to resume sport participation. However, completion times for remaining agility task were similar between groups and demonstrate that athletes completing EXiT upon medical clearance following SRC recovery have similar objective and subjective outcomes as healthy athletes. These findings provide preliminary concurrent validity for EXiT outcomes.

Based on group mean scores, the CONCUSS group had worse visual memory ImPACT composite score than the CONTROL group. All patients were medically cleared based on the comprehensive evaluation including neurocognitive, vestibular ocular screening, and completion of EXiT in accordance with routine clinical practice. In addition, in an earlier report comparing EXiT outcomes between patients at RTP/A and healthy controls (without matching) revealed a lower symptom severity for dynamic component and EXiT total score (EXiT #1). In the current study, healthy athletes were more likely to exceed clinical symptoms cut-offs than athletes at medical clearance during the dynamic component whereas the aerobic component and total EXiT symptoms were equivocal between groups. These findings contribute to the growing evidence of

tolerable symptom provocation during structured exertion [104, 109, 183] (EXiT #1, Chapters 4-5).

Limitations

The current study is limited in sample size and may not be reflect the heterogeneous clinical subtypes of concussion due to individualized responses to injury. Despite sufficient sample sizes for HRV outcomes, post-SRC impairments are heterogeneous and there exists the likelihood that a subset of individuals experienced persistent autonomic nervous system dysfunction. Future research with EXiT would benefit from evidence suggesting the prevalence of autonomic nervous system dysfunction across clinical subtypes. We were unable to control for motivation and effort which may have also contributed to our findings. In addition, individuals that obtained medical clearance greater than 90 days from SRC or non-sport related injuries were excluded, so our findings are not applicable to athletes returning to sport following more prolonged recoveries or injuries sustained from motor vehicle collisions, falls, assaults, and accidents. The current study required a 4-hour period of abstaining from caffeine whereas a 12-hour period has been recommended for HRV investigations[76], and participants may have had caffeine or other substances that may have influence physiological responses to exertion. Lastly, HRV was sampled during the 5-minute prior to and following a ~20-minute exertion assessment and most stressors in ANS research are short-duration tasks (e.g., standing, isometric handgrip, etc.), it is unknown if the HRV responses are a reliable and robust measure of ANS functioning post- EXiT.

Based on these findings, EXiT is a generalizable and objective approach to inform return to play/activity decision making following SRC recovery. Additionally, there is a need to further investigate the etiology of subjective responses during structured exertion to improve the clinical interpretation of exceeding minimal detectable change scores for endorsed symptoms. Future

studies should examine the potential causes for symptoms during provocative movements whilst controlling for exertion type, intensity, and duration to further inform clinical research for exertion-based interventions for SRC [86, 116]. An examination of the EXiT physiological, performance, and clinical outcomes among patients following prolonged recoveries is also of interest.

Conclusion

Determining safe RTP/A following SRC remains a clinical decision that should be guided by interview and comprehensive evaluation of inter-related brain functioning subsystems. Compared to sport-, age-, and sex-matched controls, athletes at medical clearance to RTP/A had equivocal heart rate and blood pressure responses, faster (better) or similar agility task completion time and errors, and similar symptoms and perceived exertion throughout EXiT. Preliminary evidence supports EXiT as an objective screening of concomitant autonomic, vestibular, and ocular subsystems, and can provide objectivity to current approaches to inform clinical decision-making regarding readiness for RTP/A after SRC.

7.0 SUMMARY AND FUTURE DIRECTIONS

The overarching purpose of the current investigation was to provide empirical evidence of the EXiT as an objective dynamic exertion assessment to inform RTP/A decision making. We established the test-retest and inter-rater reliability and minimal detectable change scores across EXiT physiological, performance, and clinical outcomes. In addition, we determined that age, sex, BMI, and sport-type did not affect these outcomes and elucidate the generalizability of EXiT. Lastly, we observed post-exertion reductions in ultrashort HRV outcomes between healthy physically active adults and athletes at medical clearance to RTP/A, but EXiT physiological, performance, and clinical outcomes were similar between age-, sex-, and sport- matched athletes. Overall, the current investigation provided empirical data for the EXiT as a reliable (Chapter 4), generalizable (Chapter 5), and valid (Chapter 6) clinical assessment to inform RTP/A decision making.

In the first study we hypothesized that healthy adolescents and adults would exhibit stable physiological, performance, and clinical outcomes across repeated visits. We also hypothesized EXiT agility task completion time and errors would have high level of inter-rater agreement. Overall, physiological outcomes prior to, throughout, and following EXiT were reliable. For most agility tasks, we observed a systematic improvement between consecutive trials at each visit, and an improvement between the fastest trials at each visit. After we established the minimal detectable change for HR %max, blood pressure, agility task completion time, and endorsed symptoms for EXiT, the systematic improvement across study visits was within the margin of measurement error. We also observed a high level of inter-rater agreement across agility tasks (ICC=.842-.972), but agreement was acceptable for only Ball Toss (κ =.548) and Pro Agility (κ =.545) tasks. Errors were

discussed and established between raters prior to the study but based on our findings additional training via live demonstration or video to demonstrate errors would increase the agreement between raters.

Structured exertion to inform RTP/A decision making should also be generalizable to a diverse population. In the 2nd study we hypothesized lower (faster) agility task completion time among males compared to females and adults compared to adolescents, but physiological and clinical outcomes between age and sex would be similar. Our hypothesis was refuted for age but supported for sex: males had faster performance than females across most agility tasks, but our results indicated similar completion time between adults and adolescents. We also hypothesized that all EXiT physiological, performance, and clinical outcomes would be similar various BMI and sport-type groups. This hypothesis was supported, we did not observe differences for these outcomes between LO-BMI and HI-BMI groups and between collision, contact, and non-contact sport-types.

The restoration of affected subsystems from SRC is fundamental to ensuring safe return to sport after injury. As a result of the neurometabolic cascade and altered cerebrovascular functioning following SRC, the ANS has been of considerable interest to medical and research communities and several studies have indicated the potential value of examining HRV outcomes to inform RTP/A decisions [59, 73, 74]. In the 3rd study we hypothesized that athletes upon medical clearance to RTP/A would have similar pre- and post-EXiT ultrashort HRV in addition to EXiT physiological, performance, and clinical outcomes as healthy athletes. Our results did not support our hypothesis as we observed lower RMSSD and SDNN ultrashort HRV outcomes among athletes at medical clearance following EXiT. This findings builds on growing evidence that physiological recovery may extend beyond clinical recovery[59, 73, 213, 214, 220]. However,

remaining EXiT physiological, performance, and clinical outcomes were similar between groups in support of our hypothesis.

Since the early recommendation of 'strict rest' as a cornerstone to SRC management in 2008[21], a plethora of evidence has emerged to support the benefits of physical activity and structured exertion as an effective intervention to reduce post-concussion symptoms and recovery time following SRC [19, 91, 221-225]. Moreover, the previous decade has seen a growing number of structured exertion assessments [31, 32, 94, 96, 226] as part of the multifaceted clinical evaluation to diagnose and manage SRC [125, 171, 203, 204]. Simultaneously, the development of clinical subtypes or injury profiles has improved clinical practice to become a more active, targeted approach [3, 17]. However, several attempts to appraise the extent literature of exertion therapies for SRC report a limited quality of available evidence due to inconsistent study outcomes or intervention endpoints[24, 227]. This presents a severe risk of indirectness that will influence conclusions from future systematic reviews and meta-analyses determining the effectiveness of exertion-based interventions. EXiT is a more objective approach to inform RTP/A decision making and capable of standardizing medical clearance for sports medicine healthcare providers[228].

There are several limitations that should be considered in the design and implementation of future work with EXiT. The current investigation enrolled a heterogeneous sport sample but was limited to only 23 concussed patients and our findings may not be generalizable to all concussion subtypes. Approximately 5-10% of SRC patients experience a protracted recovery (>4 weeks) and more likely to experience cardiovascular deconditioning because of prolonged physical inactivity, but it is unknown if EXiT is appropriate for patients with longer recovery periods (greater than 90 days). Like other human performance assessments, we were unable to account for participant motivation and effort which could have affected our findings. Lastly, we enrolled a

heterogeneous sample of athletes to improve the external validity of our findings, but all concussed patients were treated at 1 outpatient clinic by 1 clinician. This limitation can be addressed with replication studies across multiple practitioners.

Overall, the current investigation coincides with recommendations from expert consensus [33] and the Institute of Medicine and National Research Council [2] to implement well-controlled studies with integrated physiological, performance, and clinical outcomes to determine the effects of exertion among recently-concussed and healthy individuals [86, 116, 227]. Moving forward, the combined use of neurocognitive [32, 171, 229, 230], vestibular[109], or ocular[231] [104] assessments with physical exertion has been suggested to improve RTP/A decision making. Future research can consider augmenting EXiT administration with brief clinical assessments to potentially prevent premature activity resumption of athletes that would otherwise receive medical clearance. Additionally, EXiT tasks can be potentially implemented in a targeted evaluation and treatment for concussion during earlier stages of recovery. Symptomatic patients completing supervised exertion challenges within 30 days of concussion experienced symptom provocation following dynamic exertion [36], but the absence of exertion standardization prohibits the possibility to replicate these findings.. Lastly, the clinical feasibility of administering EXiT is substantially reduced for health care professionals without readily accessible exertion equipment, future work should consider alternative approaches to administer the aerobic component without treadmill use. Future studies in these areas will enhance current and developing strategies to implement structured exertion as component of the RTP/A evaluation.

Due to the heterogeneity and evolving clinical presentation of post-concussion impairments, the medical diagnosis and clearance decisions are based on a multifaceted evaluation including neurocognitive, vestibular, and ocular assessments and clinical interview findings.

Given the varied clinical presentation and unavailability of a litmus test to determine full recovery, the medical clearance decision to resume unrestricted sport and activity participation remains a significant challenge for health care providers. The findings from the current investigation support dynamic exertion testing as an objective approach to inform RTP/A decision making for adolescents and adults following recovery from sport-related concussion.

Appendix A Phone Screening Scripts

CONTROL group

Hello **[NAME OF POTENTIAL PARTICIPANT-Control]**,

My name is **[NAME HERE]**, and I am a researcher at the University of Pittsburgh School of Medicine. If you are a under the age of 18 you will need a parent or legal guardian present to continue. This research will assess the effectiveness of a novel concussion assessment for athletes so clinicians can determine if an athlete is ready to return to sport following a concussion injury. The assessment includes running, agility, and other sport-specific movements with a mental task to evaluate a person's ability to function in a sport-type setting. We will also ask (you/your child) to complete cognitive, balance, eye tracking, and mood tests, as well. There are no anticipated risks associated with this project or assessment, and (your/your child's) participation would deem you eligible for up to a total of $75. If enrolled, the first and 2nd visits will be each take approximately 90 minutes to complete and each visit 3-21 days apart. The study is optional and has no influence on current or future care with UPMC. To determine if (you/your child) are/is fully eligible to participate, I will need to ask some more questions that involve inclusion and exclusion criteria for the study. All responses are confidential, will be kept in a secure location, and (you/your child's) participation in this project is completely voluntary. Do you think (you/your child) might be interested in participating in the study?

(If No): Thank you very much for listening, have a good day.

(If Yes): Before enrolling participants into this study, we need to determine if you/your child are eligible. I would like to ask you a series of questions about you (or your child's) current health status. These questions are like the standard health questions asked here at the UPMC Sports Medicine Concussion Program and American College of Sports Medicine. You also need to understand that all information that I receive from you, including your (or your child's) name and any other identifying information, will be strictly confidential and will be kept under lock and key. The purpose of these questions is only to determine whether you (or your child) are eligible for the study. You may withdraw from the study at any time. Withdrawal will not affect current or future clinical care. You will be eligible to receive up to $75 compensation for participating in the study. Do I have your permission to ask you (or you and your child) these questions?

Adult/Parent:YES / NOChild: YES / NO

Inclusion		
Question	Response*	
	Yes	**No**
Are you child currently between the ages of 14 and 35?		
Are you physically active as completing 30 minutes of moderate intensity exertion 5 days per week or 20 minutes of vigorous exertion 3 days per week?		

*"Yes" responses meet inclusion criteria

Were all inclusion criteria met? ☐ **Yes** ☐ **No**

Exclusion		
Question	Response*	
	Yes	**No**
Have you been diagnosed with a separate concussion in the past six months?		
Have you ever been diagnosed with two or more concussions?		
Have you ever had brain surgery or been diagnosed with a traumatic brain injury or TBI (based on Glasgow Coma Score of <13)?		
Have you ever been diagnosed with a neurological or seizure disorder?		
Have you ever been diagnosed with a vestibular or balance disorder or impairment?		
Have you ever been diagnosed with an ocular motor condition?		
Are you taking any antidepressant, anticoagulant, beta-blocker, or anticonvulsant prescription medications?		
Are you pregnant?		
Are you capable of running up to a speed of? Male: 8**.5 mph**/ Female: **7.0 mph** on a treadmill **OR** Running across a full-length football/soccer field in: Male: **25 seconds**/ Female **30 seconds**		
CV/Metabolic or Renal Disease Screening		
Have you been diagnosed with a cardiac, peripheral, or cerebrovascular disease, Type 1 or 2 Diabetes, or a renal disease?		
PAR-Q+ Questions		
Has your doctor ever said that you have a heart condition or high blood pressure?		
Do you feel pain in your chest or shortness of breath at rest, during your daily activities of living, OR when you do light to moderate exertion?		
Do you lose balance because of dizziness OR have you lost consciousness in the last 12 months?		
Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)?		
Are you currently taking prescribed medications for a chronic medical condition (i.e., diabetes)?		

Do you currently have (or have had within the past 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by physical activity?		
Has your doctor ever said that you should only do medically supervised physical activity?		

Were any exclusion criteria met? ☐ **Yes** ☐ **No**

Is Subject eligible for study ☐ **Yes** ☐ **No**

CONC-RTP Group

Hello **[NAME OF POTENTIAL PARTICIPANT-Recently concussed]**,

My name is **[NAME HERE]**, and I am a researcher at the University of Pittsburgh School of Medicine. If you are a under the age of 18 you will need a parent or legal guardian present to continue. Based on the information identified within (your/your child's) medical record, (you/your child) may be eligible to participate in a study investigating an exertion-based concussion assessment. This research will assess the effectiveness of a novel concussion assessment for athletes so clinicians can determine if an athlete is ready to return to sport following a concussion injury. To do so, we would like your permission to obtain the assessment results within your/your child's medical record. We will remove any personal identification information and use the clinical assessment results to compare with a separate group that will perform the same clinical assessments. There are no anticipated risks associated with this project or assessment, and (your/your child's) participation would deem you eligible for up to a total of $25. If enrolled, we will be able to use de-identified information from your record that pertain only to your concussion injury. The study is optional and has no influence on current or future care with UPMC. To determine if (you/your child) are/is fully eligible to participate, I will need to ask some more questions that involve inclusion and exclusion criteria for the study. All responses are confidential, will be kept in a secure location, and do not affect any treatment decisions from UPMC for you/your child. (You/your child's) participation in this project is completely voluntary. Do you think (you/your child) might be interested in participating in the study?

(If No): Thank you very much for listening, have a good day.

(If Yes): Before enrolling participants into this study, we need to determine if you/your child are eligible. I would like to ask you a series of questions about you (or your child's) current health status. These questions are like the standard health questions asked here at the UPMC Sports Medicine Concussion Program and American College of Sports Medicine. You also need to understand that all information that I receive from you, including your (or your child's) name and any other identifying information, will be strictly confidential and will be kept under lock and key. The purpose of these questions is only to determine whether you (or your child) are eligible for the study. You may withdraw from the study at any time. Withdrawal will not affect current or future clinical care. You will be eligible to receive up to $25 compensation for participating in the study. Do I have your permission to ask you (or you and your child) these questions?

Adult/Parent:YES / NOChild: YES / NO

Inclusion		
Question	Response*	
	Yes	No
Are you currently between the ages of 14 and 35?		
Before your injury, were you physically active as completing 30 minutes of moderate intensity exertion 5 days per week or 20 minutes of vigorous exertion 3 days per week?		
Were you diagnosed with a concussion within 14 days of your injury?		
Do you intend to return to pre-injury physical activity (i.e., sport)?		

*"Yes" responses meet inclusion criteria

Were all inclusion criteria met? ☐ **Yes** ☐ **No**

Exclusion		
Question	Response*	
	Yes	No
Did your concussion occur outside sport participation (recreational or competitive) activity? (Car crashes, falls or other accidents will be excluded.)		
Did your concussion occur more than 90 days ago?		
Have you been diagnosed with a separate concussion in the past six months (excluding current injury)?		
Have you ever been diagnosed with two or more concussions (excluding current injury)?		
Have you ever had brain surgery or been diagnosed with a traumatic brain injury or TBI (based on Glasgow Coma Score of <13)?		
Have you ever been diagnosed with a neurological or seizure disorder?		
Have you ever been diagnosed with a vestibular or balance disorder (excluding current injury)?		
Have you ever been diagnosed with an ocular motor condition (excluding current injury)?		
Are you taking any antidepressant, anticoagulant, beta-blocker, or anticonvulsant prescription medications?		
Are you pregnant?		
Are you capable of running up to a speed of? Male: 8.5 mph/ Female: 7.0 mph on a treadmill OR Running across a full-length football/soccer field in: Male: 25 seconds/ Female 30 seconds		
CV/Metabolic or Renal Disease Screening		
Have you been diagnosed with a cardiac, peripheral, or cerebrovascular disease, Type 1 or 2 Diabetes, or a renal disease?		
PAR-Q+ Questions		

Has your doctor ever said that you have a heart condition or high blood pressure?		
Do you feel pain in your chest or shortness of breath at rest, during your daily activities of living, OR when you do light to moderate exertion?		
Aside from your concussion injury, do you lose balance because of dizziness OR have you lost consciousness in the last 12 months?		
Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)?		
Are you currently taking prescribed medications for a chronic medical condition (i.e., diabetes)?		
Do you currently have (or have had within the past 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by physical activity?		
Has your doctor ever said that you should only do medically supervised physical activity?		

Were any exclusion criteria met? ☐ **Yes** ☐ **No**

Is Subject eligible for study ☐ **Yes** ☐ **No**

(If Eligible): Because you have answered "no" to all the exclusion criteria, you child is eligible to participate in this research study.

(If Ineligible): Because you have answered "yes" to [questions answered "yes"], you will ***not*** be eligible to participate in this research study.

_____

Signature of Staff Who Obtained Verbal ConsentDate / Time

Appendix B Recruitment Flyer

Healthy Controls Needed!!

For a study investigating exercise and concussions

Participants will be asked to complete concussion tests to measure symptoms, mood, concentration, memory, and an exercise test during 2 visits

(3-21 days between visits)

Participants MUST

- **14-35 years old**
  - **14-17 years old require parental permission**
- **Physically Active by completing a minimum:**
  - **30 minutes of moderate intensity exercise 5 days/week**

  OR
  - **20 minutes of vigorous exercise 3 days/week**
- **Capable of running for 15 minutes**

Participants must NOT

- **Experienced a concussion in previous 6 months**
- **2+ prior concussions**
- **Currently take prescription medication for:**
  - **Depression**
  - **Chronic health condition**

FOR MORE INFORMATION AND ELIGIIBLITY SCREENING PLEASE CONTACT:

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Compensation will be provided

Appendix C Questionnaires and Clinical Assessments

EXiT Report Sheet

UPMC Centers of Rehab Services **UPMC EXIT for Concussion Clearance**

EXIT Concussion Assessment

Assessment Information

Date _____
Start Time _____
BP pre: _____/_____
post: _____/_____
HR pre: _____
post: _____

Testing Order
1 Aerobic (HIIT)
Version (circle): 1 2 3 4 5 6
_____Dynamic Circuit
_____Ball Toss Version
_____Box Drill (Shuffle)
_____Box Drill (Carioca)
_____Zig Zag Drill
_____Pro Agility
_____Arrow Agility

Internal Use

Site:_____
☐ Past medical history reviewed on intake

Aerobic Protocol

Gender	Athlete Type	Treadmill Version	Treadmill Speed (mph) LOW	Treadmill Speed (mph) HIGH	Pacer (10 m) Version	Pacer (10 m) Time (sec) LOW	Pacer (10 m) Time (sec) HIGH
Female	Moderate	1	4.0	6.0	5	4.5	4.0
	Advanced	2	4.5	7.0			
Male	Moderate	3	4.5	7.5	6	4.0	3.5
	Advanced	4	5.5	8.5			

Aerobic Component

Time	HA	DZ	NA	RPE	HR
0 (Pre)					
2 (Warm-up)					
6:30-7					
12 (Finish)					

Assessment Notes
☐ Symptoms worsened during assessment
Inability to maintain pace/physical demands and
☐ modified, explain:
☐ discontinued, explain:
☐ Other:
End Time (if DNF):_____

Dynamic Movement Component

Task	HA	DZ	NA	RPE	HR	Errors	Time
Dynamic Circuit							
Ball Toss							
Box Drill (Shuffle)							1. 2.
Box Drill (Carioca)							1. 2.
Zig-Zag							1. 2.
Pro Agility							1. 2.
Arrow Agility							1. 2.

Assessment Notes
☐ Symptoms worsened during assessment
Inability to maintain pace/physical demands and
☐ modified, explain:
☐ discontinued, explain:
☐ Other:
End Time (if DNF):_____

Sport Specific/Contact activities:

Vestibular-Ocular Motor Screening (VOMS) Tool

Vestibular-Ocular Motor Screening (VOMS)

	Not Tested	Headache 0--10	Dizziness 0--10	Nausea 0--10	Fogginess 0--10	Comments
BASELINE	N/A					
Smooth Pursuits						
Saccades – Horizontal						
Saccades – Vertical						
Convergence (Near Point)						**(Near Point in cm):** Measure 1:_____ Measure 2:_____ Measure 3:_____
VOR – Horizontal						
VOR – Vertical						
Visual Motion Sensitivity Test						
Comments:						

Post-Concussion Symptom Scale (PCSS)

No symptoms"0"-------Moderate "3"---------Severe"6"

Time after Concussion

SYMPTOMS	Days/Hrs _____	Days/Hrs _____	Days/Hrs _____
Headache	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Nausea	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Vomiting	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Balance problems	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Dizziness	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Fatigue	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Trouble falling to sleep	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Excessive sleep	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Loss of sleep	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Drowsiness	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Light sensitivity	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Noise sensitivity	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Irritability	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Sadness	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Nervousness	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
More emotional	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Numbness	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Feeling "slow"	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Feeling "foggy"	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Difficulty concentrating	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Difficulty remembering	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
Visual problems	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6
TOTAL SCORE	_____	_____	_____

Demographic Questionnaire

ID #_____
Date of Birth MM/DD/YYYY

_____
Height (ft/in) _____
Weight (lbs) _____
Gender:

- ◻ Male
- ◻ Female

Handedness:

- ◻ Right
- ◻ Left
- ◻ Ambidextrous

Ethnicity (***optional***) Circle One
American Indian/ Alaska Native Asian Black/ African American/ Hispanic/ Latino Native Hawaiian /Pacific Islander/ White Other/

Academic History

Years of education completed (ex. High school senior=11) _____
Select if any of the following that apply:

- ◻ Received speech therapy
- ◻ Attended Special Education classes
- ◻ Repeated one or more years of school
- ◻ Diagnosed learning disability
- ◻ Diagnosed attention deficit disorder or hyperactivity

While in school, what type of student were/are you? select one

- ◻ Below average
- ◻ Average
- ◻ Above average

Sport Participation History

Current sport:

_____
Current position (ex. Quarterback or unknown)

_____
Current level of participation

- ◻ Junior high
- ◻ High school
- ◻ Collegiate
- ◻ Professional

Years of experience at current level (i.e. 0-4)

_____

Medical History

Number of times diagnosed with a concussion

_____
If one or more please answer the following:
Total number of concussions that resulted in:
___Loss of consciousness
___Confusion
___Difficulty with memory immediately following injury
___Difficulty with memory immediately before injury
___Total games missed due to all concussions combined _____
Please list the 5 most recent concussions (MM/YYYY)

_____
_____
_____
_____
_____

Indicate whether you have experienced following:

- ◻ Treatment for headaches by physician
- ◻ Treatment for migraine headache by physician
- ◻ Treatment for epilepsy/seizures
- ◻ Treatment for brain surgery
- ◻ Treatment for meningitis
- ◻ Treatment for substance/alcohol
- ◻ Treatment for psychiatric condition (depression/anxiety)

Have you ever been diagnosed with any of the following conditions?

- ◻ ADD/ADHD Y N
- ◻ Dyslexia Y N
- ◻ Autism Y N

EXiT Dynamic Component Descriptions

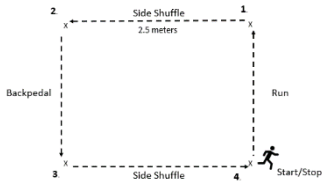
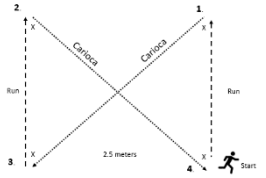
Functional Movements

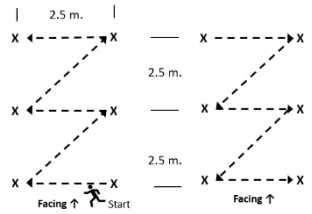
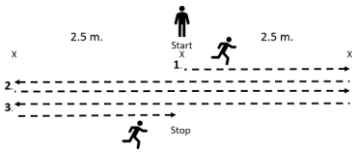
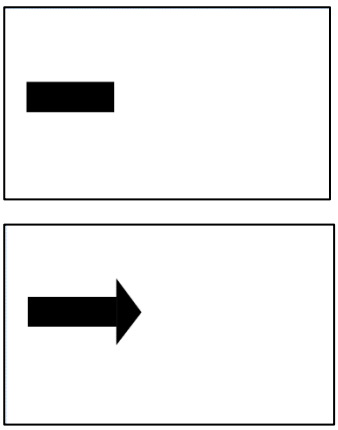
Dynamic Circuit	Athlete performs 3X10 sets of squat jumps, side-to-side pushups, and ball rotations in synchronization with a metronome (25 beat/min) and 30-second rest following each set. Errors include improper form or inability to maintain pace.
Ball Toss	While the participant standing 2.5 meters in front of administrator. After administrator calls 'left', or 'right', participant jumps and rotates 180° in the specified direction, catches a basketball tossed by the administrator, and toss back before returning to the starting position for the next trial. Conduct 10 trials (5 jumps left and 5 jumps right) and after a 30-second rest, a second round is performed whereby administrator calls direction (left or right) or 'Go' (Distractor-no response) in a random sequence (5 jumps left, 5 jumps right, and 2 distractors). A jump-turn in the wrong direction, inability to catch or toss ball back to administrator, or a jump committed after a 'Go' call are counted as errors.

Agility Tasks

Set Up: Place 6 agility cones 2.5 meters apart in a rectangle (2 rows with 3 cones each)

- Instructions and demonstrations for each task are provided during the break between tasks. All tasks will begin with a "3, 2, 1, GO" count.
- Participants complete 2 trials for each task with a 30 second rest between trials (except Pro Agility-15 seconds)
- Instances in which participants knocks a cone off the original placement, mis-navigates a cone, or does not hand-touched a cone when instructed to do so are counted as errors.

Box Drill Shuffle	Athlete will sprint forward to the first cone, side shuffle to the second cone, backpedal to the 3rd cone, and side shuffle to the "start" cone. After completing 2 "laps", immediately repeat in the opposite direction (4 total circles), rest for 30 seconds. Repeat.	
Box Drill Carioca	Athlete will sprint forward to the first corner, carioca diagonally backwards to the 3rd corner. Sprint to the 2nd corner, and carioca backwards diagonally to the "start" corner. After completing 2 "laps", rest for 30 seconds. Repeat.	

Zigzag	Athlete will side-shuffle to the left, touch the cone, and side shuffle diagonally to the right cone and repeat for remaining cones. After reaching the final cone, maintain body facing the same direction and continue to side-shuffle touch each cone in reverse order (starting with a lateral shuffle back to the right. Repeat with a backwards shuffle to the start cone. Complete 2 "laps", Rest for 30 seconds. Repeat.	
Pro Agility	Begin standing between 2 end-cones and facing perpendicular to cones. When cued, turn right, sprint to touch the right cone (2.5m), turn and sprint to the far left cone (5m), touch cone, turn and run to touch each end cone one additional time (5m each), before sprinting through the start cone (middle). Rest 15 seconds. Repeat with initial direction to left.	
Arrow Agility	Athlete begins at the same position as Pro Agility task. Administrator presents a card that has a block on the left or right side which correspond to each end cone. Subject is instructed to run, touch the cone, and return to the starting point as quickly as possible, at which point the clinician presents the next card. A series of 16 cards (8 left, and 8 right) are presented in a randomized order. Upon completion of all 16, rest for 30 seconds. During rest, athlete is instructed to repeat task, running to the direction of the arrow, regardless of its spatial location (left or right) on the card. A series of 16 cards are randomly presented, the cards include congruent (box-left/arrow-left and box-right/arrow-right) and incongruent (box-left/arrow-right and box-right/arrow-left) combinations that are each presented with 4 trials.	

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