2024-06-26

Exploring Psychological Resilience, Plasma Cortisol, and Sport-Related Concussion Outcomes Among Canadian Adolescent Sport Participants

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Exploring Psychological Resilience, Plasma Cortisol, and Sport-Related Concussion Outcomes Among Canadian Adolescent Sport Participants

by

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCE

GRADUATE PROGRAM IN NEUROSCIENCE

CALGARY, ALBERTA

JUNE, 2024

Abstract

Sport-related concussion (SRC) is a common injury among Canadian adolescent sport participants (ASP). Numerous factors potentially impact recovery from SRC, including psychological resilience and cortisol. Researchers have found low psychological resilience and low cortisol may be independently linked to increased post-SRC symptom burden and a longer duration of recovery. However, the relationship between resilience and cortisol has not yet been investigated following adolescent SRC, which was the overarching goal of this thesis.

The first aim of this study was to explore the trajectory of resilience, as measured by the Connor-Davidson Resilience Scale 10 (CDRISC-10), before and after SRC, controlling for age and sex. Following, we described the relationships between resilience and SRC outcomes, including symptom burden and length of recovery based on physician clearance to return to play. We also aimed to examine group differences in plasma cortisol (stratified by morning [before 11:00am] and basal [11:00am–6:00pm] collection times) between uninjured and post-SRC ASP, controlling for age and sex/menstrual cycle phase (male, female follicular, female luteal), and time of blood draw. We then compared post-SRC cortisol to SRC outcomes controlling for age, and sex/menstrual cycle phase. Finally, we aimed to investigate the associations between resilience and plasma cortisol before and after adolescent SRC. The analyses were stratified by time of cortisol collection as outlined above. Uninjured analyses controlled for age and sex, while post-SRC analyses controlled for age, sex, and symptom severity.

We found sex-specific trajectories of resilience following SRC, and that acute post-SRC measures of resilience may better predict SRC outcomes compared to pre-injury measures. Morning and basal cortisol were significantly lower post-SRC for males and females regardless of menstrual cycle phase. Post-SRC morning and basal cortisol demonstrated non-linear relationships with symptom burden, potentially reflecting impairment of the HPA axis and HPA axis activation in response to stress. Finally, morning cortisol decreased with increased resilience in our uninjured participants, but not in our post-SRC participants, suggesting HPA axis impairment following SRC. Overall, the results of this thesis revealed novel aspects of SRC pathophysiology and provide groundwork for future investigations into the complex relationship between resilience, cortisol, and SRC outcomes.

Key terms: Sport-related concussion, concussion, mTBI, psychological resilience, plasma cortisol, menstrual cycle, adolescents, sport participation, hypothalamic-pituitary-adrenal axis

Acknowledgements

In the spirit of reconciliation, we acknowledge that we live, work and play on the traditional territories of the Blackfoot Confederacy (Siksika, Kainai, Piikani), the Tsuut'ina, the Iyarhe Nakoda Nations, the Otipemisiwak Métis Government of the Métis Nation within Alberta District 6, and all people who make their homes in the Treaty 7 region of Southern Alberta.[1]

The efforts of numerous committed individuals made this thesis possible. A single page of acknowledgements does not fully express my heartfelt gratitude to you all.

First, I would like to thank my supervisor, Dr. Chantel Debert. I relied on your guidance as I entered the world of clinical research. Your dedication to your students, patients, and family inspires me every day. With your help, I gained valuable skills in data management and analysis, knowledge translation, scientific writing, and leadership.

This project was advanced in large part with input from my supervisory committee members, Dr. Carolyn Emery, Dr. Keith Yeates, and Dr. Michael Esser. Thank you for your support these past two years. Collaborating with esteemed researchers such as yourselves has been a remarkable opportunity.

Dr. Jason Tabor, your mentorship has been priceless. Despite your busy life, you consistently volunteered your time to support me. Thank you, sincerely.

Dr. Jean-Michel Galarneau, there is something special about planting a seed and watching it grow. You have helped me to better understand biostatistical modeling, and for that I will be forever grateful.

I would like to thank the entire team at the University of Calgary's Sport Injury Prevention Research Center. This research depended on the enthusiasm of numerous students, PIs, clinicians, research coordinators, and research assistants. A special thank you to Shane Esau, Kristina Fraser, the fluid biomarker team, and the ORCA Pod.

Also, to members of the Cumming School of Medicine Brain Neurorehabilitation Lab, your feedback and encouragement as I completed this thesis was invaluable.

Dedication

I would foremost like to dedicate this thesis to my soon-to-be wife, Laura Stefanía Niño García. You are my greatest source of strength, and the life we are building is beautiful. No matter what the future holds, I am overjoyed to be sharing it with you.

To my mother, Kathryn Livingston, your perception of justice, and dedication to upholding it, is inspiring. I promise to never lose sight of the bigger picture.

To my father, John Josafatow, you helped to inspire my scientific intrigue and work ethic.

To my siblings, you each inspire me in your own way. You are all more resilient than you know. Thank you for your unshakeable support.

Lastly, I would like to dedicate this thesis to each SHRed participant. This research would not have been possible without uninjured and post-concussion volunteers alike. In all sincerity, I hope our contribution to unravelling the pathophysiology of this injury will help to ameliorate the lives of those experiencing the effects of concussion.

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List of Abbreviations and Nomenclature

Abbreviation/Nomenclature	Definition
ACTH	Adrenocorticotropic hormone
APL	Alberta Precision Laboratories
ASP	Adolescent sport participant
ATP	Adenosine triphosphate
AYA	Adolescent and young adult
Basal Cortisol	Cortisol measured between 11:00am and 6:00pm
BBB	Blood brain barrier
CDRISC-10	Connor-Davidson Resilience Scale 10
CI	Confidence Interval
CNS	Central nervous system
CRH	Corticotropic releasing hormone
CRT-5	Concussion Recognition Tool 5
CRT-6	Concussion Recognition Tool 6
e-form	Exponential form
ECLIA	Electrochemiluminescence Immunoassay
GR	Glucocorticoid receptor
IRF	Injury Report Form
Morning Cortisol	Cortisol measured before 11:00am
MCID	Minimum clinically important difference
MR	Mineralocorticoid receptor
mTBI	Mild traumatic brain injury
PedsQL	Pediatric Quality of Life Inventory
PBQ	Pre-season baseline questionnaire
PVN	Paraventricular nucleus
RTP	Return to play
RTL	Return to learn
S/MCP	Sex/menstrual cycle phase
SCAT-5	Sport Concussion Assessment Tool 5
SCAT-5 PCSS	SCAT-5 Post-Concussion Symptom Scale
SCAT-6	Sport Concussion Assessment Tool 6
SHRed Concussions	Surveillance in High-School and Community Sport to Reduce Concussions and their Consequences
SHRed Mobile	Mobile laboratory for blood sample collection and processing
SD	Standard Deviation
SRC	Sport-related concussion
TBI	Traumatic brain injury

Preface

Data for this manuscript were collected through the SHRed Concussions (Surveillance in High-Schools to Reduce the Risk of Concussions and their Consequences) study. Ethics ID: REB18-2107. For contributions, refer to Table 9.1.

First Data Chapter (Chapter 3 in Thesis)

Title: Psychological Resilience and Adolescent Sport-Related Concussion: Consider Acute Measures

Authors: Nik Josafatow, Jason B. Tabor, Kristina Fraser, Keith Yeates, Michael Esser, Carolyn A. Emery, Chantel T. Debert

Stage: In preparation for submission to the Journal of Pediatrics

Second Data Chapter (Chapter 4 in Thesis)

Title: Morning and Basal Plasma Cortisol in Uninjured and Post-SRC Adolescent Sport Participants

Authors: Nik Josafatow, Jason B. Tabor, Julius Ho, Linden Penner, Douglas Fraser, Keith Yeates, Michael Esser, Carolyn A. Emery, Cheryl Wellington, Chantel T. Debert

Stage: In preparation for submission to the Journal of Neurotrauma

Third Data Chapter (Chapter 5 in Thesis)

Title: Investigating the Relationship Between Psychological Resilience and Plasma Cortisol in Uninjured and Acutely Post-SRC Adolescent Sport Participants

Authors: Nik Josafatow, Jason B. Tabor, Linden Penner, Kristina Fraser, Douglas Fraser, Keith Yeates, Michael Esser, Carolyn A. Emery, Cheryl Wellington, Chantel T. Debert

Stage: In preparation for submission to the British Journal of Sports Medicine

1 CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

Sport-related concussion (SRC), psychological resilience, and cortisol in adolescents are covered in this section.

1.1 INTRODUCTION

Traumatic brain injury (TBI) has been termed the 'silent epidemic', with nearly 70 million individuals sustaining a TBI globally each year.[2] Concussion, a term commonly used interchangeably with mild traumatic brain injury (mTBI), results in temporary neurological dysfunction, and over 30% of concussions occur among adolescents (10-19 years old).[3, 4] Sport-related concussion (SRC) is succinctly defined as "a traumatic brain injury caused by a direct blow to the head, neck, or body resulting in an impulsive force being transmitted to the brain that occurs in sports and exercise-related activities."[5] While much media attention has been directed to professional and collegiate athlete SRC, the 2016 consensus statement on concussion in sport called for further investigation into younger populations – an appropriate recommendation considering the greatest cohort of sports participants are adolescents.[6, 7] In response, the scientific community increased research into adolescent SRC, as reported in the more recent 2022 consensus statement on concussion in sport, though further research is needed.[5]

Several physiological and psychological factors are associated with SRC symptom burden and recovery duration. For example, both low serum cortisol and poor psychological resilience have been linked to more severe symptoms and a prolonged refer recovery following SRC in youth.[8, 9] A recent study also demonstrated cortisol may decrease following SRC, suggesting the hypothalamic-pituitary-adrenal (HPA) axis may be disrupted through the injury process.[10] Moreover, high psychological resilience has been associated with a stronger cortisol awakening response (CAR) and lower cortisol throughout the day.[11-13]

While relationships between resilience and cortisol, resilience and SRC outcomes, and cortisol and SRC outcomes have been established, no study has yet investigated the relationship between cortisol and resilience following adolescent SRC. We sought to explore the relationship between resilience and cortisol in uninjured and post-SRC adolescent sport participants (ASP). By examining this complex relationship, results from this study have the potential to inform on the pathophysiology of SRC and provide further evidence for the utility of exploring resilience-targeting therapies to improve concussion outcomes in adolescents.

1.2 SPORT-RELATED CONCUSSION IN YOUTH

"Sport-related concussion is a traumatic brain injury caused by a direct blow to the head, neck, or body resulting in an impulsive force being transmitted to the brain that occurs in sports and exercise-related activities."[5]

1.2.1 Epidemiology and Sex Differences

A 2016 study estimated that there are 1.1 – 1.9 million pediatric concussions resulting from sports and recreation annually in the US.[14] In Canada, an estimated 10% of adolescents sustain a concussion each year, with the majority being sport-related.[15, 16] Despite the seriousness and high prevalence of the injury, up to half of SRCs may go unreported.[3] The primary motivation for not disclosing SRCs include not wanting to be removed from play, but many players, even collegiate athletes, were unaware at the time of injury that an SRC had occurred.[17] Females may be at a higher risk of sustaining a concussion, even when their sports are of similar play (i.e., comparable equipment and contact regulations).[18] For example, a 2018 meta-analysis including elite-level athletes found that female ice hockey players sustained higher rates of concussion than their male counterparts, despite body checking not being allowed in the female sport.[19] This trend holds for high school sport participants, with females reporting a greater post-SRC number and severity of symptoms, and a longer duration of recovery compared to males.[6, 10, 18, 20, 21] While biomechanical and/or physiological sex differences may influence SRC (discussed below), the discrepancy in injury rates and symptom burden may also be explained by gender differences with boys being less likely to disclose injuries, and girls endorsing more symptoms even in the absence of SRC.[17] Indeed, SRC is an important injury to investigate in adolescent sport participants, and sex differences must be considered.

1.2.2 Biomechanics and Pathophysiology

Mechanisms of SRC are variable. Typically, they result following rotational and linear accelerations, and impact decelerations from contact with sporting equipment (sticks, balls/pucks, goal posts), other players, or arena surfaces (walls, turf/grass/ice).[22] The most common mechanism of injury is player to player contact.[6] It is not fully understood why females are at higher risk for sustaining SRCs and face more severe consequences following the injury. Some researchers postulate that females may suffer more severe concussions due to weaker neck muscles, and less head-neck stiffness, allowing for greater head acceleration during impact.[23] It could also be that females are at higher risk of poorer SRC outcomes due to physiological pathways, such as disturbed estrogen and progesterone production.[24]

In SRC, the biomechanically induced forces on the brain result in diffuse axonal injury due to the difference in densities of white and grey matter. As the classes of matter accelerate at different rates, the shearing forces result in mechanoporation – an increase in membrane permeability to ions, triggering a neurometabolic cascade.[25] As depicted below in Figure 1.1, the increased ion flux (potassium efflux, sodium influx, and calcium influx) depolarizes the membrane making the neurons hyperexcitable. Glutamate is then released, which binds to and activates N-methyl-D-aspartate receptors (NMDARs). The activated NMDARs allow influx of calcium, causing ion pumps to work to excrete calcium and restore the resting membrane potential. The increase in intracellular calcium overstimulates mitochondria, which generate reactive oxygen species, eventually producing tissue damage.[22] This process is compounded by hypoperfusion as blood flow may be disrupted globally, resulting in decreased availability of glucose for adenosine triphosphate (ATP) generation.[25] Of note, hyperperfusion of certain brain regions has also been reported acutely following mTBI. Therefore, findings of global disruptions may merit a more nuanced investigation.[26] Ultimately, the neurometabolic cascade depletes the cells of energy stores and triggers neuroinflammation, resulting in disrupted neural activity.[22] In moderate and severe TBI, cell death may ensue; however, this phenomenon is rare in concussion.[27]

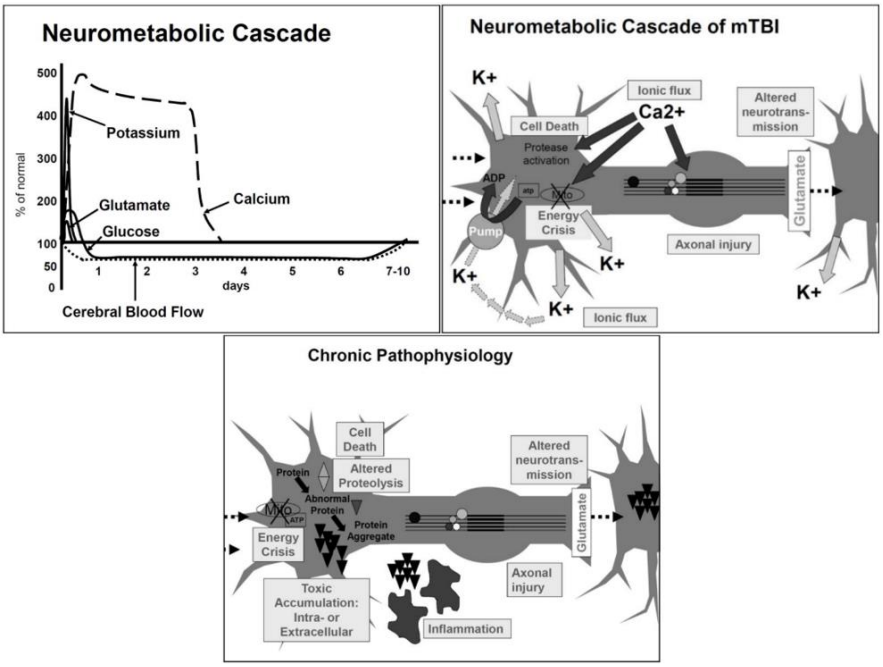

Figure 1.1 The neurometabolic cascade and chronic pathophysiology of mTBI.

Top panel illustrations showcase the neurometabolic cascade, including aberrant ionic flux and energy crisis. The bottom illustration reveals the ensuing chronic pathophysiology, including inflammation and altered neurotransmission. Figure cited with permissions from Giza and Hovda, 2014.[27] (Appendix 8.10)

1.2.3 Diagnosis

Patricios and colleagues (2023) provide a consensus for the diagnosis and clinical management of SRC.[5] The first step in concussion diagnosis is to recognize when one may have occurred. Recognition can be accomplished by an individual self-reporting a head impact, or by a teammate, coach, referee, or spectator, reporting having witnessed an impact. This step can be aided using the Concussion Recognition Tool 5 (CRT-5),[28] or the recently updated CRT-6,[29] which can be employed by non-medically trained persons to help to identify SRC red flags and provide insights on next steps. If signs or symptoms of SRC are present, the player should be removed from play and a sideline evaluation should be performed by a licensed medical professional. A recently developed tool used in such an evaluation is the Sport Concussion Assessment Tool 6 (SCAT-6),[30] though for this thesis we used the Sport Concussion Assessment Tool 5 (SCAT-5).[31] Some of the most common symptoms reported for adolescent SRC include headache, dizziness, and trouble with concentration, and, even if such symptoms are initially absent, the sport participant should be closely monitored as symptoms may evolve rapidly.[6] The injured player can only be officially diagnosed SRC by a physician or nurse practitioner based on clinical presentation.[7]

Research is underway to develop other measures to assist in the diagnosis of SRC, including functional magnetic resonance imaging (fMRI), cerebral blood flow measurements, genetic testing, and fluid biomarkers.[5, 7, 32] Tabor and colleagues' (2023) systematic review on the subject concluded that neuroimaging studies do not reveal macroscopic structural changes following SRC, though functional imaging modalities reveal alterations acutely and beyond one-month post-injury. The authors also note that several fluid biomarkers may discriminate SRC participants from controls. However, despite recent advances, none of these measurements are yet developed into tests for clinical use, and diagnosis remains reliant on self-report and clinical interpretation of signs and symptoms.[5, 7, 32]

1.2.4 Clinical Management

Considering the heterogeneous SRC pathophysiology, experts maintain that SRC clinical management should be guided by individual symptomology.[24] Indeed, the foremost predictor of recovery duration remains the acute symptom severity following injury.[7] Researchers also report that waiting to seek medical attention following injury may be associated with a longer duration of recovery.[33] Rest is generally recommended acutely following SRC, and the recent consensus sanctions that sub-symptom threshold physical activity can be started within 24 hours following injury, accompanied by return to learn (RTL) and return to play (RTP) protocols.[5]

The RTP protocol can begin within one day post-SRC, and each of the six steps takes a minimum of 24 hours before progressing to the next. The first step is symptom-limited activity, wherein the individual performs sub-symptom threshold activities of daily living. The second step is increasing the heartrate with light-to-moderate stationary aerobic activity. Third, the participant engages in sport-specific exercises which do not pose a risk of inducing further head impacts. These first three steps can be started even if some symptoms are present, maintaining that the symptoms are not exacerbated by the activity. Step four can be initiated when symptoms are no longer present. This step includes engaging in high intensity non-contact drills. For step five, individuals are cleared for full contact practice and, if no symptoms emerge, they may be cleared to proceed to step six which is a full clearance to normal game play (RTP).[5]

Though the RTP protocol may be completed within one week of injury, length of recovery from SRC is variable. Most adolescents return to their sports based on symptom resolution within one month following injury, yet some return to their sport before their symptoms have completely subsided.[5, 6] More than 20% of players may have symptoms for more than one month, at which point they deemed to have

'persistent symptoms.'[5, 6] Uninjured females tend to report higher symptoms compared to males, suggesting pre-injury symptom burdens should be considered when RTP determinations are made.[24] Ultimately, the decision of whether a player is ready to return to their sport rests with their physician.[7]

There is currently no gold-standard treatment for SRC. Nevertheless, several interventions have been proposed and several are being evaluated for their effectiveness. For example, daily sub-symptom threshold aerobic activity has been associated with faster recovery from SRC, and early vestibular therapy may decrease recovery time.[34, 35] Psychological resilience has been identified as a potentially modifiable factor which, if targeted through interventions such as cognitive-behavioral therapy, may also reduce time to recovery.[9, 36]

1.3 PSYCHOLOGICAL RESILIENCE IN YOUTH

"Resilience refers to an individual's ability to thrive despite adversity."[37]

1.3.1 Overview

Resilience is broadly the capacity to overcome hardship. There is discrepancy between 'trait-like' and 'state-like' resilience. 'Trait-like' resilience implies that resilience is a stable trait throughout life, much like personality traits, and is robust against influence from environmental factors. 'State-like' resilience suggests that resilience may develop in accordance to environmental factors, and is malleable to their influence.[38] Some researchers suggest that neither 'trait-like' nor 'state-like' resilience fully encompass the phenomenon, and a biopsychosocial approach should instead be taken to understand the development and maintenance of resilience. Indeed, as Campbell-Sills and Stein (2007) indicate, resilience has been found to be influenced by genetics, biology, psychology, and the environment.[37] Support for this model is most clearly evidenced as numerous interventions have been shown to significantly increase resilience.[23, 39, 40] Recognizing multifaceted associations between resilience and biopsychosocial factors, researchers and clinicians have been advised to consider resilience in their work, particularly when adolescents are involved.[41, 42]

For the scope of this research project, it is important to recognize that resilience may vary by age and between sexes. A 2021 cross-sectional study found that Russian male adolescents and young adults (AYA) tended to score higher in resilience than females, although there was no significant correlation between resilience and age.[43] Such sex differences have been replicated in adult and youth samples, though female resilience has been reported to decrease through adolescence.[44-47] Conversely, some researchers did not find significant sex differences in AYA samples, and others have reported female adolescents to have higher resilience than their male counterparts.[36, 37, 48, 49] Hawkley and colleagues (2021), suggest that males may *report* higher levels of resilience while females may *exhibit* higher resilience, as females tend to return to baseline levels of well-being following adversity faster than males.[45, 50] It is therefore imperative to carefully consider the interpretation of self-reported resilience measures, especially with regards to age and sex.

1.3.2 Biology of Resilience

Numerous biological factors have been associated with psychological resilience. These include, but are not limited to, medial prefrontal cortex (mPFC) and hippocampal/hypothalamic pathways.[51]

Though discussed separately, there is much overlap between these pathways. Each pathway merits more breadth than is offered below; however, the hippocampal/hypothalamic pathway is explored in the most depth as is important for interpreting sections 1.4.2 and 1.4.3 ('Cortisol and Resilience' and 'Cortisol and Concussion').

Both rodent and human studies suggest that mPFC pathways contribute to psychological resilience.[52] In fact, stimulating this region in rodents has been shown to augment their resilience in the face of physical (forced swim test) and social (chronic social defeat stress paradigm) challenges.[53, 54] While there are neural circuits leading from the mPFC which may influence resilience, such as the mPFC-dorsal raphe nucleus pathway, the precise mechanism through which the mPFC influences, and may be influenced by, resilience are yet to be fully understood.[51]

The hippocampus has also been implicated in psychological resilience, largely due to its relationship with the hypothalamic-pituitary-adrenal (HPA) axis. In their 2015 review, Levone and colleagues outline direct and indirect pathways from the hippocampus to the paraventricular nucleus (PVN) of hypothalamus.[55] Parvocellular neurons within the hypothalamus respond to stressful stimuli and release corticotrophin-releasing hormone (CRH) to promote adrenocorticotropic hormone (ACTH) release from the anterior pituitary. ACTH then enters the blood stream to promote release of glucocorticoid hormones, including cortisol, from the adrenal cortex.[55]

The HPA axis consists of negative feedback loops from the periphery to the central nervous system (CNS). From peripheral circulation, cortisol crosses the blood-brain barrier (BBB) to act on structures within the limbic system. In the limbic system, there is homeostatic balance between mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) activation which modulates the emotional response to stressful situations. In brief, in the absence of high-stress situations, the relatively low concentration of cortisol activates MRs, allowing for low-cost functioning. The increase in cortisol following stress activates the GRs, putting the system in a high-cost state which allows for memory storage and top-down emotional control.[56] The hippocampus takes part in regulating the HPA axis through negative feedback mechanisms – its MRs and GRs respond to varying concentrations of cortisol, resulting in reactions to stressors and memory consolidation, respectively.[55] Ultimately, increased memory storage in times of stress primes the system to cope with similar stressors in the future, thereby fostering psychological resilience. However, if the coping strategies do not efficiently control the stressor, the GR stimulation may

switch to bottom-up functioning, putting the individual at risk of vulnerability, as opposed to resilience.[56] While the directionality of this relationship is yet to be fully elucidated, researchers agree that resilience and cortisol interact to impact the cognitive appraisal of stressors.[57]

1.3.3 Resilience in Adversity

The importance of investigating protective factors, such as resilience, in relation to adversity in adolescence is recently being recognized. Much of the literature regarding youth mental health has focused on risk factors, such as low socioeconomic status, family dysfunction, and consumption of psychoactive substances.[58] However, a 2021 literature review of 25 studies found that higher resilience was "unanimously" associated with a decreased risk for mental health disorders in adolescents.[41] Adverse childhood experiences, such as maltreatment, have also been suggested as risk factors for later development of psychiatric illness, yet high levels of resilience may negate this effect. In fact, researchers found that psychiatric symptoms later in life were indistinguishable for participants with high resilience regardless of the level of trauma they experienced early in life, whereas individuals reporting low resilience experience significantly more psychiatric symptoms if they endured childhood trauma compared to those without.[37] Resilience has also been reported to protect against depressive symptoms in adolescents, and resilience-enhancing interventions have been proposed as an essential component in successfully managing conditions such as cancer.[59, 60]

1.3.4 Resilience and Concussion

Reported as early as 1995 by Cicerone and Kalmar, and more recently by Sullivan and colleagues (2015), low resilience has been associated with poorer outcomes following concussion in adults.[9, 61] Only recently has resilience and concussion investigated in pediatric samples. The first literature exploring this topic came from Durish, Yeates, and Brooks (2018), who found that low resilience significantly predicted persistent post-concussive symptoms in a pediatric sample (8-18 years). In fact, their research demonstrated that high resilience may protect against the development of prolonged post-concussive symptoms, even after having sustained multiple previous concussions.[62] The same researchers later confirmed this finding in adolescents (13-18 years) and suggested that resilience may indirectly modify concussion outcomes through relationships with anxiety and depressive symptoms.[36]

In 2021, Bunt and colleagues sought to explore the role of resilience in concussions specifically acquired through sport participation (SRC). In their AYA sample (13-25 years), they found that, within ten days of SRC, participants with low resilience had more severe symptoms and a higher risk of anxious and depressive symptoms. Individuals with low resilience also took longer to recover from SRC. In this study, there appeared to be a ceiling effect of resilience, wherein participants with moderate and high resilience did not differ significantly with regards to outcome measures.[9] In 2022, Ernst and colleagues confirmed that AYA athletes with low resilience took longer to recover, had more affective symptoms and perceived stress, and had more vestibular and ocular impairments following SRC. These researchers conclude that resilience is among the strongest predictors of recovery duration and suggest that it is worth considering as a staple assessment to guide clinical management following the injury.[63] However, missing from this field is prospective data with measurements collected before injury, acutely post-SRC, and throughout recovery. Due to this limitation, it is unknown whether resilience decreases acutely following SRC and, if so, when it returns to pre-injury levels. Also, measures of pre-injury resilience have not yet been explored in relation to adolescent SRC outcomes.

An overwhelming majority of studies investigating whether resilience is modifiable conclude that it is dynamic and fluctuates in response to environmental factors.[64, 65] Numerous interventions have therefore been proposed and subsequentially shown to enhance resilience, including mindfulness training, and cognitive behavioural therapy (CBT).[39, 40, 66] As resilience may be a modifiable factor associated with poor SRC outcomes, researchers have proposed resilience-targeting interventions following SRC, particularly for youth identified to have low resilience.[9] An understanding of the trajectory of resilience throughout adolescent SRC may prove useful when developing resilience-targeting treatment protocols.

1.3.5 Measurement and Analysis

Resilience is a concept which humans may understand intuitively, but have difficulty operationalizing for scientific investigation.[67] The first such scientific pursuits were undertaken in the 1970s. During these years, Michael Rutter released an article entitled 'Protective Factors in Children's Responses to Stress and Disadvantage.'[67] At the same time, Emmy Werner pioneered her research on resilience through her studies of Kauai children in Hawaii.[68, 69] Since then, numerous surveys have been developed to measure resilience. In 2011, Windle and colleagues assessed nineteen of the leading resilience measures. The researchers compared the measures across numerous domains, including content

validity, internal consistency, criterion and construct validity, and test-retest reliability. While they conclude that no single measure could be considered the stand-out survey, the Connor-Davidson Resilience Scale (CDRISC), the Resilience Scale for Adults, and the Brief Resilience Scale (BRS) were among the most psychometrically valid.[35, 37, 70, 71]

The Connor-Davidson Resilience Scale 10 (CDRISC-10) is a widely used modified version of the CDRISC. The survey consists of 10 questions which are self-reported on a 5-point Likert scale ranging from zero ("not true at all") to four ("true nearly all the time.") The questions include, "Having to cope with stress can make me stronger," and "I am not easily discouraged by failure."[37] The Cronbach's alpha for the CDRISC-10 is 0.85, indicating a reliable internal consistency.[37] Unfortunately, reference ranges for healthy Canadian ASP are not yet available. For Russian and Chinese youth, the average score has been reported approximately 25 out of the possible 40 points.[43, 44] Mean scores of 26.85 and 25.35 have been reported for Canadian male and female adolescents, respectively, though these participants were enduring post-concussive symptoms at the time of measurement.[36]

1.4 CORTISOL IN YOUTH

"The HPA axis is the main physiological system which mediates the body's stress response… cortisol [is] the end product of HPA axis activation."[72]

1.4.1 Overview

Cortisol is the end-product of the hypothalamus-pituitary-adrenal (HPA) axis. As discussed in section 1.3.2, in response to stressors, and as per a circadian rhythm, the hypothalamus' paraventricular nucleus (PVN) excretes corticotrophin-releasing hormone (CRH), modulating the anterior pituitary to the release adrenocorticotropic hormone (ACTH). ACTH enters systemic circulation and travels to the cortex of the adrenal glands where cells are stimulated to produce and release cortisol into the blood stream (see Figure 1.2A).[72, 73]

Cortisol has myriad effects including facilitating immune responses and maintaining homeostasis of glucose.[74] It also crosses the blood brain barrier (BBB) where, in the CNS, cortisol influences learning and memory through interactions with receptors throughout the limbic system – an important function during times of stress.[56] The hormone also inhibits its own production though negative feedback loops wherein it downregulates PVN and anterior pituitary activity.[72]

Cortisol follows a circadian rhythm. Concentrations peak shortly after awakening (the cortisol awakening response: CAR) and decrease throughout the day. After falling asleep, concentrations increase through the night.[75] It has been proposed that the CAR is linked to the cognitive appraisal of the day ahead, with a stronger CAR preceding more stressful days.[76] Heightened CARs have also been associated with a prolonged recovery to basal cortisol levels following an acute stressor.[77] During periods of chronic stress that lead to fatigue, the HPA axis may become overstimulated, resulting in a blunted CAR and diminished cortisol response to acute stressors.[72, 78-80] Basal cortisol refers to cortisol measurements in the absence of the CAR or acute stressors, and is measured between 11:00am and 6:00pm when investigating SRC.[81] In contrast, reactive cortisol can be measured following the administration of an experimentally stressful events, such as the Trier Social Stress Test for Children, or ACTH stimulation tests.[73, 82] Ultimately, morning, basal, and reactive measures of cortisol may all inform on HPA axis functioning.

Sex and pubertal status may also be associated with cortisol outputs during adolescence. Females are generally found to have generally higher diurnal cortisol, and may have a greater CAR compared to

males.[83, 84] As the HPA axis may be influenced by testosterone and estrogen, researchers suggest that it may appropriate to consider pubertal development in addition to age when investigating cortisol in adolescence.[85] Indeed, cortisol concentrations have been found to increase for both males and females following puberty.[86]

1.4.2 Cortisol and Resilience

As mentioned in Section 1.3.2 ("Biology of Resilience"), cortisol has been linked to psychological resilience. Researchers have found that higher resilience is associated with a stronger CAR, a greater decrease throughout the day, and generally lower basal cortisol throughout the day.[11, 12] However, some reports suggest a negative relationship between resilience and the CAR.[87] Altogether, researchers agree that high resilience is linked to healthy HPA axis performance,[87, 88] though the relationship between resilience and cortisol is complex and merits further investigation among ASP.

1.4.3 Cortisol and Concussion

For decades, researchers have been interested in the relationship between cortisol and head injury.[89] In moderate-to-severe TBI, low cortisol has been shown to predict more severe outcomes, including mortality, and up to 78% of individuals with moderate-to-severe TBI were shown to develop hypocortisolemia following their injury.[90] While cortisol may increase within six hours following concussion, the hormone has been shown to decrease in the days following concussion in adolescents, suggesting transient injury to the hypothalamic-pituitary axis.[10, 90] Moreover, low cortisol has been associated with increased symptom burden and prolonged recovery after injury in pediatric and young adult samples.[8, 10]

There are several locations along the HPA axis which may be vulnerable to disturbance following concussions. The pituitary stalk (also known as the infundibulum) is one such location. The pituitary gland is a small structure (<1 gram) and it tethered by the pituitary stalk to the hypothalamus.[91] The stalk is both fragile and highly vascularized, putting it at risk for injury from shearing and hypoxia.[91-93] Given cortisol's anti-inflammatory properties, low cortisol following concussion may be of concern.[94] To clarify, if cortisol response is diminished, the immune response following SRC may be insufficient to appropriately regulate neuroinflammation, thereby increasing risk of cellular damage and neural dysfunction, an effect illustrated in Figure 1.2B.[95] However, low cortisol following adolescent SRC has only been demonstrated with morning samples collected before 10:00am,[10] and group-level comparisons of basal cortisol have yet to

be investigated. In their young adult sample, Battista et al., (2019) did not find significantly lower basal cortisol (11:00am – 6:00pm) among SRC athletes compared to their uninjured counterparts.[81] Investigation into basal cortisol following adolescent SRC would add value to the current understanding of the pathophysiology of this injury.

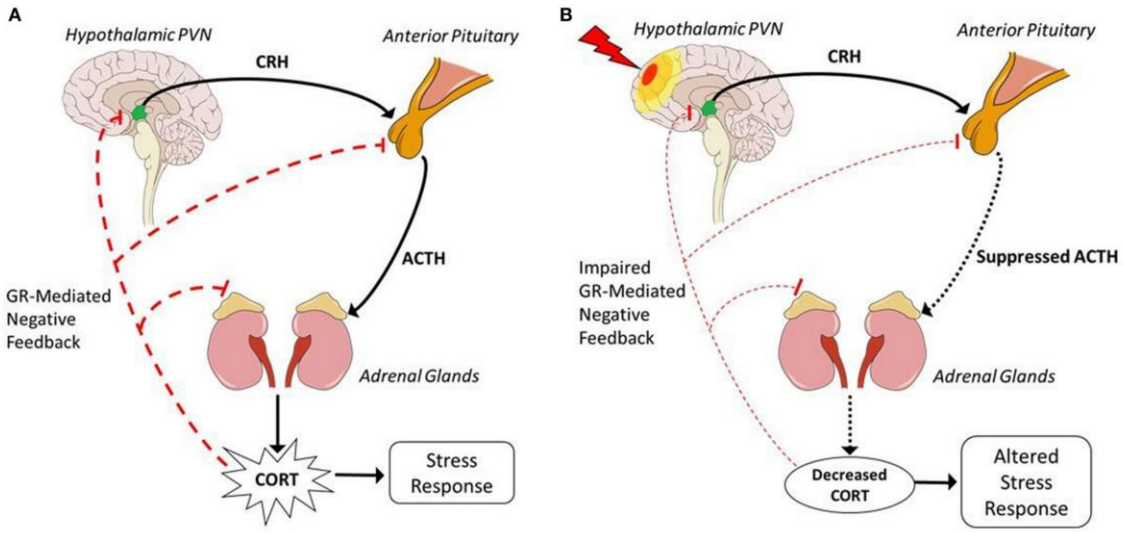

Figure 1.2. Hypothalamic-Pituitary-Adrenal (HPA) Axis.

Before (A) and after (B) traumatic brain injury (TBI). The figure outlines the potential for TBI to disrupt HPA axis function, altering cortisol release following injury. Figure cited from Tapp et al., 2019.[95] Figure cited in accordance to Creative Commons CC-BY License.[96]

1.4.4 Measurement

Some of the most common methods to measure cortisol include hair,[77, 97-99] saliva,[10, 57, 77, 83, 84, 100-107] plasma,[80, 89] and serum.[8, 108] Hair cortisol can be used to biomarker stress retrospectively over weeks to months.[98, 99] For many studies, saliva is the preferred method as it is non-invasive, can be collected by study participants, and does not cause psychological stress, as might a collection requiring venipuncture.[106, 109] However, salivary cortisol has lower concentrations compared to samples measured from blood collection as it reflects only the unbound molecule that must cross the oral mucosa for measurement.[110] In contrast, plasma and serum are considered more accurate measurements of total circulating cortisol.[109] Despite serum cortisol being somewhat lower than plasma cortisol, the two have a near perfect correlation and so are considered by some researchers to be interchangeable.[111, 112]

1.5 LINKING CONCUSSION, RESILIENCE, AND CORTISOL

To the best of our knowledge, this is the first study to investigate the interplay between adolescent psychological resilience, plasma cortisol, and SRC outcomes. As outlined above, complex relationships have been identified between resilience and SRC outcomes, cortisol and SRC outcomes, and resilience and cortisol in the absence of SRC. Examining the latter relationship following SRC has the potential to inform on the pathophysiology of this injury and embolden researchers to further explore resilience-targeting treatment interventions that may improve recovery following adolescent SRC.

2 CHAPTER 2: AIMS, HYPOTHESES, AND STUDY DESIGN

2.1 CHAPTER 2: AIMS & HYPOTHESES

2.1.1 Exploratory Aim and Hypothesis 1 & 2: Chapter 3

Exploratory Aim 1: To investigate the trajectory of resilience among adolescents pre-injury, acutely post-SRC, and at time to return to play (RTP) following SRC while controlling for age and sex.

Exploratory Hypothesis 1: We hypothesized that resilience would decrease acutely following SRC and return to near baseline conditions at time of RTP. We also expected resilience would increase with age independent of sex.

Exploratory Aim 2: To investigate the associations between resilience and SRC outcomes (symptom burden and length of recovery) following SRC in adolescent sport participants controlling for age and sex.

Exploratory Hypothesis 2: We hypothesized that high resilience would be associated with decreased symptom burden and a shorter length of recovery. We expected that females would take longer to recover and would report higher symptom burdens. Age would be negatively associated with length of recovery.

2.1.2 Exploratory Aims and Hypotheses 3 & 4: Chapter 4

Exploratory Aims 3.1 & 3.2: To investigate group differences in morning (3.1) and basal (3.2) plasma cortisol among uninjured adolescent sport participants (ASP) compared to their acute post-SRC counterparts controlling for age and sex/menstrual cycle phase.

Exploratory Hypotheses 3.1 & 3.2: We hypothesized that both morning (3.1) and basal (3.2) cortisol release would be lower acutely following SRC, and that females would have higher cortisol than males.

Exploratory Aim 4.1 & 4.2: To investigate associations between morning (4.1) and basal (4.2) cortisol SRC outcomes (symptom burden and duration of recovery) acutely following adolescent SRC controlling for age and sex/menstrual cycle phase.

Exploratory Hypotheses 4.1 & 4.2: We hypothesized that for both sexes, low morning (4.1) and basal (4.2) cortisol would be associated with more severe symptoms and a longer duration of recovery.

2.1.3 Specific Aims and Hypotheses 1 & 2: Chapter 5

Specific Aims 1.1 & 1.2: To evaluate the associations between morning (1.1) and basal (1.2) plasma cortisol and psychological resilience in the absence of injury among adolescent sport participant controlling for age and sex.

Specific Hypotheses 1.1 & 1.2: For both sexes, higher resilience would be associated with increased morning (1.1) and basal (1.2) cortisol in uninjured adolescent sport participants.

Specific Aims 2.1 & 2.2: To evaluate the associations between morning (2.1) and basal (2.2) plasma cortisol and psychological resilience acutely post-SRC among adolescent sport participant controlling for age, sex, and symptom severity.

Specific Hypotheses 2.1 & 2.2: For both sexes, higher resilience would be associated with increased morning (2.1) and basal (2.2) cortisol in adolescent sport participants acutely post-SRC.

2.2 SETTING

This project was encompassed within the pan-Canadian multicenter prospective cohort study SHRed Concussions (Surveillance in High-Schools to Reduce Concussions and their Consequences). Through study sites in Vancouver BC, Edmonton AB, Calgary AB, London ON, and Laval QC, participants were recruited as teams from high-risk-for-concussion sports. At the beginning of their sporting seasons, participants completed uninjured assessments and blood draws in the community (via the 'SHRed Mobile,' [see Image 8.1]), or in a designated phlebotomy room.

If a suspected SRC occurred, the injured participant attended a SHRed-affiliated sports-medicine clinic where they were assessed by a sports-medicine physician to confirm the diagnosis of SRC and for follow-up appointments. SRC diagnosis and management was guided by the 5th International Consensus on SRC.[7] The study was approved by the University of Calgary Conjoint Health Research Ethics Board (CHREB) # REB18-2107.

2.3 STUDY DESIGN

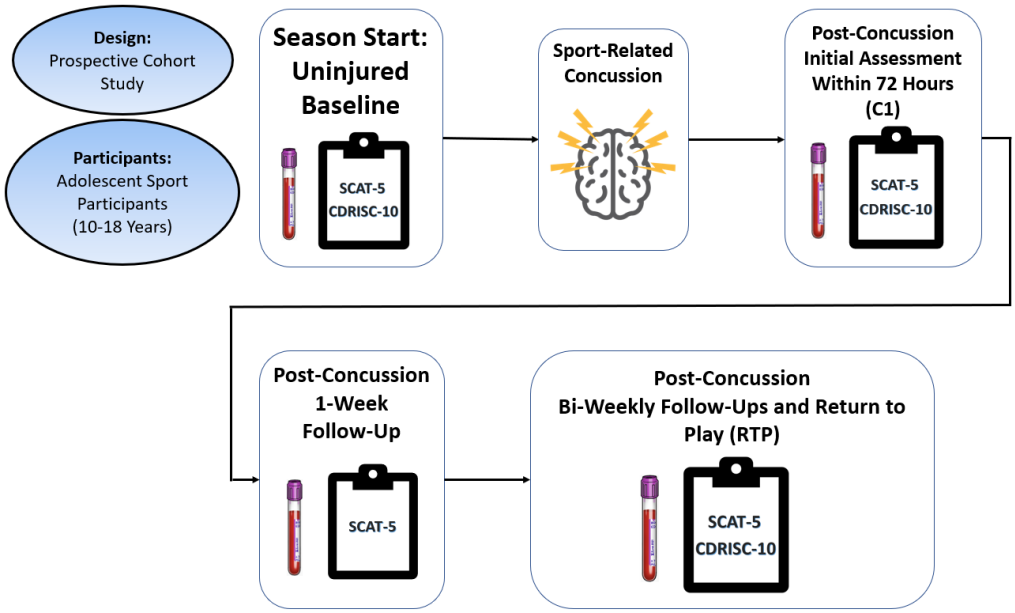

Figure 2.1. SHRed Fluid Biomarker Study Design.

SHRed Concussions fluid biomarker study design including timepoints at which plasma cortisol and assessments were collected. Blood, SCAT-5, and CDRISC-10 were completed at uninjured baseline testing, and again at the initial clinical visit following SRC. Blood and SCAT-5 were completed at the one-week follow-up, and all three measures were collected thereafter at bi-weekly follow-ups and the RTP visit. SCAT-5; Sport Concussion Assessment Tool 5, CDRISC-10; Connor-Davidson Resilience Scale 10, SRC; Sport-related concussion, RTP; Return to play.

2.4 PARTICIPANT INFORMATION

SHRED aimed for equitable representation of males and females, as well as participants of diverse ethnic and cultural backgrounds. This goal was accomplished by enrolling both male and female sports teams and encouraging participation from both urban and rural communities. Moreover, we recognized the importance of investigating sport-related injuries among gender non-conforming youth, and so such persons were not excluded from participating in the study, though they may have been excluded from analyses requiring sex as a covariate. Participants enrolled as part of a team to complete uninjured baseline testing, though some participants also enrolled upon injury. Adolescents aged 14 years and older (mature minors) provided written consent for participation in this study, whereas younger participants required written parental assent.

Adolescents aged 10-18 years enrolled in at least one sport which poses high-risk of concussion were eligible to enroll in the study. Such sports included, but were not limited to ice hockey, ringette,

rugby, football, soccer, wrestling, volleyball, and basketball. Adolescents who were unable to participate in sport due to recent broken bones and/or surgeries, and those with a history of systemic disease (e.g., heart disease, cancer) or neurological disorder (e.g., cerebral palsy) were excluded from the study. Venipuncture was not performed on youth who disclosed a history of clotting disorders.

2.5 Data Collection and Assessments

Data collection occurred primarily at two occasions: baseline (uninjured) and post-SRC. Baseline assessments occurred near the beginning of sporting seasons, whereas post-SRC assessments occurred following an SRC diagnosis. On baseline testing, participants completed the SCAT-5 accompanied by a research assistant.[31] The participants were instructed to complete the SCAT-5 Post-Concussion Symptom Scale (SCAT-5 PCSS) (see appendix Assessment 1) based on how they *typically* feel. Participants had open access to SHRed's online portal to report baseline Connor-Davidson Resilience Scale 10 (CDRISC-10) scores (see appendix Assessment 2).[37] Participants also reported medical history on the preseason baseline questionnaire (PBQ). Voluntary blood draws occurred at baseline testing sessions, at which point volunteers completed an additional Blood Draw Survey.

Upon sustaining a suspected SRC, participants attended a SHRed-affiliated sports-medicine clinic. Accompanied by a clinician, participants completed the SCAT-5 PCSS and were instructed to complete the PCSS based on how they *currently* feel. SRC diagnosis was determined by a sports-medicine physician following guidelines outlined in the 5th International Consensus of SRC.[7] The physicians also determined the time at which participants may return to their sports (return to play; RTP). Details of the injury were recorded on the Injury Report Form (IRF). Participants were encouraged to complete post-SRC CDRISC-10 assessments and were provided the opportunity to undergo voluntary venipuncture for hormone analysis. This process was repeated at follow-up appointments. (See appendix for complete SCAT-5, PBQ, Blood Draw Survey, and IRF).

While the SCAT-5 PCSS and blood draw were completed in-person, the CDRISC-10 was completed at the participant's leisure using the online portal. Participants were encouraged to complete the survey at the time they received their in-person assessments, so assessments tended to be completed in close temporal proximity; however, these assessments did not always occur on the same day. For uninjured participants, the SCAT-5, CDRISC-10, and blood draw must have occurred within 90 days for eligibility in this study. Post-SRC, assessments were included only if the measurements were completed

within three days of each other. CDRISC-10 assessments were considered RTP measurements if they were completed from 5 days before to 15 days after medical clearance to return unrestricted to their sport.

2.6 Blood Collection and Processing

Venipuncture was performed by certified phlebotomists or research nurses. Blood was collected from the antecubital fossa into 10mL K2-EDTA plasma tubes and centrifuged at 1300g for 10 minutes at room temperature. Plasma samples were aliquoted and frozen (-80°C) within two hours of collection.

Alberta Precision Labs (APL) measured plasma cortisol and progesterone concentrations using the Roche Cobas e801 analyzer. Samples were analyzed in singlicate using indirect competitive immunoassays using electrochemiluminescence (ELCIA; Roche Diagnostics, Rotkreuz, Switzerland). Cobas Elecsys Cortisol II and Cobas Elecsys Progesterone III assays were used to detect cortisol and progesterone, respectively.

2.7 Medication Reporting

Medication use was self-reported on up to 4 forms per participant: Pre-season Baseline Questionnaire (PBQ) Medical History, the SCAT-5, the Blood Survey, and the Injury Report Form (IRF). As medication use may be subject to change between sporting seasons, medication use was not cross-referenced across years of enrollment, though it was cross-referenced between the aforementioned forms within the same enrollment year. Medication use for each data chapter is summarized in the appendix.

2.8 Menstrual Cycle Phase Determination

Contraceptive use may alter cortisol concentrations.[113] Therefore, females reporting contraceptive use were excluded from analyses involving cortisol. For participants reporting no use of contraceptives, menstrual cycle phase was determined to be follicular if progesterone was <5.0 nmol/L, and luteal if progesterone was ≥5.0 nmol/L.[114]

3 CHAPTER 3: PSYCHOLOGICAL RESILIENCE AND ADOLESCENT SPORT-RELATED CONCUSSION: CONSIDER ACUTE MEASURES

3.1 ABSTRACT

Introduction: Psychological factors such as resilience contribute to recovery following sport-related concussion (SRC). Given that resilience is modifiable, it may serve as a therapeutic target to improve recovery after SRC; however, there is a lack of prospectively collected data investigating the trajectory of resilience following concussion.

Objectives: Our primary objective was to investigate the trajectory of resilience from pre-injury, to acutely post-SRC (within 10 days of injury), and to time of return to play (RTP). Secondarily, we investigated the associations between resilience and symptom burden and length of recovery.

Methods: This prospective cohort study was nested within the pan-Canadian SHRed Concussions (Surveillance in High Schools to Reduce the Risk of Concussions and their Consequences) study. Adolescent sport-participants (ages 10-18 years) completed the Connor-Davidson Resilience Scale-10 (CDRISC-10; 0-40 points) and Sport Concussion Assessment Tool-5 (SCAT-5; symptom number: 0-22, symptom severity: 0-132) prior to injury, acutely post-SRC (≤ 10 days), and at RTP. Linear mixed effect models evaluated the difference in CDRISC-10 scores between time points controlling for age and sex. Linear regressions and time to event analyses evaluated the relationships between CDRISC-10 scores and symptom burden and length of RTP.

Results: Four hundred and twenty-five adolescents (194 females, 15.88±1.29 yrs; 231 males, 15.77±1.36 years) participated. Longitudinally, there was a significant sex by timepoint interaction, whereby CDRISC-10 scores in males, but not females, decreased acutely post-SRC (β=-0.914, 95% CI: -1.721, -0.107, p=0.027). Female, but not male, scores were increased at RTP (β=2.797, 95%CI: 1.506, 4.088, p<0.001). Symptom number (β=-0.266, 95%CI: -0.429, -0.102, p=0.001), symptom severity (β=-0.922, 95%CI: -1.482, -0.361, p=0.001), and length of RTP (HR=1.042, 95% CI: 1.015, 1.071, p=0.002) decreased with increased acute CDRISC-10 scores when controlling for age and sex.

Conclusion: Male resilience was lower post-SRC, and female resilience increased at RTP. Higher resilience was associated with lower symptom burden and shorter recovery for both sexes. Our study provides evidence for resilience as a modifiable therapeutic target to improve recovery following SRC in adolescents.

3.2 INTRODUCTION

An estimated 10% of Canadian adolescents sustain a sport-related concussion (SRC) each year, presenting a significant public health concern.[15, 16] Typical recovery for adolescents is less than four weeks; however, nearly 30% remain symptomatic past one month, with females having a greater risk of prolonged recovery.[5, 115] Psychological resilience may influence recovery following SRC.[9, 63]

Resilience is broadly defined as one's ability to 'bounce back', or thrive in the face of adversity.[37] Resilience may vary by age and sex, with males typically reporting higher resilience than females, and female resilience potentially decreasing through adolescence.[43, 44, 47] However, some studies report no associations between resilience with age,[43] while others find a general increase across adolescence despite interruptions attributed to major life events, such as starting high school.[116]

Resilience among Canadian adolescent sport participants (ASPs) is not well-characterized. This topic merits further investigation as researchers have identified resilience as an important consideration for recovery following concussion. For instance, resilience predicted post-concussive symptoms at more than six-months post-injury in children,[62] and adolescent and young adult studies have demonstrated that low resilience measured within ten days following SRC was associated with increased symptom burden and duration of recovery.[9, 63] The mechanism by which resilience may influence concussion outcomes is unclear, although Durish and colleagues (2019) propose that anxiety and depressive symptoms may mediate this relationship.[36] Provided that resilience is a strong predictor of recovery, researchers recommend this measure be considered in the clinical management of SRC.[63]

To our knowledge, measures of pre-and-post SRC resilience have not yet been investigated among ASP or other populations, though Hassan et al, (2024) found that resilience was lower for children acutely following concussion compared to their orthopedic injury counterparts, suggesting that concussion may be associated with a decrease in resilience acutely post-injury.[117] A link between SRC and alterations in resilience is plausible due to post-SRC impairments in neural circuitry involved in the stress response. For instance, the homeostatic balance of mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) within the hippocampus are reported to influence resilience. These receptors respond to cortisol secretion, which may become aberrant with hypothalamic-pituitary-adrenal (HPA) axis impairment following SRC.[10, 55, 56, 90] Encouragingly, resilience has been reported as a modifiable factor that may be

improved through practices such as mindfulness training, suggesting its potential as a target for therapeutic intervention.[9, 40]

In this study, male and female ASP resilience, measured using the Connor-Davidson Resilience Scale 10 (CDRISC-10),[37] was compared at three time points: pre-injury, acutely (≤10 days) post-SRC, and at the time of medical clearance to return to play (RTP). We hypothesized CDRISC-10 scores would decrease acutely post-SRC and then return to pre-injury levels at RTP. We also hypothesized CDRISC-10 scores would be higher in males compared to females, and increase with age. Furthermore, we investigated the relationships between CDRISC-10 scores (measured pre-injury, post-SRC, and the change from pre-to-post SRC) and clinical outcomes (acute symptom burden and time to RTP), hypothesizing that pre-injury and post-SRC measures of resilience, and a greater decrease in resilience following injury, would be related to increased symptom burden and recovery time.

3.3 METHODS

3.3.1 Study Design

This observational prospective cohort study was embedded within the pan-Canadian SHRed Concussions (Surveillance in High Schools and Community Sports to Reduce Concussions and their Consequences) study. Participants (ages 10-18 years) were enrolled from high-risk-for-concussion sports (e.g., rugby, wrestling, and ringette) from multiple sites (Vancouver BC, Edmonton and Calgary AB, Winnipeg MB, London ON, and Laval, QC). Pre-injury resilience was reported through SHRed's online portal at the start of their sporting season, and post-SRC measures were completed using the portal following diagnosis of SRC by a SHRed-affiliated sports medicine physician. This study was approved by the University of Calgary Conjoint ethics board (REB18-2107).

3.3.2 Inclusion and Exclusion Criteria

For inclusion in SHRed Concussions, participants were enrolled in at least one high-risk-for-concussion sport. Individuals aged 14 years and older provided written consent, whereas younger participants required parental assent for participation in this study. For this sub-study, participants must have been diagnosed with an SRC while enrolled in SHRed and have completed at least one CDRISC-10 survey throughout their recovery. As repeat SRCs were recorded for some participants, only the first was included in this study.

Exclusion criteria included a diagnosis of systemic disease/neurological condition or a fracture/surgery within the past year that would hinder sport participation. Participants were also excluded if they did not disclose their sex as either male or female.

3.3.3 Data Collection and Clinical Assessments

Participants completed pre-injury assessments at study enrollment and the start of subsequent seasons. At those times, participants also reported demographic and medical history on pre-season baseline questionnaires (PBQs). Upon suspected SRC, participants were assessed by a sports-medicine physician. SRC diagnosis and clinical management followed guidelines outlined in the 5th International Consensus of SRC.[7] Participants completed study assessments at a one-week follow-up and every two weeks until RTP. As the CDRISC-10 was reported online, scores reported from 5 days before to 15 days after date of medical clearance were classified as RTP measures.

Two assessments were included in this study. Resilience was measured using the Connor-Davison Resilience Scale 10 (CDRISC-10).[37] The ten questions (e.g., "I believe I can achieve my goals, even if there are obstacles") were rated from on a five-point Likert scale scored from zero ("not true at all") to four ("true nearly all the time"). The maximum CDRISC-10 score is therefor 40-points. To be considered for analysis, participants must have completed at least seven of ten CDRISC-10 questions, and missing values were imputed with the mean of the answered questions.[118] Symptom burden (number and severity of symptoms) was measured at all timepoints using the Sport-Concussion Assessment Tool 5 Post-Concussion Symptom Scale (SCAT-5 PCSS).[31] The 22 symptoms (e.g., "Headache") were rated from zero ("none") to six ("severe"). The maximum number and severity of symptoms were therefore 22 and 132, respectively.

3.3.4 Statistical Analyses

Our primary analysis longitudinally compared CDRISC-10 scores at three time points (pre-injury, acute post-SRC, and RTP) using a multilevel mixed-effects linear regression including all participants within each timepoint. To further evaluate this relationship, within-subject sensitivity analysis was completed specific to participants having complete CDRISC-10 data at all three time points. Both models controlled for age (years) and sex (M/F).

Secondary analyses evaluated the association between CDRISC-10 scores (stratified by pre-injury, acute post-SRC, and pre-minus-post SRC scores) and symptom burden (number of symptoms and symptom severity) using robust generalized linear models of the family Poisson and link log. Cox proportional hazards analyses were employed to investigate associations between CDRISC-10 scores and time to RTP. Time-to-event survival plots were created to visualize recovery whereby participants were categorized as having low (0-10th percentile), average (10th-90th percentile), or high (90th-100th percentile) resilience. Statistical significance was determined a priori as alpha < 0.05. All statistical analysis was performed using STATA (v 18).[119]

3.4 RESULTS

3.4.1 Participant Characteristics

Between September 2019 and December 15th, 2023, SHRed Concussions recruited 11,226 participants reporting a total of 1661 concussions during the study. Data collection continued through the COVID-19 pandemic, though from March 2020 to July 2021, with assessments completed virtually. Summarized in Figure 3.1, the CDRISC-10 was completed at least once following 456 concussions. Final analysis included assessments reported from 425 SRCs, with a total of 289 pre-injury resilience assessments, 298 acute post-SRC assessments, and 124 assessments completed at RTP. (Figure 3.1; Table 3.1)

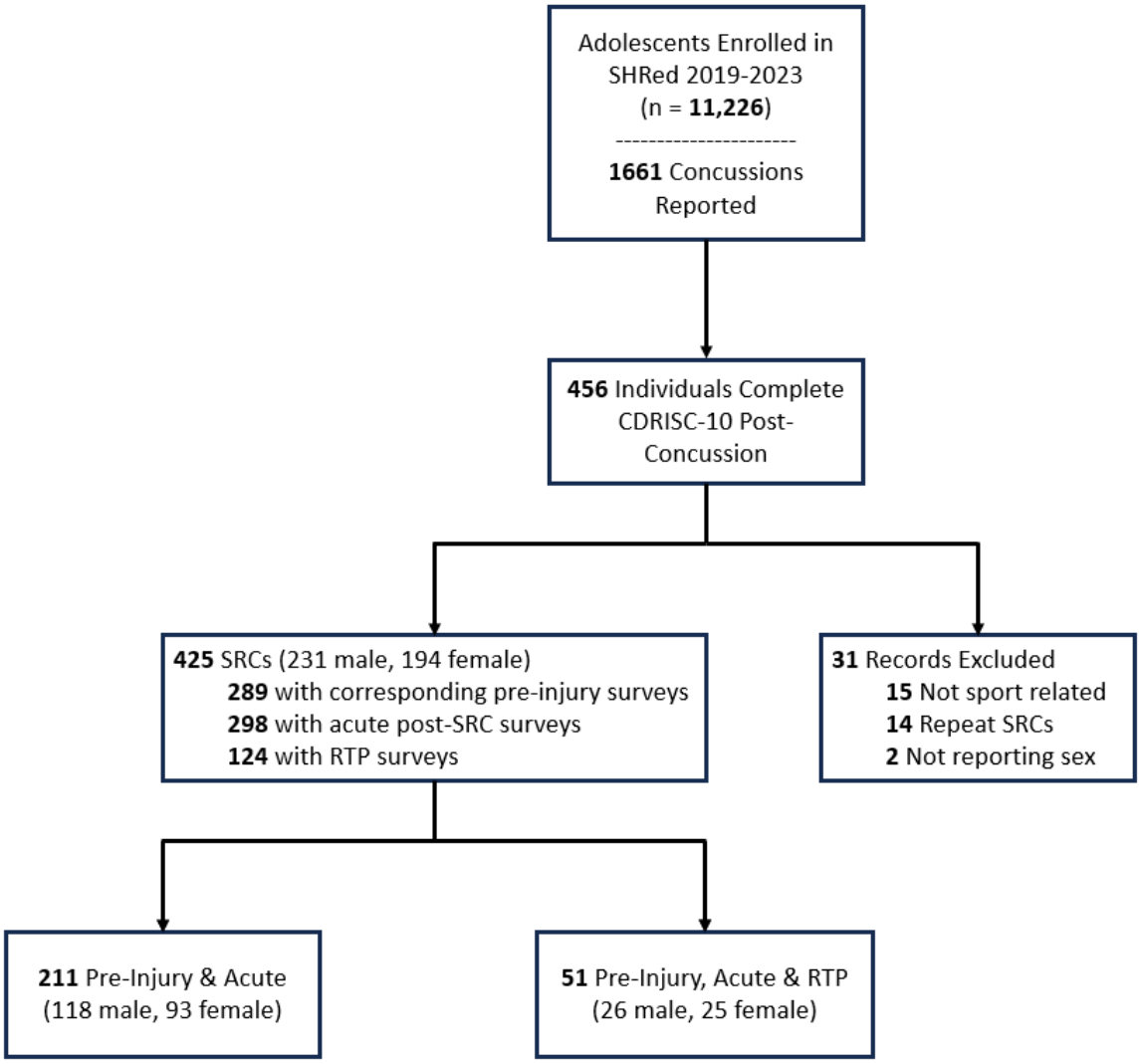

Figure 3.1: Study Flowchart of Participants.

Acute; Within 10 days post-SRC, RTP; Return to Play (Within five days prior to, to 15 days following date of medical clearance to RTP).

Table 3.1: Participant Characteristics

	Female (n=194)	**Male (n=231)**
Age (Mean, SD)	15.88 ± 1.29	15.77 ± 1.36
CD-RISC Timepoints & Scores		
Pre-Injury Measures n (%) Score (Mean, SD)	137 (70.62%) 28.23 ± 5.95	152 (65.80%) 30.45 ± 5.03
Acute Measures n (%) Score (Mean, SD)	128 (65.98%) 28.48 ± 5.36	170 (73.59%) 30.04 ± 5.27
RTP Measures n (%) Score (Mean, SD)	60 (30.93%) 31.42 ± 5.21	64 (27.71%) 30.02 ± 5.56
Pre-Injury and Acute Measures n (%) Difference in Score from Pre-Injury to Acute (Mean, SD)	93 (47.94%) 0.42 ± 4.40	118 (51.08%) 0.70 ± 5.12
Pre-Injury, Acute, & RTP CD-RISC Measures n (%)	25 (12.89%)	26 (11.26%)
Injury Characteristics		
Number of Symptoms (Median (IQR)) Missing from Acute CDRISC n (%)	13.5 (7, 19) 10 (7.81%)	9 (4, 15) 14 (8.24%)
Symptom Severity (Median (IQR)) Missing from Acute CDRISC n (%)	31 (11, 48) 10 (7.81%)	19 (6, 36) 14 (8.24)
Time to RTP (days) (Median (IQR)) Missing from Acute CDRISC n (%)	21 (15, 38) 3 (2.34%%)	18 (13, 26) 4 (2.35%)
Activity At Time of Injury		
Rugby n (%)	63 (32.47%)	57 (24.68%)
Football n (%)	10 (5.15%)	103 (44.59%)
Hockey n (%)	13 (6.70%)	36 (15.58%)
Ringette n (%)	32 (16.49%)	-
Soccer n (%)	17 (8.76%)	9 (3.90%)
Volleyball n (%)	17 (8.76%)	4 (1.73%)
Basketball n (%)	11 (5.67%)	8 (3.46%)
Wrestling n (%)	9 (4.64%)	8 (3.46%)
Synchronized Swimming n (%)	7 (3.61%)	-
PE Class n (%)	5 (2.58%)	2 (0.87%)
Other n (%)	10 (5.15%)	4 (1.73%)

Acute: Within 10 days of SRC. RTP: Return to Play (5 days prior to 15 days following date of medical clearance).
Difference in CDRISC-10 Score calculated by pre-injury CDRISC-10 score minus acute post-SRC CDRISC-10 score. A greater value indicated a greater decrease in resilience post-SRC compared to pre-injury.
Number and severity of symptoms were reported on the SCAT-5 PCSS within 10 days of SRC.
'Other' Activity at Time of Injury, three or less SRCs reported during: Skiing, Baseball, Road Cycling, Lacrosse, Ultimate Frisbee, Tobogganing, Coaching Soccer, Cheerleading, Summer Camp Games.
IQR: Inter-Quartile Range (Median (Q1, Q3))

3.4.2 Longitudinal Analyses

Primary Longitudinal Analysis

The longitudinal analysis revealed significant sex by timepoint (Wald test: $\chi2=13.85$, $p=0.001$) and sex by age (Wald test: $\chi2=24.12$, $p<0.001$) interactions. For females, there was no change in CDRISC-10 score from pre-injury to acute post-SRC, but a significant increase from pre-injury at RTP ($\beta = 2.797$, 95% CI: 1.506, 4.088, $p < 0.001$). This increase represents a 2.8-point increase in CDRISC-10 score for females at the time of RTP compared to pre-injury. Age was not associated with CDRISC-10 score in females. (Table 3.2; Figure 3.2 A&B)

For males, there was a significant decrease in CDRISC-10 score from pre-injury to acute post-SRC ($\beta = -0.914$, 95% CI: -1.721, -0.107, $p = 0.027$), indicating a 0.9-point decrease. CDRISC-10 score was similar at pre-injury and RTP in males. CDRISC-10 score for males significantly increased with age ($\beta = 0.780$, 95% CI: 0.307, 1.254, $p = 0.001$), highlighting a 0.8-point increase per year throughout adolescence. (Table 3.2; Figure 3.2 A&B)

Sensitivity Longitudinal Analysis

The within-subject sensitivity analysis including only participants with complete CDRISC-10 data at all three timepoints revealed no significant sex by timepoint or sex by age interactions, though the trends were similar to those of the primary analysis.

CDRISC-10 score for females was unchanged between pre-injury to acute measures and increased at RTP compared to pre-injury ($\beta = 3.055$, 95% CI: 0.812, 5.300, $p = 0.008$). Similar to the primary analysis, this increase represents a 3.1-point increase in CDRISC-10 score. Female CDRISC-10 score was not associated with age. (Table 3.2; Figure 3.2 C&D)

CDRISC-10 score in males was no longer significantly associated with changes from pre-injury to acute or RTP timepoints and did not increase significantly with age. Despite lack of statistical significance, the effect size of age for male resilience ($\beta = 0.661$) was comparable to the primary longitudinal analysis, suggesting an increase in CRISC-10 score of approximately 0.7 points per year for males. (Table 3.2; Figure 3.2 C&D)

Table 3.2: Longitudinal Analyses. Acute Post-SRC and RTP CDRISC-10 Scores Compared to Pre-Injury CDRISC-10 Scores.

		Female			Male		
		β	**95% CI**	***p***	***β***	**95% CI**	***p***
All Subjects Within Timepoints **n = 394** **Pre-injury: 289 obs*** **Acute Post-SRC: 298 obs*** **RTP: 124 obs***	**Acute[a]**	-0.140	-1.047, 0.766	0.772	-0.914	-1.721, -0.107	0.027
	RTP[b]	2.797	1.506, 4.088	<0.001	-0.618	-1.878, 0.642	0.337
	Age[c]	-0.173	-0.699, 0.352	0.518	0.780	0.307, 1.254	0.001
Subjects With Complete Data in all Timepoints **n = 51, 153 obs***	**Acute[a]**	0.363	-1.154, 1.881	0.639	-0.181	-1.713, 1.350	0.816
	RTP[b]	3.055	0.812, 5.300	0.008	0.741	-1.493, 2.977	0.515
	Age[c]	-0.714	-1.832, 0.404	0.211	0.661	-0.658, 1.980	0.326

The sex by timepoint interaction was significant for the first analysis (Wald test: $\chi 2=13.85$, $p=0.001$).
The sex by age interaction was significant for the first analysis (Wald test: $\chi 2=24.12$, $p<0.001$).
The sex by timepoint interaction was not significant for the second analysis (Wald test: $\chi 2=2.13$, $p=0.345$).
The sex by age interaction was not significant for second analysis (Wald test: $\chi 2=3.60$, $p=0.308$).
The effect sizes (β) represent the unit difference in CDRISC-10 scores between timepoints (pre-injury to acute ([a]), pre-injury to RTP ([b]) and per year of age ([c]).
95% CI: 95% Confidence Interval.
***obs: observations**

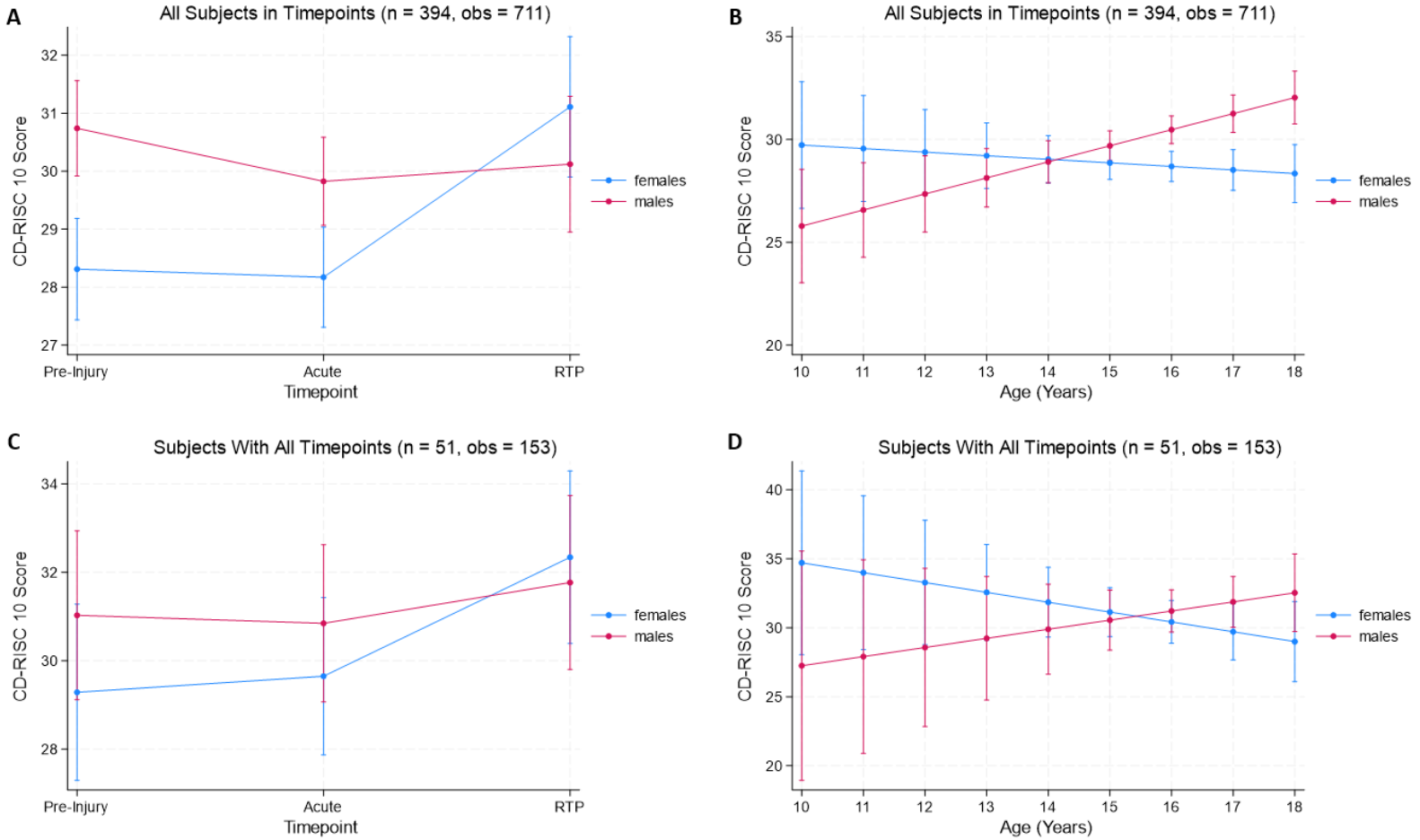

Figure 3.2: CDRISC-10 Scores: Sex by Timepoint, and Sex by Age Interactions.

(A) Primary longitudinal analysis sex by timepoint marginal means. Significant sex by timepoint interaction at RTP (Wald test: $\chi2$=13.85, p=0.001). Female CDRISC-10 score increased by 2.8-points from pre-injury to RTP (β = 2.797, 95% CI: 1.506, 4.088, p < 0.001), male CDRISC-10 score decreased 0.9-points from pre-injury to acute (β = -0.914, 95% CI: -1.721, -0.107, p = 0.027). (B) Primary longitudinal analysis sex by age marginal means. Significant age by sex interaction (Wald test: $\chi2$=24.12, p<0.001). No significant age effect for females, male CDRISC-10 score increased 0.8-points per year (β = 0.780, 95% CI: 0.307, 1.254, p = 0.001). (C) Sensitivity longitudinal analysis sex by timepoint marginal means. No significant sex by timepoint interaction at RTP (Wald test: $\chi2$=2.13, p=0.345). Female CDRISC-10 score increased 3.1-points from pre-injury to RTP (β = 3.055, 95% CI: 0.812, 5.300, p = 0.008), male CDRISC-10 score was not associated with timepoint. (D) Sensitivity longitudinal analysis sex by age marginal means. No significant age by sex interaction (Wald test: $\chi2$=3.60, p=0.308). Neither female nor male CDRISC-10 scores were significantly associated with age (see Table 3.2). Error bars represent 95% confidence intervals (CIs).

3.4.3 Resilience and SRC Outcomes

Pre-Injury CDRISC-10 Scores and SRC Outcomes

Pre-injury CDRISC-10 scores were not associated with acute post-SRC symptom severity or number of symptoms (Table 3.3) but were associated with duration of recovery (HR= 1.034, 95% CI: 1.008, 1.061, p = 0.010), controlling for age and sex. This result revealed that a 1-point increase in CDRISC-10 score was associated with a 3.4% increased likelihood of recovery, suggesting a greater likelihood of being medically cleared to RTP. (Table 3.4; Figure 3.3A)

Acute Post-SRC CDRISC-10 Scores and SRC Outcomes

CDRISC-10 scores measured acutely post-SRC were significantly associated with acute symptom severity (β = -0.922, 95% CI: -1.482, -0.361, p = 0.001), number of symptoms (β = -.266, 95% CI: -0.429, -0.102, p = 0.001) (Table 3.3), and duration of recovery (HR= 1.042, 95% CI: 1.015, 1.071, p = 0.002). These results demonstrated that a 1-point increase in CDRISC-10 score was linked to a 0.9-point decrease in symptom severity, a 0.3 decrease in total symptoms, and a 4.2% increased likelihood of recovery. (Table 3.4; Figure 3.3B)

Difference in CDRISC-10 Scores from Pre-to-Post SRC and SRC Outcomes

The difference between pre-injury CDRISC-10 scores to post-SRC CDRISC-10 scores was significantly associated with symptom severity (β = 0.971, 95% CI: 0.296, 1.646, p = 0.005) and number of symptoms (β = 0.253, 95% CI: 0.060, 0.445, p = 0.010) (Table 3.3) but not with time to RTP (Table 3.4; Figure 3.3C). The result suggested a 1-point decrease in CDRISC-10 score from pre-to-post SRC was associated with a 1-point increase in symptom severity and 0.3 more symptoms.

3.4.4 Age, Sex, and SRC Outcomes

Age and Sex Associations with Symptom Burden

Symptom severity (β = 3.629, β = 3.624, β = 3.578) and number of symptoms (β = 0.807, β = 0.807, β = 0.791) were positively associated with age across all models, suggesting a 3.6-point increase in severity of symptoms and 0.8 more symptoms with each year of age. (Table 3.3)

Symptom severity (β = -9.888, β = -8.304, β = -10.416) and number of symptoms (β = -2.222, β = -1.872, β = -2.428) were negatively associated with sex across all models. These effects indicated males reported approximately a 9-point lower symptom severity and two fewer symptoms compared to females. (Table 3.3)

Age and Sex Associations with Length of RTP

There was a significant negative relationship between age and RTP across all models (β = 0.851, β = 0.864, β = 0.863), highlighting a 15% increased likelihood of recovery with each increasing year of age. (Table 3.3)

While females tended to experience a longer recovery than males, this relationship was only statistically significant in the analysis examining the relationship between difference in resilience from pre-to-post-SRC with days to RTP (HR= 1.334, 95% CI: 1.008, 1.767, p = 0.044). This model found that males have a 33.4% increased likelihood of recovery compared to females. (Table 3.3)

Table 3.3: CDRISC-10 Scores and Symptom Burden Linear Regression Results.

Timepoint	Outcome	Independent Variables	*β*	95% CI	*p*
Pre-Injury	**Acute SCAT-5 Symptom Severity Score**	**CDRISC-10 Score**	-0.145	-0.766, 0.475	0.645
		Age	3.629	1.128, 6.129	0.004
		Sex*	-9.888	-16.619, -3.157	0.004
	Acute SCAT-5 Symptom Number	**CDRISC-10 Score**	-0.071	-0.251, 0.108	0.438
		Age	0.807	0.017, 1.598	0.045
		Sex*	-2.222	-4.159, -0.284	0.025
Acute Post-SRC	**Acute SCAT-5 Symptom Severity Score**	**CDRISC-10 Score**	-0.922	-1.482, -0.361	0.001
		Age	3.624	1.168, 6.081	0.004
		Sex*	-8.304	-14.872, -1.737	0.013
	Acute SCAT-5 Symptom Number	**CDRISC-10 Score**	-0.266	-0.429, -0.102	0.001
		Age	0.807	0.020, 1.594	0.044
		Sex*	-1.872	-3.785, 0.042	0.055
Difference from Pre-Injury to Acute	**Acute SCAT-5 Symptom Severity Score**	**Δ CDRISC-10 Score**	0.971	0.296, 1.646	0.005
		Age	3.578	1.137, 6.020	0.004
		Sex*	-10.416	-16.534, -4.297	0.001
	Acute SCAT-5 Symptom Number	**Δ CDRISC-10 Score**	0.253	0.060, 0.445	0.010
		Age	0.791	0.010, 1.571	0.047
		Sex*	-2.428	-4.293, -0.563	0.011

Margins reported from generalized linear regression models.
Acute: ≤ 10 days post-SRC.
***Sex comparisons made with females as reference.**
***β*: Beta coefficient. CI: 95% Confidence Interval.**

Table 3.4: CDRISC10 Scores and Time to RTP Time-to-Event Analysis Results

Timepoint	Independent Variables	HR	95% CI	*p*
Pre-Injury	**CDRISC-10 Score**	1.034	1.008, 1.061	0.010
	Age	0.851	0.763, 0.950	0.004
	Sex*	1.303	0.983, 1.725	0.066
Acute Post-SRC	**CDRISC-10 Score**	1.042	1.015, 1.071	0.002
	Age	0.864	0.775, 0.963	0.008
	Sex*	1.290	0.973, 1.710	0.077
Difference from Pre-Injury to Acute	**Δ CDRISC-10 Score**	0.994	0.964, 1.023	0.679
	Age	0.863	0.774, 0.964	0.009
	Sex*	1.334	1.008, 1.767	0.044

Results reported from cox proportional hazards models.
Acute: ≤ 10 days post-SRC.
***Sex comparisons made with females as reference.**
HR: Hazard Ratio. 95% CI: 95% Confidence Interval.

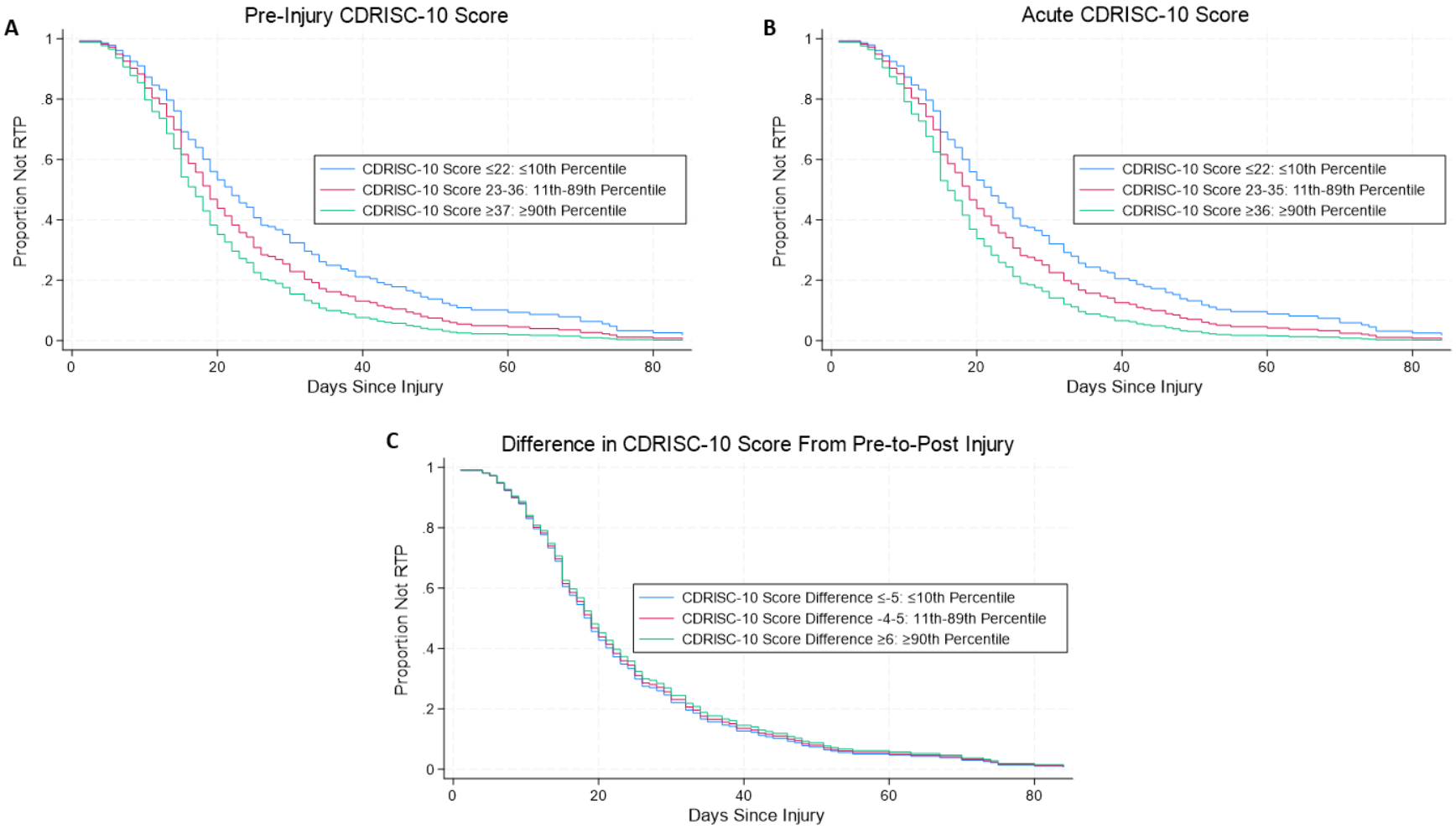

Figure 3.3: Time-to-Event Survival Plots.

Visualization of recovery time stratified by high (top 90th percentile), average (11th-89th percentile) and low (bottom 10th percentile) CDRISC-10 scores measured at (A) pre-injury (HR= 1.034, 95% CI: 1.008, 1.061, p = 0.010), (B) acute post-SRC (HR= 1.042, 95% CI: 1.015, 1.071, p = 0.002), and (C) the difference from pre-to-post-injury (HR= 0.994, 95% CI: 0.964, 1.023, p = 0.679).

3.5 DISCUSSION

This was the first study to evaluate the changes in resilience from pre-injury and throughout recovery in adolescent sport-participants (ASP) following SRC. We also explored the associations between resilience and symptom burden and length of RTP. Our primary longitudinal analysis found that male resilience decreased acutely post-SRC, although this finding was not confirmed in the sensitivity analysis, and female resilience increased at time of RTP compared to pre-injury levels. Secondary analyses revealed that pre-injury resilience was associated with length of RTP when controlling for age and sex, acute post-SRC resilience was associated with both symptom burden and length of RTP, and the difference between pre-injury and post-SRC resilience was positively associated with symptom burden. These results suggest resilience may be altered following SRC in ASP, and a lower resilience may contribute to a higher symptom burden and longer duration of recovery.

3.5.1 Age and Resilience

The literature regarding the development of resilience through adolescence is conflicting. Some authors report that resilience does not significantly fluctuate through adolescence, while others report that female resilience may decrease through these years.[43, 44] We found an interaction between sex and age, with resilience increasing with age in males, but not in females (Table 3.2, Figure 3.2B). The increase in resilience with age for males is an encouraging finding, revealing that males may become more confident in their ability to overcome adversity throughout adolescence. Considering reports that female resilience may decrease through adolescence,[44] our null finding in this regard is likewise encouraging. The females in our study were engaged in sport participation, potentially providing evidence for the positive impact of sport on adolescent mental health. As male, but not female, resilience increased with age, preventative resilience-targeting therapies may also be considered of greater utility for females compared to males through adolescence.

3.5.2 Sex and Timepoint Interactions with Resilience

We also observed a significant sex by timepoint interaction in CDRISC-10 scores. Males reported overall higher resilience compared to females, consistent with previous literature.[43-47] However, the trajectory of resilience across timepoints differed for male and female participants. Male resilience was 0.9 points lower acutely post-SRC, and female resilience was 2.8 points higher time of RTP compared to pre-injury (Table 3.2; Figure 3.2A). The minimum clinically important difference (MCID) for the

CDRISC-10 among ASP is not yet available, though the MCID for a similar 10-point resilience scale specific to cancer (the RS-SC-10) is two points.[120] While we took caution in comparing between target populations (cancer patients versus ASP), this 2.8 point increase at time of RTP is likely clinically significant. We indicate above that preventive resilience-targeting therapies may be more beneficial for adolescent females, yet this finding suggests that such interventions may be of more benefit for males post-SRC, as females increased in resilience at time of RTP, whereas males did not. Moreover, if future research identifies causal factors which prompt increased female resilience at RTP, these may become points of leverage for improving male resilience through recovery from SRC.

Our sensitivity analysis revealed similar trends as the primary longitudinal analysis, though many relationships were not statistically significant, and male resilience was not found to decrease acutely post-SRC. Still, these findings suggest that the results in the primary analysis are unlikely to be due to sampling bias within each timepoint.

3.5.3 Resilience and SRC Outcomes

This was the first study to compare resilience measured pre-injury and post-SRC in ASP. The strength of this study design allowed us to evaluate three important factors: 1) whether pre-injury resilience relates to post-SRC outcomes; 2) whether post-SRC resilience relates to SRC outcomes; and 3) whether the change from pre-injury to post-SRC resilience relates to SRC outcomes. We found that pre-injury resilience was significantly associated with time to RTP but not with symptom burden. In contrast, the change in resilience from pre-to-post-SRC was associated with acute symptom burden but not time to RTP. Acute post-SRC resilience was associated with both acute symptom severity and time to RTP, suggesting that this measure may be the most useful for informing on concussion outcomes. Overall, acute resilience may be the best timepoint to inform on concussion outcomes, a measure researchers suggest should be considered in the clinical management of SRC.[63]

Similar to our findings, previous studies report low resilience is linked to poorer SRC outcomes compared to those with high resilience.[9, 36] In fact, Ernst and colleagues (2022) found low resilience to be the strongest predictor of SRC recovery in their analysis.[63] However, in their study investigating adolescent and young adult (ages 13-25 years) resilience following SRC, Bunt et al., (2021) revealed a ceiling effect of resilience, wherein participants reporting high and average resilience did not differ in SRC outcomes, whereas individuals with low resilience had an increased symptom burden and longer

duration of recovery. Our study revealed no such ceiling effect, potentially owing to our choice of measure. The CDRISC-10 consists of 10 questions, whereas the referenced study used the Brief Resilience Scale (BRS), which contains only six questions.[71] It may therefore be that the CDRISC-10 captures greater variation in resilience and better protects against ceiling effects.

The mechanisms through which resilience and SRC outcomes interact are not well understood. Two studies have found relationships between depressive and anxiety symptoms and resilience following concussion, despite different timings of clinical measures.[9, 36] One study found depressive and anxiety symptoms mediate the relationship between resilience and SRC outcomes beyond one month post-injury.[36] The other found associations between such symptoms and SRC outcomes within 10 days post-SRC, though they did not perform a mediation analysis.[9] It is likely that anxiety and depressive symptoms may mediate the relationship between resilience and SRC outcomes in the acute and prolonged stages of SRC.

3.5.4 Resilience in Relation to Other Health Measures

While we speculate above that resilience may influence SRC outcomes, this is likely a bidirectional relationship. Considering that resilience may be influenced by biopsychosocial factors,[37, 38] we postulate that the decrease in resilience for males following SRC may be due in part to biological factors, such as disrupted neural circuits which contribute to resilience. The HPA axis, for example, may become impaired following SRC, as evidenced by lower cortisol (the end product of the HPA axis), post-SRC compared to uninjured measures.[10, 90] The hippocampus' MR and GR maintain homeostatic balance through feedback loops with cortisol, and the balance of these receptors is reported to influence psychological resilience.[55-57] If cortisol release is impaired acutely following SRC, it is likely to influence psychology through such feedback mechanisms.

Other factors may also be related to the observed fluctuations in resilience post-SRC. Considering that resilience is related to adolescent quality of life, our finding that female resilience was higher at RTP is harmonious with reports that adolescent quality of life may return to above normative values at time of RTP following SRC.[121, 122] Notably, Hassan and colleagues (2024) found that both male and female resilience increased from acute measures (within one-week of concussion) at three-month and six-month timepoints.[117] Our results therefor suggest that this increase may be evident at time of RTP for females, whereas the increase may occur for males between time of RTP and the three-month timepoint, a

measurement we did not capture. Future investigation of biopsychosocial factors related to resilience and SRC could reveal the mechanisms through resilience and SRC outcomes interact. Encouragingly, neither male nor female resilience was lower at RTP compared to pre-injury measures, suggesting that SRC may not negatively influence long-term resilience among ASP, though follow-up beyond RTP to assess resilience stability and future quality of life post-SRC is warranted.

3.5.5 Strengths and Limitations

This study had many strengths. One of the greatest strengths was the sample size and diversity. Of the 425 SRCs included, 289 had completed pre-injury resilience surveys, providing within-subject comparisons across timepoints. Moreover, our sample originated from pan-Canadian sites within British Columbia, Alberta, Ontario, and Quebec, with participants of both sexes being injured in a diverse array of sports, increasing generalizability to Canadian adolescent sport participants. As well, our participants were clinically managed by SHRed-affiliated sports-medicine physicians, potentially increasing the validity of SRC diagnoses and RTP determinations.

There were limitations to the study. First, while the CDRISC-10 has a strong internal consistency (Cronbach's alpha of 0.85),[37] the survey remains at risk of self-report biases. Indeed, our observed sex differences may be explained by reporting bias as males potentially overestimate while females underestimate their resilience.[45] Also, only 13% of females and 11% of males in our sample reported CDRISC-10 scores in all three timepoints, possibly resulting in our sensitivity analysis being statistically underpowered. Another limitation was the time since injury in which participants reported CDRISC-10 scores. While we aimed to collect assessments within 72 hours of injury, clinical research is confined by practicality, and so the range of initial assessments was broad post-injury. We therefore restricted acute measures to ten days post-SRC. Similarly, as participants reported the CDRISC-10 through an online portal at their leisure, we allotted a range of five days prior to, to fifteen days following the date of medical clearance for an assessment to be considered RTP.

3.5.6 Conclusion

This study was the first to investigate resilience measured pre-injury and throughout recovery following SRC in adolescent sport participants. We captured important sex by age and sex by timepoint interactions which should be considered in future investigations involving psychometric measures and

SRC. We found resilience scores measured at pre-injury, post-injury and the change from pre-to-post injury were associated with symptom burden and length of RTP, though resilience measured acutely post-SRC had the most robust relationship with SRC outcomes, suggesting future studies should include acute resilience as an influential psychometric measure in recovery following SRC. Overall, we have shown that resilience is a modifiable factor, and holds potential as a target for therapeutic intervention following adolescent SRC.

4 CHAPTER 4: MORNING AND BASAL PLASMA CORTISOL IN UNINJURED AND POST-SRC ADOLESCENT SPORT PARTICIPANTS

4.1 ABSTRACT

Introduction: Ten percent of Canadian adolescent sport participants (ASP) sustain an SRC each year. Previous research suggests cortisol release may be lower following SRC in some athletes, which has been associated with increased symptom burden and longer recovery. In this study, we aimed to investigate differences in cortisol (morning and basal) between uninjured and acute post-SRC ASP. We also aimed to investigate the relationship between cortisol and symptom burden and time to return to play (RTP) following SRC.

Methods: As part of the pan-Canadian SHRed Concussions (Surveillance in High-Schools to Reduce Concussions and their Consequences) study, we collected plasma cortisol and SCAT-5 symptom reports from uninjured ASP (aged 10-18 years) at the start of their sporting season, and again acutely post-SRC (≤10 days). We used generalized linear models to investigate differences in cortisol (stratified as morning [≤11:00am] or basal [11:00am-6:00pm] collection times) between uninjured and post-SRC ASP controlling for age (years), sex/menstrual cycle phase (S/MCP; male, female follicular, female luteal), and time of day. Secondary analyses investigated the associations between cortisol and symptom burden (i.e., number and severity of symptoms), controlling for age and S/MCP. Finally, time-to-event analyses were conducted to analyze the relationship between cortisol and time to medical clearance to return to play (RTP; days), controlling for age and S/MCP.

Results: The uninjured sample consisted of 762 participants (n=103 morning cortisol, n=659 basal cortisol; aged 15.96±1.25 years, 67.7% male). The post-SRC sample consisted of 208 participants (53 morning cortisol, 155 basal cortisol; aged 15.99±1.41 years, 60.6% male). We found that both morning (Effect Size: -49.874, β=0.815, 95%CI: 0.722, 0.919, p=0.001) and basal (Effect Size: -47.673, β=0.794, 95%CI: 0.736, 0.856, p<0.001) cortisol were significantly lower following SRC. Following SRC, we also found a significant non-linear relationship between morning cortisol and symptom burden, revealing symptoms decreased from 78-210 nmol/L cortisol, increased from 210-305 nmol/L, and decreased again from 305-410 nmol/L. Morning cortisol was not associated with length of RTP. Basal cortisol had a significant non-linear relationship as symptom burden decreased from 61-295 nmol/L and increased from

295-416 nmol/L. Lower basal cortisol following SRC was significantly associated with longer time to RTP (Cox Regression HR=1.002, 95% CI: 1.000, 1.004, p =0.029).

Conclusion: Cortisol was found to be lower among post-SRC participants, suggesting impairment to HPA axis functioning post-SRC. Non-linear relationships between both morning and basal cortisol and symptom burden were evident, and lower basal cortisol following SRC was associated with longer recovery times. Altogether, our findings may suggest ideal cortisol ranges for optimal recovery following SRC in ASP.

4.2 INTRODUCTION

Sport-related concussion (SRC) is a traumatic brain injury (TBI) sustained during sport. The injury typically results in transient neurological disfunction accompanied by symptoms such as headache, dizziness, and neck pain. Typical recovery occurs within 30 days, after which point symptoms are deemed to be 'persistent.'[5] SRC is common in Canadian adolescents participating in high-risk sports such as hockey, football, and ringette.[123, 124] Experts at the 2022 International Conference on Concussion in Sport have therefor called for continued investigation into adolescent SRC.[5]

Cortisol is a corticosteroid associated with SRC recovery.[8, 10] Released as the end-product of the hypothalamic-pituitary-adrenal gland (HPA) axis, cortisol follows a diurnal variation. In brief, within the hypothalamus, the paraventricular nucleus (PVN) releases corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH). ACTH enters the blood stream to promote release of cortisol from the adrenal glands.[125] Peak cortisol is measured 30-45 minutes after awakening, a phenomenon termed the cortisol awakening response (CAR), after which concentrations decrease to basal levels throughout the day.[82] Additionally, increased sympathetic activation promotes cortisol release, termed 'reactive cortisol,' which provides anti-inflammatory effects in response to stress.[126]

Researchers have identified a temporally biphasic response of cortisol following SRC. Because concussion is a stressful event, peripheral cortisol concentrations increase in the six hours following injury.[108] However, within the days following adolescent SRC, morning cortisol has been reported to decrease in some athletes, suggesting insult to the HPA axis.[10] Also, low cortisol had been found to associate with poorer SRC outcomes, including increased symptom burden and a longer duration of

recovery.[8, 10] While unconfirmed in adolescent samples, adult basal cortisol (measured between 11:00 AM and 6:00 PM) was not found to be significantly lower following SRC, although low post-SRC basal cortisol was associated with more severe symptoms in this study.[81]

Finally, menstrual cycle phase is an important consideration when investigating cortisol and SRC as cortisol fluctuates with the menstrual cycle. Summarized by Hamidovic and colleagues, (2020), during the luteal phase, the progesterone metabolite allopregnanolone may excite $GABA_A$ receptors within the CRH, thereby dampening HPA axis activity at the PVN, the downstream effect of which is decreased cortisol compared to the follicular phase.[125] Females injured in the luteal phase may face worse concussion outcomes compared to those injured in the follicular phase,[127] although whether menstrual cycle phase influences the relationship between cortisol and SRC outcomes among adolescent sport participants (ASP) has yet to be investigated.

This study had two objectives. First, we investigated whether there were differences in cortisol (stratified by morning and basal collection times) between uninjured ASP and those with acute (within 10 days) SRC. Next, we sought to characterize the associations between plasma cortisol and symptom burden and time to return to play (RTP) following SRC. We hypothesized that cortisol release would decrease following SRC, reflecting transient injury to the HPA axis, and that low cortisol would be associated with increased symptom burden and prolonged recovery following SRC.

4.3 METHODS

4.3.1 Study Design

This study was an adjunct to the fluid biomarker division of the SHRed Concussions (Surveillance in High Schools to Reduce Concussions and their Consequences) study, a pan-Canadian multicenter prospective cohort study surveying adolescent sport participants (ASP; ages 10-18) at sites in British Columbia, Alberta, Ontario, and Quebec. Participants of high-risk-for-concussion sports completed uninjured baseline assessments at the beginning of their sporting season. If a participant reported a suspected SRC, they attended a SHRed-affiliated sports-medicine clinic where SRC diagnosis was confirmed by a physician and follow-up took place. SRC diagnosis and management was guided by the 5th International Consensus on SRC.[7] SHRed aimed to assess patients in the clinic within 72 hours of injury, though for this sub-study participants were eligible if their first appointment occurred within 10

days post-SRC. This study was approved by the University of Calgary Conjoint ethics board (REB18-2107).

4.3.1 Inclusion and Exclusion Criteria

To be included in this study, participants were aged 10-18 years and engaged in a high-risk-for-concussion sport. Participants 14 years of age and older (mature minors) provided written consent for participation in this study, and younger participants required written parental assent. Participants provided a blood sample before 6:00pm, and post-SRC assessments were completed within ten days of a physician-diagnosed SRC.

Adolescents were excluded if they reported a history of systemic disease (e.g., heart disease, cancer), neurological disorder (e.g., cerebral palsy), or recent broken bones and/or surgeries. Blood samples were not collected from participants who disclosed a history of clotting disorders. Specific to this sub-study, participants were excluded if they did not disclose their sex, and females reporting use of contraceptives were excluded as such medications have been reported to alter cortisol concentrations.[113].

4.3.2 Data Collection and Clinical Assessments

Near the start of their sporting season, participants underwent baseline testing and reported demographic and medical history information on preseason baseline questionnaires (PBQs). Participants completed the Sport Concussion Assessment Tool 5 Post-Concussion Symptom Scale (SCAT-5 PCSS)[31] and underwent blood collection for hormone analysis on the same day. The SCAT-5 PCSS examines 22 post-SRC symptoms rated on a 7-point Likert scale ranging from zero ("none") to severe ("severe"). The maximum symptom number is therefore 22, with a maximum symptom severity of 132. Within 10 days of sustaining a physician diagnosed SRC, participants completed the SCAT-5 PCSS to determine number and severity of symptoms and had a blood draw for cortisol and progesterone analysis.

Plasma progesterone levels were analyzed to objectively determine menstrual cycle phase. Menstrual cycle phase was determined to be follicular if progesterone was <5.0 nmol/L and luteal if progesterone ≥5.0 nmol/L.[114]

4.3.3 Blood Collection and Processing

Baseline blood samples were collected a mobile laboratory, the 'SHRed Mobile,' or an office designated for phlebotomy. Post-SRC sample collection occurred in SHRed-affiliated sports-medicine

clinics. Venipuncture was performed by certified phlebotomists or research nurses. Samples were collected from the antecubital fossa into K2-EDTA plasma tubes (10 mL) and centrifuged at 1300g for 10 minutes at room temperature. The supernatant was aliquoted and frozen at -80°C within two hours.

Using the Roche Cobas e801 analyzer, Alberta Precision Labs (APL) measured plasma cortisol (assay: Cobas Elecsys Cortisol II) and progesterone (assay: Cobas Elecsys Progesterone III). Both assays used indirect competitive immunoassays using electrochemiluminescence (ELCIA; Roche Diagnostics, Rotkreuz, Switzerland) for signal detection.

Considering that cortisol concentrations are highest in the morning,[128] investigations regarding basal cortisol seek to minimize the effects of elevated morning cortisol. To measure reactive cortisol, researchers may perform assessments between 12:00pm and 5:00pm to minimize the effects of diurnal variation.[77] However, cortisol drops steeply after 6:00pm.[129] Specific to SRC, there is precedence to collect basal samples between 11:00am and 6:00pm.[81] Therefore, to minimize the effects of diurnal variation, we grouped cortisol as morning (before 11:00am) and basal (11:00am-6:00pm).

4.3.4 Statistical Analysis

Uninjured to Post-SRC Cortisol Group Comparisons

We employed generalized linear models (GLM) (family: gamma, link: log, robust, exponential form [e-form]) to compare group-level cortisol concentrations (nmol/L) between uninjured and post-SRC participants. Models were stratified by time of blood sample collection (morning/basal, as outlined above), controlling for age (years), sex/menstrual cycle phase (S/MCP; male, female follicular, female luteal), and time of collection.

Post-SRC Cortisol and Symptom Burden

Controlling for age and S/MCP, we used GLMs (family: gamma, link: log, robust, exponential form [e-form]) to investigate the relationships between post-SRC cortisol (stratified by morning/basal collection times) and symptom burden. Models were further stratified by number of symptoms (/22) and symptom severity (/132). We first visually inspected the Lowess curves between cortisol and symptom burden, and restricted spline knots were identified at points of inflection (see Figure 4.3). We tested

significance of the restricted splines using Wald tests, which were reported for all models (see bottom of Table 4.4).

Post-SRC Cortisol and Length of RTP

Lastly, we utilized robust Cox Proportional Hazards analyses to investigate the association between cortisol and time to RTP (days). Participants were categorized as having low (0-10th percentile), average (10th-90th percentile), or high (90th-100th percentile) cortisol for visualization of recovery time by cortisol levels using time-to-event survival curves.

Effect sizes were derived from the margins of statistical models. Significant alpha was determined a priori as less than 0.05. All statistical analysis was performed using STATA (v 18).[119]

4.4 RESULTS

4.4.1 Participant Characteristics

Between September 2019 and December 15, 2023, 11,226 participants were recruited in the SHRed Concussion study. However, the study was interrupted in March 2020 due to the COVID-19 pandemic, from which point until July 2021 data were collected virtually. Of the 1319 baseline samples collected, 762 met criteria for this study (Figure 4.1; Table 4.1). A total of 1661 SRCs were reported by SHRed participants, 208 of which met criteria for this study. (Figure 4.1; Table 4.2).

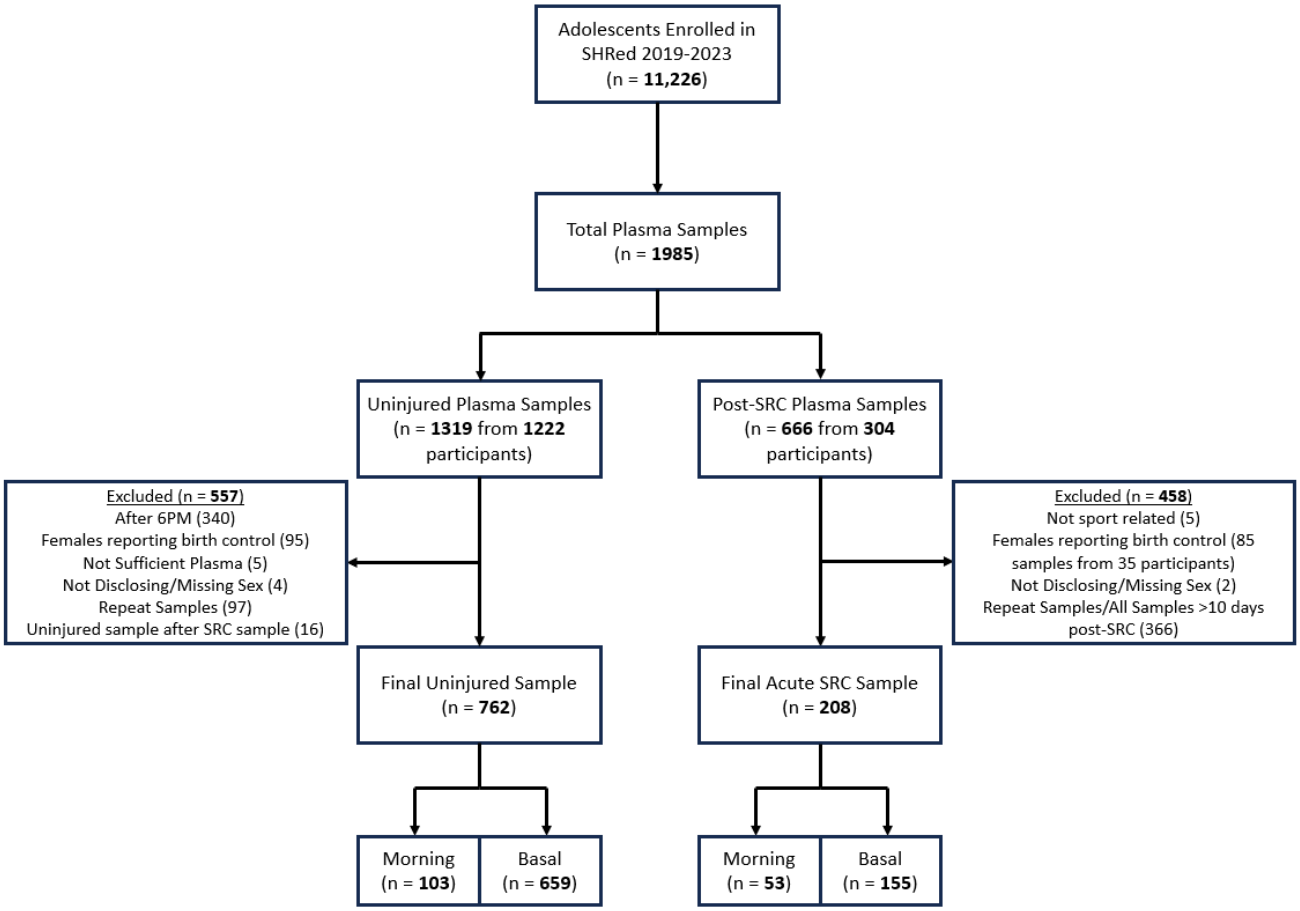

Figure 4.1: SHRed Concussions Participant Recruitment Flowchart.

SRC; sport-related concussion, Acute; within 10 days of SRC.

Table 4.1: Uninjured Participant Characteristics.

	Morning Cortisol (Before 11:00am) (n = 103)			**Basal Cortisol (11:00am-6:00pm) (n = 659)**		
	Female Follicular (n=20)	**Female Luteal (n=12)**	**Male (n=71)**	**Female Follicular (n=154)**	**Female Luteal (n=60)**	**Male (n=445)**
Age (Years) (Mean, SD)	16.14 ± 0.75	16.16 ± 1.62	15.29 ± 1.11	16.01 ± 1.45	16.03 ± 1.44	16.03 ± 1.14
Cortisol (nmol/L) (Mean, SD)	354.95 ± 135.34	235.67 ± 91.60	241.46 ± 97.71	229.39 ± 114.38	215.73 ± 96.50	208.28 ± 86.68
Blood Draw Time (0-24 Hrs) (Mean, SD)	9.93 ± 0.53	10.21 ± 0.37	10.11 ± 0.60	15.51 ± 1.87	15.63 ± 1.60	15.28 ± 1.88
Sport Participation n (%)						
Rugby	10 (50%)	4 (33.3%)	6 (8.5%)	67 (43.5%)	33 (55.0%)	108 (24.3%)
Football			21 (29.6%)	4 (2.6%)	3 (5.0%)	289 (64.9%)
Hockey	3 (15%)	2 (16.7%)	31 (43.7%)	2 (1.3%)	1 (1.7%)	12 (2.7%)
Ringette	2 (10%)	1 (8.3%)		9 (5.8%)	5 (8.3%)	
Soccer			2 (2.8%)	6 (3.9%)	1 (1.7%)	2 (0.5%)
Volleyball	3 (15%)	4 (33.3%)		5 (3.2%)	1 (1.7%)	11 (2.5%)
Basketball			2 (2.8%)	12 (7.8%)	2 (3.3%)	1 (0.2%)
Wrestling	1 (5%)	1 (8.3%)	9 (12.7%)	18 (11.7%)	6 (10.0%)	21 (4.7%)
Lacrosse	1 (5%)					1 (0.2%)
Field Hockey				22 (14.3%)	6 (10.0%)	
Cheerleading					1 (1.7%)	
Artistic Swimming				9 (5.8%)	1 (1.7%)	

Table 4.2: Acute Post-SRC Participant Characteristics.

	Morning Cortisol (Before 11:00am) (n = 53)			**Basal Cortisol (11:00am-6:00pm) (n = 155)**		
	Female Follicular (n=15)	**Female Luteal (n=3)**	**Male (n=35)**	**Female Follicular (n=45)**	**Female Luteal (n=19)**	**Male (n=91)**
Age (Years) (Mean, SD)	15.85 ± 1.26	16.65 ± 0.85	15.53 ± 1.55	15.89 ± 1.47	16.34 ± 1.09	16.14 ± 1.40
Cortisol (nmol/L) (Mean, SD)	222.27 ± 90.47	206.67 ± 116.80	234.91 ± 70.78	183.93 ± 67.08	146.79 ± 31.46	185.14 ± 76.84
Blood Draw Time (24 Hours) (Mean, SD)	9.64 ± 0.85	9.48 ± 0.96	9.63 ± 0.68	13.50 ± 1.83	13.72 ± 2.08	13.59 ± 1.81
Injury Characteristics						
Time Since SRC (Days) (Median (IQR))	4 (2, 8)	4, (2, 10)	5 (3, 7)	4 (2, 6)	3 (2, 4)	4 (3, 6)
Symptom Severity (Median (IQR)) Missing n (%)	39 (17, 48) -	70 (12, 85) -	13 (8, 22) 2 (5.7%)	25 (12, 37) -	21 (5, 58) -	24 (6, 43) -
Number of Symptoms (Median (IQR)) Missing n (%)	15 (6, 17) -	21 (7, 22) -	9 (7, 12) 2 (5.7%)	13 (7, 18) -	10 (5, 22) -	13 (5, 18) -
Time to RTP (days) (Median (IQR)) Missing n (%)	29 (17, 49) -	12 (6, 25) -	20 (14, 33) -	19 (15, 32) -	19.5 (11, 30) 1 (5.3%)	20 (13, 26) 2 (2.2%)

Table continued on next page…

…Table 4.2 continued						
Activity at Time of Injury						
Rugby n (%)	6 (40.0%)	2 (66.75)	10 (28.6%)	19 (42.2%)	5 (26.3%)	28 (30.8%)
Football n (%)			17 (48.6%)	3 (6.7%)	2 (10.5%)	40 (44.0%)
Hockey n (%)	1 (6.67%)		4 (11.4%)	3 (6.7%)		4 (4.4%)
Ringette n (%)	1 (6.67%)			8 (17.8%)	5 (26.3%)	
Soccer n (%)	2 (13.3%)			7 (15.6%)		6 (6.6%)
Volleyball n (%)	1 (6.67%)			2 (4.4%)	3 (15.8%)	
Basketball n (%)			1 (2.9%)	1 (2.2%)	2 (10.5%)	1 (1.1%)
Wrestling n (%)	1 (6.67%)		1 (2.9%)		1 (5.3%)	5 (5.5%)
Synchronized Swimming n (%)	3 (20.0%)			1 (2.2%)	1 (5.3%)	
PE Class n (%)			1 (2.9%)	1 (2.2%)		1 (1.1%)
Kayaking n (%)			1 (2.9%)			
Outdoor Activities n (%)		1 (33.3%)				
Baseball n (%)						2 (2.2%)
Field Hockey n (%)						1 (1.1%)
Lacrosse n (%)						2 (2.2%)
Skiing						1 (1.1%)

Acute: Within 10 days of Sport-Related Concussion (SRC).
IQR: Inter-Quartile Range (Median (Q1, Q3)).
RTP: Return to Play.

4.4.2 Group Differences between Uninjured and Post-SRC Cortisol

We found morning cortisol was 49.9 nmol/L lower in the post-SRC group compared to the uninjured group (β = 0.815, 95% CI: 0.722, 0.919, p = 0.001). Morning cortisol also 29.5 nmol/L higher with each year of increased age (β = 1.124, 95% CI: 1.077, 1.173, p < 0.001). (Table 4.3; Figure 4.2A)

Basal cortisol was 47.7 nmol/L lower in the post-SRC group compared to the uninjured group (β = 0.794, 95% CI: 0.736, 0.856, p < 0.001). Follicular females had 15.3 nmol/L higher basal cortisol compared to males (β = 1.075, 95% CI: 1.001, 1.154, p = 0.046). Basal cortisol increased by 9.2 nmol/L with each year of age. (Table 4.3; Figure 4.2B)

Table 4.3: Group Analyses. Margins reported from GLMs.

Cortisol Measurement	Comparison	Effect Size (nmol/L)	Exp(B)	95% CI	*p*
Morning Cortisol	**Group (Uninjured vs. Acute Post-SRC)**	-49.874	0.815	0.722, 0.919	0.001
	Male vs Female Follicular	34.957	1.141	0.984, 1.322	0.080
	Male vs Female Luteal	-41.398	0.833	0.678, 1.022	0.081
	Age (year)	29.458	1.124	1.077, 1.173	< 0.001
	Time of Day (hour)	-25.351	0.904	0.818, 0.999	0.048
Basal Cortisol	**Group (Uninjured vs. Acute Post-SRC)**	-47.673	0.794	0.736, 0.856	< 0.001
	Male vs Female Follicular	15.255	1.075	1.001, 1.154	0.046
	Male vs Female Luteal	-3.128	0.985	0.891, 1.088	0.760
	Age (year)	9.197	1.045	1.018, 1.074	0.001
	Time of Day (hour)	-5.824	0.972	0.957, 0.987	< 0.001

95% CI: 95% Confidence Interval.
Morning Cortisol: Before 11:00am. Basal Cortisol: Between 11:00am and 6:00pm.
Acute: ≤ 10 days post-SRC

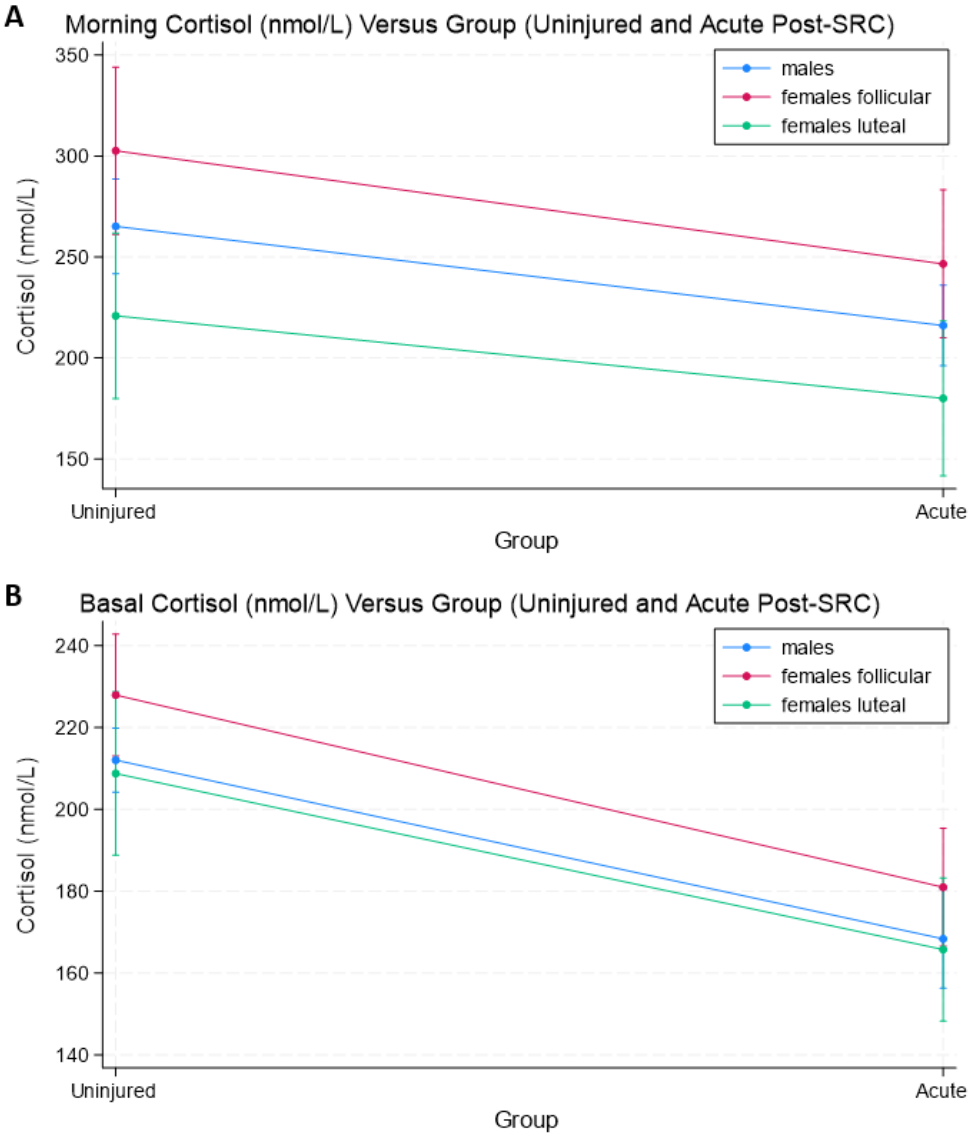

Figure 4.2: Group differences between uninjured and post-SRC cortisol samples.

(A) Acute post-SRC morning cortisol was 49.9 nmol/L lower than uninjured morning cortisol (β = 0.815, 95% CI: 0.722, 0.919, p = 0.001) controlling for sex/menstrual cycle phase, age, and time of day. (B) Acute post-SRC basal cortisol was 47.7nmol/L lower than uninjured basal cortisol (β = 0.794, 95% CI: 0.736, 0.856, p < 0.001) controlling for sex/menstrual phase, age, and time of day. Female follicular basal cortisol was 15.3 nmol higher than male basal cortisol (β = 0.972, 95% CI: 0.957, 0.987, p < 0.001). GLM marginal means reported. Error bars represent 95% CIs.

4.4.3 Morning Cortisol and SRC Outcomes

Visual inspection of the relationship between post-SRC morning cortisol and symptom burden revealed a non-linear relationship. Based on visual inspection of the Lowess curves, restricted spline knots were set at 210 nmol/L and 305 nmol/L (Figure 4.3 A&B). Symptom severity decreased by 0.25 points per unit increase in cortisol through Spline 1 (78-210 nmol/L; β = 0.990, 95% CI: 0.983, 0.997, p = 0.007), increased by 0.30 points per unit increase in cortisol along Spline 2 (210-305 nmol/L cortisol; β = 1.012, 95% CI: 1.001, 1.023, p = 0.029), and decreased by 0.55 points per unit increase at Spline 3 (305-410 nmol/L; β = 0.979, 95% CI: 0.963, 0.995, p = 0.013) (Table 4.4). Number of symptoms followed a similar trend, decreasing by 0.08 symptoms per unit increase in cortisol along Spline 1 (β = 0.992, 95% CI: 0.988, 0.997, p = 0.001), increasing by 0.10 symptoms per unit increase in cortisol at Spline 2 (β = 1.009, 95% CI: 1.001, 1.017, p = 0.026), though the association between number of symptoms and cortisol was not significant along Spline 3 (Table 4.4). The Cox analysis found no significant association between morning cortisol and duration of recovery (Table 4.5; Figure 4.4A).

4.4.4 Basal Cortisol and SRC Outcomes

Visual inspection of post-SRC basal cortisol and symptom burden also revealed a non-linear relationship. A spline knot was set at 295 nmol/L (Figure 4.3 C&D). Symptom severity decreased by 0.09 points per unit increase in cortisol through Spline 1 (61-295 nmol/L nmol/L cortisol; β = 0.997, 95% CI: 0.988, 0.997, p = 0.001), and increased by 0.25 points per unit increase in cortisol along Spline 2 (61-295 nmol/L cortisol; β = 1.009, 95% CI: 1.001, 1.017, p = 0.026) (Table 4.4). Similarly, number of symptoms decreased by 0.03 symptoms per unit increase in cortisol along Spline 1 (β = 0.998, 95% CI: 0.996, 1.000, p = 0.022), and increased by 0.06 symptoms per unit increase in cortisol for Spline 2 (β = 1.005, 95% CI: 1.001, 1.009, p = 0.017) (Table 4.4). The Cox analysis revealed that participants had a 10% greater likelihood of recovery per 50 nmol/L increase in cortisol (HR: 1.002, 95% CI: 1.000, 1.004, p = 0.029). This relationship was illustrated in the survival curves (Table 4.5; Figure 4.4B).

Table 4.4: Post-SRC Cortisol and Symptom Burden Linear Regression Results.

Outcome	Cortisol Measurement	Independent Variable	Effect Size	Exp(*β*)	95% CI	*p*
Symptom Severity	**Morning Cortisol**	**Cortisol Spline 1 (78-210 nmol/L)**	-0.250	0.990	0.983, 0.997	0.007
		Cortisol Spline 2 (210-305 nmol/L)	0.302	1.012	1.001, 1.023	0.029
		Cortisol Spline 3 (305-410 nmol/L)	-0.545	0.979	0.963, 0.995	0.013
		Age (year)	2.700	1.111	0.960, 1.286	0.159
		Males Vs. Females Follicular	23.267	2.208	1.333, 3.659	0.002
		Males Vs. Females Luteal	8.818	1.458	0.745, 2.854	0.271
Number of Symptoms	**Morning Cortisol**	**Cortisol Spline 1 (78-210 nmol/L)**	-0.082	0.992	0.988, 0.997	0.001
		Cortisol Spline 2 (210-305 nmol/L)	0.097	1.009	1.001, 1.017	0.026
		Cortisol Spline 2 (305-410 nmol/L)	-0.141	0.987	0.973, 1.002	0.090
		Age (years)	0.690	1.065	0.968, 1.171	0.198
		Males Vs. Females Follicular	4.753	1.488	1.016, 2.179	0.041
		Males Vs. Females Luteal	0.827	1.085	0.748, 1.574	0.668
Symptom Severity	**Basal Cortisol**	**Cortisol Spline 1 (61-295 nmol/L)**	-0.090	0.997	0.994, 0.999	0.015
		Cortisol Spline 2 (295-416 nmol/L)	0.253	1.009	1.001, 1.017	0.022
		Age (years)	1.335	1.048	0.925, 1.188	0.462
		Males Vs. Females Follicular	5.349	1.201	0.896, 1.610	0.220
		Males Vs. Females Luteal	2.161	1.081	0.684, 1.709	0.738
Number of Symptoms	**Basal Cortisol**	**Cortisol Spline 1 (61-295 nmol/L)**	-0.025	0.998	0.996, 1.000	0.022
		Cortisol Spline 2 (295-416 nmol/L)	0.060	1.005	1.001, 1.009	0.017
		Age (years)	0.167	1.014	0.918, 1.120	0.783
		Males Vs. Females Follicular	1.204	1.104	0.898, 1.356	0.349
		Males Vs. Females Luteal	-0.275	0.976	0.701, 1.359	0.887

Morning cortisol to symptom severity restricted spline Wald test: $\chi 2=11.03$, $p=0.012$
Morning cortisol to symptom number restricted spline Wald test: $\chi 2=12.44$, $p=0.006$
Basal cortisol to symptom severity restricted spline Wald test: $\chi 2=7.80$, $p=0.020$
Basal cortisol to symptom number restricted spline Wald test: $\chi 2= 7.12$, $p=0. 0.028$
Exp(*β*) is the exponential form (e-form) beta-coefficient from the GLMs.
Effect sizes derived from margins.

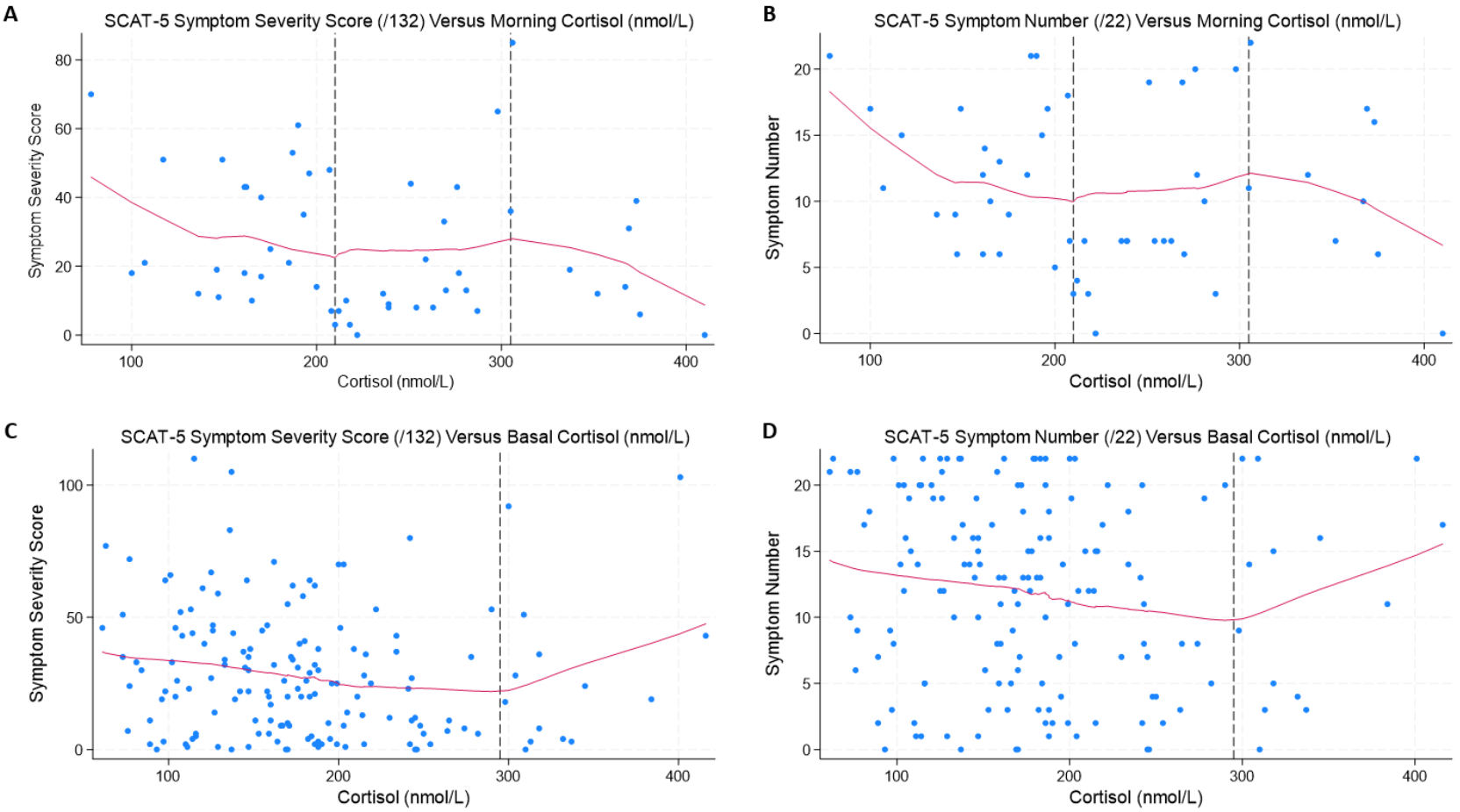

Figure 4.3: Lowess curves of post-SRC cortisol and symptom burden.

(A) SCAT-5 symptom severity score versus morning cortisol, (B) SCAT-5 number of symptoms versus morning cortisol, (C) SCAT-5 symptom severity score versus basal cortisol, and (D) SCAT-5 number of symptoms versus basal cortisol. Vertical dashed lines represent spline knots at 210 nmol/L and 305 nmol/L (A&B), and 295 nmol/L (C&D).

Table 4.5: Post-SRC Cortisol and RTP. Results from Cox Proportional Hazard Models.

Cortisol Measurement	Independent Variables	HR	95% CI	*p*
Morning Cortisol	**Cortisol (nmol/L)**	0.997	0.993, 1.001	0.183
	Age (year)	1.015	0.838, 1.229	0.878
	Males Vs. Females Follicular	0.513	0.266, 0.989	0.046
	Males Vs. Females Luteal	2.359	0.649, 8.573	0.192
Basal Cortisol	**Cortisol (nmol/L)**	1.002	1.000, 1.004	0.029
	Age (years)	0.965	0.848, 1.098	0.591
	Males Vs. Females Follicular	0.791	0.544, 1.151	0.221
	Males Vs. Females Luteal	1.026	0.631, 1.668	0.917

HR: Hazard Ratio. 95% CI: 95% Confidence Interval

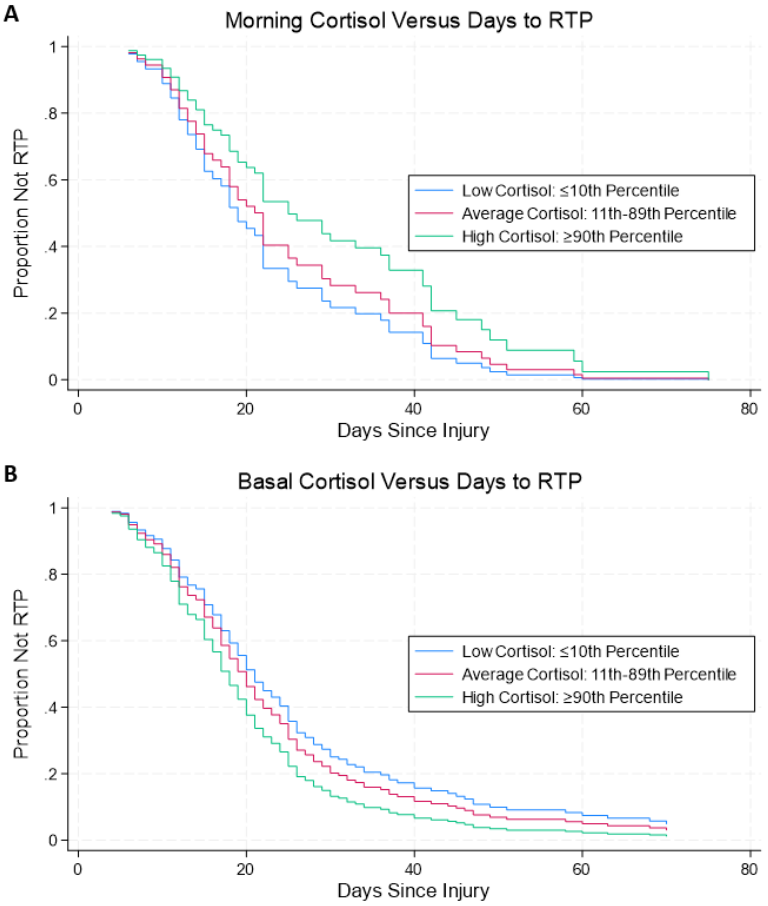

Figure 4.4: Survival Curves Produced by the Cox Proportional Hazards Models.

Visualization of recovery time stratified by high (top 90th percentile), average (11th-89th percentile) and low (bottom 10th percentile) acute. (A) Morning cortisol (Cox Regression HR = 0.997, 95% CI: 0.993, 1.001, p = 0.183), and (B) basal cortisol (Cox Regression HR = 1.002, 95% CI: 1.000, 1.004, p =0.029).

4.5 DISCUSSION

In this study, we investigated group differences in morning and basal plasma cortisol between uninjured ASP and their post-SRC (≤ 10 days) counterparts. We found that both morning and basal cortisol levels were significantly lower following SRC. We also investigated the relationships between cortisol and symptom burden and length of RTP following SRC. We found non-linear relationships between both morning and basal cortisol and post-SRC symptom burden. Morning cortisol was not associated with length of RTP, whereas lower basal cortisol was significantly related to a longer duration of recovery. Lastly, we found cortisol increased with age, and the highest cortisol concentrations were measured among females in the follicular phase.

4.5.1 Uninjured versus Post-SRC Group Differences in Morning and Basal Cortisol

Previous research has found peripheral morning cortisol to decrease following SRC.[10] Of interest, the pituitary stalk is among the most vulnerable structures along the HPA axis. Also known as the infundibulum, the stalk is highly vascularized and sensitive to shearing, making it a likely target of insult following SRC.[91-93] Disturbed pituitary function may result in diminished ACTH release, thereby disrupting adrenal cortisol production.[125] Low cortisol would be of concern following SRC as the hormone provides anti-inflammatory support and, without sufficient cortisol, neuroinflammation may persist without appropriate regulation, resulting neuronal dysfunction.[94, 95] Consistent with this hypothesis and previous literature, we found that morning cortisol was nearly 50 nmol/L lower following SRC. (Table 4.3; Figure 4.2A)

If damage to the HPA axis occurs post-SRC, we would likewise expect basal cortisol to be lower following injury. However, reports on basal cortisol conflict with this hypothesis. Battista et al., (2019) found that basal cortisol (11:00am-6:00pm) among 26 young adults post-SRC (285.5 nmol/L cortisol) was not significantly lower than their uninjured sample (306.0 nmol/L). Although, the lack of statistical significance was likely due to their small sample size.[81] With our larger post-SRC sample (n=155), we found that basal cortisol was close to 50 nmol/L lower compared to uninjured ASP, a comparison that was statistically significant (Table 4.3; Figure 4.2B). Our finding suggests that measurements of cortisol can be completed at a variety of times throughout the day and still reflect HPA axis dysfunction post-SRC, strengthening our hypothesis of transient injury to the HPA axis after SRC.

4.5.2 Sex and Menstrual Cycle Phase Cortisol within Uninjured and Post-SRC Adolescence

Previous research has revealed cortisol varies between males and females, and across the menstrual cycle. Cortisol in females is often reported as higher than in males, and cortisol in follicular females is reported as higher than in luteal females.[83, 84, 125] This is the first study to report uninjured and post-SRC cortisol differences adjusting for sex and menstrual cycle phase. We found that morning and basal cortisol were lower for post-SRC males and females regardless of menstrual cycle phase (Table 4.3, Figure 4.2). We also revealed that females in the follicular, but not luteal, phase had higher basal cortisol than males. However, this relationship was not statistically significant in our morning samples, likely due to the relatively small number of follicular females in each model. (Table 4.3; Figure 4.2)

Studies have also shown females sustaining a concussion in the luteal phase compared to the follicular phase have more severe post-concussion symptoms beyond one month following injury.[127] Our data indicating that cortisol is lower in the luteal compared to follicular phase (Table 4.3; Figure 4.2) is consistent with previous literature.[125] Considering cortisol's anti-inflammatory properties,[94, 95] we suspect the higher cortisol during the follicular phase may provide increased neuroprotection during SRC. While we did not capture the menstrual cycle phase at time of injury, our findings may indirectly feature this relationship. Indeed, females with a blood draw in the follicular phase had higher symptom burdens and longer recovery times, though these relationships were only statistically significant for our morning samples (Tables 4.4&4.5). Considering our samples were collected within the 10 days following SRC, these participants may have been more likely to be injured during the luteal phase when their cortisol would have been lower. Ultimately, both menstrual cycle phase at time of injury and at time of sample collection may be important considerations for unravelling the pathophysiology of adolescent SRC.

4.5.3 Cortisol and SRC

Considering the potential for HPA axis insult following SRC, the relationship between morning and basal cortisol and SRC outcomes should be closely investigated. Indeed, adolescent morning cortisol and young adult basal cortisol have both been associated with symptom burden and length of RTP – lower morning cortisol linked to a longer recovery, and lower basal cortisol relating to increased symptoms.[10, 81] Likely contributing to this effect is cortisol's role in neuroinflammation, only an appropriate amount of which is beneficial for recovery.[94, 95] However, to the best of our knowledge, and contrary to our

expectations, we were the first to report non-linear relationships between cortisol and SRC symptom burden.

4.5.4 Morning Cortisol, Symptom Burden, and Length of RTP Post-SRC

While we have predominantly discussed insult to the HPA axis following injury based on group averages, we cannot ignore that cortisol release may still increase typically in response to stressors for some individuals. Such complexity may result in a polyphasic relationship between cortisol and post-SRC symptom burden. Indeed, for morning samples, we found that from 78-210 nmol/L cortisol (Spline 1), symptom burden decreased with increased cortisol; from 210 to 305 nmol/L (Spline 2), symptom burden increased with increased cortisol; and from 305-410 nmol/L (Spline 3), symptom burden again decreased with increased cortisol (Table 4.4; Figure 4.3 A&B). The relationships along Splines 1 and 3 align with the hypothesis that decreased cortisol following SRC may be of concern due to its role in dampening inflammation, and that higher levels of morning cortisol may be neuroprotective.

However, the relationship at Spline 2 was surprising. One report found that the degree of elevation of morning cortisol may reflect the perceived stress of the day ahead.[76] We therefore suspect that Spline 2 represents participants without insult to the HPA axis, who may be experiencing normal cortisol release dependent on life stressors. In this range, there may be an increase in perceived stress with increased symptom burden, resulting in increased morning cortisol production. Though, this effect was possibly influenced by high-symptom outliers near the upper-cortisol range of Spline 2 (Figure 4.3 A&B). This is a complex hypothesis that merits future investigation.

Considering that one study found that lower morning cortisol may associate with a longer duration of recovery,[10] it was interesting to find that morning cortisol did not associate with time to RTP in our sample (Table 4.5; Figure 4.4A). However, demographic considerations may explain this discrepancy. The referenced study included only ice hockey players with a mean age of 13.8 years, whereas our sample participated in a diverse array of sports and were aged 15.9, 16.7, and 15.5 years for follicular females, luteal females, and males, respectively. We, along with other research groups,[86] found that cortisol increased with age through adolescence (Table 4.3), so particular attention to the age of participants should be taken when comparing between studies of adolescent SRC and cortisol.

4.5.5 Basal Cortisol, Symptom Burden, and Length of RTP Post-SRC

While low basal cortisol has been linked to more severe SRC symptoms among young-adult athletes,[81] this associations has not yet been investigated following adolescent SRC. We found at lower basal cortisol concentrations (Spline 1: 61- 295 nmol/L; Table 4.4; Figure 4.3 C&D), symptom burden decreased linearly as cortisol increased. Along Spline 1, it may therefore be that participants benefit from increased cortisol considering the corticosteroid's anti-inflammatory properties. However, there emerged a biphasic 'Goldilocks' effect, as symptoms increased with increased cortisol from 295-416 nmol/L (Spline 2; Table 4.4; Figure 4.3 C&D). The relationship between symptom burden and cortisol along Spline 2 may again capture reactive cortisol as the increased symptom burden may promote cortisol release due to increased stress of higher symptoms. These findings may indicate an optimal range of basal cortisol following SRC, and adolescents with too low or too high of basal cortisol may be at risk of experiencing higher post-SRC symptom burdens.

In their young-adult post-SRC sample (n=26), Battista et al., (2019) did not find basal cortisol to be significantly related to time to RTP. Conversely, we found that lower basal cortisol was significantly related to a longer duration of recover (Table 4.5; Figure 4.4B). This discrepancy may be due to the differing demographics of our samples (young adults versus adolescents), and our larger sample (n=155). Our finding suggests that increased basal HPA axis activation following SRC may be neuroprotective,[94, 95] thereby furthering the notion that diminished post-SRC basal cortisol is particularly concerning. Ultimately, basal cortisol should not be overlooked as an important consideration when investigating SRC pathophysiology and clinical management.

4.5.6 Strengths and Limitations

Our study had several strengths. Notably, we were the first to investigate morning and basal cortisol among uninjured and post-SRC ASP within the same study. This factor allowed for consistent interpretation of cortisol group differences. Also, particularly for our basal samples, we had large sample sizes with diverse representation of male and female sport participants engaged in numerous sports across Canada. Using the "SHRed Mobile," we accessed participants in communities that may have otherwise been unable to engage in such research opportunities. Therefore, our findings are highly generalizable to Canadian adolescent sport participants. We also used robust GLM modeling, decreasing the likelihood of misspecification error in our statistical models.

Our results also have limitations. First, we did not collect serial samples of cortisol within the same participant throughout the day. Without serial sampling, we could not determine peak cortisol, or the slope between peak and basal cortisol – two constructs often investigated in cortisol research that may provide further insights into SRC pathophysiology.[75, 130] Also, we did not record the time at which participants awoke, and our timing of blood draws covered a broad range. Particularly important for morning samples, we do not know if the cortisol measurement reflects the CAR. However, we controlled for time of day in our group comparisons and found that morning cortisol decreased more steeply than basal cortisol (25.4 nmol/L per hour and 5.8 nmol/L per hour, respectively; Table 4.3). Moreover, considering the difference in means between morning and basal cortisol (Tables 4.1&4.2), we captured elevated morning cortisol before 11:00am, and our timing for basal cortisol limited the effects of diurnal variation.

4.5.7 Conclusion

This was the first study to stratify morning and basal cortisol for comparison between uninjured and post-SRC (≤ 10 days) ASP while controlling for age, sex, time of sample collection, and menstrual phase. We found that morning and basal cortisol were significantly lower among post-SRC participants for males, and females in both phases of the menstrual cycle, providing convincing evidence for transient HPA axis impairment following SRC. Females in the follicular phase had the highest basal cortisol. Moreover, we identified significant non-linear relationships between morning and basal cortisol and symptom burden. These findings suggest a complex relationship between cortisol's anti-inflammatory properties and release in response to stress. Basal cortisol was significantly associated with length of RTP, with lower basal cortisol relating to a longer recovery. Our findings reinforce plasma cortisol as a research tool to investigate SRC pathophysiology and as a potential clinical biomarker of symptom burden and recovery following SRC in ASP.

5 CHAPTER 5: INVESTIGATING THE RELATIONSHIP BETWEEN PSYCHOLOGICAL RESILIENCE AND PLASMA CORTISOL IN UNINJURED AND ACUTELY POST-SRC ADOLESCENT SPORT PARTICIPANTS

5.1 ABSTRACT

Background: Up to 10% of Canadian adolescents are affected by sport-related concussion (SRC) each year. Recovery from SRC is associated with psychological and biological factors, including psychological resilience and cortisol. Researchers have identified associations between resilience and cortisol, though no study has investigated this relationship following SRC.

Objectives: To explore the relationship of morning (before 11:00am) and basal (11:00am-6:00pm) cortisol concentrations with resilience in uninjured and acutely (within 10 days) post-SRC male and female adolescent sport participants (ASP).

Methods: Embedded within the pan-Canadian SHRed Concussion (Surveillance in High Schools to Reduce the Risk of Concussions and their Consequences) prospective cohort study, we recruited ASP (aged 10-18) to report uninjured Connor-Davidson Resilience Scale-10 (CDRISC-10) and Sport Concussion Assessment Tool-5 Post-Concussion Symptom Scale (SCAT-5 PCSS) scores and provide a blood draw for plasma cortisol analysis. Within 10 days of SRC, the CDRISC-10, symptom severity scale, and blood draw were repeated. Using GLM analyses controlling for age and sex (all models) and symptom severity (post-SRC models only), we evaluated the relationship between plasma cortisol (morning/basal) and resilience among uninjured and post-SRC ASP.

Results: Uninjured participants (samples: 80 morning, 458 basal, 33% female, aged 15.97±1.21 years) and post-SRC participants (26 morning, 85 basal, 36% female, aged 16.38±1.19) were evaluated. In our uninjured group, morning cortisol showed a negative association with CDRISC-10 scores (β = -6.405, 95% CI: -10.598, -2.212, p = 0.003), but basal cortisol showed no association. In the post-SRC group, neither morning nor basal cortisol were associated with CDRISC-10 scores.

Conclusion: Lower morning cortisol was associated with increased resilience in uninjured ASP. This relationship was not present post-SRC, potentially reflecting HPA axis impairment following SRC.

5.2 INTRODUCTION

Termed the 'silent epidemic,' traumatic brain injury (TBI) affects approximately 70 million people annually worldwide.[2] Concussion, the most common form of TBI, typically results in transient neurological dysfunction.[5, 7, 131] Standard recovery from sport-related concussion (SRC) takes less than one month, after which point the symptoms are deemed to be prolonged.[5] As 30% of concussions take place during adolescence, experts have called for increased investigation into adolescent SRC.[4, 5, 7]

The hypothalamic-pituitary-adrenal (HPA) axis may be impaired following SRC, resulting in altered pituitary hormone response.[10] Cortisol, the end-product of the HPA axis, is one such hormone.[74] Cortisol is an anti-inflammatory corticosteroid that follows a diurnal rhythm. The molecule's peripheral concentration slowly increases overnight, peaks 30-45 minutes after awakening during the cortisol awakening response (CAR), then decreases throughout the day.[130] Cortisol also increases in response to external stressors, such as social stress or exogenous adrenocorticotropic hormone (ACTH) administration.[73, 132]

In the days following the SRC, pediatric morning cortisol may decrease below typical values, suggesting impairment of the HPA axis.[10] In both adult and pediatric samples, low cortisol has been associated with more severe symptoms and longer recovery following SRC.[8, 81] Indeed, cortisol has been suggested as a potential biomarker for youth concussion.[10] However, investigation into basal cortisol following pediatric SRC is limited. In their 2019 study, Battista and colleagues found significant associations between low basal cortisol within one week of injury and increased symptoms following young adult SRC.[81] Ritchie et al., (2018) investigated cortisol samples between 07:30-14:00 within one week following pediatric SRC. The authors noted that the four of their fourteen participants that had significantly low cortisol also had increased symptom severity and a longer duration of recovery.[8]

Psychological resilience is the ability to succeed in the face of adversity and has been suggested to influence outcomes following concussion.[9, 63] Often, studies capture resilience based on self-report, and so resilience is operationalized as one's *perceived* ability to overcome adversity. Reported first in 1995, Cicerone and Kalmar revealed that low resilience relates to poorer concussion outcomes in adults.[61] However, this topic has only recently been explored in pediatrics.[36, 62] The first research group to do so were Durish, Yeates, and Brooks (2018). Their study revealed that persistent concussion symptoms were significantly predicted by low resilience measured beyond one month post-injury.[62] The same group later

found that anxiety and depressive symptoms mediate associations between resilience and prolonged concussion outcomes.[36] However, these studies were not specific to SRC and did not capture self-reported resilience acutely following injury. Two studies have since reported on acute adolescent and young adult (AYA) resilience following SRC. Bunt et al., (2021) and Ernst et al., (2022) found that low self-reported resilience acutely (within 10 and 14 days, respectively) following SRC was associated with greater symptom burdens and prolonged recoveries.[9, 63] Published in 2024, Hassan and colleagues found that resilience measured within one week of injury was lower for children reporting to Canadian emergency departments compared to their orthopedic injury counterparts, and that resilience increased at three and six month timepoints post-concussion.[117] The relationships between post-SRC resilience and physiological factors, such as cortisol, however, remain to be explored.

Resilience and cortisol have been explored in other domains. Chi and colleagues (2015) found that, among children (ages 6-17 years) of parents living with HIV, those with higher resilience demonstrated an increased CAR and a steeper decrease throughout the day. The authors also found cortisol output throughout the day was higher for more resilient children, though they suspect this effect was influenced by the increased CAR.[133] Similarly, in undergraduate students, higher resilience was associated with a stronger CAR and a greater decrease throughout day.[11] In contrast, among parents of children with autism spectrum disorder, higher resilience was associated with lower morning cortisol.[87] Also, among parents of at least one child, resilience was negatively associated with mean cortisol throughout the day (measured upon awakening, at noon, and at bedtime).[12] Evidently, the relationship between cortisol and psychological resilience is complex, though there is general agreement that higher resilience is related to more efficient activation and deactivation of the HPA axis.[87, 134] Exploring this relationship post-SRC may provide unique insights into SRC pathophysiology.

While considering variation by age and sex, the primary purpose of this paper was to investigate the relationships between psychological resilience and morning and basal cortisol in adolescent sport participants (ASP). We first investigated these relationships in uninjured ASP, expecting that higher resilience would be associated increased morning and basal cortisol. We next explored these associations within 10 days post-SRC, including the additional covariate of post-concussion symptom severity. We again expected that higher resilience would be associated with increased morning and basal cortisol.

5.3 METHODS

5.3.1 Study Design

This study was nested within the multicenter prospective cohort SHRed Concussions (Surveillance in High Schools to Reduce Concussions and the Consequences) study. Participants were enrolled as a team from sports posing high risk for concussion (e.g., hockey, football, and wrestling). The participants, aged 10-18 years, performed baseline testing at the start of their sporting seasons. Following a suspected SRC, participants reported to a SHRed-affiliated sports medicine clinic where post-SRC assessments were recorded and diagnosis was confirmed by sports-medicine physicians guided by the 5th International SRC Consensus Statement.[7] Participants returned for follow-up appointments after one week, and every two weeks thereafter until medically cleared for unrestricted to return to play (RTP). For participants who underwent multiple baseline blood draws across numerous sporting-seasons with SHRed, we included only their most recent cortisol sample, or their cortisol sample immediately preceding an SRC. This study was approved by the University of Calgary conjoint ethics board (ID: REB18-2107).

5.3.2 Inclusion and Exclusion Criteria

For inclusion in SHRed Concussions, participants were enrolled in a high-risk-for-concussion sport. Participants younger than 14 years of age had parental assent, while older participants (mature minors), provided written consent. For inclusion in this sub-study, participants consented to a blood draw collected before 6:00pm. Uninjured participants completed the Connor-Davison Resilience Scale 10 (CDRISC-10)[37] within 90 days of blood draw. Post-SRC participants completed the CDRISC-10 within three days of the blood draw and no more than ten days post-SRC.

Participants were excluded from participation in SHRed Concussions for a history of systemic disease, neurological disorder, or recent injury (fracture or surgery) that may have impaired sport participation. Participants were excluded from this sub-study if their sex was not disclosed. Females reporting use of hormonal contraceptives were excluded due to known influence on cortisol.[113]

5.3.3 Data Collection and Clinical Assessments

Participant characteristics, demographic information and questionnaires were collected during baseline assessments. Participant and demographic characteristics included date of birth, sex, medication use, and medical history. Recorded injury characteristics included confirmation of physician diagnosis,

date of injury, and activity at time of SRC. At the baseline testing, and at post-SRC appointments, participants reported symptoms on the Sport-Concussion Assessment Tool 5 Post-Concussion Symptom Scale (SCAT-5 PCSS)[31] and their perceived resilience on the CDRISC-10.[31, 37] The SCAT-5 PCSS included 22 symptoms (e.g., Neck Pain, Dizziness, and Drowsiness) reported on a Likert scale rated from 0 ("none") to 6 ("severe"). The maximum symptom severity was therefore 132 points. The CDRISC-10 consisted of 10 questions (e.g., "I am not easily discouraged by failure") reported on a Likert scale rated from 0 ("not true at all") to 4 ("true nearly all the time"). The maximum CDRISC-10 score was therefore 40 points. Missing values for the CDRISC-10 were imputed with the mean of the answered values if a minimum of seven responses were completed.[118]

5.3.4 Blood Collection, Processing, and Analysis

Certified phlebotomists performed standard venipuncture to collect blood samples into 10 mL K2-EDTA plasma tubes. Samples were centrifuged for 10 minutes at 1300g at room temperature (21-23°C). In 0.5mL increments, the supernatant was pipetted into individual aliquot tubes that were then frozen at -80°C within two hours of collection.

Analyzing samples in singlicate, Alberta Precision Labs (APL; Calgary, AB, Canada) measured plasma cortisol using the Cobas Elecsys Cortisol II electrochemiluminescence immunoassay (ECLIA) with the Roche Cobas e801 immunoassay analyzer (Roche Diagnostics, Rotkreuz, Switzerland).

Cortisol is commonly stratified as morning or basal for clinical and research purposes. APL, for example, provides cortisol references ranges for morning samples collected before 10:00am, and basal samples collected between 3:00pm-6:00pm.[135] Beyond 6:00pm, cortisol may decrease sharply, prompting researchers to begin collection of evening cortisol after this time.[129] Therefore, to decrease the likelihood of inadvertently capturing elevated morning cortisol, or decreased evening cortisol, SRC researchers investigate basal cortisol collected between 11:00am and 6:00pm. [81] We followed this precedence, and categorized samples as morning (before 11:00am) and basal (11:00am-6:00pm).

5.3.5 Statistical Analysis

For uninjured sample analysis, we stratified by morning and basal cortisol collection times, as outlined above based on clinical and research precedents. Controlling for age (years) and sex

(male/female), we employed generalized linear models (GLM; gaussian family and identity link) to investigate the associations between plasma cortisol (nmol/L) and CDRISC-10 score.

For post-SRC sample analysis, we also stratified by morning and basal cortisol collection times. Controlling for age, sex, and symptom severity (SCAT-5 PCSS), we employed generalized linear models (GLM; gaussian family and identity link) to investigate the associations between plasma cortisol and CDRISC-10 score.

Marginal means were reported and plotted for each model. Statistical significance was determined a priori as alpha < 0.05. All statistical analysis was performed using STATA (v 18.0).[119]

5.4 RESULTS

5.4.1 Uninjured Sample

The uninjured sample is summarized in Figure 5.1 and Table 5.1. From September 2019 to December 2023, SHRed Concussions enrolled 11,226 ASP to the study. Despite interruption starting in March 2020 due the COVID-19 pandemic, assessments continued virtually and resumed in-person July 2021. Of the 1319 participants with uninjured blood samples, 538 met the criteria for inclusion in this study. One uninjured female basal sample was excluded as an outlier with cortisol over 800 nmol/L.

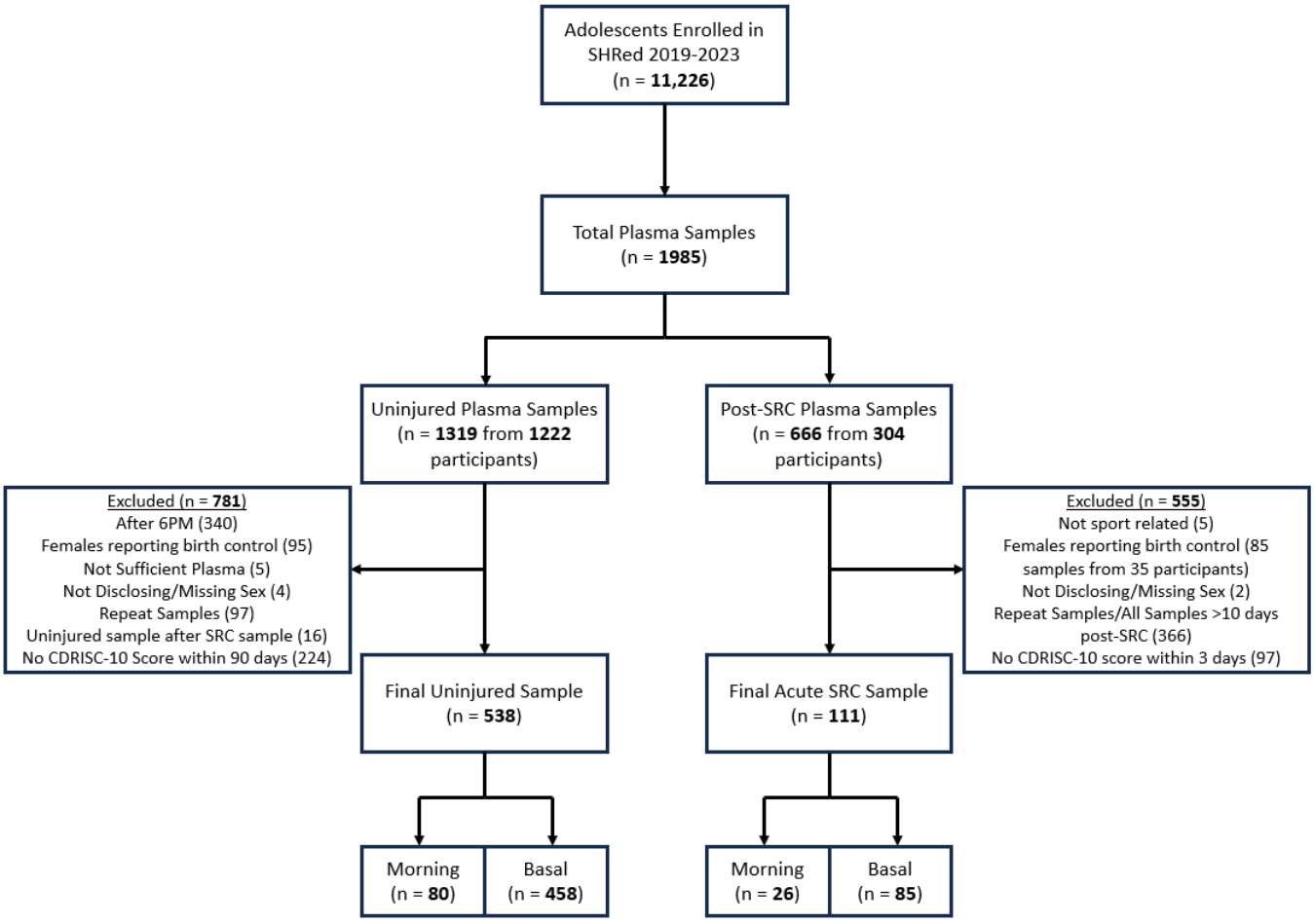

Figure 5.1: SHRed Participant Recruitment Flowchart.

CDRISC-10; Connor-Davidson Resilience Scale 10, SRC; sport-related concussion, Acute; within 10 days of SRC.

Table 5.1: Uninjured Participant Characteristics.

	Female Morning (n=22)	Male Morning (n=58)	Female Basal (n=154)	Male Basal (n=304)
Age (Mean, SD)	16.17 ± 0.77	15.38 ± 1.10	16.04 ± 1.38	16.04 ± 1.13
Cortisol (nmol/L) (Mean, SD)	303.91 ± 125.67	256.57 ± 99.62	227.94 ± 112.51	209.08 ± 87.93
Cortisol Time of Collection (Hrs) (Mean, SD)	10.04 ± 0.52	10.19 ± 0.47	15.55 ± 1.70	15.13 ± 1.96
CDRISC-10 Score (Mean, SD)	33.64 ± 4.95	31.12 ± 5.39	28.99 ± 6.24	30.90 ± 5.69
Sport Participation				
Rugby n (%)	11 (50%)	5 (8.6%)	71 (46.1%)	66 (21.7%)
Football n (%)	-	21 (36.2%)	6 (3.9%)	205 (67.4%)
Hockey n (%)	2 (9.1%)	21 (36.2%)	3 (1.9%)	8 (2.6%)
Ringette n (%)	3 (13.4%)	-	6 (3.9%)	-
Soccer n (%)	-	1 (1.7%)	6 (3.9%)	1 (0.3%)
Volleyball n (%)	4 (18.2%)	-	2 (1.3%)	2 (0.7%)
Basketball n (%)	-	2 (3.4%)	13 (8.4%)	1 (0.3%)
Wrestling n (%)	2 (9.1%)	8 (13.8%)	22 (14.3%)	20 (6.6%)
Lacrosse (%)	-	-	-	1 (0.3%)
Artistic Swimming n (%)	-	-	6 (3.9%)	-
Cheerleading n (%)	-	-	1 (0.6%)	-
Field Hockey	-	-	18 (11.7%)	-

Morning Cortisol: before 11:00am.
Basal Cortisol: between 11:00am and 6:00pm.
All participants completed the CDRISC-10 and blood draw no more than 90 days apart.

5.4.2 Uninjured CDRISC-10 Score and Morning Cortisol

We found a significant negative relationship between morning cortisol and CDRISC-10 score (β = -6.405, 95% CI: -10.598, -2.212, p = 0.003), with the effect size indicating a 6.4 nmol/L decrease in cortisol per unit increase in CDRISC-10 score. We also noted a 26.0 nmol/L increase in morning cortisol per increased year of age (β = 26.017, 95% CI: 4.432, 47.601, p = 0.018). (Table 5.2; Figure 5.2A)

5.4.3 Uninjured CDRISC-10 Score and Basal Cortisol

Uninjured basal cortisol was not associated with the CDRISC-10 score. Basal cortisol increased 9.5 nmol/L with each year of age (β = 9.533, 95% CI: 2.617, 16.450, p = 0.007). (Table 5.2; Figure 5.2B)

Table 5.2: Uninjured Morning and Basal Cortisol Compared to Uninjured CDRISC-10 Scores.

Outcome	Independent Variable	β	95% CI	p
Uninjured Morning Cortisol (nmol/L)	**CDRISC-10 Score**	-6.405	-10.598, -2.212	0.003
	Age	26.017	4.432, 47.601	0.018
	Sex*	-30.131	-81.942, 21.680	0.254
Uninjured Basal Cortisol (nmol/L)	**CDRISC-10 score**	0.399	-1.051, 1.847	0.590
	Age	9.533	2.617, 16.450	0.007
	Sex*	-15.526	-33.558, 2.506	0.092

***Sex comparisons made with females as reference.**

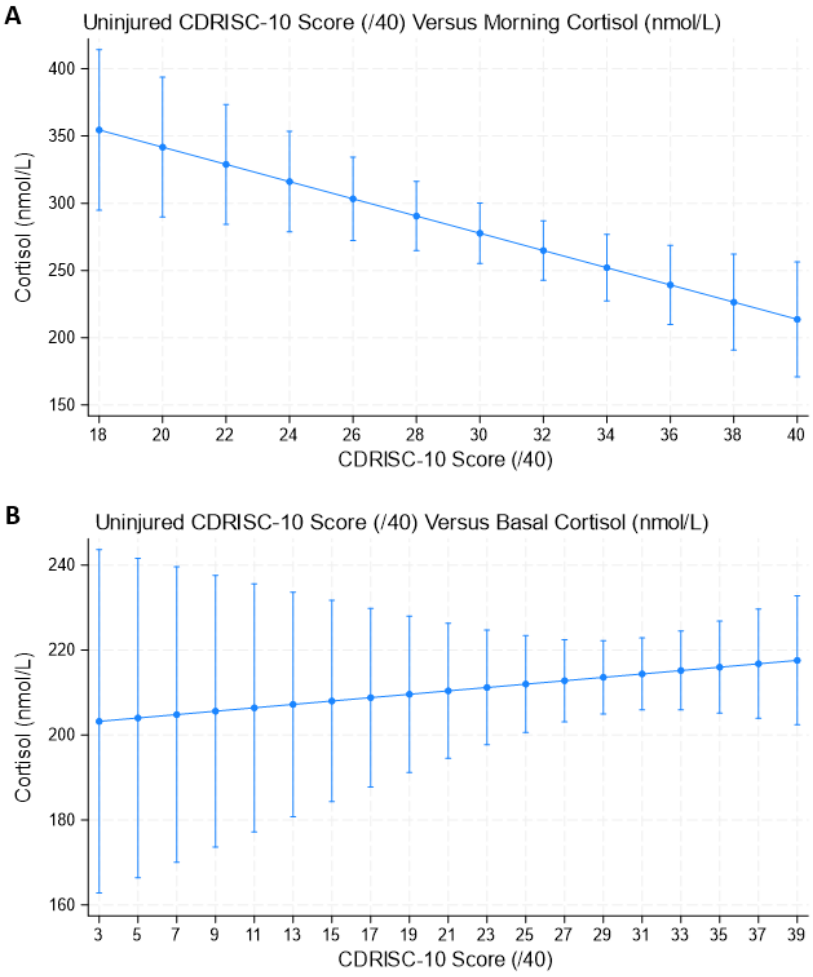

Figure 5.2: Uninjured Cortisol and CDRISC-10 Score.

A) Marginal means of the relationship between uninjured morning cortisol and CDRISC-10 score. Uninjured morning cortisol was significantly associated with CDRISC-10 score, revealing a 6.4 nmol/L decrease in cortisol per unit increase in CDRISC-10 score (β = -6.405, 95% CI: -10.598, -2.212, p = 0.003). (B) Marginal means of the relationship between uninjured basal cortisol and CDRISC-10 score. Uninjured basal cortisol was not associated with CDRISC-10 score (β = 0.399, 95% CI: 1.051, 1.847, p = 0.590). Error bars represent 95% CI.

5.4.4 Post-SRC Sample

The post-SRC sample is summarized in Figure 5.1 and Table 5.3. Within the same SHRed recruitment outlined at the start of this section, SHRed participants reported 1661 SRCs, 111 of which met the criteria for inclusion in this study.

Table 5.3: Post-SRC Participant Characteristics.

	Female Morning (n=10)	**Male Morning (n=16)**	**Female Basal (n=30)**	**Male Basal (n=55)**
Age (Mean, SD)	16.55 ± 0.99	16.37 ± 0.81	16.58 ± 1.02	16.24 ± 1.40
Cortisol (nmol/L (Mean, SD)	218.90 ± 82.49	247.06 ± 67.59	178.70 ± 62.84	181.51 ± 73.07
Cortisol Time of Collection (Hrs) (Mean, SD)	9.68 ± 0.80	9.49 ± 0.71	13.38 ± 1.91	13.86 ± 1.92
CDRISC-10 Score (Mean, SD)	33.10 ± 2.47	31.19 ± 5.00	28.5 ± 3.85	31.04 ± 4.62
Injury Characteristics				
Symptom Severity (Median (IQR))	41 (14, 53)	15.5 (8, 39.5)	26.5 (10, 53)	27 (6, 43)
Missing (n%)	-	1 (6.25%)	-	3 (5.45%)
Number of Symptoms (Median (IQR))	15 (6, 21)	8 (6.5, 15.5)	12 (7, 20)	13 (4, 17)
Missing (n%)	-	1 (6.25 %)	-	3 (5.45%)
Time to RTP (Days) (Median (IQR))	20 (11, 25)	21 (14.5, 35)	20 (15, 30)	19 (13, 26)
Missing (n%)	-	-	-	2 (3.64%)

Table continued on next page…

…Table 5.3 continued				
Activity at Time of Injury				
Rugby n (%)	4 (40%)	8 (50%)	13 (43.3%)	20 (36.4%)
Football n (%)		6 (37.5%)	2 (6.7%)	24 (43.6%)
Hockey n (%)			1 (3.3%)	2 (3.6%)
Ringette n (%)	1 (10%)		8 26.7%)	
Soccer n (%)	1 (10%)		1 (3.3%)	
Volleyball n (%)			3 (10.0%)	
Basketball n (%)			1 (3.3%)	1 (1.8%)
Wrestling n (%)		1 (6.3%)	1 (3.3%)	3 (5.5%)
Swimming n (%)	3 (30%)			
PE Class n (%)		1 (6.3%)		
Summer Camp Games n (%)	1 (10%)			
Baseball n (%)				1 (1.8%)
Lacrosse				1 (1.8%)
Skiing				1 (1.8%)

Morning Cortisol: before 11:00am.
Basal Cortisol: between 11:00am and 6:00pm.
Acute: Within 10 days of injury.
All participants completed the CDRISC-10 and blood draw no more than 3 days apart.

5.4.5 Post-SRC CDRISC-10 Score and Morning Cortisol

Post-SRC morning cortisol was not significantly associated with CDRISC-10 score. Post-SRC morning cortisol was likewise not associated with age, sex, or symptom severity. (Table 5.4; Figure 5.3A)

5.4.6 Post-SRC CDRISC-10 Score and Basal Cortisol

We found no significant association between post-SRC basal cortisol and CDRISC-10 score, and age, sex, and symptom severity were not significant in this model. (Table 5.4; Figure 5.3B)

Table 5.4: Post-SRC Morning and Basal Cortisol to CDRISC-10 Score.

Outcome	Independent Variables	β	95% CI	p
Post-SRC Morning Cortisol (nmol/L)	**Cortisol**	2.429	-5.208, 10.066	0.533
	Symptom Severity	0.175	-1.312, 1.662	0.818
	Age	23.877	-10.018, 57.772	0.167
	Sex*	40.175	-27.832, 108.182	0.247
Post-SRC Basal Cortisol (nmol/L)	**Cortisol**	-0.750	-4.152, 2.651	0.665
	Symptom Severity	-0.510	-1.139, 0.119	0.112
	Age	10.502	-1.057, 22.062	0.075
	Sex*	4.510	-27.614, 36.635	0.783

***Sex comparisons made with females as reference.**

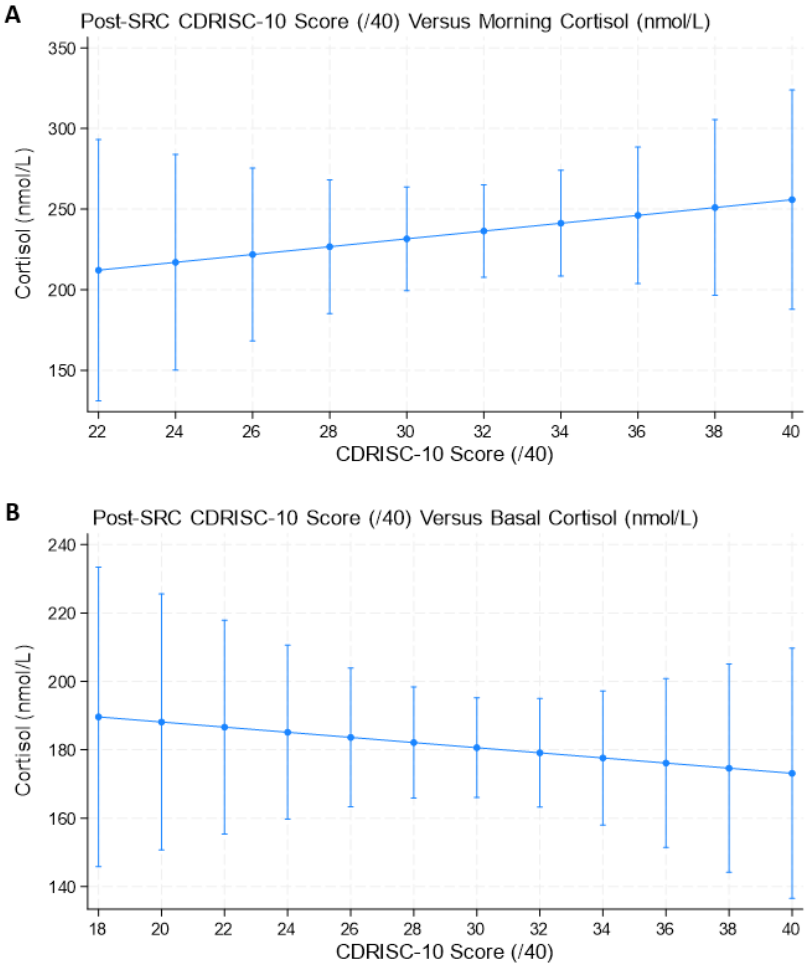

Figure 5.3: Post-SRC Cortisol and CDRISC-10 Score.

(A) Marginal means of the relationship between post-SRC morning cortisol and CDRISC-10 score. Post-SRC morning cortisol and CDRISC-10 score were not significantly related (β = 2.429, 95% CI: -5.208, 10.066, p = 0.533). (B) Marginal means of the relationship between post-SRC basal cortisol and CDRISC-10 score. Post-SRC morning basal and CDRISC-10 score were not significantly related (β = -0.750, 95% CI: -4.152, 2.651, p = 0.665). Error bars represent 95% CI.

5.5 DISCUSSION

In this paper, we investigated the relationships between morning and basal cortisol and psychological resilience, as measured by the CDRISC-10, in uninjured and post-SRC ASP. Among uninjured participants, we found that morning cortisol decreased with increased resilience, and age was positively related to both morning and basal cortisol. However, we found no relationship between basal cortisol and resilience among uninjured ASP. Following SRC, neither morning cortisol nor basal cortisol was associated with resilience. Symptom severity, age, and sex did not significantly relate to cortisol post-SRC. Our results suggest that the relationship between morning cortisol and resilience may become disrupted following SRC, and that basal cortisol does not associate with uninjured or post-SRC resilience.

5.5.1 Uninjured and Post-SRC Resilience and Morning Cortisol

Previous literature involving morning cortisol and resilience has shown conflicting results. Morning cortisol is commonly reported to increase with increased resilience in pediatric and young adult samples.[11, 133] However, there is nuance to this relationship, as the opposite effect has been reported in adults.[12, 87] Our results align with the latter findings. We found that uninjured morning cortisol decreased by 6.4 nmol/L with each unit increase in CDRISC-10 score (Table 5.2; Figure 5.2A). Succinctly, uninjured participants with higher resilience had lower morning cortisol.

Elevations in morning cortisol have been reported to reflect the perceived stress of the day ahead, and more resilient adolescents and young adults have been found to disclose less perceived stress.[63, 76] Therefore, our finding may be explained by more resilient individuals perceiving the stress of the day ahead as lower, resulting in decreased morning cortisol output. Of note, pediatric and young adult studies reveal that, in addition to a stronger CAR, highly resilient individuals demonstrate a steeper decline throughout the day.[11, 133] Considering our relatively broad range of morning sample collection (before 11:00am), it may be that we captured participants on the downslope from morning to basal cortisol. Cortisol may therefore be lower among ASP with greater resilience by virtue of a steeper decline in morning cortisol, although this hypothesis cannot be confirmed without serial sampling of morning cortisol to measure the CAR and slope to basal output.

We were the first to report on the relationship between morning cortisol and resilience acutely post-SRC. Both low morning cortisol and low resilience have independently been linked to poorer SRC

outcomes.[8-10, 62] We therefore hypothesized a positive relationship between the two measures. Contrary to our expectations, we found no significant associations between morning cortisol and resilience measured within ten days following adolescent SRC (Table 5.4; Figure 5.3A). As outlined above, we found a significant relationship between morning cortisol and resilience in our uninjured sample, and not replicating this relationship among our post-SRC sample suggests the relationship between the HPA axis and resilience may be disrupted following SRC.

5.5.2 Uninjured and Post-SRC Resilience and Basal Cortisol

Research between basal cortisol and resilience is likewise conflicting. Some studies report that total cortisol output measured by serial sampling may be higher for more resilient children and young adults,[11, 133] although single samples of basal cortisol have been shown to be higher among more resilient young men.[13] In their systematic review, Aizpurua-Perez and colleagues (2022) conclude that only a single measure of cortisol may be insufficient to capture the relationship between basal cortisol and resilience. In our uninjured sample, despite our large sample size, we indeed found no significant relationship between basal cortisol and resilience (Table 5.2; Figure 5.2B). We conclude single point-measurements of basal cortisol do not relate to resilience among uninjured ASP.

Considering reports that low basal cortisol and low resilience may independently predict increased symptom burden in young-adult SRC,[9, 63, 81] we expected to find a positive relationship between resilience and basal cortisol acutely post-SRC. However, our analyses revealed no relationship between basal cortisol and resilience in our injured sample (Table 5.4; Figure 5.3B), aligning with results from our uninjured basal cortisol analysis. In further agreement with Aizpurua-Perez and colleagues (2022), single point-measurements of basal cortisol may lack sensitivity and specificity for determination of the relationship between the HPA axis and resilience.[134] We suggest further exploration of the relationship between resilience and cortisol using serial sampling of cortisol throughout the day to advance a more nuanced understanding of the relationship between HPA axis functioning and psychological resilience in uninjured and post-SRC ASP.

5.5.3 Strengths and Limitations

This study had several strengths. First, we measured resilience acutely post-SRC, which Ernst and colleagues (2022) report is among the best indicators of SRC outcomes.[63] Another strength was that we investigated both morning and basal cortisol in uninjured and post-SRC participants within the same study

design. This strength allowed us to clearly depict the relationships between cortisol and resilience at two time points during the day in uninjured ASP, and to effectively compare these relationships to post-SRC findings. Moreover, this study included diverse representation of ASP from across Canada. Data was collected from sites in BC, AB, ON, and QC, from uninjured participants of both sexes engaged in numerous sports. SRCs also occurred in diverse sporting activities, increasing the generalizability of our findings to encompass ASP across the nation.

Our study should be interpreted considering some limitations. First is our small post-SRC morning sample. Consisting of only 26 participants, the null relationship between post-SRC morning cortisol and CDRISC-10 score may be due to lack of statistical power. We also had different participants in our uninjured compared to post-SRC groups, resulting in the potential for selection bias to influence the findings between groups. Another limitation related to our sample was not controlling for the phase of menstrual cycle for females, as it has been reported that cortisol is lower in the luteal phase compared to the follicular phase.[125] With a larger sample size, testing for influence by menstrual cycle phase may yield further insights into SRC pathophysiology. A final limitation was considering only one cortisol sample per participant. Considering cortisol's diurnal variation,[130] it may be preferable to collect at minimum two samples through the day, with the first 30-45 minutes after awakening.[128] Such a design would allow for investigation of the associations between resilience and the CAR, the slope between CAR and basal cortisol, and the basal cortisol levels, potentially revealing important features of relationship between resilience, cortisol, and SRC outcomes.[128, 134]

5.5.4 Conclusion

To the best of our knowledge, this was the first study to investigate associations between cortisol and resilience within ten days post-SRC. We found a negative relationship between morning cortisol and resilience in uninjured ASP, but not post-SRC, suggesting HPA axis impairment and disruption in the relationship between cortisol and resilience. There was no significant relationship between basal cortisol and resilience in uninjured or post-SRC ASP, suggesting morning cortisol, or collection of multiple cortisol values throughout the day, may better capture the relationship between cortisol and resilience. This study elucidated novel aspects of SRC pathophysiology, and future studies should collect cortisol serially throughout the day, starting shortly after awakening, with a larger sample size to gain a greater understanding of this complex and important relationship.

6 CHAPTER 6: CONCLUSIONS, STRENGTHS/LIMITATIONS, & FUTURE DIRECTIONS

6.1 THESIS CONCLUSIONS

Adolescent sport-related concussion (SRC) is influenced by psychological and physiological factors. This thesis sought to investigate the relationship between psychological resilience, plasma cortisol, and sport-related concussion symptom burden and length of recovery among Canadian adolescent sport participants (ASP). Leveraging data collected through SHRed concussions, in Chapter 3 we found that resilience decreased for males acutely post-SRC and increased for females at the time of medical clearance to return to play (RTP). We noted that post-SRC measures of resilience had a stronger relationship to symptom burden and length of recovery compared to pre-injury measures of resilience. Chapter 4 revealed a significant decrease for both morning and basal cortisol in participants acutely post-SRC compared to their uninjured counterparts, and we found complex non-linear relationships between cortisol and SRC symptom burden. In brief, lower morning cortisol was related to increased symptom burden and higher morning cortisol was associated with lower symptom burden, though there was a positive association with symptom burden through the mid-range of cortisol. Further, we revealed a 'Goldilocks' effect with basal cortisol, as symptoms increased both at higher and lower basal cortisol concentrations, whereas lower symptoms were found in the mid-range of basal cortisol. We also found that lower post-SRC basal cortisol was associated with a longer recovery. Finally, in Chapter 5 we found that uninjured morning cortisol was negatively associated with resilience, though this relationship did not persist following SRC. Basal cortisol was not associated with CDRISC-10 score among uninjured or post-SRC participants. Ultimately, this thesis revealed novel aspects of SRC pathophysiology, and provided evidence for the utility of exploring resilience-modifying therapeutics to benefit adolescents following SRC.

6.1.1 Chapter 3: Resilience

Chapter three of this thesis (in preparation for submission to The Journal of Pediatrics) was a prospective cohort study investigating the trajectory of resilience across three timepoints: pre-injury, acutely post-SRC, and at time of RTP. Resilience from different timepoints (pre-injury, acutely post-SRC,

and the difference between the two) was compared to SRC symptom severity, number of symptoms, and duration of recovery.

We identified a significant sex by age interaction, with resilience increasing through adolescence for males but not for females. We also revealed a sex by timepoint interaction, with resilience decreasing acutely post-SRC for males, and increasing at time of RTP for females. The trends of these results were confirmed using a within-subject sensitivity analysis; however, many of the relationships in the sensitivity analysis were not statistically significant, likely due to the smaller sample size. Considering these sex differences through adolescence and SRC recovery, we suspect females may benefit more from preventive resilience-targeting therapies, while males may benefit more from such interventions following-SRC.

Considering that resilience has been associated with hypothalamic-pituitary-adrenal (HPA) axis functioning,[11] we hypothesize that the decrease in male resilience may be linked to impaired post-SRC HPA axis functioning, which has been reported following adolescent SRC.[10] We suspect the increase in resilience at RTP for females may be related to quality of life, which has likewise been shown to be higher among adolescents at time of RTP compared to normative measures.[121] However, exploring the directionality of these relationships is a topic for future research.

Moreover, we found that lower pre-injury measures of resilience were related to increased duration of recovery from SRC, but not to symptom burden following injury. Acute measures of resilience associated with both symptom burden and duration of recovery. A greater decrease from pre-to-post-SRC measures of resilience was linked to a greater symptom burden, but not duration of recovery. Acute measures of resilience may therefore better inform on SRC outcomes compared to pre-injury reports. Altogether, resilience may be an informative indicator of SRC outcomes. Taking sex differences into consideration, effort should be directed at exploring the utility of implementing resilience measures in the clinical management of adolescent SRC, and research should continue into exploring resilience-targeting therapeutics following this injury.

6.1.2 Chapter 4: Cortisol

Chapter four (in preparation for submission to Journal of Neurotrauma) was a cross-sectional study that primarily sought to investigate group differences in cortisol between uninjured and post-SRC ASP. We also explored the relationship between cortisol and SRC outcomes.

Stratified by time of day (morning; before 11:00am, and basal; 11:00am-6:00pm) and controlling for age and sex/menstrual cycle phase, we found a significant decrease of nearly 50 nmol/L for both morning and basal cortisol among participants acutely post-SRC compared to their uninjured counterparts, suggesting SRC may result in transient impairment of the HPA axis.

We reported significant associations between post-SRC morning cortisol and symptom burden. Symptom number and severity decreased with increased cortisol from 78-210 nmol/L (Spline 1), increased with cortisol from 210-305 nmol/L (Spline 2), and decreased with cortisol from 305-410 nmol/L (Spline 3). These results suggest that lower morning cortisol may increase risk of more severe symptoms, while increased morning cortisol may be of benefit. The positive relationship between morning cortisol and symptom severity along Spline 2 may indicate a stress response to increased symptom burden, though it may also have been influenced by high-symptom outliers, and investigation with a larger sample size is warranted. Morning cortisol was not associated with duration of recovery.

Post-SRC basal cortisol was also significantly associated with symptom burden, though it demonstrated a 'Goldilocks' effect. Number and severity of symptoms decreased with increased basal cortisol from 61-295 nmol/L (Spline 1) and increased with cortisol thereafter (295-416 nmol/L; Spline 2). Both low and high cortisol were therefore coupled with increased symptom burden. Furthermore, in contrast to a study involving collegiate athletes,[81] we found that higher basal cortisol was related to a shorter recovery. Considering our finding that symptom severity increased beyond 295 nmol/L for some individuals, a more granular approach may be warranted to investigate whether these individuals likewise experienced a longer recovery, or if there exists a differential effect between cortisol and symptom severity and duration of recovery. However, considering our group-level analyses, we conclude basal cortisol may provide a neuroprotective effect following adolescent SRC.

As the first to report such non-linear relationships between morning and basal cortisol following adolescent SRC, we ultimately revealed that lower cortisol may perpetuate increased symptom burden and longer recovery. We suspect this effect is due in part to cortisol's role in inflammation – lower cortisol may result in a less appropriate anti-inflammatory response, thereby increasing symptom burden.[10, 95] However, along the mid-range of morning cortisol concentrations (Spline 2), and beyond 295 nmol/L basal cortisol, this relationship may switch. We suspect the positive associations through these cortisol ranges may be the result of cortisol being released in response to experiencing increased symptoms burdens. While our data cannot confirm the directionality of these relationships, we provide this niche of

SRC pathophysiology grounds for further targeted investigation into the polyphasic relationships between cortisol and SRC outcomes.

6.1.3 Chapter 5: Resilience and Cortisol

In chapter five (in preparation for submission to the British Journal of Sports Medicine), a cross-sectional study, we investigated the relationships between cortisol and resilience, stratified by morning (before 11:00am) and basal (11:00am-6:00pm) cortisol samples among uninjured and post-SRC participants, controlling for age and sex. We included symptom severity as an additional covariate for post-SRC analyses.

In our uninjured group, there was a significant relationship between resilience and morning cortisol, revealing morning cortisol was lower with increased resilience. Morning cortisol elevates in response to the perceived stress of the day ahead.[76] It may be that the more resilient individuals in our sample perceived lower stress, thereby releasing lower concentrations of morning cortisol. However, this finding may have been influenced by the timing of our morning cortisol collections, and merits further investigation.

Following SRC, the relationship between morning cortisol and resilience was not significant. This result could be owing to our small post-SRC morning sample size; however, it may also suggest a disruption in the typical relationship between the HPA axis and resilience. The HPA axis may become impaired following SRC, resulting in lower post-SRC cortisol,[10] thereby disturbing its typical relationship with resilience. Although, this null finding may also reflect a protective effect of resilience, which is discussed below.

Despite our large sample size, the relationship between uninjured resilience and basal cortisol was not significant. While this finding may indicate there is no relationship between basal cortisol and resilience among uninjured ASP, it can also be interpreted as evidence that single point-measures of cortisol within this population may be insufficient to capture the relationship between HPA axis function and psychological resilience. Similarly, post-SRC basal cortisol was not associated with resilience. This null finding furthers the notion that single basal measures of basal cortisol may not relate to psychological resilience. Ultimately, measures of morning cortisol, or serial measures throughout the day, may be more appropriate for capturing the relationship between the HPA axis and resilience.

As mentioned, uninjured individuals with higher resilience may release lower cortisol due to less perceived stress. However, resilience is the ability to adapt to challenges.[12] Although speculative, it may therefore be that individuals with greater resilience are better able to mount a strong stress response *when needed*, such as following SRC. Indeed, although not statistically significant, we found that morning cortisol increased with increased resilience post-SRC (Table 5.4; Figure 5.3A). As such, individuals with greater resilience may benefit more from cortisol's anti-inflammatory properties by virtue of the ability to initiate an appropriate stress response, even in the face of SRC. We postulate, therefore, that the relationship between resilience and SRC outcomes may be mediated by cortisol. We describe in Section 6.3.3 how future researchers may test this hypothesis.

6.2 THESIS STRENGTHS AND LIMITATIONS

There were numerous strengths of our study. First, our samples were well-representative of Canadian adolescent sport participants (ASP). Our data collection for uninjured cortisol was greatly enhanced through use of the 'SHRed Mobile' (see Image 8.1). The 'SHRed Mobile' was our mobile laboratory that allowed for traveling collection of blood samples within communities that may otherwise have been unable to participate. For chapter four, the result was a large sample of 762 uninjured participants meeting our inclusion criteria for cortisol analysis. These participants also engaged in a diverse array of sports. Additionally, we included a large proportion of female participants in each analysis. In doing so, we identified important sex-specific effects when investigating resilience and found that cortisol may be lower following SRC regardless of menstrual cycle phase. Our age range was also a strength, with data collected from participants aged 10-18 years. Altogether, our sample was highly generalizable to Canadian ASP.

Another strength of our sample was the clinical management of our participants post-SRC. SRC diagnosis was confirmed by sport-medicine physicians within ten days of injury, and follow-up was managed by these physicians in conjunction with a team of SHRed clinicians.

Further, cortisol and progesterone were analyzed by Alberta Precision Labs (APL). Assay management was therefore of the highest standard, and the Cobas Elecsys Cortisol II electrochemiluminescence immunoassay (ECLIA) is a commonly used cortisol assay in research and clinical settings. These factors, in addition to our blood samples being collected in strict accordance with our Standard Operating Procedure (see Appendix), make our results comparable across multiple centers.

Lastly, the timepoints at which we collected measurements strengthened this thesis. We were the first to investigate resilience measured both pre-injury and post-SRC. This factor allowed for a strong trajectory analysis of resilience through adolescent SRC and revealed that post-SRC measures of resilience may be superior predictors of SRC outcomes compared to pre-injury measures. Moreover, we were the first to include stratified analyses of morning and basal cortisol from uninjured and post-SRC ASP within the same study. This feature decreased the potential of study-design-related confounding factors to influence results when comparing between these groups.

This thesis should be interpreted in the light of some general limitations. Firstly, the CDRISC-10 was completed through an online portal, often as participants completed other questionnaires requested by SHRed. Misinterpretation of survey questions and survey fatigue may have influenced the results.

Likewise, the CDRISC-10 captures one's self-reported perceived ability to overcome adversity, and so may be biased by participants over-or-underestimating their actual ability to overcome adversity. Some studies operationalize resilience by participants' observed ability to overcome adversity.[50] Overcoming adversity within this study could be therefore operationalized using duration of recovery as a proxy (i.e., a shorter recovery suggests higher resilience). We found that individuals reporting higher resilience acutely post-SRC also recovered more quickly, suggesting that self-report bias within our sample was limited, and that the CDRISC-10 is a measure with high construct validity.

Another limitation was the potential for selection bias. As participation in this research was voluntary, participants completing their surveys may differ in resilience compared to those who failed to report these measures. In a similar vein, participants willing to undergo venipuncture may have differed in resilience and symptom severity compared to those who declined. Addressing the latter consideration, in Chapter 3, we included all participants reporting post-SRC resilience scores, regardless of whether they had completed a blood draw. However, it is likely that individuals refusing venipuncture post-SRC had lower resilience and/or higher symptom burdens, potentially diminishing representation of cortisol samples for low resilience and high symptom burden participants.

Furthermore, some participant characteristics that may have confounded results. For example, concussion history was not included. Considering that we found resilience to increase in females at time of RTP, and that Hassan et al., (2024) found resilience to increase at three-and-six months post-concussion, we expect that a history of concussion would be associated with increased resilience.

Finally, we collected only a single cortisol sample for analysis. Cortisol is highly variable both across the day and in response to stress, resulting in single cortisol measurements potentially underestimating the true frequency of low cortisol following head injury.[90] We addressed this issue by treating cortisol as a continuous variable in all models, rather than stratifying participants has having abnormally high or low cortisol; however, collecting two or more cortisol samples throughout the day may provide greater insights into the relationships between cortisol and resilience following SRC.

6.3 THESIS FUTURE DIRECTIONS

6.3.1 CDRISC-10 MCID

Future research should calculate the minimal clinically important difference (MCID) for CDRISC-10 scores specific to ASP following SRC. An established MCID for adolescent CDRISC-10 scores is not yet available, though such a determination may prove useful when considering resilience as a measure to inform on the clinical management of SRC. There is a reported two-point MCID for a similar 10-point resilience scale adapted to cancer patients,[120] though it may not be appropriate to generalize this study to our sample considering the difference in target populations. Concisely outlined by Franceschini et al., (2023), there are numerous methods to determine a measure's MCID.[136] Similar to the study by Ye et al., (2020), researchers could calculate the CDRISC-10 MCID among ASP by calculating the increase in the CDRISC-10 score associated with a one point-increase in a quality of life survey, such as the Pediatric Quality of Life Inventory (PedsQL).[120, 137]

To elucidate the utility of such a determination, in Chapter 3, we found male CDRISC-10 scores increased by 0.78-points per year through adolescence, suggesting a potential 6-point increase from a 10-year-old to an 18-year-old male. Also, females increased by 2.8 points from pre-injury to RTP measures, and we found that a one-point increase in post-SRC CDRISC-10 score related to a 0.9-point decrease in symptom severity score. While these findings are statistically significant, it was difficult to interpret their clinical relevance without an established CDRISC-10 MCID for ASP. Such an investigation should consider other factors which may relate to adolescent resilience, including measures of interpersonal relationships, life stressors, and social supports following SRC.

6.3.2 Cortisol Serial Sampling

The next step for examining cortisol in the context of adolescent SRC may be to investigate serial samples throughout the day. Acutely post-SRC, cortisol should be sampled immediately upon awakening, and again at 30 and 45 minutes to measure the cortisol awakening response (CAR).[75] Peak morning cortisol output could be compared to existing references ranges, and participants presenting with a blunted CAR could undergo a reactive-cortisol stress test to confirm suspected adrenal insufficiency.[73, 138] Afternoon measures should also be incorporated to capture basal cortisol output. The slope between the CAR and basal cortisol output could then be calculated, with a steeper slope suggesting a more efficient activation and deactivation of the HPA axis. Overall, such a study design would allow for a more granular

investigation between numerous constructs of cortisol output (i.e., the CAR, basal output, the slope from peak CAR to basal output, and peak reactive cortisol) and SRC outcomes. However, such serial sampling is both experimentally demanding, and burdensome for participants. Therefore, salivary cortisol may be considered as opposed to collection through venipuncture.

6.3.3 Resilience and Cortisol Within-Subject Design

Future studies investigating the relationship between cortisol, resilience, and SRC outcomes should aim to capture cortisol concentrations (as per the method outlined above) and CDRISC-10 scores within the same individuals pre-injury and acutely post-SRC. In Chapter 5, while we compared resilience and cortisol in uninjured and post-SRC ASP within the same study design, participants differed between the groups, introducing risk of sampling bias. By investigating the same participants before and after SRC, researchers could be more confident that potential differences in the relationships between cortisol and resilience pre-and-post-SRC would be by virtue of the injury. A major benefit of such a study would be that the mechanisms of the relationships between resilience, cortisol, and SRC outcomes could be investigated by employing prospective, hypothesis-driven causal mediation analyses.

Altogether, with an MCID for the CDRISC-10 specific to ASP and SRC, serial cortisol sampling throughout the day, and pre-and-post-SRC comparisons made within the same participants, future researchers will be well equipped to tackle the complex relationships between resilience, cortisol, and SRC outcomes.

6.4 Thesis Significance

Leveraging data collected within the largest investigation into Canadian adolescent SRC, SHRed Concussions, we found male resilience decreased from pre-injury to acute post-SRC measures, and female resilience was higher at RTP compared to pre-injury measures. For males, females in the follicular phase, and females in the luteal phase, we found that both morning and basal cortisol were significant lower acutely post-SRC compared to their uninjured counterparts. Both resilience and cortisol independently associated with SRC symptom burden and duration of recovery, suggesting these measures may be leveraged to facilitate clinical management of this injury. We found morning cortisol decreased with increased resilience among uninjured participants, though this relationship was absent following SRC, suggesting an alteration in the relationship between the HPA axis and psychology post-SRC, perhaps as a consequence of HPA axis impairment. SRC pathophysiology remains a complex subject for future research, and results from this thesis have the potential to guide targeted investigations and treatments exploring the interplay between psychology and physiology following adolescent sport-related concussion.

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8 APPENDIX

8.1 ETHICS APPROVAL

Conjoint Health Research Ethics Board
Research Services Office
2500 University Drive, NW
Calgary AB T2N 1N4
Telephone: (403) 220-2297
chreb@ucalgary.ca

CERTIFICATION OF INSTITUTIONAL ETHICS APPROVAL

Ethics approval for the following research has been renewed by the Conjoint Health Research Ethics Board (CHREB) at the University of Calgary. The CHREB is constituted and operates in compliance with the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS 2); Health Canada Food and Drug Regulations Division 5; Part C; ICH Guidance E6: Good Clinical Practice and the provisions and regulations of the Health Information Act, RSA 2000 c H-5.

Ethics ID:	REB18-2107_REN5
Principal Investigator:	Carolyn Emery
Co-Investigator(s):	Catherine Lebel Kati Pasanen Darren Stefanyshyn Sarah Kenny Bradley Gordon Goodyear Luz Palacios-Derflingher Chantel Debert Brent Hagel Alberto Nettel-Aguirre Keith Yeates Jonathan Smirl Jeffrey Dunn William Bridel Tyler Cluff Matthew Jordan Sean Dukelow Amanda Black Ashley Harris Kathryn Schneider
Student Co-Investigator(s):	Courtney Kennedy Heidi Morrison Stephen West Julius Ho Destiny Lutz Mark McKenzie Christy Fehr

Aisha Siddiqui
Robert Graham
Devon Stuart
Srijal Gupta
Kenzie Friesen
Olivia Galea
Lan Tran
Emily Heming
Alexandra Sobry
Kirsten Holte
Paul Eliason
Elizabeth Fletcher
Alana Madrid
Carlyn Stilling
Jocelyn McCallum
Joshua Burkart
Clodagh Toomey
Mark Pankow
Lauren Church
Haley Truscott
Lauren Miutz
Berlyn Seselja
Jason Tabor
Nik Josafatow
Paul McKenzie
Alexis Cairo
Matthias Scheid-Wiltshire
Ishaan Cheema
Andrew Lapointe
Ashley Kolstad
Justin Tan
Mackenzie Vaandering
Sagar Grewal
Reid Syrydiuk
Jacalyn Moore
Delowar Hossain
Isla Shill
Heather Shepherd
Meghan Critchley
Jada Kiss
Rylen Williamson
Linden Penner
Taylor Price

Study Title: Surveillance in High School to Reduce Concussions and Consequences of Concussions in Canadian Youth

Sponsor: National Football League's Scientific Advisory Board

Effective: 26-Feb-2024 **Expires:** 26-Feb-2025

Restrictions:

This Certification is subject to the following conditions:

1. The research as described in the application is approved.
2. Proposed modifications must be approved prior to implementation.
3. An application for renewal must be made annually.
4. Closure requests must be submitted when the research is complete or terminated.

Approved By: **Date:**

Stacey A. Page, PhD, Chair, CHREB 6-Feb-2024 12:34 PM

Note: This correspondence includes an electronic signature (validation and approval via an online system).

8.2 PARTICIPANT CONSENT FORM

Consent Form for Participants

TITLE: Surveillance in High Schools to Reduce Concussions and Consequences of Concussions in Canadian Youth – SHRed Concussions

FUNDING: National Football League's Scientific Advisory Board

INVESTIGATORS:

Principal Investigator: Dr. Carolyn Emery

This consent form is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, please ask. Take the time to read this carefully and to understand any accompanying information. A copy of this form can be downloaded for your records.

BACKGROUND

Sport is good for youth, but there is always a chance of getting injured. One of the injuries that can happen is a concussion. There has been research on concussion in some Canadian youth sports, such as hockey. This research has looked at why some youth may be more likely to get a concussion, what affects the amount of time it takes to recover from concussion, and ways to prevent concussions in sports. This helps researchers and health professionals develop strategies that can be used to educate teachers, coaches, parents, and students in schools about concussions.

WHAT IS THE PURPOSE OF THE STUDY?

This study has six major goals:

(1) Collect information on injuries and concussions in school-aged students
(2) Determine why some students may have a higher risk of concussion than others
(3) Examine recovery following a concussion
(4) Evaluate what students, teachers, coaches, and parents know about concussion, and how they manage concussion
(5) Create a concussion education program for high school teachers, coaches, and students, and evaluate if it works
(6) Create sport-related concussion prevention programs and evaluate if these programs work

To accomplish these goals, we will be comparing children who sustain a concussion to those who do not through their school-aged years. These comparisons include a number of measures that look at how you feel about sport, concentration, physical measures such as flexibility, vision, coordination and balance. Biological measures including MRI and blood tests will also be done. Testing may occur at school, at the University or in a clinic.

WHAT WOULD I HAVE TO DO?

We will be asking 6000 school-aged students participating in at least one high-risk concussion sport (e.g. ice hockey, rugby, football, soccer, basketball, volleyball, wrestling, field hockey, ringette, cheerleading, lacrosse, sledge hockey, acrobatic dance , artistic swimming, alpine skiing, wheelchair basketball, including ages 8-18 in community sport) or a low-risk sport (competitive swimming) across Canada to be in the study.

We will follow these participants through their years at school. (next 2 years) All participating youth will be asked to attend a baseline testing session at the time of study recruitment during which they will be asked to complete a variety of measurements. This will take approximately 3 hours to complete and will occur in a combination of your

school or community sport location, University of Calgary, Faculty of Kinesiology (Sport Medicine Centre and Sport Injury Prevention Research Centre), and/or community sport medicine clinic setting. Most of the baseline tests/questionnaires will be repeated once per year over 3 years.

Measurements for all participants will include:

1. Completion of the following questionnaires online
    a. Baseline Questionnaire (e.g., demographics, medical history, sport participation). Completed by you.
    b. Weekly self-report of participation hours in sport and any physical complaints and injuries that you sustain.
    c. Connor-Davidson Resilience Scale (this measures the "ability to "thrive in the face of adversity."). Completed by you only.
    d. The Strength and Difficulties Questionnaire is a brief emotional and behavioral screening questionnaire for children and young people.
    e. The Pediatric Quality of Life Inventory, (this measures health related quality of life in youth and adolescent and is completed by you and your parent)
    f. Phlebotomy questionnaire (some medical and growth information)
    g. Cambridge Brain Sciences (CBS), (this is a computerized test of attention and is completed by you)
    h. 8-item PROMIS sleep-disturbance and sleep-related impairment short-forms completed by you.
    i. Concussion Knowledge, Beliefs and Behaviour Questionnaire (completed by you and your parent)

2. The following tests and physical assessments of you administered by qualified research staff when it is deemed feasible and safe based on AHS and University of Calgary guidelines.. The location of testing will be virtual or at the school, university or clinic
    a. Sport Concussion Assessment Tool 5 (SCAT5) (virtual, school, university or clinic)
    b. Cervical spine evaluation including measures of range of motion, strength, endurance, head and neck position sense and neuromotor control
    c. Vision assessment including tests of smooth pursuit, saccadic eye movement, convergence, optokinetic nystagmus, and stereo visual acuity test
    d. Vestibular, balance and strength measures will include the head thrust test, dynamic visual acuity, the Functional Gait Assessment, vertical jump height and grip strength
    e. Walking While Talking Test, which involves walking at a normal pace, walking and reciting the alphabet, and walking and reciting every other letter of the alphabet
    f. 20-metre shuttle run, which involves travelling 20m distances within a set time. The set time decreases as the test progresses. You will initially be walking to complete the 20m distance, and eventually progress to jogging/running. The test ends when you can no longer complete the distance in the set time. You will be asked to wear a heart rate monitor during the whole 20-metre shuttle run to identify their maximum heart rate as well as their heart rate 5 minutes after they have completed the test.
    g. KINARM Robot assessment, which involves performing arm movements, including reaching and target hitting tasks
    h. Blood test to help identify presence of biomarkers (chemicals) associated with concussion. Blood will be taken by a trained phlebotomist or nurse with experience in pediatric phlebotomy, who can help answer any questions, concerns or anxiety you may have about the blood test. A maximum of two attempts will be made at each session. If you are uncomfortable or anxious about the blood test, or if you want to stop for any reason, they may do so. Your permission is being asked to store

blood specimens in a biobank for future studies, which may include sharing the specimen, stripped of all identifying information, with other investigators for research purposes. We will also be asking you to have your blood taken in the mid-season of their sport year.

Some measurements and assessments will only be undertaken on specific athlete groups:

a. Football, ice hockey, ringette or lacrosse athletes will be asked to have their helmet fit assessed. This currently will be conducted virtually using MS Teams or Zoom, but may include assessment where the assessor is distanced (>3m) from the participant.
b. Rugby, hockey, wrestling, ringette and/or football athletes may be asked to participate in a study where they will be asked to wear a mouthguard including wearable technology to measure body and head impacts

A study therapist (Certified Athletic Therapist and/or physiotherapist) will be visiting your school or practice on a weekly basis. If you suffer any injury during the year, you will be able to have your injury assessed by the study therapist. If the study therapist suspects that you may have a concussion, they will refer you to a study physician with expertise in youth sport-related concussion.

3. For those participants who have sustained a suspected concussion, the following examinations and assessments will occur:

If you, your parent, the coach, or other team personnel suspects that you have sustained a concussion, you will have the opportunity to follow-up with a SHRed aligned physician specializing in concussion within 72-hours. The SHRed aligned physician will assess and diagnose your injury and recommend what you should do to recover from it fully before returning to sports. You can continue seeing the physician until cleared to return to playing sports.

You will be asked to repeat the baseline measurements described above (except the 20m shuttle run). The following additional assessments will be conducted:

a. Illness Perception Questionnaire,
b. Behavioral Avoidance Scale,
c. Behavioral Response to Illness Questionnaire
d. Graded Aerobic Treadmill Test, a standardized incremental treadmill test. You may also be asked to have your blood pressure, heart and breathing rates monitored before, after and during the test. For these tests you will wear a small cuff on your finger, three electrodes attached just under your collar bones and near the bottom of your ribs (electrocardiography [ECG]), and breathe into a mouthpiece.
e. Actigraph which is a wearable technology monitor of physical activity to be worn around the waist following initial appointment (within 72 hours) with physician following concussion to monitor sleep and levels of physical activity (light-moderate- intense). You may be asked to wear the Actigraph 30 days after the concussion and 6 months after the concussion.
f. Blood tests following concussion (acutely within 72 hours, 1 week, and every 2 weeks until physician clearance to return to sport). Your permission is being asked to store blood specimens in a biobank for future studies, which may include sharing the specimen, stripped of all identifying information, with other investigators for research purposes.
g. MRI – as soon as possible after the injury and 30 days following concussion, you will be asked to undergo an MRI. If you are ineligible to undergo an MRI scan (braces or claustrophobic for example), they will be offered the ability to have an fNIRS and EEG analysis.

h. Finally, you may be invited to participate in interviews or small group discussions about their knowledge, beliefs, and behaviours towards concussion. Information from interviews and groups discussions will be used to help develop a concussion education program.
You sport team may be selected to participate in the evaluation an injury prevention strategy. In this case, additional information will be provided to you and specific consent for participation in the program will be sought at that time.

4. Uninjured/healthy comparison group

We are trying to learn about the differences between children who experience a concussion and those who do not. At the time any study participant sustains a concussion, an athlete participating in the study who has not had a concussion will also be asked to undergo an MRI assessment and/or complete the treadmill exercise test and/or wear an Actigraph and/or be asked to provide a fluid biomarker sample and/or be asked to participate in the KINARM assessment. This athlete will be selected to be similar to the student with a concussion regarding age, sex, and sport participation. This approach will help us to determine if MRI can help diagnose concussion. Wearing the Actigraph will help us determine the difference in activity and sleep levels between individuals who have or have not sustained a concussion. The KINARM assessment is a measure of neuro-motor control and will allow us to measure any differences between concussed individuals and those who did not suffer a concussion.

WHAT ARE THE RISKS TO ME?

Due to the COVID-19 pandemic, all of the research, with the exception of clinic related activities due to concussion or injury, will be moving online. As such, we wanted to inform you that with the shift to online, research related risks may include privacy and security of the IT/communication platforms used. With the switching to online meeting tools the research team will be enhancing the data security provisions through the use of institutional online platform accounts which require a password for meetings and if recording, ensure data is stored locally.

As the research team will be instituting virtual meetings with participants, there are no new risks related to transmission of the COVID-19 virus. If the participant requires clinical assessment due to a concussion or other injury, there are risks of transmission of the COVID-19 virus. The research team and clinic staff will take all precautions necessary, including use of PPE by team members and participants to mitigate the possibility of transmission.

For those participants who are undergoing concussion or injury assessments, and when face to face interactions are allowed by both the University of Calgary and your school board or sport governing body (where applicable), the following are the risks to participants:

COVID-19 - There are risks of transmission of the COVID-19 virus. Researchers and clinic staff will mitigate the possibility of transmission through:

- use of secure, remote interactions/methods where feasible
- screening those people attending in-person appointments
- use/provision of PPE for both research staff and research participants (e.g., masks, gloves)
- use/provision of hand sanitizer for both research staff and research participants (e.g., masks, gloves)
- single use research apparatus where possible
- physical distancing measures
- sanitization of surfaces and multi-use equipment between patients/participants

Physical Assessments – All physical assessments will be done under close supervision and every effort will be made to ensure your safety. As with any physical activity, there is the possibility of a muscle strain for tests, such as running. Some testing may result in dizziness or muscle fatigue for a short time following the tests. You may also experience mild discomfort when the tester prepares your skin for electrode placement. You may also find breathing through a mouthpiece while exercising slightly more difficult than breathing without a mouthpiece. The risk of injury will be reduced by careful supervision by trained research team members during testing procedures. The neck, balance, vestibular, eye movement and other tests are ones that are typically used in clinical practice. These tests will all be done by clinicians who have training in the tests. If an increase in discomfort occurs above what is typically expected during testing or if you wish to stop testing, you should let the tester know. If you do have any symptoms at any time during testing, you should let the tester know and the test will be stopped.

Blood tests - The blood tests will be done following standardized laboratory procedures. The person taking your blood will be a trained technician. Although very rare, there is a possibility of local infection within days of having blood taken. There is also a remote possibility of fainting. There is a possibility of a slight bruise at the needle site.

Magnetic resonance imaging (MRI) is a technique that uses magnets and radio waves, not radiation, to take pictures of the body. MRI has no known harmful effects as long as you have none of the risk factors that will be screened for by the MRI technologist. Specifically, you should not have an MRI if they have a pacemaker or certain other metal objects inside their body (including dental braces), because the strong magnets in the MR scanner might cause these to heat up or move, causing harm. You will also need to remove all metal from their clothing and pockets; otherwise these objects could be pulled into the magnet and cause harm. No metal can be brought into the magnet room at any time, since the magnet is always "on". During the MRI session, you will lie on a padded table and be asked to hold as still as possible while pictures are being taken. The MRI technologist will be carefully monitoring the session and will answer any questions or concerns that you or your parent may have during the session. When the scan begins, you will hear a loud knocking noise (like a drum beat) that can change at times during the scan. If you cannot lie still enough to complete a high-quality scan, are uncomfortable or anxious, or want to stop for any reason, you can be removed from the scanner immediately. Further, MRI will not be performed if you feel too claustrophobic to enter the scanner.

Near-Infrared (NIR) light can be used to measure blood flow responses in the brain. Near-infrared spectroscopy (NIRS) systems offer a non-invasive and safe way to measure oxygen content in the brain. This is done by shining light into the tissue. Different light is absorbed differently by blood. The light is measured using fiber optics. These fiber optics will be placed on the head using a head cap.

Electroencephalography (EEG) can be used to measure neuronal activity in the brain. EEG offers a non-invasive and safe way to measure brain activity. This is done by attaching electrodes to the scalp. These electrodes are sensitive to electric signals and thereby record electrical signals in their vicinity. The electrodes will be placed on the head using a head cap. An electrocardiogram (ECG) monitors heart function by measuring electrical activity of the heart. This is achieved through the placement of electrodes on three positions on the chest.

If you consent to be part of this study, we will use fNIRS/EEG/ECG to examine brain activity, cardiac rhythm, and oxygen levels. Furthermore, we will examine these measures in relation to questionnaires relating to chronic and acute stress, pain, fatigue, and concussion history.

The EEG, fNIRS, and ECG techniques are very safe and there are no risks to them.

WILL I BENEFIT IF I TAKE PART?

There are some direct benefits to you. The information we get from this study will give researchers a better understanding of school-aged students' injuries. This information will help develop strategies that can be used to prevent sport and recreational injuries in the future. The schools or clubs of athletes participating in the study will have access to a study therapist (athletic therapist or physiotherapist) one day per week to facilitate concussion educational opportunities. The study therapist will assess any injury sustained by a study participant in the previous week and make recommendations for follow-up. All study participants will have access to follow-up with a study physician with expertise in youth sport-related concussion within 72 hours of sustaining a suspected concussion.

If you participate in the MRI, SHRED Concussions will supply you with a life-size 3-D print of your brain (your choice of color).

It is possible that you and/or your parent may learn more about injuries and concussions. If you get injured during the study, you will be assessed by a study therapist. If the study therapist suspects that you may have a concussion, they will refer you to a study physician.

Incidental findings

In the unlikely scenario that a researcher observes a suspected abnormality in your results (i.e. images, blood tests), a study physician will be consulted and provided with you and your parent's information. He or she will make a determination of its potential significance to your health and welfare. If considered to be a finding of potential clinical significance, you will be informed and the physician will make recommendations for follow-up.

DOES I HAVE TO PARTICIPATE?

No, you do not have to be in the study. Participation in the study is voluntary and you may withdraw from the study at any time by contacting the study coordinator. If you leave the study, you may also request to withdraw your data. You may request to have any stored blood specimens destroyed if you decide to withdraw from the study. Your involvement in your team or school will not be affected if you choose not to consent to take part in the study. You will be informed if there is new information available through this study.

You may be contacted in the future and be invited to take part in other aligned research studies in which separate consent will be sought. Data collected during this study may be combined and reported with data from other future studies conducted by this research team. We will not share your identifying information with anyone outside the research team.

WILL THERE BE FINANCIAL COMPENSATION, OR WILL THERE BE COSTS FOR ME?

There will be no financial compensation or costs to you or your parent as a participant in this study. At the time of study related visits at a university or clinic, parking will be paid for you. In addition, juice and snacks will be available to you at the time of blood draw.

We will be offering pizza parties, as well as having random draws for participants for U of Calgary Dinos, Calgary Hitmen, or other games.

WILL MY RECORDS BE KEPT PRIVATE?

All information collected throughout the study period will be de-identified and will remain strictly confidential. Only the investigators responsible for this study, the research team members directly supervised by a study

investigator, and the team statistician who will analyze the data, the University of Calgary, and the Conjoint Health Research Ethics Board will have access to this information. Data will be collected primarily through an online web-based customized surveillance platform (athlete monitoring) with authentication for users, encryption, and password protection in accordance with Personal Health Information Protection and Privacy Act (HIPPA) guidelines and in accordance with University of Calgary information Security Control Requirements approval and stored on an OVH Canada dedicated server in compliance with University of Calgary requirements.

Confidentiality will be protected by using only study identification numbers in the database. Any results of the study, which are reported, will in no way identify study participants. Online surveys may ask for personal identifiers or information that may be used to identify you. However, no direct link is made between their information and their data. De-identified data may be used in future studies in alignment with this project. No medical data outside of study data collection will be accessed by the research team.

IF I SUFFER A RESEARCH RELATED INJURY, WILL WE BE COMPENSATED?

In the unlikely event that you suffer an injury because of participating in this research, the University of Calgary, or the researchers will provide no compensation. You still have all your legal rights. Nothing said here will alter your right to seek damages.

SIGNATURES

Your signature on this form indicates that you have understood to your satisfaction the information regarding you participation in the research project. In no way does this waive your legal rights nor release the investigators or involved institutions from their legal and professional responsibilities. You and/or your parent are free to withdraw from the study at any time without jeopardizing health care and/or education. If you have further questions related to this research, please contact:

Study Research Coordinator at SHRedConcussions@ucalgary.ca or Carolyn Emery 403-220-4608
If you have any questions concerning your rights as a possible research participant, or research in general, or if you feel you are being mistreated, please contact the Chair of the Conjoint Health Research Ethics Board, University of Calgary, at 403-220-7990.

Participant's Name	Signature & Date
Birthdate	Email Address
Investigator/Delegate's Name	Signature and Date
Witness' Name	Signature and Date
Parent/Guardian's Name	Parent Email Address
Parent Phone Number	

Please check this box if you are willing to be contacted for future studies ☐

The University of Calgary Conjoint Health Research Ethics Board has approved this research study.

8.3 SHRED BLOOD BIOMARKER QUESTIONNAIRE

SHRed Concussions – Fluid Biomarkers Blood Questionnaire

Where is blood draw occurring?

- Clinic
- Community
- School

Pre-Blood Draw Questions (Completed by RA)

1) Timing for blood draw? (Baseline, Mid-season Baseline, Post Concussion/Injury)
2) Did the participant agree to have blood taken (Yes/No)
3) Is this blood being taken as part of a camp or baseline testing session (Yes/No)

Blood Draw Details (Completed by RA)

4) Number of blood draw attempts? (1 or 2)
5) Was the blood draw successful? (Yes/No)
6) Phlebotomist/Physician who drew the blood? (Drop down list of names)
7) Collection Completion Data & Time (specify)
8) Samples taken (Serum only, Plasma only, Serum & Plasma)
9) Draw comments? (specify)

Blood Processing Details (Completed by RA)

1) Centrifuge Date & Time (date/time)
2) Freezing Date & Time (date/time)
3) Processing Time (hours/mins)
4) Sample processing comments (specify)

Blood Draw Questionnaire at each blood draw (Self-Report by Participant)

<u>Exercise Questions:</u>

1) Have you exercised in the last 24 hours? (Yes/No)
2) What type of exercise? Aerobic (e.g., running, biking, swimming) Anaerobic (e.g., weightlifting, climbing) (Answers: Aerobic, Anaerobic, Both)
3) Did you complete the exercise in the last: 3 hours, 6 hours, 12 hours, 24 hours (select one)

<u>Menstruation Questions (females only):</u>

1) When was the start of your first menstrual cycle? (Age in years and months)
2) Have you been regular over the last 12 months? (Yes/No)
3) If you are regular, how long is your cycle? (days)
4) Where are you in your current cycle/when was the start of their most recent cycle? (approx. date)
5) Are you currently using any intervention for birth control (including birth control pills, injectables, and/or IUD and other methods)? (Yes/No. If yes, specify)

<u>Medication Questions:</u>

1) Are you taking any prescription oral/inhaled/injectable/topical medications on a regular basis? (Yes/No. If yes, specify)
2) Are you taking any over the counter medications as needed such as Advil, Aleve, or Tylenol? (Yes/No. If yes, specify)
    a. If yes: How much and how often have you taken it over the last week? (E.g. 500 mg of Tylenol 3 times/day) (Amount and frequency)

3) Are you taking any vitamins or supplements? (e.g., vitamins, protein powder, creatine, probiotics) (Yes/No. If yes, specify)
4) Are you taking any performance enhancing substances? (Yes/No. If yes, specify)

Other: (Questions 2 & 3 to only be asked if blood draw in the clinic)

1) Have you had any caffeine today? (Yes/No)
    a. If yes: How much (e.g. 2 cups of coffee, 1 energy drink)
2) Do you regularly smoke, chew, or vape tobacco/nicotine products? (Yes/No)
3) Do you regularly smoke, eat, or vape cannabis products? (Yes/No)

COVID-19 Test Positivity Questions:

1) Have you ever tested positive for COVID-19 (either PCR [lab], rapid test [antigen], or serology [antibodies]) (Yes/No)
2) If yes, what was the most recent date (approximate)? – (day/month/year)
3) Have you ever tested positive (either PCR [lab], rapid test [antigen], or serology [antibodies) AND been symptomatic with COVID-19 – (Yes/No)
4) If yes, what was the most recent date (approximate)? – (day/month/year)

The next questions are about changes that may be happening to your body. These changes normally happen to different young people at different ages. If you do not understand a question or do not know the answer, just select "I don't know."

1. Would you say that your growth in height:
    a. has not yet begun to spurt
    b. has barely started
    c. is definitely underway
    d. seems completed
    e. I don't know
2. And how about the growth of your body hair? ("body hair" means hair any place other than your head, such as under your arms.) Would you say that your body hair growth:
    a. has not yet begun to grow
    b. has barely started to grow
    c. is definitely underway
    d. seems completed
    e. I don't know
3. Have you noticed any skin changes, especially pimples?
    a. skin has not yet started changing
    a. skin has barely started changing
    b. skin changes are definitely underway
    c. skin changes seem completed
    d. I don't know

Female

4. Have you noticed that your breasts have begun to grow?
    a. have not yet started growing

b. have barely started growing
c. breast growth is definitely underway
d. breast growth seems complete
e. I don't know

5. Have you begun to menstruate (started to have your period)?
Yes/No
5a. If yes, how old were you when you started to menstruate? (age in years)

Male:

4. Have you noticed a deepening of your voice?
a. voice has not yet started changing
b. voice has barely started changing
c. voice changes are definitely underway
d. voice changes seem complete
e. I don't know

5. Have you begun to grow hair on your face?
a. facial hair has not yet started growing
b. facial hair has barely started growing
c. facial hair growth has definitely started
d. facial hair growth seems complete
e. I don't know

8.4 THE SPORT CONCUSSION ASSESSMENT TOOL – 5TH ADDITION

BJSM Online First, published on April 26, 2017 as 10.1136/bjsports-2017-097506SCAT5

SCAT5©

SPORT CONCUSSION ASSESSMENT TOOL – 5TH EDITION

DEVELOPED BY THE CONCUSSION IN SPORT GROUP

FOR USE BY MEDICAL PROFESSIONALS ONLY

supported by

FIFA

Patient details

Name: _____

DOB: _____

Address: _____

ID number: _____

Examiner: _____

Date of Injury: _____ Time: _____

WHAT IS THE SCAT5?

The SCAT5 is a standardized tool for evaluating concussions designed for use by physicians and licensed healthcare professionals[1]. The SCAT5 cannot be performed correctly in less than 10 minutes.

If you are not a physician or licensed healthcare professional, please use the Concussion Recognition Tool 5 (CRT5). The SCAT5 is to be used for evaluating athletes aged 13 years and older. For children aged 12 years or younger, please use the Child SCAT5.

Preseason SCAT5 baseline testing can be useful for interpreting post-injury test scores, but is not required for that purpose.Detailed instructions for use of the SCAT5 are provided on page 7. Please read through these instructions carefully before testing the athlete. Brief verbal instructions for each test are given in italics. The only equipment required for the tester is a watch or timer.

Recognise and Remove

A head impact by either a direct blow or indirect transmission of force can be associated with a serious and potentially fatal brain injury. If there are significant concerns, including any of the red flags listed in Box 1, then activation of emergency procedures and urgent transport to the nearest hospital should be arranged.

Key points

- Any athlete with suspected concussion should be REMOVED FROM PLAY, medically assessed and monitored for deterioration. No athlete diagnosed with concussion should be returned to play on the day of injury.
- If an athlete is suspected of having a concussion and medical personnel are not immediately available, the athlete should be referred to a medical facility for urgent assessment.
- Athletes with suspected concussion should not drink alcohol, use recreational drugs and should not drive a motor vehicle until cleared to do so by a medical professional.
- Concussion signs and symptoms evolve over time and it is important to consider repeat evaluation in the assessment of concussion.
- The diagnosis of a concussion is a clinical judgment, made by a medical professional. The SCAT5 should NOT be used by itself to make, or exclude, the diagnosis of concussion. An athlete may have a concussion even if their SCAT5 is "normal".

Remember:

- The basic principles of first aid (danger, response, airway, breathing, circulation) should be followed.
- Do not attempt to move the athlete (other than that required for airway management) unless trained to do so.
- Assessment for a spinal cord injury is a critical part of the initial on-field assessment.
- Do not remove a helmet or any other equipment unless trained to do so safely.

IMMEDIATE OR ON-FIELD ASSESSMENT

The following elements should be assessed for all athletes who are suspected of having a concussion prior to proceeding to the neurocognitive assessment and ideally should be done on-field after the first first aid / emergency care priorities are completed.

If any of the "Red Flags" or observable signs are noted after a direct or indirect blow to the head, the athlete should be immediately and safely removed from participation and evaluated by a physician or licensed healthcare professional.

Consideration of transportation to a medical facility should be at the discretion of the physician or licensed healthcare professional.

The GCS is important as a standard measure for all patients and can be done serially if necessary in the event of deterioration in conscious state. The Maddocks questions and cervical spine exam are critical steps of the immediate assessment; however, these do not need to be done serially.

Name: _____

DOB: _____

Address: _____

ID number: _____

Examiner: _____

Date: _____

STEP 1: RED FLAGS

RED FLAGS:

- **Neck pain or tenderness**
- **Double vision**
- **Weakness or tingling/ burning in arms or legs**
- **Severe or increasing headache**
- **Seizure or convulsion**
- **Loss of consciousness**
- **Deteriorating conscious state**
- **Vomiting**
- **Increasingly restless, agitated or combative**

STEP 2: OBSERVABLE SIGNS

Witnessed ☐ Observed on Video ☐

Lying motionless on the playing surface	Y	N
Balance / gait difficulties / motor incoordination: stumbling, slow / laboured movements	Y	N
Disorientation or confusion, or an inability to respond appropriately to questions	Y	N
Blank or vacant look	Y	N
Facial injury after head trauma	Y	N

STEP 3: MEMORY ASSESSMENT MADDOCKS QUESTIONS[2]

"I am going to ask you a few questions, please listen carefully and give your best effort. First, tell me what happened?"

Mark Y for correct answer / N for incorrect

What venue are we at today?	Y	N
Which half is it now?	Y	N
Who scored last in this match?	Y	N
What team did you play last week / game?	Y	N
Did your team win the last game?	Y	N

Note: Appropriate sport-specific questions may be substituted.

STEP 4: EXAMINATION

GLASGOW COMA SCALE (GCS)[3]

Time of assessment			
Date of assessment			
Best eye response (E)			
No eye opening	1	1	1
Eye opening in response to pain	2	2	2
Eye opening to speech	3	3	3
Eyes opening spontaneously	4	4	4
Best verbal response (V)			
No verbal response	1	1	1
Incomprehensible sounds	2	2	2
Inappropriate words	3	3	3
Confused	4	4	4
Oriented	5	5	5
Best motor response (M)			
No motor response	1	1	1
Extension to pain	2	2	2
Abnormal flexion to pain	3	3	3
Flexion / Withdrawal to pain	4	4	4
Localizes to pain	5	5	5
Obeys commands	6	6	6
Glasgow Coma score (E + V + M)			

CERVICAL SPINE ASSESSMENT

Does the athlete report that their neck is pain free at rest?	Y	N
If there is NO neck pain at rest, does the athlete have a full range of ACTIVE pain free movement?	Y	N
Is the limb strength and sensation normal?	Y	N

In a patient who is not lucid or fully conscious, a cervical spine injury should be assumed until proven otherwise.

Davis GA, *et al*. *Br J Sports Med* 2017;**0**:1–8. doi:10.1136/bjsports-2017-097506SCAT5

OFFICE OR OFF-FIELD ASSESSMENT

Please note that the neurocognitive assessment should be done in a distraction-free environment with the athlete in a resting state.

STEP 1: ATHLETE BACKGROUND

Sport / team / school: _____

Date / time of injury: _____

Years of education completed: _____

Age: _____

Gender: M / F / Other

Dominant hand: left / neither / right

How many diagnosed concussions has the athlete had in the past?: _____

When was the most recent concussion?: _____

How long was the recovery (time to being cleared to play) from the most recent concussion?: _____ (days)

Has the athlete ever been:

Hospitalized for a head injury?	Yes	No
Diagnosed / treated for headache disorder or migraines?	Yes	No
Diagnosed with a learning disability / dyslexia?	Yes	No
Diagnosed with ADD / ADHD?	Yes	No
Diagnosed with depression, anxiety or other psychiatric disorder?	Yes	No

Current medications? If yes, please list:

_____

_____

_____

_____

_____

_____

Name: _____

DOB: _____

Address: _____

ID number: _____

Examiner: _____

Date: _____

2

STEP 2: SYMPTOM EVALUATION

The athlete should be given the symptom form and asked to read this instruction paragraph out loud then complete the symptom scale. For the baseline assessment, the athlete should rate his/her symptoms based on how he/she typically feels and for the post injury assessment the athlete should rate their symptoms at this point in time.

Please Check: ☐ **Baseline** ☐ **Post-Injury**

Please hand the form to the athlete

	none	mild		moderate		severe	
Headache	0	1	2	3	4	5	6
"Pressure in head"	0	1	2	3	4	5	6
Neck Pain	0	1	2	3	4	5	6
Nausea or vomiting	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Blurred vision	0	1	2	3	4	5	6
Balance problems	0	1	2	3	4	5	6
Sensitivity to light	0	1	2	3	4	5	6
Sensitivity to noise	0	1	2	3	4	5	6
Feeling slowed down	0	1	2	3	4	5	6
Feeling like "in a fog"	0	1	2	3	4	5	6
"Don't feel right"	0	1	2	3	4	5	6
Difficulty concentrating	0	1	2	3	4	5	6
Difficulty remembering	0	1	2	3	4	5	6
Fatigue or low energy	0	1	2	3	4	5	6
Confusion	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
More emotional	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6
Nervous or Anxious	0	1	2	3	4	5	6
Trouble falling asleep (if applicable)	0	1	2	3	4	5	6
Total number of symptoms:							of 22
Symptom severity score:							of 132
Do your symptoms get worse with physical activity?						Y	N
Do your symptoms get worse with mental activity?						Y	N
If 100% is feeling perfectly normal, what percent of normal do you feel?							

If not 100%, why?

_____

_____

_____

Please hand form back to examiner

STEP 3: COGNITIVE SCREENING

Standardised Assessment of Concussion (SAC)[4]

Name: _____

DOB: _____

Address: _____

ID number: _____

Examiner: _____

Date: _____

ORIENTATION

What month is it?	0	1
What is the date today?	0	1
What is the day of the week?	0	1
What year is it?	0	1
What time is it right now? (within 1 hour)	0	1
Orientation score		of 5

IMMEDIATE MEMORY

The Immediate Memory component can be completed using the traditional 5-word per trial list or optionally using 10-words per trial to minimise any ceiling effect. All 3 trials must be administered irrespective of the number correct on the first trial. Administer at the rate of one word per second.

Please choose EITHER the 5 or 10 word list groups and circle the specific word list chosen for this test.

I am going to test your memory. I will read you a list of words and when I am done, repeat back as many words as you can remember, in any order. For Trials 2 & 3: I am going to repeat the same list again. Repeat back as many words as you can remember in any order, even if you said the word before.

List	Alternate 5 word lists					Score (of 5) Trial 1	Trial 2	Trial 3
A	Finger	Penny	Blanket	Lemon	Insect			
B	Candle	Paper	Sugar	Sandwich	Wagon			
C	Baby	Monkey	Perfume	Sunset	Iron			
D	Elbow	Apple	Carpet	Saddle	Bubble			
E	Jacket	Arrow	Pepper	Cotton	Movie			
F	Dollar	Honey	Mirror	Saddle	Anchor			
					Immediate Memory Score			of 15
					Time that last trial was completed			

List	Alternate 10 word lists					Score (of 10) Trial 1	Trial 2	Trial 3
G	Finger Candle	Penny Paper	Blanket Sugar	Lemon Sandwich	Insect Wagon			
H	Baby Elbow	Monkey Apple	Perfume Carpet	Sunset Saddle	Iron Bubble			
I	Jacket Dollar	Arrow Honey	Pepper Mirror	Cotton Saddle	Movie Anchor			
					Immediate Memory Score			of 30
					Time that last trial was completed			

CONCENTRATION

DIGITS BACKWARDS

Please circle the Digit list chosen (A, B, C, D, E, F). Administer at the rate of one digit per second reading DOWN the selected column.

I am going to read a string of numbers and when I am done, you repeat them back to me in reverse order of how I read them to you. For example, if I say 7-1-9, you would say 9-1-7.

Concentration Number Lists (circle one)					
List A	List B	List C			
4-9-3	5-2-6	1-4-2	Y	N	0
6-2-9	4-1-5	6-5-8	Y	N	1
3-8-1-4	1-7-9-5	6-8-3-1	Y	N	0
3-2-7-9	4-9-6-8	3-4-8-1	Y	N	1
6-2-9-7-1	4-8-5-2-7	4-9-1-5-3	Y	N	0
1-5-2-8-6	6-1-8-4-3	6-8-2-5-1	Y	N	1
7-1-8-4-6-2	8-3-1-9-6-4	3-7-6-5-1-9	Y	N	0
5-3-9-1-4-8	7-2-4-8-5-6	9-2-6-5-1-4	Y	N	1
List D	List E	List F			
7-8-2	3-8-2	2-7-1	Y	N	0
9-2-6	5-1-8	4-7-9	Y	N	1
4-1-8-3	2-7-9-3	1-6-8-3	Y	N	0
9-7-2-3	2-1-6-9	3-9-2-4	Y	N	1
1-7-9-2-6	4-1-8-6-9	2-4-7-5-8	Y	N	0
4-1-7-5-2	9-4-1-7-5	8-3-9-6-4	Y	N	1
2-6-4-8-1-7	6-9-7-3-8-2	5-8-6-2-4-9	Y	N	0
8-4-1-9-3-5	4-2-7-9-3-8	3-1-7-8-2-6	Y	N	1
		Digits Score:			of 4

MONTHS IN REVERSE ORDER

Now tell me the months of the year in reverse order. Start with the last month and go backward. So you'll say December, November. Go ahead.

Dec - Nov - Oct - Sept - Aug - Jul - Jun - May - Apr - Mar - Feb - Jan	0 1
Months Score	of 1
Concentration Total Score (Digits + Months)	of 5

4

STEP 4: NEUROLOGICAL SCREEN

See the instruction sheet (page 7) for details of test administration and scoring of the tests.

Can the patient read aloud (e.g. symptom check-list) and follow instructions without difficulty?	Y	N
Does the patient have a full range of pain-free PASSIVE cervical spine movement?	Y	N
Without moving their head or neck, can the patient look side-to-side and up-and-down without double vision?	Y	N
Can the patient perform the finger nose coordination test normally?	Y	N
Can the patient perform tandem gait normally?	Y	N

BALANCE EXAMINATION

Modified Balance Error Scoring System (mBESS) testing[5]

Which foot was tested (i.e. which is the non-dominant foot) ☐ Left ☐ Right

Testing surface (hard floor, field, etc.) _____

Footwear (shoes, barefoot, braces, tape, etc.) _____

Condition	Errors
Double leg stance	of 10
Single leg stance (non-dominant foot)	of 10
Tandem stance (non-dominant foot at the back)	of 10
Total Errors	of 30

Name: _____

DOB: _____

Address: _____

ID number: _____

Examiner: _____

Date: _____

5

STEP 5: DELAYED RECALL:

The delayed recall should be performed after 5 minutes have elapsed since the end of the Immediate Recall section. Score 1 pt. for each correct response.

Do you remember that list of words I read a few times earlier? Tell me as many words from the list as you can remember in any order.

Time Started _____

Please record each word correctly recalled. Total score equals number of words recalled.

_____

_____

_____

Total number of words recalled accurately: of 5 or of 10

6

STEP 6: DECISION

Domain	Date & time of assessment:		
Symptom number (of 22)			
Symptom severity score (of 132)			
Orientation (of 5)			
Immediate memory	of 15 of 30	of 15 of 30	of 15 of 30
Concentration (of 5)			
Neuro exam	Normal Abnormal	Normal Abnormal	Normal Abnormal
Balance errors (of 30)			
Delayed Recall	of 5 of 10	of 5 of 10	of 5 of 10

Date and time of injury: _____

If the athlete is known to you prior to their injury, are they different from their usual self?
☐ **Yes** ☐ **No** ☐ **Unsure** ☐ **Not Applicable**
(If different, describe why in the clinical notes section)

Concussion Diagnosed?
☐ **Yes** ☐ **No** ☐ **Unsure** ☐ **Not Applicable**

If re-testing, has the athlete improved?
☐ **Yes** ☐ **No** ☐ **Unsure** ☐ **Not Applicable**

I am a physician or licensed healthcare professional and I have personally administered or supervised the administration of this SCAT5.

Signature: _____

Name: _____

Title: _____

Registration number (if applicable): _____

Date: _____

SCORING ON THE SCAT5 SHOULD NOT BE USED AS A STAND-ALONE METHOD TO DIAGNOSE CONCUSSION, MEASURE RECOVERY OR MAKE DECISIONS ABOUT AN ATHLETE'S READINESS TO RETURN TO COMPETITION AFTER CONCUSSION.

CLINICAL NOTES:

Name: _____
DOB: _____
Address: _____
ID number: _____
Examiner: _____
Date: _____

CONCUSSION INJURY ADVICE

(To be given to the person monitoring the concussed athlete)

This patient has received an injury to the head. A careful medical examination has been carried out and no sign of any serious complications has been found. Recovery time is variable across individuals and the patient will need monitoring for a further period by a responsible adult. Your treating physician will provide guidance as to this timeframe.

If you notice any change in behaviour, vomiting, worsening headache, double vision or excessive drowsiness, please telephone your doctor or the nearest hospital emergency department immediately.

Other important points:

Initial rest: Limit physical activity to routine daily activities (avoid exercise, training, sports) and limit activities such as school, work, and screen time to a level that does not worsen symptoms.

1) Avoid alcohol

2) Avoid prescription or non-prescription drugs without medical supervision. Specifically:

   a) Avoid sleeping tablets

   b) Do not use aspirin, anti-inflammatory medication or stronger pain medications such as narcotics

3) Do not drive until cleared by a healthcare professional.

4) Return to play/sport requires clearance by a healthcare professional.

Clinic phone number: _____

Patient's name: _____

Date / time of injury: _____

Date / time of medical review: _____

Healthcare Provider: _____

Contact details or stamp

INSTRUCTIONS

Words in *Italics* throughout the SCAT5 are the instructions given to the athlete by the clinician

Symptom Scale

The time frame for symptoms should be based on the type of test being administered. At baseline it is advantageous to assess how an athlete "typically" feels whereas during the acute/post-acute stage it is best to ask how the athlete feels at the time of testing.

The symptom scale should be completed by the athlete, not by the examiner. In situations where the symptom scale is being completed after exercise, it should be done in a resting state, generally by approximating his/her resting heart rate.

For total number of symptoms, maximum possible is 22 except immediately post injury, if sleep item is omitted, which then creates a maximum of 21.

For Symptom severity score, add all scores in table, maximum possible is 22 x 6 = 132, except immediately post injury if sleep item is omitted, which then creates a maximum of 21x6=126.

Immediate Memory

The Immediate Memory component can be completed using the traditional 5-word per trial list or, optionally, using 10-words per trial. The literature suggests that the Immediate Memory has a notable ceiling effect when a 5-word list is used. In settings where this ceiling is prominent, the examiner may wish to make the task more difficult by incorporating two 5–word groups for a total of 10 words per trial. In this case, the maximum score per trial is 10 with a total trial maximum of 30.

Choose one of the word lists (either 5 or 10). Then perform 3 trials of immediate memory using this list.

Complete all 3 trials regardless of score on previous trials.

"I am going to test your memory. I will read you a list of words and when I am done, repeat back as many words as you can remember, in any order." The words must be read at a rate of one word per second.

Trials 2 & 3 MUST be completed regardless of score on trial 1 & 2.

Trials 2 & 3:

"I am going to repeat the same list again. Repeat back as many words as you can remember in any order, even if you said the word before."

Score 1 pt. for each correct response. Total score equals sum across all 3 trials. Do NOT inform the athlete that delayed recall will be tested.

Concentration

Digits backward

Choose one column of digits from lists A, B, C, D, E or F and administer those digits as follows:

Say: *"I am going to read a string of numbers and when I am done, you repeat them back to me in reverse order of how I read them to you. For example, if I say 7-1-9, you would say 9-1-7."*

Begin with first 3 digit string.

If correct, circle "Y" for correct and go to next string length. If incorrect, circle "N" for the first string length and read trial 2 in the same string length. One point possible for each string length. Stop after incorrect on both trials (2 N's) in a string length. The digits should be read at the rate of one per second.

Months in reverse order

"Now tell me the months of the year in reverse order. Start with the last month and go backward. So you'll say December, November … Go ahead"

1 pt. for entire sequence correct

Delayed Recall

The delayed recall should be performed after 5 minutes have elapsed since the end of the Immediate Recall section.

"Do you remember that list of words I read a few times earlier? Tell me as many words from the list as you can remember in any order."

Score 1 pt. for each correct response

Modified Balance Error Scoring System (mBESS)[5] testing

This balance testing is based on a modified version of the Balance Error Scoring System (BESS)[3]. A timing device is required for this testing.

Each of 20-second trial/stance is scored by counting the number of errors. The examiner will begin counting errors only after the athlete has assumed the proper start position. The modified BESS is calculated by adding one error point for each error during the three 20-second tests. The maximum number of errors for any single condition is 10. If the athlete commits multiple errors simultaneously, only one error is recorded but the athlete should quickly return to the testing position, and counting should resume once the athlete is set. Athletes that are unable to maintain the testing procedure for a minimum of five seconds at the start are assigned the highest possible score, ten, for that testing condition.

OPTION: For further assessment, the same 3 stances can be performed on a surface of medium density foam (e.g., approximately 50cm x 40cm x 6cm).

Balance testing – types of errors

1. Hands lifted off iliac crest
2. Opening eyes
3. Step, stumble, or fall
4. Moving hip into > 30 degrees abduction
5. Lifting forefoot or heel
6. Remaining out of test position > 5 sec

"I am now going to test your balance. Please take your shoes off (if applicable), roll up your pant legs above ankle (if applicable), and remove any ankle taping (if applicable). This test will consist of three twenty second tests with different stances."

(a) Double leg stance:

"The first stance is standing with your feet together with your hands on your hips and with your eyes closed. You should try to maintain stability in that position for 20 seconds. I will be counting the number of times you move out of this position. I will start timing when you are set and have closed your eyes."

(b) Single leg stance:

"If you were to kick a ball, which foot would you use? [This will be the dominant foot] *Now stand on your non-dominant foot. The dominant leg should be held in approximately 30 degrees of hip flexion and 45 degrees of knee flexion. Again, you should try to maintain stability for 20 seconds with your hands on your hips and your eyes closed. I will be counting the number of times you move out of this position. If you stumble out of this position, open your eyes and return to the start position and continue balancing. I will start timing when you are set and have closed your eyes."*

(c) Tandem stance:

"Now stand heel-to-toe with your non-dominant foot in back. Your weight should be evenly distributed across both feet. Again, you should try to maintain stability for 20 seconds with your hands on your hips and your eyes closed. I will be counting the number of times you move out of this position. If you stumble out of this position, open your eyes and return to the start position and continue balancing. I will start timing when you are set and have closed your eyes."

Tandem Gait

Participants are instructed to stand with their feet together behind a starting line (the test is best done with footwear removed). Then, they walk in a forward direction as quickly and as accurately as possible along a 38mm wide (sports tape), 3 metre line with an alternate foot heel-to-toe gait ensuring that they approximate their heel and toe on each step. Once they cross the end of the 3m line, they turn 180 degrees and return to the starting point using the same gait. Athletes fail the test if they step off the line, have a separation between their heel and toe, or if they touch or grab the examiner or an object.

Finger to Nose

"I am going to test your coordination now. Please sit comfortably on the chair with your eyes open and your arm (either right or left) outstretched (shoulder flexed to 90 degrees and elbow and fingers extended), pointing in front of you. When I give a start signal, I would like you to perform five successive finger to nose repetitions using your index finger to touch the tip of the nose, and then return to the starting position, as quickly and as accurately as possible."

References

1. McCrory et al. Consensus Statement On Concussion In Sport – The 5th International Conference On Concussion In Sport Held In Berlin, October 2016. British Journal of Sports Medicine 2017 (available at www.bjsm.bmj.com)
2. Maddocks, DL; Dicker, GD; Saling, MM. The assessment of orientation following concussion in athletes. Clinical Journal of Sport Medicine 1995; 5: 32-33
3. Jennett, B., Bond, M. Assessment of outcome after severe brain damage: a practical scale. Lancet 1975; i: 480-484
4. McCrea M. Standardized mental status testing of acute concussion. Clinical Journal of Sport Medicine. 2001; 11: 176-181
5. Guskiewicz KM. Assessment of postural stability following sport-related concussion. Current Sports Medicine Reports. 2003; 2: 24-30

CONCUSSION INFORMATION

Any athlete suspected of having a concussion should be removed from play and seek medical evaluation.

Signs to watch for

Problems could arise over the first 24-48 hours. The athlete should not be left alone and must go to a hospital at once if they experience:

- Worsening headache
- Drowsiness or inability to be awakened
- Inability to recognize people or places
- Repeated vomiting
- Unusual behaviour or confusion or irritable
- Seizures (arms and legs jerk uncontrollably)
- Weakness or numbness in arms or legs
- Unsteadiness on their feet.
- Slurred speech

Consult your physician or licensed healthcare professional after a suspected concussion. Remember, it is better to be safe.

Rest & Rehabilitation

After a concussion, the athlete should have physical rest and relative cognitive rest for a few days to allow their symptoms to improve. In most cases, after no more than a few days of rest, the athlete should gradually increase their daily activity level as long as their symptoms do not worsen. Once the athlete is able to complete their usual daily activities without concussion-related symptoms, the second step of the return to play/sport progression can be started. The athlete should not return to play/sport until their concussion-related symptoms have resolved and the athlete has successfully returned to full school/learning activities.

When returning to play/sport, the athlete should follow a stepwise, **medically managed exercise progression, with increasing amounts of exercise.** For example:

Graduated Return to Sport Strategy

Exercise step	Functional exercise at each step	Goal of each step
1. Symptom-limited activity	Daily activities that do not provoke symptoms.	Gradual reintroduction of work/school activities.
2. Light aerobic exercise	Walking or stationary cycling at slow to medium pace. No resistance training.	Increase heart rate.
3. Sport-specific exercise	Running or skating drills. No head impact activities.	Add movement.
4. Non-contact training drills	Harder training drills, e.g., passing drills. May start progressive resistance training.	Exercise, coordination, and increased thinking.
5. Full contact practice	Following medical clearance, participate in normal training activities.	Restore confidence and assess functional skills by coaching staff.
6. Return to play/sport	Normal game play.	

In this example, it would be typical to have 24 hours (or longer) for each step of the progression. If any symptoms worsen while exercising, the athlete should go back to the previous step. Resistance training should be added only in the later stages (Stage 3 or 4 at the earliest).

Written clearance should be provided by a healthcare professional before return to play/sport as directed by local laws and regulations.

Graduated Return to School Strategy

Concussion may affect the ability to learn at school. The athlete may need to miss a few days of school after a concussion. When going back to school, some athletes may need to go back gradually and may need to have some changes made to their schedule so that concussion symptoms do not get worse. If a particular activity makes symptoms worse, then the athlete should stop that activity and rest until symptoms get better. To make sure that the athlete can get back to school without problems, it is important that the healthcare provider, parents, caregivers and teachers talk to each other so that everyone knows what the plan is for the athlete to go back to school.

Note: If mental activity does not cause any symptoms, the athlete may be able to skip step 2 and return to school part-time before doing school activities at home first.

Mental Activity	Activity at each step	Goal of each step
1. Daily activities that do not give the athlete symptoms	Typical activities that the athlete does during the day as long as they do not increase symptoms (e.g. reading, texting, screen time). Start with 5-15 minutes at a time and gradually build up.	Gradual return to typical activities.
2. School activities	Homework, reading or other cognitive activities outside of the classroom.	Increase tolerance to cognitive work.
3. Return to school part-time	Gradual introduction of school-work. May need to start with a partial school day or with increased breaks during the day.	Increase academic activities.
4. Return to school full-time	Gradually progress school activities until a full day can be tolerated.	Return to full academic activities and catch up on missed work.

If the athlete continues to have symptoms with mental activity, some other accomodations that can help with return to school may include:

- Starting school later, only going for half days, or going only to certain classes
- More time to finish assignments/tests
- Quiet room to finish assignments/tests
- Not going to noisy areas like the cafeteria, assembly halls, sporting events, music class, shop class, etc.
- Taking lots of breaks during class, homework, tests
- No more than one exam/day
- Shorter assignments
- Repetition/memory cues
- Use of a student helper/tutor
- Reassurance from teachers that the child will be supported while getting better

The athlete should not go back to sports until they are back to school/learning, without symptoms getting significantly worse and no longer needing any changes to their schedule.

Sport concussion assessment tool - 5th edition

Br J Sports Med published online April 26, 2017

8.5 Assessment 1: The Sport Concussion Assessment Tool 5 Symptom Evaluation

STEP 2: SYMPTOM EVALUATION

The athlete should be given the symptom form and asked to read this instruction paragraph out loud then complete the symptom scale. For the baseline assessment, the athlete should rate his/her symptoms based on how he/she typically feels and for the post injury assessment the athlete should rate their symptoms at this point in time.

Please Check: ☐ **Baseline** ☐ **Post-Injury**

Please hand the form to the athlete

	none	mild		moderate		severe	
Headache	0	1	2	3	4	5	6
"Pressure in head"	0	1	2	3	4	5	6
Neck Pain	0	1	2	3	4	5	6
Nausea or vomiting	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Blurred vision	0	1	2	3	4	5	6
Balance problems	0	1	2	3	4	5	6
Sensitivity to light	0	1	2	3	4	5	6
Sensitivity to noise	0	1	2	3	4	5	6
Feeling slowed down	0	1	2	3	4	5	6
Feeling like "in a fog"	0	1	2	3	4	5	6
"Don't feel right"	0	1	2	3	4	5	6
Difficulty concentrating	0	1	2	3	4	5	6
Difficulty remembering	0	1	2	3	4	5	6
Fatigue or low energy	0	1	2	3	4	5	6
Confusion	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
More emotional	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6
Nervous or Anxious	0	1	2	3	4	5	6
Trouble falling asleep (if applicable)	0	1	2	3	4	5	6
Total number of symptoms:							of 22
Symptom severity score:							of 132
Do your symptoms get worse with physical activity?						Y	N
Do your symptoms get worse with mental activity?						Y	N
If 100% is feeling perfectly normal, what percent of normal do you feel?							

If not 100%, why?

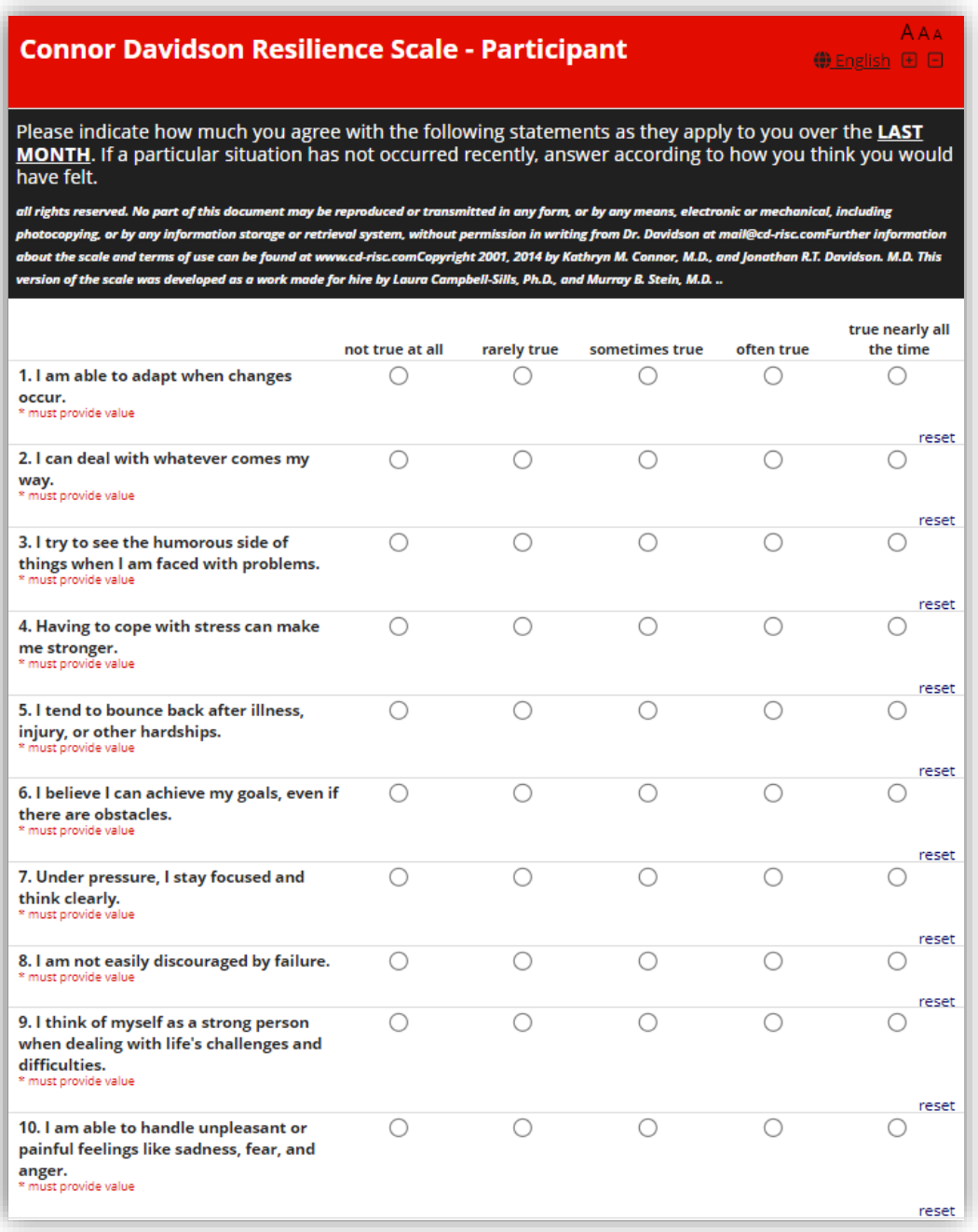
_____

_____

_____

Assessment 1: The Sport Concussion Assessment Tool 5 (SCAT-5) Symptom Evaluation Scale.[31, 139]

8.6 Assessment 2: The Connor Davidson Resilience Scale 10 (CDRISC-10)



Connor Davidson Resilience Scale - Participant

A A A

English

Please indicate how much you agree with the following statements as they apply to you over the **LAST MONTH**. If a particular situation has not occurred recently, answer according to how you think you would have felt.

	not true at all	rarely true	sometimes true	often true	true nearly all the time
1. I am able to adapt when changes occur. * must provide value	○	○	○	○	○ reset
2. I can deal with whatever comes my way. * must provide value	○	○	○	○	○ reset
3. I try to see the humorous side of things when I am faced with problems. * must provide value	○	○	○	○	○ reset
4. Having to cope with stress can make me stronger. * must provide value	○	○	○	○	○ reset
5. I tend to bounce back after illness, injury, or other hardships. * must provide value	○	○	○	○	○ reset
6. I believe I can achieve my goals, even if there are obstacles. * must provide value	○	○	○	○	○ reset
7. Under pressure, I stay focused and think clearly. * must provide value	○	○	○	○	○ reset
8. I am not easily discouraged by failure. * must provide value	○	○	○	○	○ reset
9. I think of myself as a strong person when dealing with life's challenges and difficulties. * must provide value	○	○	○	○	○ reset
10. I am able to handle unpleasant or painful feelings like sadness, fear, and anger. * must provide value	○	○	○	○	○ reset

Assessment 2: The Connor Davidson Resilience Scale 10 (CDRISC-10).[37]

8.7 SHRED CONCUSSIONS PRESEASON BASELINE QUESTIONNAIRE (PBQ)

SHRED Concussions

Today's Date
(DD/MM/YY)_____/_____/_____

SSID:_____

Baseline Questionnaire

This form collects information regarding various demographic information, physical activity, injury and medical history, utilization of health care services. This data will help us determine which factors may contribute to an increased risk of **injury** in youth. We would appreciate your cooperation by taking approximately 15 mins to complete the questionnaire in full. All information collected will be kept confidential as outlined in the consent form. **If you need help completing his please consult your parent/guardian or the research team.**

DEMOGRAPHICS		
Your full name:		Birthdate: (DD/MM/YY) _____/_____/_____
Your Email:		Your Phone #:
Street Address:	Postal Code	Parent/Guardian 1 Phone #:
Parent/Guardian 1 Name:	Parent/Guardian 2 Name:	Parent/Guardian 1 Email:

Sex: ☐Male ☐Female ☐ Other ☐I prefer not to respond	Dominant hand: ☐Right ☐Left Dominant leg: ☐Right ☐Left	Height:_____ft/inches OR _____cm Weight:_____ lbs OR _____kg
Gender: ☐Male ☐Female ☐Transgender Male ☐Transgender Female ☐Non-Binary ☐ prefer not to say ☐other identity (describe)		
If Female: Please complete ONLY if this section applies to you, and you feel comfortable doing so:	Have you started to Menstruate? ☐ Yes ☐No ☐ Prefer not to answer **If Yes:** At what age did you begin to menstruate? ___ (number)	Are your periods regular (i.e. approx. once/month) ☐ Yes ☐No On average how many periods do you have per year? _____ On average how many periods do you have per year? ☐ 0-3 ☐ 4-6 ☐ 7-9 ☐ 10+

What levels of education have been completed by your parents/guardians?	Parent/Guardian 1	Parent/Guardian 2
	☐Junior high or less ☐High school diploma ☐Technical/trade certificate ☐Undergraduate degree ☐Graduate degree ☐Unknown	☐Junior high or less ☐High school diploma ☐Technical/trade certificate ☐Undergraduate degree ☐Graduate degree ☐Unknown

SCHOOL	
School Name:	Grade: ☐9 ☐10 ☐11 ☐12 ☐ CEGEP

INJURY HISTORY

Have you had any **injuries** requiring medical attention **OR** at least 1 day of missed participation from sport or physical activity in the past **12 months**?

☐No If **no**, continue to next question
☐ Yes If **yes,** please list below

Injury Date (approx. if unknown) (DD/MM/YY)	**Activity at the time of injury** (e.g. skiing, hockey, playing tag)	**Type of Injury** (e.g. fracture, sprain, dislocation)	**Body Part Injured** (e.g. Knee, finger)	**Describe any treatment for the injury** (e.g. physio, ice, surgery)	Number of **days** before **FULL** return to physical activity

Do you have any incompletely healed injuries? (i.e. an injury that has not 100% healed/recovered)

☐No If **no**, continue to next question

☐ Yes If **yes,** please describe injury/injuries

If **yes**, are you currently receiving treatment for this injury/these injuries?

☐No If **no**, continue to next question

☐ Yes If **yes,** please describe treatment

INJURY HISTORY Continued

Have you had a **concussion** (either diagnosed or not) or been "knocked out" or had your "bell rung"?

☐No If **no**, continue to next question
☐ Yes If **yes,** please list below

Injury Date (approx. if unknown) (DD/MM/YY)	Activity at the time of injury (e.g. skiing, hockey, playing tag)	Time unconscious		Memory Loss?	Number of **days** before **FULL** return to physical activity	Was the concussion diagnosed by a doctor
		Minutes	Seconds			
				☐Yes ☐ No		☐Yes ☐ No
				☐Yes ☐ No		☐Yes ☐ No
				☐Yes ☐ No		☐Yes ☐ No

If yes, do you have persistent problems with	Memory? ☐Yes ☐ No	Dizziness? ☐Yes ☐ No	Headaches? ☐Yes ☐ No

MEDICAL HISTORY			
Have you ever been diagnosed by a physician with any of the following;		Describe	Year of Diagnosis
Patellar tendonitis or anterior knee pain?	☐No ☐ Yes		
Achilles tendonitis or Achilles tendon pain?	☐No ☐ Yes		
Bone fracture, arthritis, or other muscle or bone condition?	☐No ☐ Yes		
Systemic Disease (e.g., cancer, thyroid disease, heart disease)?	☐No ☐ Yes		
Respiratory Condition (e.g., Asthma, chronic respiratory failure, congenital lung abnormalities)?	☐No ☐ Yes		
Circulation or Heart Problem (e.g. murmur, congenital deformity, irregular beat)?	☐No ☐ Yes		
Neurological Disorder (e.g., cerebral palsy, pinched nerve, "stinger", MS)?	☐No ☐ Yes		
Have you ever experienced headaches?	☐No ☐ Yes		
If yes, are they associated with; (check all that apply)	☐Nausea ☐ Vomiting ☐ Light Sensitivity ☐ Noise Sensitivity ☐ None of the above		
Does anyone else in your family experience headaches?	☐No ☐ Yes	If **yes**, please indicate who_____	
Have you ever been concerned that you may have an attention or learning issue?	☐No ☐ Yes	If **yes**, please describe	

Have you ever been diagnosed by a health care professional with any of the following;

☐ Cognitive delay	☐ Oppositional defiant disorder
☐ Communication Disorder	☐ Conduct disorder
☐ Persuasive developmental disorder	☐ Mood disorder
☐ ADHD	☐ Depression
☐ Learning disability	☐ Bi-polar disorder
☐ Anxiety disorder	☐ Developmental Coordination Disorder
☐ Disruptive behavior disorder	☐ Other:_____

Are you currently taking;	
Medications (e.g., inhaler, Tylenol, antidepressants, birth control)?	☐No If **no**, continue to next question ☐ Yes If **yes,** please list below
Supplements (e.g., vitamins, minerals, protein powder)?	☐No If **no**, continue to next question ☐ Yes If **yes,** please list below

HEALTH CARE UTILIZATION

Please indicate whether or not you have visited the following practitioners or received the following service for **any reason in the past 12 months** (exclude visits and services received as an inpatient in a hospital)

Practitioners and Services	No Visits ☑	Visited ☑	Number of visits
Physician – emergency room doctor	☐	☐	
Physician – general practitioner/family	☐	☐	
Physician – sport medicine doctor	☐	☐	
Surgeon	☐	☐	
Physiotherapist	☐	☐	
Chiropractor	☐	☐	
Massage therapist	☐	☐	
Athletic therapist	☐	☐	
Magnetic resonance imaging (MRI)	☐	☐	
Computer tomography (CT scan)	☐	☐	
Radiographs (x-rays)	☐	☐	
Other (please specify) _____	☐	☐	

In the past 12 months, have you been **admitted** to the hospital for any reason, including emergency department visits?

☐No If **no**, continue to next questions

☐ Yes If **yes,** please list below

Primary reason for hospital visit	Number of nights in hospital	Did you have surgery while in the hospital	If **yes**, please describe
		☐No ☐ Yes	
		☐No ☐ Yes	
		☐No ☐ Yes	

PHYSICAL ACTIVITY PARTICIPATION – Physical Education

In the past 6 weeks how many weeks did you participate in school Physical Education Class?	Number of Weeks:
In a typical week, how many Physical Education classes do you participate in?	Number of Classes:
How long is each Physical Education class?	Length in Hours:
Do you **currently** fully participate in physical education class?	☐No ☐ Yes
How many **hours per week** do you participate in physical activity **during school hours**, outside of Physical Education class. (e.g., at lunch break, during other class time)	Hours per week:

Mild intensity physical activity	**Moderate** intensity physical activity	**Vigorous** intensity physical activity
(Breathing is normal & you are not working hard enough to break into a sweat)	(Breathing slightly harder than normal & working hard enough to break into a light sweat)	(Breathing hard & fast & working so hard that you are sweating heavily)
_____hours/week	_____hours/week	_____hours/week

PHYSICAL ACTIVITY PARTICIPATION – Sport and Recreation			
Not including Physical Education Class	Please indicated the **average hours per week** you participated in the following activities?		Please indicated the **total number of weeks** you participated in the
	In the past 6 weeks	**Past 12 Months**	**Past 12 Months**
Aerobics			
Alpine skiing			
Badminton			
Baseball			
Basketball			
Boxing/Kickboxing			
Cross-country skiing			
Cycling (road or mtn.)			
Dance			
Dirt biking			
Diving			
Field hockey			
Figure skating			
Floor hockey			
Football			
Golf			
Gymnastics			
Hiking/Scrambling			
Hockey			
Horse riding			
Lacrosse			
Martial arts			
Rock climbing			
Rollerblading			
Rugby			
Running			
Skate/long boarding			
Snowboarding			
Soccer			
Squash			
Speed skating			
Swimming			
Tennis			
Track and field			
Volleyball			
Water polo			
Weight training			
Wrestling			
Other (specify)*:			
I did **NOT** participate in any activities ☐			

THANK YOU!
Thank you for your time in completing this questionnaire.

8.8 SHRED CONCUSSIONS INJURY REPORT FORM (IRF)

Injury Report Form

On this form, please report any injury (new or recurrent) or any suspected concussion occurring during physical activity which either requires:

1) Medical attention **and/or**
2) Results in the inability to complete the session of activity in which the injury occurred **and/or**
3) Results in the player missing at least one day of sporting activity

Person completing form: ☐Mother ☐Father ☐Player ☐Team Therapist ☐Other_____
Injury ID: _____
Parent phone #: _____
Parent e-mail: _____

1. Student name: _____
2. SSID#: _____
3. School: _____
4. Team: _____
5. Grade: ☐ 8 ☐ 9 ☐ 10 ☐ 11 ☐ 12
6. Today's date (MM/DD/YY): _____/_____/_____
7. Injury date (MM/DD/YY): _____/_____/_____ **Time:** _____
8. Birthdate: (MM/DD/YY): _____/_____/_____
9. Injury status: *(*Note: this is also recorded on platform)*
☐ New injury
☐ Recurrence of injury from this year
☐ Recurrence of injury from previous year

10. Did the player return to the same game, practice, or physical activity in which they were hurt?
☐Yes, the player fully completed the session
☐Partially, player tried to complete the session but had to stop before the end of the session because of the injury
☐Partially, player stopped immediately after the injury, rested and returned prior to the end of the session
☐No
☐N/A, the injury happened at the end of the session

11. Injury occurred during which physical activity? *(*Note: this is recorded on platform)*_____
☐ Occurred in school related activity ☐ Occurred outside school

12. Injury occurred during: *(*Note: this is recorded on platform)*
☐ Practice/Sport specific training
☐ Game/Competition (☐Regular season, ☐Tournament, ☐Playoff, ☐Exhibition)
☐ PE Class
☐ Active transport *(e.g., biking to school)*
☐ Other *(eg, recreational activity)* Please specify:_____

→Type of game *(*Sport specific game types (players on field))*

13. Equipment at the time of injury? (check all that apply)
Mouthguard: ☐Yes ☐No ☐Don't know
If yes, specify: ☐ Dentist custom-fit ☐ Boil and bite
Brace: ☐Yes ☐No ☐Don't know
if yes, worn on(circle R/L): ☐ Knee ☐Ankle ☐Wrist
☐Other:_____
Tape: ☐Yes ☐No ☐Don't know
if yes, worn on (circle R/L): ☐(R/L) Knee ☐(R/L) Ankle ☐(R/L) Wrist
☐Other:_____
Helmet/Headgear: ☐Yes ☐No ☐Don't know
Type: ☐Bicycle ☐Hockey ☐Football ☐Lacrosse ☐Skateboard ☐Equestrian ☐Rugby headgear (scrum cap) ☐Ski/snowboard ☐Soccer headgear ☐Other:_____
Helmet age: ☐New this year ☐New last year ☐2-3 years old ☐ >3 years old
Footwear Type: ☐Barefoot ☐Skates ☐Running Shoes ☐Cleats ☐ Wrestling shoes ☐Other_____ ☐Don't know
If yes to cleats, type of cleats: ☐Turf ☐Indoor ☐Outdoor:
If outdoor: ☐Multi-stud ☐6stud ☐Blades ☐Multisurface ☐Other____

14.Have you changed any equipment (since baseline?)
☐Yes, _____ ☐No ☐No baseline-entering study at injury

15. This injury involved:
☐ Sudden onset & contact with another player
☐ Sudden onset & NO contact with another player
☐ Gradual Onset/Overuse ☐ Unknown

16. When were you injured while participating in your sport?
☐ During warm-up ☐ At the beginning ☐ In the middle ☐ At the end
☐ During cool-down ☐ Other_____ ☐ N/A ☐ Unknown

→Position playing at time of injury: *(*Sport specific positions options)*
→Where on the field did the injury occur: *(*Sport specific field diagrams)*

17. General Cause of injury (check all that apply):
☐ Intentional player contact
☐ Unintentional contact with another person or their equipment
☐ Contact with the environment, NOT another person
☐ No contact ☐ Unknown

→Sport specific Mechanisms: *(*Sport specific mechanism options)*

18. Head Injury Mechanism of injury (check all that apply)
☐ Direct blow to head: ☐Right ☐Left ☐Front ☐Back
☐ Fell & hit head: ☐Back ☐Forward ☐Side
☐ Hit head: ☐On boards ☐On post ☐On net ☐On other:_____
☐ Other:_____
☐ Non-head injury

19. Did the player anticipate contact prior to injury? ☐Yes ☐No ☐N/A ☐ Unknown

20. If concussion, did any of the following visible signs occur?
☐Yes ☐No ☐This is NOT a concussion
If YES which signs (check all that apply):
☐ Loss of consciousness ☐Slow to get up ☐Unsteady ☐Fall to ground
☐ Clutch of head ☐Dazed ☐Blank look ☐Cut/bleeding on face
☐ Other (Please Describe)_____

21. Did you do a warm-up? ☐No ☐Yes
If yes, FIFA 11+ or (similar adapted NMT program)?
☐No ☐Yes ☐Maybe ☐Unknown

22. What was the weather like where you were playing? (Check all that apply)
☐ Raining ☐ Snowing ☐ Dry ☐ Windy
☐ Calm ☐ Indoors ☐ Can't Remember
☐Other:_____

23. Surface of play:
☐ Grass ☐ Turf - Outdoor ☐ Turf – Indoor ☐ Dirt ☐ Cement ☐ Indoor carpet ☐ Gym floor ☐ Padded mat ☐ Sand ☐ Gravel ☐Snow ☐ Water ☐ Ice ☐ Rock
☐Other:_____
Surface Weather conditions: ☐ Wet ☐ Muddy ☐ Pot-holed ☐ Even ☐ Uneven ☐ Rough ☐ Slippery ☐ Cracked
☐Other:_____

24. Was a foul, penalty or violation called directly related to the injury event? *(*Note: Type of violation is linked to sport specific questions)*
☐No ☐Yes

→Sport specific penalties and violations: *(*Sport specific penalty options)*

25. Describe events surrounding injury:
_____

Injury Report Form

On this form, please report any injury (new or recurrent) or any suspected concussion occurring during physical activity which either requires:

1) Medical attention **and/or**
2) Results in the inability to complete the session of activity in which the injury occurred **and/or**
3) Results in the player missing at least one day of sporting activity

Person completing form: ❑Mother ❑Father ❑Player ❑Team Therapist ❑Other_____
Injury ID: _____
Parent phone #:_____
Parent e-mail: _____

	_____ _____ _____

26. Injury location for each type of injury (check all boxes that apply AND circle which side the injury occurred on): *(*Note: this is recorded on platform)*

Type of Injury	Head	Face	Ears (L/R)	Eye (L/R)	Nose	Teeth	Neck	Throat	Shoulder (L/R)	Collarbone (L/R)	Upper arm (L/R)	Elbow (L/R)	Forearm (L/R)	Wrist (L/R)	Hand (L/R)	Finger (L/R)	Back	Side (L/R)	Ribs (L/R)	Chest	Abdomen	Pelvis	Hip (L/R)	Groin (L/R)	Genitals	Upper Leg (L/R)	Knee (L/R)	Lower leg (L/R)	Ankle (L/R)	Foot (L/R)	Toes (L/R)	Other:_____
Knocked out																															
Concussion																															
Bruise																															
Burn																															
Bleeding																															
Abrasion/scrape																															
Cut																															
Blister																															
Joint swelling																															
Joint/ligament sprain																															
Disclocation																															
Broken bone																															
Muscle Strain																															
Tendonitis																															
Other:_____																															

STOP! The following section should be completed by the school study therapist

The following section is to be completed by the school study therapist

Note: In order to complete all fields in this form, study therapist may need to follow-up with student, or parent/guardian or TD after initial assessment, once the student has returned fully to normal activities and has completed all injury-related care.

27. Date of full medical clearance for return to: Normal daily activities (MM/DD/YY)**:** _____/_____/_____

Non-contact sports (full participation) (MM/DD/YY)**:** _____/_____/_____

Collision/contact sports (full participation) (MM/DD/YY)**:** _____/_____/_____

28. Who provided clearance to return to play? ☐Physician ☐Therapist ☐Coach ☐Parent ☐Self ☐Other: _____

29. Total # of days/hours the student's parent or guardian missed work as a direct result of the injury:

_____ days _____ hours ☐ Check box if parent/guardian was not working during this time period

30. Parent/guardian's occupation:_____ ☐Not working

31. Was an ambulance called? ☐Yes ☐No

If yes a) Did the player ride to the hospital in the ambulance? ☐Yes ☐No

b) Was the student seen by a health professional at the location the injury occurred? *(field, rink, track, etc)* ☐Yes ☐No

32. Was the student admitted to the hospital for this injury (other than an emergency department visit)? ☐Yes ☐No

If yes, a) Primary reason for hospitalization:_____ b) # nights in the hospital:_____

c) Did the player have surgery in the hospital? ☐Yes ☐No Name or describe the surgery:_____

33. Did the student see any health care professional(s) for assessment/treatment of this injury?: ☐Yes ☐No

☐On-site first aid	Total # visits:_____	☐Paediatrician	Total # visits:_____	☐Massage Therapist	Total # visits:_____
☐EMT/Paramedic	Total # visits:_____	☐Surgeon	Total # visits:_____	☐Dentist	Total # visits:_____
☐Family Physician/GP	Total # visits:_____	☐Radiologist	Total # visits:_____	☐Chiropractor	Total # visits:_____
☐ER Physician	Total # visits:_____	☐Physiotherapist	Total # visits:_____	☐Other:_____	Total # visits:_____
☐Sport Med. Physician	Total # visits:_____	☐Athletic Therapist	Total # visits:_____	_____	

34. Did the student have any tests or receive any other treatment for this injury? ☐Yes ☐No If yes, check all that apply:

☐MRI	# of times:_____ Body part:_____	☐Cast	# of casts:_____ Body part:_____ Type:_____
☐X-ray	# of times:_____ Body part:_____	☐Brace	# of braces:_____ Body part:_____ Type:_____
☐CT scan	# of times:_____ Body part:_____	☐Splint	# of splints:_____ Body part:_____ Type:_____
☐Bone scan	# of times:_____ Body part:_____	☐Taping	# of tape rolls:___ Body part:_____ Type:_____
☐Other:__	_____	☐Crutches	

35. Did the student take any medications for this injury? ☐Yes ☐No

If yes, a) Name:_____ b) Type (eg, oral, injected):_____ c) Duration (days):_____

36. Does the student take any medications for other reasons (i.e. not for injuries) on a regular basis? ☐Yes ☐No

If yes, please list (*e.g., asthma inhaler, antidepressants, acne medication, etc*): _____

SHRED Injuries- INJURY ASSESSMENT FORM (Study Therapist) *Note could be recorded on platform

Student name: _____ Injury ID:_____

Date of assessment (MM/DD/YY): _____/_____/____

Patient's specific complaint:
History (including any previous injury to structure(s)):
Observation:
Functional tests:
Special tests:
Palpation:

Impression/Assessment:_____

(e.g. Right AC Joint 2nd degree sprain) Side Region Type of injury

SMC Diagnostic Code(s):

1	
2	
3	

Referral: ☐Physician ☐Hospital ☐Medi-clinic ☐Chiropractor ☐Study Sport Medicine Physician
☐Massage ☐Therapist ☐Physiotherapist ☐Dentist ☐Athletic Therapist ☐Other:_____

Injury Severity Score: At time of injury:_____ At return to play:_____
(MM/DD/YY): _____/_____/____ (MM/DD/YY): _____/_____/____

Assessor's signature: _____

Did the attending therapist advise the participant to refrain from returning to activity on medical grounds? ☐Yes ☐No Date: _____

Was the physician's recommended level of function attained before return to play? ☐Yes ☐No

Injury severity score: Legend
1: unable to perform any normal daily activities *(i.e. walk, go to school)*
2: unable to participate in sport or recreational activity *(i.e. practice)*
3: able to practice but unable to compete in sport *(modified activities)*
4: able to compete or participate in recreational activities but performance is impaired
5: fully able to compete or participate as if there was never an injury

If the player sees a physician, therapist, or other practitioner, have this healthcare provider complete the following section (unless a fee is involved). Upon completion, return to your Team Safety Designate or study personnel.

SHRed Study		Player's Name:
Medical practitioner's name:_____ Occupation: ☐Sport Med. Physician ☐Family Physician/GP ☐ER Physician ☐Athletic Therapist ☐Physiotherapist ☐Other:_____		**Date** (MM/DD/YY): _____/_____/_____ Diagnosis/clinical impression (check both if needed): ☐Concussion ☐Other:_____
Treatment plan: ☐Rest until asymptomatic ☐Begin return to play (RTP) steps ☐Return to full participation ☐Other:		
Conditions of clearance: ☐Asymptomatic ☐Complete RTP steps ☐Other:		
ONCE PLAYER IS CLEARED TO RETURN TO UNRESTRICTED COMPETITION: Date of clearance (MM/DD/YY): _____/_____/_____		*Office use only* IID:_____ UCDC:_____

8.9 STANDARD OPERATING PROCEDURE FOR BLOOD COLLECTION AND PROCESSING

Guidelines for Phlebotomy Room Health & Safety

Before blood can be safely collected for the study, a number of protocols and safety issues must be addressed in full. With strict adherence to the safety protocols and procedures detailed here, blood may be safely and securely collected. If any of these requirements are absent, then blood collection may not proceed.

Contact Information:

In the event of any incident happening in the lab (e.g., participant feels unwell, accidental needle stick, broken glass/biohazard spill, the provincial study coordinator must be informed, and the project coordinator/primary investigator **must** be contacted. See Fainting Protocol in participant flow section. Ensure each site has an approved protocol for accidental needle-stick.

Primary Investigator: Carolyn Emery (403-510-1454)

Safety Controls

Appropriate phlebotomy chairs: Size and positioning of phlebotomy chair are important to a successful blood draw. Ensure the participant is seated in a stationary (non-rolling) chair prior to venipuncture.

Washable surfaces: When performing a collection, ensure that there is no cloth or towels on hand. Some phlebotomists prefer to use cloth to prop a participant's arm, but this poses a significant health risk, as the material is easily contaminated, and notoriously difficult to sanitize.

Safety-engineered needles: BD UltraTouch push button blood collection butterfly needles are preferred (BD #367365 or #367364 (21G or 23G x 0.75", 12" tubing) for superior participant comfort and safety. An alternative needle to BD UltraTouch is the BD Safety-Lok blood collection butterfly needles (BD #367281 or #367283 (21G or 23G x 0.75", 12" tubing) which offers a safety shield as opposed to the push button format. Once the blood collection is complete, immediately push the yellow shield forward until the safety shield is in locked in place and then discard into a yellow sharp-resistant biohazard bucket.

Puncture-resistant sharps containers: Sharps containers must be placed in each phlebotomy room. Needles should be disposed of here, immediately after completion of the blood draw. (This means before labeling tubes, bandaging patient, or doing anything other than placing gauze over the open wound.)

Hand hygiene facilities: Each phlebotomy room contains hand sanitizer, a hand washing station, and paper towels. It is required that workers wash hands before each new participant, and between every participant

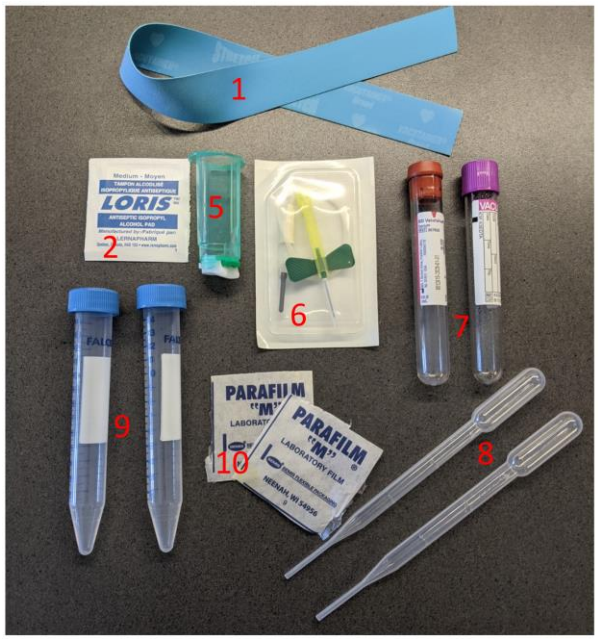
Any spills: cover/wipe up and clean with bleach solution. Refer to biosafety protocol for spills/contact with human fluid.

Disposal: After blood collection, you must ensure that yellow biohazard bins are picked up when full according to your institution's guidelines.

Administrative controls

Blood Collection Kits to be acquired by the study site should include:

1. Disposable non-latex tourniquet (one tourniquet used per participant and discarded after use)
2. Disinfecting 70% alcohol pad
3. Sterile gauze or cotton balls
4. Band-Aid
5. Single-use vacutainer for needle attachment
6. Two BD butterfly needles: either 21g (BD UltraTouch #367365 or Safety-Lok #367281) or 23g (BD UltraTouch #367364 or Safety-Lok #367283). Save the unopened needle for another draw or if a second attempt is required.
7. BD Vacutainer plastic blood collection tubes (1 Red top non-additive tube and 1 Lavender EDTA tube)
8. 2 Plastic transfer pipettes (1 for serum, 1 for plasma)
9. 2 Falcon 15mL (17 x 120mm) conical centrifuge tubes (Fisher Scientific #14-959-53A) (1 for serum, 1 for plasma)
10. 2 squares of Parafilm M Wrapping film (Fisher Scientific #537440)



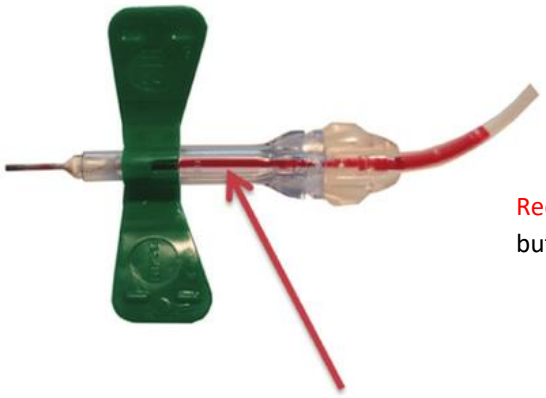
Standard Operating Procedure

Prior to collecting blood, please ensure both BD vacutainer collection tubes are properly labeled with the participant ID, timepoint, and collection time.

A. Collecting specimens

- Disinfect working area with alcohol or disinfectant spray or wipe.
- Introduce yourself and identify participant (confirm name and date of birth as it appears on the form/requisition). Ensure subject ID code is on the requisition (and matches labels attached).
- Ensure participant is comfortable and explain procedure.
- Prepare tubes in order of draw, first serum (red top) then plasma (lavender top).

- Wash hands and don latex-free gloves (latex may cause an allergic reaction).
- Apply a tourniquet to assess and select appropriate vein (assess median cubital vein first). Participant may have a preference for which arm/vein. Palpate the vein (even if it's visible).
- Once the vein has been selected, release the tourniquet and prepare the participant's arm in the correct position. *Do NOT leave tourniquet on for more than one minute during collection.
- Ensure equipment is positioned within reach. Attach the needle to the vacutainer. The tube can also be pre-assembled with the vacutainer prior to insertion (tube wedged on, so long as seal remains unbroken).
- Position the participant's arm downwards and re-apply tourniquet a few (3-4) inches above the puncture site.
- Re-palpate the vein and then cleanse the site with 70% alcohol pad. Allow skin to dry. Immobilize or anchor the vein with non-needle hand. You may instruct the participant to close their hand gently into a fist but do NOT encourage participant to pump their fist (this may result in hemolysis).
- Verbally inform the participant that you are about to puncture the skin. With a steady hand, guide the needle into the vein as smoothly as possible at a 15-30º angle, with the needle bevel facing up. Look for the



Red arrow indicates the 'flash' of blood when the butterfly needle is correctly inserted in the vein.

Image: https://www.researchgate.net/figure/Blood-collection-device-with-flash-visualization-butterfly-left-needle-with-a-visible_fig3_326378790

immediate "flash" of blood in the butterfly sheath (just below the wings) to ensure that the needle is in the vein. See the image below:

- Gently push the blood collection tube stopper (lid) to connect with the needle utilizing lip of vacutainer to help push the tube on and off; blood should flow freely through the lining of the butterfly needle.
- When collection is complete, gently release tourniquet and place clean cotton ball or gauze at the site and gently remove the needle. Tell participant to continue applying pressure to prevent formation of a hematoma. Do NOT allow participant to bend their elbow.
- Dispose of the needle in appropriate sharps container immediately – Do NOT recap needles. Dispose of all visibly contaminated materials, including gloves, bandages and cotton balls into an autoclavable biohazard bag. All other waste can go into regular garbage.
- Gently invert all blood tubes 5-10x, each with one complete turn of the wrist 180 degrees and back, taking ~1 second per inversion.
- Fill out the lab requisition for the collection component. Adhere the tube labels on the collected blood tubes. The long side of the label should run vertically down the sample, as straight as possible (you should be able to read the label from left to right if you hold the rubber stopper in your left hand). Make sure the label does not wrap completely around the tube as this will make it harder to aliquot later. Set tubes in a rack upright for processing.
- Disinfect the area using the same cleaning products used prior to initial collection.

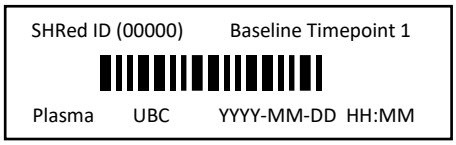
- Offer juice/cookie to participant.

B. Processing Specimens

***Note:** The recommended processing time for blood specimens (from time of collection, to centrifugation and to storage) is **≤ 2 hours**. Please make note of the exact time of collection, time of centrifugation and time when placed into a -80ºC freezer. All information should be included on your SHRed blood collection/processing form.

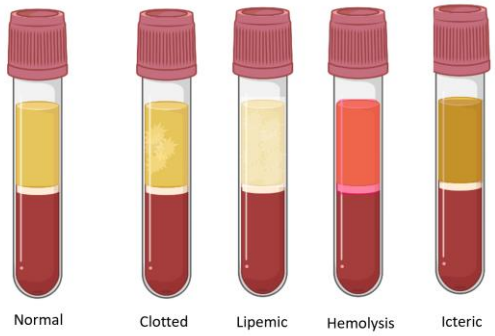
If specimens need to be transported to another location for centrifugation, place specimens in a rack or in a biohazard bag on ice or an ice pack into a secondary leak-proof container with an absorbent liner and sealable lid. Place this container into a dedicated cooler or other rigid outer packaging with a secure lid. Mark the outer packaging on both sides with the name and contact information of the principal investigator at the relevant institution. Additionally, adhere a label for "Exempt Human Specimens" on the outer packaging. An individual certified in the Transportation of Dangerous Goods (Class 6.2 – Infectious Substances) will transport samples to a University laboratory.

- Label falcon tubes for long term storage prior to sample processing. Labeles should contain:
  - Timepoint
  - SHRed Subject ID
  - Matrix (plasma or serum)
  - Date and Time of sample collection
  - Collection Site
  - Barcode (randomly generated 12-character number/letter code)
  - Example label:



- Note sample ID, timepoint, collection date and time on SHRed blood processing/collection form
- **Serum:** Allow blood to clot at room temperature for a minimum of 30 min prior to centrifuging.
- **Plasma:** Specimen can be centrifuged immediately (after proper inversion).
- Centrifuge each specimen for 10 minutes @ 1300g, at room temperature. Note the time of centrifugation on the SHRed blood processing/collection form
- Transfer the serum and plasma from their primary collection tubes to corresponding labeled 15ml falcon tubes:
  - Take one blood tube at a time, remove the top; set aside.
  - Using a plastic transfer pipette, carefully pipette the entire serum component and transfer it into the labelled 15mL centrifuge tube designated for serum. Repeat this for the plasma tube using a separate transfer pipette. ***Make sure you do NOT pipette/transfer any red cells into either tube*. If layer between serum/plasma supernatant and cells is breached causing the sample to mix, re-centrifuge the sample and attempt to separate again
  - Replace caps on blood tubes and dispose, along with pipettes, into a biohazard bag. Cap both falcon tubes and parafilm around the lids.
  - Note the approximate volume collected from each sample on the SHRed blood processing/collection form
- When transferring please note any anomalies in the sample on the SHRed blood processing/collection form, these can include but are not limited to:
  - Clots – may appear to have a snotty texture and come out in a clump. Attempt to extract or rim the clot using a wooden applicator stick (do NOT remove the entire clot from serum as it could affect

the testing phase). If layer between serum/plasma supernatant and cells is breached causing the sample to mix, re-centrifuge the sample and attempt to separate again
    - Lipemia – caused by a high blood content of lipids, sample will appear turbid to an almost milky looking consistency
    - Hemolysis – caused by breakdown of red blood cells, sample will appear pink to red in colour
    - Icteric – caused by the presence of excess bilirubin in the blood stream, sample will appear to be a darker yellow colour



    -
- Place falcon tubes upright into -80 freezer until ready to ship on dry ice to Cheryl Wellington's laboratory at UBC. Do NOT freeze the tube on its side or upside down. Use a rack or a storage box to keep samples upright. Note the time samples were placed in the freezer on SHRed blood processing/collection form.

*If any clarification is required for the processing procedure, please contact Mohammad (mohammad.ghodsi@ubc.ca) or Jennifer (jennifer.cooper@ubc.ca) by e-mail

Personal Protective Equipment

- Phlebotomists should have a white lab coat on for each and every subject.
- Workers are expected to wash hands before/between every subject (even when changing gloves between subjects). Hand sanitizer is available and should be used liberally.
- Lab-rated safety goggles should be worn during sample processing.
- Full-length pants and closed-toe shoes should be worn every session.

Worker's Qualification & Miscellaneous

1. Worker Qualification
    a. Workers must be a certified phlebotomist. This may occur through a laboratory assistant (MLA) or nursing program, EMT specialization, or from individual courses tailored to the required techniques. Certifications should be on file with project coordinators.
    b. As per University requirements, workers should be certified in Biosafety courses 1 & 3, as well as the WHMIS safety course, and Laboratory Safety course.
    c. Workers must be absent of illness or any flu-like symptoms to be eligible to perform venipuncture blood collection.
    d. Workers must be up to date on immunizations, including hepatitis B, measles, mumps, rubella, pertussis, and diphtheria. Of this list, only hepatitis B is not standard for most Canadians.

2. Participant Evaluation
    a. Prior to beginning the procedure, check that participant is comfortable and feeling well.
    b. Ask participant if they have a preferred arm, or any medical issues that would preclude one arm from use. Adjust venipuncture site accordingly.

c. If participant is at all tense, or seems apprehensive, remind them the study is completely voluntary, and they may continue the study without completing the blood collection portions.

Complications

In the event that a participant has a negative reaction, immediately inform the project coordinator for the site, and inform the provincial project head, Carolyn Emery (403-510-1454) and Cheryl Wellington (604-827-3769). The most common event is faintness during or after the collection. In the event that the participant feels faint while sitting in the chair, have them rest their head on the chair's arm rest. Ask someone to grab a cold compress (i.e. paper towel dampened with cold water) and place it on the back of the participant's neck. If the chair has no arm rest, have the participant lower their head between the knees to recirculate blood to their head and proceed with the cold compress on the back of the neck. Have the participant lie down for no less than 15 minutes and insist that they have some of the juice/cookies available with the study materials. This reaction disqualifies them from further participating in the individual study session and must be reported. A reaction will not disqualify the participants from future blood draws.

8.10 FIGURE 1.1 COPYRIGHT PERMISSIONS

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Jun 26, 2024

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Title of new work	Exploring Psychological Resilience, Plasma Cortisol, and Sport-Related Concussion Outcomes Among Canadian Adolescent Sport Participants
Institution name	University of Calgary
Expected presentation date	Jun 2024
Portions	Figures 1, 2 and 3

8.11 THE SHRED MOBILE

Image 8.1: The 'SHRed Mobile.'

SHRed Concussion's mobile laboratory equipped for phlebotomy and blood processing in the community. Image by Nikolas Josafatow.

8.12 PHLEBOTOMY INFOGRAPHIC

Infographic 1: For player, parent, and coach education of the SHRed Blood Biomarker Study.

8.13 RESILIENCE CHAPTER MEDICATION USE

Table 8.1: Resilience Chapter Medication Use.

	Female (n=194)	**Male (n=231)**
Medication Use (yes) n (%)		
Birth Control (e.g., Oral, IUD)	43 (22.16%)	N/A
Anti-Depressants/Anti-Anxiety/Anti-Psychotics/Neurostimulants	46 (23.71%)	32 (13.85%)
Anti-Epileptic Medications	1 (0.52%)	-
Cardiovascular Medications	2 (1.03%)	-
Endocrine Medications	4 (2.06%)	4 (1.73%)
Headache/Migraine Management	5 (2.58%)	2 (0.87%)
Metabolic Medications	-	1 (0.43%)
Pain Management (e.g., Tylenol/Advil)	110 (56.70%)	111 (48.05%)
Antihistamines	18 (9.28%)	18 (7.79%)
Disease-Modifying Antirheumatic Drugs	1 (0.52%)	1 (0.43%)
Gastrointestinal Medication	3 (1.55%)	2 (0.87%)
Vitamins/Supplements	76 (39.18%)	105 (45.45%)
Sleep Medications	2 (1.03%)	4 (1.73%)
Acne Medication	6 (3.09%)	7 (3.03%)
Other Medications	22 (11.34%)	10 (4.33%)

8.14 CORTISOL CHAPTER MEDICATION USE

Table 8.2: Cortisol Chapter, Uninjured Medication Use.

	Morning Cortisol (Before 11:00am)			Basal Cortisol (11:00am-6:00pm)		
	Female Follicular (n=20)	**Female Luteal (n=12)**	**Male (n=71)**	**Female Follicular (n=154)**	**Female Luteal (n=60)**	**Male (n=445)**
Medication Use n (%)						
Anti-Depressants/Anti-Anxiety/Anti-Psychotics/Neurostimulants	2 (10%)	1 (8.3%)	3 (4.2%)	15 (9.7%)	11 (18.3%)	39 (8.8%)
Anti-Epileptic Medication	1 (5%)					
Endocrine Medications (e.g., insulin)				2 (1.3%)	2 (3.3%)	3 (0.7%)
Headache/Migraine Management		1 (8.3%)		3 (2.0%)	1 (1.7%)	1 (0.2%)
Hormone Replacement Therapy (HRT)						1 (0.2%)
Pain Management (e.g., Tylenol/Advil)			1 (1.4%)	25 (16.2%)	17 (28.3%)	22 (4.9%)
Antihistamines			3 (4.2%)	13 (8.4%)	6 (10.0%)	21 (4.7%)
Vitamins/Supplements	1 (5%)		16 (22.5%)	32 (20.8%)	15 (25.0%)	84 (18.9%)
Topical Creams				1 (0.7%)		
Sleep Medications	1 (5%)			2 (1.3%)		
Acne Medication	1 (5%)		1 (1.4%)	2 (1.3%)	1 (1.7%)	11 (2.5%)
Other Medications	1 (5%)			2 (1.3%)	3 (5.0%)	7 (1.6%)

Table 8.3: Cortisol Chapter, Post-SRC Medication Use.

	Morning Cortisol (Before 11:00am)			Basal Cortisol (11:00am-6:00pm)		
	Female Follicular (n=15)	**Female Luteal (n=3)**	**Male (n=35)**	**Female Follicular (n=45)**	**Female Luteal (n=19)**	**Male (n=91)**
Medication Use n (%)						
Anti-Depressants/Anti-Anxiety/Anti-Psychotics/Neurostimulants		1 (33.3%)	9 (25.7%)	5 (11.1%)	2 (10.5%)	16 (17.6%)
Anti-Epileptic Medication			1 (2.9%)			
Endocrine Medications (e.g., insulin)		1 (33.3%)	1 (2.9%)	2 (4.4%)	2 (10.5%)	1 (1.1%)
Headache/Migraine Management	3 (20.0%)			1 (2.2%)	1 (5.3%)	1 (1.1%)
Pain Management (e.g., Tylenol/Advil)	8 (53.3%)	2 (66.7%)	23 (65.7%)	28 (62.2%)	13 (68.4%)	58 (63.7%)
Antihistamines	1 (6.7%)		1 (2.9%)	4 (8.9%)	2 (10.5%)	9 (9.9%)
Disease-Modifying Antirheumatic Drugs			1 (2.9%)			
Gastrointestinal Medication					1 (5.26%)	3 (3.3%)
Vitamins/Supplements	7 (46.7%)	1 (33.3%)	20 (57%)	21 (46.7%)	8 (42.1%)	48 (52.8%)
Topical Creams				1 (2.2%)		
Sleep Medications			1 (2.9%)	1 (2.2%)		1 (1.1%)
Acne Medication			3 (8.6%)	3 (6.7%)		4 (4.4%)
Other Medications			2 (5.7%)	1 (2.2%)		2 (2.2%)

8.15 RESILIENCE AND CORTISOL CHAPTER MEDICATION USE

Table 8.4: Resilience and Cortisol Chapter, Uninjured Medication Use.

	Morning Cortisol (Before 11:00am)		Basal Cortisol (11:00am-6:00pm)	
	Female Morning (n=22)	**Male Morning Basal (n=58)**	**Female Basal (n=154)**	**Male Basal (n=304)**
Medication Use n (%)				
Anti-Depressants/Anti-Anxiety/Anti-Psychotics/Neurostimulants	3 (13.6%)	3 (5.2%)	16 (10.4%)	30 (9.9%)
Endocrine Medications (e.g., insulin)			4 (2.6%)	3 (1.0%)
Headache/Migraine Management			4 (2.6%)	1 (0.3%)
Hormone Replacement Therapy (HRT)				1 (0.3%)
Pain Management (e.g., Tylenol/Advil)		1 (1.7%)	30 (19.5%)	16 (5.3%)
Antihistamines		3 (5.2%)	14 (9.1%)	17 (5.6%)
Gastrointestinal Medication				
Vitamins/Supplements	1 (4.6%)	15 (25.9%)	42 (27.3%)	61 (20.0%)
Sleep Medications	1 (4.6%)		1 (0.7%)	
Acne Medication	1 (4.6%)	1 (1.7%)	3 (2.0%)	10 (3.3%)
Other Medications	1 (4.6%)		3 (2.0%)	3 (1.0%)

Table 8.5: Resilience and Cortisol Chapter, Post-SRC Medication Use.

	Morning Cortisol (Before 11:00am)		Basal Cortisol (11:00am-6:00pm)	
	Female Morning (n=10)	**Male Morning (n = 16)**	**Female Basal (n = 30)**	**Male Basal (n = 55)**
Medication Use n (%)				
Anti-Depressants/Anti-Anxiety/Anti-Psychotics/Neurostimulants	1 (10%)	3 (18.8%)	3 (10%)	9 (16.4%)
Endocrine Medications (e.g., insulin)	1 (10%)	1 (6.3%)	2 (6.7%)	
Headache/Migraine Management	1 (10%)		2 (6.7%)	1 (1.8%)
Pain Management (e.g., Tylenol/Advil)	7 (70%)	11 (68.8%)	19 (63.3%)	34 (61.8%)
Antihistamines			4 (13.3%)	6 (10.9%)
Gastrointestinal Medication			1 (3.3%)	3 (5.5%)
Vitamins/Supplements	4 (40%)	12 (75.0%)	15 (50%)	28 (50.9%)
Topical Creams			1 (3.3%)	
Sleep Medications		1 (6.3%)		1 (1.8%)
Acne Medication		2 (12.5%)	2 (6.7%)	3 (5.5%)
Other Medications		1 (6.3%)	1 (3.3%)	2 (3.6%)

9 PROGRAM ENGAGEMENT, REQUIREMENTS, AND CERTIFICATES

9.1 PROGRAM ENGAGEMENT

Event	Details	Date
Phlebotomy Certificate	Completed phlebotomy certification through SAIT. Partially funded by HBI's REALIZE External Module Registration Award.	August, 2022
Blood Processing / Phlebotomy	Train (new) and organize a team of phlebotomists and blood processors for baseline and post-injury blood collection and processing.	Blood processing: May 2022 – January 2024 Phlebotomy: August 2022 – January 2024
BDNF Analysis	Analysed samples for BDNF at ACH with Biocore Lab. BDNF manuscript in preparation.	August/September 2022
Conferences	Canadian Traumatic Brain Injury Research Consortium (CTRC; oral) (x3) GSA PEER Beyond (oral) UBC Next Generation Rehabilitation Interventions for Pediatric Concussion (oral) Mathison-Littmann Research Day (poster) Canadian Academy of Sport and Exercise Medicine (poster, published abstract) Hotchkiss Brain Institute Research Day (poster) NFL Annual Meeting (oral) Community and Research Engagement Symposium (oral) Alberta Children's Hospital Research Retreat (poster)	January & June 2023, February 2024 February 2023 February 2023 March 2023 March 2023 June 2023 September 2023 September 2023 December, 2023
Awards	1. HBI Graduate Recruitment Scholarship in Neuroscience ($10,000/yr) 2. CGS-M: CIHR ($17,500/yr) 3. Alberta Graduate Excellence Scholarship ($15,000): Deferred 4. CTRC Travel Award	January 2023 (Renewed May 2024) May 2023 June 2023 February 2023
Mentor and Training Roles	1. Summer and Honours student – Julius Ho. 2. New phlebotomists/research nurses – Ashley Nelson, Emily Bennett, Jess Neufeld. 3. New blood processors – Anoush Rehmani, Connor Hass, Emily Bennett, Gavin McLellan, Grace Kelly, Haley, Joseph, Joseph Carere, Maddy Allard, Rebecca Suits, Safiya Nazir, Stefanía García 4. Tri-Council Masters Scholarship Peer Mentor Matching – Asmal Rajan	2022-2024
Knowledge Translation	Nelson Mandela High-School SHREDUCATION	September 20th, 2023
First Aid Training	Standard First Aid & CPR	Online: Nov 19th, 2023 In person: Dec 5th, 2023
MOOC	Concussion: Prevention, Detection, and Management	March 10th, 2024 – April 29th, 2024

9.2 NEUROSCIENCE GSE PROGRAM REQUIREMENTS

Program Requirement	Comments	Proposed completion date
Supervisory committee meetings (2/year)	1st Committee Meeting 2nd Committee Meeting (Proposal Defense) 3rd Committee Meeting	April 11th, 2023 July 19th, 2023 March 15th, 2024
Research Integrity Day	Complete in Year 1	February 24th, 2023
CIHR Sex and Gender Module	Complete in Year 1	November 2022
Research In Progress (1/year)	Year 1: GSA Peer Beyond Year 2: CTRC	March 11, 2023 February, 2024
Annual Progress Report	Due May 31 Each Year	May 2023 May 2024
Journal Club (1/year)	1/year	SIPRC, November 2022 ABIJC, January 2023 SIPRC, November 2023 ABIJC, December 2023
Graduate Classes MDSC 619.01/619.02		Neuro 1 (MDSC 619.01; Grade: A) Neuro 2 (MDSC 619.02; Grade: A+) Biostats Workshop (May 2023)
Thesis proposal		Submitted August 2023
Permission to write		January 2024
Request to set up thesis defense	*6 weeks prior to defense date*	May 2024
Thesis submitted to committee	*3 weeks prior to defense date*	May 15th, 2024
Thesis defense		June 5th, 2024

9.3 CERTIFICATES

PANEL ON RESEARCH ETHICS
Navigating the ethics of human research

TCPS 2: CORE 2022

Certificate of Completion

This document certifies that

Nik Josafatow

successfully completed the Course on Research Ethics based on the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2: CORE 2022)

Certificate # 0000822142 **16 May, 2022**

CIHR IRSC Institute of Gender and Health / Institut de la santé des femmes et des hommes

This is to certify that

Nikolas Josafatow

has successfully completed the CIHR Institute of Gender and Health Core Competency Module for Sex and Gender in Primary Data Collection with Human Participants.

CIHR IRSC

Cara Tannenbaum

Cara Tannenbaum, MD, MSc
Scientific Director
CIHR Institute of Gender & Health

One Health at UCalgary

UNIVERSITY OF CALGARY

CERTIFICATE
OF COMPLETION

This certificate is presented to

Nikolas Josafatow

for successfully participating in

Fundamentals of Biostatistics

30 instructional hours

DATE COMPLETED: MAY 19, 2023

Dr. Herman Barkema
DIRECTOR

Katherine Burak
INSTRUCTOR

Samantha Larose
MANAGER

UNIVERSITY OF CALGARY

Confirmation of Completion

This confirms that

Nikolas Oak Josafatow

has successfully completed

Biosafety (Program) Training

as of 06-01-2023

UNIVERSITY OF CALGARY

Confirmation of Completion

This confirms that

Nikolas Oak Josafatow

has successfully completed

Harassment and Violence Awareness Training

as of 05-06-2022

UNIVERSITY OF CALGARY

Confirmation of Completion

This confirms that

Nikolas Oak Josafatow

has successfully completed

Biosafety (Bloodborne Pathogens) Training

as of 06-01-2023

UNIVERSITY OF CALGARY

Confirmation of Completion

This confirms that

Nikolas Oak Josafatow

has successfully completed

Hazard Assessment Training

as of 05-06-2022

Signed: Leanne Elizabeth Renwick

UNIVERSITY OF CALGARY

Confirmation of Completion

This confirms that

Nikolas Oak Josafatow

has successfully completed

Occupational Health and Safety Orientation

as of 05-06-2022

Signed: Leanne Elizabeth Renwick

Date Online Completed: **19 Nov 2023**

Ticket Number: **e4b313cdb664c3cdf25780dbc1f43c4a**

Congratulations

Nik Josafatow

You have completed the online portion of

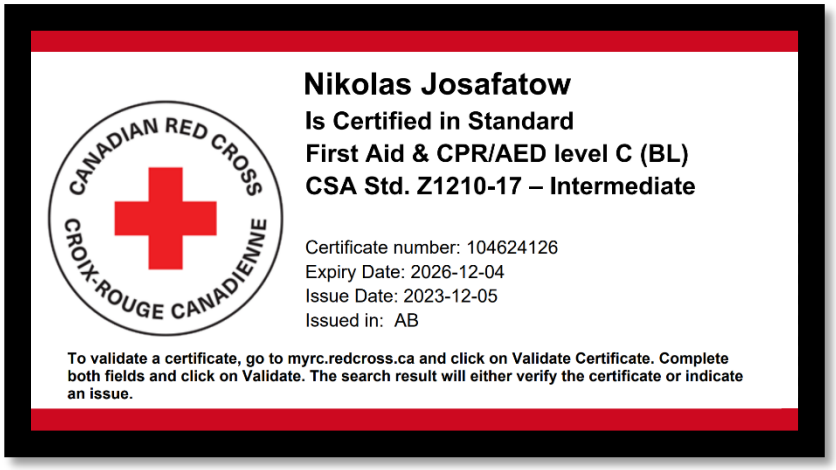
Standard First Aid & CPR - Online

You are now required to attend and successfully complete a skills and examination session.

Please make contact or have a company coordinator contact your training provider to arrange a time for skills training and examination session.

If you have further inquiries, please contact: myrcsupport@redcross.ca or 1-877-356-3226

Please note: This is not a certificate, it is a ticket validation of the completion of the online portion of training. Please print this ticket and present it at the skills training and examination session.



Nikolas Josafatow

Is Certified in Standard
First Aid & CPR/AED level C (BL)
CSA Std. Z1210-17 – Intermediate

Certificate number: 104624126
Expiry Date: 2026-12-04
Issue Date: 2023-12-05
Issued in: AB

To validate a certificate, go to myrc.redcross.ca and click on Validate Certificate. Complete both fields and click on Validate. The search result will either verify the certificate or indicate an issue.