METABOLISM, ENERGY BALANCE, AND HEALTH-RELATED QUALITY OF LIFE AFTER SPORT-RELATED CONCUSSION

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APPROVAL OF THE DISSERTATION

This dissertation, “Metabolism, Energy Balance, and Health Related Quality of Life after Sport-Related Concussion,” has been approved by the Graduate Faculty of the Curry School of Education & Human Development in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

Sport concussion (SC) has gained a lot of attention in recent years from scholars, clinicians, athletes, school districts, parents and mainstream media. This increased attention has led to improved recognition of the injury, but there is still understanding to be elucidated regarding the pathophysiology, clinical presentation, and recovery after SC. Patient sex, age, and prior concussion history are all reported to modify recovery trajectories, but the empirical evidence for these claims is mixed. Moreover, there is emerging evidence that physiologic recovery may not align with the typical clinical course of recovery. Most of what is known about pathophysiologic consequences of SC stem from rodent models of experimental brain injuries, and the evidence linking altered physiology to the clinical syndrome that is observed by clinicians and experienced by athletes with SC is sparse.

In the following studies, we examined whole-body metabolism through resting metabolic rate and carbohydrate metabolism, both measures of the physiologic response to SC. Additionally, we estimated physical activity and dietary intake in order to assess energy balance between daily energy consumption and total daily energy expenditure. We examined metrics of clinical recovery in the time to symptom resolution and the time to full return to play. In addition to the physiologic, demographic, and symptom-based measures, we incorporated patient-reported outcomes of sleep disturbance, fatigue, anxiety,

perceived resilience and stigma, and appetite. We included high school and collegiate participants diagnosed with SC acutely following their injury and serially assessed these individuals throughout their recovery. Moreover, we matched these participants to non-injured control participants based on age, height, weight, sex and sport in order to provide a meaningful comparator in lieu of a pre-injury baseline assessment.

The results of our studies will direct future research efforts to examine potential new avenues for clinical assessment and intervention after SC. Participants with SC had an energy surplus due to an overconsumption of calories in the initial 10 days following injury. This surplus related to symptom burden and perceived stigma. Males with SC had a lesser magnitude of energy surplus than females, and males who had greater carbohydrate utilization were slower to recover from injury. This suggests that altered fuel utilization and insufficient energy supply may be indicative of more severe injury and may affect recovery. Females with SC in our study recovered faster than their male counterparts. Lastly, sleep disturbance, fatigue, and stigma were all affected by SC acutely and improved throughout recovery. This study corroborates previous research findings in nascent areas of investigation and also reveals new ideas regarding the roles of perceptual, behavioral, and energetic responses to SC.

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WHOLE-BODY METABOLISM, CARBOHYDRATE UTILIZATION, AND CALORIC ENERGY BALANCE THROUGHOUT RECOVERY FROM SPORT CONCUSSION

ABSTRACT

Context: Traumatic brain injury (TBI) such as sport concussion (SC) causes an energy crisis in the brain characterized by increased energy demand, decreased energy supply, and a shift in metabolic fuel sources. Whole-body resting metabolic rate (RMR) is elevated in patients after moderate and severe TBI, and this phenomenon may be measurable after SC as well. This study was designed to observe energy-related changes in collegiate athletes following SC compared to matched controls and in relation to clinical recovery.

Methods: 20 collegiate athletes with SC (19.3±1.08 years old, 1.77±0.11 meters, 79.6±23.37 kg, 55% female) were matched with 20 controls (20.8±2.17 years old, 1.77±0.10 meters, 81.9±23.45 kg, 55% female) in this longitudinal case-control study. RMR, percent carbohydrate use (%CHO), and energy balance (EBal; the ratio between total caloric consumption and total expenditure) were collected at three time points: T_1 was within 72 hours of SC, T_2 was 7 days after T_1, and T_F was after symptom resolution. A 2x2x3 (Group x Sex x Time) MANOVA was used to assess RMR, %CHO, and EBal. Change in RMR, %CHO, and EBal between T_1, and T_F were correlated with days to symptom-free (DSF) and days to return to play (DRTP) for the whole SC group and each sex separately.

Results: Females reported symptom-free (median[full range]=6[3-10]) four days sooner than males (11[7-16]). RMR and %CHO were not different across time, between groups, or for the group by sex interaction (p>0.05). Participants with

SC had higher EBal than controls at T_1 (p=0.016, d=0.79) and at T_2 (p = 0.010, d = 0.85). In males with SC, increased %CHO utilization over time was significantly correlated with DSF (ρ=0.735, p=0.038) and DRTP (ρ=0.829, p=0.021).

Conclusions: This was the first study to examine whole-body metabolism and diet following SC. Participants with SC were in energy surplus in the first 10 days following their injury. Females recovered quicker than males yet did not differ from males with regard to energetic outcomes across time. However, males with SC took longer to recover when they used a lower proportion of carbohydrate for energy acutely following injury. Our study shows that males and females may differ in their physiologic response to SC and that there may be a role for dietary intervention to improve clinical outcomes following SC.

INTRODUCTION

The pathophysiology of traumatic brain injury (TBI) such as a concussion is often described as a “neurometabolic cascade” of intracranial metabolic events which occurs subsequent to trauma.[1] This neurometabolic cascade results in an intracranial metabolic disturbance characterized by increased energy demand, decreased total energy supply, and a subsequent shift in the types of metabolic substrates (i.e. fat, carbohydrate, and/or protein) being used for energy synthesis.[1-4] The whole-body metabolic response to concussion is currently unknown, though it has been recommended that patients eat a well-balanced diet

in order to facilitate recovery following injury.[5] This is a broad recommendation which has not been made more specific largely due to a lack of empirical evidence. In order to improve upon this dietary recommendation and to determine whether or not nutritional intervention may have a meaningful impact on the recovery from a concussion, it is imperative as a first-step to understand the whole-body metabolic response to these injuries.

The typical human brain is about two-and-a-half percent of one's total body mass, but accounts for up to 20% of the total body resting metabolic rate (RMR), which is the amount of energy required for a person to maintain vital functions (i.e. heart rate, respiratory rate, and chemical processes) at rest.[6,7] At the cellular level, energy systems in the brain are similar to those in skeletal muscle where adenosine triphosphate (ATP) is created through aerobic and anaerobic metabolism.[6] Nerve cells in particular rely heavily on glucose as their primary source of fuel for ATP synthesis.[6,8] Aerobic glycolysis involves a tandem of aerobic pathways known as the Krebs cycle and electron transport chain resulting in the net production of up to 32 molecules of ATP.[9] Anaerobic glycolysis results in the production of two molecules of ATP, lactate, and hydrogen ions.[6] Glucose may also enter the pentose phosphate pathway (PPP) which is anaerobic and whose products facilitate the creation of ATP as well as neuroprotective functions.[8,10] The brain also utilizes both lactate (a byproduct of anaerobic glycolysis) and ketone bodies (created by fatty acid oxidation in the liver) as fuel sources during activities of daily living and in states of high energy demands such as development[11], intense physical activity[12], and injury[13].

Non-glucose fuel sources may be used more during these times of increased energy demand such as injury in order to spare glucose for the PPP to help maintain homeostasis of the cellular and extracellular environment through the production of antioxidants and nucleic acids.[10] The neurometabolic cascade of concussion has been described through rodent models of experimentally-induced TBI and incorporates rapidly spreading depolarization of nerves, axonal stretching, disruption of phospholipid membranes, and the opening of ion channels which leads to poorly controlled ionic flux across nerve membranes.[1,14-18] In an effort to restore ionic homeostasis, the brain enters an initial *hyper*metabolic state (minutes to hours) which then depletes the available glucose supply and ultimately leads to a subsequent and prolonged *hypo*metabolism (hours to days).[1-4] Calcium ions enter neuronal mitochondria and linger for a matter of days, which further impairs aerobic glycolysis.[17,18] Glucose and oxygen for aerobic metabolism are delivered to the brain through circulation of blood, which has been shown to decrease after TBI. As a result, glucose utilization initially increases through use of stored glycogen and subsequently decreases as the demand outpaces the supply from blood flow, necessitating the use of alternate fuel sources.[1,2]

To date, studies of whole-body energy regulation following TBI have focused on patients in the moderate to severe aspects of the TBI spectrum. Moderate and severe TBI are defined by Glasgow Coma Scale scores (GCS) less than 13.[19] Elevated RMR has consistently been observed following moderate to severe TBI when compared to predicted values.[20-23] Specifically,

RMR has been measured at up to 200% of average predicted values in the initial days following injury and may remain elevated (116% to 200%) for several weeks.[20-23] Concordantly, higher concentrations of peripherally measured lactate and ketone bodies have also been documented within nine days immediately following moderate to severe TBI.[4,24] Like the brain, this increased availability of non-glucose substrates (i.e., lactate and ketone bodies) may represent a whole-body response to an increased overall demand for energy that is not met by glycolysis alone, though the cause of this shift is not yet known. To date, literature describing whole-body energy expenditure following milder forms of TBI (GCS of 13 to 15) such as sport concussion (SC) is lacking. Moreover, biologic sex may influence clinical recovery from SC, but the physiologic determinants of this difference are not well understood.[25]

Therefore, the purpose of our study was to examine whether SC alters whole-body energy expenditure in relation to energy balance during recovery. We also sought to investigate potential sex differences associated with clinical and energy-related recovery. We hypothesized that we would measure increases in whole-body energy expenditure and dietary energy consumption during the initial days following SC, and that these values would normalize throughout recovery. Similarly, we hypothesized that we would observe decreased carbohydrate fuel utilization acutely which would return to typical proportions after recovery and when compared to matched control participants. Additionally, we hypothesized that a greater magnitude of change in energy expenditure would relate to longer time to symptom resolution and that males and females

would have similar clinical and physiological recovery patterns. The findings from this study could illuminate potential avenues for dietary intervention following SC. Moreover, our findings will provide information for the ongoing discussions of physiologic versus clinical recovery trends, as well as the presence or absence of sex-related differences in the physiologic recovery from concussion.

METHODS

Participants

This study was approved by institutional review board of the University of Virginia. Students between 18 and 29 years of age were recruited from the Department of Athletics. For the purpose of our study, the definition of concussion was consistent with that provide by the Concussion in Sport group at the time of diagnosis.[26,27] Concussed participants were referred to the research team by their respective certified athletic trainer following diagnosis of their injury. These participants reported for their first assessment within 72 hours of their injury. Healthy control participants were matched by sex, age, height and weight, and according to their sport/habitual physical activity (i.e. varsity athletic team) when possible. All participants provided informed consent prior to their participation in the study. Participants were excluded if they self-reported that they were receiving treatment for an acute musculoskeletal injury (i.e. fracture), were diagnosed with any pathology known to affect metabolism (i.e. thyroid dysfunction), or if they had sustained a brain injury within six months prior to their first assessment.

Outcome Measures

We used a VMax® Encore metabolic cart (Carefusion, Yorba Linda, CA) to capture and monitor the exchange of oxygen and carbon dioxide gases (indirect calorimetry).[6] The VMax® Metabolic Cart is a valid measure of RMR when compared to an industry standard (no significant differences in measured RMR values between devices) and has shown small intra-subject changes in day-to day measurement (coefficient of variation = 8.4%), indicating that it is also a reliable assessment of RMR.[28] Both RMR (kcal/day) and fuel utilization were measured through indirect calorimetry. RMR was normalized to body mass (RMR/kg) prior to our analyses. The estimated proportions of carbohydrate utilization (%CHO) were calculated through the following equation[29];

$$\%CHO = [(RER - 0.71) \div 0.29] \times 100$$

In this equation, RER stands for "Respiratory Exchange Ratio" which is the relationship between the volumes of expired carbon dioxide and inspired oxygen and is used to approximate the type of fuels being used by the body.[6] RER values may be interpreted in the following way: 0.70 = fats are the primary fuel source, 0.82 = fuel sources are mixed, and 1.00 = carbohydrates (i.e. glucose) are the primary fuel source.[6] RER was also measured through the indirect calorimetry assessment. The proportion of RMR not represented by %CHO represents the use of alternate fuel sources such as fat.

Total daily energy expenditure (TEE; kcal/day) was calculated by multiplying RMR by an analogous physical activity level correction factor and was normalized to body mass (TEE/kg). The physical activity correction factor was based on activity level and sex (% above RMR; “Sedentary” men = 15%, women = 15%; “Lightly Active” men = 40%, women = 35%; “Moderately Active” men = 50%, women = 45%; “Very Active” men = 85%, women = 70%; and “Exceptionally Active” men = 110%, women = 100%).[30] Participants were given a Fitbit Charge HR or Charge 2 (Fitbit, Inc., San Francisco, CA) and asked to track step counts for each day of assessment and the subsequent two days. Step counts during these days were averaged to represent each time point’s physical activity level.[30,31] The Fitbit Charge HR has good evidence of validity when compared to a handheld step counter (Intraclass Correlation Coefficients [95% confidence interval] as high as 0.74 [0.54,0.87]) and reliability (Intraclass Correlation Coefficients [95% confidence intervals] $\geq$ 0.70 [0.46, 0.86]) in the measurement of walking steps.[32] Additionally, participants self-reported physical activities when the Fitbit was not worn and the physical activity level correction factor was elevated by one level to account for this activity (i.e. from “Very Active” to “Exceptionally Active” for a participant who played in a lacrosse game and therefore could not wear the Fitbit). As an example: a male control participant who recorded 8,000 steps on his Fitbit and participated in two hours of football practice would be considered “Very Active” and his measured RMR would accordingly be multiplied by 1.85 for that day.

Participants were provided instructions to complete a dietary recall journal by self-reporting all food and beverage intake for the day of assessment and the subsequent two days. Self-reported food records most often result in underreporting of true energy intake in athletes.[33] To address this and other sources of measurement error, it is recommended that assessment with these tools occur over at least three days and be interpreted with caution.[33,34] Participant-reported dietary intake was entered into the MyFitnessPal (MyFitnessPal, Inc., Baltimore, MD) online portal by the study team. MyFitnessPal is similar to traditional standardized paper-based dietary recall with regard to overall caloric intake ($p > 0.61$).[35] Energy consumption (EC; kcal/day) was estimated as the average number of calories consumed by the participant on the day of each assessment and the subsequent two days. EC was also normalized to body mass (EC/kg). Energy balance (EBal) was calculated as the ratio between EC and TEE (EC/TEE). A value greater than 1.0 indicated that the participant consumed more energy than they expended (energy surplus) and a value less than 1.0 indicated an energy deficit.

For concussed participants, days to reporting symptom free and days to full return to participation were determined through electronic record review (varsity student-athletes) or by self-report (for one non-varsity student-athlete). Participants were each asked to self-report their concussion-related symptomology using the Revised Head Injury Scale (HIS-r). The HIS-r includes three symptom-related outcomes: the presence of 22 symptoms, the duration (from brief to constant) and severity (not severe at all to as severe as possible)

over the previous 24 hours. The duration and severity of symptoms have been demonstrated to have strong sensitivity (77.5%) and specificity (100%) in recognizing the presence of a clinically diagnosed concussion in collegiate athletes.[36]

Procedures

All participants reported for their initial assessment within 72 hours of their injury (T_1), 7 days after their initial assessment (T_2), and again 7 days after their second assessment (T_3). Participants who were still experiencing symptoms at their third assessment were asked to report for a fourth assessment (T_4) after reporting symptom free. Assessment time points for our analyses included T_1, T_2, and the final assessment time point (T_F). T_F was considered to be the last assessment for individuals after reporting symptom free to their athletic trainer (T_3 for most, and T_4 for one participant). Control participants were assessed at three time points each, separated by at least three days between sessions to allow no overlap with regard to recording dietary intake and step counts.

Participants reported to each assessment between the hours of 0600 and 0900 in the morning. They were instructed not to eat or drink anything but water after midnight prior to each visit. Participants completed a detailed medical history form which included demographic questions and items specific to their concussion history. Next, participants self-reported their symptoms using the HIS-r. This was followed by measuring height (T_1 only) and weight. Participants were then instructed to lay supine, resting on a treatment table for 20 to 30

minutes with a clear plastic canopy placed over their head which was connected to the VMax® metabolic cart for indirect calorimetry assessment. Following indirect calorimetry, participants were asked to record step counts and dietary intake for the day of assessment and the two days following the assessment.

Missing Data

In cases of missing RMR, EC, and %CHO data, imputations were made by calculating person-specific values based on the group average change values between time points. For example: after EC was normalized to body mass, the group average difference between assessment time points (i.e. -5.01 kcal/day/kg in concussed males between T_2 and T_F) would be multiplied by that participant's most recently measured body mass and then added to the most recently measured RMR value in the following equation:

$$Group\ Average\ Change(RMR\ per\ kg) \times Last\ Measured\ Mass + Last\ Measured\ RMR = Participant's\ Estimated\ RMR$$

TEE and EBal were calculated for these individuals using the imputed RMR and EC values. When physical activity was missing, the median group correction factor was used in the calculation of TEE.

Analyses

To assess group-level RMR/kg, %CHO, and EBal outcomes over time, we performed a 2x2x3 MANOVA consisting of group (concussed vs. control) by sex

(female vs. male) by time (T_1, T_2, T_F) comparisons. Effect sizes were calculated as partial eta-squared (η_p^2) and were interpreted as small ($\leq$ 0.06), medium (0.06 to 0.13), or large ($\geq$ 0.14).[37] Post-hoc comparisons were performed using Tukey's Honestly Significant Difference (HSD) with Cohen's *d* effect sizes, which were interpreted as no effect (< 0.2), small effect (0.2 to 0.49), medium effect (0.5 to 0.79), or large effect ($\geq$ 0.8).[37] As described previously, EBal is a construct of physical activity, TEE, and EC; therefore, significant findings in EBal led to subsequent analyses of these individual components. Physical activity was assessed through χ^2 tests with Cramer's *V* effect sizes, interpreted as small ($\leq$ 0.06), medium (0.06 to 0.17), or large ($\geq$ 0.29).[38] TEE and EC were assessed with repeated measures ANOVAs and subsequent independent *t*-tests (group and sex differences) or paired *t*-tests (differences over time). Finally, we calculated Spearman's ρ correlations to examine the relationships between T_1 to T_F changes in RMR/kg, %CHO, EBal, days to symptom free and days to return to full participation. All analyses were performed in SPSS version 25 (Armonk, NY) with statistical significance set a priori with $\alpha \leq 0.05$.

RESULTS

A total of 20 concussed participants (9 males, 11 females) and 20 matched control participants were included in the study (Table 1). One female participant was initially enrolled in the control group and sustained a concussion the day after her initial visit. She was re-enrolled as a concussed participant and matched with a new control. Another male concussed participant completed the

first two assessments and declined to participate in the third assessment. Outcomes for this participant's T_F time point were imputed as described above. One male control participant was only able to complete two assessments because he sustained a foot fracture and so his T_F outcomes were also imputed.

Females reported symptom free an average four days sooner than males, and returned to full sport participation an average of five days sooner than males in our sample (Table 1). At T_1 (mean $\pm$ standard deviation, 2.1 $\pm$ 0.83 days after injury), no concussed participants had symptom resolution and none had returned to play. At T_2, 15 out of 20 (75%) reported being symptom free and three (15%) had returned to full sport participation. Two male participants had protracted recovery ($\geq$ 42 days to reporting symptom free) and did not return to their respective sports. For our analyses, we used outcome scores from the third assessment (T_3) to represent T_F for these participants. Another male participant reported symptoms for 29 days following injury, was able to return to full sport participation, and completed a fourth assessment (T_4). Dates of reporting symptom free and full return to participation were missing for two female participants; however they did return to full sport participation during the same season that they sustained their SC and participated in this study, and the date of symptom resolution was obtained for one of them. The remaining 16 participants all reported being symptom free at T_F and 15 of those 16 had returned to full participation.

We did not observe any differences in RMR/kg or %CHO over time, between groups, or regarding the interaction of sex and group. However, EBal (Figure 1) was different between groups over time ($F_{(9,28)}$ = 2.304, p = 0.044, η^2_p = 0.425). The concussed group had lower EBal ($t_{(19)}$ = 3.840, p = 0.001, d = 0.88 [0.23-1.53]) at T_F (mean ± standard deviation: 0.96 ± 0.30) compared to T_1 (1.26 ± 0.38) indicating a caloric surplus at T_1 and relative caloric balance at T_F. Control EBal significantly increased ($t_{(19)}$ = -3.113, p = 0.006, d = 0.62 [0.01-1.26]) from T_2 (0.87 ± 0.21) to T_F (1.01 ± 0.24). Concussed and control group EBal was significantly different at T_1 ($t_{(38)}$ = 2.509, p = 0.016, d = 0.79 [0.15-1.43]; 1.26 ± 0.38 and 0.99 ± 0.30, respectively) and at T_2 ($t_{(38)}$ 2.706, p = 0.010, d = 0.85 [0.20-1.49]; 1.13 ± 0.38 and 0.87 ± 0.21, respectively), but not T_F (p = 0.542).

Further exploration of physical activity indicated that the concussed group were less physically active in the first two assessment time points, and effect sizes were large for all time points (Figure 2; T_1: $\chi^2_{(5)}$ = 16.640, p = 0.005, V = 0.65; T_2: $\chi^2_{(5)}$ = 11.800, p = 0.038, V = 0.54; T_F: $\chi^2_{(5)}$ = 4.956, p = 0.421, V = 0.35). Related to physical activity, TEE/kg was lower in the concussed group (22.2 ± 3.49) compared to the control group (26.8 ± 3.87) at T_1 ($t_{(38)}$ = -3.938; p < 0.001; d = 1.25[0.57-1.93]). Additionally, TEE/kg significantly increased over time in the concussed group from T_1 to T_2 ($t_{(19)}$ = -3.269, p = 0.004, d = 0.56 [-.07 – 1.20]; 22.2 ± 3.49 and 24.4 ± 4.28, respectively), and from T_1 to T_F ($t_{(19)}$ = -3.723, p = 0.001, d = 0.96 [0.31 – 1.62]; 22.2 ± 3.49 and 26.8 ± 5.78, respectively), but did not change in the control group. Energy consumption did not change over

time or differ between groups across time points ($F_{(2)} \leq 2.554$; $p \geq 0.085$; $\eta^2_p \leq .066$).

Changes over time for RMR/kg, %CHO, and EBal in the full concussed group were not correlated with days to symptom free or days to return to play ($p \geq 0.066$). Specifically in males, an increase in %CHO utilization over time was significantly correlated with both days to reporting symptom free ($\rho = 0.735$, $p = 0.038$, $n = 8$) and days to return to play ($\rho = 0.829$, $p = 0.021$, $n = 7$) (Figure 3). In females, there were no significant correlations between clinical recovery and change over time in RMR/kg, %CHO, or EBal.

DISCUSSION

We found that whole-body metabolic rate (RMR/kg) was not affected by concussion. However, we observed changes over time in energy balance and a relationship between %CHO utilization and recovery in males alone. The EBal values greater than 1.0 at the first two time points were indicative of concussed participants over-consuming energy (hypercaloric state) compared to their relative energy expenditure within the first 10 days following their injury, but this group of individuals returned to an isocaloric state after reporting symptom-free. Female participants in our study recovered sooner than males by an average of five days for symptom recovery and six days to return to play. Related to sex differences in recovery, lower acute metabolic rates of carbohydrates in males (as evidenced by the change in %CHO over time) were strongly correlated with greater lengths of recovery. This relationship was not observed in females. We

did not observe any meaningful relationships between clinical recovery and RMR or EBal.

Our study was the first to examine whole-body energy expenditure in a sample of collegiate athletes diagnosed with SC (*mild* TBI). Based on previous studies in patients with moderate or severe TBI, we expected that we would observe changes in metabolic rate as a result of SC. This was not the case; however, and the reasons could be related to many factors. Specifically, our sample of participants with SC did not resemble those included in prior studies of more severe TBI. In studies of energy expenditure with similarly-aged patients, many were receiving prescription medications to preserve life-sustaining functions, most had severe extra- or intracranial injuries (i.e. skull fracture and/or hematoma), and all were bed-ridden.[24,39] Our participants were not hospitalized and were free of co-morbidities. It is possible that the severity of injury in our sample was not great enough to elicit a measurable whole-body metabolic rate disturbance. Additionally, rodent models of TBI that describe the timeline of metabolic alterations in experimental injury indicate that the hypermetabolic state is transient and may resolve in a matter of hours.[2-4] In this case, we may have missed the window to recognize such a shift of energy expenditure in our participants.

Of particular note was the reported overconsumption of energy in the first two time points following injury as evidenced by elevated EBal ratios. Acutely, average EC was almost 130% of TEE, and this value returned to relative caloric

balance after participants reported symptom-free. EBal is calculated using measured RMR, physical activity and EC. Physical activity was different between groups and appeared to increase over time in the concussed group. Concurrently, there was a non-significant trend of increased EC in concussed participants compared to controls and a decline over time in the concussed group with a moderate effect size. A recent meta-analysis of dietary intake reporting in athletic samples indicated that there is a tendency for athletes to underreport the amount of energy they consume by an average of 19% across studies.[33] If underreporting was also true in our study, then we may have also underestimated our present EBal ratios. Though we did not validate EC with a physiologic biomarker, we did observe isocaloric EBal at the first and final assessment time points in our control group. From this, we can infer that any present error was systematic within our study design. Decreased physical activity contributed to the disparity in TEE, and when combined with increased EC, EBal was significantly affected by SC. At this time, it is unknown if the overconsumption of energy in people with SC has a protective or healing effect, if it is a response to changes in physiology or behavior, or both.

Currently, no well-established intervention for SC exists. We observed that an increase in the utilization of carbohydrates over time in males with SC was related to a longer recovery. This change may indicate an acute shift toward non-glucose metabolic fuels (i.e. lactate and/or ketones) which may be reflective of greater neurophysiologic disturbance. In clinical practice and rodent models, ketone supplementation and ketogenic diets (i.e. high fat proportions with

relatively low or no carbohydrates) may be beneficial to facilitate recovery from severe TBI and reduced seizures in epilepsy, but the mechanisms for these results are not clear and warrant further investigation in humans.[40,41] The vagus nerve (cranial nerve X) is responsible for autonomic regulation of the gut, and it is possible that concussion affects this signaling axis. Altered signaling from the vagus nerve may have effects on appetite and mood.[42] Relatedly, the hormones leptin and ghrelin, which are responsible for hunger and satiety regulation, act through the hypothalamus and therefore may also be affected by brain injury.[43,44] Future investigations should evaluate the effectiveness of dietary interventions in attenuating the burden of SC and facilitating recovery.

Our study has definite limitations. We did not obtain pre-injury baseline assessments of energy expenditure, physical activity, or dietary intake. In lieu of these measures, we matched concussed participants to healthy, control participants based on age, height, weight, sex, and sport. The control group was consistent across time with regard to our outcomes of interest and was similar to the concussed group following their clinical recovery. This supports the use of a control group as a meaningful comparator in lieu of pre-injury assessments when assessing whole-body metabolic rate. It is important to note that step count as a measure of physical activity was also a meaningful limitation of the study. Many athletes could not wear the prescribed Fitbits during typical athletic activities (i.e. football practice, swimming, etc.). The actual amount of energy expended during each of these activities was not measured, though we did make corrections to account for activity that wasn't measured through Fitbits. Moreover, step counts

were measured as high as 28,042 steps in a single day, which is over two times the criterion value for placement at the highest physical activity group (12,500 steps per day). It is feasible that larger activity modifiers would be more accurate in the assessment of physical activity for those individuals who had higher step counts.

Lastly, estimated dietary intake may have been impacted by the ability of concussed individuals to keep track of the type and amounts of foods consumed. Dietary recall journals, even when used in healthy and alert adults, are associated with underreporting of dietary intake, and the potential to influence eating behavior.[33,45] Due to financial restrictions and considerations of practicality for our participant sample, we did not attempt to validate self-reported diets using physiological biomarkers of intake. Therefore, we were unable to determine the direction or magnitude of self-reporting errors or the presence of bias in this study. In an effort to delimit these sources of error, we encouraged participants to report their dietary intake consistently and truthfully, and a member of the research team was regularly available to address questions or concerns.

CONCLUSION

We sought to explore changes in whole-body metabolism following SC in collegiate students. We found that collegiate athletes with sport concussion consumed more energy than they expended in the initial days following injury, and that this could be partially explained by decreased physical activity. It is

unknown whether this pattern relates to the burden of injury or recovery from SC. Moreover, we found that a lower rate of carbohydrate metabolism was related to a longer duration of symptoms and time to return to play in males, but not females. We did not detect any differences between sexes with regard to metabolic rate or energy balance, but we did observe that females recovered five to six days sooner than males.

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TABLES

Table 1. Demographics. Means ± standard deviations are presented for age, height, and mass. Medians and full ranges are presented for the remaining demographic variables. T_1 = First assessment, T_2 = Second Assessment, T_F = Final Assessment, BMI = Body Mass Index.

	Concussed Females (n = 11)	**Concussed Males (n = 9)**	**All Concussed (n = 20)**	**Control Females (n = 11)**	**Control Males (n = 9)**	**All Controls (n = 20)**
Age	19.0 ± 1.10	19.7 ± 1.00	**19.3 ± 1.08**	19.9 ± 1.30	21.8 ± 2.64	**20.8 ± 2.17**
Height	1.70 ± 0.096	1.85 ± 0.076	**1.77 ± 0.112**	1.72 ± 0.083	1.82 ± 0.083	**1.77 ± 0.096**
Weight at T_1	65.7 ± 10.21	96.5 ± 24.13	**79.6 ± 23.37**	69.1 ± 9.69	97.6 ± 26.14	**81.9 ± 23.45**
Weight at T_2	65.6 ± 10.26	96.9 ± 24.27	**79.7 ± 23.65**	69.9 ± 9.75	97.3 ± 26.19	**82.2 ± 23.14**
Weight at T_F	65.6 ± 10.16	96.7 ± 24.31	**79.6 ± 23.56**	69.8 ± 9.83	98.0 ± 26.93	**82.5 ± 23.75**
BMI at T_1	22.5 ± 1.66	28.0 ± 5.20	**25.0 ± 4.55**	23.3 ± 1.98	29.1 ± 5.93	**25.9 ± 5.07**
BMI at T_2	22.5 ± 1.62	28.1 ± 5.17	**25.0 ± 4.57**	23.6 ± 2.01	29.0 ± 5.96	**26.0 ± 4.98**
BMI at T_F	22.5 ± 1.58	28.0 ± 5.22	**25.0 ± 4.55**	23.6 ± 1.93	29.0 ± 5.67	**26.0 ± 4.81**
Concussion History	1, 0-3	1, 0-6	**1, 0-6**	0, 0-3	0, 0-2	**0, 0-3**
Days to Reporting Symptom Free	6, 3-10	10, 4-29	**6, 3-29**	-	-	**-**
Days to Full Return to Play	11, 7-16	16, 10-42	**14, 7-42**	-	-	**-**

FIGURES

Figure 1. Energy Balance over Time. T1 – First assessment time point, T2 – Second assessment time point, TF – Final assessment time point. Total *n* = 40. Conc = Concussed group (*n* = 20), Ctrl = Control group (*n* = 20), F = Female participants, M = Male participants, * Significant reduction in EBal from T1 to TF in the Concussed group (*p* = 0.001), † Concussed and control groups different at T1 (*p* = 0.016), ‡ Concussed and control groups different at T2 (*p* = 0.010).

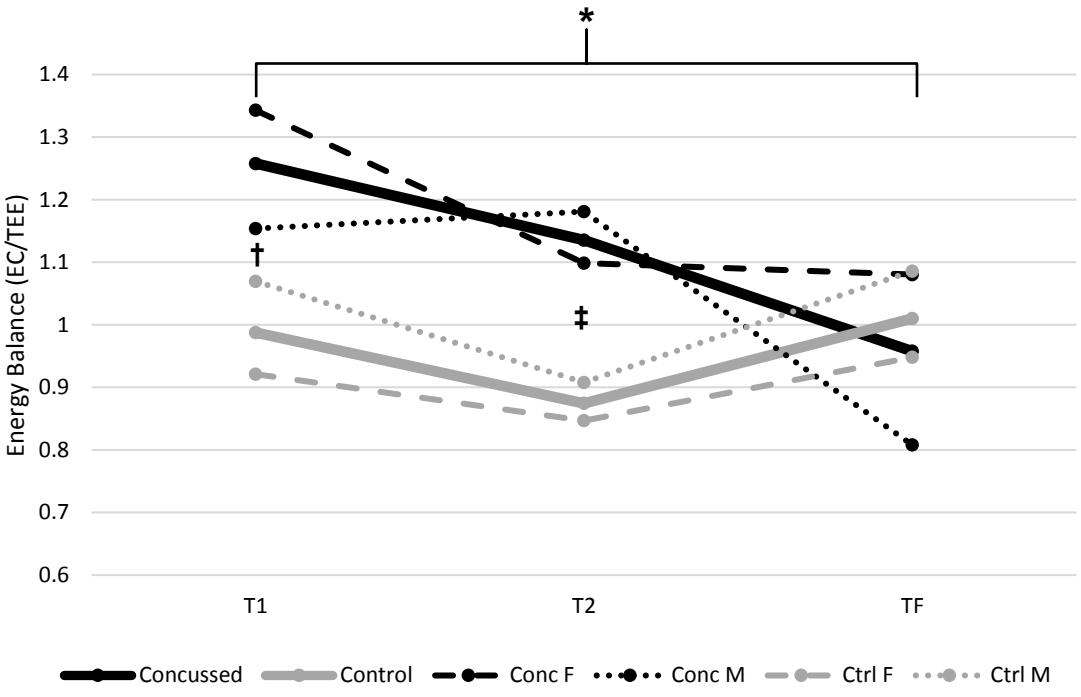
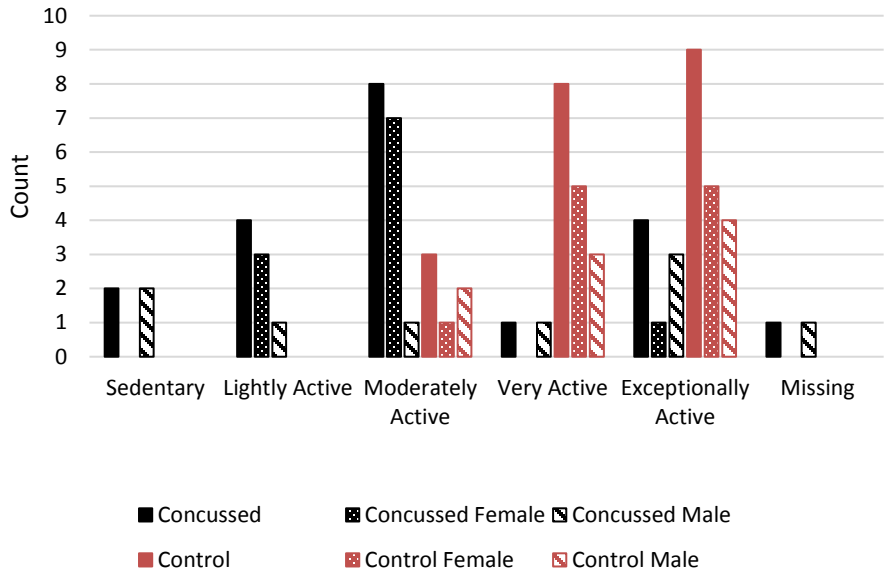
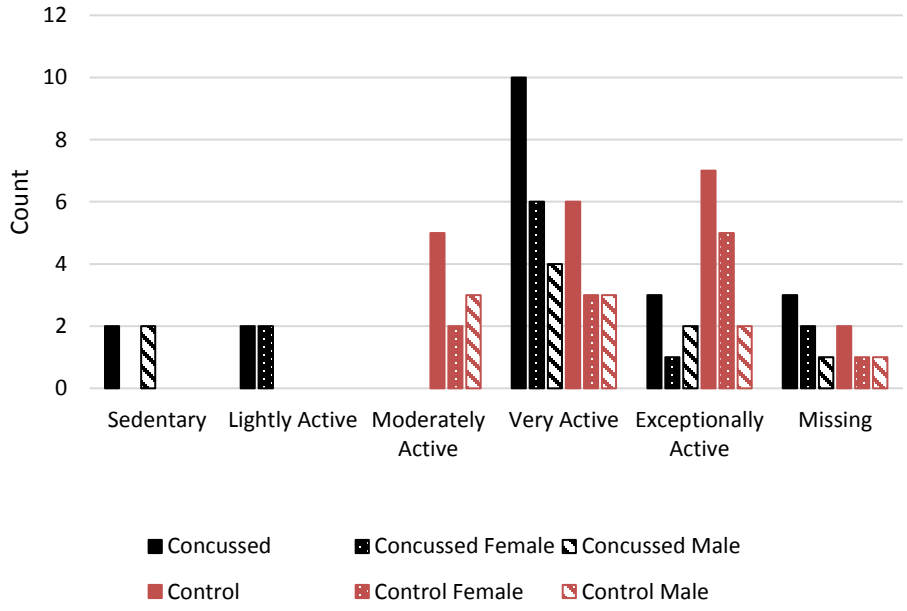


Figure 2. Physical Activity Levels

2a: Physical Activity Levels at T1. Concussed and control groups were significantly different ($\chi^2_{(5)} = 16.640$, $p = 0.005$).



2b: Physical Activity Levels at T2. Concussed and control groups were significantly different ($\chi^2_{(5)} = 11.800$, $p = 0.038$).



2c: Physical Activity Levels at the Final Assessment Time Point. Concussed and control groups were not significantly different ($\chi^2_{(5)} = 4.956$, $p = 0.421$).

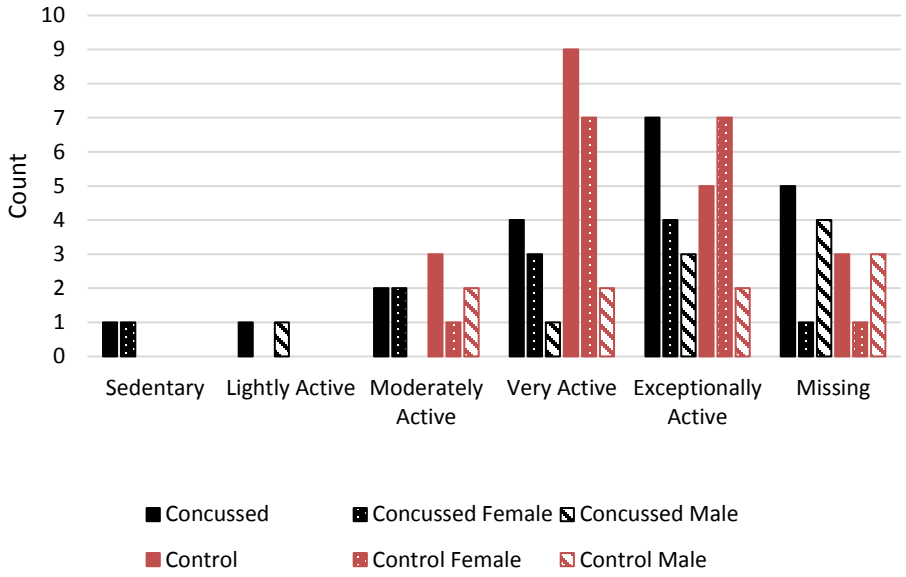
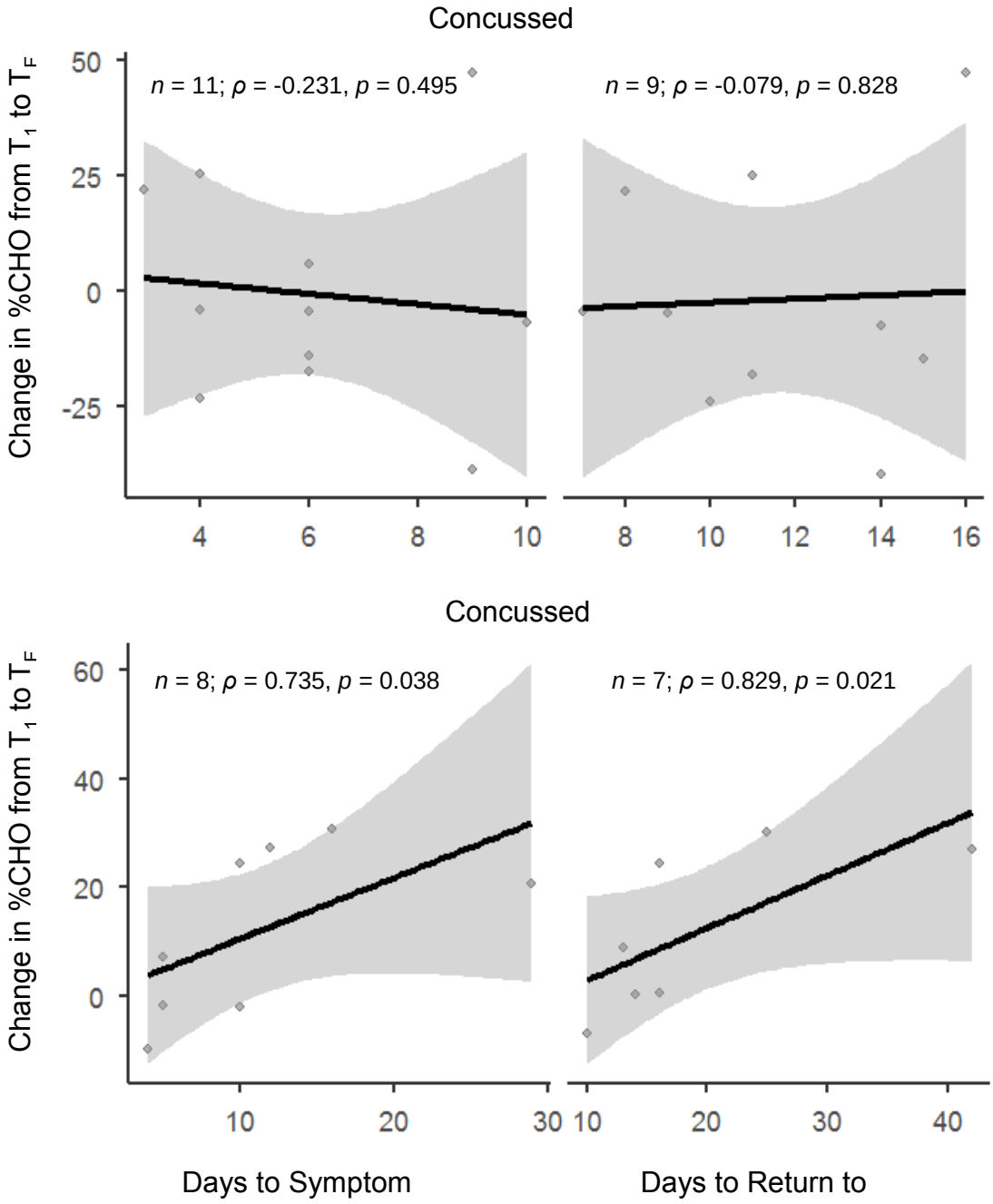


Figure 3. Correlations between Percent Carbohydrate Change over Time and Clinical Recovery in Concussed Females and Males. %CHO = The proportion of resting metabolic rate that comes from the metabolism of carbohydrates. T_1 = The first assessment time point. T_F = The final assessment time point. Black lines indicate the line of fit for each bivariate correlation. Grey areas represent the 95% confidence interval for the line of fit.



SECTION II: MANUSCRIPT II

FACTORS AFFECTING METABOLISM AND DIETARY INTAKE FOLLOWING CONCUSSION IN ACTIVE HIGH SCHOOL AND COLLEGIATE ATHLETES

ABSTRACT

Context: Sport concussion (SC) is characterized by a neurometabolic cascade of events that result in an energy crisis in the brain, and whole-body energy-related changes are measurable acutely following more severe brain injuries. Additionally, recovery from SC may be mediated by age, prior concussion history, and symptom burden, but there is little evidence regarding the physiologic mechanisms for these differential recovery trajectories. This study was designed to examine whole-body energy-related outcomes acutely following SC in relation to age, concussion history, and symptom burden.

Methods: In this case-control study participants diagnosed with SC (*n*=28, aged 18.4±1.83 years, 1.76±.10 meters, 75.6±20.97 kilograms, BMI of 20.3+4.13, 50% female) were assessed within 72 hours of injury and matched to control participants (*n*=28, aged 19.4±2.90 years, 1.76±.08 meters, 77.5±21.18 kilograms, BMI of 18.8+4.79, 50% female). Participants self-reported concussion history (CH) as well as the duration and severity of symptoms over the prior 24 hours. Resting metabolic rate (RMR) was measured via indirect calorimetry and normalized to body weight (RMR/kg). Participants reported physical activity and dietary intake, and energy balance (EBal) was calculated as the ratio between calories consumed to calories expended per day. Bivariate correlations were assessed for each group separately between RMR/kg, EBal, age, CH, BMI, total symptoms, DUR, and SEV. Separate backwards step-wise multiple regression models were built for RMR/kg and EBal to determine added value of multiple predictors on RMR/kg and EBal.

Results: Age and BMI ($\rho \geq 0.436$, $p \leq 0.020$) as well as all symptom outcomes ($\rho \geq 0.721$, $p < 0.001$) were related in both groups. BMI correlated with EBal in the SC group ($\rho = -0.551$, $p = 0.003$) and with RMR/kg in the control group ($\rho = -0.499$, $p = 0.007$). Regression analyses in the SC group revealed a relationship between CH and RMR/kg ($R^2 = 0.134$), and between age, CH, BMI, symptom severity, and symptom duration and EBal (Adj. $R^2 = 0.537$).

Conclusions: Estimated increases in EBal (energy surplus) were related to age, CH, BMI, and symptoms acutely following SC, and metabolic rate was influenced by previous concussions. The role of CH and RMR/kg after SC were not determined with certainty. The observed relationships suggest that a dietary intervention acutely following SC may improve clinical outcomes.

INTRODUCTION

Sport concussion (SC) has been defined as a mild traumatic brain injury (TBI) consisting of pathophysiologic changes which affect neurologic function following a blow to the head or elsewhere on the body.[1] This pathophysiologic response has been characterized as a neurometabolic cascade that disrupts the intracranial chemical environment subsequent to trauma.[2,3] Immediately following a TBI such as SC, insulted neuronal axons stretch which leads to cell depolarization. In response to depolarization, voltage- and chemically-mediated ion channels open, thereby impairing the control of ionic flux into and out of these cells.[4-6] This leads to a rapid efflux of intracellular potassium and influx of

extracellular sodium and calcium ions. Calcium enters neuronal mitochondria and reduces the overall rate of aerobic (oxygen-requiring) metabolism, the preferred energy pathway of the brain.[7-9] This is concurrent with a reduced blood supply to the brain and a shift toward anaerobic metabolism of carbohydrates.[10,11] As a result intracranial homeostasis may take days to recover.[7,8,12,13]

Energy is required to restore homeostasis from these ionic imbalances. Immediately following a concussive insult, the brain typically undergoes a transient (minutes to hours) hypermetabolic state followed by a subsequent hypometabolic state for a period of hours to days.[12-15] The brain typically accounts for up to one fifth of the body's total resting metabolic rate (RMR), which is the requisite amount of energy required by the body to perform life-sustaining functions in an awake but resting state.[16] Studies of patients with moderate to severe TBI (Glasgow Coma Score less than 13) have been demonstrated to have increased RMR acutely after injury and throughout recovery.[17-21] Elevated RMR may increase up to two-fold when compared to predicted values in the first few days following injury, and has been demonstrated to remain elevated in some individuals for weeks.[18-21]

Clinical research findings indicate that the response to SC may differ by age. More specifically, age may influence SC-related symptom burden and performance on cognitive and balance measures.[1,22-25] Younger athletes diagnosed with SC may report a greater symptom burden and different constellations of symptoms compared to older athletes. Younger athletes may also have a longer overall recovery compared to their older counterparts.[22-25]

Additionally, age appears to be a modifier for performance on clinical post-concussion neurocognitive and balance measures, however the effect is not consistent towards overall better performance in either younger or older athletes.[22,23,25] In addition to age, a history of prior concussions may also result in an elevated acute self-reported symptom severity, specifically in physical/somatic symptoms (i.e. headache) post-concussion.[25,26] Evidence regarding the effects of prior concussion history on neurocognitive performance is mixed .[23,26] Symptom burden appears to be an integral factor in predicting the time to recovery following concussion. Patients with a higher initial symptom severity appear to take longer to recover than those with lower severities, and this may occur independently from age, sex, and concussion history.[24,27,28]

In this study, we sought to observe the acute whole-body metabolic response to SC in physically active high school and collegiate students as compared to healthy-matched controls. We wanted to observe RMR, the balance between dietary energy intake and total daily energy expenditure (EBal), their relationships to each other, and potential modifiers including age, prior concussion history, and symptom burden within 72 hours of a diagnosed SC. We hypothesized that younger (i.e. high school) athletes would self-report a greater acute symptom burden and therefore, would have higher RMR values compared to older (i.e. collegiate) athletes who were hypothesized to self-report a lesser symptom burden. We did not expect prior concussion history alone to affect RMR or EBal outcomes. We also hypothesized that participants with SC would have greater energy expenditure than control participants.

METHODS

Participants

The institutional review board of the University of Virginia approved this study. All adult participants provided informed consent prior to their participation in the study. Participants under 18 years of age provided assent and their parent or legal guardian provided consent prior to participation. Concussed students between 14 to 29 years of age were recruited from the University of Virginia and local high schools. Data were collected between the Spring of 2015 to the Spring of 2019. The diagnosis of SC was made by a certified athletic trainer or sports medicine physician according to the latest definition from the Concussion in Sport Group available at the time of diagnosis.[1,29] Following diagnosis of a SC, participants reported for their initial assessment within 72 hours of their injury as part of a larger longitudinal study. Healthy control participants were matched to those with SC based on age, height, weight, and sport when possible. Participants were excluded if they were receiving treatment for an acute musculoskeletal injury (i.e. fracture), had diagnosis of any pathology known to affect metabolism (i.e. thyroid dysfunction), or if they had sustained another concussion within six months prior to their initial assessment.

Outcome Measures

A VMax® Encore metabolic cart (Carefusion, Yorba Linda, CA) was used to capture and monitor the exchange of respiratory gases (indirect calorimetry) for determination of RMR.[16] The VMax® Metabolic Cart provided valid

measurements of RMR when compared to an industry standard (no significant differences between devices) and has shown small changes in day-to day measurement within participants (coefficient of variation = 8.4%), indicating that it is also reliable in the assessment of RMR.[30] RMR was normalized to body mass (RMR/kg) prior to our analyses. Carbohydrate utilization (%CHO) was also calculated to assess fuel selection through the following equation[31];

$$\%CHO = [(RER - 0.71) \div 0.29] \times 100$$

where RER stands for "Respiratory Exchange Ratio" and is the relationship between the volumes of expired carbon dioxide and inspired oxygen.[16] RER is commonly used to approximate the type of fuels being used by the body and was also measured through indirect calorimetry.[16] The proportion of RMR not attributed to %CHO in our study represented the use of alternate fuel sources such as fat.

Total daily energy expenditure (TEE; kcal/day) is the product of RMR multiplied by a corresponding physical activity correction factor and was also normalized to body mass (TEE/kg). The physical activity correction factor was based on both physical activity volume and sex as a proportion above strict physical rest (i.e. percent above RMR for "Moderately Active" individuals; men = 50%, women = 45%).[32] Participants were given a Fitbit Charge series wristband device (Fitbit, Inc., San Francisco, CA) and asked to track step counts for each day of assessment and the subsequent two days. Step counts for these days were averaged to represent each time point's physical activity level[32]. The Fitbit

Charge HR has good validity evidence when compared to a handheld step counter (Intraclass Correlation Coefficients [95% confidence interval] 0.74 [0.54,0.87]) and evidence of reliability (greater than 0.70 [0.46, 0.86]) in the measurement of walking steps.[33] Additionally, participants self-reported physical activities in which the Fitbit was not worn and the physical activity level correction factor was adjusted by increasing one level of activity classification to account for this unmeasured activity. As an example: a female control participant who recorded 9,000 steps on her Fitbit and swam for two hours each day would be considered “Very Active” and her measured RMR would accordingly be multiplied by 1.70 for that day, rather than 1.45 if only the Fitbit data were used.

Energy consumption (EC; kcal/day) was estimated based on self-reported intake records as the average number of calories consumed by the participant through dietary intake on the day of each assessment and the subsequent two days. Participants were provided instructions to complete a dietary recall journal by recording all food and beverage intake for the day of assessment and the following two days. Participant-reported dietary intake was entered into the MyFitnessPal (MyFitnessPal, Inc., Baltimore, MD) online portal by the study team. MyFitnessPal is similar to traditional standardized paper-based dietary recall with regard to overall caloric intake ($p > 0.61$) and individual macronutrient caloric intake ($p < 0.05$, mean differences < 26 calories).[34] EC was also normalized to body mass (EC/kg). Energy balance (EBal) was calculated as the ratio between EC and TEE (EC/TEE). A value greater than 1.0 indicated that the

participant consumed more energy than they expended (energy surplus) and a value less than 1.0 indicated an energy deficit.

Participants were asked to self-report their concussion-related symptomology using the Revised Head Injury Scale (HIS-r).[35] The HIS-r includes three symptom-related outcomes: the presence of 22 symptoms, the duration (from brief to constant) and severity (not severe at all to as severe as possible) over previous 24 hours. The duration and severity of symptoms have shown strong sensitivity (77.5%) and specificity (100%) in recognizing sport concussion and are predictors of time to clinical recovery in collegiate athletes.[35,36]

Procedures

Participants reported to the research laboratory for their assessment between 0600 and 0900. Participants were instructed not to eat or drink anything but water after midnight prior to each appointment. A detailed health history form which included demographic, concussion-related and pertinent medical history questions was completed. This was followed by the participant self-reporting the presence of concussion-related symptoms within the previous 24 hours using the HIS-r. When a symptom was reported, the participant then indicated the duration of their experience of that symptom in the previous 24 hours on a Likert scale (brief “1” to constant “6”) as well as the severity for that symptom (not severe “0” to as severe as possible “6”). Next, each participant’s height and body mass were recorded.

Participants were then instructed to lay supine, resting on a treatment table for 20 to 30 minutes. A clear plastic canopy was placed over their head which was connected to the VMax® Encore metabolic cart to perform indirect calorimetry. Following indirect calorimetry, participants were loaned a Fitbit and the dietary recall journal. Each participant was provided instructions to record all intake of food and beverages. Collegiate participants and some high school participants completed subsequent assessments as part of a longitudinal study protocol, and these findings will be presented in related manuscripts.

Analyses

Bivariate correlation analyses were performed separately for each group (SC and control) using Pearson *r* or Spearman *ρ* (depending on normality). Comparisons were made between RMR/kg, EBal, age, number of previous concussions, total symptoms reported, total symptom duration (the sum of all individually endorsed durations), and total symptom severity (the sum of all individually endorsed severities). Separate backwards step-wise multiple regression models were built for RMR/kg and EBal to determine potential added predictability of age, number of prior concussions, and symptom outcomes for each group. Prior to regression analyses, we assessed for the normality of each of the symptom outcomes by using Shapiro-Wilk's test. Total symptom duration was not normally distributed (Shapiro-Wilk = 0.843, $p = 0.004$) and was subsequently transformed by calculating its square root. The square root of duration was deemed to be normally distributed (Shapiro-Wilk = 0.908, $p = 0.058$) and was included in our regression analyses. Lean body mass is a strong

predictor of RMR, but was not measured in our participants.[37] Instead, we included body mass index (BMI) as a surrogate measure for body composition to help address any mediating effect body composition may have had. All analyses were performed in SPSS version 25 (Armonk, NY) with statistical significance set a priori with $\alpha \leq 0.05$.

RESULTS

There were 28 participants in the SC group and 28 matched controls included in this study (Table 1). The most commonly reported symptoms in the SC group were headache (100%, 27/27), fatigue (75%, 21/27), drowsiness (68%, 19/27), feeling “in a fog” (64%, 18/27), difficulty concentrating (64%, 18/27), sensitivity to light (64%, 18/27), feeling slowed down (57%, 16/27), sleep disturbance (46%, 13/27), and dizziness (46%, 13/27). Participants with SC reported for their visit (mean $\pm$ standard deviation) 1.96 $\pm$ 0.85 days after their injury. Concussion history ranged from 0 prior concussions to 6 prior concussions. This range of self-reported previous injuries was categorized into groups of 0 (n = 30), 1 (n = 13), 2 (n = 8), and 3 or more (n = 5) or more previous concussions. Concussion history was not different between the control and SC groups. Energy expenditure and energy consumption outcomes for each group are presented in Table 2.

In both the SC and control groups, age was moderately correlated with BMI (SC: ρ = 0.436, p = 0.020; control: ρ = 0.572, p = 0.001) and each of the

symptom outcomes was strongly correlated with each other ($\rho \geq 0.721$, $p < 0.001$). In the SC group, BMI was moderately correlated with estimated EBal ($\rho = -0.551$, $p = 0.003$). This was not the case in the control group ($\rho = 0.200$, $p = 0.307$). BMI was moderately correlated with RMR/kg in the control group ($\rho = -0.499$, $p = 0.007$), but not in the SC group ($\rho = -0.009$, $p = 0.965$).

Separate backwards regression analyses onto RMR/kg indicated a significant relationship with concussion history in the SC group (unstandardized $\beta = 0.654$; $R^2 = 0.134$) and with BMI in the control group (unstandardized $\beta = -0.213$; $R^2 = 0.238$). Regarding EBal, there were no significant predictors in the control group. In the SC group we identified a meaningful prediction model (Adjusted $R^2 = 0.541$) incorporating age, concussion history, BMI, total symptom severity, and the square root of total symptom duration (Table 3).

DISCUSSION

In this study, we sought to explore the relationships between energy expenditure through RMR which is a direct assessment of whole-body metabolism. Similarly, we explored the relationship between SC and energy balance, which is a product of RMR, physical activity, and dietary energy intake. We acknowledge that the experience of symptoms in individuals diagnosed with SC may have influenced the self-reported physical activity and dietary intake information. Since we did not directly measure dietary intake, all values provided in this project were calculated estimates based on the information provided by the athletes.

We observed some relationships that were similar between groups of participants such as the correlations between age and BMI. The total number of reported symptoms, total severity and total duration were also highly related to each other within each group, and this was also an expected finding. We observed that an increased metabolic rate following SC related to a greater number of self-reported prior concussions. Moreover, we observed that EBal was decreased by a variety of clinically measureable outcomes including older age, greater prior concussion history, higher BMI, and greater reported symptom severity. Greater reported symptom duration related to increased EBal.

Age and BMI were associated with each other in both groups, indicating that older participants had higher BMI. This is an expected outcome as normal growth and development increases BMI throughout adolescence and into adulthood.[38] Additionally, athletes are likely to continue to gain body mass due to their training for their competitive sport participation. RMR/kg and BMI were strongly related in the control group, but not the SC group. Inversely, EBal and BMI were strongly related in the SC group but not the control group. Body composition, and specifically lean body mass, exert strong influence on metabolic rate in healthy individuals, and our findings corroborate this relationship.[37] The lack of this relationship in the SC group is an intriguing finding. It is possible that the pathophysiologic disturbance in the brain following SC increased the metabolic demand of neural tissue and reduced the proportional influence that lean mass (i.e. muscle) contributes to overall metabolic rate.[12-15]

This may explain the resultant loss of the influence of BMI on RMR/kg in the SC group.

The observed relationship of higher BMI with lower EBal in the SC group is harder to interpret. An elevated EBal (overconsumption of calories compared to expenditure) is likely the result of lower physical activity in concussed participants, and may also relate to increased feelings of hunger or food cravings. An acute phase of physical rest is among the current recommendations for management of SC, which is important to consider as physical activity is in the denominator of the equation for EBal.[1] More participants with SC were categorized into lower physical activity categories based on their reported levels of physical activity (Figure 1). Concurrently, energy consumption did not differ between groups and EBal was observed to be higher in the SC group compared to controls who were in relative energy balance (Table 2). There were also no group differences in height or body mass, which are the constituents of BMI (Table 1). Thus, it is unlikely that body size or energy consumption uniquely influenced EBal in either group.

In our multivariate regression models we observed again that lower RMR/kg was related to higher BMI in the control group. We also observed a relationship between more prior concussions and higher RMR/kg in the SC group. Recent studies have indicated that those with a history of concussion may have greater symptom burden following injury compared to student-athletes without a concussion history, and higher symptom burden is associated with longer recovery times.[24,25,27,28] In our study, we observed that more prior

concussions were related to greater energy expenditure in those with SC. This finding supplies evidence for a more exaggerated physiological response to a new SC injury in those with more previous concussions. At this time, it is unknown if this metabolic response represents a more serious pathophysiological consequence of injury, a protective adaptation, or some combination thereof. For example, a theoretical pathological consequence would be that prior concussion(s) have uncoupled glial cells from the neurovascular junctions and synaptic clefts where they are responsible for the transport of metabolites and neurotransmitters.[9] Inversely, perhaps the elevated metabolic response to a new insult is in fact a more efficient response enabled through prior experience with the altered neurochemical environment.[39] Future studies should seek to identify whether or not this elevated metabolic rate is a deleterious or facilitative type of response to SC.

Energy balance was calculated using self-reported dietary intake and we did not observe and statistically significant relationships with any of our clinical predictors in the control group. In participants with SC we observed strong combined influences of age, BMI, concussion history, total symptom severity and total symptom duration on EBal. This model was able to explain approximately 54% of the variance associated with EBal. Specifically, older age, higher BMI, greater concussion history, and greater acute symptom severity reduced EBal in the SC participants. Although the reasons for these influences are yet to be determined, prior studies have indicated that younger athletes and those with higher symptom burden may take longer to recover from SC. This suggests that

a positive EBal (overconsumption of energy) may be related to shorter time to clinical recovery if our observed relationships are true.[24,27,28] This particular theory was not assessed in the current study, and future research should investigate the potential for beneficial effects of a hypercaloric diet on recovery following SC.

With regard to self-reported symptoms, duration refers to the length of time over the previous 24 hours that each specific symptom was experienced. A significant positive correlation was observed between total symptom duration and total symptom severity. However, SC participant symptom duration and severity were observed to have an inverse significant relationship in terms of EBal. The most frequently reported symptoms were primarily in the somatic (i.e. headache, fatigue, drowsiness) and neurocognitive (i.e. feeling “in a fog”, difficulty concentrating) domains. These symptoms were reported for longer durations than many other symptoms, but may not likely affect appetite. Interpreted as such, the relationship with increased EBal could stem from the reduction of physical activity and not energy consumption, thus resulting in a caloric surplus as opposed to being the consequence of total symptom severity. Though not specifically assessed in this study, higher symptom severities, specific to other symptom constructs, could affect appetite and thus may reduce energy consumption. The relationship of specific symptoms and their respective domains on energy consumption and energy expenditure following SC warrants investigation.

Our study is not without limitations. The measurement of physical activity may have been under- or over-estimated. Many athletes did not wear the Fitbits during their normal athletic activities (i.e. lacrosse games) and the exact amount of energy expended during each of these sporting activities was not determined. However, we incorporated participant-reported activities into our estimates of total energy expenditure. Energy consumption was assessed according to self-reported dietary recall. This method has risks for poor compliance, biased reporting of dietary intake, and the potential to unintentionally influence eating behavior. Especially in concussed, young individuals, the effect of the SC symptoms on subject's ability to accurately report all foods consumed may have affected our energy intake estimates. However, we did not collect any objective measures of diet, such as biomarkers of intake, and can therefore not hypothesize if individuals over- or underreported consumption and the direction or magnitude of any reporting discrepancies. We encouraged all participants to report their food as accurately and consistently as possible in order to mitigate these risks.

CONCLUSION

Taken together, our study examined the relationships between clinical outcomes, metabolism, and energy consumption following SC. Concussed athletes self-reported consumption of a hypercaloric diet acutely following injury relative to their activity levels. We found that increased consumption of calories was related to age, concussion history, body composition and acute symptom burden. Our results suggest that there may be a meaningful clinical relationship

between energy consumption and symptomology acutely following SC. Additionally, we found that self-reported prior history of concussion was related to an elevated metabolic rate in participants with SC. These data imply that dietary intervention acutely following SC may help improve clinical outcomes.

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TABLES

Table 1. Demographics and Self-Reported Symptoms. Means ± standard deviations are presented for age, height, and mass. Medians and full ranges are presented for the remaining variables. Only 27 concussed participants and 26 control participants completed the HISR. *Collegiate participants as compared to high school participants. †Symptoms outcomes were significantly different between groups (Mann-Whitney *U*; $p < 0.001$). There were no other between group differences.

	Concussed ***n* = 28**	**Control** ***n* = 28**
Sex (Females: n, %)	14, 50%	14, 50%
Collegiate* (vs. High School n, %)	20, 71.4%	20, 71.4%
Age (years)	18.4 ± 1.83	19.4 ± 2.90
Height (meters)	1.76 ± 0.102	1.76 ± 0.084
Mass (kilograms)	75.6 ± 20.97	77.5 ± 21.18
Body Mass Index	22.7, 20.3-37.2	24.7, 18.8-36.9
Concussion History	1, 0-6	0, 0-3
Total Symptoms	8† (3-20)	0 (0-7)
Total Symptom Duration	22† (3-73)	0 (0-14)
Total Symptom Severity	19† (3-55)	0 (0-13)

Table 2. Energy Expenditure and Energy Consumption. All values are mean ± standard deviation. Values were normalized by dividing raw measures by participant body mass. RMR = Resting Metabolic Rate, TEE = Total Energy Expenditure, EC = Energy Consumption, Energy Balance = EC/TEE. *Concussed group significantly lower than controls ($p \leq 0.022$). ^Concussed group significantly higher than controls ($p = 0.009$).

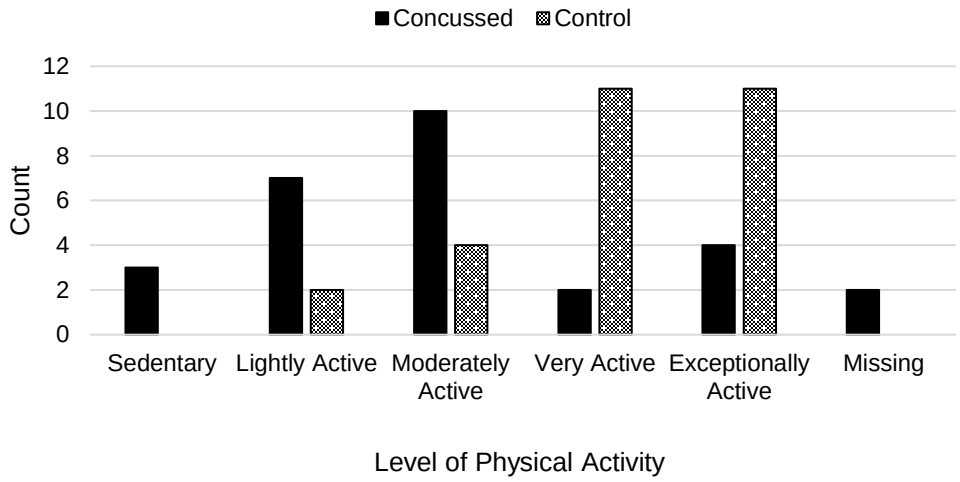
Outcome	Concussed ***n* = 28**	Control ***n* = 28**
RMR *(kilocalories per day)*	1076.6 ± 306.09	1141.8 ± 262.48
Normalized RMR *(kilocalories per kilogram per day)*	14.3 ± 2.11	14.9 ± 2.03
TEE *(kilocalories per day)*	1683.1 ± 652.06*	2087.4 ± 617.83
Normalized TEE *(kilocalories per kilogram per day)*	21.9 ± 4.72*	27.2 ± 5.69
EC *(kilocalories per day)*	2069.1 ± 693.68	2121.9 ± 810.36
Normalized EC *(kilocalories per kilogram per day)*	28.2 ± 8.38	27.3 ± 6.62
Energy Balance *(ratio)*	1.33 ± 0.42^	1.05 ± 0.35

Table 3. Regression Model for Energy Balance. Adjusted R^2 = 0.541, *p* = 0.001.

Predictor	Unstandardized Beta	Standardized Beta
Constant = 2.978		
Age	-0.077	-0.348
Concussion History	-0.132	-0.349
Body Mass Index	-0.032	-0.322
Total Symptom Severity	-0.057	-1.591
Square Root of Total Symptom Duration	0.542	1.500

FIGURES

Figure 1. Physical Activity in Acutely Concussed (≤ 72 hours after injury) and Matched Control Participants. Physical activity in the Concussed group was significantly less than in the Control group ($\chi^2_{(5)} = 19.847$, $p = 0.001$).



SECTION II: MANUSCRIPT III

HEALTH-RELATED QUALITY OF LIFE AND WHOLE-BODY METABOLIC CHANGES THROUGHOUT RECOVERY FROM SPORT CONCUSSION

ABSTRACT

Context: The neuropathological consequences of sport concussion (SC) are understood in part by alterations to intracranial as well as whole-body metabolism. However, the impact that alterations in metabolism have on mood, behavior, and socio-environmental factors is unknown. The purpose of this study was to measure these factors in individuals throughout recovery from SC and comparted to matched-controls in effort to improve clinical care related to altered physiology.

Methods: Twenty collegiate athletes with SC (19.3±1.08 years old, 1.77±0.11 meters, 79.6±23.37 kg, 55% female) were matched with 20 controls (20.8±2.17 years old, 1.77±0.10 meters, 81.9±23.45 kg, 55% female) in this longitudinal case-control study. Resting metabolic rate (RMR) was assessed with indirect calorimetry and normalized to body mass (RMR/kg), percent carbohydrate use (%CHO), and energy balance (EBal; the ratio between total caloric consumption and total expenditure) were collected at 3 time points: T_1 was within 72 hours of SC, T_2 was 7 days after T_1, and T_F was after symptom resolution. Additionally, self-reported symptoms, and healthy-related quality of life (HRQOL) measures of sleep disturbance, fatigue, anxiety, resilience, stigma and appetite were self-reported during these same visits. Changes in HRQOL outcomes between T_1 and T_F were assessed for group differences and for group by sex interactions across time via repeated measures ANOVAs with partial-eta-squared (η^2_p) effect sizes, post-hoc Tukey's HSD tests (between group differences) and paired-sample *t*-tests (changes over time) with Cohen's *d* effect sizes. Multiple linear

least-squares regressions for HRQOL outcomes that significantly changed over time in the SC group only were performed with three initial models: 1) sex and concussion history; 2) changes in symptom outcomes over time; and 3) changes in RMR/kg, %CHO, and EBal over time. When predictors from separate models were significant, they were combined into a single post-hoc model to determine the added value of each component.

Results: In SC participants, sleep disturbance ($F_{(2)}$=5.269; p=0.008; η^2_p=0.149), fatigue ($F_{(2)}$=3.464; p=0.038; η^2_p=0.110), and stigma ($F_{(2)}$=3.683; p=0.031; η^2_p=0.116) improved throughout recovery. The SC group had significantly greater sleep disturbance than controls at T_1 (p=0.001; d=1.21), and endorsed greater perceived stigma at all assessment time points ($p \leq 0.31$; $d \geq 0.80$). Change in symptom duration was related to the reduction in fatigue over time (R^2=0.347; standardized β=-0.589). Male sex (R^2=0.263; standardized β=-0.513), change in symptom severity (R^2=0.276; standardized β=-0.525), and change in EBal (R^2=0.374; standardized β=-0.611) were all individually related to the change in stigma. No predictor was associated with change in sleep disturbance over time.

Conclusions: Relative to controls, sleep disturbance and fatigue were worse in injured participants acutely following SC, but improved over time. Stigma is a potential predictor for clinical recovery from SC, especially regarding its relationship with EBal.

INTRODUCTION

A sport concussion (SC) is a mild traumatic brain injury (TBI) defined by its neuropathological effects on the brain subsequent to physical trauma.[1] These effects involve a neurometabolic cascade that manifests as a clinical syndrome unique to each individual including concussion-related signs and symptoms, impaired neurocognition, motor performance, and behavioral and psychological functions.[1-5] Due to the heterogeneity in clinical presentation among those who sustain a SC, experts recommend a multidimensional assessment battery including a combination of measures to better identify the above impairments and manage injured athletes.[1,6] Unfortunately, a consensus has not been reached in terms of the most appropriate clinical measures for each of the aforementioned domains. This lack of agreement has resulted in clinical assessments of SC that consist of highly variable constellations of clinical measures.

A truly comprehensive biopsychosocial assessment of SC would entail measures of physiologic disturbance (i.e. altered blood flow, altered whole-body metabolism), neuropsychological and behavior changes (i.e. worse memory, sleep disturbance), and psychological factors (i.e. resilience).[5] The research techniques utilized in studies to assess intracranial physiology after SC are pre-clinical, cost-prohibitive, and lack sufficient evidence to support their clinical use at this time. However, findings from these studies provide context for the other aforementioned domains of measurement in the biopsychosocial model. Intracranial physiological disturbance following SC has been associated with concussion-related symptoms and mood disturbance. Additionally, physiological disturbances such as reduced cerebral blood flow may persist beyond an

athlete's return to "pre-injury" values on current clinical measures of SC and subsequent unrestricted return to sport.[7] Furthermore, it is unknown whether these changes are indicative of a pathological process, an adaptive response to injury, or myriad other factors (i.e. anxiety and/or depression).[8]

Similar to intracranial metabolic changes, a whole-body physiologic disturbance after moderate and severe TBI has been demonstrated using resting metabolic rate (RMR) throughout recovery.[9-11] RMR is the amount of energy needed to sustain life in an awake but resting state.[12] Evidence is mixed regarding alterations in RMR in recent studies of SC in collegiate and high school student-athletes, yet energy consumption has been reported to exceed total energy expenditure in these individuals.[13,14] The ratio of energy consumption through dietary intake to the total amount of energy expenditure is known as "energy balance" (EBal).[13,14] These data regarding RMR and EBal indicate that measurement of whole-body metabolism and diet may add clinical value to the assessment of patients with SC.

Neuropsychological, mood, and behavior changes following SC are more well-known.[1] As such, neuropsychological assessments are a mainstay in the clinical assessment of SC and their use has been widely recommended.[1,15] Additionally, mood and behavioral disturbances following mild TBI and specifically in SC have garnered increasing attention in recent years.[16-22] Perceived social roles and support structures are measures of environmental factors that may influence recovery from SC, but this line of inquiry is only just beginning.[16] Whole-body metabolism, diet, mood, behavior, and social

environments may be interrelated and it would be conceivable that impairment in one domain could influence one or more other domains. These relationships warrant investigations following SC as they may present clinicians with meaningful routes for intervention.

There is divergent evidence of sex differences regarding the physiologic disturbances and clinical recovery periods following SC.[23] Simultaneously, the National Institute of Mental Health indicates higher prevalence rates of pre-injury mood disorders in females, and studies have shown that males may be less likely to report their concussion-related symptoms than females due to their perceived impact on teammates and coaches.[24,25] These observations indicate that sociobehavioral factors differ between sexes even in the absence of injury which may influence clinical recovery times following SC. Thus, the current study was designed to gather a better understanding of the holistic individual responses to SC through measurements of whole-body metabolism, diet, mood, behavior, and social environments.

In the current study, we investigated health-related quality of life (HRQOL) measures of sleep disturbance, fatigue, anxiety, resilience, stigma and appetite following SC as well as their relationships with whole-body energy-related outcomes. These energetic outcomes included RMR, carbohydrate metabolism as a proportion of RMR (%CHO), and EBal. In this way, we sought to explore the interplay between whole-body physiologic disturbance (RMR, %CHO, EBal, fatigue), mood and behavior changes (anxiety, and appetite), and perceptual factors (resilience and stigma) throughout recovery from SC in collegiate

students. We hypothesized that each of the included HRQOL constructs may affect metabolic disturbance and may recursively influence metabolism. Therefore, our study was observational rather than mechanistic in nature, seeking to explore rather than explain observed relationships.

METHODS

Participants

The current study was approved by the institutional review board of the University of Virginia as part of a larger research protocol.[14] All participants provided informed consent prior to their participation in the study. Students between 18 to 29 years of age were recruited from the University's Division I collegiate athletes as well as recreationally active undergraduate students enrolled in courses instructed within the Department of Kinesiology. For participants diagnosed with SC, referral was made by their certified athletic trainer. Athletes were diagnosed with SC based on the most recent definition from the Concussion in Sport Group at the time of injury.[1,26] Concussed participants reported to our research laboratory for their initial assessment within 72 hours of their diagnosed injury. Control participants were matched to a specific concussed participant according to sex, reported age, measured height and weight, and according to their sport/habitual physical activity (i.e. varsity athletic team). Participants were excluded if they were receiving treatment for an acute musculoskeletal issue (i.e. fracture), had diagnosis of any pathology known

to affect metabolism (i.e. thyroid dysfunction), or if they had sustained a SC less than six months prior to their first assessment.

Outcome Measures

Resting Metabolic Rate (RMR; kcal/day) was measured through indirect calorimetry and was normalized to body mass (RMR/kg) to allow for comparisons between sexes that were not biased by total body mass. Respiratory Exchange Ratio (RER) (i.e. the volume of expired carbon dioxide in relation to the inspired volume of oxygen) was used to approximate the type of fuels being used by the body.[12] Carbohydrate utilization (%CHO) was also calculated based on RER using the following equation[27]:

$$\%CHO = [(RER - 0.71) \div 0.29] \times 100$$

The remaining proportion of RMR not represented by %CHO would consist of other fuel sources such as lactate or ketone bodies. Total daily energy expenditure (TEE; kcal/day) was calculated by multiplying RMR by an analogous physical activity level correction factor which was both activity level- and sex-specific as has been described previously.[14] Energy consumption (EC; kcal/day) was estimated as the three day average number of calories consumed by the participant, including the day of each assessment and the following two days. Energy balance (EBal) was calculated as the ratio between EC and TEE (EC/TEE). A value greater than 1.0 indicated that the participant consumed more energy than they expended, and a value less than 1.0 indicated a negative caloric balance. For concussed participants, days to reporting symptom free and

days to full return to sport were determined through medical record review or through direct communication with the appropriate athletic trainer (student-athletes), or by self-report (for one recreational athlete).

Each of the HRQOL outcomes scales consisted of individual items which were endorsed on 5-point Likert scales. The fatigue and anxiety scales each consisted of 10 items with a possible range of scores from 10 to 50, where a greater score indicated a greater level of fatigue or anxiety, respectively.[28] The sleep disturbance scale consisted of eight items with a possible range of scores from 10 to 40, where a greater score indicated a greater level of sleep disturbance.[29] Similarly, the stigma scale contained seven items, with a possible range of 10 to 35, where a greater score indicated that the participant perceived that others treated them differently as a result of their injury.[28] Resilience was also measured on a 10-item scale with scores ranging from 10 to 50 where higher scores indicated a greater ability to overcome their injury, and therefore a better outcome.[28] To minimize subject burden, the potential effect of SC on dietary intake behavior was estimated using an “appetite” score, which combined the concepts of feelings of hunger and feelings of fullness. The two appetite-related questions were written by the current research team as, “Regarding your appetite: Which best describes how you feel at this moment?” and, “Which best describes how you feel in a typical day at this time?” The appetite outcome score was the difference between typical and current appetite such that a range of -4 to +4 was possible. A negative number indicated that the participant was feeling

less hungry than typical and a positive value that they were more hungry than typical.

Procedures

All participants completed three time points. The first time point (T_1) occurred within 72 hours of a concussed subject's diagnosis. The second time point (T_2) occurred 7 days after their initial assessment, and the third time point (T_3) took place 7 days after their second assessment. If a participant reported symptoms at T_3, they were asked to attend a fourth assessment (T_4) after reporting symptom free to their respective certified athletic trainer. Assessment time points for our analyses were T_1, T_2, and the final assessment time point (T_F). T_F was defined as the last assessment time point for each individual after reporting symptom free to their athletic trainer (T_3 for most, and T_4 for one participant). Control participants similarly participated in three time points each, separated by at least three days to avoid overlap with regard to recording dietary intake and step counts. The procedures for each assessment time point were nearly identical with the exceptions of providing informed consent and measuring height. Participants reported for T_1 between 0600 and 0900 and were instructed not to eat or drink anything but water after midnight prior to each appointment. After providing informed consent, a detailed health history form was completed which included demographic, concussion, and pertinent medical history questions. Next, participants completed the Revised Head Injury Scale (HIS-r) which is a self-reported symptom inventory.[30] To complete the HIS-r, participants indicated which concussion-related symptoms they had experienced during the

past 24 hours. For those items endorsed, participants then ranked each item on a Likert scale of duration (brief “1” to constant “6”) and severity (not severe “0” and most severe “6”) during the last 24 hours. After the completion of all inventories, each participant’s height, weight, and body composition were measured.

Participants were then instructed to lay supine, resting on a treatment table for 20 to 30 minutes. A clear plastic canopy was placed over their head which was connected to a VMax® Encore metabolic cart (Carefusion, Yorba Linda, CA) in order to capture and monitor the exchange of oxygen and carbon dioxide gases (indirect calorimetry).[12] The VMax® Metabolic Cart is a valid measure of RMR when compared to an industry standard (no significant differences in measured RMR values between devices) and has shown small intra-subject changes in day-to day measurement (coefficient of variation = 8.4%), indicating that it is also a reliable assessment of RMR.[31]

Following indirect calorimetry, participants were given a Fitbit Charge HR or Charge 2 (Fitbit, Inc., San Francisco, CA). Participants were asked to record step count for the day of assessment and the two days following the assessment. The Fitbit Charge wristband has been shown to have good evidence of validity when compared to a handheld step counter (Intraclass Correlation Coefficients [95% confidence interval] as high as 0.74 [0.54,0.87]) and reliability (Intraclass Correlation Coefficients [95% confidence intervals] $\geq$ 0.70 [0.46, 0.86]) in the measurement of walking steps.[32] Participants manually reported the number of steps they took each day as well as the duration and type of physical activity in

which they were not able to wear the Fitbit (e.g., practices or competitions). Participants were provided instructions to complete a dietary recall journal by recording all food and beverage intake for the day of assessment and the subsequent two days. Participant-reported dietary intake was entered into the MyFitnessPal (MyFitnessPal, Inc., Baltimore, MD) online portal by the study team. MyFitnessPal has is similar to traditional standardized paper-based dietary recall with regard to overall caloric intake ($p > 0.61$) and individual macronutrient caloric intake ($p < 0.05$, mean differences < 26 calories).[33]

Missing Data

In cases of missing RMR, EC, and %CHO data, imputations were made by calculating person-specific values based on the group average change values between time points. For example: after EC was normalized to body mass, the group average difference between assessment time points (i.e. -5.01 kcal/day/kg in concussed males between T_2 and T_F) would be multiplied by that participant's most recently measured body mass and then added to the most recently measured RMR value in the following equation:

$$Group\ Average\ Change(RMR\ per\ kg) \times Last\ Measured\ Mass + Last\ Measured\ RMR = Participant's\ Estimated\ RMR$$

TEE and EBal were calculated for these individuals using the imputed RMR and EC values. When physical activity was missing, the median group correction factor was used in the calculation of TEE. Missing HRQOL scores were not imputed.

Analyses

To assess the changes over time in HRQOL outcomes for concussed males and females compared to their healthy matched controls, we performed six separate group (concussed, control) by sex (male, female) by time (T_1, T_2, T_F) repeated measures analyses of variance (ANOVAs) with partial eta-squared (η^2_p) effect sizes. We computed post-hoc one-way ANOVAs with Tukey's HSD assessments and Cohen's *d* effect sizes when there were significant differences between groups or for interactions between group and sex. We also utilized post-hoc paired samples *t*-tests with Cohen's *d* effect sizes for changes over time. Next, we performed three separate multiple linear least-squares regressions for HRQOL outcomes which significantly changed over time. The first model included sex and concussion history as predictors, the second model included the changes in total symptom severity and duration from T_1 to T_F as well as days to reporting symptom free, and the final model included the changes in RMR, RER, and EBal from T_1 to T_F.). Lastly, significant individual predictors in each of the clinical and metabolic models were then combined into a final mixed outcomes model to determine if clinical and metabolic measures uniquely predicted changes in HRQOL throughout recovery from SC.

Anxiety outcome scores violated Mauchly's Test of Sphericity (W = 0.777; p = 0.026) and therefore we used the Greenhouse-Geisser statistic to evaluate these scores over time. The square root of stigma change (Shapiro-Wilk = 0.889;

p = 0.095) was used in our regression analyses as the raw change in stigma scores was not normally distributed (Shapiro-Wilk = 0.835; p = 0.018). Symptom severity, duration, and days to symptom-free were non-normally distributed (significant Shapiro-Wilk with $p < 0.05$) and were therefore transformed into the normalized variables of the square root of symptom severity change, the cubed root of symptom duration change, and the natural log of days to symptom free as these were deemed to be normal (non-significant Shapiro-Wilk with $p > 0.05$. All analyses were performed in SPSS version 25 (Armonk, NY) with statistical significance set a priori with $\alpha \leq 0.05$.

RESULTS

A total of 20 participants with SC (9 males and 11 females) and 20 control participants (9 males and 11 females) were included in this study (Table 1). One male concussed participant completed the first two assessments and declined to participate in the third assessment. RMR, EC, and %CHO data were imputed for this participant's final time point. Similarly, one male control participant was only able to complete two assessments because he sustained a foot fracture and his T_F outcomes were similarly imputed. Interestingly, three males reported symptoms at T_3 in the SC group, one returned for a fourth assessment, and two never returned to sport participation. Only one of those who did not return for a fourth assessment reported symptom-free, and the third assessment time point for each of these individuals was included in the T_F analyses. All female

participants in the SC group returned to play, but the date of return to full participation was missing for two participants and the date to reporting symptom free was missing for one participant.

Participants with SC reported for their first visit (mean ± standard deviation) 2.1 ± 0.83 days after their injury. Overall, these participants reported symptom free (median [interquartile range]) 6 [4-10] days after their injury and returned to full participation 14 [10-16] days following their injury. More specifically, females reported symptom free 6 [4-9] days while males reported symptom free 10 [5-15] days following their injury. A similar pattern was observed regarding return to full participation, where females (11 days [8.75-14.25 days]) returned quicker than males (16 days [13-25 days]).

Sleep Disturbance

Sleep disturbance decreased over time only in participants with SC ($F_{(2)}$ = 5.269; p = 0.008; η^2_p = 0.149; Figure 1 In this group, sleep disturbance was improved over time from T_1 to T_2 (p < 0.001; d = 0.95 [0.19-1.70]) and from T_1 to T_F (p < 0.001; d = 1.60 [0.78-2.43]). The change from T_2 to T_F was not statistically significant, but the effect size was moderate (p = 0.074; d = 0.52 [-0.20-1.25]). Additionally, the SC group had significantly greater sleep disturbance than controls at T_1 (p = 0.001; d = 1.21 [0.47-1.94]), but not at the remaining two assessment time points (p > 0.180; Table 3). There were no significant relationships identified with any of the predictor variables in the regression models.

Fatigue

Fatigue decreased over time only in participants with SC ($F_{(2)}$ = 3.464; p = 0.038; η^2_p = 0.110; Figure 1). In this group, there was significant improvement in fatigue between T_1 and T_F (p = 0.019; d = 0.94 [0.15-1.74]). The improvements between T_1 and T_2 (p = 0.082; d = 0.59 [-.19-1.36]) and between T_2 and T_F were not statistically significant (p = 0.055; d = 0.35[-0.42-1.13]). There were no significant differences between groups, between sexes, or for the interaction between group and sex (p > 0.05; Table 3). There were no significant relationships between the change in fatigue over time and sex, concussion history, symptom severity, days to symptom free, metabolic rate, carbohydrate utilization, or EBal. Greater symptom duration change was related to the reduction in fatigue over time (R^2 = 0.347; standardized β for the cubed root of symptom duration change = -0.589).

Anxiety

Anxiety improved over time in both groups ($F_{(1.635)}$ = 7.428; p = 0.003; η^2_p = 0.198), but there was no difference between groups, between sexes, or for the interaction between group and sex (p > 0.05; Table 3). Change over time was not unique to the SC group and therefore we did not further assess relationships with potential predictors using the regression models.

Resilience

Resilience improved over time in all participants ($F_{(2)}$ = 5.558; p = 0.006; η^2_p = 0.156), but there was no difference between groups, between sexes, or for the interaction between group and sex (p > 0.05; Table 3). Like anxiety, the improvement over time was observed in both groups and subsequent analyses were not performed.

Stigma

We observed group differences ($F_{(2)}$ = 3.683; p = 0.031; η^2_p = 0.116) across time with regard to perceived stigma (Figure 2). Stigma was not improved in the SC group between T_1 and T_2 (p = 0.395; d = 0.17 [-0.57-0.92]), but showed significant improvement from T_2 to T_F (p = 0.032; d = 0.57 [-0.18-1.33]) and from T_1 to T_F (p = 0.010; d = 0.84 [.07-1.62]). Those with SC endorsed greater perceived stigma at all assessment time points ($p \leq 0.031$; $d \geq 0.80$; Table 3).

Each of the three regression analyses revealed one significant relationship with stigma: a) male sex (R^2 = 0.263; standardized β = -0.513), b) change in symptom severity (R^2 = 0.276; standardized β for the square root of symptom severity change = -0.525), and c) change in EBal (R^2 = 0.374; standardized β = -0.611). There were no observed relationships with concussion history, symptom duration, days to symptom free, metabolic rate, or carbohydrate utilization. When sex, change in symptom severity and change in EBal were entered into a single combined backwards regression model, only change in EBal was maintained as a predictor (R^2 = 0.374; standardized β = -0.611).

Appetite

Based on the limited data we collected, there were no statistically significant changes in appetite over time, nor did we observe differences between groups, between sexes, or in the group by sex interaction (Table 3). In the SC group, 44% (7/16) of the participants and 30% (6/20) of the control participants endorsed differences between their “typical” appetite and the appetite they had in the moment they were attending their first visit. At T_2, 63% (10/16) of the SC participants and 20% (4/20) of the control participants endorsed differences in appetite, and 25% (4/16) of SC participants and 40% (8/19) of control participants endorsed differences in appetite in their final visit.

DISCUSSION

In this study, we sought to explore the relationships between measures of HRQOL and SC in collegiate athletes. We anticipated that each of our chosen self-reported measures would show changes over time in participants with SC, but not in our matched controls. This pattern was true for sleep disturbance, fatigue, and stigma, and resilience and anxiety improved over time in both groups. As these symptoms associated with SC may affect an individual’s memory and ability to focus, a short and crude measure for “Appetite” was developed. Based on these short-term self-reported data, athlete’s perception of typical feelings of hunger or fullness did not significantly change over time and were not statistically different between groups. Moreover, we expected to see significant differences between sexes in many of our outcomes, which was not

the case for any of our HRQOL outcomes. It should be noted, however, that resilience appeared to be slightly higher in concussed females compared to concussed males throughout recovery, although not statistically significant. This is interesting in large part because these females reported symptom free approximately 4 days earlier and returned to play on average 5 days sooner than their male counterparts.

We observed sleep disturbance and fatigue differences between groups and changes across time in the SC group. While sleep was unrelated to any of the clinical or energetic predictor variables assessed in this study, the change in fatigue over time was related to a reduction in total symptom duration. We cannot conclude from our current data whether symptom relief preceded improvements in fatigue, or vice versa. Our findings regarding sleep and fatigue are similar to previous work in SC. Hoffman et al. reported that collegiate athletes with acute SC who slept fewer hours at night than they had before their pre-injury baseline testing session reported greater acute symptom burdens, though this sleep pattern was not related to length of recovery.[18] Similarly, a recent study by Howell et al. indicated that adolescent athletes who self-reported trouble falling asleep also had greater symptom burden within the first week following SC.[19] A recent matched-control study by Hoffman et al. integrated self-reported sleep quality indices with sleep quality measured by actigraphy.[17] Our findings were similar to their study in that sleep was most disturbed 2-3 days after sustaining a SC.[17]

Resilience and stigma are psychological factors that are not commonly assessed in SC literatureas compared with military and general population base studies related to recovery from injury or illness.[20,21,34] Resilience has been operationally defined as, “the sum total of psychological processes that permit individuals to maintain or return to previous levels of well-being and functioning in response to adversity.”[35] Resilience has shown positive association with neurobehavioral and symptom outcomes in former military service members with mild TBI.[21] In our study, self-reported resilience improved over time in both the SC and control groups. When mirrored with perceived stigma in the SC group (Figure 2), it appeared as though the internal ability to overcome (resilience) related to external sources of social pressures (stigma).

The construct of stigma measured in this study most readily relates “self-stigma”, which is the internalization of perceived stereotyping, prejudice, and discrimination from others as a result of injury or illness.[36] A qualitative study in ice hockey players revealed that there was a “cultural” stigma surrounding mental illness and concussion that labeled these issues as signs of weakness.[20] In a separate study of 85 community members with a history of TBI, stigma was a significant predictor of social anxiety.[34] Social anxiety was not measured in our current study, but may preclude typical social integration and support, which are factors linked to HRQOL outcomes after mild TBI.[16,22] In our study, we observed that elevated self-reported stigma was associated with the diagnosis of SC, and that this stigma was not significantly reduced until the majority of participants had returned to full participation in sport at T_F. The reduction in stigma over time also

related to the reduction in EBal, where participants with SC moved from consuming more than they were expending at T_1 to an isocaloric state at T_F (these data in this exact sample were previously published in a related paper).[14] There is no direct physiologic explanation for the relationships between EBal and stigma that we are aware of at this time, but we speculate these two factors each most likely relate directly to clinical recovery.

Finally, we observed no statistical differences between groups or over time with regard to self-reported appetite. We defined an atypical appetite as any discrepancy between current and typical appetite as endorsed by a participant during a given assessment time point. We found that the proportion of concussed participants who endorsed an atypical appetite during the first two assessments was higher than in control participants. Estimated EBal has been reported as an energy surplus at in the acute phase of SC, indicating that concussed participants consume more calories through their diet than they expend through daily activities.[14] Potential reasons for this could be reduced physical activity levels, autonomic dysregulation via the vagus nerve (cranial nerve X), or improper signaling from the hunger and satiety regulating hormones leptin and ghrelin.[14,37-39] The relationships between appetite, dysregulation of neuroendocrine function, and dietary intake following SC have not been investigated. Future studies should seek to determine the efficacy of dietary intervention for mild TBI and SC as there may be potential for clinical intervention following injury.[40,41]

Our study has several limitations. First, all measures were self-reported and no objective assessments of the validity or reliability of the information provided by participants were performed. The Neuro-QoL (sleep disturbance) and TBI-QOL (fatigue, anxiety, resilience, and stigma) measures used for this study are part of the National Institutes of Health Toolbox for neurologic conditions and TBI, but have not yet been validated in the setting of acute SC. The appetite measure utilized in our study was designed to mimic the five-point Likert-scale structure of the Neuro-QoL and TBI-QoL measures, but has not been previously validated. Additionally, reporting biases and inconsistencies could have influenced both physical activity and energy consumption behaviors, which are integral to the computation of EBal. It is somewhat likely that the very symptoms the subjects reported for the HRQOL outcome also affected their ability to accurately report their feelings of both current and typical hunger and fullness. We gave every participant verbal and written instructions to complete each outcome measure and one investigator was appointed as a contact for any questions or concerns from the participants regarding all aspects of the study. Each outcome was optional for study participants and some did not to complete certain questionnaires throughout their involvement. As a result, some HRQOL and energetic data were missing.

CONCLUSION

In conclusion, our findings that sleep disturbance and fatigue were greater in concussed participants and that they improved throughout the course of recovery are in line with the nascent body of research in this area. Our

investigations into self-reported measure stigma shows a promising trend in its relationship with clinical recovery as this construct is an area that can be addressed by healthcare providers in the setting of SC. Both appetite and the relationship between energy intake and output represent a new line of inquiry in the realm of SC, where dietary behavior coupled with physical activity may be a novel approach to augment recovery. In sum, our study, though limited by the reliability of self-reported measures, offers new insights for the management of SC. Our findings corroborate previous research findings and raise important novel questions for future investigations into the perceptual, behavioral, and energetic responses to SC.

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TABLES

Table 1. Demographic Information. Means ± standard deviations are presented for age, height, and mass. Medians and ranges are presented for the remaining demographic variables.

	Concussed Females (n = 11)	Concussed Males (n = 9)	All Concussed (n = 20)	Control Females (n = 11)	Control Males (n = 9)	All Controls (n = 20)
Age	19.0 ± 1.10	19.7 ± 1.00	19.3 ± 1.08	19.9 ± 1.30	21.8 ± 2.64	20.8 ± 2.17
Height	1.70 ± 0.096	1.85 ± 0.076	1.77 ± 0.112	1.72 ± 0.083	1.82 ± 0.083	1.77 ± 0.096
Weight	65.7 ± 10.21	96.5 ± 24.13	79.6 ± 23.37	69.1 ± 9.69	97.6 ± 26.14	81.9 ± 23.45
BMI	22.5 ± 1.66	28.0 ± 5.20	25.0 ± 4.55	23.3 ± 1.98	29.1 ± 5.93	25.9 ± 5.07
Concussion History	1, 0-3	1, 0-6	1, 0-6	0, 0-3	0, 0-2	0, 0-3
Days to Reporting Symptom Free	6, 3-10	10, 4-29	6, 3-29	-	-	-
Days to Full Return to Play	11, 7-16	16, 10-42	14, 7-42	-	-	-

Table 2. Changes in Energetic Measures between the First and Last Assessments in Participants with Sport Concussion. Resting Metabolic Rate is presented in units of kilocalories expended per day per kilogram of body mass. Proportion of carbohydrate use is a percentage of total resting metabolic rate. Energy balance is the ratio of total energy consumption to total energy expenditure per day.

	Change Score (Mean ± Standard Deviation)		
	Resting Metabolic Rate	Proportion of Carbohydrate Use	Energy Balance
All Concussed Participants	0.19 ± 1.37	4.18 ± 21.22	-0.30 ± 0.349
Concussed Males	0.20 ± 1.54	10.41 ± 15.42	-0.35 ± 0.368
Concussed Females	0.18 ± 1.29	-0.91 ± 24.54	-0.26 ± 0.347

Table 3. Health-Related Quality of Life over Time. Values represent the raw scores for each outcome measure. T_1 – First assessment time point; T_2 – Second assessment time point; T_F – Final assessment time point.

Health-Related Quality of Life Outcome Measure		Assessment Time Point T_1	T_2	T_F
Sleep Disturbance	Concussed	17.5 [12.5-21.5]	12.5 [9.3-16.8]	10 [8-14]
Median [Interquartile Range]	Concussed Males	19 [15.5-22.8]	11 [8-22]	10.5 [7.8-20.3]
	Concussed Females	17 [15-19]	13 [10.5-15.5]	10 [8-13]
	Control	13 [12-17.5]	12 [10-14]	11 [10-13]
	Control Males	15 [12.5-18]	12 [10-14]	11 [9.3-14.8]
	Control Females	13 [11-14]	12 [10-15]	11 [10-13]
Fatigue	Concussed	22 [19-28]	19 [11.5-23.5]	13 [10-20]
Median [Interquartile Range]	Concussed Males	23.5 [19.8-34]	19 [12.5-33]	12 [10-30.3]
	Concussed Females	21 [18-26]	19 [11-22]	13 [10-18.5]
	Control	14 [12-18]	13 [11-15]	13 [11-15]
	Control Males	16 [13.5-19.5]	14 [12-16]	13 [10.3-15]
	Control Females	13 [12-15]	12 [14-16]	13 [12-18]
Anxiety	Concussed	14.5 [11.5-23]	11.5 [10-17.8]	10 [11-13]
Median [Interquartile Range]	Concussed Males	14 [13-20]	11 [10-21]	10 [10-12.5]
	Concussed Females	15 [10.5-25]	12 [10-17.5]	11 [10-14.5]

	Control	13 [11-16.5]	11.5 [10-14]	11 [10-13]
	Control Males	13 [11-16]	12 [10-13.5]	11 [10-13.5]
	Control Females	13 [11-17]	12 [14-16]	13 [12-18]
Resilience **Median [Interquartile Range]**	Concussed	36 [31.5-43]	39.5 [35-42.8]	44 [38-48]
	Concussed Males	34 [31-37]	36 [35-40]	39.5 [34.3-45.5]
	Concussed Females	38 [32.5-44]	42 [35.5-47]	46 [38-49]
	Control	43.5 [40.3-47.5]	42 [38.5-47.8]	48 [40-49]
	Control Males	42 [39-44]	42 [36-46.5]	46.5 [37.8-48.8]
	Control Females	44 [41-49]	43 [40-50]	49 [40-50]
Stigma **Median [Interquartile Range]**	Concussed	9 [8-12]	7 [7-12]	7 [7-10]
	Concussed Males	9 [8.5-11]	9.5 [7-12.5]	8 [7-10.5]
	Concussed Females	10 [7.5-16]	7 [7-13]	7 [7-8.5]
	Control	7 [7-7]	7 [7-7]	7 [7-7]
	Control Males	7 [7-7]	7 [7-7]	7 [7-7]
	Control Females	7 [7-7.5]	7 [7-7]	7 [7-7]
Appetite **Median [Interquartile Range]**	Concussed	0 [0-1]	.5 [0-2]	0 [0-0]
	Concussed Males	0 [0-2]	1 [0-2]	0 [-.25-.25]
	Concussed Females	0 [0-.5]	0 [-.5-1.5]	0 [0-.5]
	Control	0 [0-0]	0 [0-0]	0 [0-1]

Control Males	0 [0-0]	0 [0-0]	0 [-.5-.25]
Control Females	0 [0-1]	0 [0-0]	0 [0-1]

FIGURES

Figure 1. Sleep Disturbance and Fatigue. T1 = first assessment, T2 = second assessment, TF = final assessment. Sleep disturbance in the Sport Concussion group decreased from T1 to TF (n = 15, $p < 0.001$) and was different from Controls at T1 (Control n = 19, $p = 0.001$), Fatigue in the Sport Concussion group decreased from T1 to TF (n = 13, $p < 0.019$) but was not different from Controls (Control n = 19, $p \geq 0.05$). Error bars represent one standard deviation.

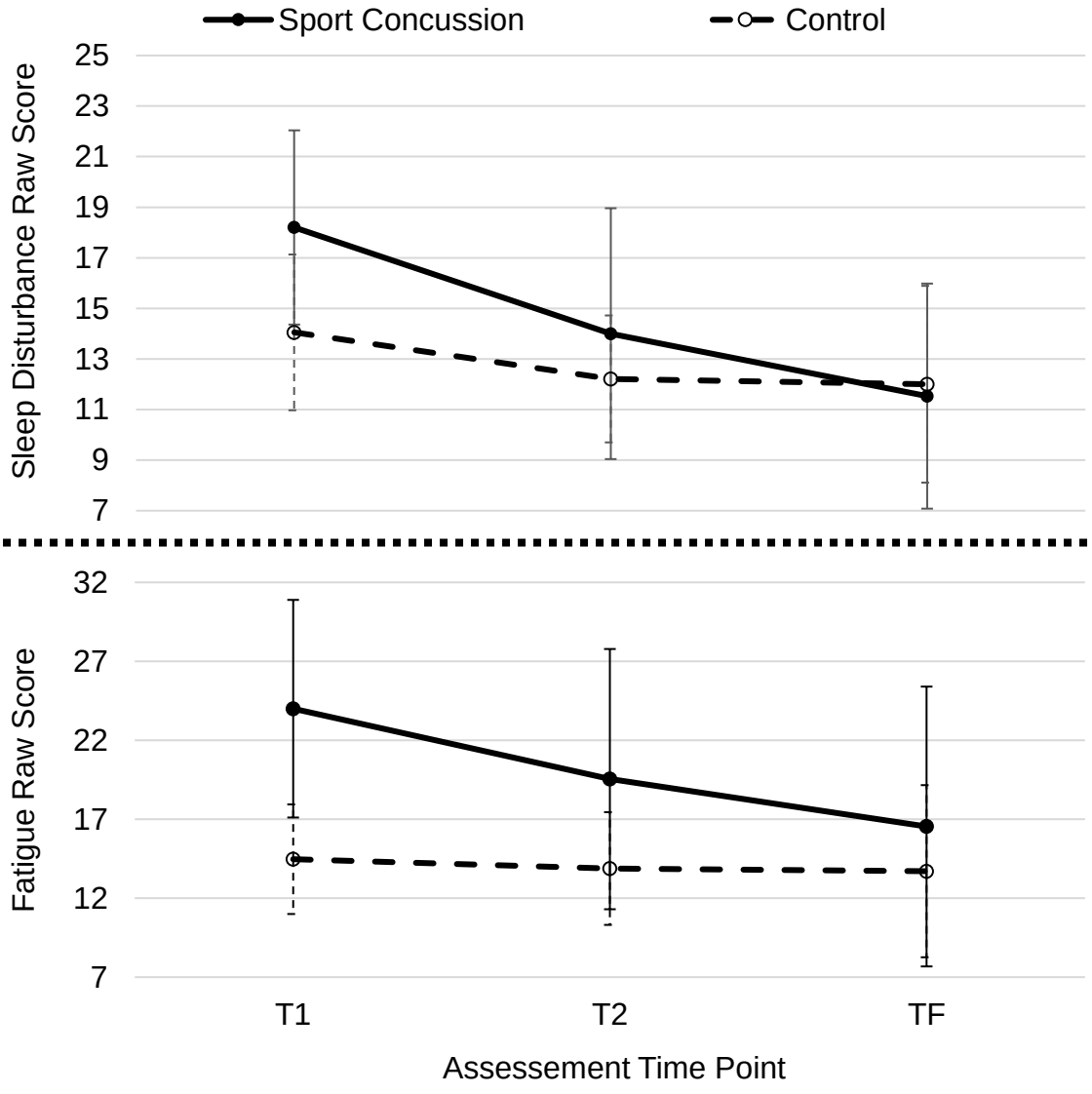
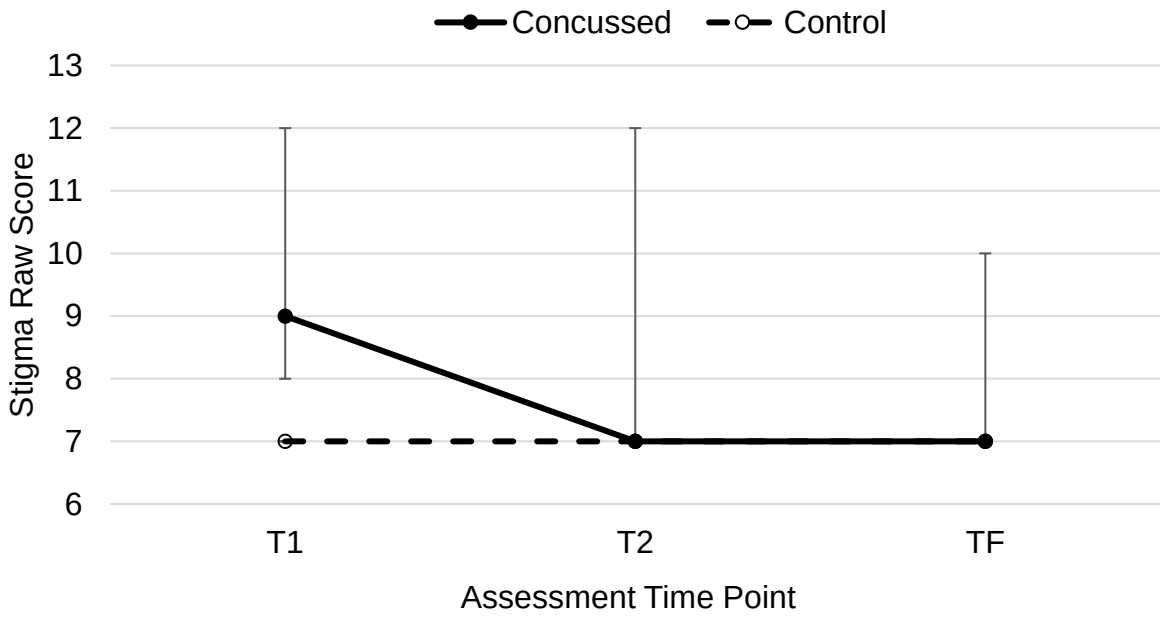


Figure 2. Stigma after Sport Concussion. Assessment time points: T1 = first assessment, T2 = second assessment, TF = final assessment. Points are median scores for each group. Error bars are the full range of scores. There were 13 Concussed participants and 19 control participants. Stigma significantly declined from T1 to T3 in the Concussed group (n = 13; p = 0.01), but not the Control group (n = 19; p > 0.05).



SECTION III: APPENDICES

APPENDIX A: THE PROBLEM

STATEMENT OF THE PROBLEM

Concussions have emerged as a major health concern for active individuals in youth, high school, collegiate, and professional sport settings.[1] Following a concussion, brain cells are vulnerable to metabolic dysfunction due to ionic shifts, altered metabolite utilization and availability, impaired connectivity and changes in neurotransmission.[2-6] In experimental animal models with moderate to severe traumatic brain injury (TBI), an immediate intracranial *hyper*metabolic state ensues that is followed by a *hypo*metabolic state. An emergent body of research has demonstrated that moderate and severe TBI may also result in a shift in whole-body metabolism. A specific measure of whole-body metabolism is resting metabolic rate (RMR), which is the base amount of energy required by the body to sustain life in an awake but rested state.[7] RMR has been reported at up to 200% of predicted values in the first days following TBI and may remain elevated for up to four weeks or more.[8] To date, there is very little

evidence regarding the full-body metabolic changes following mild TBI or concussion, and there are no studies of RMR centered in these concussed populations. Moreover, it is unknown how these changes in resting energy expenditure may relate to dietary intake, physical activity, clinical recovery, symptom burden, and health-related quality of life (HRQOL). Time to return to play, symptom burden, and HRQOL outcomes may differ between sexes and age after a concussion, but the evidence for this phenomenon remains equivocal. Thus, our data may provide unique insight into clinical management strategies for each injury and individual.

RESEARCH QUESTIONS

1. Does concussion alter energy expenditure or energy balance in physically active collegiate students as compared to healthy-matched controls?
2. Are there sex differences in the energy expenditure or energy balance responses to concussion?
3. How do energy expenditure and energy balance changes relate to clinical recovery from concussion?
4. Are acute energy expenditure and energy balance related to age, concussion history, or symptom burden following injury?

5. How are self-reported HRQOL outcomes of fatigue, sleep, anxiety, appetite, resilience, and stigma affected by concussion throughout recovery as compared to healthy-matched controls?
6. Do these HRQOL outcomes differ by sex, concussion history, or symptom burden throughout recovery?
7. How do energy expenditure, energy balance, and time to clinical recovery relate to HRQOL outcomes measured throughout recovery?

EXPERIMENTAL HYPOTHESES

1. Collegiate students diagnosed with a sport concussion will experience significantly altered RMR, substrate utilization, and dietary intake during the acute phase of recovery and throughout recovery compared to similarly matched controls.
2. The effects of sport concussion on RMR, substrate utilization, and dietary intake will be greater in females than males. Both male and female concussed participants will significantly differ from their matched controls initially, and only males will be similar to matched controls after returning to full participation in sport.
3. Participants with sport concussion exhibiting greater magnitudes of change in RMR and substrate utilization will have longer times to resolution of symptoms and return to sport participation. Greater

magnitudes of RMR and substrate utilization changes will coincide with greater initial symptom burden.

4. Energy balance, the ratio of energy consumed to energy expended, will indicate caloric deficit in concussed participants. Younger participants and those with greater symptom burden will have the greatest deficits.
5. Concussed participants will self-report greater levels of fatigue, sleep disturbance, anxiety, and stigma compared to matched controls throughout recovery, but not after reporting symptom-free.
6. Males will have lower anxiety than females. No other HRQOL outcomes will differ between sexes. Anxiety will be higher in concussed participants with greater symptom burden, and will be negatively correlated to concussion history. Those with higher symptom burden will have greater fatigue and lower resilience.
7. Higher RMR and energy consumption will relate to greater levels of anxiety, fatigue, and sleep disturbance. Acutely, greater levels of anxiety, fatigue, and sleep disturbance will relate to longer time to resolution of symptoms and time to return to play. Greater resilience and lower stigma in the acute phase will relate to quicker resolution of symptoms and time to return to play.

ASSUMPTIONS

- Clinical diagnoses of concussion will be appropriate according to the most recent guidelines established by the International Consensus on Concussion in Sport Group.[1,9]
- Concussion history will be accurately reported by each participant as it relates to total number and time since last concussion.
- Matched-control participants will accurately reflect “normal” function for each of the concussed participants.
- Participants will not consume anything but water prior to arrival for each assessment.
- Participants will accurately report their symptom burden, HRQOL experiences, and appetite, and will not withhold any information or downplay the severity of their symptoms.
- Participants will accurately report their dietary intake.
- The act of completing a food journal will not affect a participant’s eating behaviors.
- Participants will wear their Fitbits for the duration of each day they are asked to, and they will report any physical activities in which they were not able to wear the device.
- Step counts are an accurate reflection of daily physical activity.
- Physical activity modifiers accurately account for total daily caloric expenditure.

DELIMITATIONS

- Concussed participants will be assessed at pre-specified time points following injury.
- Control participants were matched to concussed participants by height, weight, age, sport (and sport position when possible) and school (e.g., high school participants).
- Participants were excluded if they had a previous concussion within the previous 6 months, had an acute illness or musculoskeletal injury, or had a medical condition such as diabetes or thyroid dysfunction that would affect metabolism.
- Participants were limited to those at the University of Virginia, or local high schools where a certified athletic trainer was present.
- A subset of participants completed a 24-hour dietary recall over the phone with the PI as a comparison for the self-reported dietary intake journal.

LIMITATIONS

- Assessment of High school control participants at only a single time point.
- High school participants did not complete HRQOL outcome assessments.
- The number of high school participants was not similar to the number of collegiate participants.

- While prospective in nature, there were no pre-injury baseline assessments of energy expenditure, physical activity, dietary intake, or the HRQOL measures for concussed participants.
- Two concussed participants withdrew from the study after they had clinically recovered and their follow-up assessments were not obtained. Two more participants completed the initial three assessments, were not recovered at the third assessment, and never completed their fourth assessment as they had not clinically recovered. These two individuals did not return to their respective sports. All four of these participants were male.
- One control participant sustained a fracture in their foot prior to their third visit, which precluded their completing that final assessment time point.
- The health-related quality of life (HRQOL) measures were optional and some participants skipped certain items or whole scales completely (intentionally or unintentionally). As a result, not all participants completed each of the measures, and a little over half of the concussed group completed each measure at all three time points.
- Step count as measured via Fitbit may not be the best predictor for total energy expenditure, as many athletes could not wear them during typical athletic activities (i.e. football practice, swimming, etc.). The actual amount of energy expended during each of these activities is unknown.
    - Moreover, step counts were measured at up to 2x the criterion value (12,500 steps) for placement the highest physical activity

group. It is feasible that larger activity modifiers would be more accurate in the assessment of physical activity for those individuals who had higher step counts.

- Body composition was only measured in a subset of the collegiate participants, and in none of the high school participants. This precluded the assessment of lean body mass as a modifier of energetic outcomes in this study.

OPERATIONAL DEFINITIONS

- Aerobic Metabolism[7]: Energy transduction dependent of the presence of oxygen.
- Anaerobic Metabolism[7]: Energy transduction that does not require oxygen.
- Concussion[1]: A complex pathophysiological process affecting the brain, induced by biomechanical forces.
- Resting Metabolic Rate[7] (RMR): Minimum amount of energy needed to sustain the vital functions of the body while aroused and at rest throughout the course of a 24-hour period. RMR is measured in kilocalories per day.
- Total Energy Expenditure[7,10] (TEE): Total amount of energy used throughout an entire 24-hour period accounting for RMR and physical activity. TEE is measured in kilocalories per day.
- Indirect Calorimetry[7]: Measurement of energy expenditure via assessment of respiratory gases (i.e. oxygen).

- Caloric Intake (CI): The amount of energy from food and beverages consumed by an individual throughout the course of a 24-hour period. CI is measured in kilocalories per day.
- Energy Balance (EBal): The difference between CI and TEE such that a positive value indicates a positive value is indicative of an energy surplus and a negative value is indicative of an energy deficit. EBal is measured in kilocalories per day.
- Health-Related Quality of Life (HRQOL): Behavioral, psychological, social, and perceptual aspects of daily life which may be affected by disease, or the lack thereof.
- Physical Activity[11,12]: Measured through self-reported steps per day (Fitbit) and sport participation or exercise in which it was not appropriate to wear the Fitbit.

SIGNIFICANCE OF THE STUDY

Currently, a multidimensional approach (i.e. neurocognitive, balance, and symptoms measures) is recommended to diagnose and manage concussion.[1,9] However, this multifaceted approach may only assess clinical rather than physiological recovery.[13] Our novel study investigated a novel approach to assess the physiologic response to concussion. The measurement of energy expenditure in this study is promising in that it is both objective and more direct than current clinical measures used in concussion management. Additionally, the

study of physiologic evidence for different recovery patterns between males and females following concussion supplies evidence to promote personalized patient care. Sex differences in recovery from concussion are widely debated, yet there is a dearth of strong empirical research evidence corroborating or refuting the pattern of females having longer recovery times than males.[14]

Our study is an important first step that will lead to future investigations into novel interventions to facilitate a more complete recovery following concussion. Knowledge of mediating demographic (age, sex, and BMI), injury-related (total symptom score, total symptom duration, total symptom severity, and previous concussion history), and HRQOL (sleep disturbance, fatigue, anxiety, resilience, stigma, and appetite) factors will help clinicians better understand who may be more susceptible to metabolic impairment in the acute phase of injury and throughout recovery. By combining each of these perspectives, we may be able to establish a holistic assessment of the biopsychosocial consequences of concussion. This knowledge will help to guide patient-specific treatments such as specific diets (i.e. ketogenic), education and counseling to improve domain-specific (i.e. sleep disturbance), as well as overall HRQOL. Our data will assist clinicians in understanding which factors may negatively affect recovery from concussion as well as potential pathways to intervene to improve patient-related outcomes.

APPENDIX B: LITERATURE REVIEW

PART I. OVERVIEW OF SPORT CONCUSSION

The clinical presentation of traumatic brain injury (TBI) incorporates a broad spectrum of injury severities which are typically classified according to the Glasgow Coma Score GCS.[15] The GCS consists of three separate scales of responsiveness including eye opening, verbal, and motor responses that generate a summary score ranging from three to 15. This GCS summary score was intended to be used as a research tool and to inform guideline development, but has also been used to classify injury severity according to the following ranges: Severe TBI being GCS scores equal to or below eight, moderate TBI from nine to 12, and mild TBI from 13 to 15.[15,16] Concussion, (and more specifically, sport-related concussion [SC]) is currently defined as mild TBI with the absence of clinical findings on traditional neuroimaging.[1] This description, however, only begins to describe the measurable clinical outcomes regarding the severity of the injury.

The purpose of this review is to present the etiology, neuropathology, and clinical assessment of SC as we know it today. These topics are presented along with an overview of the evolution of the SC definition, known incidence rates, and

a basic understanding of how SC affects normal human neurologic and metabolic functions. Finally, a discussion regarding the holistic assessment of SC and future research directions will be presented.

Concussion Definition

Over the past 20 years, the definition of sport concussion (SC) has evolved. In 1997, the American Academy of Neurology (AAN) defined concussion as, “a trauma-induced alteration in mental status,” wherein confusion and amnesia were considered imperative and the severity of injury was graded on a three-tiered scale relative to loss of consciousness and the duration of acute symptoms.[17] In 2001, a multidisciplinary group of expert international researchers convened for the initial International Consensus Conference on Concussion in Sport. This international group of thought-leaders would later be recognized as the Concussion in Sport Group (CISG). The initial CISG meeting resulted in a consensus statement and defined SC as, “a complex pathophysiological process affecting the brain,” which could be separated into three “grades” which was predicated on the presence and duration of concussion-related signs (loss of consciousness) and symptoms (headache, dizziness, post-traumatic amnesia).[18] The definition from the CISG also accounted for the functional, rather than structural, nature of SC in that signs, symptoms, and neurological impairment are present in the absence of remarkable findings on structural neuroimaging (e.g., commuted tomography or magnetic resonance imaging) studies.

The definition of concussion from the CISG later evolved during the 2004 CISG meeting. The 2004 CISG definition added concussion-related symptoms may persist beyond the time of injury.[18] Another change was the elimination of the three-tiered grade scale and the adoption of a dichotomized subtyping paradigm. SCs were now classified as “simple” (e.g., symptom resolution within seven to 10 days with no specific interventions) and “complex” concussions (e.g., persistent symptoms beyond 10 days of injury). In 2004, the National Athletic Trainers’ Association (NATA) released its first position statement on the management of SC. The NATA’s position statement called for athletic trainers (ATs) to become familiar with the signs and symptoms of all forms of TBI and to take even the mildest suspected injuries seriously.[19] The CISG reconvened in 2008, where it abandoned the “simple” and “complex” categorizations and discussed the possibility of the term “concussion” being used synonymously with “mild TBI”.[20]

In 2012, the CISG agreed that the terms “concussion”, “mild TBI”, and “commotio cerebri” (a synonym used in parts of the world outside of North America) were acknowledged to be used interchangeably.[9,20] Furthermore, it was agreed upon that SC should be considered, “a brain injury … defined as a complex pathophysiological process affecting the brain.”[9] This new definition retained the construct of the injury as a physiological process while acknowledging the gravity of cultural misconceptions that SC was not a serious TBI. Similar to the discussion at the CISG meeting in 2012, the AAN updated its practice parameters in 2013 acknowledging that the definition of concussion in

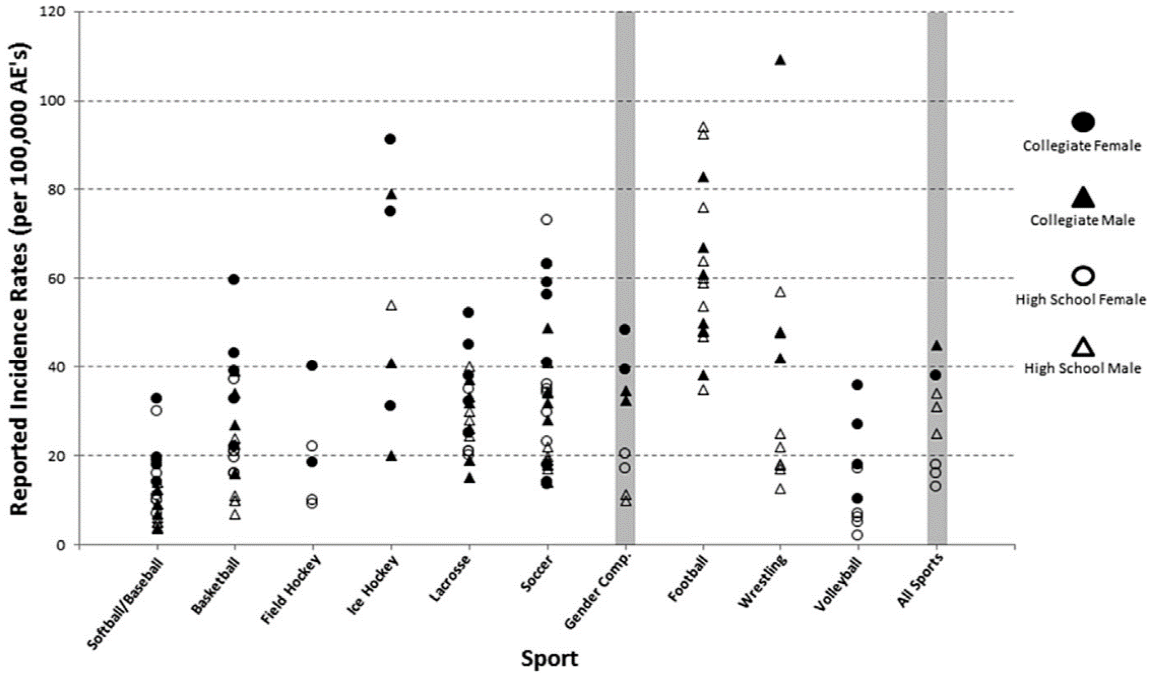
peer-reviewed literature was not consistent, but was also not dissimilar enough to warrant a separate discussion of how to best classify these injuries.[21] In 2014, the NATA also updated its practice parameters. In doing so, they acknowledged the strength of the updated, and more specific definition of SC resulting from the 2012 meeting of the CISG.[22]

Today, SC is recognized as a form of mild TBI that is caused by injurious force(s) applied to the brain from a direct blow to the head or an indirect blow elsewhere in the body.[1] These forces result in impairment of normal neuronal function that is characterized by the onset of signs and/or symptoms that are specific to each individual.[1,23] These signs and symptoms may appear immediately or may be delayed by hours or days. The majority of concussed athletes reported symptom free within a period of a few weeks. The time to physiologic recovery is not well understood, but clinical recovery typically occurs within two weeks for adults, and may take three to four weeks in the majority of adolescents and children.[1,13] Additionally, concussion-related signs and symptoms must not be able to be explained by comorbidities (e.g. migraine, dehydration, pre-existing medical conditions) or concurrent substance use (e.g. alcohol). The most current CISG definition of SC incorporates defining characteristics of what the injury is, and also what it is not. In some cases, SC may be initially suspected and not clinically diagnosed or verified until hours or days following insult. The delay in recognition highlights the current ambiguity of SC from a pathological standpoint.[24]

Epidemiology of Concussion

It was once thought that up to 3.8 million individuals in the United States sustained mTBIs each year.[25] More recently, the Centers for Disease Control and Prevention (CDC) have estimated that this number may account for only 1/9th of the true incidence which suggests that up to 38 million concussions may occur in the United States each year.[26] SC can occur at any level of sport. The majority of peer-reviewed epidemiological studies over the past 30 years have focused on high school and collegiate levels of participation. To understand the incidence rate (IR) of SC, researchers compare the number of injuries sustained to the number of athletic exposures (AE). One AE is equivalent to one athlete participating in one competition or training session.

Figure 1. Concussion Incidence Rates by Sport, Gender, and Level of Participation.



A recent review article by Resch et al. assessed the reported IRs (per 100,000 AEs) in high school and collegiate student athletes from 19 different

studies (Figure 1).[14,27-43] Overall IRs ranged from 2.0 in high school girl's volleyball to 109.2 in collegiate men's wrestling. Reported IRs were higher in collegiate athletes when compared with high school athletes, and overall IRs were higher in males compared to females. This effect was driven by the high IR of SC in football and wrestling, which are male-dominated sports. Conversely, in sports where females and males have equivalent or similar rules (i.e. soccer, lacrosse, etc.), the IRs for females were higher than those of their male counterparts. The rationale for these phenomena are currently unknown but are purported to be related to differences in symptom reporting behaviors, neck strength (with regard to force attenuation), and/or hormonal influences on SC-related outcomes.[44-46]

PART II. BRAIN PHYSIOLOGY IN HEALTHY INDIVIDUALS

Typical Neuronal Anatomy and Physiology

The typical neuron consists of a body (soma) and neurites (dendrites and axons).[47] The neuronal soma contains the organelles (i.e. mitochondria, etc.) that sustain the life of the cell and the neurites are primarily responsible for sending and receiving communications among cells in neural and other tissues. The neuronal membrane is phospholipid bilayer that separates the intracellular structures from the extracellular space and selectively allows passage of ions and chemicals into and out of the cell. The basic function of a neuron is to initiate or facilitate communication between organs. To perform this function, chemical or electrical signals are received (or generated) in the dendrites and/or cell body are

transmitted along the nerve's axon(s) toward a target tissue. This transmission of signal is called an action potential.

At rest, the resting electrical potential of the neuronal membrane is approximately -60 to -70 milliVolts (MVs) depending on the function/type of neuron.[47] This electrical potential describes a negatively charged intracellular space in comparison to the extracellular space. The word, "potential" is descriptive of the tendency for electric charge to flow from areas of positive charge to areas of negative charge. In the neuron, this resting potential is maintained by the selective permeability of the cell membrane to ion flux across the membrane as well as the active (energy requiring) work of specific protein channels and "pumps". In the typical action potential, sufficient electric or chemical signal is imparted to the nerve's cell membrane via temporal summation (repeated signal over a short period of time in one area) or spatial summation (multiple signals at one time in different locations) that causes a positive shift in the cell's membrane potential. Once this voltage shift reaches a certain threshold ("capacitance") it causes an all-out depolarization of the nerve membrane in the location the received signal is induced. This depolarization is the aforementioned action potential that travels from the point of initiation to the terminal portions of the axon, thereby ultimately releasing chemical transmitters (neurotransmitters [e.g., dopamine]) that interact with the target tissue and the extracellular space. Depolarization is facilitated by the binding of glutamate to N-methyl-D-Aspartate (NMDA) receptors within the cell membrane in order to increase the flux of ions across the membrane.[48]

The released neurotransmitters are received by the target tissue, left in the extracellular space around the axon terminals, or are taken back up into the neuron at the axon terminals.[47] Neurotransmitters that are left in the extracellular space may be chemically converted into other molecular compounds or collected by glial cells in the brain. There are many types of glial cells with a variety of functions. For example, Astrocytes have a role in the storage of neurotransmitters and recycling of those chemicals back to neurons to be used in future transmissions.[47,48] While this process is occurring, the signal-sending neuron returns to its resting potential in preparation to receive and transmit a future signal. The nerve experiences an immediate absolute refractory period in which it is near impossible for it to be depolarized again. This is followed by a short-lived relative refractory period of depolarization that can occur again before the resting membrane potential is reached. However, an increase in signal to the nerve would be required to overcome the excessively negative charge and reach its capacitance for depolarization.[47] These refractory periods are characterized by rates of ionic shift as a result of the action potential (highly negative to slightly positive intracellular charge).

The slightly positive state that results after the action potential is mitigated through active ion channels (i.e. sodium-potassium pump), requiring energy to restore the homeostatic ion concentrations on either side of the neuronal cell membrane.[47] Ion pump activity is high initially during the absolute refractory period as sodium and calcium ions that entered during the action potential are delivered to the extracellular space and potassium is delivered to the intracellular

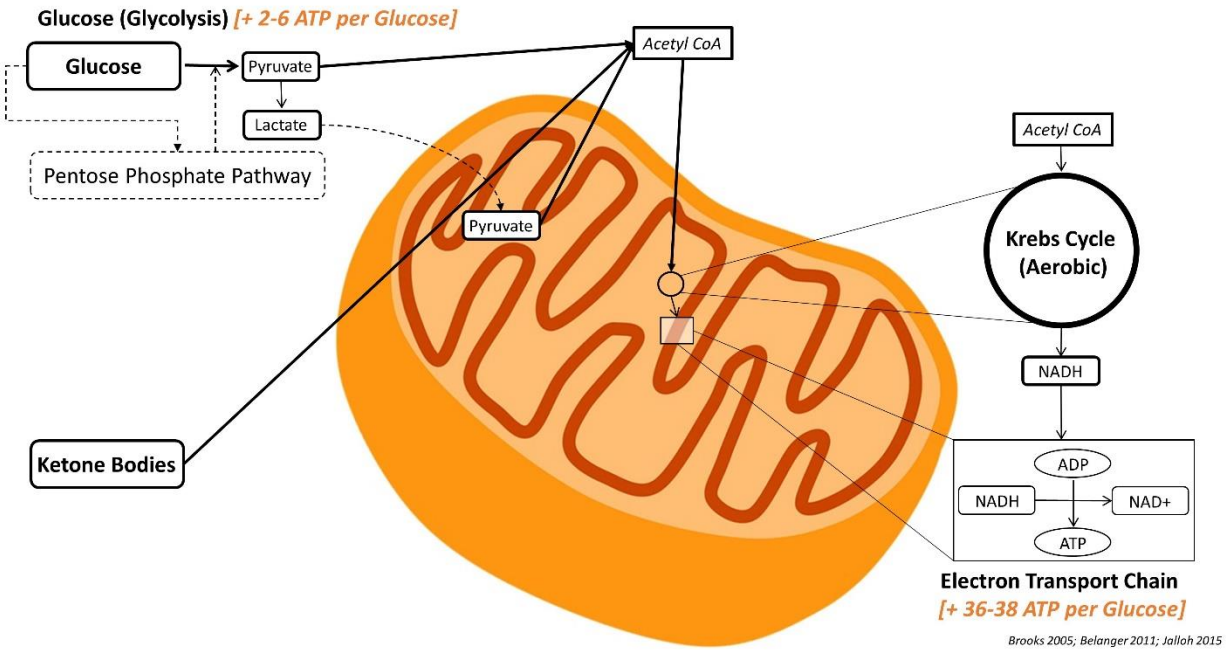
space. The relative refractory period reflects a state where the membrane potential is near resting and the active ion pumps have slowed in their activity. The fueling of ion pumps and the active recovery of released neurotransmitters require a lot of energy under normal conditions, and typically regional blood flow to active neurons is sufficient to meet these energy needs.[48]

Bioenergetics of the Brain in Healthy Individuals

Energy Basics

The human brain contributes approximately two-and-a-half percent to one's total body mass, but may utilize 20-25% of the body's aerobic (oxygen-requiring) energy resources.[49-51] The cerebral metabolic rate of glucose appears to be higher in females than males.[52,53] Glucose is the primary source of energy for the brain; however, alternative substrates such as ketone bodies and lactate may be used in states of high stress such as injury, intense physical activity, and even development (Figure 2).[48,54-56] The conversion of glucose into energy is a process known as "glycolysis", where a glucose molecule is phosphorylated by the enzyme hexokinase, thereby becoming glucose-6-phosphate (G6P).[7] G6P will typically then follow one of two different metabolic pathways in neurons: 1) aerobic metabolism via the Kreb's Cycle, or 2) the Pentose Phosphate Pathway (PPP). Alternatively, G6P may be returned to the storage form of glucose (glycogen) to be stored in astrocytes until more energy is needed.[48]

Aerobic and Anaerobic Glycolytic Pathways



Generally, glycolysis results in the production of lactate or pyruvate. Anaerobic processes do not require oxygen to be carried out, where aerobic processes do.[7] The net result of anaerobic glycolysis is typically two molecules of adenosine triphosphate (ATP) and two molecules of lactate. ATP is the most common basic unit of energy supply in the human body and is produced to greater extents when oxygen availability is adequate. Pyruvate molecules typically continue into the mitochondria to be used in a cyclical aerobic pathway known as the Krebs cycle. Pyruvate that are not taken into mitochondria may be converted to lactate. In addition to glycolysis, the pyruvate molecule gets converted to acetyl-CoA and enters the Krebs cycle to produce reducing equivalents. These reducing equivalents are nicotinamide adenine dinucleotide (NADH) and flavine adenine dinucleotide ($FADH_2$). Each glucose molecule yields

10 and two molecules of NADH and $FADH_2$, respectively, which ultimately enter the Electron Transport Chain (ETC). The ETC then results in the generation of additional ATP molecules through oxidation of the reducing equivalents. The total aerobic processes together garner a net gain of 30-32 ATP per glucose molecule compared to a net gain of 2 ATP molecules from glycolysis alone.[57] While the aerobic processes produce more energy, they are performed more slowly than anaerobic glycolysis.[7]

The Pentose Phosphate Pathway (PPP) is an alternative to anaerobic glycolysis in the human body.[48,58] The PPP is similarly anaerobic, but it does not produce energy itself. Rather, G6P is utilized in the PPP as a complementary resource to anaerobic glycolysis by converting a single nicotinamide adenine dinucleiotide phosphate (NADP+) into NADPH and intermediate substances such as fructose-6P or glyceraldehyde-3P.[48,58] NADPH serves to provide energy to the initial step of glycolysis where glucose is phosphorylated by hexokinase, and the intermediate substances can be directly utilized by glycolysis along the pathway to forming pyruvate or lactate.[7,48] NADPH may also function to assist in ameliorating oxidative stress, a state in which the breakdown of oxygen containing particles (such as would occur in normal aerobic metabolism) creates highly reactive particles that may interfere with normal chemical functions.[58] Another by-product of the PPP, ribose 5P, has been reported to participate in nucleic acid (i.e. DNA, RNA) and fatty acid synthesis and therefore may be neuroprotective.[58,59]

Lactate is an Important Fuel Source for the Brain

Each type of metabolic pathway is utilized when it is most efficient given the availability of energy substrates, mitochondria, and enzymes, but not necessarily the availability of oxygen.[7] During exercise or an injury, lactate may accumulate as a by-product of anaerobic glycolysis. Lactate may enter mitochondria by way of a transporting protein known as a “lactate shuttle”. Once in a mitochondrion, lactate will be converted into pyruvate by lactate dehydrogenase (LDH), and subsequently used in the Krebs cycle. The lactate shuttle mechanism enables the utilization of the lactate from glycolysis and also increases the rate of the high energy producing aerobic metabolism in times of need.[7]

There is evidence to show that lactate is utilized as an energy substrate in the brain under normal resting conditions, and the proportion of lactate use increases when circulating blood lactate levels are increased.[55] That is to say, an increased availability of lactate in the body increases the utilization of lactate in the brain. One recent study provided evidence that exercise-induced increases in blood lactate corresponded with improved executive function as measured with a Stroop task, irrespective of glucose, brain-derived neurotrophic factor, and hormonal fluctuations.[60] These findings suggest that neurons may rely on lactate, via the lactate shuttle mechanism, in order to facilitate increased energy demands.[7,60] This preference toward lactate in times of increased energy demand may spare glucose for use in the PPP by astrocytes that would subsequently ameliorate the increase in oxidative stress by facilitating antioxidant function as well as provide energy for nucleic acid synthesis.

Ketone Bodies as an Alternative Substrate

Ketone bodies (KBs) are derived from the oxidation of free fatty acids to acetyl-CoA, and are another important fuel for the brain during times of physiological stress.[61] Specifically, acetoacetate (AcAc) and *β*-hydroxybutyrate (*β*HB) are KBs produced in the liver that enter the brain as an energy resource, especially in times of need (e.g., starvation). Metabolism of KBs involves a series of reactions that result in the formation of two acetyl CoA that can enter directly into the Krebs cycle.[7] A foundational study by Ruderman et al. in 1974, illustrated the following relationships: 1) while glucose is the primary substrate used by the brain in a fed state, starved states induced an increase in the proportion of KB use; 2) in a starved state, lactate release was increased, suggesting lower rates of pyruvate use and increased conversion of pyruvate to lactate; 3) injection of a KB catabolizing enzyme increased lactate, *β*HB, and AcAc utilization but did not affect glucose utilization; and 4) the availability of KBs and the rate of their diffusion from the periphery into the brain is likely responsible for the metabolic rate of KBs.[61] These relationships imply that physiological stress (i.e. injury) and dietary intake are both highly influential in the type and rate of substrate metabolism in the brain.

In congruence with the discussion of lactate metabolism above, it appears that the brain (specifically neurons and astrocytes) rely heavily, but not solely, on glucose as an energy source. Moreover, these observations suggest that the availability of non-glucose sources of energy such as lactate, *β*HB, and AcAc, allow the brain to spare glucose/glycogen resources for the maintenance of

homeostasis by neurons and glia. In clinical practice and rodent models, ketone supplementation and ketogenic diets (i.e. high fat and protein proportions with relatively low or no carbohydrates) may be beneficial to the facilitation of recovery from conditions such as severe TBI and seizure reduction in epilepsy, but the mechanisms for these results are not clear.[62-64]

Measuring Brain Metabolic Activity In-Vivo

Measurement of cerebral blood flow (CBF) and the cerebral metabolic rate (CMR) of glucose (CMRglu) are possible through advanced neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).[65] These tools allow scientists to measure regional CBF and CMRglu in relation to functional activity, revealing a close relationship with regard to activity and both CBF and CMRglu. For example, upon neuronal depolarization the increased demand for energy to return to- and maintain homeostasis results in an increased regional CBF and similar increase in CMRglu.[48,66] However, the CMR of oxygen ($CMRO_2$) does not respond proportionately in kind to metabolic demand increases, and therefore the sources of normal glucose oxidation are thought to be more than just aerobic and may include other pathways (i.e. PPP) and substrates (lactate, glutamate, and KBs) even within a healthy brain.[7,66] Current advanced neuroimaging technology may therefore only be able to capture part of a much larger picture of the bioenergetic environment in the brain. Further work is required to understand the whole picture of both typical and pathological metabolism.

While neuroimaging has promise in the recognition of intracranial metabolic alterations following TBI, biofluid markers may also support our understanding of whole body changes following injury.[67-69] Specifically, circulating metabolites and hormones in blood and other body fluids may help clinicians observe physiologic changes subsequent to injury and perhaps address the mechanistic nature of these changes as well. For instance, human metabolism is regulated by hormones such as cortisol, and the signaling pathways for controlling these hormones pass through the midbrain and pituitary gland.[7,70,71] Therefore, it would be rational to suggest that hormonal dysfunction may follow mild TBI such as concussion in a similar fashion to moderate and severe TBI as will be discussed later in this review. In order to understand the effects of hormone dysfunction following injury, we will first discuss a basic understanding of hormone function in humans.

The Pituitary Axes and Mechanisms of Hormonal Control

Hormone Basics

A hormone is a chemical substance that is produced and stored in glandular tissue.[7] Hormones are released into body fluids in order to signal systemic reactions (via multiple organs) or in specific target tissues (i.e. brain, liver, kidneys, etc.). Regarding their chemical constructs, there are two basic types of hormone: 1) Steroids, which come from the adrenal cortex on the kidneys or the gonads, and are made from cholesterol bases; and 2) Polypeptides, which stem from the endocrine glands (i.e. pituitary) and are

constructed with amino acid bases.[7] While there are a variety of glands, hormones, and functions, the most relevant to this particular review are those relating to the hypothalamus and pituitary gland. This relevance is due to the physical location of the pituitary gland and subsequently, the short- and long-term hormonal dysfunction(s) that may be caused or mediated by TBI.[70-72]

The Pituitary Gland

The pituitary gland and hypothalamus are responsible for the vast majority of hormonal signaling and homeostasis.[7,47,73] The pituitary gland is located on the ventral aspect of the brain and sits within the sella turcica, a boney encasement nested within the sphenoid bone of the skull. The pituitary gland is tethered to the brain via the infundibulum. The infundibulum is the primary means of communication between the pituitary gland itself and the hypothalamus. The pituitary gland consists of three lobes, each with its own signaling pathway: the adenohypophysis (anterior pituitary), the intermediate lobe, and the neurohypophysis (posterior pituitary).[47,73] Each lobe has unique functions and neural control of pituitary function occurs by way of two distinct pathways: 1) neurons from the hypothalamus project into the neurohypophysis to communicate directly with pituicytes (pituitary gland cells) that go on to regulate the release of secretory products into the bloodstream via the inferior hypophyseal artery; and 2) through portal veins stemming from the superior hypophyseal artery and projecting directly from the hypothalamus to the adenohypophysis via tropic hormones. These tropic hormones are hormones (i.e. adrenocorticotropic hormone, thyroid stimulating hormone, etc.) that stimulate the

release of other hormones via an endocrine gland.[47,73] In this instance, tropic hormones are released from the hypothalamus. The intermediate lobe is a minute portion of the total pituitary volume, consists primarily of overlapping tissues from the anterior and posterior lobes, and may not have relevance beyond fetal development.[17,73,74]

Pituitary Hormone Functions and Controls

The adenohypophysis is responsible for the release of six primary hormones: thyroid stimulating hormone (TSH), corticotropin/adrenocorticotropic hormone (ACTH), gonadotropins such as follicle stimulating hormone (FSH) and luteinizing hormone (LH), growth hormone (GH), prolactin (PRL), and Opiomelanocortin (POMC). TSH stimulates the thyroid to release thyroxine (T4), triiodothyronine (T3), and thyroglobulin. These hormones regulate body temperature, metabolism and heart rate.[47,73,75]

TSH is regulated by TRH (Thyrotropin-Releasing Hormone) from the hypothalamus and peaks around midnight. Somatostatin inhibits the release of TRH, and both pituitary and hypothalamic T3 and T4 concentrations provide negative feedback, limiting their release when concentrations are elevated.[75,76]

ACTH stimulates the release of glucocorticoids such as cortisol from the adrenal cortex, which increases metabolism and arousal as well as suppresses inflammatory responses. ACTH is regulated by corticotropin-releasing hormone (CRH) from the hypothalamus that peaks around two to four hours before waking and follows a diurnal pattern.[76,77] There is an increased output of ACTH during

times of physical and emotional stress, and overall concentration is self-regulated via negative feedback in the hypothalamus and pituitary. POMC is a precursor glycoprotein produced primarily in the hypothalamus that can be broken down to derive peptides such as ACTH and α-melanocyte-stimulating hormone (MSH).[78] The beneficial effects of MSH include neuroprotection, anti-inflammatory processes, and maintenance of metabolism. [79-81]

FSH and LH stimulate gonads of both males (testes) and females (ovaries) for reproductive and growth functions. Release of these gonadotropins are stimulated by gonadotropin-releasing hormone (GnRH). [76,77] Diurnal, life cycle, and menstrual cycle variations each correspond with regulation of gonadotropins. [77] Inhibin in the gonads also limits FSH release. [43]

GH is the most abundant hypophyseal hormone. [82] It has a direct role in human development and growth as well as in the stimulation of insulin-like growth factor I (IGF-I) and II (IGF-II) production. These hormones are typically most abundant in utero (IGF-II) and throughout adolescence (IGF-I & GH). [83] GH acts to increase metabolic rate, increase insulin resistance in skeletal muscle, stimulate protein synthesis for increase of lean body mass, and decrease body fat. [83] Additionally, GH deficiency has been related to impairments in memory, motor skills, anxiety and worse quality of life. [84-86] PRL release is inhibited by the hypothalamus via dopamine or PRL release-inhibiting hormone, a control mechanism which is contrary to the other adenohypophyseal hormones where release is stimulated.[47] PRL is primarily involved in post-natal functioning (i.e.

inhibition of reproductive functions in both sexes), but may also have regulatory roles in calcium ion balance and dopaminergic cell proliferation in the brain. [87]

The neurohypophysis is the site of two primary hormones: oxytocin and vasopressin, which is also known as antidiuretic hormone (ADH). [47,73] In women, oxytocin stimulates the release of milk from breast tissue and causes contraction of the uterine smooth muscles during labor and delivery. In both sexes, oxytocin assists with stimulation of smooth muscle contractions that aid in conception during reproductive activities.[47] The primary function of ADH is the retention of water. To accomplish this end, water is retained in the kidneys, vascular smooth muscle is constricted, and cardiac output is reduced. [73] Hemorrhage, pain, emotions, exercise, and nausea may all stimulate ADH, while alcohol consumption may inhibit its release. [73]

PART III. PATHOPHYSIOLOGY OF TRAUMATIC BRAIN INJURY

"Neurometabolic Cascade" and Metabolic Crisis in the Brain

In 2001 and 2014, Giza and Hovda described the "Neurometabolic Cascade of Concussion", which is based predominantly on rodent models of experimentally-induced moderate and severe TBI.[23,88] This neurometabolic cascade incorporates the chemical and ionic changes in the brain that occur subsequent to trauma. These changes are coupled with bioenergetic alterations in neurons that lead to a metabolic crisis consisting of an increased demand for energy with a diminished energy supply. Subsequent to biomechanical trauma, affected neurons are depolarized, axonal stretching occurs, the phospholipid

membranes are disrupted, and both voltage- and chemically-mediated (i.e. glutamate binding to N-methyl-D-aspartate [NMDA] receptors) ion channels are opened leading to poorly controlled ionic flux across the nerve membrane.[2-4]

In accordance with the previous discussion of the bioenergetic response to stress in the brain (*Section II.*), hyperglycolysis depletes glycogen stores, an increase in extracellular lactate is observed, and a subsequent reduction in the CMRglu (hypoglycolysis) occurs.[23,88-92] Concurrently, calcium ion influx into neuron mitochondria is present immediately and sometimes lingers for a matter of days.[5,6] This sequestration of calcium in the mitochondria is thought to impair aerobic glycolysis and potentially lead to programmed cell death (apoptosis).[6] Greater concentrations of extracellular lactate as well as circulating Ketone Bodies (KBs) may be utilized as energy sources by neurons, thereby sparing glucose for preserving cognitive function and astrocyte antioxidant production.[48,69,93-95] Studies showing decreases in CMRglu and $CMRO_2$ may indicate shifts in substrate utilization rather than an overall decrease in total cerebral metabolic rate.[69,96]

Whole-body Metabolism Changes after Traumatic Brain Injury

Metabolic Rate

No literature currently exists profiling the whole-body changes in metabolism following concussion specifically, but studies focused on the whole spectrum of TBI or specifically in moderate to severe TBI provide important information regarding the potential for systemic dysfunction following injury.

Glenn et al. reported an increase in whole body carbohydrate metabolism with a concomitant increase in arterial lactate concentration within six days following moderate to severe TBI.[69] Interestingly, those participants who were shown to have a higher rate of both $CMRO_2$ and brain lactate uptake relative to arterial lactate concentration (i.e. the ability to use available alternate energy resources) had better neurological outcomes six months following their injuries. Several studies have also shown an increase in systemic KB and protein-derived substrate utilization (i.e. amino acids) for the first two to nine days following moderate to severe TBI.[97-99] The increased use of non-glycolytic energy substrates likely represents the body's response to an increased overall demand for energy that cannot be supplied by glycolysis alone.

Whole-body resting metabolic rate (RMR) is the amount of energy needed to support the body's essential functions while aroused and at rest.[7] Patients with mild to severe TBI have elevated RMR following injury when compared to predicted values. Specifically, RMR in patients with primarily moderate or severe TBI may be measured at up to 200% of average predicted values in the first days following injury, and elevated RMR (116% to 200%) may last for weeks or months.[8,100-102] These observations indicate a whole-body physiological response to brain injury, and more work is needed to determine if there is a "dose-response" regarding the magnitude of metabolic changes in relation to the severity of injury. To date, there are few pieces of evidence regarding the full-body energy expenditure or fuel utilization changes following mTBI, though full-body metabolism can be measured serially after concussion and there is an

emerging field of metabolomics which may someday be able to predict the presence and/or severity of injury.[67,68,103,104]

Altered Macronutrient Metabolism

Limited studies have examined TBI-related hormonal changes and have included measures of lipid and carbohydrate metabolism profiles. Giuliano et al. observed mild to severe TBI patients who were either one year post-injury or greater than five years post-injury.[105] Between 35% and 45% of these participants were classified as having GH dysfunction. When compared to those without GH dysfunction, these participants had higher BMI, percentages of body fat, fasting glucose, low-density lipoprotein (LDL cholesterol), and triglycerides, while exhibiting decreased high-density lipoprotein (HDL) concentration. Prodam et al. observed that 13% of their TBI participants had similar lipid (LDL, HDL, and triglyceride) profiles to those patients in the Giuliano study.[106] Prodam et al. additionally identified 9.3% of their TBI participants to have insulin resistance to the point of diagnosis of either pre-diabetes or type II diabetes mellitus or pre-diabetes. On the group level, participants with TBI-induced hormone dysfunction (hypopituitarism) had greater insulin resistance compared to TBI patients without hypopituitarism, and the magnitude of insulin resistance was correlated with time since injury.[106]

Finally, in a study of former NFL players with history of presumably football-induced TBI, 50% were observed to have a pre-diabetes or metabolic syndrome, with similar profiles to those described in the Giuliano et al. and

Prodam et al. studies.[107] These three studies were all cross-sectional at a single assessment time point, and cannot infer causation. Longitudinal studies are needed to identify and track TBI-induced metabolic changes and differentiate them from other factors such as physical inactivity, diet, etc. In summary, these studies indicate that whole-body metabolic rate and substrate utilization may be altered after TBI and there is clinically-based evidence implicating the potential roles of hormone deficiency and dysregulation in these metabolic changes.

Hormonal Changes after TBI

Over the last 15 years, the body of evidence regarding hormonal control changes and hypopituitarism following TBI has grown. While general patterns appear to be recognizable with regard to immediate and long-term hormonal dysfunction, relationships between outcomes are unclear and the etiology of hormonal dysfunction has yet to be well-understood.[70] The few studies that do longitudinally assess patients following TBI have relatively little consistent overlap with each other regarding serial assessment time points (i.e. three months and 12 months following injury). [108-113] Many other studies present only small time frames for serial measures (two to 10 days), single cross-sections, or multiple cross-sections with only some or no overlap between patient groups at each time point. [86,105-107,114-120] Moreover, this body of literature is based on samples that are predominately (67% to 100%) male. As such, group level results should be interpreted with some caution in cases where male and female analyses were not separated, especially with regard to gonadotropic hormone-related outcomes. Lastly, much of the literature regarding hormonal changes

following injury was based predominantly in moderate to severe TBI patients, although many studies did include small proportions of mild TBI. Therefore extrapolation of study results to mild TBI alone would be remiss, so the findings presented herein are meant to broadly represent the spectrum of TBI unless otherwise noted.

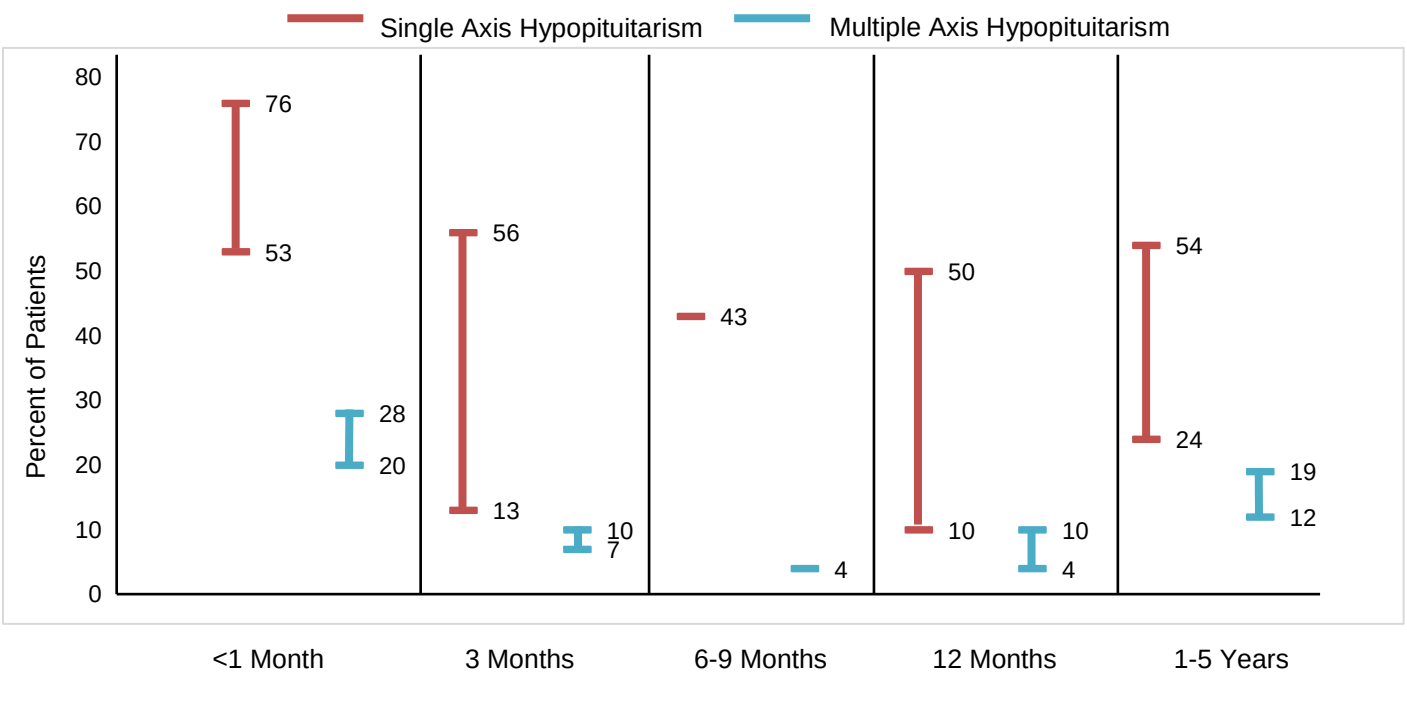
Rates of Overall Hypopituitarism Following Traumatic Brain Injury

Figure 3 summarizes the reported rates of isolated, single axis hypopituitarism as well as multiple axis hypopituitarism. In the acute phase and up to three weeks following TBI, reports of at least one deficient hormone axis has ranged from 53% to 76% in study patients, with 20% to 28% having dysfunction in more than one axis. [111,113,120] Around three months following a traumatic brain injury, the proportion of at least one deficient axis has been reported to be between 13% and 56%, with seven to 10% having more than one affected axis. [109-112] Between six and nine months after TBI, one study reported dysfunction in at least one axis in 43% of patients and in multiple axes in four percent of their sample. [110] These numbers are lower than the 53% and seven percent which the same authors reported at three months, respectively. Twelve months following injury, the reported proportions of 10% to 50% of patients being affected in at least one axis and four to ten percent being affected in multiple axes are similar to those proportions reported at three months. [108,109,111-113,120] In patients assessed between one to five years post-injury, cross-sectional studies have reported that 24% to 54% are have at least one dysfunctional axis and 12% to 19% have multiple affected axes. [106,107,115,119] It is important to note that two of

these studies contained samples that were all male former National Football League athletes or male former active-duty military members with history of multiple blast exposures in Afghanistan and/or Iraq theaters. [107,119] The other two studies with cross-sections beyond one year represented patient populations that were 70% or 80% male. [106,115]

A limited number of longitudinal studies have provided evidence that most patients who have hypopituitarism following TBI recover within the first three to 12 months; however, some studies indicated that new dysfunctions may take three months or more to develop and many who experience dysfunction may not recover at all within the first year. [109,111,113,120] Interestingly, Krahulik et al. observed a relationship in their patients between the development of hormonal dysfunction and the presence of a condition representing small pituitary volume known as “empty sella syndrome” as viewed with MRI.[120] While the single MRI

Figure 3. Reported Rates of Hypopituitarism Following Severe, Moderate and Mild Traumatic Brain Injury



measurement was not enough to infer a causal relationship, this finding provides rationale for the essence of the pituitary gland's health with relation to systemic hormonal control following moderate or severe TBI. It also appears that the severity of TBI, but not necessarily the type of injury or time since injury, is related to the presence of hypopituitarism in TBI patients. [107,109,111,112,115,119] Few studies indicated the influence of overall age on poorer hormonal functioning following TBI. [106,108,112,115] Of the evidence that does exist, conflicting findings have been reported. Similarly, reports highlight that higher BMI is associated with hormonal dysfunction (i.e. GH), although other studies observed no relationship. [108,112,114,115,118,119]

Changes in the Somatotropic Axis – GH and IGF-I

In the first hours and days following all severities of TBI, GH dysfunction has been reported in 13% to 37% of patients. [113,114,117,118,120] In studies of acute moderate and severe TBI, serial assessments of GH indicate that the typical pattern of diurnal variation may disappear initially (within 24 hours of injury) but likely return between four and ten days post-injury. [117,118] Like GH, IGF-I concentrations may be low in up to 77% of moderate and severe TBI patients initially, but may return to near-normal values within ten days. [118] Around three months after mild to severe TBI, rates of somatotropic dysfunction are reportedly similar to acute rates (nine to 39%) of, but may decrease between six and nine months post-injury (13% to 18%). [86,108-110,112] These reports differ remarkably from those at one year post-injury (10% to 63%) and up to five years post-injury (19% to 48%).[105-107,109,111-113,115,119,120]

The few studies that observed longitudinal outcomes reported relatively unchanging group proportions of somatotropic axis dysfunction over time, or reported an increase in the proportion affected from the acute phase to one year post-injury. [109,110,112,113] It's important to state that none of the patients in these longitudinal studies received therapy for GH dysfunction throughout the course of the respective studies, and therefore the findings may not represent clinical outcomes in typical patients who may receive hormone replacement therapy. GH dysfunction has been clinically associated with worse patient-reported depression, emotional well-being, fatigue, pain, physical health and general health. [84-86] The benefits of treatment with hormone replacement, exercise, and dietary therapies should be investigated in order to improve patient outcomes.

Changes in the Gonadotropic Axis – LH, FSH, Testosterone, and Estrogen

Acute and subacute findings indicate that there is a decline in LH concentration in 33% to 67% of all patients diagnosed with a TBI across the spectrum of injury. [111,113,117,118,120] Evidence regarding FSH concentrations in this time-frame is mixed, but are reported to be present in up to 46% of males and 40% of females, most of whom were suffering from moderate or severe TBI. [111,117,118] Testosterone concentrations have been observed to significantly drop acutely in 77% to 100% of males with all severities of TBI. [111,113,114,117,118] Estrogen concentrations may significantly decline in 39% to 90% of women with moderate to severe TBI. [114,118] Wunderle et al. discuss the potential role of the hormone progesterone in women as having a neuroprotective effect following mild TBI. [121] Specifically, they discuss a "withdrawal hypothesis" in that women in

the luteal phase of their menstrual cycle (where progesterone is typically elevated) may experience a sudden drop in progesterone which may worsen clinical outcomes following injury. Along with a recent study by Gallagher et al., there is some preliminary evidence that hormonal control via synthetic progesterone supplementation (i.e. common birth control medications) may help to reduce the negative impact of mild TBI on symptom burden and recovery time outcomes.[121,122]

Around three months following TBI, 17% to 32% of individuals may experience some type of gonadotropic dysfunction (LH and/or FSH). [109,110,112] Slightly lower rates (10% to 23%) have been reported between six and nine months post-injury, which is similar to reported rates at one year (eight to 26%).[108-110,112,113,120] Beyond one year and up to five years post-injury, rates appear to be a bit lower overall, ranging between nine and 18%.[106,107,115,119] Greater severity of TBI has been associated with the presence of gonadotropic dysfunction and there is mixed evidence with regard to the role of age. [108,109,112,113,118] Gonadotropic dysfunction may manifest in sexual dysfunction, and in conjunction with somatotropic deficiencies, healing and energy production may be impaired. [107,118] Thus, dysfunction in this axis could affect both physiologic recovery and quality of life.

Changes in the Corticotropic Axis – Cortisol and ACTH

A handful of studies have assessed hypocorticotropism acutely following injury with assessments within hours or days after mild to severe TBI.

[111,113,114,116,117,120] Cortisol and ACTH appear to lose their diurnal variation and have been measured at their highest within 24 hours of TBI and at their lowest between two and three days following injury. [116] Likely due to the marked fluctuation of Cortisol and ACTH within such a short time frame, the reported proportions of acute corticotropic axis dysfunctions in patients varies widely from four to 70%.[111,113,114,116,117,120] Between three months and one year post-injury, proportions of corticotropic axis dysfunctions appear to be more consistently between two and 19%.[108-110,112,113] Longitudinal studies show disparate changes in the proportions of individuals over the course of months who have corticotropic axis dysfunction, with one study showing an increase in proportion over a year, two studies showing relatively little to no change in proportion over six to nine months, and two studies showing a decreased proportion of those with dysfunction over the course of three to nine months. [108-110,112,113] Only one study addressed the presence of hypocorticotropism in moderate to severe TBI patients beyond one year after injury, reporting that 13% of their participants had some sort of corticotropic axis dysfunction. [106] Impaired corticotropic axis functioning could theoretically lower overall metabolic rate and alter the catabolism of certain substrates like lipids, which would in part explain metabolic dysfunction following TBI. [105-107]

Changes in the Thyrotropic Axis – TSH, T3 and T4

Initially following mild to severe TBI, three to 52% of patients have been reported to have thyrotropic axis dysfunction, but there is mixed evidence regarding which of TSH, T3, and/or T4 are deficient when compared to controls.

[111,113,114,117,120] Up to five years following TBI, thyrotropic axis dysfunction has been reported consistently between two and 18% of all patients, with the majority of reports between three and eight percent. [106,108-110,112,113,115] Similar to the earliest assessment time points, it is unclear which component(s) of this axis consistently contribute to the measured dysfunction. This suggests that individual patient variability and study methodology are potentially important factors. [106,108,110,111,113,115] Thyrotropic axis dysfunction over time within individual longitudinal studies were also inconsistent. [111,113] These hormones are directly involved in regulating metabolic rate, and like each of the previously discussed axes, impaired thyrotropic axis function could meaningfully alter whole-body metabolism.

Hyperprolactinemia – An Increase in PRL

Prolactin is dissimilar to the majority of the hormones discussed above as dysfunction following injury involves a sustained increase in concentration (hyperprolactinemia) rather than a decrease. This is due to the hypothalamic control of PRL being an inhibitory process rather than an excitatory one.[47] Significantly elevated PRL has been reported acutely at proportions between 12% and 87% across the TBI spectrum. Specifically measured in females, this range might be 40% to 87%, and slightly less in males at 24% to 72%.[111,113,114,117] These rates are drastically less around three months post-injury at four percent for a mixed sample, 26% in females alone, and two percent in males alone.[109,110] Between six and 12 months, the proportions appear to be higher in a reported range of six to 15% in mixed samples, where the female

proportion was reportedly decreased to eight percent, and males increased to 12% in the six to nine month time frame.[108-110,113] Longitudinal studies of PRL concentrations throughout the first year following injury have revealed a decrease in the proportion of hyperprolactinemic patients over time. [108,110,114] Few studies have investigated hyperprolactinemia beyond one year in mild to severe TBI and found that 16% of patients were outside of normal limits, but eight percent had hyperprolactinemia while the other eight percent were below typical values.[115]

Changes in Neurohypophyseal Function – Vasopressin/ADH

Neurohypophyseal function was directly assessed by measurement of ADH or by assessment of urine osmolality, specific gravity, and/or the presence of diabetes insipidus. Diabetes insipidus is a condition in which fluid intake and urination volumes increase. Following TBI, the onset of this condition is inferred to be indicative of an inadequate amount of circulating ADH. Within three weeks of injury, 14% to 26% of all patients were observed to have changes indicative of ADH dysfunction.[114,115,120] Between three and 12 months, proportions of patients with ADH dysfunction ranged between one and 11%, and studies with multiple assessments in this time frame indicated a reduction in the proportion over time. [109,110,112,120] Beyond one year after TBI, one study reported no changes in osmolality or specific gravity of urine, while two studies reported irregularities (high or low concentrations) in ADH volume in six percent and 23% of participants. [106,115,119]

General findings from studies on patients with mild to severe TBI as described in this section indicate that hormonal dysfunction and hypopituitarism occur frequently. Rates of hypopituitarism were observed between 43% and 76% of all TBI patients in at least one axis as measured acutely or years after their injury. The majority of the patients in these studies suffered from moderate to severe TBI, however, even patients with mild TBI presented with dysfunction. Many patients recovered over time in longitudinal studies, but many did not present with symptoms until months had passed following their injuries, and some patients had lingering dysfunction up to years afterward. Each hormonal axis may be affected differently, but these changes have influence on metabolic, cognitive, and quality of life functioning. Pituitary and hormone function screening is not part of standard clinical practice in patients who suffer from SC, but future studies investigating these phenomena may eventually elucidate pathways for intervention in those who do not recover typically. Currently, assessment of impairment following SC is multifactorial and is targeted toward domains of clinical presentation of SC as will be discussed in the following section.

PART IV. CLINICAL PRESENTATION OF CONCUSSION

Measurement Properties of Assessment Tools

Reliability and Validity

Before addressing the clinical presentation of SC, it is vital to present the measurement properties of the common instruments which clinicians use to recognize and evaluate functional impairments. Among these properties are

objectivity, stability, and validity.[123] Objectivity is synonymous with interrater reliability in that it represents an instrument's ability to consistently measure a certain construct regardless of who is performing the assessment.[123,124] Stability, also known as test-retest reliability or intrarater reliability, refers to the consistency of a measurement obtained repeatedly by the same individual.[123,124] There is no widely-recognized threshold for clinically applicable stability values, but suggested thresholds have included correlation values greater than 0.60, 0.75, and 0.90, where 0.00 indicates no relationship, and 1.00 indicates a perfect correlation. [125,126] [127] Validity is a broad term which incorporates many facets, or sub-categories. Broadly, validity evidence determines the degree to which an instrument accurately measures what it is purposed to measure.[123] A threshold for the validity of an instrument has not been established; therefore, validity assessments should be interpreted according to their strengths in the context of the clinical evaluation rather than as meeting a certain criterion value.

Of particular importance are construct validity, convergent validity, discriminant validity, sensitivity, and specificity. Construct validity and convergent validity are similar, and sometimes synonymous.[123,124] Specifically, construct validity refers to the ability of an instrument to measure a certain property (i.e. balance). New instruments will often be compared to an established "gold standard" that is more onerous than the new instrument in order to determine how much agreement (convergent validity) exists in the two instruments' ability to measure that certain property.[123,124] Discriminant validity represents how related two instruments are when they should be measuring different constructs.[124] In

this case, in order to avoid redundancy in an assessment battery, instruments that are intended to measure different constructs should have weaker relationships with each other.[123]

Lastly, sensitivity and specificity represent the ability of an instrument to distinguish those with a certain condition (i.e. presence of concussion) from those without that condition, and are measured in percentages of correctly identified individuals. When evidence of sensitivity is high (closer to 100%), the instrument is able to identify impairment in concussed individuals without falsely identifying impairment in those who are not concussed.[123] When evidence of specificity is high (closer to 100%), an instrument is able to determine those who are not impaired due to concussion as compared to those who are impaired due to concussion.[123]

Measurement Error

The multiple types of reliability and validity, are affected by measurement error. There are two primary classifications of error: systematic and random.[123] Systematic error refers to influential factors that are typically non-modifiable, such as those inherent to an instrument itself (i.e. computerized scoring algorithms) or a test-taker (i.e. learning disability). Random error is that which is independent of the instrument and/or is modifiable (i.e. distractions in the testing environment). Multiple authors have recommended that clinicians controlling testing environments and procedures in order to reduce random error and thus improve the reliability and validity of baseline and post-injury concussion

assessments.[123,128-130] Instruments used to assess impairment from concussion are directly affected by the measurement properties as discussed above. Therefore, the following discussion of the clinical presentations of concussion will include measurement properties of instruments that are used to assess each type of outcome as they relate to understanding those outcomes.

Signs and Self-Reported Symptoms

The Concussion in Sport Group (CISG) emphasizes signs and symptoms that follow concussion injury with regard to the definition and recognition of injury, as well as in the evaluation of recovery.[1] Signs and symptoms of concussion are typically observed to have a rapid onset following insult to the brain and usually resolve in seven to 10 days.[131,132] However, symptom onset may take minutes or hours, and in 10-30% of cases, symptoms may linger beyond the typical 10 day recovery window.[9,133] A universally accepted definition of “prolonged” symptoms has not yet been established, but the CISG has recommended that symptom presence beyond 10-14 days in adults or beyond four weeks in children is suggestive of protracted recovery time.[134] Common symptoms of concussion (Table 1) can be separated into four domains: Physical, Cognitive, Emotional/Affective, and Sleep.[135-139] The endorsement of symptoms at baseline and following injury are known to differ depending on sex/gender and age.[132,140-144]

Table 1. Commonly Assessed Concussion Symptoms

Domain	***Symptom***
Physical	Headache
	"Pressure in Head"
	Neck Pain
	Nausea or Vomiting
	Dizziness
	Visual Problems
	Balance Problems
	Sensitivity to Light
	Sensitivity to Noise
	Numbness or Tingling
Cognitive	Feeling "Slowed Down"
	Feeling "in a Fog"
	"Don't Feel Right"
	Difficulty Concentrating
	Difficulty Remembering
	Confusion
Emotional/Affective	Feeling More Emotional
	Irritability
	Sadness
	Depression
	Nervous or Anxious
Sleep	Fatigue or Low Energy
	Drowsiness
	Trouble Falling Asleep
	Sleeping More/Less Than Usual

In screening for the presence of a concussion, symptom assessment is arguably the most sensitive measure, but this relies heavily on patient report and the symptoms are not specific to concussion as they may have other potential causes.[145,146] Patient reporting of symptoms is subject to their ability and willingness to recognize and divulge their experience of symptoms. Commonly endorsed reasons for not reporting symptoms are due to one's lack of knowledge about the symptoms being indicative of injury, not believing concussions are serious enough to report, not wanting to miss playing time, not wanting to let down the team or hurt team performance, and uncertainty regarding the effect of taking time off on one's team role.[147-150] For the diagnosis of concussion, an important criterion stated by the CISG is that the signs and symptoms must not be able to

be explained by a co-morbid factor (i.e. migraine) or substance use (i.e. alcohol).[1] As such, symptoms play a valuable role in the conservative recognition and care of concussed patients, but their role may be less clear in determining recovery as secondary pathologies or co-morbidities may cause symptoms to linger and the presence of symptoms in uninjured individuals is typical.[132,140,144,151]

Neurocognitive Impairment

The terms “neuropsychological” and “neurocognitive” have been used interchangeably in peer-reviewed literature regarding the measurement of cognitive processes following TBI. Neuropsychological assessment typically includes assessments of affect and motivation in addition to measurement of cognition; however, neuropsychological assessment protocols for SC typically consist of primarily cognitive testing alone.[152] There is a wealth of assessment instruments that may be used to measure a variety of cognitive functions and there are several types of media that can be used for assessment. The patient being tested may interact with a clinician through verbal and/or paper & pencil formats, or they may be assessed with a computer program.

Recommendations for assessing cognitive impairment following concussion include batteries of tests consisting of multiple domains of measurement.[1,22,152] For example, the Immediate Postconcussion Assessment and Cognitive Testing (ImPACT) battery is a computerized neurocognitive assessment battery that includes verbal and visual memory outcomes along with visual motor speed and reaction time.[135] Paper & pencil tests have been around

for decades and therefore have been validated in various settings, with an array of healthy and clinical samples.[153] Some proposed advantages of computerized tests are the inclusion of many versions of test forms, quick and easy assessment and evaluation of performances, the ability to assess groups of individuals simultaneously, centralized normative databases, and objectivity beyond the paper and pencil format by removing the clinician's contribution to random error.[123,128,152] However, the widespread use of computerized neurocognitive assessment has not been well-supported by the empirical measurements of reliability or validity for those instruments.[123,152,154]

As an example, the ImPACT test is the most commonly used computerized neurocognitive test (CNT), with multiple surveys indicating that over 90% of athletic trainers who perform neurocognitive testing use the ImPACT.[155-157] Despite this high usage rate, the psychometric properties of the test warrant caution with its use. The stability of the ImPACT's clinical outcomes ranges from 0.12 to 0.91 (Pearson's *r* and Intraclass Correlation Coefficients) as measured across a single day to multiple years, and the most reliable outcomes are the reaction time and visual motor speed outcomes.[151,158-164] There is a similarly wide range of reported sensitivity (53.8%-97.3%) and specificity (69.1%-97.3%) values.[146,151,165-168] These properties are possibly due to variability in test administration and interpretation practices between institutions and/or the participant samples used in these studies.

Motor Control Deficits

Another important component to the multidimensional assessment battery for concussion is an evaluation of motor control. This has been recommended by the CISG and the NATA, and typically takes the form of balance assessment.[1,22,155] The Sensory Organization Test (SOT) is considered to be the balance assessment standard to which newer, more cost- and time-effective assessments may be compared, but it is not time or cost effective.[169] The SOT assesses each of the visual, vestibular, and somatosensory systems, which are required to maintain balance, and it does so by way of a digitized force plate. The Balance Error Scoring System (BESS) was proposed Riemann and Guskiewicz as an affordable and effective alternative to the SOT and the BESS (or a modified version) has been recommended as part of clinical assessment following suspected or diagnosed concussion.[1,22,170,171] On its own, the SOT has a stability measure of up to 0.83 and has been reported sensitivity of 50% to 72% and specificity of 80%.[146,168,172-175] BESS stability over a one to two year span has been reported to be 0.41 to 0.42.[176] Sensitivity of the BESS (45% to 60%) and modified BESS (47% to 71%) are relatively low, and the specificity of these measures (BESS: 61% and modified BESS: 63% to 66%) are similar.[177,178] A recent study with a large sample of collegiate athletes indicated that removing the modified BESS from an assessment battery did not affect the sensitivity or specificity of that battery[179]. Another assessment of postural control that has had more recent attention is the Timed Tandem Gait (TTG).[178] With a reported stability measure of 0.46 over a one to two week span along with sensitivity and

specificity of 63% and 61%, respectively, TTG may only add a limited amount of value to the assessment of postural control.[178,180]

Reaction time and visual motor speed/processing speed are simultaneously neurocognitive and motor control outcomes which are commonly evaluated as a part of CNTs and/or in the form of a simple reaction time task like a “puck drop”.[181] These types of assessment typically involve a motor response to a given cognitive task such as clicking a computer mouse in response to a visual stimulus or the clasping of fingers in response to a dropping “puck”.[135,181] Stability of the motor aspects of CNTs have been reported to have correlation values (Pearson’s *r* and Intraclass Correlation Coefficients) between 0.32 to 0.91 for motor speed and 0.34 to 0.89 for reaction time.[151,159,161,163,164,168,182-184] Stability of the puck drop testing has been reported to similarly range between 0.32 to 0.87.[176,185,186] Eckner et al. reported the greatest combined sensitivity and specificity of the puck drop test at the 80% (57% sensitive, 86% specific) and 90% (50% sensitive, 79% specific) confidence levels, indicating that this assessment may be effective in ruling in a concussion within the first 48 hours of injury.[187]

Oculomotor functioning, specifically, control of saccadic movements has been reported to be a useful screening assessment following concussion. Tools like the King-Devick rapid number-naming test (K-D) and the Vestibular/Ocular Motor Screen (VOMS) have made their way into the sports medicine market.[188,189] It is believed that approximately half of the cerebral cortex is involved in vision, and this is the foundation of the use of visual assessments

using the K-D and VOMS tools.[47,190] Acutely following a concussion, the K-D and VOMS have shown variable diagnostic accuracies (20% to 100% sensitivity and 39% to 100% specificity) and also present rates of "false-positive" findings in healthy individuals of up to 36%.[149,191-201] Higher sensitivity and specificity values (> 80%) were reported solely in studies where only a few participants sustained a concussion ($n \leq 14$).[149,192-195,199] Worse K-D and VOMS performance has also been shown to correlate with symptom assessments and other common assessment tools after a concussion (including with each other) and therefore the amount of unique information that each test adds to an assessment battery is potentially limited.[188,196,198-200,202] Moreover, as decline in performance following injury is the primary outcome of the K-D and false positives are common, pre-injury baseline testing is necessary, which takes time and resources to administer.[189]

Multidimensional Assessment Batteries

The CISG consensus guidelines and NATA position statement on the management of concussion in sport recommend that multiple aspects of neurological function be assessed in order to screen for and diagnose concussion, as well as to inform the return to daily and athletic activities.[1,22] In large part, this is due to the absence of any sufficiently reliable and valid single measure to determine the presence or absence of a concussion as has been previously discussed in this review. In 2004, the CISG combined screening questions (Maddocks questions), the Glasgow Coma Scale for level of alertness, a graded symptom checklist, Standardized Assessment of Concussion (SAC) for

cognitive function, and a modified BESS assessment into a single tool: the Sport Concussion Assessment Tool (SCAT).[15,77,203,204] The SCAT has been updated over the past 15 years to the most recent version: SCAT-5, but the primary components remain the same.[1,9,20] A child version of the SCAT-5 has also been developed as the components of the adult version may not be appropriate for children.[205]

While the SCAT-5 is recommended as a sideline screening tool, the majority of evidence for the tool comes from the second and third versions. This research has shown individual components of the SCAT battery to be moderately reliable (correlation measures of 0.34 to 0.66) and sensitive to the presence of concussion (73% to 100%).[145,176,206-209] Studies consistently reported that symptoms were the most sensitive component of the SCAT tools (96% to 100%), followed by the SAC (27% to 57%), modified BESS (46% to 53%), and TTG (18% to 55%) components.[206-209] Two studies incorporating of self-reported symptoms, the SOT and the ImPACT into a single clinical assessment battery have shown combined sensitivity and specificity values up to 100%, which was in contrast to lower values in each measure individually.[146,168] As diagnostic accuracy for the multidimensional assessment battery supersedes that of individual measures, the recommendation for this approach is sound. However, the best diagnostic batteries include assessments that are time and cost-prohibitive for many clinicians.[146,168] This means that more work is needed to identify parsimonious and accurate assessment batteries for clinicians with varying access to resources. There is emerging evidence that simultaneous task

demands such as dual-task walking while performing a cognitive test may be able to detect impairments that single tasks alone may not, and this also warrants further investigation.[180]

Return to Play Criteria

There is no clear consensus on whether or not pre-injury "baseline" testing is an essential component of concussion management paradigms, although it likely adds value to the clinical decision-making process.[210-212] The "Sports as an Assessment Laboratory Model", also known as the SLAM, was initiated by Macciochi and Barth in 1989 and instituted baseline testing as a comparator for post-injury neurocognitive performance in university athletes.[213] Years later, the disparity in measures of stability, sensitivity, and specificity of neurocognitive tests like ImPACT has led clinicians and researchers to reconsider the practice of baseline assessment and instead compare post-injury outcomes to normative databases alone.[210,214] Similar caution is warranted in the case of clinical decisions based on normative data comparisons as not all individuals or institutions may fit the normative data provided by test manufacturers, thereby increasing the risks of misclassifying the presence of impairment.[210,211,215] Lastly, typical recovery of neurocognitive function following concussion occurs before the resolution of symptoms, which necessitates the use of neurocognitive assessment as part of a multidimensional assessment battery and not as a standalone tool.[1,22,131,146,168,216,217]

Before beginning the progression to return to play within the CISG's recommended return-to-sport protocol (Table 2), a patient should present with normal neurologic functioning upon physical exam and with regard to neurocognitive and motor performance on one or more of the aforementioned clinical measures. It is also recommended that student-athletes also return to full academic participation before entering into full sport participation.[1] Progression from one stage of the return-to-sport protocol to the next is driven by symptom exacerbation, or rather the lack thereof. It is recommended that patients are first given a period of 24-48 hours of physical and cognitive rest before starting the protocol. If a given level of exertion does not exacerbate symptoms within 24 hours of the activity, the patient may move on to the next stage of progression (i.e. from light aerobic exercise to sport-specific exercise). Therefore, symptoms largely dictate the return to participation in sport. Similarly, academic reintegration may require that the student be allowed adjustments or accommodations due to their symptoms, and is therefore also symptom-limited.

Table 2. Recommended Return to Sport Progression (CISG)[1]

Stage	***Aim***	***Activity***	***Goal***
1	Symptom-Limited Activity	Activities of daily living which don't exacerbate symptoms.	Reintroduce daily activities gradually.
2	Light Aerobic Exercise	Walking/stationary cardio, no resistance training.	Elevate heart rate.
3	Sport-Specific Exercise	Exercise related to sport, no head impact activities.	Increase movement.

4	Non-Contact Training Drills	Increase drill difficulty, may begin resistance training.	Increase exercise complexity and exertion.
5	Full Contact Practice	Following medical clearance, resume normal training.	Functional assessment and confidence building.
6	Return to Sport	Typical ” sport participation	Unrestricted participation.

Psychosocial Consequences of Concussion

Decreased functioning in multiple domains of health-related quality of life (HRQOL) have been observed acutely and across years in individuals diagnosed with one or more previous concussions.[218-227] Common HRQOL domains in these studies consist of physical (ex. pain), emotional (ex. depression), social (ex. getting along with peers), cognitive (ex. sustaining attention), sleep (ex. trouble falling asleep), and other related functions. There are no specific assessment tools for HRQOL functioning in those with SC that are standard in clinical practice, and the recommendation for their use is supplementary at this time.[228] This being said, general tools commonly used in research literature include the Pediatric Quality of Life Inventory™-Version 4.0 (PedsQL)[229], the Short Form 36 (SF-36)[230], the Profile of Mood States-Brief (POMS-B)[231], the Hospital Anxiety and Depression Scale (HADS)[232], the Beck Depression Inventory-II (BDI-II), the Patient Health Questionnaire-9 (PHQ-9)[233], and the Pittsburgh Sleep Quality Index (PSQI[234]. The PedsQL and SF-36 are multidimensional HRQOL assessment tools. The POMS-B, HADS, BDI, and PHQ-9 are assessments of mood states, specifically, and the PSQI assesses multiple components of sleep quality. While none of these were designed for

assessing patients with neurologic disorders or TBI, newer tools such as the Neuro-QoL and TBI-QoL batteries incorporate a multitude of domains respectively intended for these patients.[219,220] However, the Neuro-QoL and TBI-QoL have not yet been utilized in studies specific to SC.

Prior to injury, higher levels of depression assessed with the BDI-II may negatively influence neurocognitive function and may be associated with endorsement of more cognitive types of symptoms.[141] However, only a single study has observed this relationship, and a similar study found little to no evidence to support this pattern of neurocognitive impairment associated with mood state with the POMS-B.[235] Immediately following injury, lower sleep duration has been associated with greater concussion-related symptom severity and neurocognitive performance, but not longer time to return to play.[223] Mood states have been shown to decrease acutely following SC, and worse function on all domains of the PedsQL were significantly related to greater symptom severity between days three and 10 post-SC as well as with a longer time to return to play.[218,224-226,236]

Specifically, Russell et al. found that adolescents aged (mean $\pm$ standard deviation) 14.6 $\pm$ 1.17 years who went on to have concussion-related symptoms for months after their injury endorsed significantly worse function on the PedsQL within the first week following their injury.[224] This difference in PedsQL function scores was found to be maintained at weeks four, eight and 12 in pediatric patients who sustained a mild TBI and had persistent symptoms when compared to those patients who did not have persistent symptoms.[221] In a sample of 39

patients who were assessed 18 months after sustaining a mild TBI, higher rates of anxiety and depression (HADS) were observed in conjunction with worse SF-36 functional domains of pain, vitality, social aspects, and mental health when compared to matched controls.[227] A study of adult patients with various forms of mild TBI who were assessed years after their injury observed that most participants had abnormal sleep quality as indicated on the PSQI, which was related to higher levels of depression (BDI-II), fatigue, and to being of the female sex.[237] In this particular study, social and behavioral outcomes were not found to be correlated to hormonal dysfunction; however, the authors did not assess the relationships between sleep, fatigue, or depression and hormone dysfunction.

The body of literature investigating HRQOL outcomes following SC is nascent. Currently, the data surrounding HRQOL impairments stem from predominantly cross-sectional studies and are therefore largely descriptive. Even longitudinal studies have not yet mechanistically described the etiology of the HRQOL burden of TBI. Likely causes of these burdens are hypothesized to be related to hormonal disturbance(s), altered blood flow to the brain, environmental factors, perception of injury, and/or intrapersonal history of pre-injury comorbidities such as depression.[137,226,238-241] There are currently no validated therapeutic interventions to assist in recovery from concussion; however, gaining insight into specific areas of HRQOL deficit may allow for the development of QOL-related interventions. This will require obtaining knowledge of the physiologic, psychological, and environmental factors that contribute to or mediate HRQOL functioning in healthy and injured individuals.

Defining Recovery after Concussion

As discussed previously, typical recovery of self-reported symptoms occurs within three days to two weeks; however, 10 to 30% of patients will experience lingering symptoms.[131-133,141,216,242] Cognitive function may take anywhere from two to 10 days to return to normal,[131,141,223,242-244] and balance may similarly take three to 10 days to recover.[131,242,245] Return to play protocols for athletes that follow the CISG guidelines will begin after patients have returned to normal function on these measures and have reported symptom-free.[1] This indicates that return to sport participation should occur at least five days later, leading to a roughly eight to 20 day return to sport following the diagnosis of concussion. There is no consensus on what defines “recovery” and researchers have varied by using return to symptom-free, return to activities of daily living, day of written clearance to return to sport activity, or actual return to full sport participation as their recovery metrics.

In addition to the previously discussed long-term hormonal changes and HRQOL disturbances that may last for weeks to years after concussion, there is emerging evidence that physiologic changes may outlast clinical recovery. Significantly altered cerebral blood flow has been observed after return to normal on clinical assessments of symptoms, cognition, and balance in young athletes when compared to baseline and to healthy controls.[246-248] Similarly, studies have shown ongoing metabolic disturbance in the brain compared to healthy-matched controls, even after the resolution of symptoms.[249-251] Studies of brain electrical activity and motor signaling have shown impairments also lasting beyond clinical

recovery time frames.[217,252-254] Moreover, assessments of single and dual-task postural control paradigms indicate that motor function may be altered beyond clinical recovery which may or may not lead to future injury risk.[180,255,256]

PART V. FUTURE DIRECTIONS

The Biopsychosocial Model of Concussion

The sequelae of concussion injury include both physiologic and psychological factors. Given the evidence described above, the biopsychosocial model of the sequelae from concussion would include the following domains[257,258]: 1) intracranial physiologic disturbance (i.e. altered blood flow, hormonal deficiency), 2) whole-body physiologic disturbance (i.e. altered metabolism or impaired balance), 3) neuropsychological and behavior changes (i.e. worse memory, sleep disturbance), and 4) Perceptual factors (i.e. factors affecting reporting behaviors). Each of these domains may be interrelated and it would be conceivable that impairment in one domain could influence the factors in other domains.[257,258] Therefore, a holistic understanding of each of these factors and how they relate to each other is warranted in future research.

Novel Assessment of the Biopsychosocial Model of Concussion

The ability to measure intracranial metabolism is time and cost-prohibitive as it requires advanced neuroimaging and assessment techniques, and these measurements may only be able to address certain types of oxygen-requiring

metabolism and not the use of non-oxidative substrates.[48,65] However, whole-body metabolism (i.e. RMR) can be measured via indirect calorimetry and may represent an objective measurement of the physiological response to injury.[103] Indirect calorimetry is the measurement of oxygen consumption by an individual that reflects not only RMR, but also an estimate of fuel usage through the respiratory exchange ratio (i.e. RER).[7] As RMR has been shown to increase after moderate to severe TBI, and biofluids assessments of whole-body substrate shifts have been observed, indirect calorimetry may be a useful means to determine changes following mild TBI such as concussion.[8,97-99]

If whole-body metabolism or substrate use is affected by injury, it's possible that dietary changes may also occur if the body and brain are in communication regarding the need for alternative energy substrate to carbohydrates. Therefore, assessment of patient diet following concussion would provide information not only for the amount of energy being consumed, but also whether or not the total energy intake inflects with total energy expenditure, and if the type of fuels consumed relate to the types of fuels being utilized throughout recovery. A recent review has pieced together evidence that implicates the vagus nerve (responsible for visceral autonomic functioning) as a potential avenue for neuronal signal disruption as a contributor to altered appetite and mood disturbances through its input to the hypothalamus and regulation of gut microbiota.[259] Relatedly, the hormones leptin and ghrelin, which are responsible for hunger and satiety regulation, act through the hypothalamus and therefore may also be affected by injury.[260,261] Low carbohydrate (ketogenic) diets in

rodents improve concussion recovery outcomes in adolescents, while having equivocal effects in adults. This implies that the response to injury and diet intervention my differ by age.[63]

These novel assessments of energy metabolism, consumption, and eating behavior are avenues that have yet to be explored in human patients with concussion. Measurement of energy use and fuel utilization warrants further study in humans to ascertain whether intervention with a therapeutic diet may have beneficial effects in concussed patients. RMR and RER are objective physiologic measures, and would therefore not be readily influenced by self-report or effort on behalf of the patient being assessed. When combined with assessments of subjective dietary intake, physical activity, behavior (i.e. sleep), mood (i.e. anxiety), injury perception (i.e. resilience and stigma), and clinical outcomes of self-reported symptoms and time to return to play, this model can provide a picture of the holistic effects of concussion on an individual. With this information, targeted and patient-specific interventions may be elucidated, thus providing avenues to enhance patient care after injury.

APPENDIX C: ADDITIONAL METHODS

Table C1. University of Virginia Institutional Review Board Approved Protocol (IRB-HSR 17960)

IRB-HSR PROTOCOL

Investigator Agreement

BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

1. I am not currently debarred by the US FDA from involvement in clinical research studies.
2. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
3. That if this study involves any funding or resources from an outside source, or if you will be sharing data outside of UVA prior to publication that you will contact the Dean's office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
4. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.
5. That no personnel will be allowed to work on this protocol until they have completed the IRB-HSR On-line training and the IRB-HSR has been notified.
6. That all personnel working on this protocol will follow all IRB-HSR Policies and Procedures as stated on the IRB-HSR Website http://www.virginia.edu/vprgs/irb/ and on the School of Medicine Clinical Trials Office Website: http://knowledgelink.healthsystem.virginia.edu/intranet/hes/cto/sops/sop_index.cfm
7. I will ensure that all those delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training , experience or credentialing to undertake those tasks.
8. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.
9. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment
10. That any materials used to recruit subjects will be approved by the IRB-HSR prior to use.

11. That all subjects will sign a copy of the most current consent form that has a non-expired IRB-HSR approval stamp.
12. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.
13. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
14. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
15. That any serious deviation from the protocol will be reported promptly to the Board in writing.
16. That any data breach will be reported to the IRB, the UVa Corporate Compliance and Privacy Office , UVa Police as applicable.
17. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
18. That the IRB-HSR office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.
19. That a new PI will be assigned if the current PI will not be at UVA for an extended period of time. If the current PI is leaving UVa permanently, a new PI will be assigned PRIOR to the departure of the current PI.
20. All study team members will have access to the current protocol and other applicable documents such as the IRB-HSR Application, consent forms and Investigator Brochures.
21. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept at least 6 years after completion of the study.
22. No data/specimens may be taken from UVa without a signed Material Transfer Agreement between OSP/SOM Grants and Contracts Office and the new institution. Original study files are considered institutional records and may not be transferred to another institution. I will notify my department administration regarding where the originals will be kept at UVa. The material transfer agreement will delineate what copies of data, health information and/or specimens may be taken outside of UVa. It will also approve which HIPAA identifiers may be taken outside of UVa with the health information or specimens.
23. If any member of study team leaves UVa, they are STRONGLY ENCOURAGED to use Exit Checklist found on IRB-HSR website at http://www.virginia.edu/provost/facultyexit.pdf.

<u>The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.</u>

<u>Investigators Experience</u>

Dr. Jacob Resch: Dr. Resch achieved his doctorate in exercise science with an emphasis on sports medicine at the University of Georgia. Dr. Resch led a large (N=2600) longitudinal study consisting of middle and high school students at the University of Texas at Arlington prior to moving to UVa. The purpose of the longitudinal study was to address sport concussion. Dr.

Resch is also a certified athletic trainer and possesses several years of experience working with pediatric and adult participants, specifically with sport concussion.

Dr. Steve Malin: Dr. Malin achieved his doctorate at the University of Massachusetts in Kinesiology and completed his post-doctoral fellowship at the Cleveland Clinic. Dr. Malin possesses expertise in bioenergetics. More specifically, interventions designed to treat insulin resistance associated with diabetes. Dr. Malin possesses several years of experience working with human subjects, specifically in regards to assessment of metabolic rate/activity.

Dr. Susan Saliba: Dr. Saliba achieved her doctorate at the University of Virginia following the completion of her Physical Therapy degree from Hahnemann University. Dr. Saliba possesses expertise in therapeutic modalities and exercise. Dr. Saliba also has experience working with pediatric patients in regards to measures the effects of sport concussion and assessing various measurement instruments used to assess the magnitude of hits to the head during sport.

Samuel Walton: Mr. Samuel Walton is a third year doctoral candidate within the Department of Kinesiology. Mr. Walton is currently completing his doctorate under the direction of Dr. Jacob Resch. Mr. Walton has several years of a clinical experience working as a certified athletic trainer and via conducting clinical research specifically addressing sports-related concussion.

Signatures

Principal Investigator

_____	_____	_____
Principal Investigator	Principal Investigator	Date
Signature	Name Printed	

The Principal Investigator signature is ONLY required if this is a new protocol, a 5 year update or a modification changing the Principal Investigator.

Department Chair

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

1. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
2. That the Principal Investigator is qualified to perform this study.
3. That the protocol is scientifically relevant and sound.

_____	_____	_____
Department Chair or Designee	Department Chair or Designee	Date
Signature	Name Printed	

The person signing as the Department Chair cannot be the Principal Investigator or a sub-investigator on this protocol.

The Department Chair or Designee signature is ONLY required if this is a new protocol or a modification changing the Principal Investigator.

Brief Summary/Abstract

Sport concussion has been defined as a metabolic crisis. Following a concussive blow to the head a hyper- followed by a hypometabolic event ensues leading to a variety of signs and symptoms for up to 15 days in young participants. The aforementioned metabolic crisis has been solely demonstrated to occur intracranially following injury in animal models. The purpose of this study is to investigate the metabolic consequences of concussion systemically rather than isolated to the cranium and to assess caloric intake following injury. Our hypotheses include that a hypermetabolic state will exist throughout the recovery from a concussion and that participants will report consuming significantly fewer calories compared to 1) their predicted healthy caloric expenditure 2) the actual caloric state as measured in the proposed study and 3) compared to a healthy similarly matched control participant. In order to address these hypotheses high school participants from St. Anne's Belfield, Charlottesville, Albemarle, West Albemarle, and Monticello High schools, as well as young adults from UVA and the surrounding community will be recruited to participate in our study following diagnosis of a concussion by their healthcare provider. Upon gaining consent/assent from each participant, regardless of recruitment site and their parent/guardian (if appropriate and regardless of recruitment site) he/she will report to the UVa Exercise Science Laboratory located within Memorial Gymnasium within 72 hours of their diagnosed concussion (session 1). The participant will then be asked to lie in a supine position and will be fitted with a noninvasive and comfortable hood which is a component of the Vmax Metabolic Cart. After being fitted the hood participants will be asked to breathe normally for thirty minutes. If the participants choos, they can fall asleep during this time. Following the first measurement, participants will be asked to complete a 3 day dietary recall in order to assess caloric intake and be asked to wear a FitBit to assess the activity level of the participant throughout the study duration. Participants will be asked to report to Memorial Gymnasium to conduct the same procedures 7 days after the first assessment (session 2), 7 days following the second assessment (session 3), and upon reporting no further concussion related symptoms to their healthcare provider and/or study team (session 4; only for concussed participants if symptom resolution happens after session 3). In addition the actual measured resting metabolic expenditure and the actual caloric

intake; a predicted caloric intake will be calculated using the Harris-Benedict equation. Concussed participants will be matched with healthy participants who will be asked to undergo the same methodology at similar time points as their injured counterparts. Adult participants (18 years of age and older) will be asked to complete health-related quality of life outcomes during each visit. Our data analyses will consist of a mixed model analyses of variance to assess within and between subject caloric expenditure and intake as well as within and between subject health-related quality of life outcomes. We will also use demographic variables to regress onto resting energy expenditure and caloric intake variables to see which factors best predict changes in these measures following injury. All analyses will be performed with $\alpha = .05$.

Background

1. Provide the scientific background, rationale and relevance of this project.

Concussion is a complex pathophysiological process induced by biomechanical forces secondary to direct or indirect forces to the head. [1] Concussion is defined as a biomechanically induced neurological injury, resulting in an alteration of mental status, such as confusion or amnesia, which may or may not involve a loss of consciousness. [2] Disturbance of brain function is related to a neurometabolic dysfunction rather than a structural injury and is typically associated with normal structural neuroimaging findings. [2] Concussion has also been described as a neurometabolic cascade of events that involves bioenergetics challenges, cytoskeletal and axonal alterations, impairments in neurotransmission, vulnerability to delayed cell death and chronic dysfunction. [3] Concussion is classified from mild to severe on the basis of specific symptoms. [4]

Concussion gives rise to early ionic and neurotransmitter perturbations that initiate a cascade of events that disrupt normal cellular function, including changes in glucose metabolism, free radical production and mitochondrial dysfunction. [6] Disruption of normal cell membrane function results in increased intracellular calcium, vasoconstriction, decreased cerebral blood flow, and decreased glucose delivery. [4] Prolonged exposure to high levels of calcium leads to oxidative cell injury that stops the production of adenosine triphosphate (ATP). [4] Also, in an attempt to restore normal cell membrane function large amounts of ATP are requires which requires glucose metabolism. [4] This ATP deficiency creates an energy crisis. [4] Hypermetabolism, a measured rate that is at least 10% above the predicted healthy rate, has been noted in a variety of brain injuries.[7] The degree of inflammatory response is a major predictor of hypermetabolism.[7]

Changes in Ionic Fluxes

Normal transmission of signals involves neurotransmitter-mediated activation of receptors and subsequent controlled ionic changes in the postsynaptic membranes. [6] Ionic changes across the bilipid membrane are regulated by energy-dependent sodium-potassium

(Na^+-K^+) ATPase pumps.[6] A concussive event initiates a complex cascade of neurometabolic events.[2,3] Concussion causes an increased flux of glucose through the pentose phosphate pathway (PPP) during this post-injury time, possibly in response to the oxidative stress induced by a concussive event.[11] The younger brain may also be more vulnerable to these oxidative challenges due to an 'underdeveloped' mitochondrial antioxidant capacity.[9] Potassium efflux, and sodium and calcium influx occurs due to mechanoporation of lipid membranes at the cellular level.[3] Initial ionic flux and depolarization can then trigger voltage- or ligand-gated ion channels, creating a diffuse 'spreading depression-like' state that may be the biological substrate for very acute postconcussive impairments.[3] These transient cell membrane disruptions will also lead to redistribution of ions and neurotransmitters, particularly excitatory amino acids (EAAs), resulting in a further ionic flux.[2,6] The Na^+-K^+ ATP-dependent pump then works at maximal capacities to reestablish ionic balance, depleting energy stores via anaerobic glycolysis.[2] This increased demand for energy occurs in a setting of normal or decreased blood flow, resulting in a uncoupling between energy supply and demand.[3] Intracellular calcium flux, which occurs early and may persist longer than other ionic disturbances, is accommodated by impounding of calcium into mitochondria and can result in mitochondrial dysfunction, which can exacerbate problems with oxidative metabolism and ultimately worsen the cellular energy crisis.[3]

Changes in Glucose Metabolism

Ionic imbalance induces a transient increase in the cerebral metabolism of glucose (CMRglc) followed by a prolonged phase of depressed CMRglc, as well as an increased anaerobic glycolysis reflected by tissue and extracellular accumulation of lactate.[8] The duration of this phase of decreased glucose metabolism varies with injury severity, type, and age at injury.[9] The alterations in glycolytic enzyme functioning following a concussion ultimately decrease the ability for glucose to be processed efficiently for oxidative metabolism, which in turn, contributes to the post-concussion metabolic crisis.[6] Brain injury has also been shown to exacerbate the normal age differences in substrate transporters and metabolism.[13]

Some thoughts that have been suggested for this immediate post injury increase in CMRglc have been that it is caused by an increased energy demand to maintain cellular membrane ionic balance.[8] The cause of the post-injury period of depressed CMRglc is still unknown but has been observed in different experimental injury models as well as clinically.[8] Some possible mechanisms include: Ca^{++}-induced mitochondrial disruption, ionic flux disruptions, reduced cerebral blood flow or lactic acid accumulations.[9] DNA oxidative damage that also occurs after injury will increase the consumption of poly ADP-ribose polymerases (PARP), which will deplete cystolic nicotinamide adenine dinucleotide (NAD^+)[8,10], resulting in glyceraldehyde-3-phosphate (GAPDH) inhibition and glycolytic dysfunction.[11] When this occurs, glucose may not be a sufficient cerebral energy source[8,9] and the use of an alternative fuel

source during this critical period of inflammation may improve cell vitality and enhance functional outcome.[8] Early nutritional support in the care of head-injured patients, may allow for a more rapid neurological recovery from injury.[11] A sizable increase in energy expenditure in children with TBI has been noted, indirectly suggesting the importance of adequate nutrition.[5] Published pediatric TBI guidelines have even gone as far as identifying nutrition as a key issue for future investigation.[5]

In humans, local cerebral metabolic rates for glucose have been shown to be increased within the first 30 minutes (30-46% above control levels) and then after 6 hours, a hypometabolism ensues that may last up to 5 days.[2] The prolonged glucose metabolic depression reflects a period of time during which glucose uptake into the brain is compromised which could cause downstream negative effects if the energy demands of the brain are not sufficiently met.[6] Animal studies have shown the duration of CMRglc depression to last for 7-10 days before returning to sham levels in adult rats, whereas recovery has been observed within three days post-injury in pre-weaning rats.[3,4,8] This hypometabolic period has been associated with behavioral impairments in spatial learning.[3] Animal studies have also seen the accumulation of calcium within the mitochondria to peak at 2 days post injury and resolve within 4 days.[4] Furthermore, oxidative metabolism in the cortex is restored by 10 days post injury; however, a reduction has still been noted in the hippocampus.[4] It has also been noted in rats that the susceptibility to metabolic crisis following brain injury is age dependent and that a slower developing metabolic crisis in the younger brains may provide a greater window for therapeutic intervention.[8] Injury models with different age groups have also expressed that younger brains show earlier recovery of glucose metabolic rates than adults and suggests age-related differences in metabolic coping strategies or metabolic trafficking.[9] The time period of energy crisis creates a biological vulnerability and is associated with the current practice of delaying return to contact.[3] If a second injury were to occur during this metabolic vulnerability following the initial concussion, the severity of both hypometabolism and memory impairment would be greater.[3] However, if the second injury occurs after full metabolic recovery from the first injury, the two injuries will act like single and separate injuries.[3]

To determine nutritional adequacy in patients, the total amount of calories taken in by the patient is compared to the patients predicted total energy expenditure (TEE).[11] The TEE is an adjustment in the basal energy expenditure, which accounts for activity and injury.[11] The use of calorimetry, a method of assessing the amount of energy expended by measuring the amount of heat produced by the body, is a useful assessment to more accurately reveal the TEE of the patient on which to base nutritional support.[11] Some studies have shown a higher frequency of unhealthy eating behaviors in participants when compared to non-participants.[12] There is also evidence to suggest that a high prevalence of unhealthy eating behaviors exist in adolescent non-participants and participants when compared to the adult population.[12] There are a variety of different ways to assess caloric intake, nutrition, and metabolism. There is no perfect method for assessing dietary intake in children.[13] Food frequency questionnaires (FFQs) are often used in epidemiological studies since they are relatively easy to administer, less expensive, and are

easily adaptable for certain populations. [13] In FFQs respondents are asked to report the frequency of consumption and sometimes portion size for a defined list of foods. [13] Diet histories are also frequently used but are more qualitative than quantitative in that diet histories assess the past diet of an individual in the form of usual meal patterns, food intake, and food preparation practices through and extensive interview or questionnaire. [13] Food records are written accounts of actual intake of the food and beverages consumed during a specified time period (usually 3, 5, or 7 days), and by collecting the information at the time of consumption, error due to memory loss is reduced and thus food records serve as a validation standard. [13]

Indirect calorimetry is a technique that provides accurate estimates of energy expenditure from measures of carbon dioxide production and oxygen consumption during rest and steady-state exercise. [11,14] This measure can provide invaluable information regarding the energy requirements and what fuels are being oxidized at rest. [11] Indirect calorimetry is carried out on an individual basis, which makes this a fairly time-consuming process ideal for smaller studies. [19] Resting metabolic rate (RMR) and respiratory exchange ratio (RER) are important for both clinical and research settings because they provide invaluable information regarding energy requirements and what fuels are being oxidized at rest. [15] Age, body size and composition, and sex are known determinants of resting metabolic rate. [10] Resting energy expenditure (REE) can also be estimated by using various equations. [16] The White formula had the most acceptable estimates of REE followed by the Harris-Benedict formula, however, the degree of metabolic stress can be variable and difficult to accurately predict and therefore, the calculation of optimal nutrition requirements for critically ill children should be based on measurement rather than estimation of energy expenditure.[17]

Health-Related Quality of Life

Increased daily self-reported symptom (SS) burden and decreased health-related quality of life (HRQOL) have been reported both acutely and chronically after one or more SRCs.[18-21] Likely causes of these phenomena are thought to be related to hormonal disturbance(s), environmental factors and/or intrapersonal history of comorbidities such as depression.[19,22-24] Females have been reported to have greater SS both before and after SRC and have a higher baseline prevalence of mood disorders.[25-27] There is emerging evidence to say that both sleep quality and the presence of social support structure have influences on short and long-term HRQOL in those who have sustained SRC.[28-30] The acute and on-going effects of SRC on an individual's HRQOL warrant further study.

The National Institutes of Health and the National Institute on Disability and Rehabilitation Research has developed and validated a series of HRQOL measures specific to traumatic brain injury: the Traumatic Brain Injury – Quality of Life (TBI-QOL) tool.[31-34] This tool includes 22 individual measures which encompass mood and symptoms, social aspects, and

physical and mental functioning. The TBI-QOL was established in order to provide common data elements to those conduction research regarding traumatic brain injury. It has been recommended in the assessment of concussion, though only one such study has been performed to date which focused on military veterans 6 months or more after mild or moderate traumatic brain injury.[35]

To date, little to no research has addressed the resting metabolic rate and caloric intake of concussed participants. Additionally, our study will address HRQOL changes in student-participants diagnosed with sport concussion and how these relate to their individual metabolic responses. Findings from our pilot study will potentially lead to future research addressing this issue and may lead to nutritional interventions following sport concussion.

Hypothesis to be Tested

The objectives of this study include to examine the systemic metabolic rate following concussion and to determine if young participants are consuming enough calories to account for both a predicted healthy resting metabolic rate and the actual metabolic rate as measured by the VMax Metabolic Cart. Additionally, we are seeking to observe if these metabolic changes relate to self-reported measures of health-related quality of life. Our hypotheses are as follows:

Hypothesis 1: Concussed participants will be observed to have a significantly elevated resting metabolic rate throughout the typical (≤ 15 days) recovery from concussion**.**

Hypothesis 1a: Concussed participants will be observed to have significantly elevated resting metabolic rates as measured by the VMax Metabolic Cart compared to predicted resting metabolic rate within 72 hours and 7 days of their diagnosed injury.

Hypothesis 1b: Concussed participants will be observed to have significantly elevated resting metabolic rates within 72 hours and 7 days following injury compared to healthy matched controls at the same time points.

Hypothesis 2: The reported caloric intake of concussed participant's will be significantly less than predicted and measured resting metabolic rates as well as values reported by matched controls at within 72 hours, 7 days, and upon reporting symptom free.

Hypothesis 3: Age, sex, symptom severity, concussion history, and body mass index will be related to the amount of change in resting metabolic rate.

Hypothesis 4: Concussed participants will be observed to have significantly worse self-reported health-related quality of life throughout the typical (≤ 15 days) recovery from concussion**.**

Study Design: Biomedical

1. **Will controls be used?** Yes

►IF YES, explain the kind of controls to be used.

Control participants will be matched to concussed participants based on age, sport, position, height and weight. Healthy control participants will be matched retrospectively based on the demographic information for each concussed participant. Control participants will be excluded if they have been diagnosed with a concussion within 6 months or anytime during their participation in the proposed study or if they sustain any other musculoskeletal injury during the study as it may influence their metabolic rate.

2. **What is the study design?** Cohort Study

3. **Does the study involve a placebo?** No

Human Participants

Ages: 14 to 29 years of age

Sex: Male and Female
Race: All races are eligible to participate in the current study

Subjects- see below

1. **Provide target # of subjects (at all sites) needed to complete protocol.**

50 concussed participants (26 collegiate-aged [18 to 29 years of age, not enrolled in high school], 24 high school [14 to 18 years of age]) and 26 collegiate-aged healthy controls will be enrolled in the current study.

2. **Describe expected rate of screen failure/ dropouts/withdrawals from all sites.**

Due to the current working relationship between UVa and St. Anne's Belfield, Charlottesville, Albemarle, West Albemarle, and Monticello High schools as well as the University of Virginia, we expect a very low if non-existent failure/dropout/withdrawal rate for the proposed study. Attrition for the current study is expected to be $\leq$ 10%.

3.How many subjects will be enrolled at all sites? 84

50 concussed participants and 26 healthy matched participants will be enrolled in the proposed study.

4. How many subjects will sign a consent form under this UVa protocol? 84

All eligible participants (concussed and healthy) will be asked to provide assent (in participant is under 18 years of age) and/or consent (parent/guardian/participant over 18 years of age) for the proposed study. Eight additional participants will be recruited to account for attrition.

5. Provide an estimated time line for the study.

100% of participants are to be enrolled and completed (including all follow-up points) By March 15th, 2019. 100% of data analysis will be completed by March 31st, 2019.

Inclusion/Exclusion Criteria

1. List the criteria for inclusion

Eligible concussed participants:

- 14 to 29 years of age.
- Concussed participants will be identified and diagnosed based on the Concussion in Sport Consensus Panel definition by the University of Virginia's, or St. Anne's Belfield, Charlottesville, Albemarle, West Albemarle, and Monticello High schools' certified athletic trainer when the participant is an athlete. Participants who are recruited from UVA's Emergency Department (concussed adult participants only) or Student Health Department (concussed adult participants only) will be diagnosed by a healthcare practitioner (physician, nurse practitioner, etc.).
- Participants must report English as their primary language.

Eligible matched controls:

- 14 to 29 years of age
- Report English as their primary language.
- Eligible matched control participants will be matched based on age, gender, sport, and position as identified by the concussed participant if appropriate. Healthy-matches will be recruited by word of mouth from the University's student, staff and faculty populations.

2. List the criteria for exclusion

Participants receiving treatment for another injury which may influence resting metabolic rate (e.g. ankle or knee injuries). Participants diagnosed with a co-morbid pathology that may affect metabolism (e.g. diabetes or thyroid dysfunction).

3. List any restrictions on use of other drugs or treatments.

No restrictions will exist for the use of other drugs (e.g. medication used to manage ADHD).

Statistical Considerations

1. Is stratification/randomization involved? No

2. What are the statistical considerations for the protocol?

The study design is a repeated measured mixed model design. This statistical design will be used to investigate the following hypotheses:

Hypothesis 1: Concussed participants will be observed to have a significantly elevated resting metabolic rate throughout the typical (≤ 15 days) recovery from sport concussion.

Hypothesis 1a: Concussed participants will be observed to have significantly elevated resting metabolic rates as measured by the VMax Metabolic Cart compared to predicted resting metabolic rate within 72 hours and 7 days of their diagnosed injury.

Hypothesis 1b: Concussed participants will be observed to have significantly elevated resting metabolic rates within 72 hours and 7 days following injury compared to healthy matched controls at the same time points.

Hypothesis 2: The reported caloric intake of concussed participant's will be significantly less than predicted and measured resting metabolic rates as well as values reported by matched controls at within 72 hours, 7 days, and after reporting symptom free.

Hypothesis 3: Younger age, male sex, increased symptom severity, having a concussion history, and a lower BMI will predict higher energy expenditure and increased caloric intake.

Hypothesis 4: Self-reported health-related quality of life scores will indicate poorer quality of life at within 72 hours and 7 days for those concussed participants.

Our analyses will be based on group membership (concussed or healthy) and assess predicted and measured metabolic rate, caloric intake, and quality of life outcomes. Participants will also be compared based on activity level as measured by a FitBit (steps per day).

This study will use a mixed model design. Sample size for Hypotheses 1, 2, and 4 was predicted using a power = .80, a desired effect size of .75, and three time points. The total sample size required to meet these criteria is 52 participants. Additional participants will be recruited (n = 8) in order to account for attrition and to reduce any error associated with these study hypotheses. An additional 24 concussed participants (50 all together) will be recruited to allow for the inclusion of 5 predictors in the regression models for Hypothesis 3 (10:1 ratio of participants to predictors). All analyses will be conducted with $\alpha = .05$.

3. Provide a justification for the sample size used in this protocol.

This study will use a mixed model design. Sample size for Hypotheses 1, 2, and 4 was predicted using a power = .80, a desired effect size of .75, and three time points. The total sample size required to meet these criteria is 52 participants. Additional participants will be recruited (n = 8) in order to account for attrition and to reduce any error associated with these study hypotheses. An additional 24 concussed participants (50 all together) will be recruited to allow for the inclusion of 5 predictors in the regression models for Hypothesis 3 (10:1 ratio of participants to predictors). All analyses will be conducted with $\alpha = .05$.

4. What is your plan for primary variable analysis?

Hypothesis 1: Concussed participants will be observed to have a significantly elevated resting metabolic rate throughout the typical (≤ 15 days) recovery from sport concussion.

> **Hypothesis 1a:** Concussed participants will be observed to have significantly elevated resting metabolic rates as measured by the VMax Metabolic Cart compared to predicted resting metabolic rate within 72 hours and 7 days of their diagnosed injury.
>
> **Analysis:** A repeated measures ANOVA will be used to assess rested and predicted metabolic rates across time points.
>
> **Hypothesis 1b:** Concussed participants will be observed to have significantly elevated resting metabolic rates within 72 hours and 7 days following injury compared to healthy matched controls at the same time points.

Analysis: An ANOVA will be used to compare measured and predicted metabolic rates of concussed and healthy participants.

Hypothesis 2: The reported caloric intake of concussed participant's will be significantly less than predicted and measured resting metabolic rates as well as values reported by matched controls at within 72 hours, 7 days, and upon reporting symptom free.

Analysis: An ANOVA will be used for each time point to assess differences between caloric expenditure and intake between groups.

Hypothesis 3: Younger age, male sex, increased symptom severity, having a concussion history, and a lower BMI will predict higher energy expenditure and increased caloric intake: Separate linear least-squares regression models for RMR, TEE and EBal at assessment time point 1. Backwards step-wise removal will begin with all 5 of the independent variables included in the full model.

Hypothesis 4: Self-reported health-related quality of life scores will indicate poorer quality of life at within 72 hours and 7 days for those concussed participants: An ANOVA will be used for each time point to assess differences between health-related quality of life measures between groups.

5. What is your plan for secondary variable analysis?

All analyses have been addressed in Item 4.

6. Have you been working with a statistician in designing this protocol?

No, Dr. Resch completed his doctorate in measurement which will be adequate for the analyses proposed for this study.

7. Will data from multiple sites be combined during analysis?

Participants will be recruited from St. Anne's Belfield, Charlottesville, Albemarle, West Albemarle, Monticello High school, and the University of Virginia but data will only be collected at Memorial Gymnasium.

Biomedical Research

1. What will be done in this protocol?

Participants will be recruited upon being diagnosed with a concussion by their Athletic Trainer or other certified health care provider. All healthy matched control participants will be matched retrospectively based on the injured participant's demographics.

The following procedures will take place after a concussive event at St. Anne's Belfield, Charlottesville, Albemarle, West Albemarle, Monticello High school and/or UVa:

- Following the diagnosis of a sport concussion the participant (and their parent/ guardian when the participant is under 18 years of age) will be provided a study summary.
- If the parent/guardian and participant express interest in the study the healthcare provider at St. Anne's Belfield, Charlottesville, Albemarle, West Albemarle, Monticello High schools and/or at UVa Athletics, Emergency Department or Student Health will contact Dr. Jacob Resch or Samuel Walton to arrange an appointment within the following 72 hours of injury at the Memorial Gymnasium Exercise Science Laboratory. Additionally, participants will be asked to fast from 12:00 AM that evening until the completion of the study the following morning between 6:00 and 9:00 AM. Participants will be asked to bring a "standard breakfast" to this session so they can eat immediately following the protocol.

Session 1

- Upon arriving at Memorial Gymnasium, parents and participants will meet with and investigator in order to have the study explained and to provide the consent/assent document(s). The investigator will make sure the subject had fasted from the night before beginning the study.
- After obtaining consent/assent, the participant will complete a health and symptom questionnaire followed by collection of anthropometrics: height, weight, body composition using a Tanita In-Body bioelectrical impedance measuring device.
- Next, participants will be asked to lie on an examination table while they are fitted with the VMax Metabolic Cart canopy. This canopy is designed to be minimally invasive. From the investigators' past experience, most participants can fall asleep during the assessment. Participants will be fitted with a dome-like structure that will only have tubes exiting the exterior surface. Participants will not be asked to use a mouthpiece or any other invasive equipment. Participants will then be asked to breathe normally for the next 30 minutes as O2/Co2 are being measured via the canopy.
- Following the 30 minute data collection period, participants will be encouraged to eat while they complete about 30 minutes worth of health-related quality of life measures (**adult participants only, with the exception of the HIS-r, which will be completed by all participants**):
    - Neuro-QOL v1.0 - Sleep Disturbance SF_
    - Revised Head Injury Scale (HIS-r; self-reported symptom inventory)

- TBI-QOL v1.0 Ability to Participate in Social Roles and Activities SF10a
- TBI-QOL v1.0 Anxiety SF10a
- TBI-QOL v1.0 Attention-Concentration SF6a
- TBI-QOL v1.0 Communication SF9a
- TBI-QOL v1.0 Depression SF10a
- TBI-QOL v1.0 Emotional Behavorial Dyscontrol SF 10a
- TBI-QOL v1.0 Fatigue SF10a
- TBI-QOL v1.0 Headache Pain SF10a
- TBI-QOL v1.0 Positive Affect Well Being SF 9a
- TBI-QOL v1.0 Resilience SF10a
- TBI-QOL v1.0 Satisfaction with Social Roles and Activities SF 10a
- TBI-QOL v1.0 Self-Esteem SF10a
- TBI-QOL v1.0 Stigma SF7a
- Tampa Scale of Kinesiophobia-11
- Two questions about current and "normal" appetite
- A general question regarding how they feel as a percentage of normal.

- The investigator will then explain the remainder of the procedures. At the conclusion of session 1, participants will be asked to record via paper and pencil their food intake for the next three days. The subject will take home a dietary recall journal (which is attached) and return the completed 3 day journal to the investigator. The information will then be entered into a caloric assessment program to calculate and average total caloric intake. Participants will also be asked to wear a FitBit to assess the number of steps per day while participating in the proposed study. At the end of each day, participants will record the number of steps they have taken on a sheet of paper. Data collected will not be entered into the FitBit cloud. At the conclusion of the study, participants will be asked to return the FitBit to the research team. Compensation for participation will be given upon the receipt of the dietary and step-count by the investigator.

Session 2

- Participants will then return to Memorial Gymnasium seven days following their injury for their second assessment and initially complete solely the symptom inventory. Participants will be asked to fast beginning at 12:00 AM the night prior to their visit as described in session 1.
- Participants will then be measured for anthropometrics and subsequently be placed in a supine position and will be fitted with the VMax metabolic cart canopy as described for session 1.
- Following the participant's caloric expenditure measurement using the VMax Metabolic Cart they will then be asked to answer the quality of life questions and record their caloric intake for the next three days as described in session 1. Compensation for participation will be given upon the receipt of the dietary and step-count by the investigator.

Session 3

- This session will be identical to session 2. Compensation for participation will be given upon the receipt of the dietary and step-count by the investigator.

Session 4 (only for concussed subjects whose symptoms resolve after session 3 AND matched controls)

The final assessment will occur when concussed participants report no further concussion related symptoms, but only if they reported experiencing symptoms during session 3. Participants will undergo the same procedures as described for the second and third sessions including an overnight fast starting at 12:00 AM the night prior to their appointment.

After completion of the three day diet recall following their symptom free assessment (either session 3 or session 4) participants will have completed all study components. Compensation for participation will be given upon the receipt of the dietary and step-count by the investigator.

Participants will have the option to withdrawal from participation at any point of the study without any type of penalty from UVa athletics, St. Anne's Belfield, Charlottesville, Albemarle, West Albemarle, Monticello High schools, and/or the UVa Emergency Department and Student Health.

2. List the procedures, in bullet form, that will be done for research as stipulated in this protocol.

ALL

3. Will you be using data/specimens in this study that were collected previously, with the use of a research consent form, from another research study? No

4. Will any of the procedures listed in item # 2 have the potential to identify an incidental finding? No

5. Do any of the procedures listed above, under question # 2, utilize any imaging procedures?

No

6. Will you be using viable embryos? No

7. **Will you be using embryonic stem cells?** No

8. **Are any aspects of the study kept secret from the participants?** No

9. **Is any deception used in the study?** No

If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study. NA

10. Will your study involve measures used to screen or assess for depression and/or suicidality <u>for research purposes? Yes</u>

NOTE: Answer this question YES if any of the following apply:

1) *The protocol has a research purpose to study suicide, suicidal ideation, depression or trauma*
2) *The protocol has a research purpose to study traumatic life events that may evoke powerful emotion or induce mood changes in participants;*
3) *The protocol includes **assessments** or tools (e.g. Surveys, exams, questionnaires, etc.) that can be used to screen or identify **depression (C-SSRS/BID/SCID, questions related to mood, etc.) and/or suicidal ideation** (thoughts of suicide, either active or passive), plan (the means or mechanism) or intent (the expressed desire and willingness to act on the plan).*

a) Which research staff members will be available to provide appropriate referral for further care or intervention if the study tools indicate this need?
Answer by position with study (e.g. PI, sub investigator etc. Do not include names in answer.
Answer/Response: Dr. Resch, Mr. Walton and Mr. Erdman are licensed healthcare professionals. One of the aforementioned investigators will be present during all study assessments and will be able to provide the appropriate referral when necessary. The PI and Mr. Walton and Erdman are licensed athletic trainers who are familiar with the referral process.

b) Include specific guidelines for intervention or further assessment based on tools and rating scales used in this study (i.e. based on score of xxx or response of X, subject will be assessed further by the PI for suicide risk or referred urgently to an ED, crisis center, or clinic immediately).
Answer/Response: If a participant endorses anything other than "Never" on the TBI-QOL v1.0 Depression SF10a question: "I felt I had no reason for living", they will be referred immediately for help.
   (i) If they are a student-athlete (or collegiate) their athletic trainer will be contacted and referral will be coordinated through that athletic trainer.
   (ii) If the participant is not a student-athlete, but are enrolled at the University of Virginia they will be referred to Student Health: Counseling and Psychological Services.
   (iii) Participants who were recruited from the University of Virginia Emergency Department, if not a student at a participating high school or at the University of Virginia, will be referred to the University of Virginia Emergency Department and/or University of Virginia Department of Psychiatry and Neurobehavioral Sciences.

c) Describe a plan to link participants to psychological help if needed and include written materials listing those resources as an attachment to the protocol. State how imminent risk of harm will be handled. (i.e. may include a list of local psychiatry/psychotherapy providers at UVA)
Answer/Response: The PI or a licensed athletic trainer sub investigator will refer any participant who fits the abovementioned criteria (section b.) to the appropriate provider for psychological help.
   (i) If a participant is a student-athlete at UVa, their athletic trainer will be notified and will subsequently refer them to Dr. Jason Freeman, who is a licensed neuropsychologist working within UVa athletics.
   (ii) If the participant is a non-athlete, they will immediately be referred to Counseling and Psychological Services (CAPS) through UVa's Student Health Center. The phone number for CAPS is (434) 243-5150 and is available 24/7. Alternatively, the investigator may contact emergency services through calling 911.
   (iii) Participants who were recruited from the University of Virginia Emergency Department, if not a student at a participating high school or at the University of Virginia, will be referred to the University of Virginia Emergency Department (911) and/or University of Virginia Department of Psychiatry and Neurobehavioral Sciences (434.924.2718).

d) If your subjects will be patients at UVA Medical Center, confirm you plan to adhere to **Medical Center Policy 0140 Judicial Treatment Order and 0197 Suicide Risk Assessment and Prevention.**
Answer/Response: N/A

e) Will subjects, who discontinue or are withdrawn secondary to suicidal ideations/depression prior to study completion, be asked to come to the site for an early withdrawal visit as soon as possible?
Answer/Response: No

If No, provide outline of plan for follow-up or indicate if follow up is not required.
Follow-up will not be required for this study.

Data and Safety Monitoring Plan

This study has been deemed minimal risk. Because this study poses minimal risk to the subject, **adverse events will only be collected or recorded if a causal relationship to the study intervention is suspected.** If any adverse event is considered serious and unexpected, the event must be reported to the IRB-HSR within 7 days from the time the study team receives knowledge of the event.

1. Definitions

1.1 How will you define adverse events (AE)?

Do not change this answer

An adverse event will be considered any undesirable sign, symptom or medical condition considered **related to the intervention**. Medical condition/diseases present before starting the intervention will be considered adverse events only if they worsen after starting the study and that worsening is considered to be related to the study intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research.

1.2 How will you define an unanticipated problem?

Do not change this answer

An unanticipated problem is any issue that involves increased risk(s) to participants or others. This means issues or problems that cause the subject or others to be placed at greater risk than previously identified, even if the subject or others do not incur actual harm. For example if a subject's confidentiality is compromised resulting in serious negative social, legal or economic ramifications, an unanticipated problem would need to be reported. (e.g serious loss of social status, loss of job, interpersonal conflict.)

1.3 What are the definitions of a protocol violation and/or noncompliance?

Do not change this answer

A protocol violation is defined as any change, deviation, or departure from the study design or procedures of research project that is NOT approved by the IRB-HSR prior to its initiation or implementation**.** Protocol violations may be major or minor violations.

Noncompliance can be a protocol violation OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulation**s.** Noncompliance may be serious or continuing

Additional Information: see the IRB-HSR website at http://www.virginia.edu/vpr/irb/HSR_docs/Forms/Protocol_Violations_%20Enrollment_Exceptions_Instructions.doc

1. What is the definition of a data breach?

Do not change this answer

A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Additional Information may be found on the IRB-HSR Website: Data Breach

2. What risks are expected due to the intervention in this protocol?

Expected Risks related to study participation	**Pick One**
There is a small risk that breaches of privacy and/or confidentiality might occur. The risk of violation of subject privacy and confidentiality is minimal due to the requirements of the privacy plan in this protocol.	Occurs rarely

3. When will recording and reporting of unanticipated problems/adverse events begin?

__x___After subject signs consent

_____After subject begins study intervention

_____Other Specify Answer/Response:

4. When will the recording/reporting of unanticipated problems/adverse events end?

_x____Subject completes participation in the protocol

_____End of intervention

_____30 days post intervention

_____Subject completes intervention and follow up period of protocol

_____Other: Specify Answer/Response:

5. What is your plan for safety monitoring?

Do not change this answer

Safety monitoring and aggregate review of adverse events, unanticipated problems, protocol violations and any data breach will be performed by the PI and IRB-HSR through continuation review at least annually.

6. What is your plan for reporting a Unanticipated Problem, Protocol Violation or Data Breach?

Do not change this answer

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?

Unanticipated Problems tha are not adverse events or protocol violations This would include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc)*
Protocol Violations/Noncompliance (*The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.)* **OR** **Enrollment Exceptions**	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation, Noncompliance and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html* *Go to 3rd bullet from the bottom.*
Data Breach of Protected Health Information	The UVa Corporate Compliance and Privacy Office ITC: if breach involves electronic data UVa Police if breach includes	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html Police: phone- (434) 924-7166

	items that are stolen		

Payment

1. Are subjects being reimbursed for travel expenses (receipts /mileage required)**?** No

►IF NO, Do you confirm you are aware of the following procedures to follow for reimbursements? Yes

2. Are subjects compensated for being in this study? YES

►IF YES, answer the following questions (2a-2d).

2a. What is the maximum TOTAL compensation to be given over the duration of the protocol?

For concussed subjects: Up to $40 in Amazon gift cards.

For control subjects: Up to $40 in Amazon gift cards.

2b. Explain compensation to be given.

Participants will receive one gift card after each testing session. Most participants will complete only three time points. If a participant completes a fourth time point (in the instance that they are still experiencing symptoms during the third assessment), they will receive a gift card for participation in this session as well. Gift cards will be given upon receipt of the 3 day dietary recall following each assessment.

2c. Is payment pro-rated?

Yes - as explained above

If No, explain why payment cannot be pro-rated.
Answer/Response:

2d. Is money paid from UVa or State funds (including grant funds) or will items such as gift cards be distributed through UVa? Yes

►IF YES, answer the following questions [2d(i)-2d(ii)].

2d(i). How will the researcher compensate the subjects?

__x___ Gift card/Debit Card

2d(ii). Which category/ categories best describes the process of compensation?

Choose one of the following 3 options

_____ All compensation will be made via check issued to participant via UVA Oracle or State system

The preferred method

____ __ Compensation will include an alternative method (petty cash, gift card, other) and tax information will be collected, securely stored, and submitted electronically to Procurement Services as required.

►If this box is checked and an alternate method will be used, justify why you are unable to issue checks through the UVa Oracle or state system.

Guidance to answer this question.

See question: When is it justifiable to provide compensation using an alternative method of payment while still collecting tax information?

IMPORTANT: If you check this box you will be required to submit the subjects' name, Social Security number, full address and amount of payment to Procurement at the end of each calendar year. The Office of the VP for Research will send you instructions on this procedure at a later date.

If the sponsor is providing the gift card/debit card and sending to UVA study team for distribution, please include the statement "SPONSOR REQUEST" under the request for justification.

__x___ Compensation will include an alternative method (petty cash, gift card, other) and tax information cannot be collected. Total possible compensation per participant for participating in the research study over one year is limited to <=$50.

INSTRUCTIONS: If the subject will receive <$50/year in this study check this option and insert the following answer to both questions below. Subjects will be compensated $50 or less per year for this protocol and subjects may hesitate to enroll in the study if it requires they share their Social Security number for such a small amount of money.

►If an alternate method will be used justify why you are unable to issue checks through the UVa Oracle or state system:

Guidance to answer this question.

See question: When is it justifiable to provide compensation using an alternative method of payment while still collecting tax information?

Answer/Response: Subjects will be compensated $50 or less per year for this protocol and subjects may hesitate to enroll in the study if it requires they share their Social Security number for such a small amount of money.

►If you are unable to collect the tax information justify why it cannot be collected.

Answer/Response: Subjects will be compensated $50 or less per year for this protocol and subjects may hesitate to enroll in the study if it requires they share their Social Security number for such a small amount of money.

Guidance to answer this question.

See question: When is it justifiable to provide compensation if the tax information cannot be collected?

Risk/ Benefit Analysis

1. What are the potential benefits for the participant as well as benefits which may accrue to society in general, as a result of this study?

There are no direct benefits for participants if they participate in the current study. Information gained during this study will also benefit participants with concussion as this will serve as the basis for a nutritional intervention if our alternative hypotheses are accepted.

2. Do the anticipated benefits justify asking subjects to undertake the risks?

Yes, participants will be under the supervision of Dr. Jacob Resch, who possesses expertise in sport concussion. Participation will be of minimal risk and allow parents/participants to ask questions to Dr. Resch or Mr. Walton regarding their/their child's condition.

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APPENDIX: Legal/Regulatory

Recruitment

The following procedures will be followed:

- Finders fees will not be paid to an individual as they are not allowed by UVa Policy.
- All recruitment materials will be approved by the IRB-HSR prior to use. They will be submitted to the IRB after the IRB-HSR has assigned an IRB-HSR # to the protocol.
- Only those individuals listed as personnel on this protocol will recruit and or conduct the consenting process with potential subjects.

Retention Incentives

Any item used by the sponsor/ study team to provide incentive to a subject to remain in the study, other than compensation identified in the Payment section, will be submitted to the IRB for review prior to use. The IRB-HSR will provide the study team with a Receipt Acknowledgement for their records. Retention incentive items are such things as water bottles, small tote bags, birthday cards etc. Cash and gift cards are not allowed as retention incentives.

Clinical Privileges

The following procedures will be followed:

- Investigators who are members of the clinical staff at the University of Virginia Medical Center must have the appropriate credentials and been granted clinical privileges to perform specific clinical procedures whether those procedures are experimental or standard.
- The IRB cannot grant clinical privileges.
- Performing procedures which are outside the scope of the clinical privileges that have been granted may result in denial of insurance coverage should claims of negligence or malpractice arise.
- Personnel on this protocol will have the appropriate credentials and clinical privileges in place before performing any procedures required by this protocol.
- Contact the Clinical Staff Office- 924-9055 or 924-8778 for further information.

Sharing of Data/Specimens

Data and specimens collected under an IRB approved protocol are the property of the University of Virginia. You must have "permission" to share data/ specimens outside of UVa other than for a grant application and or publication. This "permission" may come in the form of a contract with the sponsor or a material transfer agreement (MTA) with others. A contract/ MTA is needed to share the data outside of UVa even if the data includes no HIPAA identifiers and no code that could link the data back to a HIPAA identifier.

- No data will be shared outside of UVa, beyond using data for a grant application and or publication, without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.
- No specimens will be shared outside of UVa without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.

Prisoners

If the original protocol/ IRB application stated that no prisoners would be enrolled in this study and subsequently a subject becomes a prisoner, the study team must notify the IRB immediately. The study team and IRB will need to determine if the subject will remain in the study. If the subject will remain in the study, the protocol will have to be re-reviewed with the input of a prisoner advocate. The prisoner advocate will also have to be involved in the review of future continuations, modifications or any other reporting such as protocol violations or adverse events.

Prisoner- Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.

For additional information see the OHRP website at
http://www.hhs.gov/ohrp/policy/populations/index.html

Compensation in Case of Injury

If a subject requests compensation for an injury, the study team should notify the IRB-HSR (924-9634/2439847) the UVa Health System Patient Relations Department (924-8315). As a proactive

courtesy, the study team may also notify UVa Health System Patient Safety and Risk Management (924-5595).

On request, the study team should provide the Risk Management Office with the following information/documents:

- Subject Name and Medical Record Number
- Research medical records
- Research consent form
- Adverse event report to IRB
- Any letter from IRB to OHRP

Subject Complaints

During a research study, the study team may receive complaints from a subject. If the study team is uncertain how to respond to a complaint, or is unable to resolve it with the subject, the study team may contact the IRB-HSR (924-9634/243-9847), the UVa Health System Patient Relations Department (924-8315).

Request for Research Records from Search Warrant or Subpoena

If the study team receives a request for research records from a search warrant or subpoena, they should notify UVa Health Information Services at 924-5136. It is important to notify them if information from the study is protected by a Certificate of Confidentiality.

APPENDIX: Unapproved Device Use
(Unapproved Device being used but not evaluated)

1. **List name of device(s) being used in an unapproved manner in this protocol**.

Per the statute: Federal Food, Drug, and Cosmetic Act Sec 201.h [21USC321]

DEVICE: (h) The term "device" (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c)) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—
(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Answer/Response: Vmax Metabolic cart

2. **Do you confirm the device is only being USED and NOT being evaluated in this study?** Yes

3. **Is the device a Research Use Only (RUO) device?** No

►If the device is NOT a RUO device, is the device currently approved for any indication?
Answer/Response: Yes, to assess indirect calorimetry for a variety of populations.

►If the device is currently approved list the indication:

INSTRUCTIONS: Also submit the Manufacturer's Brochure

Answer/Response: see above

►If the device is currently approved, do you confirm that results will not be used in clinical care of the subject (e.g. will not be used for diagnosis or treatment?)
Answer/Response: yes

4. **In how many humans has this device been used previously as it is being used in this study?**
Extensively, as this is considered a gold standard for measuring metabolic rate.

5. **Describe pertinent human data that is available regarding the safety of this device as you are using it in this protocol.**
The device used in this study is equivalent to that used by the Exercise Physiology Core Laboratory in the School of Medicine. Dr. Malin, CO-I has used this device extensively to assess metabolic rate (Malin 2013 Journal of Applied Physiology, Malin 2014 Medicine and Science & Sports and Exercise). Our team employs standard procedures to ensure subject safety, including routine calibration and subject familiarization of equipment.

6. **If this protocol will be used in children, describe any previous use of this device with children of a similar age range as it is being used in this study.**
Indirect Calorimetry is routinely used in children to assess metabolic rate during rest, exercise, and fed conditions (Chu 2011 Eru J Appl Physiol; Timmons Appl Physiol Nutr Metab 2007). In this protocol, we will perform resting measures only following our routine protocols.

7. **What steps will be taken to minimize risk?**
   The device will be used according to the brochure.

8. **Would you consider the use of this device to be minimal risk? Why or why not?**
   Yes. Participants simply lie on a comfortable examination table while wearing an "astronaut" type helmet. The helmet sits two feet away from the participant's nose. Participants are simply asked to breathe normally and often fall asleep during the measurement.

APPENDIX: Recruitment

Recruitment includes identifying, review of records to determine eligibility or any contact to determine a potential subjects interest in the study.

*The UVa HIPAA covered entity is composed of the UVa VP Office of Research, the Health System, School of Medicine, School of Nursing, Nutrition Services (Morrisons), the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory and the Exercise Physiology Laboratory.

1. **How do you plan to <u>identify</u> potential subjects?**

- To "identify" a potential subject refers to steps you plan to take to determine which individuals would qualify to participate in your study. This does NOT include steps to actually contact those individuals.
- If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being identified by the given method.
- Check the methods you plan to utilize:

a.____ Chart Review/ Clinic Schedule Review/ Database Review from a database established for health care operations (departmental clinical database) or an Improvement Project (*e.g. Performance Improvement, Practice Improvement, Quality Improvement*).

<u>If you plan to obtain data from the UVa Enterprise Data Warehouse (EDW) please see option b below.</u>

<u>DHHS:</u> Study team requests Waiver of Consent to identify potential subjects.

<u>HIPAA:</u> Allowed under Preparatory to Research if PHI to be accessed.

IMPORTANT

Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

--a UVa student working in the UVa HIPAA Covered Entity*

--a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

b_X__ Review of a database that was established to keep data to be used for future research such as the CDR, departmental research database or use of data from a separate current active research protocol.

If you plan to obtain data from the UVa Enterprise Data Warehouse (EDW) you are required to submit your request to the CDR. The CDR staff will work with the EDW to obtain the data you need.

DHHS: Study team requests Waiver of Consent to identify potential subjects.

HIPAA: Allowed under Preparatory to Research if PHI to be accessed.

IMPORTANT

Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they who meet one of the following criteria:

--a UVa student working in the UVa HIPAA Covered Entity*

--a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

The information from which you are obtaining potential subjects must also have an IRB protocol approval. If this item is checked, enter the IRB # below.

IRB# _20052 (for healthy participants only)

If obtaining information from the Clinical Data Repository (CDR) insert IRB # 10797

c. ____ Patients UVa health care provider supplies the UVa study team with the patients contact information without patients' knowledge.

DHHS: Study team requests Waiver of Consent to identify potential subjects.

HIPAA: Allowed under Preparatory to Research if PHI will be shared by the health care provider.

IMPORTANT

Keep in mind that PHI may only be given to individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

--a UVa student working in the UVa HIPAA Covered Entity*

--a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

d. ____ Patient obtains information about the study from their health care provider. The patient contacts the study team if interested in participating. (Health care provider may or may not also be the a member of the study team)

DHHS: NA

HIPAA: Allowed under Health Care Operations

If this choice is checked, check 3d-INDIRECT CONTACT below.

e. ___x_ Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure etc.

If this choice is checked, check 3d- INDIRECT CONTACT below.

DHHS & HIPAA: NA

f. _____ Potential subjects have previously signed a consent to have their name in a registry/database to be contacted for future studies of this type.

IRB# of registry/ database: _____

DHHS & HIPAA: NA

_X___ Other*:* Patient obtains information about the study from their healthcare provider upon being diagnosed with a concussion. Healthy controls matched will be informed about the current study via word-of-mouth or via flyer.

Referring providers for each site include:

a. High Schools – Certified athletic trainer in charge of care for that school's student-athlete population.
b. UVA Varsity Athletics - Certified athletic trainer employed by UVA in charge of care for each particular sport.
c. UVA Emergency Department (Concussed adults only) – Dr. Joshua Easter.
d. UVA Department of Student Health (Concussed adults only) – Dr. Christopher Holstege.
e. Healthy Adults (to be matched to ED and Student Health concussed participants) – This study's investigators (Dr. Jacob Resch and Sam Walton)

Upon the parent and the participant both expressing interest in participating in the current study, the healthcare provider or adult patient will contact Mr. Walton in order to implement the initial phases of the study protocol.

If item # a, b or c is checked above and if this protocol involves the use of protected health information do you confirm the following to be true?

- The use or disclosure is sought solely to review protected health information as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the UVa covered entity.
- The PHI that the researcher seeks to use or access is necessary for the research purposes.

Answer/Response: Yes

2. How will potential subjects be <u>contacted?</u>

To "contact" a potential subjects refers to the initial contact you plan to take to reach a potential subject to determine if they would be interested in participating in your study. This may include direct contact by such methods as by letter, phone, email or in-person or indirect contact such as the use of flyers, radio ads etc.

If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being contacted by the given method.

Check the methods below you plan to utilize:

a.__X__ Direct contact of potential subjects by the study team via letter, phone, direct e-mail. Members of study team ARE NOT health care providers of patients. Information will not be collected from psychotherapy notes.

<u>Note:</u> Letter, phone, direct email scripts must be approved by IRB prior to use. See IRB-HSR Website for templates.

<u>DHHS/HIPAA:</u> Study team requests a Waiver of Consent and Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:

Keep in mind that if PHI was collected during the identification phase that contact with potential subjects may only be performed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

- a UVa student working in the UVa HIPAA Covered Entity*
- a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

b.____Potential subjects will be approached while at UVa Hospital or Health Clinic by a person who is NOT a member of their health care team. Information will not be collected from psychotherapy notes.

DHHS & HIPAA: Study team requests a Waiver of Consent and a Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:

Keep in mind that contacting individuals in a clinical setting may only be performed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

a UVa student working in the UVa HIPAA Covered Entity*

a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

You should share the following information with the potential subject:

- Your name
- Who you are: physician, nurse etc. at the University of Virginia.
- Why you want to speak with them
- Ask if you have their permission to explain the study to them
- If asked about how you obtained their information use one of the following as an option for response.
    - DO NOT USE THIS RESPONSE UNLESS YOU HAVE OBTAINED PERMISSION FROM THEIR UVa PHYSICIAN: Your doctor, Dr. insert name wanted you to be aware of this research study and gave us permission to contact you.

- We obtained your information from your medical records at UVa.
- Federal regulations allow the UVa Health System to release your information to researchers at UVa, so that we may contact you regarding studies you may be interested in participating. We want to assure you that we will keep your information confidential.

- IF THE PERSON SEEMS ANGRY, HESITANT OR UPSET, THANK THEM FOR THEIR TIME AND DO NOT ENROLL THEM IN THE STUDY. YOU MAY ALSO REFER THEM TO THE IRB-HSR AT 924-9634.

c.____Direct contact of potential subjects by the study team by approaching in person at UVa or via letter, phone, direct e-mail. Members of study team contacting potential subjects ARE health care providers of patients.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.

See IRB-HSR Website for templates.

DHHS: Study team requests a Waiver of Consent to contact potential subjects

HIPAA: Allowed under Health Care Operations.

d._x___ Indirect contact (flyer, brochure, TV, broadcast emails, patient provided info about the study from their athletic trainer and either the patient contacts study team or gives their athletic trainer permission for the study team to contact them.)

The indirect method used (flyer, brochure, TV, broadcast emails) must be approved by the IRB prior to use. The IRB does not need to review any type of script to use when the potential subject responds to the indirect method.

DHHS & HIPAA: NA

e. X Potential subjects are not patients. The study does not include obtaining subjects health information. Subjects will be contacted directly via email, phone, letter or presentation in group setting with consent then obtained individually in a private setting.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.

See IRB-HSR Website for templates.

DHHS: Study team requests a Waiver of Consent to contact potential subjects.

HIPPA: NA

3. **Will any additional information be obtained from a potential subject during "prescreening"?** No

4. **Do you plan to ask the subjects to do anything, other than answering questions, for the study prior to signing a consent?** Yes

►**IF YES, explain in detail what you will ask them to do**.

Answer/Response: Fast until the first visit

5. **How will the consenting process take place with either the prospective subject, the subject's legally authorized representative or parent/legal guardian of a minor (if applicable)?**

Parents/guardians and subject will be asked to provide written consent/assent following a detailed explanation of the current study. Following my explanation, the parent followed by the minor will be asked if they have any additional questions prior to providing consent/assent.

For those participants between the ages of 18 and 29, their healthcare provider will briefly ask about their interest in participating in the study following the diagnosis of a concussion. If interested, the research team will meet the

participant at Memorial Gymnasium and provide the consent form coupled with an in depth explanation of the study in order to obtain consent.

6. Will subjects sign a consent form for any part of the study? Yes

7. Will the study procedures be started the same day the subject is recruited for the study? Yes. After obtaining consent/assent, the participant will begin the outlined protocol.

►IF YES, explain in detail why the subject cannot be given more time to make a decision to consent.

Answer/Response: The study aims to study young participants who have experienced a concussion. Beginning in the study is time sensitive as there is a narrow window until the condition resolves.

►IF YES, explain in detail what will be done to assure the potential subject has enough time to make an informed decision.

Answer/Response: Subjects will be given the option to return the following day if they feel they need more time to decide.

8. Is there the potential to recruit economically or educationally disadvantaged subjects, or other vulnerable subjects such as students or employees?

Answer/Response: Yes

IF YES, what protections are in place to protect the rights and welfare of these subjects so that any possible coercion or undue influence is eliminated?

Answer/Response: Students are not under the direct supervision of the PI or any other research team member. Neither the PI or research influences any outcome following the participant's injury either academically or in regards to sport participation.

9. Do you need to perform a "dry run" of any procedure outlined in this protocol? No

APPENDIX: Participation of Children

In the state of Virginia a person under the age of 18 is considered a child.

1. Explain why this research topic is relevant to children.

Answer/Response: Concussion has gained an exponential amount of media and research attention especially in regards to management and long-term effects. This study will address a novel question regarding metabolic expenditure in young participants. If caloric expenditure is noted to be above normal resting rates, a nutritional intervention may be appropriate and may lead to a more full recovery.

2. Is the knowledge being sought in this study already available for children or is it currently being acquired through another ongoing study?

Answer/Response: No evidence currently exists regarding this line of scientific inquiry.

3. Provide data that is available in adults in order that the IRB may judge the potential risk in children. If there is no adult data available, provide reasons why not. If this information is available in a sponsor's protocol, you may reference the section # here and not duplicate the information.

Given this specific line of research, no current research exists addressing resting metabolic rate in either children or adults. That said, a pilot study conducted at the University of Texas at Arlington performed on 5 adolescent student-athletes diagnosed with sport concussion demonstrated an approximately increase of 500 calories beyond predicting resting state metabolic rate.

4. **Is the potential subject population likely to include wards of the state or children who are more at risk for becoming a ward of the state?** No

4a. Is the research is this protocol related to the childs' status as a ward of the state?

No

4b. Is the research to be conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards? Yes

4c. Are you aware of the following requirement?

If the consent form contains a signature line for both parents the study team will notify the IRB immediately, if at any time during the course of the research, it becomes known that a potential subject is a ward of the state or that a child already enrolled in this protocol becomes a ward of the state.

Answer/Response: Yes

5. **Does this study involve a placebo arm?** No

6. **Will UVa researchers conduct the study outside the state of Virginia?** No

APPENDIX: Privacy Plan for Studies With Consent

1. Answer the questions below (1A-1F) to describe the plan to protect the data from improper use and disclosure.

1A. How will data be collected?

1A(1)._Yes____ Collection of data onto an individual-use device (e.g. smart phone app, tablet, laptop)

If checked answer the following questions:

- What kind of device is it (e.g. laptop, tablet, desktop computer)? Desktop_____
- Who manages / supports the device (e.g., Health Systems Computing Services (HS/CS), Information Technology Services (ITS), self)? _Eric Cosner (ekc2p) providers support for this device. Besides the ETO support team, I am the only other individuals with administrative rights to this device. ___ The data collected to the laptop will be subject-coded and will NOT contain any other HIPAA-regulated identifers besides a subject code that is unconnected to any PII or PHI of the subject.
- How long with the data remain on the device before it is downloaded to a server managed by HS/CS, ITS or SON SECUREnet? _Until study completion____
- Will anyone other than study team members have access to the data on the device? _No____
- Will data be downloaded to UVa in an encrypted secure manner such as the use of SFTP or HTTPS? _No____

- Are any backups made of the information on the device? _Yes____
- After information is downloaded will you delete all UVa subject data from the device? _Yes____
- Does the owner of the device (e.g. phone service provider/ app developer) have any rights to use or access the data either individually or in aggregate? No

1A(2.)_____ Collection of data via web-based format (e.g. online consent, online surveys) via a Non- UVa Secure Server (e.g. HS/CS, ITS or SON SECUREnet)

See 1A(6) below for an exception.

If checked answer the following questions:

- Provide the web address (URL): _____
- How long with the data remain on the Non- UVa Secure Server before it is downloaded to a server managed by HS/CS, ITS or SON SECUREnet? _____
- Will anyone other than study team members have access to the data on the Non UVa Secure Server? _____
- Will data be downloaded to a UVa Secure Server in an encrypted secure manner such as the use of SFTP or HTTPS? _____
- Are any backups made of the information on the Non- UVa Secure Server? _____
- After information is downloaded will you delete all UVa subject data from the Non- UVa Secure Server? _____
- Do the owners of the Non- UVa Secure Server have any rights to use or access the data either individually or in aggregate? _____
- If the data are regulated by HIPAA, is there a Business Associates Agreement (BAA) with the provider? _____

1A(3)._____ Directly to a server managed by the principal investigator's department or school that is configured to store data regulated by HIPAA or highly sensitive data. If checked, please provide the name of the server: _____

1A(4)._____ Directly to a Health Systems Computing Services (HS/CS), or School of Nursing SECUREnet with I Key managed server that is configured to store data regulated by HIPAA.If checked, please provide the name of the server: _____

NOTE: for HS/CS must have HSCS in the URL of the server name .

1A(5)._____ Directly to an Information Technology Services (ITS) managed server that is configured to store data regulated by HIPAA.

If checked, please provide the name of the server: _____

NOTE: must have ITS in the URL of the server name.

1A(6)._____ Directly to a server managed by the sponsor or CRO in which the data will be sent and stored in an encrypted fashion (e.g. must be shared and stored via Secure FX, Secure FTP, HTTPS, PGP)

1.A(7).__x___ Paper

YES	NO	HIPAA Identifier
		1. Name
		2.Postal address information, other than town or city, state, and zip code
		3. Age or Date of Birth if over the age of 89
		4. Telephone numbers
		5. Fax numbers
		6. Electronic mail addresses
		7. Social Security number
		8. Medical Record number
		9. Health plan beneficiary numbers
		10. Account numbers
		11. Certificate/license numbers
		12. Vehicle identifiers and serial numbers, including license plate numbers
		13. Device identifiers and serial numbers
		14 Web Universal Resource Locators (URLs)
		15. Internet Protocol (IP) address numbers
		16. Biometric identifiers, including finger and voice prints
		17. Full face photographic images and any comparable images

		18. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)
		19. Any other information that could be used alone or in combination with other information to identify an individual.

►If you checked any of the items 1A(1) through 1A(3) will the data include any of the HIPAA identifiers listed below? ANWER QUESTION IN TABLE BELOW

INSTRUCTIONS: If any item above is checked, the study team must verify with the UVa Office of Information Security, Policy & Records Office (ISPRO) that adequate security is in place to collect highly sensitive data. www.virginia.edu/ispro Email: IT-Security@Virginia.edu

Submit ISPRO approval with new protocol submission.

1B. How will data be stored?

INSTRUCTIONS: Choose only one of the following options:

_____ Data, which may include health information, or other highly sensitive data will be stored with HIPAA identifiers.

INSTRUCTIONS: You MUST choose this option if case report forms will include such items as initials.

__x___ Data, which may include health information or other highly sensitive data will NOT be stored with any HIPAA identifier except date(s). This means:

- Documents such as case report forms will have NO HIPAA identifiers except dates (e.g. no initials or medical record #)
- HIPAA identifiers, except dates will be stored in a different place than the health information/specimens. A code such as subject # 1 will be used to link the identity of the individual (HIPAA identifiers) with the persons health information.

EXAMPLE: The HIPAA identifiers with the code (e.g.- John Doe=subject #1) will be stored in one location (computer drive, paper file, memory stick, CD) and the health information (diagnosis,

radiology results) will be stored in a different location (different computer drive, paper file in a different file cabinet, memory stick).

1C. Will specimens be stored by the UVa study team? No

1D. Will any of the data be stored electronically? Yes

►IF YES, will it include storage of any health information or other sensitive data?

Answer/Response: Yes

►IF YES, will the data include any of the HIPAA identifiers listed below?

ANWER QUESTION IN TABLE BELOW

YES	NO	HIPAA Identifier
x		1. Name
		2.Postal address information, other than town or city, state, and zip code
x		3.Age or Date of Birth if over the age of 89
x		4. Telephone numbers
		5. Fax numbers
		6. Electronic mail addresses
		7. Social Security number
		8. Medical Record number
		9. Health plan beneficiary numbers
		10. Account numbers
		11. Certificate/license numbers
		112. Vehicle identifiers and serial numbers, including license plate numbers
		13. Device identifiers and serial numbers
		14 Web Universal Resource Locators (URLs)
		15. Internet Protocol (IP) address numbers
		16. Biometric identifiers, including finger and voice prints
		17. Full face photographic images and any comparable images
		18. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)
		19. Any other information that could be used alone or in combination with other information to identify an individual. (*e.g. rare disease, study team or company has access to the health information and a HIPAA identifier or the key to the code*)

1E. If you answered YES to any HIPAA identifier above, where will the data be stored?

_____ a Health Systems Computing Services (HS/CS) managed server that is configured to store data regulated by HIPAA.

- If checked, please provide the name of the server: _____

_____ a Information Technology Services (ITS) managed server that is configured to store data regulated by HIPAA.

- If checked, please provide the name of the server: _____

_____ a server managed by the principal investigator's department or school that is configured to store data regulated by HIPAA or highly sensitive data.

- If checked, please provide the name of the server: _____
- If checked, see Instructions below

- Data will be deidentified and free of all HIPPA regulated identifiers which will be replaced with a code (e.g. Bill Smith 001) and stored on an encrypted external hard drive. Participant identifiers will be kept in a paper format and kept within a locked file cabinet within a secure office (Memorial Gymnasium 223A). The data stored on this external drive be subject-coded and will NOT contain any other HIPAA-regulated identifers besides a subject code that is unconnected to any PII or PHI of the subject.

INSTRUCTIONS: The study team must verify with the UVa Office of Information Security, Policy & Records Office (ISPRO) that the server they plan to use is configured to store highly sensitive data. www.virginia.edu/ispro Email: IT-Security@Virginia.edu

Submit ISPRO approval with the new protocol submission.

_____ a server managed by the sponsor or CRO in which the data will be sent and stored in an encrypted fashion (e.g. must be shared and stored via Secure FX, Secure FTP, HTTPS, PGP)

INSTRUCTIONS: The study team should confirm the security of the site with the sponsor, CRO or other outside group.

NOT ALLOWED if you have answered YES to any HIPAA identifier above and data will not be sent/stored in an encrypted manner.

_____ Cloud (UVaBox, UVa-Collab)

- If checked, please provide the name of the service: _____

INSTRUCTIONS: Not allowed if you have answered YES to any HIPAA identifier above.

NOTE: No research data may be stored in a non- UVa licensed cloud provider such as Dropbox, Google Drive, Survey Monkey etc.

1F. Will any of the data be collected or stored in hard copy format by the UVa study team (*e.g. on paper***)?** Yes

►IF YES, where will it be stored?

_____ case report forms will be stored in a secure area with limited access.

_x____ questionnaires/ surveys will be stored in a secure area with limited access.

_____ other - Specify Answer/Response: All participants will be coded upon obtaining consent/assent. From that point, a numerical identifier (001) will be used for all data entry. A paper copy will be kept with the subject's name and identifier in a locked cabinet within the PI's office (Memorial Gymnasium 223A) with access only permitted to research team members.

1G. The following procedures will also be followed.

- Only investigators for this study and clinicians caring for the patient will have access to the data. They will each use a unique login ID and password that will keep confidential. The password should meet or exceed the standards described on the Information Technology Services (ITS) webpage about *The Importance of Choosing Strong Passwords.*
- Each investigator will sign the University's Electronic Access Agreement forward the signed agreement to the appropriate department as instructed on the form.

  If you currently have access to clinical data it is likely that you have already signed this form. You are not required to sign it again.

- UVa University Data Protection Standards will be followed
- http://www.virginia.edu/informationsecurity/dataprotection.
- If identifiable data is transferred to any other location such as a desktop, laptop, memory stick, CD etc. the researcher must follow the University's "Electronic Storage of Highly Sensitive Data Policy". Additional requirements may be found in the Universities Requirements for Securing Electronic Devices.
- If identifiable health information is taken away from the UVa Health System, Medical Center Policy # 0218 will be followed.

- The data will be securely removed from the server, additional computer(s), and electronic media according to the University's Electronic Data Removal Policy.
- The data will be encrypted or removed if the electronic device is sent outside of UVa for repair according to the University's Electronic Data Removal Policy.
- If PHI will be faxed, researchers will follow the Health System Policy # 0194.
- If PHI will be emailed, researchers will follow the Health System Policy # 0193 and University Data Protection Standards .
- The data may not be analyzed for any other study without additional IRB approval.
- If you are using patient information you must follow Health System Policy # 0021.
- Both data on paper and stored electronically will follow the University's Record Management policy and the Commonwealth statute regarding the Destruction of Public Records.

Summary of Requirements to Comply with UVa Health System, Medical Center and University Policies and Guidance as noted above:

Highly Sensitive Data is:

-personal information that can lead to identity theft if exposed or

-health information that reveals an individual's health condition and/or history of health services use.

Protected Health Information (PHI) a type of Highly Sensitive Data, is health information combined with a HIPAA identifier

Identifiable Health Information under HIPAA regulations is considered to be *Highly Sensitive Data*

A **Limited Data Set** (LDS) under HIPAA regulations is considered to be *Moderately Sensitive Data. The only HIPAA identifiers associated with data: full dates and or postal address information including town or city, state, and zip code.*

Highly Sensitive Data **(Identifiable Health Info per HIPAA)**	**Moderately Sensitive Data** **(Limited Data Set and De-identified data per HIPAA)**
General Issues	*General Issues*
Discussions in private Do not share with those not on the study team or those who do not have a need to know.	Do not share with those not on the study team or those who do not have a need to know
Password protect	Password protect
Physically secure (lock) hard copies at all times if not directly supervised. If not supervised hard copies must have double protection (e.g. lock on room OR cabinet AND in building requiring swipe card for entrance).	Physically secure (lock) hard copies at all times if not directly supervised.
For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.	For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.
Encrypt See encryption solutions guidance. *Files on Health System Network drives are automatically encrypted. If not stored there it is study teams responsibility to make sure data are encrypted.*	
If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVa Purchase order.	If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVa Purchase order.
Store files on a network drive specifically designated for storing this type of data, e.g. high-level security servers managed by Information Technology Services or the “F” and “O” managed by Heath Systems Computing Services. You may access it via a shortcut icon on your desktop, but you are not allowed to take it off line to a local drive such as the desktop of your computer (e.g. C drive) or to an individual Use Device*. May access via VPN	

Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract/ MTA is in place	Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract/ MTA is in place
If collected without consent/ HIPAA authorization will NOT be allowed to leave UVa HIPAA covered entity unless disclosure is approved by the IRB and the disclosure is tracked in EPIC	If collected without consent/ HIPAA authorization will NOT be allowed to leave UVa HIPAA covered entity unless disclosure is approved by the IRB and an MTA is in place prior to sharing of data

Highly Sensitive Data **(Identifiable Health Info per HIPAA)**	**Moderately Sensitive Data** **(Limited Data Set and De-identified data per HIPAA)**
Individual-Use Device	*Individual-Use Device*
Do not save to individual-use device* without written approval of your Department AND VP or Dean. If approval obtained, data must be password protected and encrypted.	
Do not save an email attachment containing HSD to an individual use device (e.g. smart phone)	
E Mail	*E Mail*
Do not share via email with Outlook Web/ or forward email using other email vendors like Gmail/ Yahoo	
Do not send via email on smart phone unless phone is set up by Health System	
Email may include name, medical record number or Social Security number only if sending email to or from a person with * HS in their email address. *NOTE: VPR & IRB staff do not meet this criteria!*	In addition to sharing LDS, may include initials if persons sending and receiving email work within the UVa HIPAA covered entity.**
FAX	*FAX*
Verify FAX number before faxing	Verify FAX number before faxing
Use Fax Cover Sheet with Confidentiality Statement	Use Fax Cover Sheet with Confidentiality Statement
Verify receiving fax machine is in a restricted access area	Verify receiving fax machine is in a restricted access area
Verify intended recipient is clearly indicated	Verify intended recipient is clearly indicated
Recipient is alerted to the pending transmission and is available to pick it up immediately	Recipient is alerted to the pending transmission and is available to pick it up immediately

Electronic Data Collection and Sharing	*Electronic Data Collection and Sharing*
(e.g. smart phone app, electronic consent using tablet etc.) MUST consult with ISPRO or Health System Web Development Office: 434-243-6702 ▪ University Side: IT-Security@virginia.edu ▪ Health System: Web Development Center: Contract must include required security measures.	
May NOT be stored in places like UVaBox, UVaCollab, QuestionPro. May also NOT be stored in non-UVa licensed cloud providers, such as Dropbox, Google Drive, Survey Monkey, etc.	
LOST OR STOLEN:	*LOST OR STOLEN:*
Must report in accordance with protocol/ in accordance with the Information Security Incident Reporting Policy (See Privacy Plan section of this protocol)	Must report in accordance with protocol/ in accordance with the Information Security Incident Reporting Policy (See Privacy Plan section of this protocol)

** Individual Use Device – examples include smart phone, CD, flash (thumb) drive, laptop, C drive of your computer,*

***The UVa HIPAA covered entity is composed of the UVa VP Office of Research, the Health System, School of Medicine, School of Nursing, Nutrition Services (Morrison's), the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory and the Exercise Physiology Laboratory.*

2. Describe your/central registry's plan to destroy the HIPAA identifiers at the earliest opportunity consistent with the conduct of the research and in accordance with any stipulations in the research sponsor contract and UVa records management guidelines.

Check one option below:

_x____ HIPAA identifiers will be destroyed with the data after all retention requirements per sponsors' requirements, UVa Records Management Policies and IRB-HSR Record

Retention Requirements have been met. If data and HIPAA identifiers from this study are to be kept and used in future research, a Database Protocol will be established to protect the data before this protocol is closed.

_____ This is a Database Only study. All data including HIPAA identifiers will be destroyed or de-identified per HIPAA regulations (e.g. no HIPAA identifiers will be kept) when this protocol is closed. *Do not check this option if the protocol has a hypothesis*

3. **Do you confirm that you will not reuse the identifiable data (HIPAA identifiers or health information) or disclose any of this information to any other person or entity except as outlined in this protocol, except as required by law, for authorized oversight of the research study, or use it for other research unless approved by the IRB-HSR?** Yes

This means that after the study is closed at UVa:

- You cannot contact the subject by any method (you cannot call them, send a letter, talk to them in person about the study, etc.) without additional IRB approval
- You cannot use the data for any research that is not already described in your IRB protocol without additional IRB approval (if you change your hypothesis you must modify your protocol)
- You cannot share your research data with another researcher outside of your study team without additional IRB approval
- Any health information with HIPAA identifiers will be shredded or discarded by using recycling bins for confidential material found in clinic settings. For large item disposal of confidential material contact Environmental Services at 2-4976 or University Recycling at 2-5050.

TABLE A: HIPAA Identifiers (Limited Data Set)

1. Name
2. Postal address information, other than town or city, state, and zip code
3. Age or Date of Birth if over the age of 89
4. Telephone numbers
5 Fax numbers
6. Electronic mail addresses
7. Social Security number
8. Medical Record number
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plate numbers
13. Device identifiers and serial numbers
14. Web Universal Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints
17. Full face photographic images and any comparable images
18. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)

Table C2. University of Virginia Institutional Review Board Approved Concussed Consent Form

Consent of an Adult to Be in a Research Study

In this form "you" means a person 18 years of age or older who is being asked to volunteer to

Parents' or Guardians' Permission for Your Child to Be in a Research Study

Agreement of a Child to Be in a Research Study (age 15-17)

In this form "you" means the child in the study *and* the parent or guardian.

- ✓ If you are the parent or guardian, you are being asked to give permission for your child to be in this study.
- ✓ If you are the child, you are being asked if you agree to be in this study.

In this form "we" means the researchers and staff involved in running this study at the University of Virginia.

In this form "you" means the person (your child) who is being asked to be in this study. As the parent or guardian, you are being asked to give permission for your child to be in this study.

Participant's Name_____

Principal Investigator:	**Jacob E. Resch, Ph.D.** Memorial Gymnasium 223A The University of Virginia 210 Emmet St S. Charlottesville, VA 22901 Office: 434.243.6525 Cell: 434.242.2013 E-mail: jer6x@virginia.edu
Sponsor:	**The Mid-Atlantic Athletic Trainers' Association** **The University of Virginia**

What is the purpose of this form?

This form will provide you with information about this research study. You do not have to be in the study if you do not want to. You should have all your questions answered before you agree to be in this study.

Please read this form carefully. If you want to be in the study, you will need to sign this form. You will be given a signed copy of this form.

Who is funding this study?

This study is being funded by the Mid-Atlantic Athletic Trainers' Association and the University of Virginia.

Why is this research being done?

The purpose of this study is to investigate the calories used following the diagnosis of a concussion in young individuals (aged 14-29 years). Additionally, this study will address how many calories are consumed following a concussion throughout your recovery.

A concussion is defined as a hyper- followed by a hypometabolic event. This means that someone who suffers a concussion will use more calories right after an injury than compared to the number of calories they normally use. After the first few days someone with a concussion

may use fewer calories than their normal healthy state. This has been shown only in animal studies but not in humans.

For this study we will be predicting the amount of calories you normally use and compare that to the actual measurement of calories used. We will also be comparing the amount of calories you use to the amount of calories used by another individual who has not had a concussion.

You are being asked to be in this study, because you has been diagnosed with a concussion by your healthcare provider.

Up to *84 (54 injured and 30 healthy)* people will be in this study at UVA.

What will happen if you are in the study?

If you agree to be in this study, you will sign this consent form before any study related procedures take place.

STUDY PROCEDURES

Following the diagnosis of a concussion you will be provided a study summary. If you express interest in our study, you or your healthcare provider will contact Mr. Sam Walton or Dr. Jacob Resch to arrange an appointment within 72 hours immediately following your injury at the Memorial Gymnasium Exercise and Sport Injury Laboratory. Additionally, if you express interest in our study you will be asked to fast (no food or drink) the night prior starting at midnight (12:00 AM) until following morning between 6:00 and 9:00 AM. You will be asked to bring a typical breakfast to this session for you so you can eat immediately following the protocol.

After providing consent/assent, you will be asked to complete a health history and symptom questionnaire. Then you will be asked to lie on an examination table while you are fitted with a clear plastic dome. This dome is designed to be minimally invasive and extra comfortable for you. Most participants can fall asleep after being fitted with this dome. You will then be asked to breathe normally for the next 30 minutes as caloric expenditure is being measured. Following the 30 minute data collection period, you will be encouraged to eat the breakfast you brought.

Following the first assessment, you will be asked to complete some questionnaires. After this, you will be asked to record on paper your food intake for the next three days. You will be provided a food journal to record this information. You will also be provided and asked to wear a FitBit to assess the number of steps per day while participating in our study. At the end of each day, you will record the number of steps you have taken on a sheet of paper. Data collected on the FitBit will not be entered into the FitBit cloud. At the conclusion of the study you will be asked to return your FitBit to the research team.

You will then be asked to return to Memorial Gymnasium seven days following your first assessment for your second assessment, and again seven days after your second assessment for a third assessment. If you are still experiencing symptoms during your third assessment, we will ask you to return one more time after reporting no further concussion related symptoms. You will be asked to not have anything to eat or drink from 12:00 AM the night prior to your assessment as you did for your first session. You will then complete the same steps as the first assessment.

You will have the option to withdraw from participating at any point of the study without any type of penalty from St. Anne's Belfield School, Charlottesville High School, Albemarle High School, West Albemarle High School or Monticello High School or the University of Virginia (Athletics, Student Health, or Emergency Department).

During this study, you will be asked to fill out some questionnaires. These questionnaires ask about:

- Your demographics (height, weight, age)
- Your health History
- History of any learning disabilities
- Any medications you may be taking
- Your symptoms
- Your mood and behavior **(only participants 18 years of age or older)**
- Your feelings about exercise and injury **(only participants 18 years of age or older)**
- Your social functioning **(only participants 18 years of age or older)**

If you are an adult participant (age 18 or older), It will take about 35 minutes to complete the questionnaires.

If you are not an adult participant, It will take about 10 minutes to complete the questionnaires.

You do not have to answer all of these questions to remain in the study. If you choose not to answer any questions, please tell a member of the study team.

For adults, some of the questions deal with how you feel (your mood). After reviewing your answers, if the study team feels that you may benefit from talking to a counselor, they will direct you to counseling services at UVA if you are not a student-athlete.
UVA Counseling and Psychological Services (CAPS): (434) 243-5150 is available 24/7 for enrolled UVA students.
Participants who were recruited from the University of Virginia Emergency Department, if not a student at a participating high school or at the University of Virginia, will be referred to the University of Virginia Emergency Department (911) and/or University of Virginia Department of Psychiatry and Neurobehavioral Sciences (434-924-2718).

Study Schedule

	Assessment 1	**Assessment 2**	**Assessment 3**	**Assessment 4** (if needed)
Informed Consent	x			
Measurement of Calories Used	x	x	x	x
Medical History	x			
Questionnaires	x	x	x	x
Recording of diet (3 days after each session)	x	x	x	x
Use of Fitbit (Every Day Between Assessments)	x	x	x	x

WHAT ARE YOUR AND YOUR PARENT/LEGAL GUARDIAN'S RESPONSIBILITIES IN THE STUDY?

You and your parent/legal guardian have certain responsibilities to help ensure your safety.

These responsibilities are listed below:

- Your parent/legal guardian must bring you to each assessment or otherwise organize your transportation to and from each assessment.
- You and your parent/legal guardian must be completely truthful about your health history.
- Follow all instructions given.
- You or your parent/legal guardian should tell the study PI (Dr. Jacob Resch) or study staff about any changes in your health or the way you feel.
- Ensure that you has fasted a minimum of six hours before each assessment.
- Ensure that the FitBit is worn each day of study participation.
- Ensure the three day diet journal is filled out honestly and is complete.

How long will this study take?

Your part in this study will require 3-4 study assessments over about a two week period (or longer if you are still experiencing symptoms at your third assessment). Each assessment will last about 90 minutes.

What are the risks of being in this study?

The only possible risk is hunger from fasting overnight. To reduce this risk, we encourage you to bring a premade breakfast to each assessment to eat after the first part of the test.

Could you be helped by being in this study?

You may or may not benefit from being in this study. Possible benefits include understanding more about your injury and understanding of their caloric intake following injury. In addition, information researchers get from this study may help others in the future.

What are your other choices if you do not join this study?

You do not have to be in this study to be treated for your illness or condition. You can get the usual treatment even if you choose not to be in this study. The usual treatment for student-athletes would include:

- Computerized Neurocognitive Testing
- Balance Assessment
- Assessment of Self-reported Symptoms

These measures are part of UVa's, St. Anne's Belfield School's, Charlottesville High School's, Albemarle High School's, West Albemarle High School's, and Monticello High School's concussion management protocol.

Usual treatment for adult non-varsity athletes will be provided by your referring healthcare provider.

Will you be paid for being in this study?

You will be paid up to a maximum $40 in Amazon gift cards for finishing this study.

You will receive a $10 Amazon gift card when you turn in your food log and step count following each assessment.

Will being in this study cost you any money?

All of the procedures in this study will be provided at no cost to you or your health insurance. You will be responsible for the cost of travel to come to any study assessment and for any parking costs.

What if you are hurt in this study?

If you are hurt as a result of being in this study, there are no plans to pay you for medical expenses, lost wages, disability, or discomfort. The charges for any medical treatment you receive will be billed to your insurance. You will be responsible for any amount your insurance does not cover. You do not give up any legal rights, such as seeking compensation for injury, by signing this form.

What happens if you leave the study early?

You can change your mind about being in the study any time. You can agree to be in the study now and change your mind later. If you decide to stop, please tell us right away. You do not have to be in this study to get services you can normally get at the University of Virginia.

Even if you do not change your mind, the study leader can take you out of the study. Some of the reasons for doing so may include

a) Your study physician is concerned about your health

b) Your concussion symptoms get worse

c) The study sponsor closes the study for safety, administrative or other reasons

If you decide to stop being in the study, we will ask you to please contact Dr. Jacob Resch.

How will your personal information be shared?

The UVa researchers are asking for your permission to gather, use and share information about you for this study. If you decide not to give your permission, you cannot be in this study, but you can continue to receive regular medical care at UVA.

If you sign this form, we may collect any or all of the following information about you:

- Personal information such as name, address and date of birth
- Social Security number ONLY IF you are being paid to be in this study
- Your health information if required for this study. This may include a review of your medical records and test results from before, during and after the study from any of your doctors or health care providers.

Who will see your private information?

- The researchers to make sure they can conduct the study the right way, observe the effects of the study and understand its results
- People or groups that oversee the study to make sure it is done correctly

Some of the people outside of UVa who will see your information may not have to follow the same privacy laws that we follow. They may release your information to others, and it may no longer be protected by those laws.

The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy. No one will be able to find out from the article that you were in the study.

What if you sign the form but then decide you don't want your private information shared?

You can change your mind at any time. Your permission does not end unless you cancel it. To cancel it, please send a letter to the researchers listed on this form. Then you will no longer be in the study. The researchers will still use information about you that was collected before you ended your participation.

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Jacob Resch

Kinesiology, Curry School of Education

Memorial Gymnasium Office 223A

210 Emmet St. S

Charlottesville, VA 22901

Telephone: (434)243-6525

What if you have a concern about this study?

You may also report a concern about this study or ask questions about your rights as a research subject by contacting the Institutional Review Board listed below.

University of Virginia Institutional Review Board for Health Sciences Research

PO Box 800483

Charlottesville, Virginia 22908

Telephone: 434-924-9634

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the IRB-HSR Number (at the top of this form), and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

Signatures

What does your signature mean?

Before you sign this form, please ask questions about any part of this study that is not clear to you. Your signature below means that you have received this information and all your questions have been answered. If you sign the form it means that you agree to join the study. You will receive a copy of this signed document.

Consent From Adult

_____	_____	_____
PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

To be completed by participant if 18 years of age or older.

Parental/ Guardian Permission

By signing below you confirm you have the legal authority to sign for this child.

_____	_____	_____
PARENT/GUARDIAN (SIGNATURE)	PARENT/GUARDIAN (PRINT NAME)	DATE

Assent from Child (less than 18 years of age)

Consent from the parent/guardian MUST be obtained before approaching the child for their assent.

_____	_____	_____
PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

Person Obtaining Assent of the Child (15-17 years of age)

Consent from the parent/guardian MUST be obtained before approaching the child for their assent.

By signing below you confirm that the study has been explained to the child (less than 18 years of age), all questions have been answered and the child has voluntarily agreed to participate.

_____	_____	_____
PERSON OBTAINING ASSENT (SIGNATURE)	PERSON OBTAINING ASSENT (PRINT)	DATE

Table C3. University of Virginia Institutional Review Board Approved Concussed Assent Form

Participant's Name_____ Medical Record # _____

ASSENT FORM TO BE IN A RESEARCH STUDY
(age 7-14)

Doctors at the University of Virginia are trying to learn more about concussion. This is called a research study.

The reason to do this research study is to understand how many calories are used after a concussion which occurs as a result of participation in sport. Additionally, this research will help us understand how many calories athletes diagnosed with a concussion use following their diagnosis.

You are being asked to be in this research study because you are a healthy athlete who has been identified as a match by your certified athletic trainer for a participant in our study. You are a match because you have a similar height, weight, sport, and age as another participant in our study.

The research doctor in charge of this study is Dr. Jacob E. Resch.

This study will take place here at Memorial Gymnasium on the campus of the University of Virginia. This study will last approximately two weeks in which you be asked to participate in three separate testing sessions.

This is what will happen during this study: You will be asked to come to Memorial Gymnasium the morning after you have been identified as a match for another participant. The night before you come to Memorial Gymnasium we ask that you do not having anything to eat after 12:00 AM the night prior to your first visit. Water is fine. The following morning after arriving at Memorial Gymnasium you and your

parent/guardian will answer questions about your height, weight, age, health history and symptoms.

It will take about 10 minutes to answer these questions.

You do not have to answer all of the questions to stay in the study. If you choose not to answer any questions, please tell a member of the study team.

After reviewing your answers, if we feel that you may benefit from talking to a counselor, we will refer you to a counselor.

Next, we will ask you to lie on a table while we place a clear plastic dome over your head. You will be able to breathe normally under the dome. We will then ask you to breathe normally for the next 30 minutes. After 30 minutes, you will be done with the first part of the test.

After you finish the first part of the test you can eat whatever snack you may have brought with you while we explain the rest of the study. We will ask you to wear a FitBit (a small device worn around your wrist to measure your footsteps) during the remainder of the study. This will help us understand how active you are. We will also ask you to record how much food you eat (after each meal) by writing it down for the next three days. We will provide a food journal for you to record this information.

We will ask you to come to Memorial Gymnasium and complete the same steps as explained above seven days after your first session and again seven days after your second session which includes an overnight fast starting at 12:00 AM the night before visit. Your certified athletic trainer will assist in arranging these times for you.

Sometimes things happen to people in research studies that may hurt them or make them feel bad. These are called risks. The risks of this study are minimal. You may experience hunger until we are done with the first part of the study (where you lie on a table for 30 minutes). To reduce this risk we would like you to bring a snack or your breakfast with you so you can eat soon after you are done with the first part of our study.

People also may have good things happen to them because they are in research studies. These are called benefits. Possible benefits include understanding more about your food intake.

You do not have to be in this study if you do not want to be.

You may stop being in the study at any time. If you decide to stop, no one will be angry or upset with you.

You will receive a $10 Amazon gift card for completing each session of this study. You will receive up to $30 if you complete all three sessions of this study.

Please ask as many questions as you need to make sure you understand the study before you sign this form.

Assent from Child (age 7-14)

_____	_____	_____
CHILD (SIGNATURE)	CHILD (PRINT NAME)	DATE

Consent from the parent/guardian MUST be obtained before approaching the child for their assent.

If the child is not able to read English, the minor should not sign this form. There should be written documentation in the study file noting that study was explained to the child, all questions were answered and the child verbally agreed to participate in the study.

Person Obtaining Assent of the Child

By signing below you confirm that the study has been explained to the child (less than 18 years of age), all questions have been answered and the child has voluntarily agreed to participate.

_____	_____	_____
PERSON OBTAINING ASSENT OF THE CHILD (SIGNATURE)	PERSON OBTAINING ASSENT OF THE CHILD (PRINT NAME)	DATE

Parental/ Guardian Permission

By signing below you confirm you have the legal authority to sign for this child.

_____	_____	_____
PARENT/GUARDIAN (SIGNATURE)	PARENT/GUARDIAN (PRINT NAME)	DATE

Table C4. University of Virginia Institutional Review Board Approved Healthy Consent Form

Consent of an Adult to Be in a Research Study

In this form "you" means a person 18 years of age or older who is being asked to volunteer to

Parents' or Guardians' Permission for Your Child to Be in a Research Study

Agreement of a Child to Be in a Research Study (age 15-17)

In this form "you" means the child in the study *and* the parent or guardian.

- ✓ If you are the parent or guardian, you are being asked to give permission for your child to be in this study.
- ✓ If you are the child, you are being asked if you agree to be in this study.

In this form "we" means the researchers and staff involved in running this study at the University of Virginia.

In this form "you" means the person (your child) who is being asked to be in this study. As the parent or guardian, you are being asked to give permission for your child to be in this study.

Participant's Name_____

Principal Investigator:	**Jacob E. Resch, Ph.D.** Memorial Gymnasium 223A The University of Virginia 210 Emmet St S. Charlottesville, VA 22901 Office: 434.243.6525 Cell: 434.242.2013 E-mail: jer6x@virginia.edu
Sponsor:	**The Mid-Atlantic Athletic Trainers' Association** **The University of Virginia**

What is the purpose of this form?

This form will provide you with information about this research study. You do not have to be in the study if you do not want to. You should have all your questions answered before you agree to be in this study.

Please read this form carefully. If you want to be in the study, you will need to sign this form. You will be given a signed copy of this form.

Who is funding this study?

This study is being funded by the Mid-Atlantic Athletic Trainers' Association and the University of Virginia.

Why is this research being done?

The purpose of this study is to investigate the calories used following the diagnosis of a concussion in young individuals (aged 14-29 years). Additionally, this study will address how many calories are consumed following a concussion throughout your recovery.

A concussion is defined as a hyper- followed by a hypometabolic event. This means that an someone who suffers a concussion will use more calories right after an injury than compared to the number of calories they normally use. After the first few days someone with a concussion

may expend fewer calories than their normal healthy state. This has been shown only in animal studies but not in humans.

For this study we will be predicting the amount of calories you normally use and compare that to the actual measurement of calories used. We will also be comparing the amount of calories you use to the amount of calories used by another individual who has not had a concussion.

You are being asked to be in this study, because you are healthy and have not had a concussion recently.

Up to *84 (54 injured and 30 healthy)* people will be in this study at UVA.

What will happen if you are in the study?

If you agree to be in this study, you will sign this consent form before any study related procedures take place.

Before you can start in the study, there will be a screening period. You will have tests and procedures during this time to make sure you are eligible and it is safe for you to participate. These include the following:

- You must be identified as a match based on height, weight, age, and sport (where applicable) to another participant diagnosed with a concussion.

If these items show you are eligible, you will be asked to report for assessment within 72 hours to begin the study.

STUDY PROCEDURES

After being identified as being a match for a concussed participant, you will be provided a study summary by a member of the study team. If you express interest in our study you or your healthcare provider will contact Mr. Sam Walton or Dr. Jacob Resch to arrange an appointment within the following 72 hours of your identification at the Memorial Gymnasium Exercise Science Laboratory. Additionally, if you express interest in our study your will be asked to fast the night prior starting at 12:00 AM until end of

the first part of our study between 6:00 and 9:00 AM. You will be asked to bring a typical breakfast to this session so you can eat immediately following the protocol.

After providing consent/assent, you will then complete a health history and symptom questionnaire. Then you will be asked to lie on an examination table while you are fitted with a clear plastic dome. This dome is designed to be minimally invasive and extra comfortable for you. Most participants can fall asleep after being fitted with this dome. You will then be asked to breathe normally for the next 30 minutes as caloric expenditure is being measured. Following the 30 minute data collection period, you will be encouraged to eat the snack you brought.

Following the first assessment, you will be asked to complete some questionnaires. After this, you will be asked to record on paper your food intake for the next three days. You will be provided a food journal to record this information. You will also be provided and asked to wear a FitBit to assess the number of steps per day while participating in our study. At the end of each day, you will record the number of steps you have taken on a sheet of paper. Data collected on the FitBit will not be entered into the FitBit cloud. At the conclusion of the study you will be asked to return your FitBit to the research team.

You will then be asked to return to Memorial Gymnasium seven days following the first assessment for your second assessment and again seven days following your second assessment for your third assessment. You may be asked to return for a fourth assessment if you are matched with a concussed participant who meets the criteria to do so. You will be asked to fast starting at 12:00 AM the night before as you did in session one. You will then complete the same steps as the first assessment for each of the second and third assessments.

You will have the option to withdrawal from participation at any point of the study without any type of penalty from St. Anne's Belfield School, Charlottesville High School, West Albemarle High School, Monticello or Albemarle High School or the University of Virginia (Athletics, Student Health, or Emergency Department).

During this study, you will be asked to fill out some questionnaires. These questionnaires ask about:

- Your demographics (height, weight, age)
- Your health History
- History of any learning disabilities
- Any medications you may be taking
- Your symptoms
- Your mood and behavior **(only participants 18 years of age or older)**
- Your feelings about exercise and injury **(only participants 18 years of age or older)**
- Your social functioning **(only participants 18 years of age or older)**

If you are an adult participant (age 18 or older), it will take about 35 minutes to complete the questionnaires.
If you are not an adult participant, it will take about 10 minutes to complete the questionnaires.

You do not have to answer all of these questions to remain in the study. If you choose not to answer any questions, please tell a member of the study team.

For adults, some of the questions deal with how you feel (your mood). After reviewing your answers, if the study team feels that you may benefit from talking to a counselor, they will direct you to counseling services at UVA if you are not a student-athlete.
UVA Counseling and Psychological Services (CAPS): (434) 243-5150 is available 24/7 for enrolled UVA students.
Participants who were recruited from the University of Virginia Emergency Department, if not a student at a participating high school or at the University of Virginia, will be referred to the University of Virginia Emergency Department (911) and/or University of Virginia Department of Psychiatry and Neurobehavioral Sciences (434-924-2718).

Study Schedule

	Assessment 1	**Assessment 2**	**Assessment 3**	**Assessment 4** (if needed)
Informed Consent	x			
Measurement of Calories Used	x	x	x	x
Medical History	x			
Questionnaires	x	x	x	x
Recording of diet (3 days after each session)	x	x	x	x
Use of Fitbit (Every Day Between Assessments)	x	x	x	x

WHAT ARE YOUR AND YOUR PARENT/LEGAL GUARDIAN'S RESPONSIBILITIES IN THE STUDY?

You and your parent/legal guardian have certain responsibilities to help ensure your safety.

These responsibilities are listed below:

- Your parent/legal guardian must bring you to each assessment or otherwise organize your transportation to and from each assessment.
- You and your parent/legal guardian must be completely truthful about your health history.
- Follow all instructions given.
- You or your parent/legal guardian should tell the study PI (Dr. Jacob Resch) or study staff about any changes in your health or the way you feel.
- Ensure that you has fasted before each assessment.
- Ensure that the FitBit is worn each day of study participation
- Ensure the three day diet journal is filled out honestly and is complete.

How long will this study take?

Your part in this study will require 3-4 study assessments over about a two week period (or longer if you are matched with a concussed participant who is still experiencing symptoms at their third assessment). Each assessment will last about 90 minutes.

What are the risks of being in this study?

Risks associated with the current study are minimal. The only foreseeable risk is hunger associated with the overnight fast. To minimize this risk, we encourage you to bring a premade breakfast to each assessment to eat after the initial part of the test.

Other unexpected risks:

You may have side effects that we do not expect or know to watch for now. Call the study leader if you have any symptoms or problems.

Could you be helped by being in this study?

You may or may not benefit from being in this study. Possible benefits include understanding more about your caloric intake. In addition, information researchers get from this study may help others in the future. Your will also be eligible to receive $10 to $30 in iTunes gift cards for participation in the current study.

What are your other choices if you do not join this study?

You do not have to be in this study. Participation is voluntary but appreciated.

Will you be paid for being in this study?

You will be paid up to a maximum of $40 in Amazon gift cards for finishing this study.

You will receive a $10 Amazon gift card when you turn in your food log and step count following each assessment.

Will being in this study cost you any money?

All of the procedures in this study will be provided at no cost to you or your health insurance. You will be responsible for the cost of travel to come to any study assessment and for any parking costs.

What if you are hurt in this study?

If you are hurt as a result of being in this study, there are no plans to pay you for medical expenses, lost wages, disability, or discomfort. The charges for any medical treatment you receive will be billed to your insurance. You will be responsible for any amount your insurance does not cover. You do not give up any legal rights, such as seeking compensation for injury, by signing this form.

What happens if you leave the study early?

You can change your mind about being in the study any time. You can agree to be in the study now and change your mind later. If you decide to stop, please tell us right away. You do not have to be in this study to get services you can normally get at the University of Virginia.

Even if you do not change your mind, the study leader can take you out of the study. Some of the reasons for doing so may include

a) Your study physician is concerned about your health

b) The study sponsor closes the study for safety, administrative or other reasons

If you decide to stop being in the study, we will ask you to please contact Dr. Jacob Resch.

How will your personal information be shared?

The UVa researchers are asking for your permission to gather, use and share information about you for this study. If you decide not to give your permission, you cannot be in this study, but you can continue to receive regular medical care at UVA.

If you sign this form, we may collect any or all of the following information about you:

- Personal information such as name, address and date of birth
- Social Security number ONLY IF you are being paid to be in this study
- Your health information if required for this study. This may include a review of your medical records and test results from before, during and after the study from any of your doctors or health care providers. This may include mental health care records,

Who will see your private information?

- The researchers to make sure they can conduct the study the right way, observe the effects of the study and understand its results
- People or groups that oversee the study to make sure it is done correctly

Some of the people outside of UVa who will see your information may not have to follow the same privacy laws that we follow. They may release your information to others, and it may no longer be protected by those laws.

The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy. No one will be able to find out from the article that you were in the study.

What if you sign the form but then decide you don't want your private information shared?

You can change your mind at any time. Your permission does not end unless you cancel it. To cancel it, please send a letter to the researchers listed on this form. Then you will no longer be in the study. The researchers will still use information about you that was collected before you ended your participation.

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Jacob Resch

Kinesiology, Curry School of Education

Memorial Gymnasium Office 223A

210 Emmet St. S

Charlottesville, VA 22901

Telephone: (434)243-6525

What if you have a concern about this study?

You may also report a concern about this study or ask questions about your rights as a research subject by contacting the Institutional Review Board listed below.

University of Virginia Institutional Review Board for Health Sciences Research

PO Box 800483

Charlottesville, Virginia 22908

Telephone: 434-924-9634

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the IRB-HSR Number (at the top of this form), and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

Signatures

What does your signature mean?

Before you sign this form, please ask questions about any part of this study that is not clear to you. Your signature below means that you have received this information and all your questions have been answered. If you sign the form it means that you agree to join the study. You will receive a copy of this signed document.

Consent From Adult

_____	_____	_____
PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

To be completed by participant if 18 years of age or older.

Parental/ Guardian Permission

By signing below you confirm you have the legal authority to sign for this child.

_____	_____	_____
PARENT/GUARDIAN (SIGNATURE)	PARENT/GUARDIAN (PRINT NAME)	DATE

Assent from Child (15-17 years of age)

Consent from the parent/guardian MUST be obtained before approaching the child for their assent.

_____	_____	_____
PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

Person Obtaining Assent of the Child (less than 18 years of age)

Consent from the parent/guardian MUST be obtained before approaching the child for their assent.

By signing below you confirm that the study has been explained to the child (less than 18 years of age), all questions have been answered and the child has voluntarily agreed to participate.

_____	_____	_____
PERSON OBTAINING ASSENT (SIGNATURE)	PERSON OBTAINING ASSENT (PRINT)	DATE

Table C5. University of Virginia Institutional Review Board Approved Healthy Assent Form

Participant's Name_____ Medical Record # _____

ASSENT FORM TO BE IN A RESEARCH STUDY
(age 7-14)

Doctors at the University of Virginia are trying to learn more about concussion. This is called a research study.

The reason to do this research study is to understand how many calories are used after a concussion which occurs as a result of participation in sport. Additionally, this research will help us understand how many calories athletes diagnosed with a concussion use following their diagnosis.

You are being asked to be in this research study because you are a healthy athlete who has been identified as a match by your certified athletic trainer for a participant in our study. You are a match because you have a similar height, weight, sport, and age as another participant in our study.

The research doctor in charge of this study is Dr. Jacob E. Resch.

This study will take place here at Memorial Gymnasium on the campus of the University of Virginia. This study will last approximately two weeks in which you be asked to participate in three separate testing sessions.

This is what will happen during this study: You will be asked to come to Memorial Gymnasium the morning after you have been identified as a match for another participant. The night before you come to Memorial Gymnasium we ask that you do not having anything to eat after 12:00 AM the night prior to your first visit. Water is fine.

The following morning after arriving at Memorial Gymnasium you and your parent/guardian will answer questions about your height, weight, age, health history and symptoms.

It will take about 10 minutes to answer these questions.

You do not have to answer all of the questions to stay in the study. If you choose not to answer any questions, please tell a member of the study team.

After reviewing your answers, if we feel that you may benefit from talking to a counselor, we will refer you to a counselor.

Next, we will ask you to lie on a table while we place a clear plastic dome over your head. You will be able to breathe normally under the dome. We will then ask you to breathe normally for the next 30 minutes. After 30 minutes, you will be done with the first part of the test.

After you finish the first part of the test you can eat whatever snack you may have brought with you while we explain the rest of the study. We will ask you to wear a FitBit (a small device worn around your wrist to measure your footsteps) during the remainder of the study. This will help us understand how active you are. We will also ask you to record how much food you eat (after each meal) by writing it down for the next three days. We will provide a food journal for you to record this information.

We will ask you to come to Memorial Gymnasium and complete the same steps as explained above seven days after your first session and again seven days after your second session which includes an overnight fast starting at 12:00 AM the night before visit. Your certified athletic trainer will assist in arranging these times for you.

Sometimes things happen to people in research studies that may hurt them or make them feel bad. These are called risks. The risks of this study are minimal. You may experience hunger until we are done with the first part of the study (where you lie on a table for 30 minutes). To reduce this risk we would like you to bring a snack or your breakfast with you so you can eat soon after you are done with the first part of our study.

People also may have good things happen to them because they are in research studies. These are called benefits. Possible benefits include understanding more about your food intake.

You do not have to be in this study if you do not want to be.

You may stop being in the study at any time. If you decide to stop, no one will be angry or upset with you.

You will receive a $10 Amazon gift card for completing each session of this study. You will receive up to $30 if you complete all three sessions of this study.

Please ask as many questions as you need to make sure you understand the study before you sign this form.

Assent from Child (age 7-14)

_____	_____	_____
CHILD (SIGNATURE)	CHILD (PRINT NAME)	DATE

Consent from the parent/guardian MUST be obtained before approaching the child for their assent.

If the child is not able to read English, the minor should not sign this form. There should be written documentation in the study file noting that study was explained to the child, all questions were answered and the child verbally agreed to participate in the study.

Person Obtaining Assent of the Child

By signing below you confirm that the study has been explained to the child (less than 18 years of age), all questions have been answered and the child has voluntarily agreed to participate.

_____	_____	_____
PERSON OBTAINING ASSENT OF THE CHILD (SIGNATURE)	PERSON OBTAINING ASSENT OF THE CHILD (PRINT NAME)	DATE

Parental/ Guardian Permission

By signing below you confirm you have the legal authority to sign for this child.

_____	_____	_____
PARENT/GUARDIAN (SIGNATURE)	PARENT/GUARDIAN (PRINT NAME)	DATE

Table C6. Health Questionnaire

Health Questionnaire

Please answer the following questions as accurately and as thoroughly as you can.

NAME: Last:_____Middle Initial:_____First:_____

Telephone number (Home) _____

What is your birth date? Month: _____ Day: _____ Year: _____

What is your current age? _____ Circle your biological sex: Male Female

What is your RACE/ETHNICITY?

(Check one)

- ❑ White (not of Hispanic origin)
- ❑ Black (not of Hispanic origin)
- ❑ Hispanic
- ❑ Asian or Pacific Islander
- ❑ American Indian or Alaskan Native
- ❑ Arabic, Middle Eastern or North African
- ❑ Multiple (please explain) _____
- ❑ Unknown/Other: _____

3. Have you ever had a concussion? (CIRCLE ONE) YES NO

4. How many times have you had a concussion?

(CIRCLE ONE) 0 1 2 3 4 5 More than 5

If so, what is the year of your most recent concussion? Year: _____

5. Are you physically sick (cold, flu, allergies) today? **(CIRCLE ONE)** YES NO

6. Are you currently receiving treatments for any type of injury?

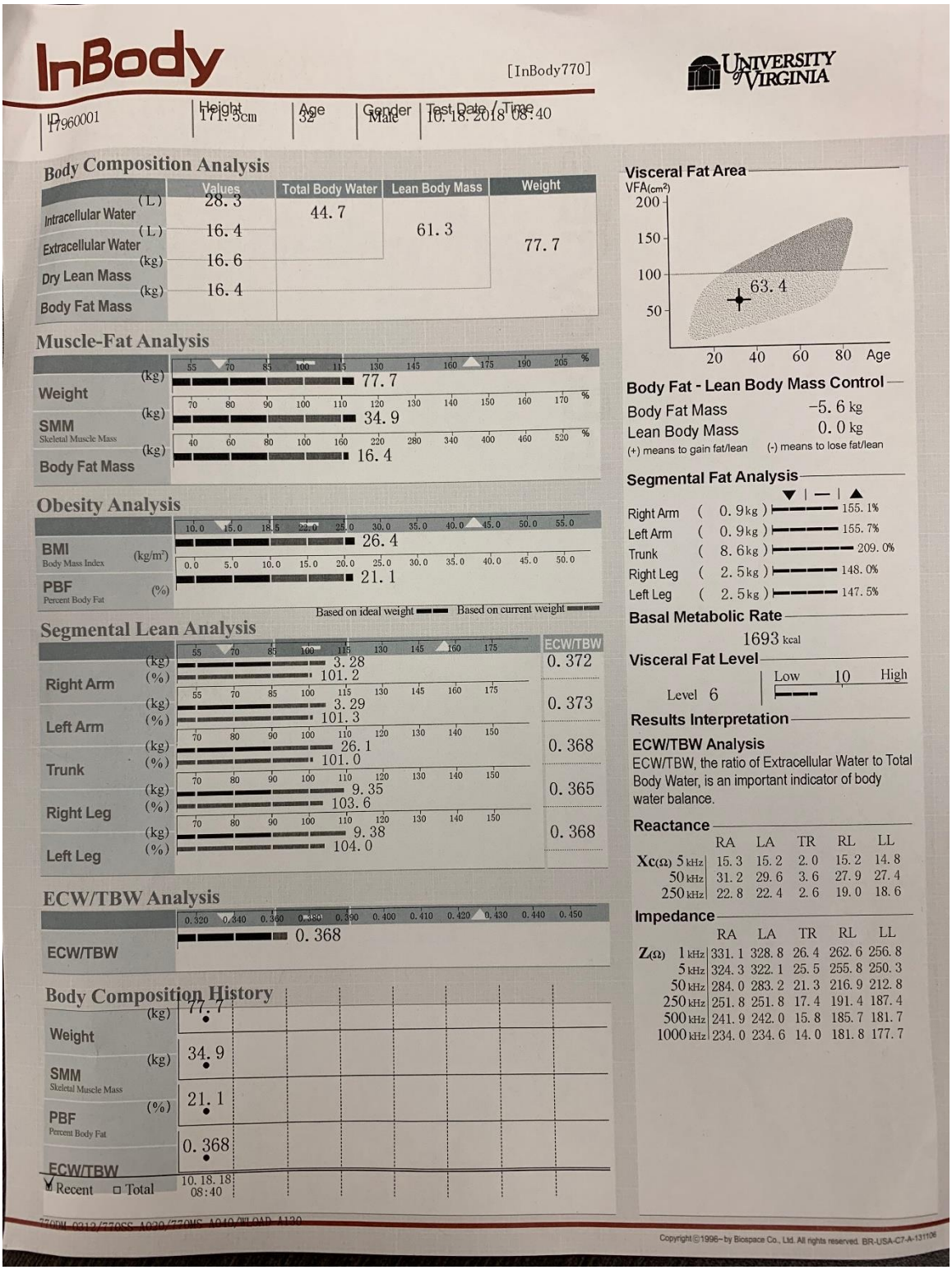
(Example: ankle sprain, bruise, pulled muscle) **(CIRCLE ONE)** YES NO

7. Have you participated in any physical activities today? **(CIRCLE ONE)**YES NO

8. Do you consume anything containing nicotine? **(CIRCLE ONE)** YES NO

If yes, have you done so within the last 3 hours? **(CIRCLE ONE)**YES NO

Table C7. Sample InBody Body Composition Analysis Form



InBody [InBody770]

UNIVERSITY of VIRGINIA

ID 17960001 | Height 171.5cm | Age 32 | Gender Male | Test Date / Time 10.18.2018 08:40

Body Composition Analysis

	Values	Total Body Water	Lean Body Mass	Weight
Intracellular Water (L)	28.3	44.7	61.3	77.7
Extracellular Water (L)	16.4			
Dry Lean Mass (kg)	16.6			
Body Fat Mass (kg)	16.4			

Muscle-Fat Analysis

Weight	(kg)	77.7
SMM Skeletal Muscle Mass	(kg)	34.9
Body Fat Mass	(kg)	16.4

Obesity Analysis

BMI Body Mass Index	(kg/m²)	26.4
PBF Percent Body Fat	(%)	21.1

Based on ideal weight — Based on current weight

Segmental Lean Analysis

			ECW/TBW
Right Arm	(kg)	3.28	0.372
	(%)	101.2	
Left Arm	(kg)	3.29	0.373
	(%)	101.3	
Trunk	(kg)	26.1	0.368
	(%)	101.0	
Right Leg	(kg)	9.35	0.365
	(%)	103.6	
Left Leg	(kg)	9.38	0.368
	(%)	104.0	

ECW/TBW Analysis

ECW/TBW	0.368

Body Composition History

Weight (kg)	77.7
SMM Skeletal Muscle Mass (kg)	34.9
PBF Percent Body Fat (%)	21.1
ECW/TBW	0.368

☑ Recent ☐ Total — 10.18.18 08:40

Visceral Fat Area

VFA(cm²) 200 / 150 / 100 / 50 — 63.4 — 20 40 60 80 Age

Body Fat - Lean Body Mass Control

Body Fat Mass	−5.6 kg
Lean Body Mass	0.0 kg

(+) means to gain fat/lean (-) means to lose fat/lean

Segmental Fat Analysis

Right Arm	(0.9kg)	155.1%
Left Arm	(0.9kg)	155.7%
Trunk	(8.6kg)	209.0%
Right Leg	(2.5kg)	148.0%
Left Leg	(2.5kg)	147.5%

Basal Metabolic Rate

1693 kcal

Visceral Fat Level

Level 6 | Low 10 High

Results Interpretation

ECW/TBW Analysis

ECW/TBW, the ratio of Extracellular Water to Total Body Water, is an important indicator of body water balance.

Reactance

	RA	LA	TR	RL	LL
Xc(Ω) 5 kHz	15.3	15.2	2.0	15.2	14.8
50 kHz	31.2	29.6	3.6	27.9	27.4
250 kHz	22.8	22.4	2.6	19.0	18.6

Impedance

	RA	LA	TR	RL	LL
Z(Ω) 1 kHz	331.1	328.8	26.4	262.6	256.8
5 kHz	324.3	322.1	25.5	255.8	250.3
50 kHz	284.0	283.2	21.3	216.9	212.8
250 kHz	251.8	251.8	17.4	191.4	187.4
500 kHz	241.9	242.0	15.8	185.7	181.7
1000 kHz	234.0	234.6	14.0	181.8	177.7

Table C8. Revised Head Injury Scale (HIS-r)

Day of Testing: Baseline

SRS: Day 1 2 3 4 5 6 7 ___
SRA: Day 1 2 3 4 5 6 7 ___

Name_____ **Date** _____

Symptom Checklist; ***Circle "YES" if you have experienced the symptom within the last 24 hours or "NO" if you have not experienced the symptom over the last 24 hours.***

1. Have you had a headache in the last 24 hours?	YES/NO
2. Have you experienced nausea in the last 24 hours?	YES/NO
3. Have you had difficulty balancing in the last 24 hours?	YES/NO
4. Have you experienced fatigue in the last 24 hours?	YES/NO
5. Have you experienced drowsiness in the last 24 hours?	YES/NO
6. Have you experienced sleep disturbances in the last 24 hours?	YES/NO
7. Have you had difficulty concentrating in the last 24 hours?	YES/NO
8. In the last 24 hours have you felt like you are "in a fog"?	YES/NO
9. In the last 24 hours have you felt "slowed down"?	YES/NO
10. Have your eyes been sensitive to light in the last 24 hours?	YES/NO
11. Have you felt sadness in the last 24 hours?	YES/NO
12. Have you experienced vomiting in the last 24 hours?	YES/NO
13. Have your ears been sensitive to noise in the last 24 hours?	YES/NO
14. Have you experienced nervousness in the last 24 hours?	YES/NO
15. Have you had difficulty remembering things in the last 24 hours?	YES/NO
16. Have you experienced numbness in the last 24 hours?	YES/NO
17. Have you experienced tingling sensations in the last 24 hours?	YES/NO
18. Have you experienced dizziness in the last 24 hours?	YES/NO
19. Have you experienced any neck pain in the last 24 hours?	YES/NO
20. Have you been irritable in the last 24 hours?	YES/NO
21. Have you experienced feelings of depression in the last 24 hours?	YES/NO
22. Have you experienced blurred vision in the last 24 hours?	YES/NO

	DURATION						SEVERITY						
	Briefly		Sometimes			Always	Not Severe						As Severe As Possible
1) Headache	1	2	3	4	5	6	0	1	2	3	4	5	6
2) Nausea	1	2	3	4	5	6	0	1	2	3	4	5	6
3) Difficulty balancing	1	2	3	4	5	6	0	1	2	3	4	5	6
4) Fatigue	1	2	3	4	5	6	0	1	2	3	4	5	6
5) Drowsiness	1	2	3	4	5	6	0	1	2	3	4	5	6
6) Sleep Disturbances	1	2	3	4	5	6	0	1	2	3	4	5	6
7) Difficulty Concentrating	1	2	3	4	5	6	0	1	2	3	4	5	6
8) Feeling "in a fog"	1	2	3	4	5	6	0	1	2	3	4	5	6
9) Feeling "slowed down"	1	2	3	4	5	6	0	1	2	3	4	5	6
10) Sensitive to light	1	2	3	4	5	6	0	1	2	3	4	5	6
11) Sadness	1	2	3	4	5	6	0	1	2	3	4	5	6
12) Vomiting	1	2	3	4	5	6	0	1	2	3	4	5	6
13) Sensitive to noise	1	2	3	4	5	6	0	1	2	3	4	5	6
14) Nervousness	1	2	3	4	5	6	0	1	2	3	4	5	6
15) Difficulty Remembering	1	2	3	4	5	6	0	1	2	3	4	5	6
16) Numbness	1	2	3	4	5	6	0	1	2	3	4	5	6
17) Tingling	1	2	3	4	5	6	0	1	2	3	4	5	6
18) Dizziness	1	2	3	4	5	6	0	1	2	3	4	5	6
19) Neck Pain	1	2	3	4	5	6	0	1	2	3	4	5	6
20) Irritable	1	2	3	4	5	6	0	1	2	3	4	5	6
21) Depression	1	2	3	4	5	6	0	1	2	3	4	5	6
22) Blurred vision	1	2	3	4	5	6	0	1	2	3	4	5	6

Table C9. Percent of Normal and Appetite Questionnaire

If 100% is feeling perfectly normal, what percentage of normal do you feel?

_____%

If not 100%, why?

Regarding your *appetite*:

Which best describes how you feel at this moment? (Circle One)

1. Full
2. Somewhat full
3. Neither hungry or full
4. Somewhat hungry
5. Hungry

Which best describes how you feel in a typical day at this time? (Circle One)

1. Full
2. Somewhat full
3. Neither hungry or full
4. Somewhat hungry
5. Hungry

Table C10. Neuro-QoL Sleep Disturbance Short Form

Neuro-QOL Item Bank v1.0 – Sleep Disturbance – Short Form

Sleep Disturbance – Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
NQSLP02	I had to force myself to get up in the morning……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSLP03	I had trouble stopping my thoughts at bedtime……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSLP04	I was sleepy during the daytime……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSLP05	I had trouble sleeping because of bad dreams……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSLP07	I had trouble falling asleep……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSLP12	Pain woke me up……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSLP13	I avoided or cancelled activities with my friends because I was tired from having a bad night's sleep……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSLP18	I felt physically tense during the middle of the night or early morning hours……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

English
March 6, 2014

Table C11. TBI-QoL Ability to Participate in Social Roles and Activities Short Form

TBI-QOL Item Bank v1.0 – Ability to Participate in Social Roles and Activities – Short Form 10a

Ability to Participate in Social Roles and Activities – Short Form 10a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
NQPRF03	I am able to do all of my regular family activities.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF06	I am able to do all of the family activities that I want to do.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF09	I am able to do all of my regular activities with friends.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF14	I am able to do all of the activities with friends that I want to do.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF18	I am able to do all of my regular leisure activities.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF21	I am able to do all of the community activities that I want to do.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF29	I am able to go out for entertainment as much as I want.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF32	I am able to perform my daily routines.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF35	I am able to do all of my usual work (include work at home).	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF39	I can do everything for work that I want to do (include work at home).	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Table C12. TBI-QoL Anxiety Short Form

TBI-QOL Item Bank v1.0 – Anxiety– Short Form 10a

Anxiety – Short Form 10a

Please respond to each question or statement by marking one box per row.

In the past 7 days...		Never	Rarely	Sometimes	Often	Always
EDANX53	I felt uneasy.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX46	I felt nervous.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX27	I felt something awful would happen.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX33	I felt terrified.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX54	I felt tense.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX48	Many situations made me worry.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX18	I had sudden feelings of panic.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX55	I had difficulty calming down.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX13	I had a racing or pounding heart.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX07	I felt like I needed help for my anxiety.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Table C13. TBI-QoL Attention/Concentration Short Form

TBI-QOL Item Bank v1.0 – Learning/Memory – Short Form 6a

Attention/Concentration – Short Form 6a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely (once)	Sometimes (two or three times)	Often (about once a day)	Always (several times a day)
NOCOG65	I had trouble keeping track of what I was doing if I was interrupted…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Cog_Dep_24	I had trouble keeping my mind on what I was doing…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NOCOG44	I had difficulty paying attention for a long period of time…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NOCOG60	I had trouble concentrating…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Cog136	I felt confused…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Cog_37	I had difficulty following the topic of conversation…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Table C14. TBI-QoL Communication Short Form

TBI-QOL Item Bank v1.0– Communication – Short Form 9a

Communication – Short Form 9a

Please respond to each question or statement by marking one box per row.

		None	A Little	Somewhat	A Lot	Cannot Do
Cog_123	How much DIFFICULTY do you currently have following what other people are saying?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Cog_138	How much DIFFICULTY do you currently have carrying on a conversation with more than one person?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Cog_102	How much DIFFICULTY do you currently have understanding what people say to you?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Cog_94	How much DIFFICULTY do you currently have speaking?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG04	How much DIFFICULTY do you currently have understanding family and friends on the phone?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

	In the past 7 days…	Never	Rarely (once)	Sometimes (two or three times)	Often (about once a day)	Always (several times a day)
Cog_139	I forgot what I wanted to say when talking to others…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Cog_37	I had difficulty following the topic of conversation…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG49	I had trouble saying what I mean in conversations with others…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG54	I had trouble finding the right word(s) to express myself…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Table C15. TBI-QoL Depression Short Form

Depression – Short Form 10a

Please respond to each question or statement by marking one box per row.

	In the past 7 days...	Never	Rarely	Sometimes	Often	Always
EDDEP39	I felt I had no reason for living.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP19	I felt that I wanted to give up on everything.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP04	I felt worthless.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP45	I felt that nothing was interesting.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP46	I felt that my life was empty.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP09	I felt that nothing could cheer me up.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP36	I felt unhappy.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP05	I felt that I had nothing to look forward to.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Table C16. TBI-QoL Emotional and Behavioral Dyscontrol Short Form

Emotional and Behavioral Dyscontrol – Short Form 10a

Please respond to each question or statement by marking one box per row.

	In the past 7 days...	Never	Rarely	Sometimes	Often	Always
PerEBD1	I had a problem controlling my temper.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NOPER05	It was hard to control my behavior.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NOPER06	I said or did things without thinking.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NOPER07	I got impatient with other people.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NOPER16	I had a hard time accepting criticism from other people.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NOPER17	I became upset easily.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NOPER19	I was in conflict with others.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pers_23	Other people got annoyed because I was so talkative.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pers_28	I said things that were inappropriate.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pers_29	Other people told me I did things that were inappropriate.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Table C17. TBI-QoL Fatigue Short Form

Fatigue – Short Form 10a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Not at All	A Little Bit	Somewhat	Quite a Bit	Very Much
FATIMP27	To what degree did you have trouble starting things because of your fatigue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP51	To what degree did you have trouble finishing things because of your fatigue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP42	To what degree did you feel tired even when you hadn't done anything?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP1	To what degree did you have to push yourself to get things done because ofyour fatigue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP28	How hard was it for you to carry on a conversation because of your fatigue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
FATEXP18	How often did you run out of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP26	How often were you too tired to socialize with your family?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP29	How often were you too tired to leave the house?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP20	How often did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Table C18. TBI-QoL Headache Pain Short Form

Headache Pain – Short Form 10a

Please respond to each question or statement by marking one box per row.

	In the past 7 days...	Never	Rarely	Sometimes	Often	Always
Headache1	I was irritable because of headaches.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Headache11	Headaches interfered with my daily activities.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Headache12	I had constant pain from headaches.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Headache2	I felt a pounding sensation in my head.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Headache4	I felt sharp pains in my head.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Headache5	I was unable to concentrate because of headaches.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Headache6	I felt a dull throbbing in my head.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Headache7	My head hurt.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Headache8	Headaches interfered with my ability to do things.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pain6	I was bothered by headaches.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Table C19. TBI-QoL Positive Affect and Well-Being Short Form

Positive Affect and Well-Being Short Form 9a

Please respond to each question or statement by marking one box per row.

	Lately...	Never	Rarely	Sometimes	Often	Always
NQPPF12	I felt hopeful.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPPF14	I had a sense of well-being.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPPF15	My life was satisfying.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPPF16	I had a sense of balance in my life.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPPF17	My life had meaning.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPPF19	My life was worth living.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPPF20	My life had purpose.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PPF30	I thought positively about my future.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PPF33	I was proud of everything that I have overcome.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Table C20. TBI-QoL Resilience Short Form

TBI-QOL Item Bank v1.0 – Resilience – Short Form 10a

Resilience – Short Form 10a

Please respond to each question or statement by marking one box per row.

	Lately...	Never	Rarely	Sometimes	Often	Always
Resilience_26	I was able to recognize and overcome challenges.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Resilience_9	I tried to see the positive side of things.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Resilience_12	I could adapt easily to new situations.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Resilience_25	I was confident that I could overcome my limitations.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Resilience_11	I found new things to enjoy.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Resilience_23	I felt I can get through difficult times.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Resilience_5	I used positive ways to cope with my injury.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Resilience_20	I felt the things I went through made me a stronger person.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Resilience_30	I achieved emotional balance in my life.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Resilience_7	I felt good about how I have coped with my injury.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Table C21. TBI-QoL Satisfaction with Social Roles and Activities Short Form

TBI-QOL Item Bank v1.0 – Satisfaction with Social Roles and Activities – Short Form 10a

Satisfaction with Social Roles and Activities – Short Form 10a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
NOSAT02	I am disappointed in my ability to meet the needs of my family.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NOSAT11	I am disappointed in my ability to meet the needs of my friends.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPSAT05	I am satisfied with the amount of time I spend doing leisure activities.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT08	I feel good about my ability to do things for my family.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT09	I am satisfied with my ability to do the work that is really important to me (include work at home).	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT20	I am satisfied with my ability to do things for my friends.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT21	I am satisfied with the amount of time I spend doing work (include work at home).	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT33	I am satisfied with my ability to do things for fun outside my home.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT48	I am satisfied with my ability to do things for fun at home (like reading, listening to music, etc.).	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SRPSAT49	I am satisfied with my ability to perform my daily routines.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Table C22. TBI-QoL Self-Esteem Short Form

Self-Esteem – Short Form 10a

Please respond to each question or statement by marking one box per row.

	In the past 7 days...	Never	Rarely	Sometimes	Often	Always
SelfE_12	I felt inferior to my friends or family.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SelfE_13	I felt bad about myself.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SelfE_14	I had poor self-esteem.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SelfE_15	I felt insecure.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SelfE_16	I was ashamed of my injury.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SelfE_24	I felt I was no longer a "whole person".	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SelfE_25	I felt invisible to other people.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SelfE_7	Because of my injury, I was unhappy with who I am.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SelfE_8	I felt it was difficult to achieve goals I set for myself.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SelfE_9	Because of my injury, I worried about performing tasks in front of other people.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Table C23. TBI-QoL Stigma Short Form

TBI-QOL Item Bank v1.0 – Stigma – 7a

Stigma – Short Form 7a

Please respond to each question or statement by marking one box per row.

	Lately...	Never	Rarely	Sometimes	Often	Always
Stigma_19	Because of my injury, I felt like other people were uncomfortable around me.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSTQ01	Because of my injury, some people seemed uncomfortable with me.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSTQ02	Because of my injury, some people avoided me.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSTQ08	Because of my injury, people avoided looking at me.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSTQ04	Because of my injury, I felt left out of things.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Stigma_26	Because of my injury, I felt that other people had low expectations of me.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSTQ06	Because of my injury, people made fun of me.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Table C24. Dietary Recall and Step Count Journal

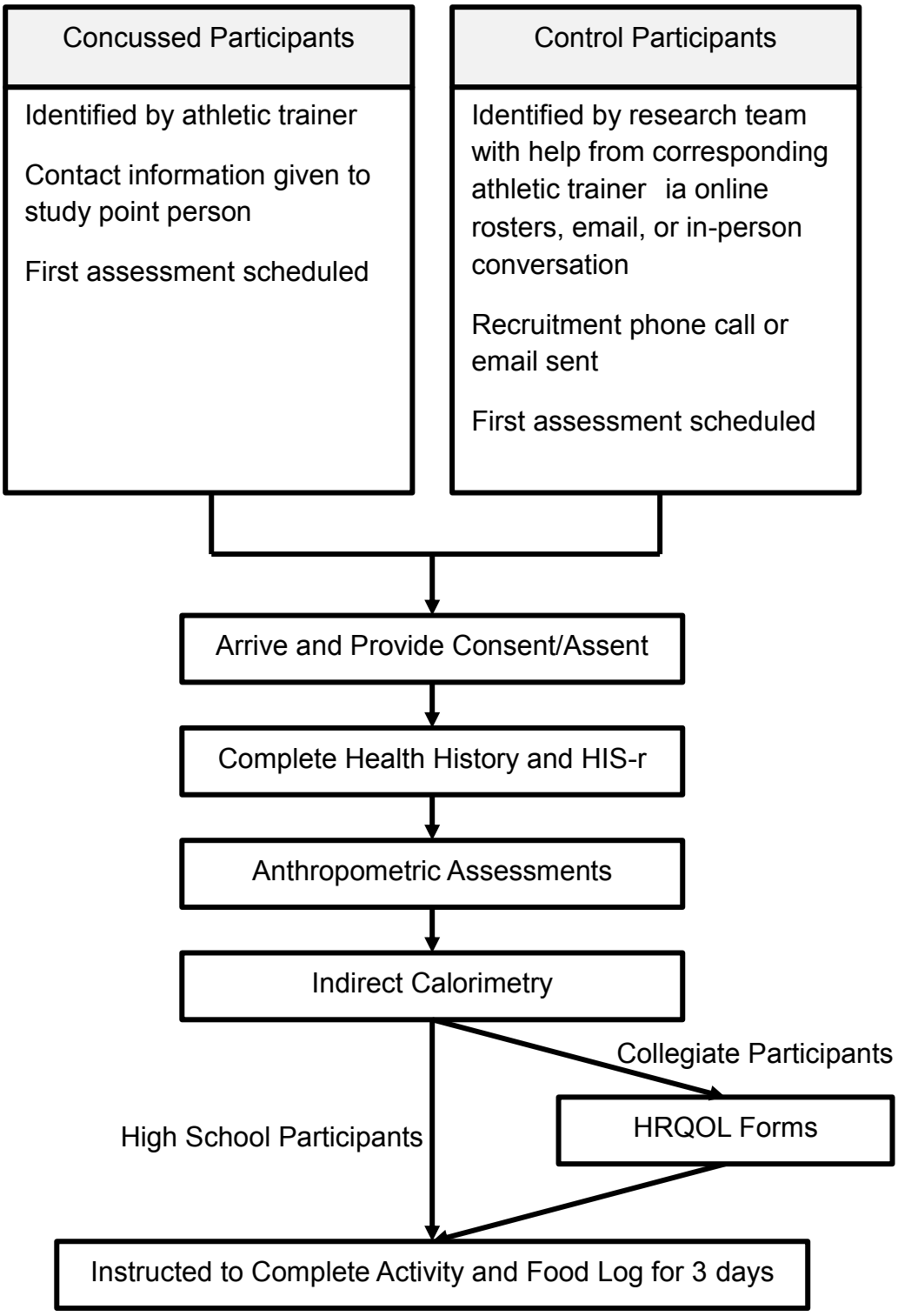
Name: _____

Each time you eat a meal, snack, or have a drink, please log the date and time. Indicate which food you ate and how many you consumed and include condiments or topings. Please indicate small, medium, or large if possible (e.g, a small serving is about the size of your palm, a medium serving is about the size of a baseball or 1 cup, and a large serving is about the size of a full plate or bowl). Please write a separate entry for each food or drink item.

Date & Time of Day	**Food/Beverage Consumed**	**Amount & Size**	**Condiments/Toppings**
11/13, 1:00pm	Cheeseburger	1- medium	Cheese, mayo, ketchup
11/13, 1:00pm	Pepsi	1- small	N/A
11/13, 3:00pm	Strawberries	Medium (1 cup)	Sugar (2 tsp)

Steps Day 1: _____ Steps Day 2: _____ Steps Day 3: _____

Figure C1. Participant Flow Chart



APPENDIX D

Table D1. MANOVA results for Group by Sex by Time comparisons of RMR/kg, %CHO, and EBal (Manuscript 1)

Multivariate Tests[a]

Effect	Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared		Noncent. Parameter		Observed Power[c]
Intercept	Pillai's Trace	.992	411.061[b]	9.000	28.000	.000	.992	3699.547	1.000
	Wilks' Lambda	.008	411.061[b]	9.000	28.000	.000	.992	3699.547	1.000
	Hotelling's Trace	132.127	411.061[b]	9.000	28.000	.000	.992	3699.547	1.000
	Roy's Largest Root	132.127	411.061[b]	9.000	28.000	.000	.992	3699.547	1.000
Group	Pillai's Trace	.425	2.304[b]	9.000	28.000	.044	.425	20.733	.800
	Wilks' Lambda	.575	2.304[b]	9.000	28.000	.044	.425	20.733	.800
	Hotelling's Trace	.740	2.304[b]	9.000	28.000	.044	.425	20.733	.800
	Roy's Largest Root	.740	2.304[b]	9.000	28.000	.044	.425	20.733	.800
Sex	Pillai's Trace	.310	1.398[b]	9.000	28.000	.236	.310	12.578	.540
	Wilks' Lambda	.690	1.398[b]	9.000	28.000	.236	.310	12.578	.540
	Hotelling's Trace	.449	1.398[b]	9.000	28.000	.236	.310	12.578	.540
	Roy's Largest Root	.449	1.398[b]	9.000	28.000	.236	.310	12.578	.540
Group * Sex	Pillai's Trace	.389	1.979[b]	9.000	28.000	.081	.389	17.808	.723
	Wilks' Lambda	.611	1.979[b]	9.000	28.000	.081	.389	17.808	.723
	Hotelling's Trace	.636	1.979[b]	9.000	28.000	.081	.389	17.808	.723
	Roy's Largest Root	.636	1.979[b]	9.000	28.000	.081	.389	17.808	.723

a. Design: Intercept + Group + Sex + Group * Sex
b. Exact statistic
c. Computed using alpha = .05

Table D2. Correlations between changes in RMR/kg, %CHO, and EBal with Days to Symptom Free and Days to Full Return to Play

Correlations

Correlations

		days_sxfree	days_rtp	RMRkgchange	CHOchange	EBalchange
days_sxfree	Pearson Correlation	1	.706**	-.238	.333	.267
	Sig. (2-tailed)		.002	.325	.163	.270
	N	19	17	19	19	19
days_rtp	Pearson Correlation	.706**	1	-.061	.406	-.175
	Sig. (2-tailed)	.002		.815	.106	.502
	N	17	17	17	17	17
RMRkgchange	Pearson Correlation	-.238	-.061	1	-.066	-.472*
	Sig. (2-tailed)	.325	.815		.782	.035
	N	19	17	20	20	20
CHOchange	Pearson Correlation	.333	.406	-.066	1	.106
	Sig. (2-tailed)	.163	.106	.782		.656
	N	19	17	20	20	20
EBalchange	Pearson Correlation	.267	-.175	-.472*	.106	1
	Sig. (2-tailed)	.270	.502	.035	.656	
	N	19	17	20	20	20

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Nonparametric Correlations

Correlations

			days_sxfree	days_rtp	RMRkgchange	CHOchange	EBalchange
Spearman's rho	days_sxfree	Correlation Coefficient	1.000	.787**	-.242	.289	.084
		Sig. (2-tailed)	.	.000	.318	.230	.732
		N	19	17	19	19	19
	days_rtp	Correlation Coefficient	.787**	1.000	-.166	.456	-.293
		Sig. (2-tailed)	.000	.	.523	.066	.253
		N	17	17	17	17	17
	RMRkgchange	Correlation Coefficient	-.242	-.166	1.000	-.099	-.433
		Sig. (2-tailed)	.318	.523	.	.677	.056
		N	19	17	20	20	20
	CHOchange	Correlation Coefficient	.289	.456	-.099	1.000	.078
		Sig. (2-tailed)	.230	.066	.677	.	.743
		N	19	17	20	20	20
	EBalchange	Correlation Coefficient	.084	-.293	-.433	.078	1.000
		Sig. (2-tailed)	.732	.253	.056	.743	.
		N	19	17	20	20	20

**. Correlation is significant at the 0.01 level (2-tailed).

Table D3. Correlations between RMR/kg, TEE/kg, EC/kg, EBal, Age, Concussion History, Total Symptom Score, Total Symptom Severity, Total Symptom Duration, and Physical Activity Factors

Descriptive Statistics

Group		Mean	Std. Deviation	N
Concussed	RMRperKg1	14.3143	2.11973	28
	TEEperkg1	21.8510	4.71628	27
	ECperKg1	28.1703	8.38168	28
	EBal1	1.3330	.42010	27
	Age	18.43	1.834	28
	ConxHxCat	1.0357	1.10494	28
	1_totalsx	8.67	3.843	27
	1_totaldur	26.52	13.902	27
	1_totalsev	20.41	11.998	27
	1pafactor	1.5287	.28510	27
Control	RMRperKg1	14.9405	2.03068	28
	TEEperkg1	27.1561	5.68661	28
	ECperKg1	27.2539	6.62235	28
	EBal1	1.0491	.34829	28
	Age	19.43	2.899	28
	ConxHxCat	.5357	.83808	28
	1_totalsx	.35	1.384	26
	1_totaldur	.65	2.785	26
	1_totalsev	.58	2.564	26
	1pafactor	1.8125	.24061	28

Parametric correlations

Correlations

Group			RMRperKg1	TEEperkg1	ECperKg1	EBal1	Age	ConxHxCat	1_totalsx	1_totaldur	1_totalsev	1pafactor
Concussed	RMRperKg1	Pearson Correlation	1	.560**	.153	-.228	.083	.255	.235	.258	.241	-.200
		Sig. (2-tailed)		.002	.436	.254	.673	.190	.237	.194	.226	.317
		N	28	27	28	27	28	28	27	27	27	27
	TEEperkg1	Pearson Correlation	.560**	1	.172	-.457*	.215	-.023	-.075	-.082	-.047	.692**
		Sig. (2-tailed)	.002		.391	.017	.283	.910	.714	.692	.821	.000
		N	27	27	27	27	27	27	26	26	26	27
	ECperKg1	Pearson Correlation	.153	.172	1	.776**	-.189	-.225	.073	.024	-.082	.054
		Sig. (2-tailed)	.436	.391		.000	.335	.250	.716	.904	.684	.791
		N	28	27	28	27	28	28	27	27	27	27
	EBal1	Pearson Correlation	-.228	-.457*	.776**	1	-.416*	-.238	.075	.061	-.060	-.376
		Sig. (2-tailed)	.254	.017	.000		.031	.231	.714	.766	.770	.054
		N	27	27	27	27	27	27	26	26	26	27
	Age	Pearson Correlation	.083	.215	-.189	-.416*	1	.157	.295	.142	.048	.259
		Sig. (2-tailed)	.673	.283	.335	.031		.426	.136	.480	.811	.193
		N	28	27	28	27	28	28	27	27	27	27
	ConxHxCat	Pearson Correlation	.255	-.023	-.225	-.238	.157	1	.124	.095	.047	-.226
		Sig. (2-tailed)	.190	.910	.250	.231	.426		.539	.638	.816	.256
		N	28	27	28	27	28	28	27	27	27	27
	1_totalsx	Pearson Correlation	.235	-.075	.073	.075	.295	.124	1	.859**	.755**	-.250
		Sig. (2-tailed)	.237	.714	.716	.714	.136	.539		.000	.000	.218
		N	27	26	27	26	27	27	27	27	27	26
	1_totaldur	Pearson Correlation	.258	-.082	.024	.061	.142	.095	.859**	1	.953**	-.273
		Sig. (2-tailed)	.194	.692	.904	.766	.480	.638	.000		.000	.178
		N	27	26	27	26	27	27	27	27	27	26
	1_totalsev	Pearson Correlation	.241	-.047	-.082	-.060	.048	.047	.755**	.953**	1	-.224
		Sig. (2-tailed)	.226	.821	.684	.770	.811	.816	.000	.000		.271
		N	27	26	27	26	27	27	27	27	27	26
	1pafactor	Pearson Correlation	-.200	.692**	.054	-.376	.259	-.226	-.250	-.273	-.224	1
		Sig. (2-tailed)	.317	.000	.791	.054	.193	.256	.218	.178	.271	
		N	27	27	27	27	27	27	26	26	26	27

Control	RMRperKg1	Pearson Correlation	1	.781**	.117	-.361	-.262	-.020	.232	.197	.208	.162
		Sig. (2-tailed)		.000	.555	.059	.178	.920	.255	.334	.308	.410
		N	28	28	28	28	28	28	26	26	26	28
	TEEperkg1	Pearson Correlation	.781**	1	-.068	-.647**	-.150	.079	.102	.108	.124	.737**
		Sig. (2-tailed)	.000		.730	.000	.445	.688	.620	.599	.545	.000
		N	28	28	28	28	28	28	26	26	26	28
	ECperKg1	Pearson Correlation	.117	-.068	1	.772**	.132	-.087	-.114	-.145	-.133	-.224
		Sig. (2-tailed)	.555	.730		.000	.504	.660	.580	.479	.518	.252
		N	28	28	28	28	28	28	26	26	26	28
	EBal1	Pearson Correlation	-.361	-.647**	.772**	1	.118	-.100	-.139	-.165	-.165	-.645**
		Sig. (2-tailed)	.059	.000	.000		.549	.614	.499	.422	.419	.000
		N	28	28	28	28	28	28	26	26	26	28
	Age	Pearson Correlation	-.262	-.150	.132	.118	1	-.022	.153	.187	.183	.080
		Sig. (2-tailed)	.178	.445	.504	.549		.912	.454	.360	.371	.687
		N	28	28	28	28	28	28	26	26	26	28
	ConxHxCat	Pearson Correlation	-.020	.079	-.087	-.100	-.022	1	.072	.081	.089	.131
		Sig. (2-tailed)	.920	.688	.660	.614	.912		.725	.694	.664	.507
		N	28	28	28	28	28	28	26	26	26	28
	1_totalsx	Pearson Correlation	.232	.102	-.114	-.139	.153	.072	1	.987**	.990**	-.076
		Sig. (2-tailed)	.255	.620	.580	.499	.454	.725		.000	.000	.713
		N	26	26	26	26	26	26	26	26	26	26
	1_totaldur	Pearson Correlation	.197	.108	-.145	-.165	.187	.081	.987**	1	.998**	-.038
		Sig. (2-tailed)	.334	.599	.479	.422	.360	.694	.000		.000	.855
		N	26	26	26	26	26	26	26	26	26	26
	1_totalsev	Pearson Correlation	.208	.124	-.133	-.165	.183	.089	.990**	.998**	1	-.021
		Sig. (2-tailed)	.308	.545	.518	.419	.371	.664	.000	.000		.918
		N	26	26	26	26	26	26	26	26	26	26
	1pafactor	Pearson Correlation	.162	.737**	-.224	-.645**	.080	.131	-.076	-.038	-.021	1
		Sig. (2-tailed)	.410	.000	.252	.000	.687	.507	.713	.855	.918	
		N	28	28	28	28	28	28	26	26	26	28

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Nonparametric Correlations

Correlations

Group				RMRperKg1	TEEperkg1	ECperKg1	EBal1	Age	ConxHxCat	1_totalsx	1_totaldur	1_totalsev	1pafactor
Spearman's rho	Concussed	RMRperKg1	Correlation Coefficient	1.000	.551**	.106	-.282	.116	.266	.243	.320	.362	-.215
			Sig. (2-tailed)	.	.003	.593	.154	.558	.171	.222	.104	.064	.282
			N	28	27	28	27	28	28	27	27	27	27
		TEEperkg1	Correlation Coefficient	.551**	1.000	.223	-.437*	.349	-.061	-.011	-.040	.029	.640**
			Sig. (2-tailed)	.003	.	.264	.023	.074	.764	.956	.845	.888	.000
			N	27	27	27	27	27	27	26	26	26	27
		ECperKg1	Correlation Coefficient	.106	.223	1.000	.698**	-.110	-.247	-.034	.002	-.155	.146
			Sig. (2-tailed)	.593	.264	.	.000	.577	.204	.866	.994	.440	.466
			N	28	27	28	27	28	28	27	27	27	27
		EBal1	Correlation Coefficient	-.282	-.437*	.698**	1.000	-.311	-.264	-.017	.054	-.147	-.299
			Sig. (2-tailed)	.154	.023	.000	.	.114	.182	.934	.793	.474	.130
			N	27	27	27	27	27	27	26	26	26	27
		Age	Correlation Coefficient	.116	.349	-.110	-.311	1.000	.118	.262	.045	.065	.270
			Sig. (2-tailed)	.558	.074	.577	.114	.	.550	.187	.823	.746	.174
			N	28	27	28	27	28	28	27	27	27	27
		ConxHxCat	Correlation Coefficient	.266	-.061	-.247	-.264	.118	1.000	.225	.126	.106	-.263
			Sig. (2-tailed)	.171	.764	.204	.182	.550	.	.259	.531	.599	.185
			N	28	27	28	27	28	28	27	27	27	27
		1_totalsx	Correlation Coefficient	.243	-.011	-.034	-.017	.262	.225	1.000	.802**	.721**	-.197
			Sig. (2-tailed)	.222	.956	.866	.934	.187	.259	.	.000	.000	.334
			N	27	26	27	26	27	27	27	27	27	26
		1_totaldur	Correlation Coefficient	.320	-.040	.002	.054	.045	.126	.802**	1.000	.942**	-.340
			Sig. (2-tailed)	.104	.845	.994	.793	.823	.531	.000	.	.000	.089
			N	27	26	27	26	27	27	27	27	27	26
		1_totalsev	Correlation Coefficient	.362	.029	-.155	-.147	.065	.106	.721**	.942**	1.000	-.289
			Sig. (2-tailed)	.064	.888	.440	.474	.746	.599	.000	.000	.	.153
			N	27	26	27	26	27	27	27	27	27	26
		1pafactor	Correlation Coefficient	-.215	.640**	.146	-.299	.270	-.263	-.197	-.340	-.289	1.000
			Sig. (2-tailed)	.282	.000	.466	.130	.174	.185	.334	.089	.153	.
			N	27	27	27	27	27	27	26	26	26	27

Control	RMRperKg1	Correlation Coefficient	1.000	.633**	.148	-.346	-.286	.033	.164	.070	.070	.060
		Sig. (2-tailed)	.	.000	.453	.071	.140	.866	.424	.736	.736	.760
		N	28	28	28	28	28	28	26	26	26	28
	TEEperkg1	Correlation Coefficient	.633**	1.000	-.097	-.660**	-.057	.260	-.148	-.044	-.044	.767**
		Sig. (2-tailed)	.000	.	.624	.000	.772	.181	.471	.830	.830	.000
		N	28	28	28	28	28	28	26	26	26	28
	ECperKg1	Correlation Coefficient	.148	-.097	1.000	.764**	-.211	.030	-.107	-.264	-.264	-.255
		Sig. (2-tailed)	.453	.624	.	.000	.282	.880	.604	.192	.192	.191
		N	28	28	28	28	28	28	26	26	26	28
	EBal1	Correlation Coefficient	-.346	-.660**	.764**	1.000	-.062	-.042	.006	-.143	-.143	-.615**
		Sig. (2-tailed)	.071	.000	.000	.	.755	.831	.979	.484	.484	.000
		N	28	28	28	28	28	28	26	26	26	28
	Age	Correlation Coefficient	-.286	-.057	-.211	-.062	1.000	.057	.119	.294	.294	.129
		Sig. (2-tailed)	.140	.772	.282	.755	.	.772	.563	.145	.145	.513
		N	28	28	28	28	28	28	26	26	26	28
	ConxHxCat	Correlation Coefficient	.033	.260	.030	-.042	.057	1.000	-.031	.055	.055	.141
		Sig. (2-tailed)	.866	.181	.880	.831	.772	.	.879	.789	.789	.473
		N	28	28	28	28	28	28	26	26	26	28
	1_totalsx	Correlation Coefficient	.164	-.148	-.107	.006	.119	-.031	1.000	.817**	.817**	-.345
		Sig. (2-tailed)	.424	.471	.604	.979	.563	.879	.	.000	.000	.084
		N	26	26	26	26	26	26	26	26	26	26
	1_totaldur	Correlation Coefficient	.070	-.044	-.264	-.143	.294	.055	.817**	1.000	1.000**	-.179
		Sig. (2-tailed)	.736	.830	.192	.484	.145	.789	.000	.	.	.382
		N	26	26	26	26	26	26	26	26	26	26
	1_totalsev	Correlation Coefficient	.070	-.044	-.264	-.143	.294	.055	.817**	1.000**	1.000	-.179
		Sig. (2-tailed)	.736	.830	.192	.484	.145	.789	.000	.	.	.382
		N	26	26	26	26	26	26	26	26	26	26
	1pafactor	Correlation Coefficient	.060	.767**	-.255	-.615**	.129	.141	-.345	-.179	-.179	1.000
		Sig. (2-tailed)	.760	.000	.191	.000	.513	.473	.084	.382	.382	.
		N	28	28	28	28	28	28	26	26	26	28

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Table D4. Symptom Outcome Frequencies

1_headache_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	25	44.6	47.2	47.2
	1	28	50.0	52.8	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_headache_duration

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	1.8	3.6	3.6
	2	3	5.4	10.7	14.3
	3	6	10.7	21.4	35.7
	4	8	14.3	28.6	64.3
	5	7	12.5	25.0	89.3
	6	3	5.4	10.7	100.0
	Total	28	50.0	100.0	
Missing	System	28	50.0		
Total		56	100.0		

1_headache_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	6	10.7	21.4	21.4
	2	5	8.9	17.9	39.3
	3	9	16.1	32.1	71.4
	4	7	12.5	25.0	96.4
	5	1	1.8	3.6	100.0
	Total	28	50.0	100.0	
Missing	System	28	50.0		
Total		56	100.0		

1_nausea_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	44	78.6	83.0	83.0
	1	9	16.1	17.0	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_nausea_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	2	3.6	22.2	22.2
	2	1	1.8	11.1	33.3
	3	4	7.1	44.4	77.8
	4	2	3.6	22.2	100.0
	Total	9	16.1	100.0	
Missing	System	47	83.9		
Total		56	100.0		

1_nausea_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	1	1.8	11.1	11.1
	1	1	1.8	11.1	22.2
	2	2	3.6	22.2	44.4
	3	5	8.9	55.6	100.0
	Total	9	16.1	100.0	
Missing	System	47	83.9		
Total		56	100.0		

1_diffbalancing_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	42	75.0	79.2	79.2
	1	11	19.6	20.8	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_diffbalancing_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	2	3.6	18.2	18.2
	2	4	7.1	36.4	54.5
	3	4	7.1	36.4	90.9
	5	1	1.8	9.1	100.0
	Total	11	19.6	100.0	
Missing	System	45	80.4		
Total		56	100.0		

1_diffbalancing_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	4	7.1	36.4	36.4
	2	5	8.9	45.5	81.8
	3	2	3.6	18.2	100.0
	Total	11	19.6	100.0	
Missing	System	45	80.4		
Total		56	100.0		

1_fatigue_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	31	55.4	58.5	58.5
	1	22	39.3	41.5	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_fatigue_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	2	6	10.7	27.3	27.3
	3	11	19.6	50.0	77.3
	4	3	5.4	13.6	90.9
	5	2	3.6	9.1	100.0
	Total	22	39.3	100.0	
Missing	System	34	60.7		
Total		56	100.0		

1_fatigue_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	5	8.9	22.7	22.7
	2	10	17.9	45.5	68.2
	3	4	7.1	18.2	86.4
	4	1	1.8	4.5	90.9
	5	2	3.6	9.1	100.0
	Total	22	39.3	100.0	
Missing	System	34	60.7		
Total		56	100.0		

1_drowsiness_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	33	58.9	62.3	62.3
	1	20	35.7	37.7	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_drowsiness_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	1.8	5.0	5.0
	2	7	12.5	35.0	40.0
	3	5	8.9	25.0	65.0
	4	6	10.7	30.0	95.0
	6	1	1.8	5.0	100.0
	Total	20	35.7	100.0	
Missing	System	36	64.3		
Total		56	100.0		

1_drowsiness_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	6	10.7	30.0	30.0
	2	8	14.3	40.0	70.0
	3	4	7.1	20.0	90.0
	4	2	3.6	10.0	100.0
	Total	20	35.7	100.0	
Missing	System	36	64.3		
Total		56	100.0		

1_sleepdist_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	38	67.9	73.1	73.1
	1	14	25.0	26.9	100.0
	Total	52	92.9	100.0	
Missing	System	4	7.1		
Total		56	100.0		

1_sleepdist_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	3	5.4	21.4	21.4
	2	1	1.8	7.1	28.6
	3	5	8.9	35.7	64.3
	4	2	3.6	14.3	78.6
	5	1	1.8	7.1	85.7
	6	2	3.6	14.3	100.0
	Total	14	25.0	100.0	
Missing	System	42	75.0		
Total		56	100.0		

1_sleepdist_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	4	7.1	28.6	28.6
	2	3	5.4	21.4	50.0
	3	4	7.1	28.6	78.6
	4	1	1.8	7.1	85.7
	5	2	3.6	14.3	100.0
	Total	14	25.0	100.0	
Missing	System	42	75.0		
Total		56	100.0		

1_diffbalancing_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	42	75.0	79.2	79.2
	1	11	19.6	20.8	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_diffbalancing_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	2	3.6	18.2	18.2
	2	4	7.1	36.4	54.5
	3	4	7.1	36.4	90.9
	5	1	1.8	9.1	100.0
	Total	11	19.6	100.0	
Missing	System	45	80.4		
Total		56	100.0		

1_diffbalancing_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	4	7.1	36.4	36.4
	2	5	8.9	45.5	81.8
	3	2	3.6	18.2	100.0
	Total	11	19.6	100.0	
Missing	System	45	80.4		
Total		56	100.0		

1_feelinginfog_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	34	60.7	64.2	64.2
	1	19	33.9	35.8	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_feelinginfog_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	3	5.4	15.8	15.8
	2	4	7.1	21.1	36.8
	3	4	7.1	21.1	57.9
	4	5	8.9	26.3	84.2
	5	1	1.8	5.3	89.5
	6	2	3.6	10.5	100.0
	Total	19	33.9	100.0	
Missing	System	37	66.1		
Total		56	100.0		

1_feelinginfog_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	1	1.8	5.3	5.3
	1	3	5.4	15.8	21.1
	2	7	12.5	36.8	57.9
	3	3	5.4	15.8	73.7
	4	4	7.1	21.1	94.7
	5	1	1.8	5.3	100.0
	Total	19	33.9	100.0	
Missing	System	37	66.1		
Total		56	100.0		

1_feelingslowed_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	36	64.3	67.9	67.9
	1	17	30.4	32.1	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_feelingslowed_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	2	6	10.7	35.3	35.3
	3	6	10.7	35.3	70.6
	4	3	5.4	17.6	88.2
	5	1	1.8	5.9	94.1
	6	1	1.8	5.9	100.0
	Total	17	30.4	100.0	
Missing	System	39	69.6		
Total		56	100.0		

1_feelingslowed_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	4	7.1	23.5	23.5
	2	5	8.9	29.4	52.9
	3	5	8.9	29.4	82.4
	4	1	1.8	5.9	88.2
	5	2	3.6	11.8	100.0
	Total	17	30.4	100.0	
Missing	System	39	69.6		
Total		56	100.0		

1_sensitivetolight_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	35	62.5	66.0	66.0
	1	18	32.1	34.0	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_sensitivetolight_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	5	8.9	27.8	27.8
	2	1	1.8	5.6	33.3
	3	7	12.5	38.9	72.2
	4	2	3.6	11.1	83.3
	5	1	1.8	5.6	88.9
	6	2	3.6	11.1	100.0
	Total	18	32.1	100.0	
Missing	System	38	67.9		
Total		56	100.0		

1_sensitivetolight_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	1	1.8	5.6	5.6
	1	5	8.9	27.8	33.3
	2	4	7.1	22.2	55.6
	3	4	7.1	22.2	77.8
	4	2	3.6	11.1	88.9
	5	2	3.6	11.1	100.0
	Total	18	32.1	100.0	
Missing	System	38	67.9		
Total		56	100.0		

1_sadness_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	47	83.9	88.7	88.7
	1	6	10.7	11.3	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_sadness_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	1	1.8	16.7	16.7
	1	1	1.8	16.7	33.3
	2	2	3.6	33.3	66.7
	3	1	1.8	16.7	83.3
	4	1	1.8	16.7	100.0
	Total	6	10.7	100.0	
Missing	System	50	89.3		
Total		56	100.0		

1_sadness_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	2	3.6	33.3	33.3
	2	1	1.8	16.7	50.0
	3	2	3.6	33.3	83.3
	4	1	1.8	16.7	100.0
	Total	6	10.7	100.0	
Missing	System	50	89.3		
Total		56	100.0		

1_vomiting_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	52	92.9	98.1	98.1
	1	1	1.8	1.9	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_vomiting_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	1.8	100.0	100.0
Missing	System	55	98.2		
Total		56	100.0		

1_vomiting_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	1.8	100.0	100.0
Missing	System	55	98.2		
Total		56	100.0		

1_sensitivetonoise_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	40	71.4	75.5	75.5
	1	13	23.2	24.5	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_sensitivetonoise_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	1.8	7.7	7.7
	2	3	5.4	23.1	30.8
	3	4	7.1	30.8	61.5
	4	4	7.1	30.8	92.3
	5	1	1.8	7.7	100.0
	Total	13	23.2	100.0	
Missing	System	43	76.8		
Total		56	100.0		

1_sensitivetonoise_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	1	1.8	7.7	7.7
	1	2	3.6	15.4	23.1
	2	5	8.9	38.5	61.5
	3	4	7.1	30.8	92.3
	4	1	1.8	7.7	100.0
	Total	13	23.2	100.0	
Missing	System	43	76.8		
Total		56	100.0		

1_nervous_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	46	82.1	86.8	86.8
	1	7	12.5	13.2	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_nervous_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	2	3.6	33.3	33.3
	2	1	1.8	16.7	50.0
	3	1	1.8	16.7	66.7
	4	1	1.8	16.7	83.3
	5	1	1.8	16.7	100.0
	Total	6	10.7	100.0	
Missing	System	50	89.3		
Total		56	100.0		

1_nervous_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	2	3.6	33.3	33.3
	2	1	1.8	16.7	50.0
	3	2	3.6	33.3	83.3
	4	1	1.8	16.7	100.0
	Total	6	10.7	100.0	
Missing	System	50	89.3		
Total		56	100.0		

1_diffremembering_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	47	83.9	88.7	88.7
	1	6	10.7	11.3	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_diffremembering_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	1.8	16.7	16.7
	2	2	3.6	33.3	50.0
	3	2	3.6	33.3	83.3
	4	1	1.8	16.7	100.0
	Total	6	10.7	100.0	
Missing	System	50	89.3		
Total		56	100.0		

1_diffremembering_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	2	3.6	33.3	33.3
	2	2	3.6	33.3	66.7
	3	2	3.6	33.3	100.0
	Total	6	10.7	100.0	
Missing	System	50	89.3		
Total		56	100.0		

1_numbness_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	52	92.9	98.1	98.1
	1	1	1.8	1.9	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_numbness_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	1.8	100.0	100.0
Missing	System	55	98.2		
Total		56	100.0		

1_numbness_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	1.8	100.0	100.0
Missing	System	55	98.2		
Total		56	100.0		

1_tingling_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	52	92.9	98.1	98.1
	1	1	1.8	1.9	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_tingling_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	1.8	100.0	100.0
Missing	System	55	98.2		
Total		56	100.0		

1_tingling_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	1.8	100.0	100.0
Missing	System	55	98.2		
Total		56	100.0		

1_dizziness_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	40	71.4	75.5	75.5
	1	13	23.2	24.5	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_dizziness_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	3	5.4	23.1	23.1
	2	4	7.1	30.8	53.8
	3	2	3.6	15.4	69.2
	4	2	3.6	15.4	84.6
	5	2	3.6	15.4	100.0
	Total	13	23.2	100.0	
Missing	System	43	76.8		
Total		56	100.0		

1_dizziness_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	1	1.8	7.7	7.7
	1	2	3.6	15.4	23.1
	2	7	12.5	53.8	76.9
	3	2	3.6	15.4	92.3
	6	1	1.8	7.7	100.0
	Total	13	23.2	100.0	
Missing	System	43	76.8		
Total		56	100.0		

1_neckpain_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	46	82.1	86.8	86.8
	1	7	12.5	13.2	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_neckpain_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	2	3.6	28.6	28.6
	2	1	1.8	14.3	42.9
	3	2	3.6	28.6	71.4
	4	1	1.8	14.3	85.7
	5	1	1.8	14.3	100.0
	Total	7	12.5	100.0	
Missing	System	49	87.5		
Total		56	100.0		

1_neckpain_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	2	3.6	28.6	28.6
	2	3	5.4	42.9	71.4
	3	2	3.6	28.6	100.0
	Total	7	12.5	100.0	
Missing	System	49	87.5		
Total		56	100.0		

1_irritable_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	47	83.9	88.7	88.7
	1	6	10.7	11.3	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_irritable_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	1.8	16.7	16.7
	2	4	7.1	66.7	83.3
	3	1	1.8	16.7	100.0
	Total	6	10.7	100.0	
Missing	System	50	89.3		
Total		56	100.0		

1_irritable_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	3	5.4	50.0	50.0
	2	3	5.4	50.0	100.0
	Total	6	10.7	100.0	
Missing	System	50	89.3		
Total		56	100.0		

1_depression_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	49	87.5	92.5	92.5
	1	4	7.1	7.5	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_depression_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	2	3.6	50.0	50.0
	3	1	1.8	25.0	75.0
	4	1	1.8	25.0	100.0
	Total	4	7.1	100.0	
Missing	System	52	92.9		
Total		56	100.0		

1_depression_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	2	3.6	50.0	50.0
	2	1	1.8	25.0	75.0
	3	1	1.8	25.0	100.0
	Total	4	7.1	100.0	
Missing	System	52	92.9		
Total		56	100.0		

1_blurredvision_pres

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	46	82.1	86.8	86.8
	1	7	12.5	13.2	100.0
	Total	53	94.6	100.0	
Missing	System	3	5.4		
Total		56	100.0		

1_blurredvision_dur

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	3	5.4	42.9	42.9
	2	1	1.8	14.3	57.1
	3	1	1.8	14.3	71.4
	4	2	3.6	28.6	100.0
	Total	7	12.5	100.0	
Missing	System	49	87.5		
Total		56	100.0		

1_blurredvision_sev

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	4	7.1	57.1	57.1
	2	2	3.6	28.6	85.7
	5	1	1.8	14.3	100.0
	Total	7	12.5	100.0	
Missing	System	49	87.5		
Total		56	100.0		

Table D5. Physical Activity Cross-tabulation

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Group * 1palvl	56	100.0%	0	0.0%	56	100.0%

Group * 1palvl Crosstabulation

Count

		1palvl					
		Exceptionally	Lightly	Moderately	Sedentary	Very	Total
Group	Concussed	2	4	7	10	3	2	28
	Control	0	11	2	4	0	11	28
Total		2	15	9	14	3	13	56

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	19.847[a]	5	.001
Likelihood Ratio	22.786	5	.000
N of Valid Cases	56		

a. 6 cells (50.0%) have expected count less than 5. The minimum expected count is 1.00.

Symmetric Measures

		Value	Approximate Significance
Nominal by Nominal	Phi	.595	.001
	Cramer's V	.595	.001
N of Valid Cases		56	

Table D6. Multiple Regression onto RMR/kg

Model Summary

Group	Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
						R Square Change	F Change	df1	df2	Sig. F Change
Concussed	1	.464[a]	.216	-.020	1.99727	.216	.917	6	20	.503
	2	.464[b]	.215	.028	1.95001	-.001	.018	1	20	.894
	3	.461[c]	.213	.069	1.90819	-.002	.066	1	21	.799
	4	.453[d]	.205	.101	1.87506	-.007	.208	1	22	.653
	5	.441[e]	.195	.127	1.84776	-.011	.306	1	23	.585
	6	.366[f]	.134	.099	1.87745	-.061	1.810	1	24	.191
Control	1	.584[g]	.341	.132	1.94456	.341	1.636	6	19	.192
	2	.584[h]	.341	.176	1.89537	.000	.001	1	19	.976
	3	.583[i]	.340	.214	1.85107	-.001	.030	1	20	.865
	4	.572[j]	.327	.236	1.82535	-.012	.393	1	21	.537
	5	.545[k]	.297	.236	1.82505	-.030	.992	1	22	.330
	6	.488[l]	.238	.207	1.85972	-.059	1.921	1	23	.179

a. Predictors: (Constant), 1_totalsev, ConxHxCat, Age, 1BMI, 1_totalsx, TotalDurSQRT1

b. Predictors: (Constant), 1_totalsev, ConxHxCat, Age, 1BMI, TotalDurSQRT1

c. Predictors: (Constant), ConxHxCat, Age, 1BMI, TotalDurSQRT1

d. Predictors: (Constant), ConxHxCat, 1BMI, TotalDurSQRT1

e. Predictors: (Constant), ConxHxCat, TotalDurSQRT1

f. Predictors: (Constant), ConxHxCat

g. Predictors: (Constant), 1_totalsev, 1BMI, ConxHxCat, Age, TotalDurSQRT1, 1_totalsx

h. Predictors: (Constant), 1_totalsev, 1BMI, ConxHxCat, TotalDurSQRT1, 1_totalsx

i. Predictors: (Constant), 1_totalsev, 1BMI, ConxHxCat, TotalDurSQRT1

j. Predictors: (Constant), 1_totalsev, 1BMI, TotalDurSQRT1

k. Predictors: (Constant), 1_totalsev, 1BMI

l. Predictors: (Constant), 1BMI

Coefficients[a]

Group	Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
			B	Std. Error	Beta			Lower Bound	Upper Bound
Concussed	1	(Constant)	10.927	5.386		2.029	.056	-.308	22.162
		Age	.111	.245	.105	.453	.655	-.400	.622
		ConxHxCat	.560	.378	.313	1.481	.154	-.229	1.349
		1BMI	-.073	.111	-.155	-.662	.516	-.304	.158
		1_totalsx	-.028	.211	-.055	-.135	.894	-.469	.412
		TotalDurSQRT1	.616	1.120	.404	.550	.588	-1.721	2.954
		1_totalsev	-.027	.101	-.162	-.266	.793	-.237	.183
	2	(Constant)	11.318	4.427		2.556	.018	2.111	20.525
		Age	.101	.229	.096	.443	.662	-.374	.577
		ConxHxCat	.566	.367	.317	1.543	.138	-.197	1.329
		1BMI	-.076	.107	-.161	-.711	.485	-.298	.146
		TotalDurSQRT1	.530	.899	.347	.590	.561	-1.338	2.399
		1_totalsev	-.025	.098	-.153	-.258	.799	-.228	.178
	3	(Constant)	11.718	4.058		2.888	.009	3.302	20.133
		Age	.102	.224	.096	.456	.653	-.362	.566
		ConxHxCat	.591	.346	.331	1.706	.102	-.127	1.309
		1BMI	-.070	.102	-.147	-.685	.501	-.280	.141
		TotalDurSQRT1	.314	.308	.205	1.019	.319	-.324	.951
	4	(Constant)	12.977	2.923		4.440	.000	6.930	19.024
		ConxHxCat	.606	.339	.339	1.789	.087	-.095	1.307
		1BMI	-.050	.091	-.106	-.553	.585	-.238	.137
		TotalDurSQRT1	.341	.296	.224	1.153	.261	-.271	.954
	5	(Constant)	11.587	1.473		7.864	.000	8.546	14.628
		ConxHxCat	.584	.331	.327	1.762	.091	-.100	1.268
		TotalDurSQRT1	.381	.283	.250	1.345	.191	-.204	.966
	6	(Constant)	13.451	.508		26.471	.000	12.405	14.498
		ConxHxCat	.654	.333	.366	1.965	.061	-.031	1.339

Control	1	(Constant)	24.068	4.796		5.018	.000	14.030	34.106
		Age	-.005	.169	-.007	-.030	.976	-.358	.348
		ConxHxCat	-.263	.467	-.108	-.564	.579	-1.240	.713
		1BMI	-.219	.097	-.503	-2.251	.036	-.422	-.015
		1_totalsx	.342	2.074	.227	.165	.871	-3.998	4.682
		TotalDurSQRT1	-3.555	3.654	-1.003	-.973	.343	-11.204	4.094
		1_totalsev	.827	1.477	1.015	.560	.582	-2.266	3.919
	2	(Constant)	24.013	4.316		5.563	.000	15.009	33.017
		ConxHxCat	-.263	.454	-.108	-.578	.570	-1.211	.685
		1BMI	-.220	.082	-.506	-2.687	.014	-.391	-.049
		1_totalsx	.348	2.013	.230	.173	.865	-3.851	4.546
		TotalDurSQRT1	-3.563	3.553	-1.005	-1.003	.328	-10.975	3.849
		1_totalsev	.825	1.438	1.013	.573	.573	-2.176	3.825
	3	(Constant)	24.202	4.077		5.936	.000	15.723	32.682
		ConxHxCat	-.275	.438	-.113	-.627	.537	-1.187	.637
		1BMI	-.224	.078	-.514	-2.880	.009	-.385	-.062
		TotalDurSQRT1	-3.645	3.439	-1.029	-1.060	.301	-10.796	3.505
		1_totalsev	1.030	.792	1.265	1.300	.208	-.617	2.677
	4	(Constant)	23.647	3.925		6.025	.000	15.508	31.787
		1BMI	-.220	.076	-.504	-2.876	.009	-.378	-.061
		TotalDurSQRT1	-3.345	3.358	-.944	-.996	.330	-10.308	3.619
		1_totalsev	.953	.772	1.170	1.235	.230	-.647	2.553
	5	(Constant)	20.248	1.939		10.442	.000	16.237	24.260
		1BMI	-.220	.076	-.505	-2.881	.008	-.378	-.062
		1_totalsev	.198	.143	.243	1.386	.179	-.097	.493
	6	(Constant)	20.180	1.975		10.216	.000	16.103	24.257
		1BMI	-.213	.078	-.488	-2.740	.011	-.373	-.052

a. Dependent Variable: RMRperKg1

Table D7. Multiple Regression onto EBal

Model Summary

Group	Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
						R Square Change	F Change	df1	df2	Sig. F Change
Concussed	1	.760[a]	.578	.444	.31255	.578	4.329	6	19	.006
	2	.733[b]	.537	.421	.31904	-.041	1.839	1	19	.191
Control	1	.443[c]	.196	-.058	.35495	.196	.771	6	19	.602
	2	.442[d]	.196	-.006	.34603	.000	.008	1	19	.932
	3	.440[e]	.194	.040	.33805	-.002	.042	1	20	.839
	4	.418[f]	.175	.062	.33417	-.019	.498	1	21	.488
	5	.336[g]	.113	.036	.33880	-.062	1.643	1	22	.213
	6	.281[h]	.079	.040	.33802	-.034	.889	1	23	.356
	7	.000[i]	.000	.000	.34508	-.079	2.055	1	24	.165

a. Predictors: (Constant), 1_totalsev, ConxHxCat, Age, 1BMI, 1_totalsx, TotalDurSQRT1

b. Predictors: (Constant), 1_totalsev, ConxHxCat, Age, 1BMI, TotalDurSQRT1

c. Predictors: (Constant), 1_totalsev, 1BMI, ConxHxCat, Age, TotalDurSQRT1, 1_totalsx

d. Predictors: (Constant), 1_totalsev, 1BMI, ConxHxCat, Age, 1_totalsx

e. Predictors: (Constant), 1_totalsev, 1BMI, Age, 1_totalsx

f. Predictors: (Constant), 1_totalsev, 1BMI, 1_totalsx

g. Predictors: (Constant), 1_totalsev, 1BMI

h. Predictors: (Constant), 1BMI

i. Predictor: (constant)

Coefficients[a]

Group	Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
			B	Std. Error	Beta			Lower Bound	Upper Bound
Concussed	1	(Constant)	2.978	1.041		2.859	.010	.798	5.158
		Age	-.089	.038	-.405	-2.321	.032	-.170	-.009
		ConxHxCat	-.122	.059	-.322	-2.058	.054	-.246	.002
		1BMI	-.039	.018	-.393	-2.122	.047	-.077	-.001
		1_totalsx	.049	.036	.442	1.356	.191	-.027	.126
		TotalDurSQRT1	.325	.239	.901	1.359	.190	-.176	.826
		1_totalsev	-.049	.019	-1.370	-2.644	.016	-.088	-.010
	2	(Constant)	2.067	.812		2.544	.019	.372	3.762
		Age	-.077	.038	-.348	-2.015	.058	-.156	.003
		ConxHxCat	-.132	.060	-.349	-2.205	.039	-.257	-.007
		1BMI	-.032	.018	-.322	-1.776	.091	-.069	.006
		TotalDurSQRT1	.542	.182	1.500	2.977	.007	.162	.921
		1_totalsev	-.057	.018	-1.591	-3.169	.005	-.094	-.019
Control	1	(Constant)	.095	.875		.109	.915	-1.737	1.928
		Age	.020	.031	.162	.652	.522	-.044	.085
		ConxHxCat	-.016	.085	-.039	-.185	.855	-.194	.163
		1BMI	.019	.018	.266	1.081	.293	-.018	.056
		1_totalsx	.463	.379	1.859	1.224	.236	-.329	1.256
		TotalDurSQRT1	.058	.667	.099	.087	.932	-1.338	1.454
		1_totalsev	-.289	.270	-2.147	-1.072	.297	-.853	.275
	2	(Constant)	.154	.541		.285	.779	-.975	1.284
		Age	.020	.030	.163	.677	.506	-.042	.083
		ConxHxCat	-.017	.082	-.042	-.206	.839	-.188	.154
		1BMI	.019	.017	.265	1.105	.282	-.017	.055
		1_totalsx	.459	.366	1.842	1.255	.224	-.304	1.223
		1_totalsev	-.274	.199	-2.033	-1.377	.184	-.688	.141
	3	(Constant)	.132	.518		.255	.802	-.946	1.210
		Age	.021	.029	.166	.706	.488	-.040	.081
		1BMI	.019	.017	.269	1.150	.263	-.016	.054
		1_totalsx	.470	.354	1.885	1.328	.199	-.266	1.206
		1_totalsev	-.280	.192	-2.080	-1.459	.159	-.679	.119
	4	(Constant)	.387	.367		1.053	.304	-.375	1.149
		1BMI	.025	.014	.352	1.764	.092	-.004	.055
		1_totalsx	.446	.348	1.791	1.282	.213	-.276	1.169
		1_totalsev	-.264	.188	-1.962	-1.402	.175	-.655	.127
	5	(Constant)	.508	.360		1.411	.172	-.237	1.253
		1BMI	.021	.014	.294	1.492	.149	-.008	.050
		1_totalsev	-.025	.026	-.186	-.943	.356	-.080	.030
	6	(Constant)	.517	.359		1.439	.163	-.224	1.258
		1BMI	.020	.014	.281	1.434	.165	-.009	.049
	7	(Constant)	1.022	.068		15.108	.000	.883	1.162

a. Dependent Variable: EBal1

Table D8. Sleep Disturbance Repeated Measures ANOVA and Post-Hoc

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Sleep	Sphericity Assumed	333.178	2	166.589	21.360	.000	.416	42.720	1.000
	Greenhouse-Geisser	333.178	1.912	174.224	21.360	.000	.416	40.848	1.000
	Huynh-Feldt	333.178	2.000	166.589	21.360	.000	.416	42.720	1.000
	Lower-bound	333.178	1.000	333.178	21.360	.000	.416	21.360	.994
Sleep * Group	Sphericity Assumed	82.181	2	41.090	5.269	.008	.149	10.537	.816
	Greenhouse-Geisser	82.181	1.912	42.974	5.269	.009	.149	10.075	.803
	Huynh-Feldt	82.181	2.000	41.090	5.269	.008	.149	10.537	.816
	Lower-bound	82.181	1.000	82.181	5.269	.029	.149	5.269	.603
Sleep * Sex	Sphericity Assumed	4.646	2	2.323	.298	.743	.010	.596	.095
	Greenhouse-Geisser	4.646	1.912	2.429	.298	.734	.010	.570	.094
	Huynh-Feldt	4.646	2.000	2.323	.298	.743	.010	.596	.095
	Lower-bound	4.646	1.000	4.646	.298	.589	.010	.298	.083
Sleep * Group * Sex	Sphericity Assumed	7.746	2	3.873	.497	.611	.016	.993	.128
	Greenhouse-Geisser	7.746	1.912	4.050	.497	.603	.016	.950	.126
	Huynh-Feldt	7.746	2.000	3.873	.497	.611	.016	.993	.128
	Lower-bound	7.746	1.000	7.746	.497	.486	.016	.497	.105
Error(Sleep)	Sphericity Assumed	467.942	60	7.799					
	Greenhouse-Geisser	467.942	57.371	8.156					
	Huynh-Feldt	467.942	60.000	7.799					
	Lower-bound	467.942	30.000	15.598					

a. Computed using alpha = .05

Paired Samples Test

Group			Paired Differences					t	df	Sig. (2-tailed)
			Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Concussed	Pair 1	1sleeptotal - 2sleeptotal	4.313	3.928	.982	2.219	6.406	4.392	15	.001
	Pair 2	2sleeptotal - f3sleeptotal	2.467	2.748	.710	.945	3.989	3.476	14	.004
	Pair 3	1sleeptotal - f3sleeptotal	6.667	4.386	1.132	4.238	9.096	5.887	14	.000
Control	Pair 1	1sleeptotal - 2sleeptotal	1.950	3.316	.742	.398	3.502	2.630	19	.017
	Pair 2	2sleeptotal - f3sleeptotal	.211	4.289	.984	-1.857	2.278	.214	18	.833
	Pair 3	1sleeptotal - f3sleeptotal	2.053	4.129	.947	.062	4.043	2.167	18	.044

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference Lower	Upper
1sleeptotal	Equal variances assumed	.501	.484	3.631	36	.001	4.083	1.124	1.803	6.364
	Equal variances not assumed			3.594	33.049	.001	4.083	1.136	1.772	6.395
2sleeptotal	Equal variances assumed	8.609	.006	1.036	34	.307	1.325	1.278	-1.273	3.923
	Equal variances not assumed			.966	20.776	.345	1.325	1.371	-1.528	4.178
f3sleeptotal	Equal variances assumed	.723	.402	-.326	32	.747	-.467	1.432	-3.383	2.449
	Equal variances not assumed			-.321	28.020	.751	-.467	1.455	-3.448	2.514

Table D9. Fatigue Repeated Measures ANOVA and Post-Hoc

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Fatigue	Sphericity Assumed	189.118	2	94.559	4.221	.020	.131	8.442	.718
	Greenhouse-Geisser	189.118	1.766	107.067	4.221	.024	.131	7.456	.678
	Huynh-Feldt	189.118	2.000	94.559	4.221	.020	.131	8.442	.718
	Lower-bound	189.118	1.000	189.118	4.221	.049	.131	4.221	.510
Fatigue * Group	Sphericity Assumed	155.204	2	77.602	3.464	.038	.110	6.928	.626
	Greenhouse-Geisser	155.204	1.766	87.867	3.464	.045	.110	6.119	.587
	Huynh-Feldt	155.204	2.000	77.602	3.464	.038	.110	6.928	.626
	Lower-bound	155.204	1.000	155.204	3.464	.073	.110	3.464	.435
Fatigue * Sex	Sphericity Assumed	1.868	2	.934	.042	.959	.001	.083	.056
	Greenhouse-Geisser	1.868	1.766	1.057	.042	.944	.001	.074	.056
	Huynh-Feldt	1.868	2.000	.934	.042	.959	.001	.083	.056
	Lower-bound	1.868	1.000	1.868	.042	.840	.001	.042	.054
Fatigue * Group * Sex	Sphericity Assumed	27.169	2	13.585	.606	.549	.021	1.213	.146
	Greenhouse-Geisser	27.169	1.766	15.382	.606	.530	.021	1.071	.140
	Huynh-Feldt	27.169	2.000	13.585	.606	.549	.021	1.213	.146
	Lower-bound	27.169	1.000	27.169	.606	.443	.021	.606	.117
Error(Fatigue)	Sphericity Assumed	1254.507	56	22.402					
	Greenhouse-Geisser	1254.507	49.458	25.365					
	Huynh-Feldt	1254.507	56.000	22.402					
	Lower-bound	1254.507	28.000	44.804					

a. Computed using alpha = .05

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	1fatiguetotal - 2fatiguetotal	4.462	8.472	2.350	-.658	9.581	1.899	12	.082
Pair 2	2fatiguetotal - f3fatiguetotal	3.000	5.083	1.410	-.071	6.071	2.128	12	.055
Pair 3	1fatiguetotal - f3fatiguetotal	7.462	9.980	2.768	1.431	13.492	2.696	12	.019

Table D10. Anxiety Repeated Measures ANOVA

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Anxiety	Sphericity Assumed	163.415	2	81.708	7.428	.001	.198	14.857	.930
	Greenhouse-Geisser	163.415	1.635	99.926	7.428	.003	.198	12.148	.887
	Huynh-Feldt	163.415	1.890	86.474	7.428	.002	.198	14.038	.919
	Lower-bound	163.415	1.000	163.415	7.428	.011	.198	7.428	.751
Anxiety * Group	Sphericity Assumed	33.310	2	16.655	1.514	.228	.048	3.028	.310
	Greenhouse-Geisser	33.310	1.635	20.368	1.514	.231	.048	2.476	.280
	Huynh-Feldt	33.310	1.890	17.626	1.514	.229	.048	2.861	.301
	Lower-bound	33.310	1.000	33.310	1.514	.228	.048	1.514	.222
Anxiety * Sex	Sphericity Assumed	20.258	2	10.129	.921	.404	.030	1.842	.202
	Greenhouse-Geisser	20.258	1.635	12.387	.921	.388	.030	1.506	.185
	Huynh-Feldt	20.258	1.890	10.720	.921	.399	.030	1.740	.197
	Lower-bound	20.258	1.000	20.258	.921	.345	.030	.921	.153
Anxiety * Group * Sex	Sphericity Assumed	1.245	2	.622	.057	.945	.002	.113	.058
	Greenhouse-Geisser	1.245	1.635	.761	.057	.916	.002	.093	.058
	Huynh-Feldt	1.245	1.890	.659	.057	.938	.002	.107	.058
	Lower-bound	1.245	1.000	1.245	.057	.814	.002	.057	.056
Error(Anxiety)	Sphericity Assumed	659.959	60	10.999					
	Greenhouse-Geisser	659.959	49.061	13.452					
	Huynh-Feldt	659.959	56.693	11.641					
	Lower-bound	659.959	30.000	21.999					

a. Computed using alpha = .05

Table D11. Resilience Repeated Measures ANOVA

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Resilience	Sphericity Assumed	151.254	2	75.627	5.558	.006	.156	11.115	.837
	Greenhouse-Geisser	151.254	1.850	81.754	5.558	.008	.156	10.282	.815
	Huynh-Feldt	151.254	2.000	75.627	5.558	.006	.156	11.115	.837
	Lower-bound	151.254	1.000	151.254	5.558	.025	.156	5.558	.626
Resilience * Group	Sphericity Assumed	37.088	2	18.544	1.363	.264	.043	2.726	.282
	Greenhouse-Geisser	37.088	1.850	20.047	1.363	.264	.043	2.521	.271
	Huynh-Feldt	37.088	2.000	18.544	1.363	.264	.043	2.726	.282
	Lower-bound	37.088	1.000	37.088	1.363	.252	.043	1.363	.204
Resilience * Sex	Sphericity Assumed	1.044	2	.522	.038	.962	.001	.077	.056
	Greenhouse-Geisser	1.044	1.850	.564	.038	.954	.001	.071	.055
	Huynh-Feldt	1.044	2.000	.522	.038	.962	.001	.077	.056
	Lower-bound	1.044	1.000	1.044	.038	.846	.001	.038	.054
Resilience * Group * Sex	Sphericity Assumed	8.045	2	4.022	.296	.745	.010	.591	.095
	Greenhouse-Geisser	8.045	1.850	4.348	.296	.728	.010	.547	.093
	Huynh-Feldt	8.045	2.000	4.022	.296	.745	.010	.591	.095
	Lower-bound	8.045	1.000	8.045	.296	.591	.010	.296	.082
Error(Resilience)	Sphericity Assumed	816.469	60	13.608					
	Greenhouse-Geisser	816.469	55.503	14.710					
	Huynh-Feldt	816.469	60.000	13.608					
	Lower-bound	816.469	30.000	27.216					

a. Computed using alpha = .05

Table D12. Stigma Repeated Measures ANOVA and Post-Hoc

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Stigma	Sphericity Assumed	20.115	2	10.058	5.756	.005	.171	11.513	.849
	Greenhouse-Geisser	20.115	1.994	10.088	5.756	.005	.171	11.478	.849
	Huynh-Feldt	20.115	2.000	10.058	5.756	.005	.171	11.513	.849
	Lower-bound	20.115	1.000	20.115	5.756	.023	.171	5.756	.639
Stigma * Group	Sphericity Assumed	12.870	2	6.435	3.683	.031	.116	7.366	.654
	Greenhouse-Geisser	12.870	1.994	6.454	3.683	.032	.116	7.343	.653
	Huynh-Feldt	12.870	2.000	6.435	3.683	.031	.116	7.366	.654
	Lower-bound	12.870	1.000	12.870	3.683	.065	.116	3.683	.458
Stigma * Sex	Sphericity Assumed	7.191	2	3.595	2.058	.137	.068	4.116	.406
	Greenhouse-Geisser	7.191	1.994	3.606	2.058	.137	.068	4.103	.406
	Huynh-Feldt	7.191	2.000	3.595	2.058	.137	.068	4.116	.406
	Lower-bound	7.191	1.000	7.191	2.058	.163	.068	2.058	.283
Stigma * Group * Sex	Sphericity Assumed	13.276	2	6.638	3.799	.028	.119	7.598	.669
	Greenhouse-Geisser	13.276	1.994	6.658	3.799	.029	.119	7.575	.668
	Huynh-Feldt	13.276	2.000	6.638	3.799	.028	.119	7.598	.669
	Lower-bound	13.276	1.000	13.276	3.799	.061	.119	3.799	.469
Error(Stigma)	Sphericity Assumed	97.844	56	1.747					
	Greenhouse-Geisser	97.844	55.830	1.753					
	Huynh-Feldt	97.844	56.000	1.747					
	Lower-bound	97.844	28.000	3.494					

a. Computed using alpha = .05

Paired Samples Test

Group			Paired Differences					t	df	Sig. (2-tailed)
			Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Concussed	Pair 1	1stigmatotal - 2stigmatotal	.733	2.658	.686	-.739	2.205	1.068	14	.303
	Pair 2	2stigmatotal - f3stigmatotal	1.714	2.673	.714	.171	3.257	2.400	13	.032
	Pair 3	1stigmatotal - f3stigmatotal	2.357	2.951	.789	.653	4.061	2.989	13	.010
Control	Pair 1	1stigmatotal - 2stigmatotal	.222	1.166	.275	-.358	.802	.809	17	.430
	Pair 2	2stigmatotal - f3stigmatotal	.053	.229	.053	-.058	.163	1.000	18	.331
	Pair 3	1stigmatotal - f3stigmatotal	.278	1.074	.253	-.256	.812	1.097	17	.288

Table D13. Appetite Repeated Measures ANOVA

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Appetite	Sphericity Assumed	2.970	2	1.485	2.544	.088	.083	5.089	.489
	Greenhouse-Geisser	2.970	1.806	1.645	2.544	.094	.083	4.596	.462
	Huynh-Feldt	2.970	2.000	1.485	2.544	.088	.083	5.089	.489
	Lower-bound	2.970	1.000	2.970	2.544	.122	.083	2.544	.338
Appetite * Group	Sphericity Assumed	2.436	2	1.218	2.087	.134	.069	4.173	.411
	Greenhouse-Geisser	2.436	1.806	1.349	2.087	.139	.069	3.768	.389
	Huynh-Feldt	2.436	2.000	1.218	2.087	.134	.069	4.173	.411
	Lower-bound	2.436	1.000	2.436	2.087	.160	.069	2.087	.286
Appetite * Sex	Sphericity Assumed	3.474	2	1.737	2.975	.059	.096	5.951	.556
	Greenhouse-Geisser	3.474	1.806	1.923	2.975	.065	.096	5.374	.526
	Huynh-Feldt	3.474	2.000	1.737	2.975	.059	.096	5.951	.556
	Lower-bound	3.474	1.000	3.474	2.975	.096	.096	2.975	.384
Appetite * Group * Sex	Sphericity Assumed	.725	2	.363	.621	.541	.022	1.242	.149
	Greenhouse-Geisser	.725	1.806	.401	.621	.526	.022	1.122	.143
	Huynh-Feldt	.725	2.000	.363	.621	.541	.022	1.242	.149
	Lower-bound	.725	1.000	.725	.621	.437	.022	.621	.119
Error(Appetite)	Sphericity Assumed	32.687	56	.584					
	Greenhouse-Geisser	32.687	50.571	.646					
	Huynh-Feldt	32.687	56.000	.584					
	Lower-bound	32.687	28.000	1.167					

a. Computed using alpha = .05

Table D14. Sleep Disturbance Regressions

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.411[a]	.169	-.081	4.72734	.169	.677	3	10	.586
2	.406[b]	.165	.013	4.51826	-.004	.049	1	10	.830
3	.400[c]	.160	.090	4.33868	-.005	.065	1	11	.803
4	.000[d]	.000	.000	4.54767	-.160	2.283	1	12	.157

a. Predictors: (Constant), cuberootsxdurchange, LogDSF, SxSevChangesqrt

b. Predictors: (Constant), LogDSF, SxSevChangesqrt

c. Predictors: (Constant), SxSevChangesqrt

d. Predictor: (constant)

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-4.547	15.173		-.300	.771
	SxSevChangesqrt	-2.281	3.918	-.625	-.582	.573
	LogDSF	.696	2.394	.087	.291	.777
	cuberootsxdurchange	2.150	9.760	.238	.220	.830
2	(Constant)	-1.576	6.645		-.237	.817
	SxSevChangesqrt	-1.449	1.007	-.397	-1.440	.178
	LogDSF	.565	2.217	.070	.255	.803
3	(Constant)	-.342	4.374		-.078	.939
	SxSevChangesqrt	-1.460	.966	-.400	-1.511	.157
4	(Constant)	-6.714	1.215		-5.524	.000

a. Dependent Variable: SleepChange

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.304[a]	.092	-.155	4.71447	.092	.373	3	11	.774
2	.285[b]	.081	-.072	4.54177	-.011	.137	1	11	.718
3	.215[c]	.046	-.027	4.44511	-.035	.453	1	12	.514
4	.000[d]	.000	.000	4.38613	-.046	.631	1	13	.441

a. Predictors: (Constant), EBalchange, CHOchange, RMRkgchange

b. Predictors: (Constant), EBalchange, RMRkgchange

c. Predictors: (Constant), EBalchange

d. Predictor: (constant)

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	-7.891	1.707		-4.622	.001
	RMRkgchange	-.764	1.256	-.200	-.608	.555
	CHOchange	.020	.053	.107	.370	.718
	EBalchange	-4.176	4.393	-.312	-.951	.362
2	(Constant)	-7.835	1.638		-4.783	.000
	RMRkgchange	-.810	1.204	-.212	-.673	.514
	EBalchange	-4.248	4.228	-.317	-1.005	.335
3	(Constant)	-7.401	1.474		-5.022	.000
	EBalchange	-2.885	3.631	-.215	-.794	.441
4	(Constant)	-6.667	1.132		-5.887	.000

a. Dependent Variable: SleepChange

Table D15. Fatigue Regressions

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.414[a]	.171	.021	9.49039	.171	1.137	2	11	.356
2	.412[b]	.169	.100	9.09639	-.002	.024	1	11	.879
3	.000[c]	.000	.000	9.58966	-.169	2.448	1	12	.144

a. Predictors: (Constant), ConxHxCat, sexnumeric

b. Predictors: (Constant), ConxHxCat

c. Predictor: (constant)

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-10.044	10.081		-.996	.340
	sexnumeric	-.841	5.394	-.044	-.156	.879
	ConxHxCat	3.053	2.117	.403	1.442	.177
2	(Constant)	-11.507	3.531		-3.259	.007
	ConxHxCat	3.116	1.992	.412	1.565	.144
3	(Constant)	-7.500	2.563		-2.926	.012

a. Dependent Variable: FatigueChange

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.638[a]	.408	.210	8.41908	.408	2.064	3	9	.175
2	.638[b]	.406	.288	7.99447	-.001	.017	1	9	.900
3	.589[c]	.347	.288	7.99567	-.060	1.003	1	10	.340

a. Predictors: (Constant), cuberootsxdurchange, LogDSF, SxSevChangesqrt

b. Predictors: (Constant), cuberootsxdurchange, SxSevChangesqrt

c. Predictors: (Constant), cuberootsxdurchange

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	40.276	27.103		1.486	.171
	SxSevChangesqrt	6.287	7.042	.804	.893	.395
	LogDSF	.555	4.284	.034	.129	.900
	cuberootsxdurchange	-26.086	17.392	-1.355	-1.500	.168
2	(Constant)	42.141	21.800		1.933	.082
	SxSevChangesqrt	6.505	6.494	.832	1.002	.340
	cuberootsxdurchange	-26.649	15.991	-1.385	-1.667	.127
3	(Constant)	25.559	14.185		1.802	.099
	cuberootsxdurchange	-11.336	4.690	-.589	-2.417	.034

a. Dependent Variable: FatigueChange

Table D16. Stigma Regressions

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics			
					R Square Change	F Change	df1	df2	Sig. F Change
1	.678[a]	.460	.280	.90178	.460	2.553	3	9	.121
2	.657[b]	.432	.318	.87756	-.028	.470	1	9	.510
3	.611[c]	.374	.317	.87829	-.058	1.018	1	10	.337

a. Predictors: (Constant), EBalchange, CHOchange, RMRkgchange

b. Predictors: (Constant), EBalchange, RMRkgchange

c. Predictors: (Constant), EBalchange

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.866	.332		2.605	.029
	RMRkgchange	.248	.250	.272	.995	.346
	CHOchange	.007	.011	.168	.686	.510
	EBalchange	-1.596	.876	-.498	-1.821	.102
2	(Constant)	.876	.323		2.710	.022
	RMRkgchange	.245	.243	.268	1.009	.337
	EBalchange	-1.577	.852	-.492	-1.850	.094
3	(Constant)	.774	.307		2.519	.029
	EBalchange	-1.958	.765	-.611	-2.562	.026

a. Dependent Variable: StigmaChangesqrt

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.616[a]	.380	.173	2.76907	.380	1.835	3	9	.211
2	.615[b]	.379	.255	2.62862	-.001	.011	1	9	.918
3	.525[c]	.276	.210	2.70592	-.103	1.656	1	10	.227

a. Predictors: (Constant), cuberootsxdurchange, LogDSF, SxSevChangesqrt

b. Predictors: (Constant), LogDSF, SxSevChangesqrt

c. Predictors: (Constant), SxSevChangesqrt

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	-.878	8.914		-.098	.924
	SxSevChangesqrt	-1.553	2.316	-.618	-.670	.519
	LogDSF	1.704	1.409	.328	1.210	.257
	cuberootsxdurchange	.608	5.720	.098	.106	.918
2	(Constant)	-.041	3.974		-.010	.992
	SxSevChangesqrt	-1.316	.626	-.524	-2.103	.062
	LogDSF	1.667	1.295	.321	1.287	.227
3	(Constant)	3.455	2.986		1.157	.272
	SxSevChangesqrt	-1.320	.645	-.525	-2.047	.065

a. Dependent Variable: StigmaChange

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.800[a]	.640	.532	2.01859	.640	5.928	3	10	.014
2	.750[b]	.563	.483	2.12143	-.077	2.149	1	10	.173

a. Predictors: (Constant), EBalchange, SxSevChangesqrt, sexnumeric

b. Predictors: (Constant), EBalchange, SxSevChangesqrt

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	6.286	2.523		2.491	.032
	sexnumeric	-1.762	1.202	-.297	-1.466	.173
	SxSevChangesqrt	-1.036	.500	-.413	-2.072	.065
	EBalchange	4.234	1.712	.478	2.473	.033
2	(Constant)	4.489	2.318		1.936	.079
	SxSevChangesqrt	-1.256	.501	-.500	-2.505	.029
	EBalchange	4.679	1.771	.528	2.643	.023

a. Dependent Variable: StigmaChange

APPENDIX E: BACK MATTER

Recommendations for Future Research

- Incorporate advanced imaging of the brain to related metabolic changes in the brain to that of the rest of the body.
- Incorporate biomarkers to assess brain and blood-brain barrier insult, peripheral hormone concentrations, and blood-based markers of metabolism.
- Improve physical activity tracking with an actigraph or other more versatile and precise measures of both activity and physical inactivity (i.e. sedentary time) to gain insight towards exercise dose recommendations.
- Improve dietary recall with use of standardized programs and/or scripted phone calls (i.e. a 5-pass interview).
- Incorporate more sophisticated measures of sleep.
- Explore intervention of a specific diet: hypercaloric- and/or ketogenic-based interventions.
- Incorporate HRQOL measures, specifically sleep disturbance, anxiety, resilience, and stigma into a multi-site investigation in order to, A) understand the baseline in healthy athlete samples (high school and collegiate), and B) to better understand how these components change following injury and throughout recovery.

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