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Perceived Stress, Salivary Cortisol, and Depression in Adults Diagnosed with Postconcussion
Syndrome: A Pilot Study

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Abstract

PERCEIVED STRESS, SALIVARY CORTISOL, AND DEPRESSION IN ADULTS
DIAGNOSED WITH POSTCONCUSSION SYNDROME: A PILOT STUDY

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy from the School of Nursing at Virginia Commonwealth University.

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Introduction: Traumatic Brain Injury (TBI) affects approximately 1.7 million persons in the United States each year, of which an estimated 75% are categorized as mild TBI (mTBI). Most persons who experience an mTBI will recover completely, however an estimated 10% will develop Postconcussion Syndrome (PCS). PCS is chronic condition consisting of the presence of several coexisting symptoms that interfere with comfort and quality of life. Little is known regarding the development of PCS or the presence of PCS symptoms. Evidence supports a relationship between perceived stress, salivary cortisol levels, and depressive symptoms in persons after TBI; however, there are no known studies exploring these relationships in persons diagnosed with PCS. We sought to examine the relationships between perceived stress, salivary cortisol levels, and depressive symptoms in adult persons diagnosed with PCS; and to explore the potential mediating effect of cortisol between perceived stress and depressive symptoms.

Method: A sample of 17 men and women diagnosed with PCS were recruited through general advertisement from Southwest Virginia and the Richmond area. Descriptive data collection included a Demographic Information form and the Rivermead Postconcussion Questionnaire. Variables of stress and depression were measured with the Perceived Stress Scale-10, Center for

Epidemiological Studies-Depression Scale and the PROMIS Emotional Distress (ED)-Depression Short form (SF). Salivary cortisol was collected with a SalivaBio Oral Swab (SOS) Saliva Collection System from Salimetrics. Data were analyzed with Wilcoxon Rank-Sum (Mann-Whitney U) test for continuous variables and Pearson's Chi Square for categorical data. Spearman's Rank Order Correlation Coefficients were used to compare variables for correlation.

Results: We found a statistically significant relationship between stress and depression (Spearman $\rho=0.87$; $p < 0.0001$) in the study sample; however, we did not find a statistically significant relationship between stress and cortisol (Spearman $\rho=-0.11$; $p=0.6887$) or depression and cortisol as measured by the CES-D (Spearman $\rho=-0.10$; $p=0.6989$) and the PROMIS ED-Depression SF (Spearman $\rho=-0.40$; $p=0.1327$). **Conclusion:** TBI is prevalent in the US with 75% of all occurrences being mild in severity. Although most individuals recover completely, every year approximately 10% of those with mTBI will develop the chronic symptoms of PCS. In this study, we found significant relationships between perceived stress and depression but not between cortisol and perceived stress nor between cortisol and depression. While perceived stress may impact the report of depressive symptoms in persons diagnosed with PCS, much is unknown about the influence of other factors such as stress, environment and social support, in the development of this syndrome or the influence of cortisol and other biologic markers such as pro- and anti-inflammatory cytokines and C-reactive protein. More research is needed to identify underlying psychoneurobiological mechanisms behind the development and presence of PCS and PCS symptoms in order to further inform our understanding of this condition, and to apprise the development of nursing interventions and self-care strategies to enhance symptom management and improve quality of life for those who suffer with PCS.

Chapter I

Introduction

Traumatic Brain Injury (TBI) is estimated to affect approximately 1.7 million individuals in the United States each year; with those at highest risk being children under four years of age, teens between 15 and 19 years of age, and seniors greater than 65 years of age (Faul, Xu, Wald, & Coronado, 2010; Hoffman et al., 2010). TBI incidence is most commonly related to falls while TBI mortality is most commonly due to motor vehicle collisions (MVCs) (Faul et al., 2010; Hoffman et al., 2010). Diagnostically, TBI severity is classified as mild TBI (mTBI), moderate or severe. Severity of injury is determined by a combination of radiologic imaging, such as computed tomography (CT), magnetic resonance imaging (MRI), and neurological assessment (Valente & Fisher, 2011). Nationwide, approximately 75% of TBI is reported to be mild in severity, affecting approximately 600 of every 100,000 adults annually (Cassidy et al., 2004); making mTBI the prevailing diagnosis in the adult TBI population.

Symptoms associated with mTBI may include difficulty concentrating, headache, and fatigue (Prigatano & Gale, 2011). Most individuals diagnosed with mTBI will recover completely with the resolution of any reported symptoms; however, nationally, approximately 10% of patients who experience mTBI will continue to report symptoms, including distressed mood, ≥ 6 months after injury (Prigatano & Gale, 2011). When symptoms persist for a prolonged period of time after injury, the individual may meet criteria for the diagnosis of postconcussion syndrome (PCS).

Historically, PCS has been diagnosed in individuals with mTBI when symptoms, as described by the World Health Organization (WHO) (1992) have been present ≥ 3 months. Currently, however, there are two sources used for diagnosing PCS: (1) the 10th edition of the

International Classification of Disease (ICD-10); and (2) the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V). The ICD-10 defines PCS as a syndrome that occurs after head injury and consists of a constellation of symptoms that may, or may not, co-occur. Symptoms may include headache, dizziness, fatigue, irritability, difficulty concentrating, and a reduced tolerance to physiological stress (WHO, 2015). The DSM-V does not have a definition for PCS. Instead, the DSM-V defines major or minor neurocognitive disorder (NCD) related to brain injury (American Psychiatric Association [APA], 2013). Criteria required to receive an NCD diagnosis, as described in the DSM-V, include the report of decline in cognitive function ranging from mildly concerning (mild) to severe enough to interfere with daily activity (major) (APA, 2013). NCD due to TBI is suspected when an individual presents with cognitive dysfunction and has a history of TBI. To meet diagnostic criteria, the TBI must have resulted in a loss of consciousness, inability to remember events surrounding the injury (i.e., amnesia), disorientation, confusion, and/or neurological signs; such as CT or MRI results indicating brain injury, new or worsening seizure disorder, and/or visual changes. These symptoms must present immediately after injury or immediately after return to consciousness and remain after the acute post-injury period (APA, 2013, p. 624). Symptoms such as irritability, anxiety, personality change, headache, fatigue, and sleep disturbance are described as supporting this diagnosis but are not required to meet diagnostic criteria (APA, 2013, p.625).

Recent literature regarding PCS reflects diagnostic criteria per the DSM-IV-TR. According to the DSM-IV-TR, an individual is diagnosed with postconcussional disorder (PCD) if they have had a TBI and have experienced the presence of three or more co-occurring symptoms that may include headache, distressed mood, irritability, apathy, fatigue or sleep disturbances; persisting for three months or greater (APA, 2000). The benefit to the change in

ICD-10 diagnostic criteria is that more individuals who suffer persistent mTBI symptoms may receive treatment. The challenge to the DSM-V criteria is that potentially less treatment will be provided because the criteria for diagnosis relates to more severe symptomology of visual change and seizure. Thus, individuals who have been diagnosed with mTBI, but whose distressed mood or other symptoms have lasted longer than 3 months, may not meet the DSM-V criteria for PCS. Whether defined as PCS (DSM-IV-TR; ICD-10) or NCD (DSM-V), the persistent (i.e., more than 3 months) physical and psychological symptoms occurring after mTBI have been shown to negatively impact comfort and quality of life in this patient population (Emanuelson, Holmkvist, Björklund, & Stålhammar, 2003; Moran et al., 2012; Yeates et al., 2012).

Several factors have been implicated in the development of PCS following mTBI including psychosocial stress appraisal (or perception) and the physiological response to stress. Psychosocial stress refers to how an individual appraises or perceives their ability and resources to manage situations that may threaten well-being (Cohen, Kamarck, & Mermelstein, 1983; Lazarus & Folkman, 1984). Psychosocial stressors, such as an individual's reported level of perceived stress, may have a role in the ultimate development and severity of the PCS symptom of distressed mood in the form of depression. For example, following mTBI, higher reports of perceived stress have been evidenced to correlate with greater reports of depression (Strom & Kosciulek, 2007). In a study conducted by Strom and Kosciulek (2007), data was collected on $N=94$ subjects with a history of mTBI. The authors reported the mean score for the 14-item Perceived Stress Scale (PSS) to be 28.8 with scores ranging from 10 to 50. The total score possible on the PSS ranges from 0 to 56, with higher scores indicating higher levels of perceived stress (Cohen et al., 1983). The reported mean depression score as measured by the Beck

Depression Inventory-2nd edition (Beck, Steer, & Brown, 1996) was 16.7 with participant scores ranging from 0 to 63. Total scores on the 21-item BDI range from 0 to 63. A score ≤ 13 indicates no depression, a score of 14-19 indicates mild depression, a score of 20-28 indicates moderate depression, and scores ≥ 29 indicate severe depression. The mean score of 16.7 identified by the researchers indicates that subjects in this study reported mild depression. Further, the researchers reported a statistically significant ($\beta=0.67$; $p < 0.001$) correlation between the levels of perceived stress and depression, with higher levels of perceived stress being predictive of higher levels of depressive symptoms (Strom & Kosciulek, 2007).

In a study conducted by Bay, Hagerty, Williams, Kirsch, and Gillespie (2002), data on perceived stress and depressed mood was collected from $N=75$ subjects with mild ($n=27$) or moderate ($n=48$) brain injury (Bay et al., 2002; Bay, Sikorskii, & Gao, 2009). The researchers found subjects reported a mean score of 20.45 as collected on the Center for Epidemiological Studies Depression scale (CES-D) (Radloff, 1977), with 20% ($n=15$) reporting a score > 30.5 . The CES-D is a measure of symptoms related to depressed mood with scores ranging from 0-60. A score of 16-20 indicates mild depression, 21-26 indicates moderate depression and a score greater than 27 indicates severe; thus, scores as reported by Bay et al. (2002) indicated symptoms ranged from mild to severe in this study population. In a secondary analysis examining the relationship between perceived stress and depressed mood in this same study population, Bay et al. (2009) reported a significantly positive relationship ($\beta =0.51$; $p <0.01$); showing that higher reports of perceived stress correlated with higher reports of depressive symptoms. These studies suggest a relationship between psychosocial or perceived stress and the potential development of depression in persons with mTBI. In addition to psychosocial stress, the physiological response

to stress (i.e. stress response) that occurs after mTBI is also related to the development of depressive symptoms in this population (Bay, Sikorskii, & Gao, 2009; Griesbach et al., 2011).

TBI-related hypothalamic-pituitary-adrenal (HPA axis) dysfunction is thought to affect the response to acute and chronic stress. The physical stress response has been described as the neuroendocrine response to a psychosocial or physical stimulus or stressor (Chrousos & Gold, 1992; Glaser & Keicolt-Glaser, 2005; Selye, 1950). This stress response occurs with activation of the HPA axis when a psychosocial or physical stressor is experienced. As a feedback response to a stressor, the hypothalamus secretes corticotropin releasing hormone (CRH). This in turn stimulates the pituitary gland to release adrenocorticotrophic hormone (ACTH) leading to stimulation of the adrenal cortex and the release of corticosteroid hormones such as the glucocorticoid cortisol (Glaser & Kieicolt-Glaser, 2005; Selye, 1950). Research has demonstrated that this physical response to stress is altered after mTBI. For example, in rat models, Griesbach, Hovda, Tio, and Taylor (2011) identified an intensified response to acute stress after inducing mTBI, describing a higher than expected release of ACTH and less than expected corticosteroid levels after exposure to a stressor; indicating a dysfunction of this feedback mechanism related to mTBI.

In humans, HPA axis dysfunction after moderate to severe TBI has been implicated in the development of mood disorders such as depression and anxiety (Bay et al., 2009). For example, Bay et al. (2002; 2009) examined the salivary cortisol data collected from $N=75$ subjects with mild or moderate TBI. Cortisol had been collected at 4 time points within 24 hours; 8 a.m., 12 p.m., 4 p.m. and 8 p.m. Researchers reported summing the total cortisol count across time points and finding mean cortisol levels ranging from 0.17 to 0.89 nanograms per milliliter (ng/ml). Cortisol is released in a diurnal pattern, both naturally and when prompted in response to stress

(Kirschbaum & Hellhammer, 1989). Normal cortisol levels for a healthy adult may range from <0.50 to 42.8 nanomoles per liter (nM/L) with highest concentrations in the morning and lowest concentrations in the evening (Aardal & Holm, 1995). Converting the levels reported by Bay et al. (2009) from ng/ml to nM/L, demonstrated that the mean cortisol levels ranged from 0.47 to 2.46 nM/L. Subjects' cortisol levels demonstrated the presence of hypocortisolemia; one indicator of HPA axis dysfunction (Bay et al., 2009; Heim, Ehlert, & Hellhammer, 2000). Hypo- and hypercortisolemia are known to result from HPA axis dysfunction, and both have been associated with depression (Bay et al., 2009; Carroll et al., 2012; Jarcho, Slavich, Tylova-Stein, Wolkowitz, & Burke, 2013). The evidence presented by Bay et al. (2002; 2009) suggests a relationship between HPA axis dysfunction (i.e. hypocortisolemia) and depression after mild and moderate TBI.

In summary, there is a burgeoning body of evidence suggests a relationship among perceived stress, HPA axis dysfunction as indicated by cortisol levels, and the symptom of depression in the mTBI and moderate TBI populations. However, to the best of our knowledge, research is limited and further, there are no known studies examining these relationships in persons diagnosed with PCS. While there is limited data implicating cortisol as a factor in mTBI and PCS, HPA axis dysfunction has been implicated in the development of PCS symptoms such as depression. By examining the relationships among the variables of perceived stress scores, a.m. cortisol levels, and depression scores; we hoped to further elucidate underlying mechanisms of PCS symptoms. The current study provides a foundation for conducting future studies that may further our understanding of the development of PCS and PCS symptoms; studies that (a) addresses self-care strategies and symptom management, (b) contributes to evidence based practice, and (c) offer potential enhancement of patient comfort and quality of life.

Study Purpose

The purpose of the current study was to examine and describe potential relationships among levels of perceived stress, biological indicators of stress (i.e., cortisol), and levels of depression in persons diagnosed with PCS. The primary aim was to examine potential relationships among levels of perceived stress, levels of cortisol, and symptoms of depression in adults diagnosed with PCS. The secondary aim was to examine the mediating effect of cortisol between perceived stress and symptoms of depression in persons diagnosed with PCS.

Research Hypotheses

Hypothesis 1:

There is a correlation among levels of perceived stress, levels of cortisol, and depression in persons diagnosed with PCS

Hypothesis 2:

Cortisol mediates the relationship between levels of perceived stress and depression in persons diagnosed with PCS

Therefore, the specific aims of the current study were to:

1. Examine the relationships among perceived stress, salivary cortisol and symptoms of depression in persons diagnosed with PCS.
2. Examine the mediating effect of cortisol between perceived stress and levels of depression in persons diagnosed with PCS.

Conceptual Framework

The conceptual framework guiding the current study was adapted from the nursing framework of psychoneuroimmunology (PNI) (McCain, Gray, Walter, & Robins, 2005; Zeller, McCain, & Swanson, 1996). PNI, as a biobehavioral framework, is theoretically informed by the work of Selye (1950) and Ader (1981; 2000). Selye (1950; 1951) described a physiologic response to stress in his conceptual model of the General Adaptation Syndrome (GAS). This model posited that in defense of a physical stressor, the HPA axis is activated; resulting in the production of neuroendocrine hormones (i.e. CRH, ACTH, vasopressin, and cortisol). CRH stimulates the sympathetic nervous system (SNS) to release the catecholamines, epinephrine and norepinephrine, from the adrenal medulla. This neuroendocrine response is considered to be essential for adaptation and survival when exposed to a physical stressor (Selye, 1950). Ader (2000) founded the theory of PNI, which he defined as “the study of the interactions among behavior, neural and endocrine function, and immune system processes” (p. 167). One principle of this theory described a bi-directional pathway of communication between the brain and the neuroendocrine system; providing detail of a biobehavioral process whereby a psychosocial variable, such as perceived stress, may influence health outcomes (Ader, 2000). The primary objective of PNI research is to identify and describe relationships among stress, neuroendocrine and immune function, and health (Robinson, Mathews, & Witek-Janusek, 2002). When used as a framework for guiding nursing research, the PNI model supports nurse scientists in their efforts to explore and describe the multidimensional mechanisms of psychobehavioral and neuroendocrine system interactions. Within the PNI framework, the production and release of stress hormones such as cortisol is thought to be modulated by perceived stress; meaning that greater levels of perceived stress may contribute to HPA axis dysfunction as evidenced by hyper-

or hypocortisolemia (McCain et al., 2005). In the current study, the PNI framework was applied to explore potential relationships among levels of perceived stress, biological indicators of stress (i.e., cortisol), and levels of depression in persons diagnosed with PCS (see Appendix A).

Study Significance

This study has the potential to make a significant contribution to the literature in the areas of chronic illness and symptom management, nursing research, and to provide scientific evidence of relationships among biobehavioral variables in the PCS patient population. Findings from the current research study provide a description of relationships among perceived stress, levels of cortisol and depression in adults who are diagnosed with PCS. Study findings provide theoretical support for further research to inform our understanding of mechanisms related to the presence of PCS and PCS symptoms, and ultimately to support the development of symptom management strategies in this patient population. Chapter two contains a description of the conceptual framework and a review of the literature.

Chapter II

Conceptual Framework and Literature Review

The purpose of the current study was to examine and describe potential relationships between levels of perceived stress, biological indicators of stress (i.e., cortisol), and levels of depression in persons diagnosed with postconcussion syndrome (PCS). In chapter two, the conceptual framework of psychoneuroimmunology (PNI) is further explicated with a literature review related to the key variables of perceived stress, cortisol and depression.

Psychoneuroimmunology as a Nursing Framework

PNI is a biobehavioral framework integrated by McCain, Gray, Walter and Robins (2005) as a conceptual framework to guide nursing research related to mechanisms and processes surrounding symptoms and interventions for symptom management in a variety of chronic disease states including sickle cell disease (Ameringer, Elswick, & Smith, 2014), HIV (McCain et al., 2008), fibromyalgia (Menzies, Lyon, Elswick, McCain, & Gray, 2014), and cardiometabolic risk (Robins, Elswick, Sturgill, & McCain, 2015). The foundation of PNI is informed by the theoretical work of Selye (1950) and Ader (1981; 2000). Selye (1950; 1951) described the activation of the HPA axis in response to a physical stressor as part of the general adaptation syndrome (GAS) theory. According to PNI, exposure to a physical stressor may lead to an individual's inability to physically adapt. The ongoing exposure to both acute and chronic stress creates a physiologic burden on the individual leading to compromised health status, placing the individual at risk for illness. Building on the work of Selye, Ader (2000) founded the PNI theory to more clearly describe the mechanisms of communication between and among the brain, neuroendocrine system and immune system. From this perspective, the PNI serves as a structure for the study of behavior, the neuroendocrine and immune systems, and the

bidirectional process of communication that occurs between or among systems. The implication of PNI theory is that psychosocial factors, such as perceived stress, stimulate the physical stress response thereby leading to disruption in levels of circulating stress hormones ultimately leading to changes in the inflammatory response (Ader, 2000; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002).

The primary objective of nursing research based on PNI theory is to identify and describe biobehavioral relationships between psychological factors such as perceived stress and physiological indicators of neuroendocrine and immune function, and their potential impact on health and health outcomes (McCain et al., 2005; Starkweather, Witek-Janusek, & Mathews, 2005). In that light, the PNI framework has been used to guide research to examine potential relationships among variables of stress and symptoms in a variety of patient populations. For example, in a cross-sectional correlational study, researchers examined the relationship among fatigue, pain, sleep, anxiety, depression, stress and biomarkers of inflammation and oxygenation in a sample of $N=60$ subjects between the ages of 15 and 30 years of age with sickle cell disease (Ameringer, Elswick & Smith, 2014). Fatigue was measured with three scales: The Brief Fatigue Inventory (BFI) (Mendoza et al., 1999); the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) (Stein, Martin, Hann, & Jacobsen, 1998); and the PROMIS Fatigue Short Form (PROMIS, 2012). Stress was measured using the 10-item Perceived Stress Scale (PSS) (Cohen, Kamarch, & Mermelstein, 1983) and depression with the Center for Epidemiological Studies-Depression scale (CES-D) (Radloff, 1977). The researchers noted a significant correlation between stress and fatigue as measured by the BFI ($\beta=0.41$; $p \leq 0.001$), MFSI-SF ($\beta=0.69$; $p \leq 0.001$) and PROMIS fatigue short form ($\beta=0.41$; $p < 0.01$) indicating that higher reported levels of perceived stress correlated to higher reported levels of fatigue regardless of fatigue measure.

Additionally, the biomarker of hemoglobin was reported to correlate with fatigue as measured by PROMIS fatigue short form ($\beta=-0.30$; $p<0.05$). No findings were reported to describe a relationship between stress and depression in this study.

In another PNI based exploratory study, researchers used a cross-sectional correlational design to examine the relationship among stress and symptoms of pain, fatigue, depression, functional status and biomarkers of inflammation in a sample of $N=50$ women with fibromyalgia (Menzies, Lyon, Elswick, Montpetit & McCain, 2013). Stress was measured with the 10-item PSS (Cohen, et al., 1983) and depression with the CES-D (Radloff, 1977). The researchers reported significant correlation between perceived stress and depression ($\beta=0.80$; $p<0.01$) meaning higher reported levels of perceived stress correlated to higher reported levels of depressive symptoms. Additionally, a significant correlation between perceived stress and the pro-inflammatory biomarker Interleukin (IL)-1 β was reported ($r=-0.29$; $p<0.05$), suggesting a potential relationship may exist between the psychological variable of perceived stress and the immune system (Menzies et al., 2013).

While these studies seem to substantiate the presence of a biobehavioral relationship among stress, biological indicators and symptoms in those experiencing a chronic illness, to our knowledge, there are no studies reporting the use of the PNI framework to examine a potential biobehavioral relationship among variables of stress, any biologic indicator, including cortisol, and depression in persons diagnosed with PCS.

Conceptually, psychosocial or perceived stress, refers to how an individual interprets the ability and resources to manage situations that appear threatening (Cohen, Kamarck, & Mermelstein, 1983; Cohen, Kessler, & Gordon, 1997; Lazarus & Folkman, 1984). Physically, the perception of stress has been demonstrated to stimulate the hypothalamus (Glaser & Kiecolt-

Glaser, 2005; Selye, 1950). This stimulation occurs as part of the GAS as described by Selye (1950; 1951). The end result of this process is the release of cortisol (Glaser & Kiecolt-Glaser, 2005; Selye, 1950). Cortisol is a valid biological measure of HPA axis function and therefore, a valid measure of the response to stress (Heim & Nemeroff, 2002; Monroe, 2008). After mTBI, HPA axis function is theorized to be dysfunctional meaning that response to a stressor may result in a less than expected release of cortisol or hypocortisolemia (Griesbach, Hovda, Tio, & Taylor, 2011). Both hypo- and hypercortisolemia are known to result from HPA axis dysfunction, and both have been associated with depression (Bay, Sikorskii, & Gao, 2009; Carroll et al., 2012; Jarcho, Slavich, Tylova-Stein, Wolkowitz, & Burke, 2013). Individuals diagnosed with PCS are at risk for the development of symptoms that include depression and when present, depressive symptoms have been shown to negatively impact overall quality of life (Emanuelson, Holmkvist, Björklund, & Stålhammar, 2003; Moran et al., 2012; Yeates et al., 2012). While the research literature has reported a relationship between stress and biopsychosocial outcomes in illnesses other than PCS (Ameringer, et al., 2014; Menzies, et al., 2013), and because there is a known relationship between hypo- or hypercortisolemia and depression (Jarcho et al., 2013); the risk to individuals diagnosed with PCS to develop a worsening of depressive symptoms or a diagnosis of clinical depression may be linked to levels of stress as well as to levels of the neuroendocrine biomarker, cortisol. Therefore, for purposes of the current study we used the PNI construct as a guide to examine potential relationships among three PNI-focused variables, i.e., the psychosocial factors of self-reported perceived stress and depression and the potential mediating effect of cortisol, in a sample of adults (aged ≥ 21 years) who have been diagnosed with PCS. Specifically, the primary relationships to be explored using the PNI framework were those that may exist between levels of perceived stress, cortisol and depressive symptoms in this

population. The secondary relationship to be examined was the potential influence of cortisol as a mediating variable between perceived stress and depressive symptoms in this population. Study results were anticipated to provide preliminary findings upon which future interventional research will be based.

Literature Review

The following literature review reflects the PNI framework that guided the current study. The literature was explored to identify evidence of relationships among perceived stress and cortisol; cortisol and depression; and perceived stress, cortisol, and depression in the PCS patient population. The electronic databases Cumulative Index of Nursing and Allied Health Literature (CINAHL), PsychINFO and PubMed were searched for articles published between 2005 and 2016 using the initial keyword *Postconcussion Syndrome*. The search strategy included use of the additional key words *perceived stress*, *cortisol*, and *depression*, in each database to ensure identification of all available evidence. Inclusion criteria were those articles published in English, with a PCS population as subjects and included adults over age 18 years of age. Excluded were duplicates, dissertations, studies involving children, and those studies involving Post-traumatic Stress Disorder (PTSD). Additionally, the ancestry method was used, which involved reviewing the reference lists of articles that met inclusion criteria. Using the initial keyword (postconcussion syndrome) with variables of *perceived stress*, *cortisol*, and *depression* resulted in one research-related article; however, the study subjects were those with mild to moderate TBI rather than diagnosis of PCS (Bay & Xie, 2009). Thus, a secondary search using *traumatic brain injury* as a key word and the keywords of *perceived stress*, *cortisol* and *depression*, was completed in each database. A total of 6 articles were retrieved using this search strategy. After removing duplicates, a total of 29 articles were identified for review. After a

Careful review of abstracts, a total of seven articles were found to meet inclusion criteria (See Appendix B, Table 1).

Results

Of the seven articles meeting inclusion criteria, two reported varied findings, using data from the same cross-sectional design parent study. The initial report of the parent study data examined perceived stress and depression in mTBI and moderate TBI but did not include the variable of cortisol (Bay, Hagerty, Williams, Kirsch & Gillespie, 2002). The second publication of the parent study reported findings related to perceived stress, cortisol and depression (Bay, Hagerty, Williams & Kirsch, 2005). The third and fourth articles selected for inclusion in this literature review included correlational studies; one, a longitudinal design examining potential relationship(s) between perceived stress and depression in subjects diagnosed with mTBI and moderate TBI (Bay & Donders, 2008); and the second, a cross-sectional design examining potential relationships between perceived stress and depression in subjects diagnosed with mTBI only (Strom & Kosciulek, 2007). Two further articles selected for review included quasi-experimental longitudinal studies (Luo, Chai, Jiang, Chen, & Yan, 2015; Sung et al., 2016); each consisting of subjects with mTBI. The first study compared the effectiveness of interventions on symptoms of depression among three groups of subjects with mild, moderate and severe TBI (Luo et al., 2015), while the second study compared subjects with mTBI to a healthy control group (Sung et al., 2016). The final article for review was a randomized control trial (RCT) comparing a walking intervention to an attention control nutrition education intervention on perceived stress and depressive symptoms after TBI (Bellon et al., 2015). There were no studies found for the PCS patient population. Because PCS is a downstream diagnosis post mTBI, and because there was an absence of literature on our selected study population of PCS, we have

included research studies that examined our variables of interest; stress, cortisol, and depression in the TBI population (See Appendix B, Table 2). Following is further explication of the aforementioned studies.

Bay et al. (2002) reported results of a cross-sectional study with a sample of $N=75$ subjects with mild or moderate TBI. All participants had been hospitalized and diagnosed with either mTBI or moderate TBI at the time of their injury. Participants' age range was not reported; however, the mean age was reported as 37.04 years. The sample consisted of $n=39$ men and $n=36$ women who were within 2-years of injury at the time of data collection. The authors reported on variables of post-injury perceived stress and depression. Post-injury stress was measured using the 14-item PSS (Cohen et al., 1983). PSS scores range from 0 to 56 on this 14-item scale with higher scores indicating greater stress (Cohen et al., 1983). Depression was measured using the Neurobehavioral Functioning Inventory Depression sub-scale (NFI-D) (Kreutzer, Seel, & Marwitz, 1999; Seel & Kreutzer, 2003) and the CES-D (Radloff, 1977). The NFI-D is a 13-item scale with total scores ranging from 13 to 65; higher scores indicate greater depressive symptoms with risk for a diagnosis of depression at scores ≥ 28 (Kreutzer, Seel, & Marwitz, 1999; Seel & Kreutzer, 2003). The CES-D is a measure of symptoms related to depressed mood with scores ranging from 0 to 60; higher scores indicate greater report of depressive symptoms (Radloff, 1977). A score of ≥ 16 indicates potential for depression (Radloff, 1977). A significant relationship was found between stress, as measured by the PSS, and depression, as measured by the NFI-D, ($R^2=0.54$, $F=87.72$ (1, 73), $p=0.00$), indicating that higher levels of perceived stress were positively correlated with higher levels of depressive symptoms.

The second report by Bay et al. (2005), included a study sample of $N=75$ subjects with mild or moderate TBI; ages ranging from 19 to 60 years of age with a mean age of 37.04 years. The authors expanded on prior analyses through inclusion of both pre- and post-injury perceived stress as well as salivary cortisol. Pre-injury stress was measured using the Childhood Adversity Checklist (CAC), a 16-item questionnaire was designed to capture chronic stress that may have occurred in childhood or be attributed to childhood events (Kupfer & Detre, 1974; Cohen, Coyne, & Duvall, 1993). As in the Bay et al. (2002) study, post-injury stress was measured using the 14-item PSS (Cohen et al., 1983) and depression was measured using the NFI-D (Kreutzer, et al., 1999; Seel & Kreutzer, 2003). For this study, salivary cortisol was reported as having been collected at four time points over a 24-hour time period (8:00 a.m., 12:00 p.m., 4:00 p.m. and 8:00 p.m.) from $n=53$ of $N=75$ ($n=26$ men and $n=27$ women) subjects; indicating missing data from $n=22$ subjects. There were no significant relationships between salivary cortisol and post-injury stress or depressive symptoms; however, the authors reported that those individuals with mTBI had significantly ($t= 2.66$, $df 48$, $p=0.011$) greater 8:00 a.m. cortisol levels than those with moderate TBI. The authors did not discuss the significance of this difference between the two groups. The authors acknowledged the challenge of measuring cortisol in this population such as difficulty achieving 100% collection of all salivary cortisol specimens and self-report of compliance with collection protocol and stated the need for further research in this area.

In a cross-sectional study conducted by Strom and Kosciulek (2007), researchers sought to explore the potential for a relationship among perceived stress, depression and coping in individuals post TBI by testing a theoretical model titled Stress, Appraisal and Coping (SAC) (Godfrey, Knight, & Partridge, 1996). The authors collected data from $N=94$ subjects, recruited from two rehabilitation centers, who had a confirmed diagnosis of TBI. Subjects' ages ranged

from 18 to 74 years and included $n=35$ men and $n=58$ women. Perceived stress was measured using the 14-item PSS (Cohen et al., 1983) while depressive symptoms were measured using the Beck Depression Inventory 2nd edition (BDI-II) (Beck, Steer, & Brown, 1996). The BDI-II is a 21-item scale with scores ranging from 0-63 with higher scores indicating greater report of depression (Beck et al., 1996). The authors reported PSS scores ranging from 10-50 with a mean score of 28.8 indicating subjects' reported a moderate level of perceived stress. The reported mean depression score as measured by the BDI-II was 16.7 with participant scores ranging from 0 to 63, indicating subjects in this study reported mild depression. Further, the researchers reported a statistically significant ($\beta=0.67$; $p<0.001$) correlation between the levels of perceived stress scores and depression scores, with higher levels of perceived stress being predictive of higher levels of depressive symptoms.

In a separate cross-sectional study, Bay and Donders (2008) explored the role of perceived stress in the development of depressive symptoms after TBI in a sample of $N=84$ subjects recruited from eight rehabilitation centers. All participants had experienced prior hospitalization and had been diagnosed with either mTBI ($n=65$) or moderate TBI ($n=19$) at the time of their injury. Participants' age range was not reported; however, the mean age was reported as 38.02 years. The sample consisted of $n=43$ men and $n=41$ women who were between one and 36 months from injury at the time of data collection. Chronic stress was measured using the 14-item PSS (Cohen, et al., 1983) and the Impact of Event Scale (IES) (Horowitz, Wilner, & Alvarez, 1979). The IES is a 15-item scale that measures the level of distress experienced by an individual when faced with an event perceived as stressful (Horowitz, et al., 1979). Scores from the IES range from 0 to 60 with higher scores indicating higher perceived stress (Horowitz, et al., 1979). Depression was measured using the NFI-D (Kreutzer, et al., 1999; Seel & Kreutzer,

2003). The researchers also measured symptoms of pain and fatigue. Pain was measured using the McGill Pain Questionnaire Short Form (MPQ-SF) (Melzack, 1987). The MPQ-SF is a 15-item questionnaire with scores ranged from 0 to 45, with higher scores indicating greater intensity of pain (Melzack, 1987). Fatigue was measured using the Modified Version of the Fatigue Impact Scale (MFIS) (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). The MFIS is a 21-item scale with scores ranging from 0-84 with higher scores indicating greater impact of fatigue (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). The authors reported subjects' NFI-D scores ranged from 13-56 with a mean score of 31.71, noting that 58% ($n=49$) of subjects reported a score >28 , indicating the presence of depressive symptoms and 42% ($n=35$) reported scores <28 indicating no depressive symptoms. For those subjects categorized as depressed (NFI-D score >28), the mean PSS score was 27.37. For those subjects categorized as not depressed (NFI-D ≤ 28), the mean PSS score was 19.66. This finding indicates that those subjects who reported depressive symptoms also reported higher levels of perceived stress when compared to those subjects who did not report depressive symptoms. No significant relationship was reported between levels of fatigue and depression or levels of pain and depression; however, levels of perceived stress were evidenced to explain levels of depression ($R^2=0.55$) such that higher levels of perceived stress were more closely related to greater levels of depression.

A report of a RCT study by Bellon et al. (2015) compared the effect of a 12-week walking intervention to a 12-week attention control nutrition education program on reported levels of perceived stress and depressive symptoms in subjects diagnosed with mild, moderate or severe TBI. Bellon et al recruited $N=123$ subjects with a history of diagnosed TBI from the community and from the Northern California TBI model Systems database. Perceived stress was

measured using the 14-item PSS (Cohen et al., 1983) and depression was measured using the CES-D (Radloff, 1977). Potential participants were screened to assess for eligibility and ability to ambulate. Once consented, subjects were randomized to either the walking intervention group or the nutrition education group. Measures were collected at baseline, 12- weeks, and 24- weeks. The walking intervention was practiced at the subjects' home using a pedometer to track daily steps. The first week of the intervention, participants tracked their activity as usual. Each week after, the participants were asked to increase their steps by 5% until week- 8, at which time they were instructed to maintain the daily level of steps for weeks 9-12. Coaching was provided three times a week for weeks 1-3 then twice a week for weeks 4-8. Coaching was further reduced to 1-time a week for weeks 9-12. The nutrition education group served as a control group.

Participants self-identified needed improvement in eating habits and were provided with nutritional education to meet their goals. Coaching was provided on the same schedule as the walking intervention group. At the completion of the intervention (week 12), measures were again collected. At this time, participants switched groups as part of the crossover design. At 24 weeks, after completing the alternate intervention, measures were collected a final time. The authors reported that $N=69$ participants ($n=41$ men and $n=28$ women) completed the study. Study participants had a confirmed diagnosis of mild ($n=10$), moderate ($n=10$) or severe ($n=35$) TBI; $n=13$ subjects had a TBI diagnosis of unknown severity. The mean CES-D score was 16 for both groups at baseline, indicating mild depressive symptoms. At 12 weeks, the walking group reported a mean CES-D score of 12 as compared to the nutrition group, which reported a mean score of 15 indicating that the walking group had a decrease in report of depressive symptoms as compared to the nutrition group. At 24 weeks, both groups reported a mean CES-D score of 13, noted by the authors as a significant effect ($p=0.007$). The mean PSS scores at baseline were 25

for the walking group and 23 for the nutrition education group. At 12 weeks, the PSS mean score for the walking group had decreased to 20.76 whereas the mean for the nutrition education group had increased to 24.3. At completion of the study, the 24th week, the PSS mean score for both groups were reported as 21. The authors reported significant decreases in PSS scores during the walking intervention for both groups ($p=0.006$) with a significant decrease in PSS score at 24 weeks for both groups ($p=0.006$). This indicates that the 12-week walking intervention was effective in reducing scores on both the PSS and the CES-D.

In a quasi-experimental repeated measures study, exploring the effect of cortisol supplementation, psychotherapy and Citalopram on depressive symptoms after TBI; Luo, Chai, Jiang, Chen, & Yan (2015) reported on $N=68$ subjects diagnosed with depression after TBI. Participants were recruited at the first follow up appointment after discharge from the hospital post injury. The sample consisted of $n=45$ men and $n=23$ women ranging in age from 18 to 70 years. Demographic data did not include the number of participants in each category of TBI; mild, moderate or severe. The study protocol consisted of initial measurement of depressive symptoms using the BDI-II (Beck et al., 1996) at which time subjects began the initial treatment with psychotherapy. The authors reported $n=22$ subjects reported mild depression, $n=37$ reported moderate depression, and $n=9$ subjects reported severe depression at baseline prior to treatment with psychotherapy. The psychotherapy intervention consisted of one-hour sessions each week for six weeks for all subjects. At the conclusion of psychotherapy, subjects were again assessed for depressive symptoms using the BDI-II. The authors reported that $n=8$ subjects were found to report few to no depressive symptoms or a score of <13 as collected on the BDI-II. The remaining $n=60$ subjects were then assessed for hypocortisolemia and assigned to be in one of two treatment groups based on their individual serum cortisol levels. Participants found to have

hypocortisolemia ($n=32$) were placed in a group receiving psychotherapy plus the administration of two medications (i.e. the antidepressant medication Citalopram and Prednisone); those with normal cortisol levels ($n=28$) were placed in a group receiving psychotherapy and only one medication (i.e. Citalopram). A limitation to understanding this study lies in the fact that while cortisol levels were reportedly measured, specific levels were not reported. After three weeks of treatment, each group was assessed for depressive symptoms for a third time and all but one study participant in the normal cortisol level group demonstrated a decrease in depressive symptoms after treatment. Additionally, all but two study participants in the hypocortisolemia group, who received both Citalopram and Prednisone, reported a decrease in depressive symptoms after treatment. It was not reported whether cortisol levels were re-evaluated post-treatment. While data on the number of participants at each level of injury was not reported, study outcomes, as reported by Luo et al. (2015), demonstrated no significant relationship between severity of injury and severity of depression ($r=0.128$, $p>0.05$). Such findings suggest that those individuals with mTBI are just as likely to develop depressive symptoms as those with moderate or severe TBI.

Using a quasi-experimental design with two data collection time points, Sung et al. (2016), reported on heart rate variability (HRV), neuroendocrine function, and symptoms of anxiety and depression in a study comparing $N=483$ subjects with mTBI ($n=331$) to a healthy control group ($n=152$). Participants were recruited through two University hospitals. The mTBI group inclusion criteria required diagnosis of mTBI with a negative computed tomography scan of the brain. The healthy control group inclusion criteria required no history of TBI. Both groups included subjects ≥ 20 years of age. Neuroendocrine hormones, including cortisol, were collected from serum. Depression was measured with the BDI-II (Beck et al., 1996). In addition,

the researchers measured heart rate variability (HRV), a measure of autonomic nervous system (ANS) function with ANS dysfunction suggested to be related to mood disorder such as depression and anxiety (Appelhans & Luecken, 2006; Zheng & Moritani, 2008). All measures were collected at baseline and 6 weeks. Mean age of participants was reported as 27.5 years in the control group and 40 years in the mTBI group; age ranges were not reported. Median values of cortisol were reported as 10.88 $\mu\text{g/dL}$ in the healthy control group compared to a median of 10.66 $\mu\text{g/dL}$ in the mTBI group at week 1, with no significant difference in cortisol levels between groups ($p=0.698$). The authors reported that although cortisol levels in the mTBI group decreased from 10.66 $\mu\text{g/dL}$ in week 1 to 9.65 $\mu\text{g/dL}$ in week 6, this change was not significant. The authors reported finding significantly greater levels of depression in the mTBI group as compared to the healthy control group at weeks 1 ($p=0.002$) and 6 ($p<0.001$). There was no reported data suggesting statistical analysis was completed to examine correlations between cortisol and depression in this study.

Discussion

Initial review of the literature to identify studies examining a biobehavioral relationship among the variables of perceived stress, cortisol and depression in individuals diagnosed with PCS revealed no studies in the PCS population. Given the relationship between mTBI and PCS, the search was expanded to include the larger TBI population, ultimately yielding seven studies.

TBI affects approximately 1.7 million people in the United States (U.S.) each year, approximately 75% of which are categorized as mild. Therefore, it may be concluded that approximately 1.3 million people incur mTBI annually (Centers for Disease Control and Prevention [CDC], 2003; Coronado et al., 2011). Most people who sustain a mTBI will recover completely; however, as many as 10% will continue to experience symptoms such as pain,

fatigue and depression three-months after injury leading to the potential for a diagnosis of PCS (Cicerone & Kalmar, 1995; Packard, 2008).

The pathophysiology underlying the trajectory from acute injury to mTBI and the development of PCS remains unclear. One potential mechanism is HPA axis dysfunction related to brain injury (Griesbach et al., 2011; McAllistar, 2011). The HPA axis is activated in response to psychosocial and physical stressors triggering the release of neuroendocrine hormones, particularly cortisol (Glaser & Kiecolt-Glaser, 2005; Selye, 1950). HPA axis dysfunction presents as either an underactive response to stress with too little cortisol release (hypocortisolemia), or an overactive response to stress with too much cortisol release (hypercortisolemia) (Tsigos & Chrousos, 2002). While non-biologic factors that may contribute to PCS remain unclear, an emerging body of evidence indicates relationships among perceived stress and a history of depression or anxiety may explain its development (Meares et al., 2008; Ponsford et al., 2012). For example, individuals diagnosed with mTBI, moderate or severe TBI, who reported higher levels of perceived stress also reported greater levels of depression (Bay & Donders, 2008; Bay et al., 2002; Bay et al., 2005; Bellon et al., 2015; Strom & Kosciulek, 2007). Given that perceived stress has been consistently associated with an increased risk for depression in these patient populations, perceived stress may also affect the trajectory of PCS.

While the studies revealed in the literature review have included participants with varying degrees of TBI, which are antecedents to PCS, no study was found to have included subjects who have been diagnosed with PCS. We suggest that the absence of inclusion of study participants with PCS is a gap in the science that the current study sought to address. Other considerations related to outcomes of this literature review included an examination and comparison of

measures used to capture the non-biological variables of stress and depression, and the biological measure of cortisol.

Measures: Non-biological

The method of measurement for perceived stress was consistent across the studies reviewed, in that five of the seven studies exploring a relationship between perceived stress and depression measured perceived stress using either the 10-item or 14-item PSS (Bay & Donders, 2008; Bay et al., 2002; Bay et al., 2005; Bellon et al., 2015; Strom & Kosciulek, 2007). The PSS is a valid and reliable measure of perceived stress with little time burden for participants. While there was some consistency, studies varied on how depression was measured. One author reported using both the CES-D and the NFI-D to measure depression (Bay et al., 2002), whereas two authors reported using only the NFI-D (Bay & Donder, 2008; Bay et al., 2005). One author reported levels of depression as collected using only the CES-D (Bellon et al., 2015). The remaining authors reported levels of depression as collected using the BDI-II (Luo et al., 2015; Strom & Kosciulek, 2007; Sung et al., 2016). Although the NFI-D was designed for neurologic populations, the CES-D was found to significantly correlate with the NFI-D (Bay et al., 2002). The CES-D, developed for use in the general population, is a measure of symptoms listed in the DSM-V as being related to depressed mood but is not a diagnostic tool. This measure is sensitive to the presence of potentially impactful depressive symptoms even in the absence of clinical depression (Radloff, 1977; Bay, Hagerty, & Williams, 2007). Both the CES-D and the NFI-D are brief thus limiting participant burden. While the CES-D, the NFI-D and the BDI-II are valid and reliable measures, only the NFI-D is designed specifically for use in the neurologic population.

Variation in measures complicates comparison of results in this population. The use of appropriate, common measures move the science forward. A Common Data Element (CDE)

initiative promoted by the National Institute of Health (NIH) was launched to identify a common set of measures to better organize and improve the communication of research findings (NIH, 2016). As part of this initiative, the NIH developed a CDE portal (https://www.nlm.nih.gov/cde/summary_table_1.html) that provides a link to several resources reflecting the current drive to operationalize standardization of measures across patient populations. Among these are the NIH Toolbox for assessment of neurologic and behavioral function as well as the National Institute of Neurological Disorder and Stroke (NINDS) CDE (NIH, 2016). When reviewing these resources for standardized measures of perceived stress and depression, a comparative review can be made regarding CDE suggested measures and those measures used in the reviewed studies. For example, the CES-D and BDI-II, though not developed specifically for the neurologic population, are recommended for use in the TBI population as a supplemental measure of depression (NINDS, 2016); Therefore, it would be appropriate to administer these instruments to the PCS patient population. The NIH Toolbox, as accessed through the CDE portal, contains another of the variables of interest in our current study, perceived stress. The standardized instrument suggest by the NIH toolbox is identified as the 10-item perceived stress survey with items taken from the PSS (NIH & Northwestern University, 2012). Upon further examination of these resources, it was found that the use of these standardized instruments is not always free to the public. There are reported fees attached to use, therefore while inclusion of CDE standardized measures would enhance potential contributions from the current study to the science of PCS research, because of the pilot nature of this project as a first step in the research trajectory, funding for such measures was not available. Therefore, based on TBI research indicating correlation of the CES-D with the NFI-D (Radloff, 1977), and CDE support of the 10-item PSS (Cohen, Kamarck, & Mermelstein, 1983), we designed a

descriptive study using these measures to advance the science and collected measurement of perceived stress with the 10-item PSS and depression using the CES-D.

Measures: Biological

The measurement of cortisol was included as a variable in three studies, all of which identified the presence of hypocortisolemia in a portion of study participants (Bay et al., 2005; Luo et al., 2015; Sung et al., 2016). There were inconsistencies, however, in both the collection methods and reporting of cortisol among these studies. The medium of collection differed between the studies with one collecting salivary cortisol (Bay et al., 2005) and two collecting serum cortisol (Luo et al., 2015; Sung et al., 2016). The collection of salivary cortisol has the advantages of being non-invasive, easily collected by the subject in their home, and demonstrating less potential for causing a stress induced rise in cortisol (Aardal & Holm, 1995). Additionally, when comparing measurement of cortisol collected from saliva and serum, reference ranges or normal values are closely correlated (Aardal & Holm, 1995).

A limitation among the studies was a lack of standardized reporting of concentration solution units of cortisol. For example, Bay et al. (2005) reported cortisol units in nanograms per milliliter (ng/mL), Sung et al. (2016) reported cortisol units in micrograms per deciliter ($\mu\text{g/dL}$), and Luo et al. (2015) reported measuring cortisol but did not report concentration solution units. Normal cortisol values for a healthy adult, whether measured in saliva or serum, have been described as ranging from <0.50 to 42.8 nanomoles per liter (nM/L) with highest concentrations in the morning and lowest concentrations in the evening (Aardal & Holm, 1995). For example, Aardal and Holm (1995) reported a normal mean value of salivary cortisol in a healthy adult to be 11.9 nM/L at 8:00 a.m. and 1.8 nM/L at 10:00 p.m. and an equivalent normal serum cortisol to be 15.5 nM/L at 8:00 a.m. and 3.9 nM/L. Converting the salivary cortisol levels reported by

Bay et al. (2005) from ng/mL to nM/L demonstrated, therefore, that the mean cortisol levels in their study ranged from 0.47 to 2.46 nM/L with a mean value of 1.63 nM/L (0.59 ng/mL) collected at 8:00 a.m. and a mean value of 0.47 nM/L (0.17 ng/mL) collected at 8:00 p.m. This suggests underactive HPA axis function in response to stress as evidenced by hypo-cortisolemia in this study population. Both hypo- and hypercortisolemia are known to result from HPA axis dysfunction, and both have been associated with depression (Bay, Sikorskii, & Gao, 2009; Carroll et al., 2012; Jarcho, Slavich, Tylova-Stein, Wolkowitz, & Burke, 2013).

Luo et al. (2015) did not report cortisol levels, only using serum cortisol to stratify subjects into groups, i.e. a normal cortisol value group and a hypo-cortisolemia group. Sung et al. (2016) reported a normal serum cortisol reference range of 5-23 $\mu\text{g/dL}$ for their study, with mean cortisol levels found to be 10.88 $\mu\text{g/dL}$ in the healthy control group and 10.66 $\mu\text{g/dL}$ in the mTBI group at week 1. The cortisol level in the mTBI group decreased to a mean 9.65 $\mu\text{g/dL}$ in week 6. The decrease in cortisol level in the mTBI group from week 1 to week 6 was noted to not be significant. The authors did not report the hour of collection, only that collection occurred at two time points, week 1 and week 6 and no comparison was made between cortisol and depression; therefore, it is not possible to determine the significance of their study findings. When considering future studies in which cortisol is a variable of interest, such as in the current study, it will be important to thoughtfully consider methods of cortisol sampling including the data collection period and the type of medium used to collect cortisol samples, as well as include reporting of normal reference ranges and consider standardization of concentration units.

Overall, findings from this literature review have contributed to the design and methods of the current study. Prior research has elucidated both the strengths and limitations of the biologic indicator discussed regarding cortisol. The strengths include supporting the collection of

cortisol, a valid and reliable method of measuring this biological indicator of stress (Aardal & Holm, 1995; Kirschbaum & Hellhammer, 1989; Laudat et al., 1988), thus we included cortisol not only as a mediator between stress and depression, but we also examined it as the classic biologic measure of HPA axis dysfunction. Weaknesses include the identification of discrepancies among the types of medium selected for cortisol collection (i.e. saliva or serum). An additional weakness or limitation were the variation of reported concentration solution units (ng/mL and $\mu\text{g/dL}$). Both limitations challenge an accurate interpretation of collective study findings. We addressed these limitations in the current study by reporting normal cortisol levels, comparing study findings against these standardized levels and exploring appropriate laboratory resources to address the most commonly used product related to standardized salivary cortisol collection.

In summary, this literature review demonstrated that the relationships between perceived stress and cortisol, as well as those between perceived stress and depression have been examined in the TBI patient population. Despite examination of relationships between these variables, there remains a gap in the literature of studies incorporating the variables of perceived stress, cortisol and depression in the PCS population. In that light, we proposed to study the relationships between perceived stress and depression, perceived stress and cortisol including examination of cortisol as a mediating variable. This research provides pilot data on which to build further studies exploring biobehavioral mechanisms behind the presence of PCS and PCS symptoms, building to a program of interventional research. Given the symptom burden in individuals living with PCS and the evidence that perceived stress levels and depressive symptoms can be reduced with mind-body interventions such as guided imagery (Menzies et al., 2014) and tai chi (Robins et al., 2013), development of similar interventions are reasonable to

decrease symptoms in this patient population. Before such assistance can be offered to the PCS population; however, it is important to first examine and describe the presence of perceived stress and its relationship to depression in this patient population while also considering any contributions that may or may not be attributed to the neuroendocrine hormone, cortisol. In chapter three, the study methodology and design are described.

Chapter III

Research Design and Methods

A review of the literature resulted in few studies investigating the relationships among stress, cortisol and depression in the mild traumatic brain injury (mTBI) population. To date, we know of no studies examining potential relationships between these variables in adults diagnosed with post-concussion syndrome (PCS). In chapter three, we present the research methodology for the pilot study examining these relationships in adults with PCS.

Study Design

This was a descriptive, cross-sectional design to examine and describe relationships among levels of perceived stress and cortisol, cortisol and depressive symptoms, and perceived stress and depressive symptoms in persons diagnosed with PCS. The research questions addressed in this study were:

1. Is there a relationship among levels of perceived stress, cortisol and depressive symptoms in adults diagnosed with PCS?
2. Does cortisol mediate the relationship between perceived stress and depressive symptoms in adults diagnosed with PCS?

Setting and Sample

The study sample of $N=17$ adults diagnosed with PCS were recruited through general advertising efforts (See Appendix C). Recruitment sites included, Carilion Roanoke Memorial Hospital (CRMH) and Carilion affiliates, including the Carilion New River Valley (CNRV) Physical Medicine and Rehabilitation clinic and Jefferson College of Health Sciences (JCHS), Virginia Commonwealth University (VCU), and VCU Health System (VCUHS). Social media outlets including Facebook and Craigslist were added to maximize study recruitment. The

Carilion Clinic is a non-profit organization consisting of eight hospitals located in southwest Virginia (VA) and numerous care facilities within the service area, 17 of which are located in the Roanoke, VA area. CRMH is a 700+ bed hospital, and a certified level-one trauma center located in Roanoke, VA. The CRMH emergency department and the Carilion Clinic family medicine centers, together, see approximately 121,000 outpatients annually, an estimated 37,510 (31%) seen in Roanoke County alone (Roanoke Valley Community Health Needs Assessment, [RVCHNA] 2015); with at least 1,500 individuals having a diagnosis of PCS (Carilion, 2016). The CNRV Physical Medicine and Rehabilitation clinic, located in Radford, VA, is associated with CNRV Medical Center, a Carilion Clinic affiliate. The CNRV Medical Center serves more than 49,000 patients annually (New River Valley Community Health Needs Assessment, [NRVCHNA] 2016). Participants were also recruited through the distribution of recruitment brochures and flyers to Jefferson College resources (an affiliate of Carilion Clinic), by submission to the VCU TelegRAM for faculty/staff and students and VCUHS Employee Bulletin Board, by postings on Facebook and Craigslist in both the Roanoke and Richmond areas, and through snowball sampling from participants and individuals who had seen the advertisement and referred the study to family and friends. VCU is an urban university offering over 200 programs of study at the undergraduate and graduate level (Virginia Commonwealth University, 2017a). In the 2017-18 academic year, enrollment for both the main and health sciences campus was approximately 31,000 students (Virginia Commonwealth University, 2017b). The VCU Health System employs more than 12,000 individuals in the Richmond and the surrounding area (Virginia Commonwealth University Health System, 2017).

To facilitate tracking recruitment strategies, when potential study participants were contacted by the study investigator for further information, they were asked how they heard

about the study. This question was included in the standardized telephone interview script developed to answer initial contact questions (See Appendix D). It was anticipated that such data would be helpful in identifying successful recruitment options for future studies in this population.

Prior to participant recruitment and enrollment, the investigator received approval from the Institutional Review Board (IRB) of VCU. Inclusion criteria were (a) ages 21 and older; (b) diagnosis of PCS based on the 10th edition of the ICD-10 (WHO, 2015) and documented by the patient's healthcare provider; (c) ability to communicate in English; and (d) an ability to understand and sign the consent form and complete the pencil and paper measures. Exclusion criteria were (a) an inability to follow study protocol, e.g. self-collect saliva specimen and/or participate in a study visit; (b) pregnancy or possibility of being pregnant and (c) a history of severe mental illness (e.g., schizophrenia, psychosis, bipolar).

The sample size required for successful completion of the study was $N=30$ adult individuals (men or women) diagnosed with PCS. The sample size required for this study was calculated using Cohen's (1988) guidelines for small, medium and large effect sizes. Using a large effect size (0.50) for the test of the null hypothesis $H_0: r = 0$ versus the two-sided alternative $H_A: r \neq 0$ where r is the Pearson correlation coefficient with a significance level of $p=0.05$ and a desired power of 80%, it was determined that a sample size of $N=26$ was needed for this study. To account for the potential of a 20% drop-out rate, we planned to recruit $N=30$ subjects diagnosed with PCS for the study.

Procedures

Screening Procedure (Appendix D)

Volunteers who were interested and self-selected to participate in the study were screened by the student investigator by telephone (if contacted by telephone) or in person (if contacted in person) in a private place convenient to the potential participant. The study, including risks and benefits, was explained in detail and all questions raised by the potential study participant were answered. If after the telephone screening procedure, the individual met inclusion criteria and agreed to participate, an appointment was made to meet at a place and time convenient to the participant that also afforded participant confidentiality. At that time, the study was explained once again, any participant questions answered, written informed consent (See Appendix E) obtained and the data collection protocol initiated. Upon completion of signed informed consent, the participant was asked to provide proof of diagnosis of PCS in the form of a medical record or signed note from the healthcare provider. If unable to provide proof of diagnosis, the participant was asked to complete and sign a HIPAA authorization release form (Appendix E) to enable contacting the healthcare provider for proof of diagnosis. If the participant was screened in person and was interested in participating, the study was explained once again, any participant questions answered, and if the participant was willing, written informed consent was obtained. After obtaining written informed consent, the data collection protocol was initiated. After obtaining written informed consent, the participant was asked to provide confirmation of PCS diagnosis. If the participant was unable to provide proof of diagnosis with either a note from their healthcare provider or a print out of the diagnosis from medical records, the participant was asked to complete and sign a HIPAA authorization release form to enable contacting the healthcare provider for proof of diagnosis. Data was de-identified with the assignment of a subject identification number, in consecutive order starting with 1001, at the time of consent. Details of the informed consent including date and time were recorded in study records and a

copy of the informed consent document were kept in a secure locked location for IRB purposes. A copy of the informed consent document was also provided to the participant.

Following screening and informed consent, the data collection protocol was explained with study participants repeating back to the investigator the process and having time to ask questions for any points of needed clarification. A salivary cortisol collection system was provided to the participant with both verbal and written directions regarding how and when to collect the sample, and how to store the sample until pick up by the investigator. Full informed consent and collection of non-biological data was anticipated to take approximately 60 minutes.

Measures (Appendix F)

Non-biologic Measures.

Demographic and Health History Questionnaire.

Following informed consent, a self-report demographic and health history questionnaire was used to obtain information regarding age, race/ethnicity, marital status, date of original injury leading to diagnosis, date of PCS diagnosis, socioeconomic status, psychiatric history, medical history, and medication history.

The Rivermead Post Concussive Symptom Questionnaire (RPQ).

The Rivermead Post concussive Symptom Questionnaire (RPQ) (King, Crawford, Wenden, Moss, & Wade, 1995) is designed to measure postconcussive symptoms and symptom severity and was included as a method of phenotyping the study population. To be diagnosed with PCS, an individual must present with three or more symptoms of this syndrome (WHO, 2015). This self-report measure is recommended for use in the mTBI and moderate TBI population by the National Institute of Neurological Disorders and Stroke (NINDS) (Wilde et al., 2010). The RPQ is a 16-item survey measured on a 5-point Likert scale where participants

indicate and rate the experience of various PCS symptoms relative to their experience of the symptom prior to injury. Examples of symptoms that subjects are asked to rate include “headache”, “fatigue” and “restlessness”. The presence of symptoms are ranked from 0= “not experienced at all” to 4= “a severe problem” in the past 24 hours (King et al., 1995). The measure was scored with a total summed score and with the recommended method of scoring in two parts. The first part (RPQ-3) consists of scoring the first three items, which relate to early presenting symptoms of PCS (headache, dizziness and nausea and or vomiting). Scores range from 0-12 with higher scores indicating greater report of symptom severity and the need for closer symptom monitoring and assessment. The second part (RPQ-13) consists of scoring the remaining 13-items with scores ranging from 0-52; higher scores indicate greater report of symptoms and symptom severity (Eyres, Carey, Gilworth, Neumann, & Tennant, 2005). Although there is no reported statistical validity for this measure, in a sample of $n=369$ individuals with a diagnosis of TBI, test-retest reliability coefficients for the RPQ-3 and RPQ-13 was reported at 0.72 and 0.89 respectively (Eyres, Carey, Gilworth, Neumann, & Tennant, 2005). When testing reliability with a total summed score, Eyres et al. (2005) reported poor item fit ($\mu = 0.416$, $SD = 1.989$) thus supporting findings obtained from the literature to score the measure in two parts as RPQ-3 and RPQ-13 (Lannsjö, Borg, Björklund, af Geijerstam, & Lundgren-Nilsson, 2011; Potter, Leigh, Wade, & Fleminger, 2006).

Perceived Stress Scale (PSS).

The 10-item Perceived Stress Scale (PSS; Cohen et al., 1983) was used to measure perceived stress. The PSS measures the level to which situations are appraised as stressful (Cohen et al., 1983). The PSS is a valid and reliable measure in the TBI population (Bay & Donders, 2008; Bay et al., 2002; Bay et al., 2005; Bellon et al., 2015; Strom & Kosciulek, 2007).

It was anticipated that the PSS would take no more than 5 to 10 minutes to complete, thus addressing patient burden concerns (Cohen & Williamson, 1988). The 10-item PSS contains items that are measured on a 5-point Likert scale: 0 = “never”; 1= “almost never”; 2= “sometimes”; 3= “fairly often”; and 4 = “very often” over the past month. Some examples of items include “In the last month, how often have you been upset because of something that happened unexpectedly?” and “In the last month, how often have you felt that you were effectively coping with important changes that were occurring in your life?” The range of score is 0-40 with higher scores indicating higher report of perceived stress (Cohen et al., 1983). Cronbach’s alpha co-efficient for the scale has been reported as 0.87 when used in the mTBI and moderate TBI population, indicating high internal reliability (Bay et al., 2009).

The Center for Epidemiologic Studies Depressive Scale (CES-D).

The Center for Epidemiologic Studies Depressive Scale (CES-D; Radloff, 1977) was used to measure depressive symptoms. This self-report measure was designed for use in the general population to indicate depressive symptoms and is frequently used as a measure of depressive symptoms in both healthy and non-healthy populations (Radloff, 1977). The CES-D is a 20-item survey measured on a 4-point Likert scale where participants rate how they felt or behaved during the last week as “rarely”, “some”, “occasional”, or “most”; with four of the 20 items scored negatively. Some examples of statements include “I was bothered by things that don’t usually bother me” and “I felt like people disliked me”. The range of score is 0-60 with a score of 16-20 indicating mild depression, 21-26 indicating moderate depression and a score greater than 27 indicating severe depression. The CES-D has been used as a measure of depression in the mTBI and moderate TBI populations (Bay et al., 2002; Bellon et al., 2015). Although not developed specifically for the neurologic population, the CES-D is recommended

for supplemental use in the TBI population as a measure of depression (NINDS, 2016).

Cronbach's alpha co-efficient for the scale has been reported as 0.92 when used in the mTBI and moderate TBI population indicating high internal reliability (Bay, Kalpakjian & Giordani, 2012).

It was anticipated that this measure would take no more than 5 to minutes to complete (Spinal Cord Research Evidence, 2010).

The Patient Reported Outcomes Measurement Information System (PROMIS)

Emotional Distress Depression Scale- short form (PROMIS ED-Depression-SF).

The CES-D was the primary measure of depressive symptoms in this study as this measure is frequently used as a valid and reliable measure of depressive symptoms (Radloff, 1977). The PROMIS Emotional Distress (ED)-Depression-Short Form (SF) for adult individuals was included as a second measure of depression in the study. This self-report measure is designed to measure depressive symptoms listed in the DSM-V (American Psychological Association [APA], 2013). These symptoms include feelings such as sadness, loneliness and worthlessness. The PROMIS-ED-Depression-SF was developed for use in general and chronic disease populations (PROMIS, 2015). Although not developed specifically for the neurologic population, the PROMIS-ED-Depression-SF has been recommended for use in the TBI population as part of the NIH CDE initiative to promote consistency among brain injury research findings (NINDS, 2016). The PROMIS ED- Depression Scale-SF is an 8-item survey measured on a 5-point Likert scale where participants rate how they felt during the last seven days as: 1= "never"; 2= "rarely"; 3="sometimes"; 4= "often" or 5="always". Some examples of items include "I felt worthless" and "I felt helpless". Scores range from 8-40. Scores are summed then converted to a T-score. T-scores range from 37.1 to 81.1 with higher scores indicating higher report of depressive symptoms. A T-score of <55 indicates no to slight depression, a score of 55

to 59.9 indicates mild depression, a score of 60.0 to 69.9 indicates moderate depression and a score >70 indicates severe depression (APA, 2013). Cronbach's alpha co-efficient for the scale has been reported as 0.96 when used in mild, moderate and severe TBI populations indicating high reliability (Tulsky et al., 2016). As with the PSS and CES-D, we anticipated this measure could be completed within 5 to 10 minutes, thus minimizing patient burden.

Biologic measure.

Salivary Cortisol.

Salivary cortisol was collected from study participants using the SalivaBio Oral Swab (SOS) Saliva Collection System from Salimetrics (2015). The amount of saliva collected using the SOS saliva collection system is 75 μ L. Intra-assay precision for this collection system is reported to be between 4-7%, with an inter-assay precision of 3-11% and a serum cortisol correlation of 0.91 (Salimetrics, 2016). Normal awakening cortisol levels in adults range from 0.094 to 1.551 μ g/dL (Salimetrics, 2016). Although no studies have been identified exploring cortisol in the PCS population, Bay et al. (2005) explored correlations between perceived stress, salivary cortisol, and depression in $N=75$ men and women after mTBI and moderate TBI. The authors were not able to report statistically significant study findings related to salivary cortisol; however, they did report that individuals with mTBI had significantly greater 8:00 a.m. (awakening) cortisol levels ($t= 2.66$, $df 48$, $p=0.011$) as compared to those with moderate TBI. It has been determined that salivary cortisol collection has advantages when compared to serum collection. Serum collection for cortisol requires the invasive procedure of venipuncture which may confound results due to activation of the stress response, making the salivary method preferred not only due to ease and convenience of data collection and decreased patient burden, but also to limit a potential confounding effect (Kirschbaum & Hellhammer, 1989).

Data collection protocol

The student investigator obtained informed consent. Afterward, the investigator provided the non-biological self-report measures to the study participant and described the pencil and paper process. The order of completion was demographic form, RPQ, PSS, CES-D and PROMIS ED-Depression-SF. All measures, including the demographic form, were completed by the participant and collected by the investigator at this time. The student investigator then provided the participant with the salivary cortisol collection kit containing an oral swab and labeled collection tube. A biohazard bag was provided to place the collected sample prior to freezing. The student investigator explained and provided written directions on how to collect and store the salivary cortisol sample.

Salivary Cortisol Sample Collection.

Participants were asked to collect the salivary cortisol sample within seven days of having signed the consent form and completing all non-biological data collection measures. Participants were instructed to (a) write the date and time on the label or the biohazard bag provided to them along with the salivary collection kit (tube); (b) collect salivary cortisol sample in tube provided (as demonstrated to them by the investigator at the time of study enrollment); (c) place the salivary cortisol sample tube into the biohazard bag; (d) place the sealed biohazard bag with salivary cortisol sample inside into their home freezer; (e) notify the study investigator, by text, email, or phone, that they had collected the sample and arrange an agreed-upon time for the student investigator to personally collect the salivary cortisol sample. To enhance needed study protocol compliance, a method of reminding the participant to collect the sample within 30 minutes of awakening was negotiated with each study participant by the study investigator at the time of study enrollment. This was done with a reminder text or e-mail at a predetermined time.

Because stressful events the evening before collection could lead to an elevated cortisol, the participant was asked to collect the sample after what they would consider to be a 'routine' night. At the time of pick up, the investigator received the sample and maintained the sample in a frozen state until transportation to VCU School of Nursing (VCU SON) where all frozen specimens were stored at or below -80C until thawed for batch processing and analysis. At study completion, each study participant received a \$10 gift card.

Risk Reduction.

This study involved minimal risk due to the exploratory nature of the research plan. Participants were notified that they may refuse any portion of the data collection. No participant appeared to experience emotional discomfort in completing the measures. If a participant were to have experienced greater than expected emotional distress, the study visit would have been terminated and the participant withdrawn from the study. The student investigator would have remained with the participant until a support person arrived or until the emotional distress resolved. The participant would have been encouraged to speak with their healthcare provider about their distress. To further minimize risk, participants reporting CES-D scores greater than 16, indicating the potential for a diagnosis of depression (Radloff, 1977), were informed at the time of data collection or by the method of preferred communication on the day of data collection and referred to their healthcare provider for further assessment.

Data Management and Analysis

Data Management

All data was maintained electronically on a password-protected computer with secure network server access at VCU School of Nursing. Hard copy material such as the demographic form and consents containing identifiable information were maintained by the study investigator

in a locked cabinet within a locked room in the investigators Roanoke office until the study was completed. Upon study completion, the measures were transported to the principle investigators office at VCU SON to be maintained under the same conditions. Salivary cortisol samples were frozen immediately following collection and remained frozen until thawed for batch processing and analysis. Once received by the laboratory, samples were stored in a freezer at or below -80C until processing. All samples from a single participant were assayed together to reduce interassay variability. Assays were performed per manufacturer's guidelines. All study material will remain stored and locked in secure location in the office of research at VCU SON and then destroyed within seven years after study completion per VCU policy.

Data Analysis

The student investigator entered all data into the JMP Pro-14 statistical package for analysis. Statistical significance was set with an alpha of 0.05.

Step 1: Descriptive

Descriptive statistics were described with medians and ranges for variables such as the demographics of age, time since original injury leading to diagnosis of PCS, time since PCS diagnosis and RPQ scores. Race/ethnicity, marital status, sex, and socioeconomic status were described with numbers and frequencies. A comparison was made between subjects with confirmed diagnosis ($n=10$) and those without confirmation ($n=7$).

Step 2: Correlation analysis

For specific aim 1: Examine the relationships among perceived stress, symptoms of depression and cortisol levels in persons diagnosed with PCS; Spearman's Rank Order Correlation Coefficient was used to examine relationships between stress and cortisol; stress and depression; and cortisol and depression.

Step 3: Mediation analysis

For specific aim 2: Examine the mediating effect of cortisol between perceived stress and levels of depression in persons diagnosed with PCS; Spearman's Rank Order Correlation Coefficient was used to determine relationships between variables. We had planned to use mediation analysis to determine the mediating effect, if any, of cortisol. Mediation analysis is a four-step process described by Baron and Kenny (1986). The four steps are as follows: (1) perform a simple regression analysis between perceived stress and depression; (2) perform a simple regression analysis between perceived stress and cortisol; (3) perform a simple regression analysis between cortisol and depression. If relationships exist in all three steps, then (4) perform a multiple regression analysis of perceived stress, cortisol and depression. If any one of the first three steps is found to have no relationship, mediation is not likely and step four is not performed.

Step 4: Cronbach's alpha

The RPQ, PSS, CES-D and PROMIS ED-Depression short form were statistically analyzed for validity and reliability in this study population. We have reported the findings with Cronbach's alpha thus contributing to the reliability of these measures for use in the adult PCS population. Additionally, a correlation analysis was performed between the CES-D and PROMIS ED-Depression short form.

Summary

This was a feasibility study using a descriptive, cross-sectional design to examine relationships among perceived stress, cortisol levels and depressive symptoms in adult persons diagnosed with PCS; with the hopes of exploring a mediating effect of cortisol between perceived stress and levels of depression in this population. Symptom characteristics were

identified and described. Study measures, such as the PSS, CES-D and PROMIS ED-Depression SF were assessed for reliability in the PCS population. Study findings will be used to power a larger exploratory study in the PCS population and to inform a future PNI-based intervention study. In chapter four, we discuss the study findings in relation to the study hypothesis.

Chapter IV

Results

The purpose of this descriptive cross-sectional study was to explore and describe relationships among levels of perceived stress, levels of cortisol as a biological indicator of HPA axis dysregulation, and levels of depression, in persons diagnosed with PCS. The findings related to the following research questions are reported in this chapter.

1. Is there a correlation among levels of perceived stress, cortisol, and symptoms of depression in adults diagnosed with PCS?
2. Does cortisol mediate the relationship between perceived stress and symptoms of depression in adults diagnosed with PCS?

Recruitment

Following VCU IRB approval, participants were recruited from May 2017 through June 2018. Self-selection sampling was the primary strategy in participant recruitment for this study. A total of 49 persons from the New River and Roanoke Valleys, and the Richmond area, contacted the student investigator and expressed interest in the study (see Figure 1). Of the 49 interested persons, 36 persons were screened for eligibility. Inability to retrieve telephone numbers for the purpose of eligibility screening was the primary reason for not screening potentially interested persons; meaning the individual had contacted the student investigator by email to express interest in the study, however, did not return the student investigator's email requests for telephone contact information to discuss the study and potentially screen for eligibility (see Table 1). In an attempt to identify successful recruitment options for future studies in the PCS patient population, those persons who were screened for eligibility were asked

how they found out about the study. The majority of respondents became aware of the study from the Richmond Craigslist advertisement (see Table 2).

Figure 1. Participant Tracking Report from Interest through Completion of Data Collection.

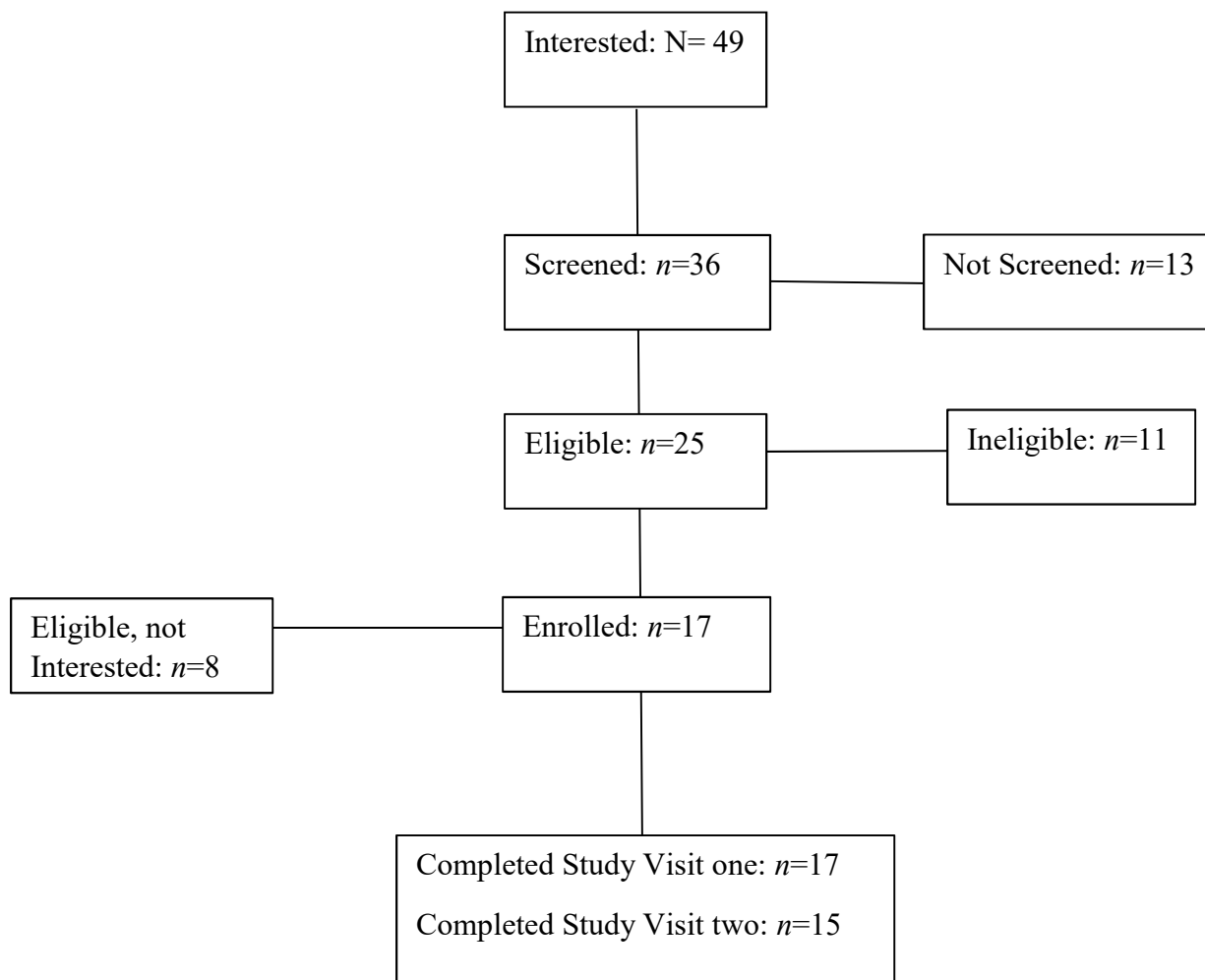


Figure 1. Participant tracking demonstrating flow from time of response to general advertisement, i.e. interest, through screening, eligibility, enrollment and study completion.

Table 1 *Rationale for not Screening Interested Persons for Eligibility*

<u>Rationale</u>	<u>Number of Persons</u>
Not responding to return call/email	<i>n</i> =7
Interested in study for a friend or family member	<i>n</i> =5
Inpatient at a rehabilitation facility	<i>n</i> =1
<hr/>	
Total	<i>N</i> =13

Table 2 *Study Advertisement Tracking Information Collected from Interested Persons who were Screened for Eligibility*

<u>Advertisement Source</u>	<u>Number</u>
Jefferson College of Health Sciences	<i>n</i> =3
Carilion and Affiliates	<i>n</i> =7
Craigslist Roanoke	<i>n</i> =6
Craigslist Richmond	<i>n</i> =14
VCU & VCUHS	<i>n</i> =3
Third Party Sources	<i>n</i> =3
<hr/>	
Total	<i>N</i> = 36

Note. VCU= Virginia Commonwealth University; VCUHS= Virginia Commonwealth University Health System

Of the 36 persons who were screened, 25 were found to meet eligibility criteria. A lack of formal diagnosis due to not seeking care for head injury and/or persistent postconcussive symptoms was the primary reason for not meeting eligibility criteria (see Table 3). Of the 25 individuals who were screened and found eligible to participate, $N=17$ ($n=13$ females; $n=4$ males) agreed to participate in the study. There were eight individuals who met inclusion criteria but declined participation related to concerns of time commitment and/or lack of financial incentive.

Table 3

Persons Screened who did not Meet Eligibility Criteria

<u>Reasons for Ineligibility</u>	<u>Number of Persons</u>
Not formally diagnosed	$n=9$
Major psychiatric history	$n=1$
Younger than 21 years	$n=1$
Total	$N=11$

Of the 17 participants who enrolled in the study, 15 ($n=11$ females; $n=4$ males) completed all study instruments and salivary cortisol sample collection at both time points. Subjects were instructed verbally and in writing to collect the salivary cortisol sample 30 to 45 minutes after awakening, after what participants considered a ‘normal’ evening, within seven days of the initial study visit and to record the date and time of collection. Salivary cortisol samples ($N=15$) were reported by the participants as being collected between 0604 and 1032 in the morning, with collection occurring within a range of 2 to 17 days (median 9 days) after the

initial study visit. Due to difficulties in obtaining proof of diagnosis with either a note from their healthcare provider or a print out of the diagnosis from medical records, $n=7$ diagnoses were not confirmable by medical record. Barriers to confirmation included a lack of response to diagnosis confirmation requests from healthcare providers, inability of the healthcare provider to confirm or deny diagnosis of PCS, and the inability of the participant to find a medical record that they believed they had possession of. All 17 participants did self-report both date of head injury and date of PCS diagnosis.

Demographic Characteristics

Despite a persistent and multi-pronged recruitment strategy, a sample size was not achieved that would power this study and we cannot assume the sample variable means are normal; therefore, demographic data is described with medians and ranges. The significance level was set at $p=0.05$. Group (healthcare provider confirmed diagnosis and unconfirmed diagnosis) medians were compared with the non-parametric Wilcoxon Rank-Sum (Mann-Whitney U) test for continuous variables and Pearson's Chi Square for categorical data. The study sample consisted primarily of Caucasian women. The median age of the total study sample was 38 years with a range of 22 to 61 years. Participants reported having experienced an mTBI between 2 months to 109 months (9 years) with a median of 14 months from the date of the first study visit. The reported time between mTBI and diagnosis of PCS for this sample ranged from 0 to 34 weeks (median of 3 months), and the time between diagnosis of PCS and the first study visit was reported between 1 week to 105 weeks (24 months) with a median of 15 months (see Table 4). The socioeconomic status of the sample varied, as did the relationship status. Notably, only one participant elected not to divulge their socioeconomic status and no participant reported being divorced or separated (see Table 5). More than half ($n=9$) of all participants reported being

diagnosed with depression and/or anxiety disorder and reported taking antidepressant or antianxiety medication. The median RPQ score was 46.

Table 4

Demographics: Continuous Variables and Group Comparison

Variable	Total Sample (N=17) Median (Range)	Confirmed Diagnosis (n=10) Median (Range)	Unconfirmed Diagnosis (n=7) Median (Range)	p-value
Age in years	38(22, 61)	46 (23, 61)	38 (22, 49)	0.2034
Time Since Head Injury in Months	13.8 (2.1, 108.6)	18.0 (3.5, 108.6)	12.7 (2.1, 72.0)	0.8073
Time between Head Injury and PCS Diagnosis in Weeks	2.7(0.0, 34.1)	5.0 (0.0, 34.1)	2.0 (0.0, 17.4)	0.4919
Time between PCS Diagnosis and Study visit one in Months	14.6(1.4, 104.7)	20.1 (3.5, 104.7)	11.1 (1.4, 72.0)	0.7327
Rivermead Postconcussion Questionnaire (RPQ)	46 (8, 57)	46 (8, 57)	36 (15, 55)	0.9610

Table 5

Demographics: Categorical Variables and Group Comparison

Variable	Total Sample (N=17)	Confirmed Diagnosis (n=10)	Unconfirmed Diagnosis (n=7)	X²	p-value
Sex				0.17	0.6818
Male	4 (24%)	2 (20%)	2 (29%)		
Female	13 (76%)	8 (80%)	5 (71%)		
Ethnicity				1.51	0.2179
Hispanic	1 (6%)	0 (0%)	1 (17%)		
Non-Hispanic	16 (94%)	10 (100%)	6 (83%)		
Race				5.20	0.1574
Asian	1 (6%)	0 (0%)	1 (14%)		
Hispanic	1 (6%)	0 (0%)	1 (14%)		
Caucasian	14 (82%)	10 (100%)	4 (58%)		
African American	1 (6%)	0 (0%)	1 (14%)		
Income				3.20	0.5249
<14,000	2 (12%)	1 (10%)	1 (14%)		
14-24,999	1 (6%)	1 (10%)	0 (0%)		
25-34,999	4 (24%)	2 (20%)	2 (29%)		
35-49,000	1 (6%)	0 (0%)	1 (14%)		
50,000 or >	8 (47%)	6 (60%)	2 (29%)		
No response	1 (6%)	0 (0%)	1 (14%)		
Relationship Status				3.78	0.1504
Living with partner	4 (24%)	4 (40%)	0 (0%)		
Married	8 (47%)	4 (40%)	4 (57%)		
Single/never married	5 (29)	2 (20%)	3 (43%)		

When comparing groups between those with confirmation of diagnosis and those without for both continuous and categorical variables, no significant differences were found. Median scores for those with a confirmed diagnosis were found to be slightly higher in the variables of age (+ 8.5 years), time since mTBI (+ 5.25 months), time between mTBI and diagnosis of PCS (+ 3 weeks), and time between diagnosis of PCS and the first study visit (+ 9 months). Those participants with a confirmed diagnosis reported a median RPQ score 10 points higher than those without a confirmed diagnosis. Of those with confirmed diagnosis, more than half ranked the

symptoms of 'fatigue' as being a severe problem since their head injury (M=4). Symptoms reported as causing a moderate problem (M=3) include 'dizziness', 'irritability', 'frustration', 'forgetfulness', 'poor concentration' and 'taking longer to think'. The symptom of depressed mood was reported as being a mild problem (M=2). These findings share similarities with findings from the unconfirmed diagnosis group, with 'fatigue', 'forgetfulness', and 'taking longer to think' reported as a severe problem (M=4), and symptoms reported as a moderate problem (M=3) including 'headache', 'sleep disturbance', 'irritability', 'feeling depressed', 'frustration', and 'poor concentration'.

Outcome Variables

Descriptive statistics for the variables of perceived stress, salivary cortisol and depression were described with medians and ranges as we cannot assume that this data is normally distributed due to the small sample size. Group medians of the study measures were compared with the non-parametric Wilcoxon Ranked-Sum (Mann-Whitney *U*) test. Although the groups, those with confirmed diagnosis and those without, are both reported; only the analysis for those with confirmed diagnosis was used for hypothesis testing. For those with confirmed diagnosis, the median score for the PSS, was 25 (range of 16 to 31). The median score for the CES-D, was 29 (range of 10 to 47) and the median measurement of salivary cortisol was 7 nM/L (range of 4 to 21 nM/L) for those with confirmed diagnosis (see Figure 2).

Figure 2. Box Plot of Salivary Cortisol Results for groups

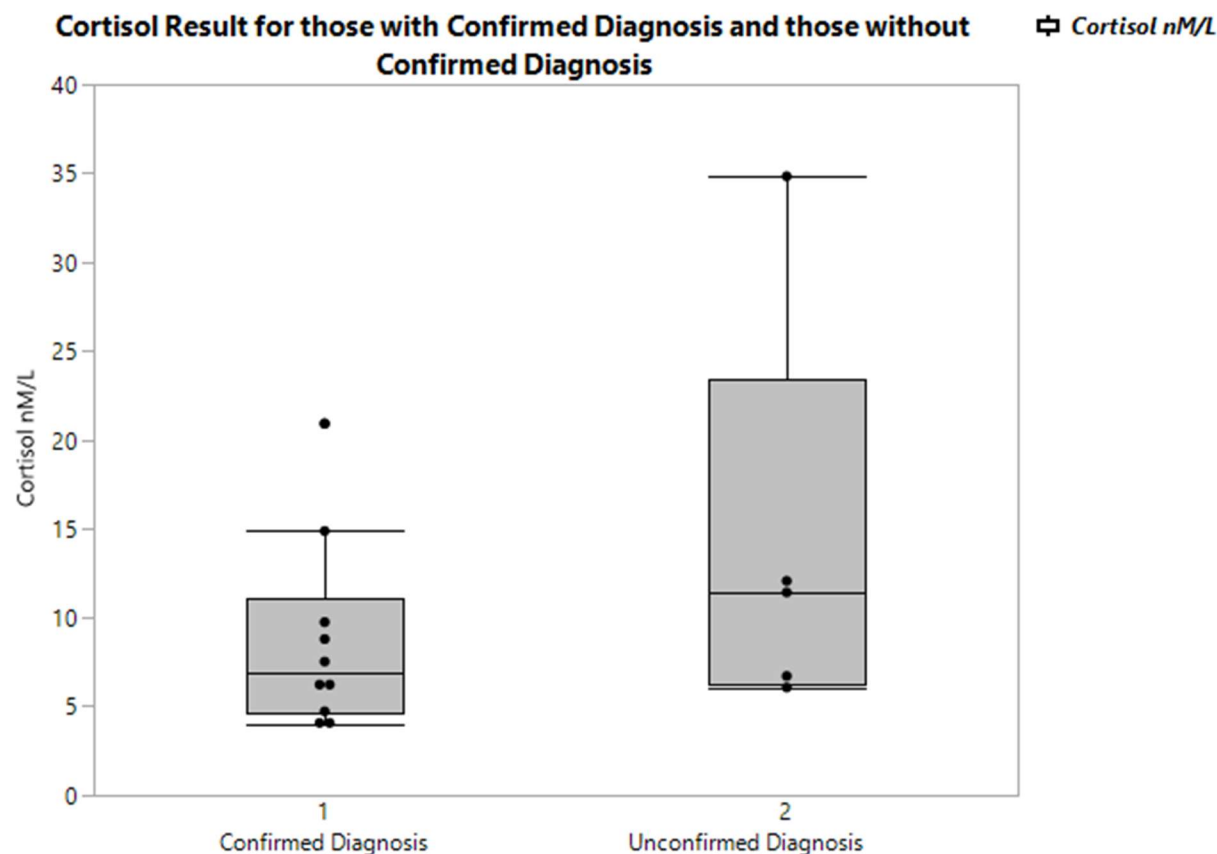


Figure 2. A Quantile Box plot of cortisol levels for those with confirmed diagnosis and those without a confirmed diagnosis. The median level for those with confirmed diagnosis was 6.9 nM/L (IQR 4.6 to 11 nM/L). The mean level was 8.7 nM/L (SD 5.4). The median level for those without confirmed diagnosis was 11.4 nM/L (IQR 6.2 to 23.4 nM/L). Note nM/L=nanomoles per liter.

When comparing descriptive statistics for outcome variables between those with and without diagnosis, we find there are no significant differences between groups (see Table 6). The medians were slightly lower for those with confirmed diagnosis for the biological variable of cortisol and slightly higher for the variables of perceived stress and CES-D as the primary measure of depression than those without confirmed diagnosis

Table 6

Descriptive Statistics for Study Measures with Group Comparison

Variable	Total Sample (N=17) Median (Range)	Confirmed Diagnosis (n=10) Median (Range)	Unconfirmed Diagnosis (n=7) Median (Range)	p-value
Perceived Stress Scale (PSS)	23 (6, 31)	25 (6,31)	22 (16, 27)	0.5901
Center for Epidemiologic Studies Depression Scale (CES-D)	25 (10, 47)	29 (10, 47)	25 (12, 38)	0.7325
PROMIS Emotional Distress-Depression Short Form (PROMIS ED-SF)	19 (8, 34)	23 (12, 34)	19 (8, 25)	0.3765
Salivary Cortisol in nanomole per liter (nM/L)	8 (4, 35)	7 (4, 21)	11 (6, 35)	0.2979

Hypothesis 1: There is a correlation among levels of perceived stress, cortisol, and depression in persons diagnosed with PCS. Spearman's Rank Order Correlation Coefficient was used to analyze relationships of the variables of perceived stress and salivary cortisol, salivary cortisol and depression, and perceived stress and depression among the study sample with a confirmed diagnosis (see Table 7). No significant relationships were found between PSS scores and cortisol levels (Spearman $\rho = -0.09$; $p = 0.8016$) or between cortisol levels and CES-D scores (Spearman $\rho = -0.09$; $p = 0.8022$), however there was a statistically significant relationship noted between PSS scores and CES-D scores (Spearman $\rho = 0.91$; $p = 0.0002$). Because no significant relationships were found in two of the three pairs of variables, we fail to reject the null

hypothesis meaning there is not enough evidence to demonstrate whether the variables do or do not correlate.

Table 7

Results of Correlational Analysis of PSS, Cortisol and CES-D for Sample with Confirmed Diagnosis

	PSS Total Score p- value	CES-D Total Score p- value	Cortisol (nM) p- value
PSS Total Score		0.0002 *	0.8016
CES-D Total Score			0.8022

*Note. PSS=Perceived Stress Scale; CES-D= Center for Epidemiological Studies Depression Scale; nM=Nanomole; *= Statistical Significance.*

Figure 3. Scatterplot Demonstrating Relationships between Stress, Depression and Cortisol Scores in the Sample with Confirmed Diagnosis

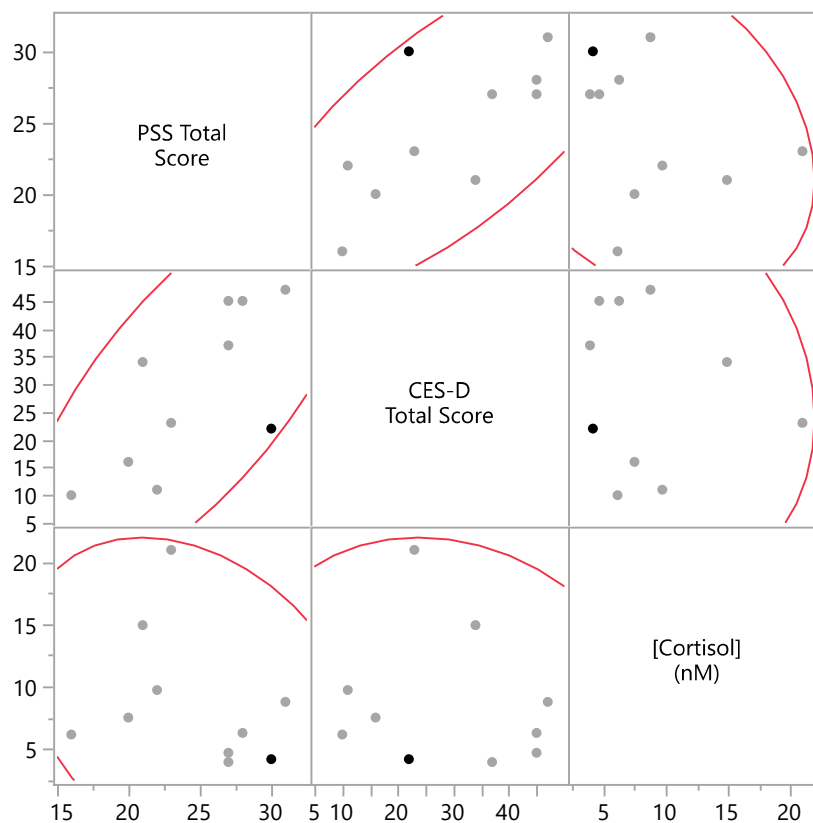


Figure 3. A visual representation of the relationships between perceived stress and depression as measured by the CES-D in the sample with confirmed diagnosis of PCS. PSS= Perceived Stress Scale; CES-D= Center for Epidemiological Studies Depression scale; nM=nanomoles; PCS=Postconcussion Syndrome.

No significant correlations were found between PSS scores and cortisol levels (Spearman $\rho = -0.11$; $p = 0.6887$), or between cortisol levels and CES-D scores (Spearman $\rho = -0.10$; $p = 0.6989$) in the total sample, however there was a statistically significant positive relationship identified between PSS scores and CES-D scores (Spearman $\rho = 0.87$; $p < 0.0001$); meaning that

higher reported levels of perceived stress appeared to correlate to higher reported levels of depression (see Table 8).

Table 8

Correlational Probability of PSS, Cortisol and CES-D for Total Sample

	PSS Total Score p- value	CES-D Total Score p- value	Cortisol (nM) p- value
PSS Total Score		0.0001*	0.6887
CES-D Total Score			0.6989

*Note. PSS= perceived stress scale; CES-D= Center for Epidemiological Studies Depression scale; *=statistically significant.*

For Hypothesis 2: Cortisol mediates the relationship between levels of perceived stress and depression in persons diagnosed with PCS. We did not perform a multiple regression of variables as significant correlation among all variables was required for the analysis of cortisol as a mediator. We did not find a significant correlation between perceived stress and cortisol, and cortisol and depression, meaning that cortisol was unlikely to mediate these relationships. Thus, we were unable to reject the null hypothesis.

Reliability of Study Measures

Non-biologic Measures

Study measures were assessed for item reliability. Multivariate analysis was used to identify the Cronbach's alpha co-efficient for each measure. In this study, the RPQ was used for descriptive purposes. The Cronbach alpha co-efficient for the instrument in this sample was 0.96 indicating high internal reliability. When exploring internal reliability of the RPQ in two parts, the RPQ-3 and RPQ-13, the instrument remains reliable with a Cronbach alpha co-efficient of

0.70 and 0.95 respectively. The Cronbach's alpha co-efficient for the PSS in this sample was 0.86, indicating high internal reliability. The Cronbach's alpha co-efficient for CES-D was 0.92 for this sample, meaning the measure demonstrated high internal reliability. The PROMIS-ED-Depression SF was used as a secondary measure of depression for the purpose of comparing reliability with the CES-D in order to contribute to the National Institutes of Health (NIH) Common Data Element (CDE) initiative. The Cronbach's alpha co-efficient for the PROMIS-ED-Depression SF in this sample was 0.96 indicating high internal reliability. When comparing total scores between the CES-D and the PROMIS-ED-Depression SF, we found a significant correlation in scores ($p < 0.0001$). When comparing reliability of the measures by group, those with a confirmed diagnosis and those without a confirmed diagnosis, we found similar results. Thus, study instruments demonstrated high internal reliability of all measures with the exception of the RPQ-3 and the PSS scores in the unconfirmed diagnosis group (see Table 9).

Table 9

Study Measure Item Reliability

	Total	Confirmed Diagnosis	Unconfirmed Diagnosis
Study Measure	Cronbach's α	Cronbach's α	Cronbach's α
RPQ Total Score	0.96	0.96	0.95
RPQ-3	0.70	0.77	0.45
RPQ-13	0.95	0.96	0.95
PSS	0.86	0.91	0.61
CES-D	0.92	0.94	0.82
PROMIS ED-SF	0.96	0.96	0.92

Note. RPQ=Rivermead Postconcussion Questionnaire; PSS= Perceived Stress Scale;

CES-D= Center for Epidemiological Studies Depression scale.

Biological Measure

Salivary cortisol was collected from participants using the SalivaBio Oral Swab (SOS) Saliva Collection System from Salimetrics (2015). Intra-assay precision for this collection system is reported to be between 4-7%, with an inter-assay precision of 3-11% (Salimetrics, 2016). The amount of saliva collected using the SOS saliva collection system was 75 μ L. The samples were analyzed by the Biobehavioral Research Laboratory at the Virginia Commonwealth University (VCU) School of Nursing (SON) using Enzyme Linked Immunosorbant Assay (ELISA) methodology. A total of $N=15$ frozen samples were delivered to the lab where they remained frozen until batch analysis. When data collection was completed, all samples were thawed. Once thawed, saliva samples were centrifuged at 1000 x g to remove any particulates, and 25 μ L pipetted into four separate wells to obtain quadruplicate data for each sample. Optic density (OD) and percent bound (B/BO) were calculated for each sample, and the mean of four values were obtained for each participant. In tandem, duplicate values were obtained for high and low controls and cortisol standards. A four-parameter curve fit was performed with a total sum of square (SST) of 0.12 and an R^2 of 0.99, indicating excellent fit. Concentrations for each sample in nM/L were calculated using the standard curve. As expected, the mean value for the low control was 4.23 nM/L and the mean value for the high control was 30.09 nM/L. The mean cortisol level for the total sample was 10.5 nM/L.

Summary

The purpose of this study was to explore and describe relationships among levels of perceived stress, cortisol as a biological indicator of stress, and levels of depression in persons diagnosed with PCS. A total $n=10$ subjects were confirmed to have a PCS diagnosis and were included in hypothesis testing. No significant differences were found between those subjects

with a confirmed diagnosis and those without diagnosis, demographically or in measurement of the outcome variables. A significant correlation was found between perceived stress and depression only. Questions remain as to a potential mediating effect of cortisol on these variables as study findings have led us to fail to reject the study H_0 . Chapter Five, includes a discussion of the study findings and the implications of these findings for nursing practice and future study.

Chapter V

Discussion and Implications

The study was a cross-sectional pilot study to (a) examine the potential relationships among the variables of perceived stress, salivary cortisol and depression in adults diagnosed with postconcussion syndrome (PCS) and (b) examine cortisol as a potential mediator between the variables of perceived stress and depression. In this chapter, the study results are discussed in relation to the hypotheses: (1) “There is a correlation between levels of perceived stress, levels of cortisol, and depression in persons diagnosed with PCS”, and (2) “Cortisol provides a mediating effect between levels of perceived stress and depression in persons diagnosed with PCS”. Study results demonstrated a statistically significant correlation between perceived stress and depressive symptoms (Spearman $\rho=0.87$; $p < 0.0001$); however, there were no reported correlations between the variables of perceived stress and cortisol (Spearman $\rho = -0.11$; $p = 0.6887$); nor between depression and cortisol as measured by CES-D (Spearman $\rho = -0.10$; $p = 0.6989$) or the PROMIS ED-Depression SF (Spearman $\rho = -0.40$; $p = 0.1327$). These findings suggest that cortisol is not likely to be a mediator between the specific variables of perceived stress and depression. We suggest that this may be due to the complexity of symptomatology associated with PCS or to a small sample size related to unexpected recruitment challenges, or perhaps, to both issues. Due to difficulty obtaining proof of diagnosis for all participants prior to data analysis, we discuss the study results by groups. Of the total sample ($N=17$), we have placed subjects in groups by diagnosis; those with confirmed diagnosis ($n=10$) and those with unconfirmed diagnosis ($n=7$). In addition to discussing study results, in this chapter we compare the study findings to previous studies in mild traumatic brain injury (mTBI) and moderate TBI populations. We discuss strengths and barriers to the recruitment strategy and enrollment, other

study limitations and reports of unexpected findings related to fatigue. Finally, we present implications for nursing practice and directions for future research.

Discussion of Study Results

Perceived Stress and Depression

In this study, there were statistically significant correlations between perceived stress as measured by the Perceived Stress Scale (PSS) and depression as measured by the Center for Epidemiological Studies Depression scale (CES-D) (Spearman $\rho = .87$; $p < 0.0001$) and perceived stress and depression as measured by the Patient Reported Outcomes Measurement Information System (PROMIS) Emotional Distress Depression Scale- short form (PROMIS ED-Depression-SF) (Spearman $\rho = .82$; $p < 0.0001$). Cronbach's alpha for all measures were strong, i.e., PSS (0.86), CES-D (0.92) and PROMIS ED-Depression-SF (0.96). Because of the very small sample size, we also examined medians and interquartile ranges (IQR) in the total sample ($N=17$) and by groups (confirmed diagnosis $n=10$; unconfirmed diagnosis $n=7$). The median (interquartile range) PSS scores were 23 [18, 27] for the total sample ($N=17$); with a median (interquartile range) of 25 [14, 30] for those with confirmed diagnosis ($n=10$); and 22 [20, 25] for those with unconfirmed diagnosis ($n=7$). These results indicate the presence of moderate levels of perceived stress in the study sample, regardless of the status of their diagnosis, with both groups reporting the experience of similar levels of perceived stress. The median (interquartile range) CES-D scores were 25 [18, 28] for the total sample; 29 [15, 45] for those with confirmed diagnosis; and 25 [19, 35] for those with unconfirmed diagnosis ($n=7$). These results suggest a study sample experiencing moderate to severe depression, with those having a confirmed diagnosis ($n=10$) reporting more severe depressive symptomology. When describing reports of depressive symptoms collected by the PROMIS ED-Depression SF, findings also suggest the

presence of moderate to severe levels of depression. That is, median (interquartile range) depression scores were 58 [54, 66] for the total sample; 61 [51, 70] for those having a confirmed diagnosis; and 58 [56, 63] for those with unconfirmed diagnosis. When exploring the report of depression scores as collected by both the CES-D and PROMIS ED-Depression SF, the study sample having a confirmed diagnosis ($n=10$) of PCS were found to report greater depressive symptomatology as described by both measures. In reporting the medians and means of perceived stress as collected by the PSS, and depressive symptoms as collected by both the CES-D and PROMIS-ED-Depression SF, we hope to add to our understanding of these variables in the PCS patient population.

To our knowledge, there are no known studies describing the relationship between perceived stress and depression in persons diagnosed with PCS. Examining the literature, we found studies examining similar variables, predominantly in the mTBI and moderate TBI patient population. For example, among research studies reporting a relationship between perceived stress and depression in the TBI population; Bay, Hagerty, Williams, Kirsch and Gillespi (2002) used a cross-sectional design to explore a potential relationship among post-injury stress and depressive symptoms in persons diagnosed with mild to moderate brain injury ($N=75$; men $n=39$; women, $n=36$). They found a significant relationship between perceived stress and depressive symptoms ($R^2=.54$; $p=.00$). In this study, the authors also reported means for variables of stress and depression; describing a mean stress score of 28 (SD 9.5) and a mean depression score of 20 (SD 13.2) in their sample. Of this study sample, the authors reported 20% ($n=15$) were found to have depression scores indicative of the presence of severe depressive symptomatology. In a secondary analysis of the data from Bay et al. (2002), Bay, Sikorskii, & Gao (2009) reported finding a positive relationship ($\beta =0.51$; $p<0.01$) between perceived stress and depression, with

higher reports of perceived stress correlating with higher reports of depressive symptoms. In a separate study, Bay and Donders (2008) used a cross-sectional design to describe the role of chronic stress in the development of depressive symptoms after a TBI in a sample of individuals diagnosed with mTBI or moderate TBI ($N=84$; men $n=43$; women $n=41$). Noting that all study participants had been diagnosed with TBI between one and 36 months from the date of data collection, the researchers reported that the presence of depressive symptoms after TBI could be explained by reported levels of perceived stress ($R^2=.55$), adding to the evidence that perceived stress shares a significant positive relationship to depression in the TBI population. While the authors did not report median or mean stress score for the total sample ($N=84$), the median depressive score was reported as 32. In this study, Bay and Donders (2008) placed subjects in groups by presence or absence of depression as identified by depression scores that identified those at risk ($n=49$) and those not at risk ($n=35$) for depression (i.e., depressed or not depressed). The authors reported mean stress scores for both the depressed group (\bar{x} 27, SD 5.5) and not depressed group (\bar{x} 20, SD 4.3). The mean depression score for the depressed group was 40 (SD 6.1) and the not depressed group was 21 (SD 4.4). These reported study results indicate that individuals in the depressed group reported higher levels of perceived stress than those in the not depressed group. Strom and Kosciulek (2007) used a cross-sectional research design to examine relationships between perceived stress and depression in individuals diagnosed with mTBI ($N=94$; men $n=35$; women $n=58$). The researchers reported a significant ($\beta=0.67$; $p<0.001$) correlation between perceived stress and depression. The mean stress score in this sample was reported to be 29 (SD 9.3) with a mean depression score of 17 (SD 10.8). The findings described by Strom and Kosciulek (2007) indicate a study sample reporting the presence of high levels of stress and mild to moderate depression. In a randomized control trial comparing the effect of a

12-week walking intervention to a 12-week control nutrition education program, Bellon et al. (2015) compared levels of perceived stress and depressive symptoms in a sample ($N=69$; men $n=41$; women $n=28$) diagnosed with mild, moderate or severe TBI. The researchers did not report comparisons of perceived stress and depression scores; however, mean scores of both measures were reported at each time point of this interventional study. The mean stress scores at baseline were reported as 26 (SD 9.5) for the interventional walking group and 23 (SD 9.2) for a control nutrition education group, indicating the presence of moderate perceived stress in both groups. The mean depression scores were reported as 16 for both the walking group (SD 12.4) and the control nutrition education group (SD 12.1) at baseline, indicating the presence of mild depressive symptoms in both groups. At study completion (24 weeks), both the intervention walking and control nutrition education groups reported a mean stress score of 21 (SD 9.5 walking group; SD 9.2 nutrition group) and a mean depression score of 13 (SD 10.5 walking group; SD 11.4 nutrition group), indicating a decrease in levels of reported perceived stress and absence of depression. These findings support the evidence of the presence of higher reported levels of perceived stress and depression in the TBI population. Additionally, the findings reported in this study demonstrate the potential clinical significance of interventions that address symptoms of perceived stress and depression in the TBI population, and potentially, in the PCS population. While collectively these studies support the presence of a relationship between perceived stress and depression in the mTBI, moderate TBI and severe TBI populations, to our knowledge, there are no known studies to support this relationship in the PCS population. Therefore, we suggest that current study findings support an association between perceived stress and depression in persons diagnosed with PCS and, in this light, study findings contribute to addressing a gap in the science of PCS research.

Cortisol as a mediator.

In this study, cortisol was hypothesized to mediate the relationship between perceived stress and depression. Analysis of study results did not evidence a significant correlation between perceived stress and cortisol (Spearman rho= -0.11; $p= 0.6887$) nor between depression and cortisol as measured by either the CES-D (Spearman rho= -0.10; $p= 0.6989$) or the PROMIS ED-Depression SF (Spearman rho= -0.40; $p=0.1327$). Because there were no statistically significant correlations between cortisol and either stress or depression, the study findings did not meet criteria for mediation analysis as described by Baron and Kenny (1986); meaning, cortisol was unlikely to mediate the relationships between stress and depression. We examined medians and means of the cortisol levels in the total sample ($N=17$) and in groups (confirmed diagnosis $n=10$; unconfirmed diagnosis $n=7$). We report median cortisol levels due to our small sample size with the understanding that the literature reports standardized values as mean values. Regardless of how reported, means or medians, we found cortisol levels in our study sample as being below the published standardized normal mean of 13.05 nM/L diurnal cortisol release patterns (Salimetrics, 2016). In congruence with the current nursing literature that reports on salivary cortisol, we report our study findings on cortisol in nanomole per liter (nM/L). The median level of salivary cortisol in the study sample was 7.5 nM/L (\bar{x} 10.5; SD 8.1). When describing findings by group, the cortisol level for those with confirmed diagnosis was 6.9 nM/L (\bar{x} 8.7; SD 5.4) and for those with unconfirmed diagnosis, 11.4 nM/L (\bar{x} 14.1; SD 11.9). Our findings demonstrated, therefore, that the mean cortisol level in the confirmed diagnosis group was 4.35 nM/L lower than the standardized morning cortisol awakening response (CAR). The limitation of small sample size combined with a one-time data collection may be contributing factors to the inability to report any significant correlations between stress and cortisol, or depression and cortisol; however,

study findings will inform future longitudinal research studies to examine more thoroughly the question of cortisol in the PCS patient population and its putative role as a mediator of stress and depression.

To our knowledge no studies have been published exploring relationships between stress and cortisol nor between depression and cortisol in the PCS population. However, a minimal number of studies have been published exploring such relationships in the mTBI population. For example, Hutchinson et al. (2017) used a cross control repeated measures study to examine variables, including perceived stress and cortisol, between university athletes with concussion injury ($n=26$; men $n=16$, women $n=10$) and a healthy matched control group ($n=26$; men $n=16$, women $n=10$). Unlike our study, the researchers collected two salivary cortisol samples, one in the morning and one in the afternoon, at three separate time points; during the first week of injury (Time 1), at resolution of concussive symptoms (Time 2), and when medically cleared to return to play (Time 3). At time 1, mean cortisol in the athletes with concussion was reported as $0.17 \mu\text{g/dL}$ (4.69 nM/L); time 2 mean cortisol was reported as $0.20 \mu\text{g/dL}$ (5.52 nM/L); and at time 3, mean cortisol was reported to be $0.18 \mu\text{g/dL}$ (4.97 nM/L) with no significant differences between this group and the matched control group ($P > 0.44$). Cortisol levels as reported by Hutchinson et al. (2017) were not mean CAR levels, but rather mean levels of samples collected at two time points, morning and afternoon. Because of this, we are unable to reliably compare our cortisol study findings, nor are we able to assess Hutchinson et al.'s (2017) cortisol levels for normality. Interestingly, Hutchinson et al. (2017) found a significant correlation between Time 1 stress scores and salivary cortisol levels ($p = 0.007$) in the concussion group as compared to healthy controls; however, they did not report such correlations for times 2 and 3. The mean time from beginning of data collection (time 1) to return to play (time 3) was 35 days (range 9 to 142

days) for the concussed athletes. Despite this individualized variance in time between injury and return to play; there was little variation in mean cortisol levels between data collection time points indicating cortisol may not mediate symptoms in this population. Hutchinson et al. (2017) noted that the correlation of stress and cortisol in their study sample may have indicated cortisol as a potential diagnostic biomarker for those concussed athletes with persistent physical symptoms of stress (pE46). Additionally, when considering that a diagnosis of PCS is received if symptoms persist beyond 90 days, the wide range of time between injury and return to play as reported in this study suggests 'recovery' from concussion injury is an individual process that places some individuals at risk for the development of chronic symptoms, e.g. PCS, after injury.

When exploring relationships between perceived stress and cortisol, and depression and cortisol; Bay et al. (2005) reported an absence of significant relationships between variables. Bay (2005) collected four salivary cortisol samples (8 a.m., 12 p.m., 4 p.m. and 8 p.m.) from a sample of $n=50$ ($N=53$) subjects with mild to moderate TBI on a single day. The authors reported an 8 a.m. salivary cortisol mean level of 0.59 ng/ml with a range of 0.02 to 2.87 ng/ml (1.63 nM/L; range 0.06 to 7.92 nM/L). This morning value is 11.42 nM/L below the standardized normal mean value for the CAR. This data suggests the presence of hypocortisolemia in this mild to moderate TBI population similar to findings in our study sample. Cortisol levels as reported by Bay et al. (2005) seemed to demonstrate a diurnal pattern with the 12 p.m. mean cortisol level reported as 0.29 ng/ml (0.8 nM/L), 4 p.m. mean cortisol level of 0.21 ng/ml (0.58 nM/L) and 8 p.m. mean cortisol level of 0.17 ng/ml (0.47 nM/L), thus contributing to the reliability and validity of their reported study findings. Nevertheless, the authors noted that the use of antidepressants may have confounded cortisol results as approximately 43% of their study participants reported being diagnosed with depression and 41% reported taking antidepressant

medications. In our study, we found similar results with more than half ($n=9$) of the study sample being diagnosed with depression and/or anxiety and taking antidepressants and/or anxiolytics.

In a longitudinal study comparing biological (heart rate variability, cortisol) and nonbiological (depression, anxiety) variables in a sample of individuals diagnosed with mTBI ($N=331$; men $n=131$, women $n=200$) and a healthy control group with no history of head injury ($N=152$; men $n=47$, women $n=105$), Sung et al. (2016) collected data at baseline (time of injury) and 6 weeks later (time 2) for the mTBI group and baseline only for the healthy control group. At baseline the researchers reported median serum cortisol levels in the mTBI sample as 10.66 $\mu\text{g/dL}$ (294 nM/L) and 9.65 $\mu\text{g/dL}$ (296 nM/L) at week six. as compared to healthy controls 10.88 $\mu\text{g/dL}$ (300.14 nM/L) at baseline. The difference between cortisol levels at baseline was minimal at only 6.14 nM/L between groups. Because the time of cortisol collection was not reported and seemed to be random, we are unable to make reliable comparisons between the cortisol levels found in our study sample with those of Sung et al.(2016); however, levels as reported by these authors appeared to be above the normal CAR value. When considering the nonbiological variables, Sung et al. (2016) reported finding significantly greater levels of depression in the mTBI group as compared to the healthy control group at weeks 1 ($p=0.002$) and 6 ($p<0.001$) but reported no statistically significant correlations between depression and any other variable in their study, including cortisol levels. Such findings indicate a potential risk for the development of depression in persons after mTBI and thus contribute to a risk for developing PCS. In summary, other researchers, with the exception of Sung et al. (2016), have predominantly reported lower cortisol levels in persons with mTBI and TBI, which aligns with our study findings. In the current study, abnormal cortisol levels may imply a dampened CAR in those with a confirmed diagnosis ($n=10$) of PCS; indicating potential HPA axis dysfunction. We

suggest comparative research studies across TBI, mTBI and PCS populations to examine the impact of stress on HPA axis function as related to diurnal patterns and potential dysfunctional cortisol production would potentially contribute meaningful insights into the underlying mechanisms that may or may not lead to the development of PCS. This includes considerations regarding the role of inflammation in the development of PCS. For example, it is understood that cortisol shares a relationship with the inflammatory response and that inflammation occurs in response to activation of the HPA axis (i.e., stress response) (Glaser & Kiecolt-Glaser, 2005; Mavroudis, Corbett, Calvano, & Androulakis, 2015). Higher levels of inflammation in the acute period of TBI have been suggested to contribute to the development of PCS (Topolovec-Vranic et al., 2011; Rathbone, Tharmaradinam, Jiang, Rathbone, & Kumbhare, 2015). Additionally, the inflammatory process has been associated with depression (Felger & Lotrich, 2013; Miller & Raison, 2016), and while in our study cortisol was not found to mediate a relationship between perceived stress and depression in the PCS sample, perhaps there are other biological indicators that intersect with, or are influenced by the presence of cortisol that lead to an inflammatory process. Therefore, comparative studies across the TBI, mTBI and PCS would further the science by also examining HPA axis dysfunction and biomarkers of inflammation including pro- and anti-inflammatory cytokines and C-reactive protein (CRP) and potential relationship to symptomology. From a biobehavioral perspective, enhancing our understanding of underlying mechanisms and their relationship to symptom development in the PCS patient population provides opportunities for developing and exploring potential benefits of targeted symptom management interventions.

Secondary Findings

The Rivermead Postconcussion Symptom Questionnaire (RPQ) (King, Crawford, Wenden, Moss, & Wade, 1995), a measure of PCS symptoms, was used to explore the symptom characteristics reported by the study sample. The RPQ is a questionnaire where participants rate the presence of a symptom in the past 24 hours relative to the presence of the same symptom prior to the injury that led to a diagnosis of PCS. Scores range from 0 (not experienced at all) to 4 (a severe problem). In the current study, an unexpected finding from data collected with the RPQ was the identification of ‘fatigue’ and ‘forgetfulness’ as the most problematic post-injury symptoms (as compared to before injury) reported by this sample, with a mean value of 3.1 for each of the variables. Ten of the 17 study participants reported fatigue as a severe problem (rated a ‘4’); $n=3$ rated it a moderate problem (rated a ‘3’) and $n=2$ a mild problem (rated a ‘2’). Only two subjects rated fatigue as no problem or no more of a problem than prior to injury. The second most common post-injury symptom reported was forgetfulness, with $n=8$ reporting it as a severe problem, $n=6$ as a moderate problem and $n=2$ as a mild problem. One study participant reported forgetfulness as no problem. Depression was reported to be a less problematic symptom, i.e. mild problem post-injury (\bar{x} 2, SD 1.1) in both the diagnosed and non-diagnosed study participants, even though, the CES-D and PROMIS ED-Depression SF scores indicated the presence of moderate to severe depression in this study sample.

Fatigue is a subjective symptom, defined as a lack of energy that ranges between feeling ‘tired’ to feeling ‘exhausted’, that interferes with daily activity and function (Ameringer et al., 2016; Ream & Richardson, 1996). Forgetfulness, defined as poor memory, is a complex concept related to cognitive dysfunction (Dwyer & Katz, 2018; Wilson, Evans & Williams, 2008). Following the impact of a TBI, difficulties with memory are typically related to learning and remembering new facts or experiences and may include reports of the loss of knowledge related

to facts and experiences that were known prior to the head injury (Wilson, Evans & Williams, 2008). Both fatigue and memory disturbance are common sequelae after TBI, regardless of severity of injury (Cronin & O'Loughlin, 2018; Rabinowitz & Levin, 2014). It is estimated that as many as 70% of persons with TBI experience fatigue (Bay & Xie, 2009; Wayne, & Shinakee, 2013). Approximately 65% of persons with TBI will experience chronic cognitive dysfunction, including impaired memory (Rabinowitz & Levin, 2014).

Less is known regarding the prevalence of these symptoms in persons diagnosed with PCS. In a study of $N=91$ (men $n=47$, women $n=44$) persons diagnosed with PCS who were patients at a university concussion clinic, Baker et al. (2012) reported approximately 70% of participants identified fatigue and 95% identified concentration or memory problems as a chronic symptom after injury. In a longitudinal descriptive study of $N=110$ (men $n=60$, women $n=50$) persons diagnosed with PCS, Hiploylee et al. (2017) divided subjects into two groups; those who recovered from PCS, meaning they were no longer experiencing symptoms ($n=30$) and those who did not recover from PCS ($n=80$), meaning persons continued to report symptoms. Of the sample that did not recover, the three highest reported symptoms in order of prevalence were headache, difficulty concentrating, and fatigue; with 52.5% reporting experiencing fatigue and 67.5% reporting difficulty concentrating as chronic symptoms since time of injury. The authors further noted that headache was the highest reported symptom among study participants (68.8%) who did not recover from PCS. In contrast to these two studies, we reported fatigue and cognitive dysfunction as the 'more problematic' prevalent symptoms. Although not measured as variables in the current study, and based on comparative study findings, future research studies that include a measure of pain, fatigue and cognitive dysfunction in conjunction with measures

of depression may contribute to moving the science forward by examining potential relationships among these symptoms in comparative studies of persons diagnosed with TBI, mTBI and PCS.

Additional Considerations

Every effort was made to reduce participant burden in this study by including brief yet valid and reliable measures; however, it seems that some burden still occurred. The study protocol required participants to complete an IRB-formatted seven-page consent, after which data was collected using a one-page demographic form with a one to three page medical and health history (depending on the extent of medical history). Participants were asked to list medical and/or psychiatric illnesses that they had experienced and to list current medications including medication name, dosage, frequency, date prescription began, and purpose for which prescription was received. Of the total sample ($N=17$), $n=3$ subjects reported no history of illness; $n=4$ reported no use of medications; $n=11$ (65%) reported having three or more medical and/or psychiatric illnesses and/or prescribed three or more medications. Some participants verbalized that reading the consent for understanding and completing the demographic and medical history forms were cognitively demanding. Such complaints seem reflective of reported post-injury symptoms of fatigue and cognitive dysfunction and may have influenced participant response on the remaining self-report data collection instruments (RPQ; PSS; CES-D; PROMIS ED-Depression SF), that, when taken together comprised a total of 54 items.

In summary, these unexpected secondary study findings may be clinically meaningful as it is unclear what impact the post-injury symptoms of fatigue and cognitive dysfunction may have had on individual performance when completing study measures. Further, it is unknown whether such symptoms may have contributed to compromised compliance with study protocol, specifically the collection of a morning salivary cortisol sample within 7-days of completing the

paper measures. When designing future studies, it is important to consider the impact of these symptoms on study participation, with thoughtful efforts made to streamline and simplify the data collection process in this population.

Study Strengths & Limitations

Study Strengths

The reliability of study measures was a strength to this study. The RPQ was scored with a total summed score along with the recommended method of scoring in two parts in order to thoroughly analyze and report the reliability of this measure in this sample. When evaluating reliability of the summed score, the measure performed well with a Cronbach's alpha of 0.96 for both the total sample and the sample with confirmed diagnosis; and a Cronbach's alpha of 0.95 for the sample with unconfirmed diagnosis. When scoring in two parts, the first three items which relate to early presenting symptoms of PCS (headache, dizziness and nausea, and or vomiting) are totaled (RPQ-3). The remaining 13 items are then totaled (RPQ-13). When evaluating reliability by scoring in two parts, the RPQ-3 and RPQ-13, we found the RPQ-3 performed satisfactorily with the total sample and with the confirmed diagnosis group ($\alpha = 0.70$ and 0.77 respectively). The RPQ-3 did not perform as well in the unconfirmed diagnosis group ($\alpha = 0.45$). This is likely due to the small sample size ($n=7$) coupled with the characteristics of the rated symptoms. The symptoms rated in the first three items, i.e. the RPQ-3, are typically experienced in the acute stage of the injury, however these symptoms may present at any time in the continuum after mTBI and during PCS (Eyres, Carey, Gilworth, Neumann, & Tennant, 2005).

The PSS-10 has been found to be reliable in the mTBI and moderate TBI populations. Cronbach's alpha co-efficient for the scale has been reported by Bay, Sikorskii, & Gao (2009) as

0.87 when used in the TBI population, indicating high internal reliability. For the current study, the Cronbach's alpha co-efficient for the scale was 0.86. Interestingly, the Cronbach's alpha for those without a confirmed diagnosis was only 0.61, below the acceptable level of $\alpha=0.70$. Perhaps the 0.61 was related to the smaller sample size ($n=7$) of the non-confirmed diagnosis group. The CES-D has been found to be reliable in the TBI population as a measure of depression. Cronbach's alpha co-efficient for this scale has been reported as 0.92 in a TBI sample (Bay, Kalpakjian & Giordani, 2012). In our study, Cronbach's alpha co-efficient for the scale was 0.92 for this sample, indicating high internal reliability. The PROMIS-ED depression SF has been found to have potential for reliability when used in mild, moderate and severe TBI populations with sensitivity for this measure reported as >0.95 (Clover et al., 2018). This short form has been validated in other populations. In a study assessing validity and reliability of the PROMIS ED-Depression SF across platforms (paper instrument, personal computer, personal digital assistant, and interactive voice response), Bjorner et al. (2014) found the PROMIS ED-Depression SF to be reliable in a sample of $N=923$ subjects with rheumatoid arthritis, depression, and chronic obstructive pulmonary disease (COPD), reporting a Cronbach's alpha of 0.95 when collected via paper instrument. In the current study, the Cronbach's alpha co-efficient was 0.96, indicating high internal reliability. When comparing reliability of the depression measures in the current study, we found a significant correlation of the scores as reported on the CES-D to scores reported on the PROMIS-ED-Depression SF ($p < 0.0001$) suggesting this 8-item scale may be just as accurate in measuring the outcome of depression as the 20-item CES-D in adults diagnosed with PCS, thus simplifying data collection in this population. To address concerns of patient burden, we recommend that future studies replicate the use of both instruments in comparative studies across TBI, mTBI and PCS patient populations with larger sample sizes.

Should study findings produce similar results, then the shorter PROMIS-ED-Depression SF scale could be used in place of longer measures such as the CES-D which would lower item burden from 54 to 34, thus addressing concerns of participant burden.

Study Limitations

As a feasibility study, we sought to identify best practice for successful recruitment and enrollment of adults with PCS. We identified challenges to enrollment including (a) potential study participants who were interested in participation but who lacked a medical diagnosis of PCS, and (b) experiencing difficulty in obtaining confirmation of PCS diagnosis by examination of a study participant's medical record once they were consented and enrolled. Many persons who were interested in participating in the study lacked a diagnosis of PCS. In total, 36 interested individuals were screened for eligibility. Of those, $n=9$ persons did not meet this inclusion criteria. Those not meeting this inclusion criteria stated they did not know they had a concussion/mTBI and therefore either they did not seek care for the injury, did not relate the chronic symptoms they were experiencing directly to the injury, or did not know chronic symptoms could occur after mTBI. These study findings support the challenge of describing the incidence of mTBI due to the failure of those experiencing an mTBI to seek care or, possibly due to under-reporting by clinicians (Powell et al., 2008; Setnik & Bazarian, 2007). In a retrospective study conducted at a level one trauma center, investigators found that approximately 56% of Emergency Department (ED) admissions identified by research staff as meeting the CDC guidelines for mild TBI were not diagnosed by ED physicians at the time of their visit (Powell et al., 2008). Along with lack of proper diagnosis, individuals may not seek health care due to uncertainty or lack of awareness of the potential problems related to mild brain injury. In a survey conducted to identify why individuals did not seek care for mTBI, researchers found that

the most common reason was simply not knowing care should be sought (Setnik & Bazarian, 2007). In the current study, of the 25 interested persons who were screened and met eligibility, only 68% ($n=17$) agreed to participate and were enrolled in the study. Reasons for deciding not to enroll included concern over the time commitment of participation and lack of financial incentive. One person did not give a reason for deciding against participation other than ‘just not interested’. Although the time commitment was clearly described in the screening script as approximately 60 minutes for the first visit and 5 minutes for the sample pick up (visit 2), concern over the issue of ‘time’ may have been related to PCS symptomology such as the presence of fatigue. Future studies will address recruitment challenges learned in the current study by adapting a medical records approach to study participant recruitment strategy rather than using general advertisement (self-selection). This adjustment in recruitment strategies would be designed to specifically target individuals diagnosed with TBI, mTBI and PCS in advance of activities directed at study recruitment, screening, consent and enrollment. We would anticipate that such a pro-active recruitment strategy could enlarge the potential sample size and address current study limitations.

Diversity.

We made every effort to address diversity in our small study sample. For example, we placed brochures and flyers advertising the study in clinics serving diverse and underserved patient populations. Additionally, those who participated in the study were asked to pass the advertisement to others who may be eligible to participate. The demographic characteristics of the study sample were similar to those studies in the mTBI and TBI population as reported by Bay (2012; 2005); that is, study participants were predominantly mid to upper class, married Caucasian females. Study recruitment strategies were initially focused on the Roanoke and New

River Valley area, which is reported to be predominantly Caucasian (86%) and African American (8%) with a population of approximately 3% Hispanic, 2% Asian and 1% other (men, 48%; women, 52%) (US Census Bureau, 2017a). To address recruitment challenges, our efforts widened to include the urban setting of Richmond, which is reported to be approximately 48% African American, 40 % Caucasian, 7% Hispanic, 2% Asian and 3% other (men, 56%; women 44%) (United States Census Bureau, 2017b).

Our study included $n=14$ Caucasian (82%), $n=1$ African American, $n=1$ Hispanic and $n=1$ Asian and of these, 13 were women (76%) and 4 were men. Given the demographics of previous studies in the mTBI and PCS populations, we predicted a larger Caucasian presence, but we could not predict the distribution of male to female subjects given the imbalance in male to female subjects reported from the literature review. The literature suggests women may be more likely than men to present with PCS symptomology and therefore more likely to be diagnosed with PCS. For example, in a study of $N= 223$ subjects with mTBI ($n=123$, men $n=91$, women $n=32$) or admitted with trauma ($n=100$, men $n=64$, women $n=36$), Ponsford et al. (2012) reported finding that women were 2.56 times more likely to report PCS symptoms than men. Additionally, in a study of $N=180$ (men $n=115$, women $n=65$) subjects with mTBI, Dischinger, Ryb, Kufera, and Auman (2009) found that 53% of the women reported PCS symptoms at three months after injury as compared to 33% of men sampled. Neither race nor ethnicity were reported in either study. When planning for recruitment in future studies, it will be important to consider methods for maximizing recruitment efforts to ensure a more diverse study sample. For example, researchers might consider reaching out to leaders of community-based organizations to offer educational programs to enhance awareness of the problem of concussion/mTBI and PCS. This strategy would not only foster awareness of the problem, but also aid in building

relationships and trust within diverse communities. Collaboration with healthcare providers serving diverse and underserved populations and with lay persons may encourage engagement of a diverse population.

Singular cortisol sample.

Collection of salivary cortisol samples over time to facilitate the evaluation of potential changes in cortisol in response to a stressor, or to examine diurnal patterns in cortisol levels, is the preferred method of sampling (Bay et al., 2009; Granger, Johnson, Szanton, Out, & Schumann, 2012); however, the current feasibility study protocol provided an opportunity to collect cortisol data at one time point, thus limiting our ability to engage study participants over time. In an effort to address this study limitation and to collect a reliable and valid sample of salivary cortisol that is limited to a one-time data point, participants in the current study were educated to the importance of the timing of the biologic data collection. The objective was to collect salivary cortisol at the known peak time point. Secretion of cortisol is diurnal, meaning secretion occurs episodically over a 24-hour cycle with the greatest secretion occurring 30 to 45 minutes after waking in the morning (Kirschbaum & Hellhammer, 1989). This peak of secretion is referred to as the cortisol awakening response (CAR) and is considered a reliable indicator of HPA axis function (Kunz-Ebrecht, Kirschbaum, Marmot, & Steptoe, 2004; Wüst, Federenko, Hellhammer, & Kirschbaum, 2000). Adherence to the study protocol for cortisol collection was a threat to validity for this study. Prior to consent, the participants were asked about their concerns related to completing the study such as in collecting and storing the salivary sample or ability to be available to the investigator at the time of sample pick up. Participant concerns were addressed, and a plan developed with each participant for successful completion of the data collection process. Despite this plan, we found collection of cortisol samples to be challenging.

Participants were reluctant to receive morning text or email reminders. A mid-week reminder was negotiated with most participants for collection of the sample to occur within seven days from completion of the paper pencil instruments. Despite all effort, the median time of salivary sample collection occurred 9 days after completion of the instruments with a range of 2 to 17 days. Two of seventeen samples were not collected due to loss of contact with subjects.

Implications for Nursing Research

In the US, TBI affects approximately 1.7 million individuals annually with the majority of injuries, nearly 75%, being classified as mTBI. Although most individuals completely recover from mTBI, approximately 10% will continue to report the persistent symptoms of PCS. While the variables of perceived stress, cortisol, and depression have reportedly been studied in the TBI population, there are very few studies examining these variables in persons with PCS. In an effort to address this gap we conducted a study using a holistic paradigm, i.e. a psychoneuroimmunology framework, to explore these factors in persons diagnosed with PCS. Given that our study findings indicated a significant relationship between perceived stress and depression but not between cortisol and perceived stress nor between cortisol and depression, we are poised to design future studies to help address our study outcomes. Within the design of future studies, we will take into consideration our unexpected findings of fatigue and cognitive dysfunction as distressing symptoms as measured by the RPQ. These findings support the current evidence that persons with PCS are at risk for developing depression; however, more comprehensive, prospective research designs are needed to contribute to our understanding of PCS symptomatology, including depression, fatigue, cognition, and pain as well as other factors, both biological and psychosocial, that have the potential to place an individual with a TBI or mTBI at risk for developing PCS. Non-biological factors would include self-reported levels of

stress, environment, family history and social support (Bay & Covassin, 2012; Dwyer & Katz, 2018). Biological factors could include cortisol and immunological biomarkers such as pro- and anti-inflammatory cytokines and C-reactive protein (Barlow, 2016; Bay et al., 2005; Rathbone, Tharmaradinam, Jiang, Rathbone, & Kumbhare, 2015). Additionally, based on our study findings, participant recruitment and retention may be more successful by lessening patient burden through the use of valid and reliable measures that minimize patient effort. For example, replacing the CES-D with the brief, and easily completed, PROMIS ED-Depression SF when measuring depression. Further, rather than general advertising for study participants and seeking post-consent confirmation of a PCS diagnosis as occurred in the current study, future research efforts aimed at interprofessional collaboration and review of medical records for identification of potential eligible study participants would contribute to a stronger study design. And finally, to enhance diversity of sample, it is important to collaborate with racially and ethnically diverse multidisciplinary research teams as well as partnering with community leaders serving diverse populations.

In summary, it would seem that the perception of stress impacts the presence of depressive symptoms in persons experiencing PCS, however much is unknown about the impact of perceived stress and stressors, or the influence of other factors on the development of PCS and the presence of PCS symptoms. Furthermore, recovery from mTBI appears to be an idiosyncratic process with some persons not fully recovering and therefore at risk for diagnosis of PCS. We have much to learn about the underlying mechanisms behind the development of PCS and the occurrence of symptoms, such as depression, in this vulnerable patient population. For example, we do not know the influence of HPA axis dysfunction and associated alterations in cortisol production, nor the impact of inflammation that occurs post-injury has on the presentation of

PCS. Both mechanisms, HPA axis dysfunction and inflammation, have been found to be present in the mTBI and TBI populations, and have been associated with the occurrence of depression; but we do not know if or how these mechanisms influence the presentation of depression or other symptoms in persons with PCS. Additionally, because we do not know if stress, stressors, or any of the biological mechanisms that may potentially influence the development of the chronic symptomology of PCS that follows a mTBI, future comparative studies that examine both mTBI and PCS patient population are warranted. Exploring HPA axis function and inflammatory processes (e.g., pro- and anti-inflammatory cytokines and CRP), psychosocial and environmental influences and associations with currently reported symptoms can provide an opportunity to further inform our understandings regarding the risk for or development of PCS. When planning future studies that include biomarkers such as cortisol, pro- and anti-inflammatory cytokines, or CRP, thoughtful planning must be considered for specimen collection time points and adherence to specimen collection protocol to ensure complete data collection and the reliability of study findings. Recruitment can be a challenge in this population, therefore strategies for enrolling a larger, more diverse sample should be fully explored. The presentation of community education programs would promote awareness of the problem and may potentially increase study enrollment. Additionally, heightened awareness of the problem may increase the probability that those persons who have experienced a mTBI will seek healthcare. By further exploring and understanding biologic and psychosocial mechanisms and processes related to the development of PCS and associated symptoms, we may then better serve this population with the induction of nursing interventions and self-care strategies to enhance symptom management and thus improve quality of life.

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Appendix A
Conceptual Framework

Figure A1. Biobehavioral Relationships Among Perceived Stress, Cortisol and Depression in Adults Diagnosed with Postconcussion Syndrome (PCS).

Figure A1 Biobehavioral Relationships Among Perceived Stress, Cortisol and Depression in Adults Diagnosed with Postconcussion Syndrome (PCS).

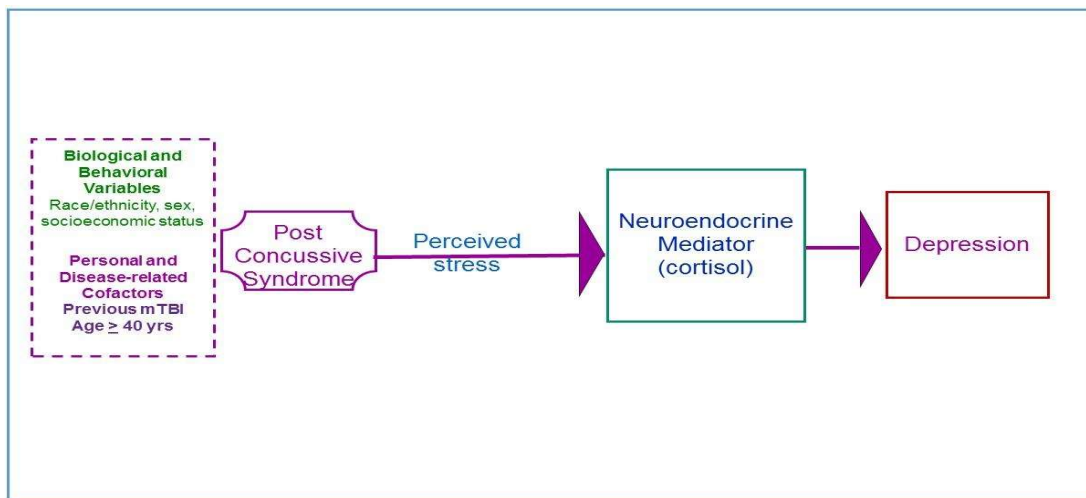


Figure A1. Conceptual framework informed by a Psychoneuroimmunology paradigm. Adapted from McCain, N.L., Gray, P.G., Walters, J.M., & Robins, J. (2005). Implementing a comprehensive approach to the study of health dynamics using the psychoneuroimmunology paradigm. *Advances in Nursing Science*, 28(4). p. 320-332. Note mTBI= mild traumatic brain injury.

Appendix B
Study Tables

Table 1 PRISMA Flow Diagram

Table 2. Literature Review Study Table



Table A.1 PRISMA 2009 Flow Diagram

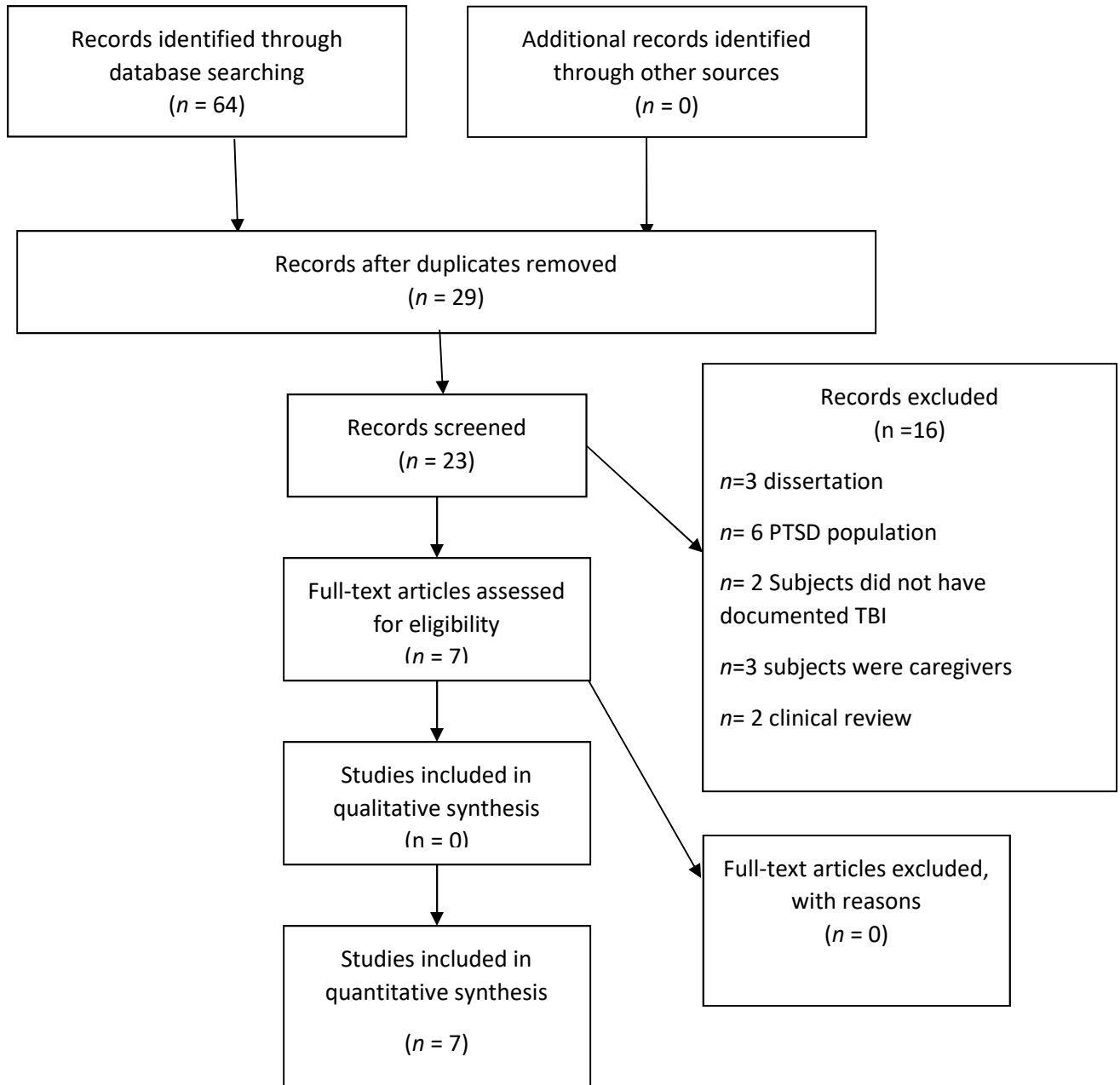


Table A.2

Literature Review Study Table

Study	Study Design	Participants	PCS/TBI definition criteria	Intervention/groups	Main Outcome Variable/Measures	Findings
Bay 2002	Non-experimental cross-sectional study	Convenience sample of $N=75$ adults (male $n=39$; female $n=36$). Recruited from 5 rehabilitation clinics with diagnosis of mild or moderate TBI and evaluated by study neuropsychologist	1993 American Congress of Rehabilitation Medicine ($n=27$ mTBI; $n=48$ moderate TBI)	N/A	Post-injury stress (PSS) Depressive Symptoms (NFI-D, CES-D) Interpersonal relatedness (IRI, Hagerty's sense of belonging Instrument)	The NFI-D and CES-D were strongly correlated ($r=.85$, $p<.00$, one-tailed). 20% subjects had CES-D scores >30.5 Significant relationship between PSS and depression, as measured by the NFI-D, ($R^2=0.54$, $F=87.72$ (1, 73), $p=0.00$)
Bay, Hagerty, Williams, & Kirsch, 2005 [Perceived stress, Cortisol, Depression & TBI]	Non-experimental cross-sectional study	Convenience sample of $N=75$ adults (male $n=39$; female $n=36$). Recruited from 5 rehabilitation clinics with diagnosis of mild or moderate TBI and evaluated by study neuropsychologist	1993 American Congress of Rehabilitation Medicine per Bay et al., 2002. ($n=27$ mTBI; $n=48$ moderate TBI)	N/A	Pre-injury chronic stress (CAC, MSLEC) Post-injury stress (PSS) Salivary Cortisol Depressive Symptoms (NFI-D) Interpersonal relatedness (IRI, Hagerty's sense of belonging instrument)	Individuals with mTBI demonstrated greater 8 am salivary cortisol levels than those with moderate TBI ($t=2.66$, df 48, $p=0.011$) 8 am ($t=2.39$, df 9.23, $p=0.04$) and noon ($t=2.18$, df 20.74, $p=0.04$) mean cortisol values were significantly greater for those reporting more pre-injury childhood adversity. 8pm cortisol level associated with frequency of pre-injury stressful life events ($r=0.38$, $p=0.01$). No relationship between salivary cortisol values and level of depression. Limitations: Small sample size

<p>Strom & Kosciulek, 2007</p> <p>[Perceived stress, Depression & TBI]</p>	<p>Non-experimental, cross-sectional</p>	<p>Convenience sample of $N=94$ subjects (male $n=35$; female $n=58$). Recruited from 2 rehabilitation centers, with confirmed diagnosis of mTBI</p>	<p>mTBI as evidenced by a Glasgow Coma Scale score of 13–15 and a period of post-traumatic amnesia of less than 60 minutes</p>	<p>N/A</p>	<p>Stressors (PSS)</p> <p>Appraisal (Hope scale)</p> <p>Coping (Problem solving inventory)</p> <p>Stress response/depression (BDI)</p> <p>Adjustment (Productivity scale of the Community Integration Questionnaire, Satisfaction with Life Scale)</p>	<p>PSS scores ranging from 10-50 with a mean score of 28.8</p> <p>BDI mean depression scores ranging from 0-63 with a mean score of 16.7</p> <p>statistically significant ($\beta=0.67$; $p<0.001$) correlation between the levels of perceived stress scores and depression scores</p>
<p>Bay & Donders, 2008</p> <p>[Perceived stress, Depression & TBI]</p>	<p>Non-experimental cross-sectional study</p>	<p>Convenience sample of $N=84$ adults (male $n=43$; female $n=41$). Recruited from eight rehabilitation centers with diagnosis of mild or moderate TBI.</p>	<p>Diagnosed TBI ($n=65$ mTBI; $n=19$ moderate TBI)</p>	<p>N/A</p>	<p>Chronic Stress (PSS, Impact of event scale-revised)</p> <p>Depressive Symptoms (NFI-D)</p> <p>Somatic symptoms (McGill pain questionnaire, modified version of the fatigue impact scale)</p> <p>Functional status (30-item PCRS)</p> <p>Pain (MPQ-SF)</p> <p>Fatigue (POMS-F)</p>	<p>NFI-D scores ranged from 13-56 with a mean score of 31.71, 58% ($n=49$) of subjects reported a score >28, and 42% ($n=35$) reported scores ≤ 28</p> <p>For those subjects categorized as depressed (NFI-D score >28), the mean PSS score was 27.37.</p> <p>For those subjects categorized as not depressed (NFI-D ≤ 28), the mean PSS score was 19.66.</p> <p>No significant relationship was reported between levels of fatigue and depression or levels of pain and depression; however, levels of perceived stress were evidenced to explain levels of depression ($R^2=0.55$)</p>

<p>Bellon, et al., 2015</p> <p>[Perceived stress, Depression & TBI]</p>	<p>Experimental RCT, cross over design</p>	<p>Purposive sample of $N=123$ adults with $n=69$ completing all time points (male $n=41$; female $n=28$). Recruited from community and from Northern California TBI model Systems database with history of TBI.</p>	<p>Diagnosed TBI ($n=10$ mTBI; $n=10$ moderate TBI; $n=35$ severe TBI; $n=13$ unknown)</p>	<p>12-week walking intervention ($n=28$) Week one-tracked their activity as usual with pedometer. Each week after, increase steps by 5% until week- 8, then maintain the daily level of steps for weeks 9-12. Coaching three times a week for weeks 1-3 then twice a week for weeks 4-8. Coaching 1-time a week for weeks 9-12.</p> <p>12-week attention control nutrition education program ($n=39$) Coaching on same schedule as intervention group</p> <p>Measures collected at baseline, 12-weeks, and 24- weeks</p>	<p>Depression (CES-D)</p> <p>Perceived stress (PSS)</p>	<p>Mean CES-D score of 16 for both groups at baseline,</p> <p>At 12 weeks, the walking group reported a mean CES-D score of 12 as compared to the nutrition group mean score of 15</p> <p>At 24 weeks, both groups reported a mean score of 13 ($p=0.007$).</p> <p>Mean PSS score of 25 at baseline for the walking group and 23 for the nutrition education group.</p> <p>At 12 weeks, the PSS mean score of 20.76 for the walking group compared to the nutrition education group mean score of 24.3.</p> <p>At 24 weeks, the PSS mean score for both groups were reported as 21.</p> <p>The authors reported significant decreases in PSS scores during the walking intervention for both groups ($p=0.006$) with a significant decrease in PSS score at 24 weeks for both groups ($p=0.006$).</p> <p>Limitations: attrition rate of 50%</p>
<p>Luo, Chai, Jiang, Chen, & Yan, 2015</p>	<p>Quasi-experimental longitudinal interventional</p>	<p>Convenience sample of $N=68$ adults (male $n=45$; female</p>	<p>Diagnosed TBI on admission to hospital.</p>	<p>Group 1: 6-week Psychotherapy</p>	<p>Severity of Injury (GCS)</p> <p>Chronicity (GOS)</p>	<p>$n=32$ subjects demonstrated hypocortisolemia</p>

[Cortisol, depression, TBI]	Study using comparison groups stratified according to cortisol	<i>n</i> =23) Recruited from neurosurgical department of a University hospital with diagnosis of depression or depressive symptoms	Severity classified by GCS on admission . 3-8: severe 9-12: moderate 13-15: mild Mild TBI defined by the ACRM.	<i>N</i> =68) Group 2: Psychotherapy and Citalopram (<i>n</i> =28) Group 3: Psychotherapy and Citalopram and Prednisone (<i>n</i> =32) <i>N</i> =8 recovered post psychotherapy; not assigned to pharmacotherapy groups	Cortisol (denote when measured) Depression (BDI-II) (measured baseline; 6 weeks; 9 weeks)	and were placed in group 3. No significant correlation between severity of injury and severity of depression ($r=0.128$, $p>0.05$). Group 1: absent depressive symptoms after treatment. Group 2: <i>n</i> =27 subjects reported decreased/absent depressive symptoms after treatment Group 3: <i>n</i> =30 subjects reported decreased/absent depressive symptoms after treatment Limitations: Lack of control, no statistical analysis of effect among the 3 groups. Cortisol levels and demographic information not reported.
Sung et al., 2016 [Cortisol, depression, TBI]	Longitudinal comparison group design Non-experimental Comparative study Prospective Chapter 9 118=	Convenience sample of <i>N</i> =483 adults (male <i>n</i> =178; female <i>n</i> =305). Recruited from a University hospital with a diagnosis of mTBI. Healthy controls with no history of TBI.	Diagnosed by medical provider. World Health Organization definition of mTBI.	mTBI group: <i>n</i> =331 Healthy control group: <i>n</i> =152	Neurohormones (ACTH, IGF-1, melatonin, cortisol) HRV Anxiety: BAI Depression: BDI-II	Greater report of anxiety in mTBI group as compared to healthy controls at 1 week ($p<0.001$) and 6 weeks ($p<0.05$). Greater report of depression in the mTBI group compared to the healthy controls at 1 week ($p=0.002$ and 6 weeks ($p<0.001$). No statistically significant change in cortisol levels from

						<p>week 1 and week 6 in mTBI group. No statistically significant differences in cortisol levels between groups ($p=0.698$).</p> <p>Did not compare cortisol to depression</p> <p>Limitations: loss of 125 mTBI subjects from week 1 to week 6 due to subjects not following up at hospital. Unequal number of male to female subjects. Healthy control group was younger than mTBI group.</p>
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Appendix C
Recruitment Material

1. Newsletter Advertisement Roanoke and New River Valley
2. Newsletter Advertisement Richmond
3. Study Flyer Pull-off Roanoke and New River Valley
4. Study Flyer Pull-Off Richmond
5. Study Flyer Publisher

Newsletter Advertisement Roanoke and New River Valley

Hardcopy and Online

Postconcussion Syndrome Study

If you are age 21 or over, and have a diagnosis of Postconcussion syndrome, you may qualify to participate in a research study conducted in the Roanoke and New River Valleys. Participants of this study will be asked to meet two times in a private area to protect confidentiality. Once to meet with the student investigator to complete four sets of questionnaires and receive a kit for collection of a sample of saliva for purposes of measuring a stress biomarker. A second shorter meeting will be required to pick up the sample of saliva. Compensation is available at completion of the study. For more information, please contact:

Christine Huson, MSN, RN

Doctoral student Virginia Commonwealth University

(540) 985-4028 or email husonc@vcu.edu.

Principal Investigator:

Victoria Menzies PhD, RN, PMHCNS-BC, FAAN

Associate Professor Virginia Commonwealth University

VCU IRB #HM20009108

Newsletter Advertisement Richmond

Hardcopy and Online

Postconcussion Syndrome Study

If you are age 21 or over, and have a diagnosis of Postconcussion syndrome, you may qualify to participate in a research study conducted in the Richmond, Va. area. Participants of this study will be asked to meet two times in a private area to protect confidentiality. Once to meet with the student investigator to complete four sets of questionnaires and receive a kit for collection of a sample of saliva for purposes of measuring a stress biomarker. A second shorter meeting will be required to pick up the sample of saliva. Compensation is available at completion of the study. For more information, please contact:

Christine Huson, MSN, RN

Doctoral student Virginia Commonwealth University

(540) 985-4028 or email husonc@vcu.edu.

Principal Investigator:

Victoria Menzies PhD, RN, PMHCNS-BC, FAAN

Associate Professor Virginia Commonwealth University

VCU IRB #HM20009108

Study Flyer Publisher

Adult Volunteers with Postconcussion Syndrome



“Perceived Stress, Salivary Cortisol and Depression in Adults with Postconcussion Syndrome: A Pilot Study “

Study purpose: To examine relationships among stress, cortisol as a biologic marker of stress, and depressive symptoms in adults 21 or older who have been diagnosed with postconcussion syndrome or PCS.

Study Plan: Volunteers from the Roanoke, New River Valleys and Richmond area who are interested in participating in this study will be screened either by phone or in person to see if they meet criteria for enrollment in the study. If volunteers meet criteria and agree to participate, informed consent will be obtained in a confidential setting. Volunteers are asked to complete four sets of questionnaires which should take no longer than 60 minutes. Volunteers will then be asked to collect a sample of saliva within their home setting. A second visit will be required for a research assistant to collect the saliva sample. This visit should take no longer than 5 minutes.



What Will Volunteers Receive?

Compensation is available at completion of the study

Who Can Volunteer?

- * **21 years of age or older**
- * **Diagnosed with PCS**
- * **Can communicate in English**
- * **Can consent and understand the study protocol**
- * **Not pregnant**

For more information, contact:

Christine Huson, MSN, RN

Student Investigator

Doctoral student Virginia Commonwealth University

(540) 985-4028; husonc@vcu.edu

Principle Investigator: Victoria Menzies PhD, RN, PMHCNS-BC, FAAN,

Associate Professor Virginia Commonwealth University

VCU IRB #HM20009108

Appendix D

1. Telephone Interview Script
2. Participant Tracking and Screening Form

Telephone Interview Script

Thank you for calling the VCU School of Nursing Postconcussion Syndrome Study. This is [Your Name], how can I help you?

Then go to this script:

Thank you for your interest in this study. May I have your name? Thank you, and may I ask how you heard about this study? Great.

I'd like to tell you a bit about the study. In the past decade there have been many advances in our understanding of concussion and mild traumatic brain injury. These advances have led to improvements in preventive measures such as concussion screening, patient education after concussion and mild traumatic brain injury and sports related improvements such as shock resistant football helmets; however we do not know exactly what causes those individuals who suffer a mild brain injury to develop persistent symptoms of PCS [you may have to explain that this is the acronym for the longer term] or why one person might experience symptoms such as depressed mood while others do not. We don't know if factors such as how people experience stress or how the release of a stress hormone might have an effect on symptoms such as depressed mood.

This study is being conducted to learn more about the relationship between perceived stress; cortisol, a hormone related to stress; and symptoms such as distressed mood that might occur among individuals with a diagnosis of PCS. To better understand a possible relationship between these variables, we are inviting adults age 21 and older, who have been diagnosed with PCS to participate in this study

[Involvement]

Generally, participation in the study involves you meeting with me to complete a consent process and to provide you with the opportunity to ask questions that we might answer for you. This may be done in your home or at another place that is comfortable to you yet offers privacy so that any information you provide remains confidential. Once we have met, and if you consent to participate in this study, all of the information I obtain will remain confidential, and will be identified by a number only. At that time, I will ask if you would be interested in further studies related to individuals with postconcussion syndrome. If you agree to be contacted for future studies, only your preferred contact information will be kept.

During your study appointment and after you have agreed and consented to participate, you will be asked to complete questions related to your health history and demographic background. Following this, you will be asked questions regarding how you think about or experience stress as well as questions related to any feelings of sadness or depression you might have experienced in the past week. For example, you will be asked to rate how often "In the past week [you] felt depressed". . You may choose not to answer questions about which you are uncomfortable.

Also, during our first study appointment and after you have agreed and signed an informed consent form to participate in the study, we will ask you to provide proof of your diagnosis of PCS with either a note from your primary healthcare provider or a print out of your medical

records. If that is not possible, we will ask you to complete a diagnosis confirmation form to enable us to contact your primary health care provider to confirm your diagnosis of PCS. A copy of this form will be provided to you.

Following this initial study visit, there will be one more step to the collection of data and that would be asking you to collect a sample of your saliva during the following week (within 7 days) of your first study visit. This one extra step will involve asking you to collect a sample of your saliva, using a simple cotton tip swap and storing it until we can retrieve it. We provide all the needed materials and instructions so as to keep it as simple as possible for you. We will use this saliva to analyze a stress hormone called cortisol. Our study plan is to compare the level of this stress hormone in your body to the answers you provide on the questionnaires we will be giving you. At the time of the first meeting, I will provide you with a saliva collection kit as well as with detailed written directions on how to collect and store your saliva. Following this, you and I, together, will make a plan for how I may retrieve this sample from you. I will explain this in more detail if you are eligible and choose to participate in this study.

All levels of participation in this study are completely voluntary. I will explain each of the tasks in more detail at the time of our meeting.

There is no cost to you to participate, other than the time you spend completing the study. Study participants will be compensated for their time. Upon completion of all study-related requests, and after I retrieve your saliva sample, you will be provided with a 10 dollar Walmart gift card.

We hope that the information gained by your participation will provide insight into how the experience of stress may influence mood in adults diagnosed with PCS.

Are there any questions I can answer for you?

NEXT:

If participant is interested, then the next step is to inform them that in order to be considered to be in the study, you need to ask them a few questions first.

If Participant states they are not interested: We want to thank you for your call and for the time you took to have this explained. Should you change your mind, or want more information, feel free to contact me at this number. Once again, thank you. .

Are you age 21 or older? **If no, then ineligible. Stop the interview and thank them for calling.**

Are you currently pregnant? **If “yes” then ineligible – stop the interview and say “It is one of our criteria that we can’t include pregnant women in this study but thank you for your interest.**

Have you been diagnosed with a severe psychiatric condition? **If person says they were hospitalized once for having had a break down, simply ask them what the diagnosis was that brought them to the hospital. If anxiety or depression or general admission then okay.**

Are you able to obtain and bring with you to the first meeting a note from your MD confirming your diagnosis of Postconcussion Syndrome? **If yes**, please bring this confirmation with you to your first study visit, should you decide to participate.

You may ask them how they will do this and/or offer the following advice: “All you need to do is call your provider’s office and ask them to document your official PCS diagnosis on a prescription form and leave it for you to pick up in an envelope at the reception desk. There should be no need to make an appointment. Then just pick it up and bring it with you to your first study visit. WE WILL SO APPRECIATE THAT!”

If interested and meet inclusion criteria, proceed to enrollment form

Participant Tracking and Screening Form

IID _____

EID _____

SID _____

Participant Interest Tracking Form
Menzies/Huson IRB# HM20009108**Response to Advertisement (Interest ID) Form**

Message Received Date: _____ Time: _____ PD: _____ Interest ID# (IID): _____

Contact Method (circle one): Phone Email

If email contact:**First attempt:**

PD email response sent (Date): _____ Time: _____

Reply email with phone # received (Date): _____ Time: _____

No reply email received: no response (nr)

Second attempt (if necessary)

PD email response sent (Date): _____ Time: _____

Reply email with phone # received (Date): _____ Time: _____

No reply email received: no response (nr)

If phone contact:**First attempt:**

PD call back (Date): _____ Time: _____

Outcome (circle one): reached person left message

If reached person, continue to screening form below:

Second attempt:

PD call back (Date): _____ Time: _____

Outcome (circle one): reached person left message

If reached person, continue to telephone script.:

How did the individual hear/read about the study? _____

Enrollment Form

If eligible, Eligibility # (EID): _____

Study appointment information:**Initial Baseline Visit:**

Appointment Date _____ Time _____ Location _____

Salivary Data Collection Visit:

Appointment Date _____ Time _____ Location _____

Appendix E

1. Study Consent Form
2. Stand-alone HIPAA Form
3. Diagnosis Confirmation Note

Study Consent Form

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: Perceived Stress, Salivary Cortisol and Depression in Adults with Postconcussion Syndrome; A Pilot Study

VCU IRB NO.: #HM20009108

INVESTIGATOR: Victoria Menzies, PhD, RN, PMHCNS-BC, FAAN

STUDENT INVESTIGATOR: Christine Huson, MSN, RN

This consent form contains important information to help you decide whether to take part in a research study. The student investigator will explain this study to you. If any information contained in this consent form is not clear, please ask the student investigator to explain any information that you do not fully understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

Please keep in mind:

- Being in a study is voluntary- your choice.
- If you join this study, you can still stop at any time.
- No one can promise that a study will help you.
- Do not join this study unless all of your questions are answered.

After reading and discussing the information in this consent form you should know:

- Why this research study is being done;
- What will happen during the study;
- Any possible benefits to you;
- The possible risks to you;
- Other options you could choose instead of being in this study;
- How your personal health information will be treated during the study and after the study is over;
- Whether being in this study could involve any cost to you; and
- What to do if you have problems during the study or questions about this study.

Please read this consent form carefully.

PURPOSE OF THE STUDY

The purpose of this research study is to learn more about the relationships between perceived stress; cortisol, a hormone related to stress; and symptoms such as distressed mood that might occur among persons with a diagnosis of postconcussion syndrome, also known as PCS. To better understand a possible relationship between these variables, we are inviting adults 21 years of age and older, who have been diagnosed with PCS to participate in this study. There will be up to 60 adults (male and female) from the Roanoke and Richmond, Virginia area who will be participating in this study. You are being asked to participate in this study because you are an adult who has been diagnosed with postconcussion syndrome.

DESCRIPTION OF THE STUDY AND YOUR INVOLVEMENT

If you decide to be in this research study, you will be asked to sign two copies of this consent form after you have had all your questions answered and understand what will happen to you during the study. One copy of this informed consent will be given to you and one retained by the PI. After you have agreed and signed the informed consent forms to participate in the study, you will be asked to provide proof of your diagnosis of PCS with either a note from your healthcare provider or a print out of your diagnosis from your medical records. If that is not possible, you will be asked to sign diagnosis confirmation form permitting the student investigator to ask your healthcare provider for confirmation of PCS diagnosis. If contacting your provider, we will make a copy of the diagnosis confirmation document that you have signed and we will send it to your identified healthcare provider with a letter from us asking for confirmation of a diagnosis of PCS. If you agree to participate in this study and after you have signed the informed consent forms, you will be assigned an identification number to which all of your information will be confidentially linked.

Volunteers who agree to participate in this study will be asked to meet two times for study appointments. The first study appointment will take approximately 60 minutes and the second study appointment approximately 5 minutes.

During your first study appointment and after you have agreed and signed an informed consent form to participate in the study, you will be asked to complete questions related to your health history and demographic background. You will be then be asked questions regarding how you think about or experience stress as well as questions related to any feelings of sadness or depression you might have experienced in the past week. For example, you will be asked to rate how often "In the past week [you] felt depressed". You may choose not to answer questions about which you are uncomfortable.

Following this initial study appointment, there will be one more step to the collection of data and that would be asking you to collect a sample of your saliva during the following week (within 7 days) of your first study appointment. This one extra step will involve asking you to collect a sample of your saliva, using a simple cotton tip swab and storing it until we can retrieve it. We provide all the needed materials and instructions at your first study appointment so as to keep it as simple as possible for you. We will ask you to collect a one-time sample of your saliva 30 minutes after you wake up in the morning. Because this sample is to collect a hormone related to stress that is present in saliva, we will ask that you collect the sample after a normal or routine evening and night of sleep. We will arrange with you to send a text or phone reminder to help you remember to collect this. After you collect the saliva sample, we will ask that you apply a label recording the date and time of collection only. You will place the swab of saliva sample in the bag that will come with the pre-assembled kit and once sealed, place in a safe space in your home freezer. After you collect the sample of saliva, we ask that you notify the student investigator at a designated, confidential telephone number that we will provide. We will work with you at that time to arrange a convenient time for retrieving this sample from you.

We will use this saliva to analyze a stress hormone called cortisol. Our study plan is to compare the level of this stress hormone in your body to the answers you provide on the questionnaires we will be giving you.

RISKS AND DISCOMFORTS

We do not expect anyone to be harmed by this study any more than they would be in daily life. There may, however, be some brief discomfort when answering questions about stress or feelings related to mood. Some of the questions you will be asked are personal and could make you feel uncomfortable. If there are questions that you do not wish to answer, you may skip those questions. There is also a potential risk for loss of confidentiality. We will minimize this risk by storing your data and samples as securely as possible.

BENEFITS TO YOU AND OTHERS

This is not a treatment study and you may not get any direct benefit from participating in this study. The information we gain from this study will not have a direct effect on you. The information learned in this study may benefit others diagnosed with PCS in the future as study findings may help us to better understand how perceptions of stress or release of the hormone cortisol affect feelings such as depressed mood in people with PCS.

USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

Your privacy is important to us. During this study, we will ask you to share identifiable health information with us. This health information is Protected Health Information, so it will be protected like your other medical records are protected. We are asking you to authorize the release of your research information in the specific situations described below:

Types of Personal Health Information That May Be Collected by This Study

The following types of information may be used to conduct this research study:

- | | | |
|------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------|
| <input type="checkbox"/> Complete health record | <input checked="" type="checkbox"/> Diagnosis & treatment codes | <input type="checkbox"/> Discharge summary |
| <input type="checkbox"/> History and physical exam | <input type="checkbox"/> Consultation reports | <input type="checkbox"/> Progress notes |
| <input type="checkbox"/> Laboratory test results | <input type="checkbox"/> X-ray reports | <input type="checkbox"/> X-ray films / images |
| <input type="checkbox"/> Photographs, videotapes | <input type="checkbox"/> Complete billing record | <input type="checkbox"/> Itemized bill |
| <input type="checkbox"/> Information about drug or alcohol abuse | <input type="checkbox"/> Information about Hepatitis B or C tests | |
| <input type="checkbox"/> Information about psychiatric care | <input type="checkbox"/> Information about sexually transmitted diseases | |
- Other (specify): medical and psychiatric conditions, current medications, symptoms of PCS, self reported levels of stress and depression, and salivary cortisol.

Expiration of This Authorization

- This authorization will expire when the research study is closed, or there is no need to review, analyze and consider the data generated by the research project, whichever is later.
- This research study involves the use of a Data or Tissue Repository (bank) and will never expire.
- Other (specify):

Authority to Request or Release Protected Health Information

The following people and/or groups may request my Protected Health Information and the Principal Investigator may release my information to them:

- Health Care Providers at the VCUHS
- Research Collaborators and Study Staff
- Data Safety Monitoring Boards
- Data Coordinators
- Study Sponsor
- Institutional Review Boards
- Government/Health Agencies
- Others as Required by Law

Once your health information has been disclosed to anyone outside of this study, the information may no longer be protected under this authorization.

Right to Revoke Authorization and Re-disclosure

You may change your mind and revoke (take back) the right to use your Protected Health Information at any time. Even if you revoke this Authorization, the researchers may still use or disclose health information they have already collected about you for this study. If you revoke this Authorization you may no longer be allowed to participate in the research study. To revoke this Authorization, you must write to the Principal Investigator.

COSTS

There are no costs for participating in this study other than the time you will spend filling out questionnaires.

PAYMENT FOR PARTICIPATION

Upon conclusion of the second study visit, when we have collected the saliva sample from you, you will be given a \$10 Walmart gift card as compensation for your time.

ALTERNATIVES

The alternative to participating in this study is to not participate.

CONFIDENTIALITY

Potentially identifiable information about you will consist of the study questionnaires.

Your data will be de-identified by the assignment of an ID number, not names, and stored separately from research data in a locked research area. All personal identifying information will be kept in password protected files and these files will be deleted within 7 years of study completion. Other records, such as the screening forms and questionnaires, will be kept in a locked file cabinet in the research offices of VCU School of Nursing for 7 years after the study ends and will be destroyed at that time. Access to all data will be limited to study personnel.

We will not tell anyone the answers you give us; however, information from the study and the consent form signed by you may be looked at or copied for research or legal purposes by Virginia Commonwealth University. Personal information about you might be shared with or copied by authorized officials of the Department of Health and Human Services or other federal regulatory bodies.

If something we learn through this research indicates that you may intend to harm yourself or others, we are obligated to report that to the appropriate authorities.

What we find from this study may be presented at meetings or published in papers, but your name will not ever be used in these presentations or papers.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide to not participate in this study. Your decision not to take part will involve no penalty or loss of benefits to which you are otherwise entitled. If you do participate, you may freely withdraw from the study at any time.

Your decision to withdraw will involve no penalty or loss of benefits to which you are otherwise entitled.

Your participation in this study may be stopped at any time by the study staff without your consent. The reasons might include:

- the study staff thinks it necessary for your health or safety;
- you have not followed study instructions;
- the sponsor has stopped the study; or
- administrative reasons require your withdrawal.

QUESTIONS

If you have any questions, complaints, or concerns about your participation in this research, contact:

Victoria Menzies, PhD, RN, PMHCNS-BC, FAAN
Associate Professor
P.O. Box 980567
Richmond, VA 23298-0567
Phone: (804) 628-3381
E-mail: vsmentzies@vcu.edu

and/or

Christine Huson, MSN, RN
Student Investigator
101 Elm Ave, SE
Roanoke, VA 24013-2222
Phone: (540) 985-4028
E-mail: husonc@vcu.edu

The researcher/study staff named above is the best person(s) to call for questions about your participation in this study.

If you have any general questions about your rights as a participant in this or any other research, you may contact:

Office of Research
Virginia Commonwealth University
800 East Leigh Street, Suite 3000
P.O. Box 980568
Richmond, VA 23298
Telephone: (804) 827-2157

Contact this number to ask general questions, to obtain information or offer input, and to express concerns or complaints about research. You may also call this number if you cannot reach the

research team or if you wish to talk with someone else. General information about participation in research studies can also be found at

http://www.research.vcu.edu/human_research/volunteers.htm.

CONSENT

I have been given the chance to read this consent form. I understand the information about this study. Questions that I wanted to ask about the study have been answered. My signature says that I am willing to participate in this study. I will receive a copy of the consent form once I have agreed to participate.

Participant name printed

Participant signature

Date

Name of Person Conducting Informed Consent Discussion
(Printed)

Signature of Person Conducting Informed Consent Discussion

Date

Principal Investigator Signature (if different from above)

Date

This study is an initial exploration of relationships among stress, cortisol and depression. Study findings have the potential to provide a foundation for a future intervention study.

If you are interested in being contacted for future studies, we ask your permission to contact you. If you agree to be contacted, we ask the method of contact you prefer.

This permission to be contacted for future studies can be withdrawn at any time by contacting the following researchers:

Victoria Menzies, PhD, RN, PMHCNS-BC, FAAN

Associate Professor

P.O. Box 980567

Richmond, VA 23298-0567

Phone: (804) 628-3381

E-mail: vsmenzies@vcu.edu

and/or

Christine Huson, MSN, RN
Student Investigator
101 Elm Ave, SE
Roanoke, VA 24013-2222
Phone: (540) 985-4028
E-mail: husonc@vcu.edu

The decision to not be contacted for future studies does not affect your ability to participate in this current study.

_____ No, I do not wish to be contacted for future studies.

_____ Yes, I would like to be contacted for future studies. My preferred contact information is:

If yes, Participant name printed

Participant signature

Date

Stand Alone HIPAA Form

Title of Document:

“Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study”

Victoria Menzies, PhD, RN, PMHCNS-BC, FAAN
Associate Professor
P.O. Box 980567
Richmond, VA 23298-0567
Phone: (804) 628-3381
E-mail: vsmenzies@vcu.edu

Christine Huson, MSN, RN
Student Investigator
101 Elm Ave, SE
Roanoke, VA 24013-2222
Phone: (540) 985-4028
E-mail: husonc@vcu.edu

Date:

RE: IRB Protocol #HM20009108

Dear Potential Study Participant:

If you sign this document, you give permission for the student investigator to confirm your diagnosis of PCS through communication with your healthcare provider,

_____ (M.D.) (D. O.) (N.P.) (P.A.) at

Address line 1

Address line 2

Telephone Number

Your signature authorizes the student investigator to use or disclose (release) your health information that identifies you for the research study described below:

Perceived Stress, Salivary Cortisol and Depression in Adults with Postconcussion Syndrome; A Pilot Study

This study is being conducted to learn more about the relationship between perceived stress; cortisol, a hormone related to stress; and symptoms such as distressed mood that might occur among individuals with a diagnosis of PCS.

The health information that we may use or disclose (release) for this research includes information that you have a confirmed diagnosis of postconcussion syndrome.

The health information listed above may be used by and/or disclosed (released) to: Dr. Victoria Menzies, Principal Investigator.

_____ (M.D.) (D.O.) (N.P.) (P.A.) is required by law to protect your health information.

By signing this document, you authorize _____, (M.D.) (D.O.) (N.P.) (P.A.) to disclose (release) your health information for this research.

Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Please note that:

- You do not have to sign this Authorization, but if you do not, you may not be eligible to participate in this study
- You may change your mind and revoke (take back) this Authorization at any time, except to the extent that _____ (M.D.) (D.O.) (N.P.) (P.A.) has already acted based on this Authorization.

To revoke this Authorization, you must write to: Victoria S. Menzies PhD, RN, FAAN, 1100 East Leigh Street, P.O. Box 980567 Richmond, VA 23298-0567

- Your health information will be used or disclosed when required by law.
- Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, and conducting public health surveillance, investigations or interventions.
- No publication or public presentation about the research described above will reveal your identity.
- If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

This Authorization does not have an expiration date.

Printed name of participant

Signature of participant

Date

Sincerely,



Victoria Menzies, PhD, RN, FAAN
Associate Professor

Diagnosis Confirmation Note

Victoria Menzies, PhD, RN, FAAN
 Associate Professor
 P.O. Box 980567
 Richmond, VA 23298-0567
 Phone: (804) 628-3381
 E-mail: vsmenzies@vcu.edu

Christine Huson, MSN, RN
 Student Investigator
 101 Elm Ave, S.E.
 Roanoke, VA 24013-2222
 Phone: (540) 985-4028
 E-mail: husonc@vcu.edu

Date:

(Healthcare Provider Name)
 (Address)
 (City State Zip)

Re: Request from your patient (patient's name), regarding IRB Protocol #**HM20009108**

Dear <<HCP >>

We are conducting a study titled, "Perceived Stress, Salivary Cortisol and Depression in Adults with Postconcussion Syndrome; A Pilot Study".

Your patient, (<<patient's name>>), has volunteered for this study, if (<<she/he>>) meets the inclusion criteria. One criterion for inclusion is a confirmed diagnosis of postconcussion syndrome from the patient's healthcare provider. Attached is a HIPAA-approved signed authorization letter from <<patient name>>, requesting that you confirm, for study purposes, (<<her/his>>) diagnosis of postconcussion syndrome.

Would you please complete and sign the information below? You may return it to the Principal Investigator, at Virginia Commonwealth University School of Nursing at the HIPAA approved confidential fax number (804) 828-2487. Thank you.

Sincerely,



Victoria Menzies, PhD, RN, FAAN

Patient's Name: _____

Diagnosis: _____

Date of Diagnosis: _____

Healthcare provider's Signature:

Today's Date:

Appendix F

1. Demographic Form and Medical History
2. Rivermead Post Concussion Symptoms Questionnaire
3. Perceived Stress Scale
4. Center for Epidemiologic Studies Depression Scale
5. PROMIS Emotional Distress Depression Short Form
6. Salivary Cortisol Instruction

Demographic Form and Medical History

Stress, cortisol and depression in Adults with PCSSubject ID: Time: **Demographic Form****Directions: Please complete the following information.**

1. Age: _____

2. What is your ethnicity?

Hispanic or Latino _____

Not-Hispanic or Latino _____

3. What is your race?

American Indian or Alaska Native _____

Asian _____

Native Hawaiian or Other Pacific Islander _____

Hispanic or Latino _____

White _____

Do not wish to answer _____

4. Current Relationship Status:

Living with a partner _____

Married _____

Single, and never been married _____

Divorced/Separated _____

Widow/Widower _____

5. What date did your head injury occur?

_ / _ / _ _ _ _

6. What date were you diagnosed with Postconcussive Syndrome?

_ / _ / _ _ _ _ (month/day/year) j

7. Please select your household income level

Less than \$14,000 _____

\$14,000 – 24,999 _____

\$25, 000 -34,999 _____

\$35,000 -49.000 _____

50.000 or more _____

8. Please list any medical and/or psychiatric illness that you have experienced (such as heart disease, diabetes, depression).

Please fill out your medication information on the following page:

Rivermead Post Concussion Symptoms Questionnaire

SID: _____

Date: _____

The Rivermead Post-Concussion Symptoms Questionnaire

After a head injury or accident some people experience symptoms which can cause worry or nuisance. We would like to know if you now suffer from any of the symptoms given below. As many of these symptoms occur normally, we would like you to compare yourself now with before the accident. For each one, please circle the number closest to your answer.

0 = Not experienced at all
1 = No more of a problem
2 = A mild problem
3 = A moderate problem
4 = A severe problem

Compared with **before** the accident, do you **now** (i.e., over the last 24 hours) suffer from:

Headaches.....	0	1	2	3	4
Feelings of Dizziness.....	0	1	2	3	4
Nausea and/or Vomiting	0	1	2	3	4
Noise Sensitivity, easily upset by loud noise	0	1	2	3	4
Sleep Disturbance	0	1	2	3	4
Fatigue, tiring more easily	0	1	2	3	4
Being Irritable, easily angered	0	1	2	3	4
Feeling Depressed or Tearful.....	0	1	2	3	4
Feeling Frustrated or Impatient.....	0	1	2	3	4
Forgetfulness, poor memory	0	1	2	3	4
Poor Concentration.....	0	1	2	3	4
Taking Longer to Think	0	1	2	3	4
Blurred Vision	0	1	2	3	4
Light Sensitivity, Easily upset by bright light	0	1	2	3	4
Double Vision.....	0	1	2	3	4
Restlessness	0	1	2	3	4

Are you experiencing any other difficulties?

1. _____ 0 1 2 3 4

2. _____ 0 1 2 3 4

Perceived Stress Scale

SID: _____

Date _____

Perceived Stress Scale

The questions in this scale ask you about your feelings and thoughts **during the last month**. In each case, you will be asked to indicate by circling *how often* you felt or thought a certain way.

0 = Never
1 = Almost Never
2 = Sometimes
3 = Fairly Often
4 = Very Often

1. In the last month, how often have you been upset because of something that happened unexpectedly?..... **0 1 2 3 4**
2. In the last month, how often have you felt that you were unable to control the important things in your life? **0 1 2 3 4**
3. In the last month, how often have you felt nervous and “stressed”?**0 1 2 3 4**
4. In the last month, how often have you felt confident about your ability to handle your personal problems? **0 1 2 3 4**
5. In the last month, how often have you felt that things were going your way?..... **0 1 2 3 4**
6. In the last month, how often have you found that you could not cope with all the things that you had to do? **0 1 2 3 4**
7. In the last month, how often have you been able to control irritations in your life?..... **0 1 2 3 4**
8. In the last month, how often have you felt that you were on top of things?. **0 1 2 3 4**
9. In the last month, how often have you been angered because of things that were outside of your control?..... **0 1 2 3 4**
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them? **0 1 2 3 4**

Center for Epidemiologic Studies Depression Scale

	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of the time (3-4 days)	Most or all of the time (5-7 days)
During the past week:				
1) I was bothered by things that usually don't bother me	0	1	2	3
2) I did not feel like eating; my appetite was poor	0	1	2	3
3) I felt that I could not shake off the blues even with help from my family and friends	0	1	2	3
4) I felt that I was just as good as other people	0	1	2	3
5) I had trouble keeping my mind on what I was doing	0	1	2	3
6) I felt depressed	0	1	2	3
7) I felt that everything I did was an effort	0	1	2	3
8) I felt hopeful about the future	0	1	2	3
9) I thought my life had been a failure	0	1	2	3
10) I felt fearful	0	1	2	3
11) My sleep was restless	0	1	2	3
12) I was happy	0	1	2	3
13) I talked less than usual	0	1	2	3
14) I felt lonely	0	1	2	3
15) People were unfriendly	0	1	2	3
16) I enjoyed life	0	1	2	3
17) I had crying spells	0	1	2	3
18) I felt sad	0	1	2	3
19) I felt that people disliked me	0	1	2	3
20) I could not get "going"	0	1	2	3

PROMIS Emotional Distress Depression Short Form

PROMIS Item Bank v1.0 – Emotional Distress – Depression–Short Form 8a

Emotional Distress – Depression – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days...

		Never	Rarely	Sometimes	Often	Always
EDDEP04 1	I felt worthless	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDDEP06 2	I felt helpless	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDDEP29 3	I felt depressed	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDDEP41 4	I felt hopeless	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDDEP22 5	I felt like a failure	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDDEP36 6	I felt unhappy	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDDEP05 7	I felt that I had nothing to look forward to .	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDDEP09 8	I felt that nothing could cheer me up.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Salivary Cortisol Instructions

Salivary Cortisol Sampling Instructions

Before Sample Collection

- Avoid foods with high sugar or acidity, immediately before sample collection;
- Document consumption of alcohol, caffeine, nicotine, and prescription/over-the-counter medications
within the prior 12 hours.
- Avoid steroid-based anti-inflammatory medications.
- Document vigorous physical activity and the presence of oral diseases or injury.
- Do not eat a major meal within 60 minutes of sample collection.
- Rinse mouth with water to remove food residue and **wait at least 10 minutes** after rinsing to avoid sample dilution before collecting saliva.

How to collect the sample

- Remove SOS from outer packaging and place in mouth.
- Keep SOS in place for 1-2 minutes to ensure that it is saturated (Do not move around in the mouth).
- Place SOS into the swab storage basket insert (upper portion of the tube).
- Replace cap and snap securely onto tube.

After Sample Collection

- Record the time and date of collection.
- Freeze samples immediately
- Samples visibly contaminated with blood should be recollected. Notify student investigator to obtain new kit.