U.S. MILITARY HEALTH: THE EPIDEMIOLOGY OF OCCUPATIONAL RISK FACTORS AND LONG-TERM HEALTH ACROSS THE LIFE-COURSE

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DEDICATION

To Cynthia Janak

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U.S. military service is associated with both health promoting (e.g. physical activity) and health compromising (e.g. psychological trauma) factors that influence health across the life-course. Therefore, understanding how military service may affect the long-term physical, psychological, and social health of service members and veterans is of public health importance. This dissertation (1) investigated the change in persistent post-traumatic stress disorder (PTSD) and post concussive symptoms (PPCS) among patients diagnosed with mild traumatic brain injury seen at a major U.S. military treatment facility from 2008-2013, (2) developed clinical prediction equations of persistent symptom change with predictor variables of interest, and (3) compared the prevalence of metabolic syndrome among veterans and civilians receiving medical evaluations at the Cooper Clinic from 1970-2013.

Paired t-tests and mean standardized differences were calculated among 257 patients to evaluate pre- to post-treatment symptom change. Results indicated that the multidisciplinary treatment program was associated with a resolution of global and domain specific persistent PTSD and PPCS. The same sample of 257 patients was used to explore

prediction equations of persistent symptom change and clinically meaningful PTSD treatment response. Results from prediction equations indicated that pre-treatment PPCS symptom burden and pre-treatment PTSD diagnosis were the only clinically meaningful predictors identified influencing post-treatment PPCS. Pre-treatment PTSD symptom burden was the only clinically meaningful predictor identified influencing post-treatment PTSD symptom burden or clinically meaningful PTSD treatment response.

Among a sample of 64,220 civilians and 1,250 veterans, the prevalence of metabolic syndrome and individual metabolic syndrome risk factors were compared. Prevalence ratios using generalized linear models were reported after adjusting for confounders. Veterans reported a lower prevalence of metabolic syndrome and two of the individual metabolic syndrome risk factors (i.e. low HDL-C and high triglyceride levels). Conversely, veterans reported a higher prevalence of one metabolic risk factor (i.e. large waist circumference).

In conclusion, evidence from this research indicates that the multidisciplinary treatment program was associated with resolution of persistent symptoms attributed to mild traumatic brain injury. Furthermore, results support existing research suggesting that a treatment approach addressing comorbidities such as PTSD is important in order to meet the needs of patients with persistent symptoms. Lastly, this research potentially supports a veteran resiliency theory suggesting that a subgroup of veterans view their military experience as a positive influence on their life that was key to instilling health promoting rather than health compromising behaviors associated with a poor metabolic risk profile.

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BACKGROUND

Introduction: Overview and Rationale for the Proposed Studies

During the first part of the 20th century, the United States (U.S.) Armed Forces became both a national institution and an occupation[1]. Membership in one of the services provides occupational benefits such as monetary compensation and specialized training; however, the norms and values of the U.S. Armed Forces also require that service members be prepared for self-sacrifice and service to their country. This includes potential exposure to a wide range of deployment-related occupational risks such as combat-related physical injuries and prolonged psychological stress. Military service also confers non-deployment related risks such as family disruption due to frequent job-relocation[2], injuries during physical training[3,4], and an occupational environment that has historically promoted negative health behaviors such as alcohol misuse[5-7] and cigarette smoking[8-10]. Thus, U.S. military service is associated with both benefits and risks that have the potential to alter long-term physical, psychological, and social health across the life-course of U.S. veterans[11-15].

The purpose of this dissertation was to examine occupational risk and protective factors associated with U.S. military service that can impact health across the life-course (Figure 1-1). The first two journal articles focused on mild Traumatic Brain Injury (mTBI), which is considered by some to be the signature wound of the current conflicts in Iraq and Afghanistan[16]. Mild TBIs are a specific micro-level military service factor that can impact the health of active-duty service members and veterans across their life-course.

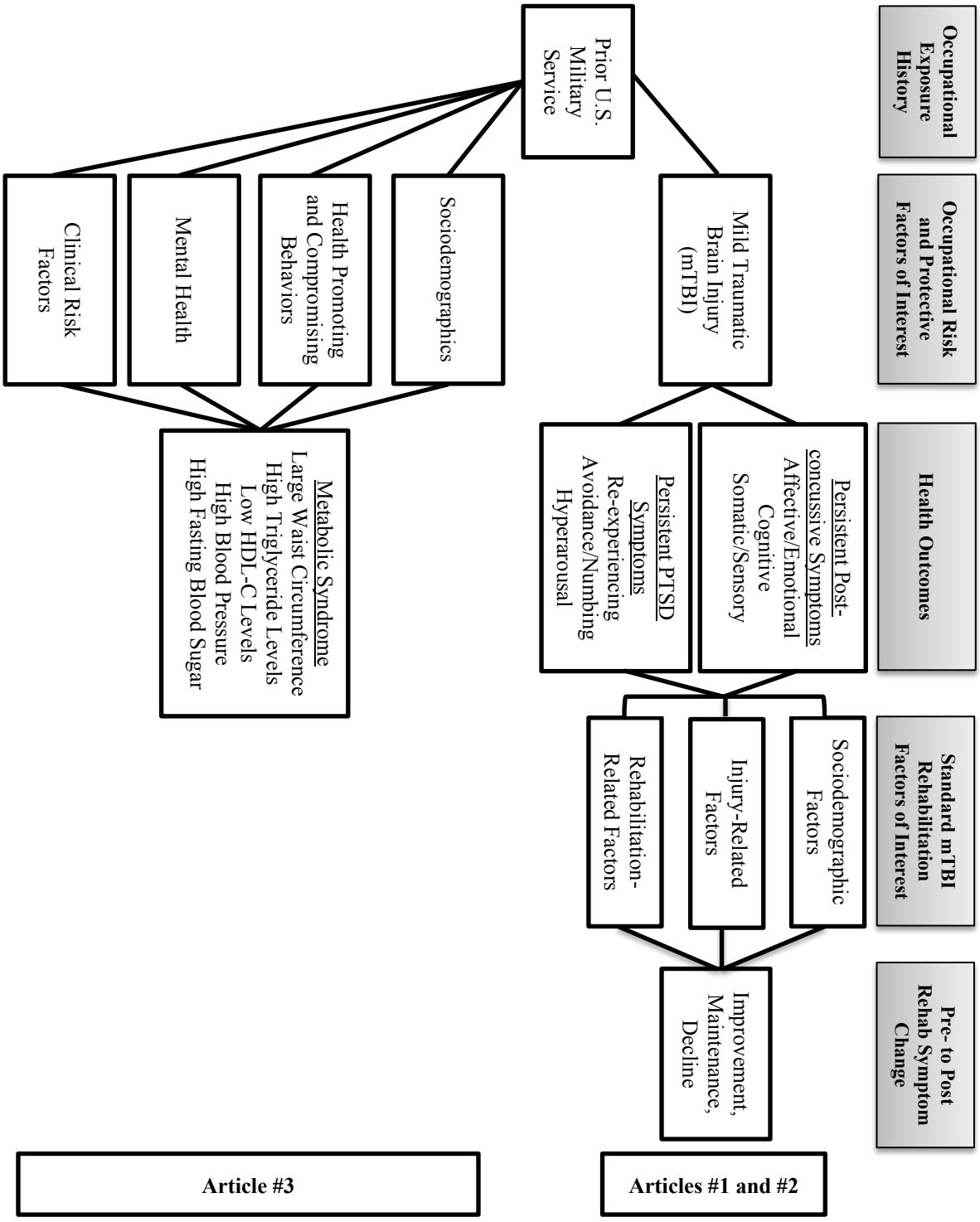


Figure 1-1. Overall U.S. Military Health Structural Framework for the Proposed Studies

The third journal article explores broader macro-level factors that can increase the long-term risk of developing common morbidities among persons with a history of military service compared with civilians with no prior military service. More specifically:

The *first journal article* describes military patients who received mTBI treatment for self-reported persistent post concussive and post-traumatic stress disorder (PTSD) symptoms at a major U.S. military hospital; describes the pre- to post-treatment change in these symptoms; and identifies sociodemographic-, injury-, and rehab-related factors associated with symptom change following successful completion of mTBI rehab.

The *second journal article* builds on the first by developing clinical prediction equations of persistent post concussive and PTSD pre- to post-treatment symptom change based on sociodemographic-, injury-, and rehabilitation-related variables of interest. It also explores a prediction equation of PTSD treatment response (yes/no).

The *third journal article* explores the association of sociodemographic variables, health compromising behaviors, health promoting behaviors, history of neuropsychiatric outcomes, and clinical variables associated with metabolic syndrome by comparing men reporting prior military service to men with no prior military history from a large cohort study.

Journal Articles 1 and 2: Mild Traumatic Brain Injury as a Micro-level Factor

Traumatic Brain Injuries (TBIs) and other non-fatal injuries have occurred in American military operations since the Revolutionary War began in 1775[17]. However, until recently, prevention of non-combat related disease and infections, the leading causes of death in all military conflicts prior to World War II, was the public health priority. As a result of advances in immunization programs and hygiene[18,19] the current priority is now injuries. Because of the relatively high incidence and potential for serious long-term consequences, TBIs garner international attention as a signature wound[16] of the recent conflicts in Iraq and Afghanistan. Because mild traumatic brain injury (mTBI), also known as concussion, represents more than 3/4ths of all TBIs among U.S. active duty service members[20] and thus warrants special attention as a focus of efforts to improve the health of U.S. warfighters.

Deployment-related research conducted during the wars in Iraq and Afghanistan greatly increased knowledge about the effects of mild traumatic brain injury. We now know that mild traumatic brain injury (mTBI) may have been the cause of the "shell shock"[21] experienced by service members in World War I (WWI). However, many of these veterans also experienced combat-related psychological trauma that can result in post-traumatic stress disorder or PTSD. Therefore, the physical (e.g. vision and hearing difficulty), somatic (e.g. nausea), emotional/behavioral (e.g. feeling anxious and depressed), and cognitive (e.g. poor concentration and slowed thinking) symptoms attributed to mTBI may have been caused by mTBI, PTSD or a combination of the two because many of the symptoms resulting from

mTBI and PTSD are the same. Thus, many modern studies of deployment-related mTBI have investigated the overlap of mTBI symptoms with those of PTSD.

For the majority of service members, with mTBI, the symptoms will resolve within 3 months,[22] but for a small yet significant proportion these symptoms will persist long-term. Persistent symptoms are associated with a variety of outcomes including chronic daily headaches[23], visual[24] and auditory impairment[25], a minimal decline in cognitive functioning[22,26], suicide[27], substance abuse[28,29], and impaired social functioning[30] (e.g. employment, quality of life, social relationships). There is suggestive evidence that mTBI is associated with long-term morbidities (i.e. Chronic Traumatic Encephalopathy, Alzheimer's type dementia, Parkinsonism)[31-33], especially among service members with a history of multiple mTBIs. Therefore, sustaining an mTBI has the potential to disrupt a service member's health and social functioning across the life-course. Because we still know relatively little about the trajectory and long-term impact of persistent post concussive and PTSD symptoms and the effectiveness of treatment for them, additional studies are warranted.

Journal Article 3: Military Experience as a Macro-Level Factor

At the macro-level, a variety of other military related occupational factors (e.g. pay raise, educational reimbursement, building leadership skills, self-efficacy, job re-location, combat exposure) may positively or negatively affect the physical, psychological, and social health of service members across the life-course. This macro-level perspective examines the

entire ecosystem of occupational factors that affect health across the life-course rather than a specific health outcome from one such factor (e.g. deployment-related mTBI) used in the micro-level approach. Some studies indicate that military service may be both a risk and a protective factor[13,34] for select morbidities[15,35,36] and mortality[14,37-39]. As a protective exposure, the military provides an economic and social support system that may promote economic independence, stable family formation, educational opportunities, responsible membership in communities[40-42], and health promoting behaviors such as physical activity[43,44]. Conversely, prior military service may increase the risk of criminality, marital difficulties, and impede economic achievement[13]. Prior military service is also associated with an increased risk of health compromising behaviors (i.e. substance abuse[45] and smoking[46,47]).

A growing body of literature has investigated the relationship between combat exposure and changes in veterans' health and social functioning across the life-course[12,48]. Combat exposure may result in long-term functional limitations and/or chronic pain from physical injuries[15,49], as well as psychological impairment associated with persistent anxiety and/or traumatic stress[50-52]. However, desirable effects include increased resilience that can mitigate the negative psychological effects of such exposure[53,54]. Thus, the impact of prior military service on health and functioning across the life-course is complex and remains unclear.

Many of the risk factor and protective factors associated with a history of military service, including negative health behaviors such as smoking and lack of physical activity, may influence the development of specific health conditions. Metabolic syndrome[55-61], a group of individual metabolic risk factors associated with cardiovascular disease, type 2 diabetes mellitus, select cancers, and all-cause mortality in the U.S.,[62-65] is one such condition that may be affected by lifelong health behaviors. With regard to smoking, military service may precipitate the adoption of this negative behavior in young adulthood[66-68], a critical developmental period for the adoption of behaviors that continue across the life-course. On the other hand, the rigorous training associated with military service may lead to high levels of physical activity, a possible health behavior that may also persist across the life course[69-71]. Because relatively little is known about the influence of lifelong habits on the risk of metabolic syndrome among former military service members compared with civilians, additional research is needed.

Public Health Significance

The Iraq and Afghanistan wars, the longest in American history, have contributed greatly to the number of deployed U.S. service members and number of veterans. As of September and October 2013 respectively, the estimated number of living U.S. veterans was approximately 22 million[72] and the number of active duty military personnel was 1.38 million[73]. The total expenditure of veteran benefits from various medical programs was $46.9 billion dollars in 2010 and the compensation for service-connected disability was $38 billion

dollars[74]. Moreover, compared to costs in 1990, the total cost of medical expenditures and service-connected disability compensation had more than quadrupled by 2010.

With regard to mTBI, the need for treatment and rehabilitation of service members returning home with persistent symptoms contributed to these growing costs. In 2008, the federal government considerably increased the disability benefits veterans received specifically related to mTBIs from a maximum of approximately $120 to $600 per month[75]. The estimated increase in the annual cost of all TBI related benefits due to this increase in monthly mTBI benefits is approximately $120 million dollars through 2017. Furthermore, the U.S. Department of Veterans Affairs (VA) is proposing a change in regulations to improve veteran access to benefits and healthcare by adding five new medical conditions to the current list of diseases automatically considered service-related based on current scientific evidence associating TBI with specific adverse health outcomes such as symptoms of Parkinson's disease[76]. Based on this proposed change in regulation, VA hospitals treating and rehabilitating veterans with mTBI would experience a significant additional increase in the burden of care and cost for these veterans.

Service members and veterans with persistent mTBI and PTSD symptoms are currently receiving treatment to manage their symptoms and to facilitate their successful reintegration into military and civilian life[77]. However, the literature describing this patient population, evaluating the effectiveness of these treatment and rehabilitation methods, or identifying specific predictors of successful symptom resolution is currently limited.

Addressing these limitations and understanding whether treatment is effective in reducing post-concussive and PTSD symptoms, which symptoms are affected, and identifying characteristics of patients that could predict treatment success or failure is vital to meeting the needs of patients with these persistent symptoms.

With regard to metabolic syndrome, the annual estimated chronic condition-attributable costs per VA patient are also high for morbidities associated with this condition such as cancer ($12,065), stroke ($7,794), heart conditions ($5,590), diabetes ($2,311), and hypertension ($929) in 2008 dollars[78]. Furthermore, the change in total VA spending from 2000 (adjusted to 2008 dollars based on the consumer price index) to 2008 increased dramatically for cancer ($1.5 billion), stroke ($209.8 million), heart conditions ($811.7 million), diabetes ($820.5 million), and hypertension ($737.6 million). Thus, identifying modifiable health behaviors and treatments for health outcomes among older veterans is vital to curbing these costs and improving quality of life.

Although considerable research has focused on the health effects of military service, studies that directly compare military service members and civilians with regard to sociodemographic characteristics, potential health promoting and health compromising behaviors, neuropsychiatric outcomes, and clinical risk factors are lacking. The greatest need is for studies that take the next step to examine whether these differences between civilians and prior military service members are associated with risk or protection from long-term chronic health outcomes. These results could help inform efforts to promote healthy

behaviors and reduce health-compromising behaviors among an aging U.S. veteran population and among active duty military personnel.

Specific Aims

The goal of this doctoral dissertation was to address these gaps in the literature by investigating factors associated with prior military service that impact health across the life-course. This included the micro-level impact of persistent post-concussive and PTSD symptoms reported following mTBI(s) as well as the macro-level occupational risk and protective factors associated with metabolic syndrome. To accomplish this, two data sets were used. The first was from patients with persistent post-concussive and PTSD symptoms attending the San Antonio Military Medical Center (SAMMC) TBI Rehabilitation Clinic. These data were used for journal articles #1 and #2 described in the following specific aims:

(1) To examine the pre- to post change in self-reported post-concussive and post-traumatic stress symptoms, and to explore potential factors associated with symptom resolution among U.S. military service members and veterans with diagnosed mild traumatic brain injury completing an initial and discharge clinical evaluation during rehabilitation treatment at the San Antonio Medical Military Center Traumatic Brain Injury Clinic from 2008-2013.

(2) To explore prediction equations of pre- to post-treatment changes in (1) persistent post-concussive and post-traumatic stress disorder related symptomology, and (2) a prediction equation of clinically meaningful PTSD treatment response among U.S. military service members and veterans with diagnosed mild traumatic brain injury

completing an initial and discharge clinical evaluation during rehabilitation treatment at the San Antonio Medical Military Center Traumatic Brain Injury Clinic from 2008-2013.

The second data set is from a cohort of men seeking preventative medical services and agreeing to participate in the Cooper Clinic Longitudinal Study (CCLS). The CCLS is a prospective study of men and women who came to the Cooper Clinic (Dallas, Texas) for a fee for service preventive medical visit and agreed to enroll in the study. This data set was used for journal article #3 described in the third specific aim below:

(3) To compare the prevalence of metabolic syndrome among men reporting and not reporting prior military service, and to investigate the association of sociodemographic factors, health promoting behaviors, health compromising behaviors, neuropsychiatric outcomes, and clinical factors with metabolic syndrome.

LITERATURE REVIEW: JOURNAL ARTICLES 1 AND 2

For the reader's convenience, a review of TBI biomechanics and pathophysiology can be found in Appendix A, and a glossary of important terms can be found in Appendix D.

What is a Traumatic Brain Injury (TBI)?

TBI definition

TBI is an alteration in brain function, or other evidence of brain pathology, caused by an external force[79]. A more detailed definition that describes the complexity of TBI is as follows:

> TBI is a traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least one of the following clinical signs immediately following the event[77]:
>
> - Any period of loss of or a decreased level of consciousness (LOC)
> - Any loss of memory for events immediately before or after the injury (post-traumatic amnesia [PTA])
> - Any alteration in mental state at the time of the injury (e.g. confusion, disorientation, slowed thinking, etc.) (Alteration of consciousness/mental state [AOC])
> - Neurological deficits (e.g. weakness, loss of balance, change in vision, praxis, paresis/plegia, sensory loss, aphasia, etc.) that may or may not be transient
> - Intracranial lesion

Persons with a history of a blow or jolt to the head (external force) who experience any of the above signs and symptoms immediately or shortly afterwards can be said to have had a TBI *event*. Of note, TBI definitions, including for concussion/mTBI, vary considerably across studies[80,81].

TBI Severity

The criteria for categorizing TBI severity are summarized in Table 1-1. TBI severity is generally categorized based on the length of time the person experiences LOC, PTA, and/or AOC and is best assessed at the time of initial injury. According to the International Work Group on Demographics and Clinical Assessment of TBI[80], assessment of these neurological changes is necessary in order to differentiate concussions/mTBIs from more severe brain injuries. At the least severe end of the spectrum is mTBI in which AOC and PTA may be very brief, in some cases lasting only a few seconds or minutes. According to these more recent definitions, *loss of consciousness* is not necessary for a diagnosis of mTBI, and it can be diagnosed in persons with *alteration* of consciousness only.

The Glasgow Coma Scale score (GCS), a measure of the injured individual's responsiveness (e.g, ability to follow simple verbal commands), is commonly used to assess initial TBI severity[82]. GCS scores range from 8 to 15, with the highest scores indicating the least severe injuries. Persons with a concussion/mTBI typically have an initial GCS score ranging from 13 to 15. A score of 15 indicates that this scale identified no deficits, yet symptoms not assessed by the scale may still be present.

The terms concussion and mTBI are often used interchangeably with concussion being used more often in sports medicine and mTBI more prevalent in clinical medicine[83]. However, "concussion" is preferred because it refers to a specific injury event that may or may not be associated with persisting symptoms. Because both are used in the literature cited here, the term "concussion/mTBI" is used in this review.

Table 1-1: Severity of Brain Injury Stratification

Criteria	Mild/Concussion	Moderate	Severe
Structural imaging	Normal[1]	Normal or abnormal	Normal or abnormal
Loss of Consciousness (LOC)	0-30 min	>30 min and < 24 hours	> 24 hrs
Alteration of consciousness/mental state (AOC)	a moment up to 24 hrs	>24 hours. Severity based on other criteria	
Post-traumatic amnesia (PTA)	≤1 day	>1 and <7 days	> 7 days
Glasgow Coma Scale (best available score in first 24 hours)[2]	13-15	9-12	3-8

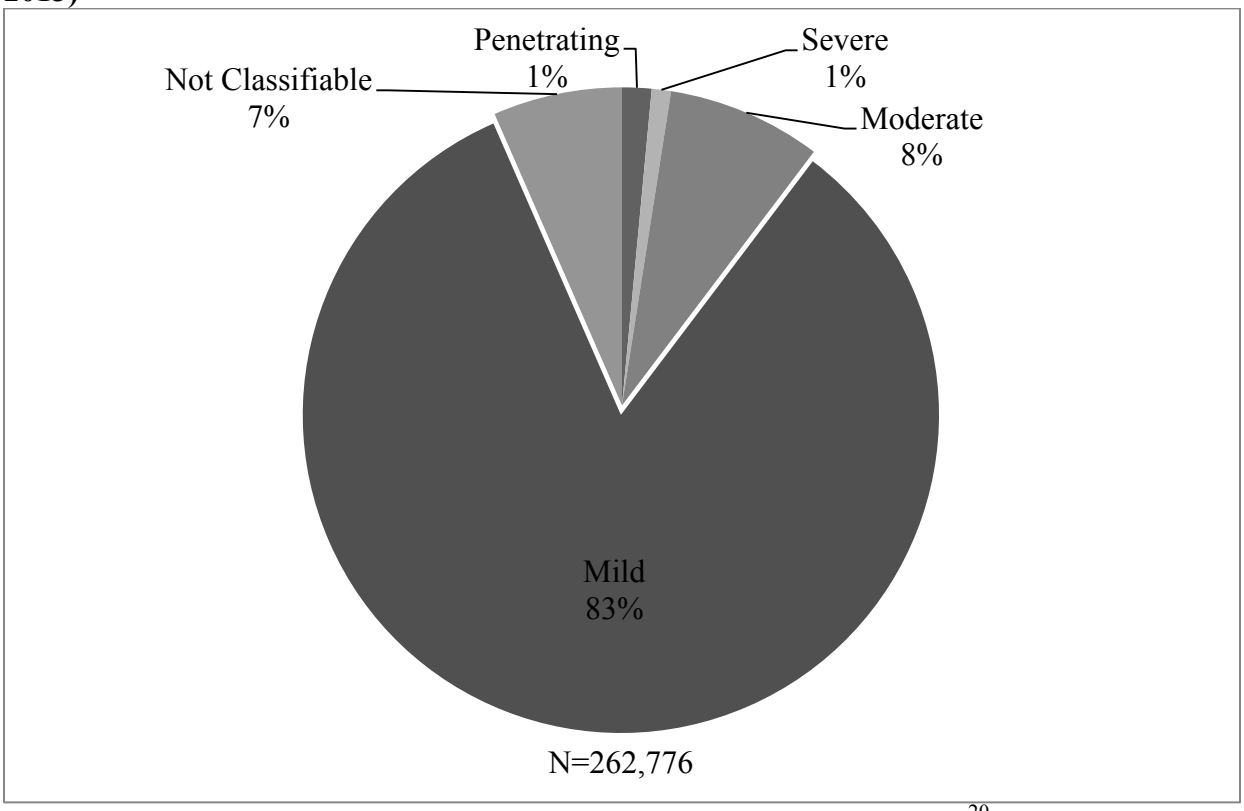
[1]Note that minor abnormalities possibly not related to the brain injury may be present on structural imaging in the absence of LOC, AOC, PTA; [2]Some studies report the best available Glasgow Coma Scale (GCS) score within the first 6 hours or some other time period.
Source: Va/DoD Clinical Practice Guideline for the Management of concussion/mTBI[77]

What is the distribution of TBIs by Severity in the U.S. Military?

The U.S. Department of Defense (DoD) Worldwide TBI Numbers Website reports that 262,776 TBIs have occurred among U.S. Service members around the world, including in Iraq and Afghanistan, since the beginning of 2001 using International Disease

Classification 9th Edition (ICD-9) codes to diagnose injury and assign severity[20]. The Website reported from 2001 through the first 2 quarters of 2013 that 224,261 (83.1%) of the incident TBIs were mild (Figure 2-1).

Figure 2-1. Percent of TBIs Among U.S. Service Members Stratified by Severity (2001-2013)



Source: Defense Medical Surveillance System, Theater Medical Data Store[20]

It is important to note that this number includes only medically diagnosed TBIs among US military personnel and includes all TBIs that occurred anywhere in the world, not just those associated with deployment to the war theater. This estimate for concussions/mTBIs among all TBIs in the U.S. military (83%) mirrors estimates for medically treated concussions/mTBIs (85%) among all TBIs in the U.S. civilian population[84].

The focus of the remaining review focuses specifically on concussions/mTBI for the following reasons: (1) the first two journal articles are restricted to patients with concussions/mTBIs, (2) the majority of TBIs in the civilian and military population are mild, and (3) concussions/mTBIs can be considered clinically and epidemiologically unique from moderate and severe TBIs[85].

How Frequent are concussions/mTBIs in the U.S. Military?

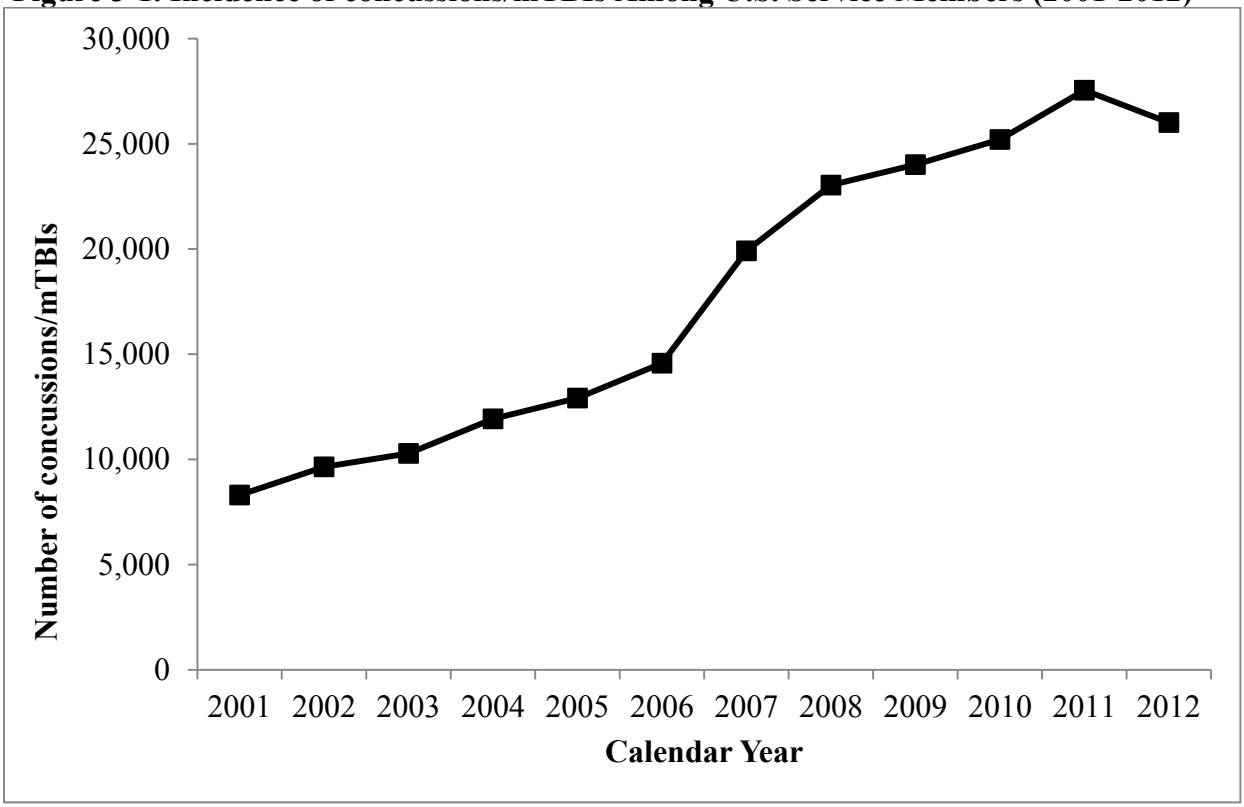
Incidence

The incidence of concussion/mTBI in the U.S. Military is defined as the number of new concussion/mTBI events within a specified time interval (e.g., annual) with symptoms that may or may not persist long-term. According to the DoD TBI Worldwide website, the annual incidence of medically diagnosed concussions/mTBI without knowing the total population at risk steadily increased from 8,306 in 2001 to 27,545 in 2011 before it began to decrease (n=26,011) in 2012 (Figure 3-1)[20]. Another study reported that concussions/mTBIs were the most common (60.6%) ICD-9 TBI diagnosis among TBI-related hospitalizations in fixed military treatment facilities from 2000-2011[86].

Information on the incidence of multiple concussions/mTBIs is limited; however, one study using data from provider-diagnosed concussion/mTBI of U.S. Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) military personnel that occurred in the combat setting reported that repeated concussions/mTBIs often occur within a short time period[87]. In fact, 20% of military personnel experienced a second event within 2 weeks of the first and

87% within 3 months. Number and timing of concussions/mTBIs is important because it may be associated with longer-term neurodegenerative outcomes such as chronic traumatic encephalopathy (CTE).

Figure 3-1. Incidence of concussions/mTBIs Among U.S. Service Members (2001-2012)



Source: Defense Medical Surveillance System, Theater Medical Data Store[20]

Prevalence

Prevalence of a history of concussion/mTBI refers to the number or percent of individuals who have "ever" experienced at least one concussion/mTBI "event" regardless of whether they have persisting symptoms or related disability. The prevalence of concussion/mTBI is currently not known due to limitations in the longitudinal surveillance of

service members. Prevalence estimates specific to a history of deployment-related concussion/mTBI range from 12%-23%[88-90].

Prevalence of "disability" from concussion/mTBI is defined as having had one or more concussion/mTBIs and living with persistent symptoms. Although no estimate has been reported specifically for mTBI/concussion, the prevalence of TBI requiring treatment for all OEF/OIF/Operation New Dawn(OND) veterans utilizing inpatient or outpatient care screened by the Veteran Health Administration from fiscal year 2009 to 2011 was 58,886 (9.6%)[91].

What are the External Causes of concussions/mTBIs?

External cause refers to the nature of how an injury occurred (e.g., motor vehicle crash or fall)[92]. The intent underlying the injury (intentional vs. unintentional), mechanism of injury (e.g. blast or explosion), and the object involved (e.g. gun), where appropriate, are important dimensions to report in order to fully capture the external cause of an injury. Among concussions/mTBIs treated in fixed military hospitals from 2000-2011, falls and motor vehicle crashes (40%) followed by unintentional gun/explosive incidents (26%) were the most frequent external causes of concussion/mTBI[86]. This is similar to the young and middle-aged civilian adult population in which motor vehicle crashes are the primary external cause of concussions/mTBIs[93].

What is the Setting?

The DoD Worldwide website does not report separately the incidence of concussion/mTBI for deployed vs. nondeployed service members but indicates that less than 20% of all TBIs combined occurred in a deployed setting[20]. In a separate study examining cause of injury records for concussion/mTBI patients treated in fixed military hospitals, only a minority (<5%) of the concussions/mTBIs were attributed to battle injuries sustained while deployed to the war theater[86]. This evidence further highlights the importance of non-combat related concussions/mTBI in the U.S. military.

What are the Acute Symptoms?

Acute symptoms of concussion/mTBI include physical, cognitive, and behavioral/emotional symptoms (Table 2-1). Based on results of civilian studies, cognitive impairment (e.g. deficits in speed of information processing, attention, and memory) is more common among persons with concussion/mTBI vs. healthy controls[94,95]. Persons with concussion/mTBI are also more likely than controls to report acute physical and behavioral/emotional symptoms[95,96]. The vast majority of persons with concussion/mTBI experience symptom resolution within the first 3 months post-injury[97,98].

Table 2-1. Acute (≤30 days) Post-Concussion/mTBI Related Symptoms

Physical Symptoms	Cognitive Symptoms	Behavioral/Emotional Symptoms
• Headache • Dizziness • Balance Disorders • Nausea • Fatigue • Sleep Disturbance • Blurred Vision • Sensitivity to Light • Hearing Difficulties/Loss • Sensitivity to Noise • Seizure • Transient Neurological Abnormalities • Numbness tingling	• Attention • Concentration • Memory • Speed of Processing • Judgment • Executive Control	• Depression • Anxiety • Agitation • Irritability • Impulsivity • Aggression

Source: Va/DoD Clinical Practice Guideline for the management of concussion/mTBI[77]

Which Acute Symptoms Persist Long-term for a Sub-group of Patients and Why?

Persistent Post-Concussive Symptoms (PPCS)

Persistent symptoms, i.e., beyond 3 months post-injury, are uncommon and according to one expert are experienced by less than 5% of all concussion/mTBI cases[22,99,100]. Among these cases sometimes referred to as the "miserable minority"[101], PPCS may be far from mild. For example, a recent case report described a 45-year old officer who was exposed to constant combat from 2006-2007 during OIF and sustained a blast-related concussion/mTBI. He reported worsening PPCS including problems with memory, attention, anger control and physical pain following the concussion/mTBI[102]. He also experienced severe functional impairments related to work performance and social relationships, which ultimately placed him on the temporary disability retirement list. It was approximately 2 years after sustaining

the concussion/mTBI before he reported an improvement in daily functioning after participating in a rehabilitation program with an emphasis on expectations of recovery; yet, he has still been unable to find post-military employment.

Cognitive Symptoms

Despite case reports and findings of substantial cognitive impairment during the acute post-injury period, recent well-designed studies show no measurable long-term effects of concussion/mTBI on cognitive functioning[26,103,104]. An example of one such study is a meta-analysis by Schretlen and Shapiro[26] that compared acute and long-term cognitive deficits between studies examining concussion/mTBI and moderate to severe TBI. The study reported that the magnitude of effect for moderate to severe TBI ($d= -0.74$) was considerably larger than for concussion/mTBI ($d= -0.24$) averaged across all follow-up periods. Further, the majority of cognitive deficits resolved completely within the first three months for concussion/mTBI; however, cognitive impairment persisted even years later for moderate to severe TBI. A more recent meta-analysis supports these results reporting a significant cognitive deficit ($d= -0.39$; $p<0.05$) within the first 7 days following concussion/mTBI; yet, no significant difference ($d= -0.07$; $p>0.05$) 3 months post-injury[103].

Studies of military service members and veterans report similar findings. For example, Lange and colleagues[105] found that military service members with uncomplicated concussion/mTBI (i.e. no identifiable intracranial lesion or depressed skull fracture on day-of-injury CT scan), complicated concussion/mTBI (i.e. presence of a visible intracranial

lesion or depressed skull fracture on day-of-injury CT scan), and moderate TBI evaluated within 6 months following the injury reported almost no significant differences on tests of neuropsychological performance (i.e. attention, memory, and intelligence). Therefore, the evidence to date indicates that acute cognitive deficits following concussion/mTBI typically resolve within the first 3 months[94].

Physical and Emotional/Behavioral Symptoms

No definitive evidence indicates that sustaining a concussion/mTBI causes persistent physical and/or emotional/behavioral symptoms because the true etiology of these symptoms cannot be disentangled from pre-morbid (e.g. demographics) or comorbid (e.g. PTSD, substance abuse, depression) conditions likely to contribute to these PPCS [85,106]. It is plausible that physical damage to the brain caused by a concussion/mTBI leads to distinct pathophysiologic events causing these PPCS, but causality has not been established to date[107].

Somatic Symptoms

Physical symptoms (e.g. sensitivity to light and hearing loss) are physiogenic, that is, they are caused by a complex pathophysiologic cascade of events following damage to the brain sustained during a concussion/mTBI. Somatic symptoms, which have a psychogenic or psychological origin, are the manifestation of physical symptoms such as headaches, nausea, and joint pain with an unknown medical pathology (i.e. not attributed to concussion/mTBI) usually attributed to psychological distress[108]. Traditionally, somatization of symptoms has

been described as either functional somatization or presenting somatization of physical symptoms[109]. Functional somatization is the *primary* manifestation of medically unexplained physical symptoms (i.e. with no known pathology) and presenting somatization is the manifestation of such symptoms *secondary* to psychological distress such as anxiety or depression.

Presenting somatization is of particular interest in the military population because service members deployed to the war theater commonly experience psychological distress. Somatic symptoms, which are often attributed to concussion/mTBI, can persist long-term but may be due to factors other than the mTBI/concussion. For example, one study surveying a large sample of soldiers 3 to 4 months post-deployment in Iraq found that those who self-reported mTBI/concussion with loss of consciousness (LOC) (i.e. a relatively more severe concussion) also reported significantly higher levels of somatic symptoms compared to soldiers with other non-concussion/mTBI injuries[89]. However, this finding was not significant after adjustment for comorbid psychiatric conditions, PTSD and depression. This highlights growing evidence indicating that persisting symptoms attributed to concussion/mTBI may at least in part be due to comorbid psychiatric conditions[110].

Psychogenic verse Physiogenic etiology of Persistent Post-concussive Symptoms

Whether the etiology of PPCS is psychogenic, physiogenic, or a combination of both[107] is currently the subject of debate. The evidence to date suggests that PPCS have a psychogenic etiology mediated by common comorbidities such as PTSD and depression

among service members deployed to the war theater[85,89,111]. However, this does not eliminate the possibility that there are subtle physiogenic factors contributing to PPCS currently difficult to distinguish with standard neuroimaging techniques. Lastly, there are both unique and overlapping regions of the brain involved in PTSD and concussion/mTBI supporting the hypothesis that that the etiology of PPCS is potentially both psychogenic and physiogenic[112].

Persistent Post-concussive Symptoms and Overlap with Other Comorbid Factors

The true causes of PPCS are difficult to disentangle because many of the effects of PPCS attributed to concussion/mTBI are the same as those that result from psychological distress caused by exposure to traumatic event(s) (Tables 3-1)[113]. Pre-concussion/mTBI patient characteristics [114], symptom exaggeration in the context of potential compensatory litigation[115-118], or misattribution of all negative symptoms to a recent trauma such as concussion/mTBI[119,120] can also confound the true association between concussion/mTBI and PPCS and should be included in studies of long-term concussion/mTBI outcomes. Because in contrast to more severe TBI and other observable trauma such as amputation no outward signs of physical injury or damage are associated with concussion mTBI, PPCS may be over-reported in an effort to validate the occurrence of the concussion/mTBI, especially among military personnel with co-occurring PTSD and depression[121]. This ultimately can lead to confusion and a misperception by patients regarding which symptoms they are expected to report to receive adequate care and how their symptoms will resolve overtime[122].

Table 3-1. Common Symptoms following Exposure to Trauma and the Overlap with PPCS*

Physical Symptoms	Cognitive Symptoms	Emotional Symptoms	Behavioral Symptoms
• Chills • Difficulty breathing • **Dizziness** • Elevated Blood Pressure • Fainting • **Fatigue** • Grinding Teeth • **Headaches** • Muscle Tremors • **Nausea** • Pain • Profuse Sweating • Rapid Heart Rate • Twitches • Weakness	• Blaming Someone • Change in Alertness • Confusion • Hyper-vigilance • Increased or Decreased Awareness of surroundings • Intrusive images • **Memory Problems** • Nightmares • **Poor Abstract Thinking** • **Poor Attention** • **Poor Concentration** • **Poor Decision-making** • **Poor Problem Solving**	• **Agitation** • **Anxiety** • Apprehension • Denial • Depression • Emotional shock • Fear • Feeling Overwhelmed • Grief • Guilt • Inappropriate Emotional Response • **Irritability** • Loss of Emotional Control	• Increased alcohol consumption • Antisocial Acts • Changes in activity • Change in communication • Change in Sexual Functioning • Change in Speech Pattern • Emotional Outbursts • Inability to Rest • Change in Appetite • Pacing • Startle reflex intensified • Suspiciousness • Social Withdrawal

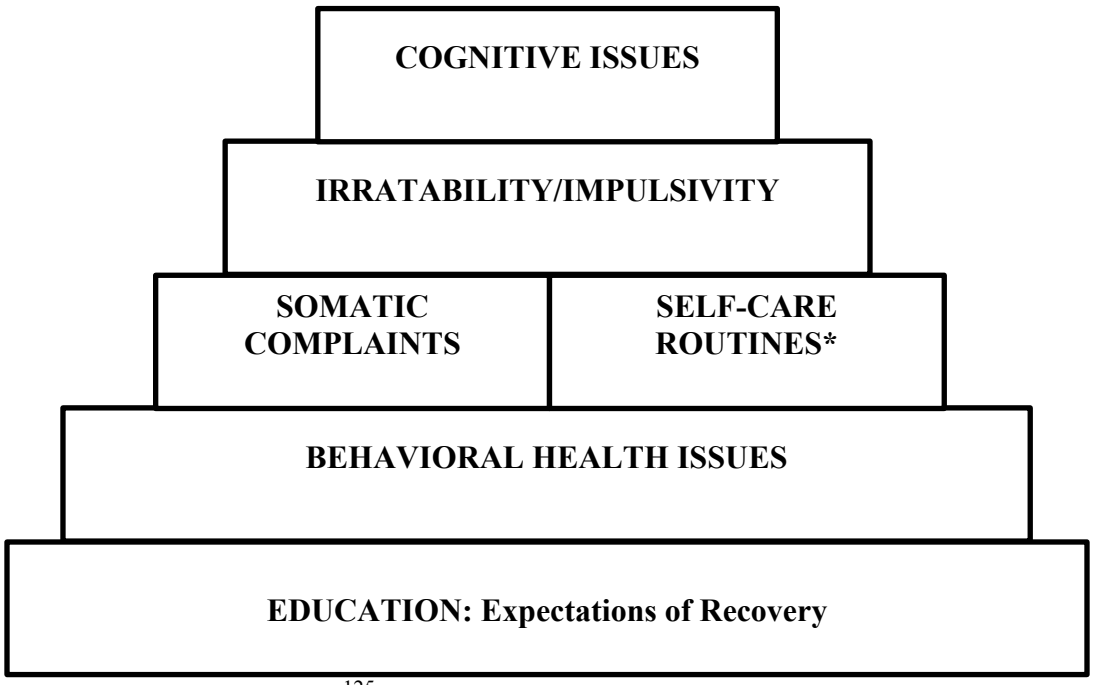
Source: Va/DoD Clinical Practice Guideline for Management of Post-Traumatic Stress[123]; ***Symptoms that are bold overlap with acute post-concussion/mTBI symptoms in Table 2-1**

What Are the General Approaches to Treating Persistent concussion/mTBI Symptoms?

A TBI step-care model was developed to specifically address the overlapping concussion/mTBI and psychological symptoms observed among soldiers returning from combat[90] in a stepwise fashion[124] (Figure 4-1). The TBI Step-care Model focuses on addressing the patient's symptoms regardless of the etiology (e.g. concussion/mTBI vs.

PTSD). Further, the model assumes that cognitive issues can best be identified and treated if other problems are alleviated first.

Figure 4-1. Traumatic Brain Injury Step-care Treatment Model



Source: Terrio et al., 2009[125]; *Includes sleep hygiene, diet, exercise, and avoiding further traumatic brain injury

First, soldiers and their family or support system are provided with educational material describing the expected recovery and potential comorbid psychiatric symptoms. Second, somatic and self-care routine problems are treated as necessary. Third, specific problems with irritability and impulsivity are treated as necessary. Typically, all of these steps are followed before cognitive interventions are explored.

Va/DoD Clinical Guidelines for persistent concussion/mTBI symptoms

The Veterans Affairs (VA) and Department of Defense (DoD) Clinical Practice Guideline for the management of concussion/mTBI[77] outside the deployed setting is consistent with the step-care models ultimate goal of successfully reintegrating military personnel into their work and social life post-injury.

Patients with symptoms that persist following the initial management of concussion/mTBI symptoms require follow-up for PPCS. Assessment of PPCS begins with a reassessment of symptom severity, functional status (e.g. employment, school, relationships, family), and a psychosocial evaluation[77]. If symptoms have improved then the current treatment plan is continued and follow-up is recommended in 3 to 4 months. However, if the symptoms have not improved then the clinical team must assess possible alternative causes of adverse symptom reporting (e.g. depression, PTSD, substance abuse), and manage the comorbid condition(s) if present. Further, the clinical team considers interdisciplinary specialty care (e.g. recreational therapy, neurology, ophthalmology) to treat persistent symptoms. Moreover, cognitive symptoms that do not respond to the initial treatments may require additional neuropsychological assessment and cognitive behavioral therapy. Lastly, occupational and community reintegration therapy should be considered for patients with persisting functional deficits. The case manager is responsible for continuing to reinforce the treatment and provide support during follow-up.

What are the Treatments and Therapies for Persistent Post-Concussive Symptoms?

A variety of treatments and therapies are used as part of the management and treatment of post-concussive symptoms described above. The majority of rehabilitation therapies are designed to address the constellation of common physical[126,127], cognitive[128-132], emotional[129,133,134], and functional/social[135-137] symptoms observed following TBI. However, the majority of these programs have been designed for patients with moderate to severe TBI. Many of these treatment programs show promise but further research using a rigorous methodology is necessary to fully evaluate the efficacy of these rehabilitation programs, especially in the concussion/mTBI patient population[128,130,134]. Furthermore, treatment among military personnel must also consider the impact of other factors on rehabilitation success (e.g. psychiatric comorbidities, pain, and sleep disturbance)[128,138].

An updated review of the literature identified 18 studies evaluating psychological interventions aimed at reducing concussion/mTBI symptoms for adults[129]. All of the studies included in this review targeted a civilian population to evaluate the efficacy of patient education (n=12 studies) or neuropsychological interventions (n=6 studies) to reduce concussion/mTBI symptoms. The review concluded that the methodology for the majority of these studies was weak with limited evidence suggesting that educational interventions administered acutely after the injury reduced concussion/mTBI symptoms. Specifically, the review indicated that patient education is often the preferred intervention to prevent delayed recovery of symptoms following a concussion/mTBI. The primary focus of patient education is an explanation of the general pathophysiology and typical sequealae and reinforcing

patients' expectations of recovery.[139]. Expectation of recovery as a method for improving concussion/mTBI outcomes based on the knowledge that the vast majority of patients recover fully, and that this expectation helps reduce the likelihood that symptoms associated with other injuries/conditions are misattributed to a past concussion/mTBI.

Only one study by Walter et al.[140] identified prospectively evaluated PPCS and PTSD symptom change for 28 veterans with comorbid TBI of all severities and PTSD at a VA Medical Center. These patients completed an initial symptom evaluation before treatment and a discharge symptom evaluation following an adapted 8-week Cognitive Behavioral Therapy program with only the Cognitive components (CPT-C). Patients completed individual and group CPT-C sessions to identify and modify maladaptive cognition from traumatic experiences. The study reported significant ($p<0.05$) symptom resolution from pre- to post-treatment for clinician assessed PTSD symptom scores (74.68 v. 48.5; potential range: 0-136), self-reported PTSD symptom scores (61.43 v. 46.71; potential range: 0-85), and self-reported post-concussive symptom scores (54.25 v. 45.36; potential range: 0-88). Lower scores indicate fewer reported post-concussive and PTSD symptoms. These results suggest that the CPT-C program was effective in reducing both PPCS and PTSD symptoms.

What Factors are Associated with Persistent Post-Concussive Symptom Change Following Rehabilitation?: Article #1

There is also limited evidence for the association between various demographic-, injury-, and rehabilitation-related factors and PPCS assessed pre- to post-rehabilitation in the

civilian or military literature. Again, the study by Walter et al.[140] examining pre- to post PPCS and PTSD symptom change following a CPT-C program reported that pre-treatment self-reported post-concussive symptom scores were positively correlated with clinician assessed PTSD symptom scores ($r=0.38$; $p<0.01$) and self-reported PTSD symptom scores ($r=0.57$; $p<0.01$). These results are consistent with scientific evidence that psychological symptoms like those of persons with PTSD may be the underlying cause of PPCS. In addition, residual differences were calculated for all three symptom scores and a positive correlation was found between PPCS resolution and PTSD symptom resolution. For example, self-reported PPCS resolution was correlated with clinician assessed PTSD-like symptom resolution ($r=0.57$; $p<0.01$) and self-reported PTSD symptom resolution ($r=0.60$; $p<0.01$). Therefore, PTSD-like psychological symptoms were not only associated with initial PPCS but also with the resolution of PPCS from pre- to post-rehabilitation. Lastly, demographic variables (i.e. age and education level) were not significantly correlated with PPCS and PTSD symptom resolution. A limitation of this study is the use of correlation as the method for analysis.

Another recent study of 125 military service members initially evaluated at Walter Reed Army Medical Center with TBI of all severities investigated the demographic, injury-related, psychological, and effort testing variables associated with meeting postconcussional disorder (PCD) symptom criteria[141]. PCD symptoms are consistent with the PPCS symptoms described earlier in this review. No demographic variable (i.e. age, pre-TBI intelligence, sex, race, education) was associated with PCD. Injury-related variables including location of

injury (OEF/OIF v. non-combat-related), mechanism of injury (blast v. non-blast), bodily injury severity, length of loss of consciousness, length of post traumatic amnesia, intracranial abnormality, and number of months tested post-injury all conferred significant risk (RR range=1.2 to 2.7) for developing PCD at initial evaluation. However, no demographic or injury-related variables were significant predictors of the initial PPCS total score across the entire sample. Rather, the total PTSD score ($p < 0.001$), depression score ($p = 0.001$), and indication of poor effort on the Word Memory Test ($p = 0.010$) were the only significant predictors of the total PPCS score accounting for 65.8% of the variance ($p < 0.001$). Therefore, similar to the findings by Walter and colleagues[140], these results indicate that factors unrelated to concussion/mTBI impact PPCS reporting. This study did not examine the association between various demographic-, injury-, and rehabilitation-related factors and symptoms assessed pre- to post-rehabilitation. However, it was the most comprehensive study evaluating these factors among a veteran population referred to a TBI clinic for initial evaluation and highlights the need for further research in this area.

The remaining evidence for factors associated with concussion/mTBI related PPCS and PTSD symptoms overwhelmingly comes from cross-sectional post-deployment evaluations[88,89,142,143], retrospective medical record reviews from post-deployment trauma registries[144-146], longitudinal surveys of recruited soldiers[147-149], and patient records from military medical treatment centers or VA Medical Centers[111,150-161]. Demographic-, injury-, and rehabilitation-related factors associated with concussion/mTBI that potentially affect PPCS and post-traumatic stress symptom change during concussion/mTBI rehab are

reviewed below due to the dearth of literature actually examining factors associated with symptom change during rehabilitation. This part of the review primarily focuses on the variables available from the SAMMC data that were used in the first two journal articles.

Demographic Factors

According to the sources described above, the majority of deployment-related concussions/mTBIs are reported among young (≤30 years), male (≥ 90%), junior enlisted (≥ 50%) military personnel. This was confirmed by a study in which the majority of veterans with TBI at any level of severity (n=55,070) who completed in-person comprehensive TBI evaluations at a VA Medical Center from October 1, 2007 to June 16, 2010 were young (≤30 years; 52%) and male (94%)[151]. Further, the majority were married or living with their partner (49%) and the highest level of education attained was high school or equivalent (56%). Importantly, this medical record review included only veterans and military personnel evaluated at the VA Medical Center.

Age

No studies specific to the military population reported an association between age and PPCS, but the civilian literature shows that older age (≥50 years) is a risk factor for poorer or delayed recovery of cognitive symptoms following concussion/mTBI[106]. Therefore, age is likely an important confounder or effect modifier to consider when examining PPCS reporting, specifically cognitive symptoms among older patients that have sustained multiple concussions/mTBIs.

Sex

No identified studies specifically examined differences in PPCS and/or health outcomes between men and women with concussion/mTBI only. One study examined the population-level association between deployment related TBI of all severities and mental health outcomes stratified by sex[153]. The final analytic sample included 654 women and 11,951 men identified with deployment related TBI. Women were at an increased risk of depression (OR=1.90; 1.61-2.24), comorbid PTSD and depression (OR=1.66; 1.40-1.96), and severe PPCS across all symptom domains compared with men.

Another study randomly surveyed 2,348 OEF/OIF veterans with probable TBI of all severities. Results indicated that the odds of self-reported probable PTSD, anxiety symptoms, and physical health symptoms were at least 2.5 times greater for female veterans compared with male veterans[162]. Although not specific to concussions/mTBIs, these results support important potential differences in reported PPCS and PTSD symptoms among male vs. female service members that need to be considered when examining symptom resolution following rehabilitation.

Comorbidities

Numerous studies have investigated the association between various comorbidities (e.g. PTSD, depression, pain) and PPCS symptom reporting. These studies suggest that civilian and military personnel with these comorbid diagnoses or symptoms report significantly greater PPCS[88,111,142,154,155,163-168]. This evidence supports the hypothesis that

PPCS attributed to concussion/mTBI are at least partially if not entirely due to these comorbid symptoms. For example, one of the few longitudinal studies surveying soldiers pre- and post-deployment reported that soldiers sustaining a concussion/mTBI during deployment were at an increased risk of reporting memory problems (OR=2.47; 1.08-5.65), ringing of the ears (OR=2.45; 1.09-5.51) and irritability (OR=2.84; 1.14-7.07) compared to controls post-deployment[149]. However, these symptoms were no longer statistically significant after adjustment for PTSD. Furthermore, clinicians performing in-person comprehensive TBI evaluations at VA Medical Centers reported that based on their opinion 23% of patient PPCS reporting was due to a behavioral health condition alone and 61% was due to a combination of TBI and a behavioral health condition[151].

Lastly, it is important to reiterate the impact of patients' pre-concussion/mTBI patient personality characteristics and comorbid psychiatric conditions (e.g. anxiety, depression)[114], symptom exaggeration in the context of potential compensatory litigation[115-118], or misattribution all negative symptoms experienced to a recent trauma such as concussion/mTBI[119,120]. These factors are often found to be more strongly associated with reporting of PPCS than with diagnosis of concussion/mTBI.

Injury-Related Factors

Injury Etiology

Evidence for the association between concussion/mTBI and injury etiology (blast-related v. non-blast-related) is mixed[152,158]. The majority of studies report no significant

differences across PPCS domains stratified by injury etiology. However, among studies that did find a statistically significant difference, hearing loss and headache are the most common symptoms associated with blast-related concussion/mTBI[150,156,169]. A study by Kontos and colleagues[158] reported PPCS and PTSD symptom severity scores among U.S. Army Special Operations Command personnel stratified by blunt, blast-related, and combination blunt and blast-related concussion/mTBI. Results from this study indicate a dose response gradient of risk for both PPCS and PTSD symptoms from blunt, blast-related, and combined blunt and blast-related, respectively.

Combat Stress and Severity of Comorbid Injuries

Some studies show that combat stress and severity of other physical injuries influence the reporting of PPCS. One recent study found that service members diagnosed with a concussion/mTBI and high-level combat stress reported significantly higher PPCS scores on the Neurobehavioral Symptom Inventory (NSI) compared with service members diagnosed with a concussion/mTBI and low-level combat stress (44.41 v.12.33; $F=190.7$, $p<0.001$)[159]. Another study found that service members with a concussion/mTBI[157] reported a decrease in PPCS as severity of other bodily injuries increased. The results of these suggest that PPCS among military service members may in fact be due to combat stress as opposed to a diagnosed concussion/mTBI. In addition, service members with no evidence of physical injury to which PPCS can be attributed may be more likely to misattribute them to concussion/mTBI.

Multiple concussion/mTBI

Limited evidence from the civilian sports injury and emergency medicine literature, indicates that multiple concussions/mTBIs and the number of previous concussions/mTBIs sustained are potential risk factors for subsequent concussion/mTBI, delayed neurological recovery, and long-term neurodegenerative diseases such as chronic traumatic encephalopathy[170-172]. Results from animal studies[173,174] and one study of concussed athletes[175] indicate that a period of cerebral metabolic depression of unknown duration following a concussion/mTBI may lead to a "window of risk" in which additional concussion/mTBIs may increase vulnerability to these adverse post-concussion outcomes. This increased vulnerability is of particular concern for service members exposed to repeated concussion/mTBIs within a short period of time, for example from multiple exposures to blasts[87] or even subconcussive blows[176,177]. This topic warrants further research.

Rehabilitation-Related Factors

No studies of the effects of rehabilitation-related factors (e.g. length of rehabilitation stay, time from injury to initial evaluation) on PPCS and/or PTSD symptoms were found in the literature.

What are the Clinical Predictors of Pre- to Post-Symptom Resolution following Rehabilitation?: Article #2

Research predicting outcomes for mortality, functional outcomes, and other global outcomes with moderate to severe TBI is a growing area of research[178-184]. However, the

literature evaluating predictive factors of successful symptom resolution following concussion/mTBI treatment is extremely limited. Three studies of predictive factors for PPCS and PTSD symptom change among patients with concussion/mTBI were identified.

Stulemeijer et al.[185] developed and validated a predictive model of "low" PPCS 6 months post-concussion/mTBI with a sample of 152 civilian hospital patients 16 years and older. "Low" PPCS was defined as reporting nothing more severe than a mild impairment that did not interfere with daily activities on 13 of the 16 questions from the Rivermead Post-Concussion Questionnaire (RPCQ). The final predictive model included a lack of pre-morbid physical comorbidity (OR =3.5; 1.6-7.8), acutely reporting "low" post-concussive symptoms after injury (OR=5.5; 2.3-13.2), and no acute post-traumatic stress post-injury (OR =10.0; 2.3-42.9) as factors increasing the odds of "low" PPCS symptoms 6 months post-concussion/mTBI. The predictive probability of this model after bootstrapping was satisfactory (AUC=0.82). This model supports both concussion/mTBI factors and non-injury factors as predictive of PPCS symptom resolution.

Ponsford et al.[186] developed predictive models for acute (1week) and subacute (3 months) post-concussive symptoms with a sample of 123 concussion/mTBI civilian hospital patients and 100 controls. Post-concussive symptoms were calculated with the ImPACT Post-concussion Symptom inventory (range: 0-132) where a higher score indicates a greater degree of impairment. At 1-week post injury, the following variables were significantly predictive of higher post-concussive scores among pre-injury and acute predictors of interest:

concussion/mTBI (OR=3.25), female (OR=2.56), and history of a psychiatric diagnosis (OR=3.7). However, at 3 months post-injury concussion/mTBI was no longer a significant predictor of higher post concussive scores, but pre-injury psychiatric diagnosis (OR=2.56) and poor pre-injury physical health (OR=1.09) were significant predictors. Furthermore, concussion/mTBI (OR=3.30), anxiety symptoms (OR=1.32), and greater pain severity (OR=1.03) were significant injury-related predictors at 1-week post injury. Again, at 3 months post-injury, concussion/mTBI was no longer a significant predictor, but anxiety symptoms at 1-week post-injury was a significant predictor (OR=1.18). Similar to the Stulemeijer study, pre-morbid variables and comorbid psychiatric variables were most predictive of PPCS, thus supporting the psychogenic etiology of PPCS.

Luis and colleagues[187] also reported findings by retrospectively predicting PPCS among a sample of Vietnam era veterans with and without self-reported concussion/mTBI. Demographic variables (i.e. age, education, race, enlistment intelligence score), early life psychiatric difficulties (e.g. anxiety and depression) and social support were the strongest predictors of PPCS explaining over 25% of the unique variance among veterans with PPCS. Thus, this study provides additional evidence that demographic and pre-morbid psychiatric conditions are important predictive factors in PPCS.

None of the identified studies developed and validated predictive models for post concussive and PTSD symptom resolution among military service members completing

concussion/mTBI rehabilitation. However, the literature supports a range of possible pre-injury, peri-injury, and post-injury factors associated with PPCS symptom resolution.

Table 4-1. Factors Associated with a Delayed Recovery/Poor Outcome Following a Sustained Concussion/mTBI

Indicator	Representative Reference(s)	Comment
• Increased age at injury	• [106]	• True of all Injury Severities
• Premorbid Psychiatric Illness	• [188,189]	
• Development of psychiatric illness after injury (e.g. depression, PTSD)	• [190-194]	• Fairly consistent association between Axis I diagnosis and increased levels of postconcussive symptoms and other outcome measures
• Compensation/Litigation	• [195-198]	• Not a universal finding. Association should not be misinterpreted as causation
• Repetitive Injuries	• [170,171,199]	• Evidence is somewhat indirect and tentative-comes from both sports injury literature and early emergency department populations[218]. See Institute of Medicine for discussion[31].
• Selected polymorphic alleles (e.g. *ANK1*, *APOE*E4*)	• [200,201]	• Several large ongoing studies should shed further light on this
• Abnormal acute neuroimaging	• [188,202,203]	• "Complicated mild TBI" has outcomes more similar to moderate TBI
• Expectation of poor outcome	• [204,205]	• Expectation of poor outcome or severity of complications associated with poor recovery
• Extracranial injuries and high initial symptom load	• [202]	• Extracranial injuries may prolong need for treatment and delay return to work but not necessarily increase "postconcussive symptoms"[185,206]

In fact, a recent book chapter presented the evidence for specific factors associated with delayed recovery or poorer outcomes following concussion/mTBI (Table 4-1)[139]. These are important variables to consider when choosing clinical predictors to include in models of pre- to post PPCS and PTSD symptom change following rehabilitation.

LITERATURE REVIEW: JOURNAL ARTICLE 3

The last section of the literature review will transition to a review of important concepts for the third and final journal article of the dissertation concerning macro-level factors associated with military service and chronic morbidities among veterans.

What are the Demographics of Veterans?

Definition

There are two important distinctions between a service member with prior U.S. military service and a U.S. veteran. A veteran must complete their full active duty service in the military or receive an early honorable discharge[74]. The full service obligation across all branches is 8 years but the minimum active duty requirement varies by service branch as follows: Army (2-5 years), Navy (2 years), Air Force (4 years), and Marines (4 years)[207]. Similarly, the definition of prior military service is branch specific[208]. For example, the Army defines prior military service as 180 days of military service or completion of military job training. The bulk of the literature including the review presented below concerns veterans.

Prevalence, Incidence and Demographics

The Department of Veterans Affairs completed an actuarial projection model of the veteran population based on data from fiscal year 2010 called the Veteran Population Projection Model 2011 (VetPop2011)[209].

Table 5-1. Projected Number of U.S. Veterans Stratified by Demographic Characteristics

	Living Veterans 2013 (n=21,972,964)	Living Veterans 2020 (n=19,604,276)	Living Veterans 2040 (n=14,462,805)	Percent Change in Incidence of Living Veterans[a.]
Sex (%)				
Male	89.7	87.6	82.3	-39.6
Female	10.3	12.4	17.6	12.1
Age (%)				
< 50 years	36.6	36.2	37.8	-32.1
≥ 50 years	63.4	63.8	62.2	-35.4
Race/Ethnicity (%)				
White Only	78.2	75.2	66.0	-44.5
Black Only	11.9	13.4	16.5	-8.8
Asian Only	1.2	1.4	1.9	1.0
Hispanic/Latino	6.3	7.4	11.4	20.2
Other	2.3	2.7	4.1	15.6
Branch (%)[b.]				
Army	43.4	41.1	36.9	-44.0
Navy	22.4	22.2	22.4	-34.3
Air Force	18.3	18.0	17.2	-38.1
Marine	10.8	11.4	13.4	-18.1
Service Era (%)[c.]				
Peacetime	25.0	24.4	36.4	-4.3
World War II	5.7	1.5	0.0	-100.0
Korean Conflict	9.4	5.0	0.0	-99.9
Vietnam War	33.4	30.9	8.9	-82.4
Gulf War	29.5	40.5	55.3	23.3
Post-Gulf War	0.0	0.6	22.6	100.0

[a.] Incidence calculated based on estimated number of living veterans from 2013 to estimated number of living veterans in 2040 (37 years); [b.] Excludes Non-Defense and Reserves; [c.] Percent greater than 100% due to veterans serving in multiple conflicts.

VetPop2011 provides key estimated prevalence projections for the estimated number of living veterans from fiscal year 2011 to 2040 (Table 5-1). The majority of veterans in 2013 are older (≥50 years; 63.4%), white (78.2%) men (89.7%) that served during the Vietnam and Gulf-War era (62.9%). The number of veterans in the U.S. is projected to decrease by approximately 34% (n=7,510,159) over the next 37 years. However, the incidence of women (12.1%), Asians (1.0%), Hispanics (20.2%), and Other races (15.6%) are projected to increase over this time. Data from the American Community Survey[209] reported that 66.5% of male and 47.3% of female veterans were married. Lastly, 15% of male and 19.6% of female veterans obtained a bachelor's degree. The rate of marriage compared to civilians was higher for male and slightly lower for female veterans.

Is Military Service Associated with Protective and Risk Factors?

Alcohol Misuse and Abuse

The prevalence rate of heavy alcohol use, defined as five or more drinks per typical drinking occasion in the last 30 days for men and four more drinks for women, ranged from 15%-20% among a large cross-sectional sample of active duty military personnel from 1980-2005[210]. Similar proportions were reported by the National Center for Health Statistics among civilian men drinking five or more drinks on at least 12 days in the past year (16%)[211]. Another study of alcohol abuse trends from 1980-1995 noted that U.S. Army personnel (61.8 per 10,000) reported similar rates of alcohol-related hospitalizations to civilians (60.4 per 10,000)[45]. However, rates of nondependent alcohol abuse (e.g. binge drinking) were higher for Army personnel (21.6 per 10,000) compared to civilians (7.6 per 10,000); and these

findings indicate that non-dependent heavy alcohol use is potentially responsible for different drinking behaviors when comparing service members and civilians.

There are several proposed hypotheses to explain differences in drinking behaviors between service members and civilians primarily based on the understanding of social norms encouraging negative drinking behaviors in the U.S. military and self-medication of service members to deal with psychological stress, specifically related to combat exposure. First, alcohol misuse and abuse among service members may be associated with a military drinking culture[6]. For example, among men and women Navy careerists, perceived peer approval for heavy drinking and usual number of drinks on liberty (or regular time off) was a significant risk for all drinking outcomes (i.e. weekly frequent heavy drinking, DSM-IV alcohol abuse, heavy drinking during most liberty, and heavy episodic drinking during most recent liberty). Importantly, the sample from this study was not young male enlistees with a higher likelihood of alcohol misuse and abuse, but Navy careerists with an average length of service of 15 years.

Moreover, ethnographic interviews of Navy careerists found the following major themes regarding social norms of drinking behavior: (1) policy and tradition, (2) hydraulic drinking model, (3) free-range behavior, and (4) work-related stress. Policy and tradition refers to the varying degree of enforcement for negative drinking related infractions (e.g. driving under the influence, drunk and disorderly behavior, and public intoxication). The Navy has a recorded history and tradition of glamorizing negative drinking behaviors as an

accepted norm of service. Therefore, the Navy has implemented policies to reverse the promotion of these norms to varying success, in part due to inconsistent enforcement of adopted penalties intended to curtail negative drinking behaviors. The hydraulic drinking model refers to Navy personnel excessively drinking during liberty to relax because alcohol is prohibited during long deployments. Navy careerists are also reported that being away from their friends, family, and community for long periods lead to free-range behavior where they felt fewer social barriers to negative drinking habits. Lastly, long deployments in confined spaces with limited privacy and demanding job tasks can cause a stressful work environment. Therefore, Navy careerists reported a need to relieve work-related stresses by heavy drinking.

Secondly, alcohol misuse and abuse is also associated with combat-related stress potentially caused by self-medication as a way to deal with combat-related trauma[212,213]. Boscarino et al.[214] reported that Vietnam veterans with combat exposure reported a significantly higher ($p<0.01$) number of binge drinking episodes compared to Vietnam era veterans with no combat exposure, other veterans, and non-veterans. Further, another study among a sample of Vietnam and Korean War veterans found that excessive alcohol abuse, defined as currently meeting the DSM-III criteria for alcohol abuse or dependence, persisted years post-deployment[215]. In addition, those veterans exposed to combat reported significantly higher levels of alcohol abuse compared to non-combat veterans ($\chi^2=9.87$; $p<0.05$). There is also evidence from the current conflicts in Iraq and Afghanistan that combat exposure increases the risk of alcohol misuse and abuse[216,217]. Based on data from the

Millennium Cohort, active duty personnel deployed to Iraq with combat exposure were at an increased risk of new onset binge drinking (OR=1.31; 1.14-1.49) compared to non-deployed personnel. Moreover, National Guard and Reserve troops deployed to Iraq with combat exposure were at an increased risk of new onset heavy drinking (OR=1.63; 1.36-1.96); binge drinking (OR=1.46; 1.24-1.71), and alcohol-related problems (OR=1.63; 1.33-2.01) compared to non-deployed soldiers.

There is evidence that prior military service is a risk factor for alcohol misuse and abuse due to a historical military drinking culture promoting negative drinking behaviors. However, the current evidence is limited and the strongest evidence comes from a study specific to the Navy; thus, results are not directly applicable to other branches of service. Furthermore, service members exposed to combat appear to be at a specific risk for alcohol misuse and abuse as a way to deal with the psychological distress experienced during combat.

Smoking

There is a long history of smoking in the U.S. military with the prevalence of ever smoking and history of heavy smoking historically higher among service members compared to civilians. For example, based on data from a large sample of approximately 225,000 veterans participating in the Behavioral Risk Factor Surveillance System (BRFSS) from the 2003-2007, the reported prevalence of smoking was higher among veterans (27%) compared to non-veterans (21%) [218]. In addition, evidence from the nationally representative National

Medical Expenditure Survey reported that 77% of veterans smoked at least 100 cigarettes in a lifetime compared to 49% of non-veterans surveyed (RR=1.29; 1.24-1.34) in 1987[46]; in addition, veterans were at an increased risk of currently smoking compared to non-veterans (RR=1.26, 1.16-1.36). This is noteworthy because service members generally voluntarily enlist or drafted early in life, and age at first cigarette is predictive of the number of cigarettes smoked in a lifetime and dependence as an adult[219].

Exposure to the military is not only associated with an increased risk of ever smoking but also an increased risk of heavy smoking. For example, based on results from the National Longitudinal Study of Youth from 1979-1984, a significantly (χ^2=17.62; p<0.007) higher proportion of current young male military personnel (19.1%) reported heavy smoking status (≥26 cigarettes/day) compared to students and those unable to work (10.2%), unemployed men (11.8%), and civilian employees (14.3%). Lastly, there is also evidence from the Millennium Cohort based on data collected before and after the conflicts in Iraq and Afghanistan indicating that combat exposure maybe a risk factor for smoking initiation among never-smokers (OR=1.63; 1.15-2.32) and smoking recidivism (OR=1.27;1.07-1.51) among past-smokers[220]. Thus, combat exposure is associated with alcohol misuse, abuse, and smoking. Other suggested hypotheses for increased rates of smoking among prior service members compared to civilians include cigarette manufacturers' extensive effort to promote and market tobacco to military personnel, reduced prices of up to 76% for a carton of cigarettes at military commissary/exchange systems, and inclusion of a four pack of cigarettes per meal in K- and C-rations until 1975[8-10].

Other Substance Abuse

A large cross-sectional sample of active duty military personnel from 1980-2005 reported the prevalence of using one of 12 categories of non-medically illicit drugs ranged from 2.4%-27.6%[210]. However, since 1980 the reported percentage of illicit drug use has dropped dramatically to approximately 3%. There is evidence that this dramatic decrease in use is at least partially due to adoption of strict anti-illicit drug policies in the military[221].

Another study based on a nationally representative sample from the World Health Survey reported the proportion of active duty military personnel using illicit drugs (i.e. marijuana, cocaine, heroin, methamphetamines) in 1992 and 1995 was relatively stable for men (13.8% and 12.1%) and nearly doubled for women (4.6% and 9.0%)[222]. Similar to the civilian population[223,224], heavy alcohol use and moderate to heavy smoking among military personnel were significant predictors of illicit drug use. The odds of illicit drug use among men were approximately 2 times greater for heavy smokers (OR=2.28; 1.45-3.57) and 10 times greater for heavy alcohol users (OR=9.93; 5.38-18.32). For women, the increased odds of illicit drug use was approximately 3.5 times greater for heavy smokers (OR=3.55; 1.18-10.74) and 6.5 times greater for heavy alcohol users (6.54; 2.56-16.72). Therefore, the negative health consequences of heavy alcohol use, smoking, and illicit drug use are a serious concern among individuals with prior military history.

PTSD/Anxiety

This part of the review will focus on the limited evidence among older veterans concerning the long-term positive and negative effects of PTSD, anxiety, and stress[225]. The long-term longitudinal changes in PTSD over time are currently unclear. A longitudinal and retrospective study of PTSD in World War II veterans found a three-phase response to war related trauma[226]. First, directly following the conclusion of the war in 1945 soldiers reported a high number of PTSD symptoms. Second, from 1946 to 1979 there was a gradual decrease in symptoms over-time. Third, in the 1980s and 1990s the symptoms began to increase again. Late-onset of PTSD symptoms during the third phase with limited to no prior history of PTSD during the first phase were uncommon. However, Davison and colleagues[51] reported evidence to support late on-set stress symptomology (LOSS) among a focus group of World War II, Korean War, and Vietnam veterans. LOSS is described as exposure to traumatic combat related experience(s) with no functional impairment or chronic stress disorder in adulthood but an increase in stress symptomology late in life as the thoughts, memories, and feelings of the trauma are contemplated. Therefore, despite not understanding the progression of PTSD and PTSD symptoms over-time, the current evidence indicates that a long-term association between combat related trauma during military service and PTSD symptoms is plausible[227]. For example, approximately 5% of Dutch Word War II veterans (n=4,057) surveyed met the criteria for PTSD 50 years after the war had ended[228]. Furthermore, U.S. World War II veterans with moderate to heavy combat exposure were at a dramatically increased risk of PTSD diagnosis 45 years after the war compared to non-combat veterans (OR=13.3; 1.4-129.7)[229].

There is also evidence that exposure to traumatic experiences during war produces positive character traits such as learning how to cope with adversity. A study by Elder et al.[34] reported more resilience and less hopelessness over time associated with military service. In addition, veterans exposed to high levels of combat reported learning how to cope with adversity (χ^2=17.2; p<0.01), self-discipline (χ^2=8.2; p<0.05), the value of life (χ^2=14.4; p<0.01), and a clearer sense of direction (χ^2=7.1; p<0.05) as positive influences from traumatic war experiences compared to veterans exposed to light or no combat. Similarly, another study reported that negative effects of PTSD were alleviated by perceived benefits from stressful events[54]; thus, supporting that combat exposure potentially also promotes resilience in a subset of veterans.

Other Health Behaviors: Dietary Intake and Physical Activity

There is limited evidence evaluating differences among veterans, active-duty personal, and civilians on non-substance abuse related health behaviors (e.g. diet and physical activity). However, it is reasonable to hypothesize that prior military service has a positive effect on health behaviors because military enlistment requires recruits meet various criteria associated with positive health outcomes (e.g. physical fitness, mental aptitude, not suffering from certain debilitating chronic diseases, and no drug dependence)[230].

A recent study based on data from the 2010 BRFSS examined the association of health behaviors stratified by military service[231]. The study reported that active-duty

(OR=0.65; 0.51-0.82) and National Guard/Reserve troops (OR=0.82; 0.71-0.96) had a lower odds of reporting no exercise compared to civilians. However, this protective benefit was not shown in veterans (OR=1.00; 0.94-1.05) compared to civilians. Another study using data from the 2003 BRFSS reported that veterans reported a statistically significant ($p<0.0001$) lower prevalence of inactivity (16.2% v. 20.5%) and higher prevalence of activity (20.8% v. 14.7%) compared to civilians after adjusting for age and sex[232]. But maintenance of long-term healthy physical activity behaviors is complicated. For example, despite recognizing the health benefits of physical activity, maintaining healthy physical activity behaviors may be difficult for veterans exposed to combat due to adverse health conditions and chronic pain post-deployment[43].

Park and colleagues[233] used the Multiethnic Cohort comprised of 45 to 75 year old participants residing in California and Hawaii to examine the health behaviors of veterans and non-veterans. There were no significant differences ($p=0.41$) in reported physical activity level (≥30 minutes/day) between veterans (31.4%) and non-veterans (32.1%). Yet, the results did suggest that veterans were heavier consumers of daily red (48.4 grams v. 45.5 grams; $p<0.0001$) and processed meat (25.1 grams v. 22.5 grams) compared to non-veterans. Furthermore, veterans consumed less fruits (241 grams v. 265 grams) and vegetables (333 grams v. 346 grams) compared to non-veterans. Further exploration of differences in health behaviors post-military service to elucidate important differences associated with long-term chronic disease is warranted.

Is Military Exposure a Risk Factor for Metabolic Syndrome?

Metabolic Syndrome

The veteran specific literature regarding metabolic syndrome is scarce with the majority of identified articles describing the association between psychiatric symptoms and/or comorbidities and metabolic syndrome. The overall prevalence of metabolic syndrome among U.S. veterans is unknown. A retrospective examination of computer based clinical records estimated that 25% of registered veterans at the Veteran Affairs Northern California Health Care System (n=51,026) met the modified Adult Treatment Panel III criteria for metabolic syndrome[234]. However, the prevalence was likely much higher due to missing data on a number of variables necessary to make an accurate diagnosis. The prevalence of metabolic syndrome among veterans with complete data was 41.6%.

Similarly, 40% of Gulf War veterans (n=253) from a clinical sample met the World Health Organization and the National Cholesterol Education Program for metabolic syndrome[60]. PTSD symptoms was the only significant sociodemographic predictor of metabolic syndrome (OR=1.01). Conversely, another retrospective study found no significant association between PTSD and metabolic syndrome among repatriated POWs from Vietnam[235]. However, the sample and methodology between the two studies were different making direct comparison difficult. Another cross-sectional study from the Vietnam Experience Study reported generalized anxiety disorder (OR=1.39; 1.02-1.89) was a risk factor for metabolic syndrome but major depressive disorder was not a significant

predictor[61]. Therefore, there is limited evidence that stress and anxiety related symptoms among service members are risk factors for metabolic syndrome.

Evidence from previous studies also indicate that psychiatric outcomes (e.g. PTSD and depression) are associated with an increased risk of individual metabolic syndrome risk factors such as obesity, elevated systolic and diastolic blood pressure, elevated triglyceride levels, and decreased HDL-C levels[236-239]. Furthermore, smoking is also associated with an increased risk of individual metabolic syndrome risk factors (i.e. elevated blood pressure, elevated triglyceride levels, decreased HDL-C levels, and glucose intolerance)[240-242]. Therefore, compared to civilians, veterans may be at an increased risk for metabolic syndrome because they are at an increased risk for these adverse neuropsychiatric outcomes and a health compromising behavior. Conversely, evidence indicates that veterans may engage in higher levels of physical activity compared to civilians[44,232], which is a health promoting factor inversely associated with metabolic syndrome[57]. In addition, cardiovascular fitness, which is correlated with physical activity[243], is associated with lower levels of abdominal obesity[244], low systolic blood pressure[245], decreased triglyceride levels and increased HDL-C levels[246-248]. Therefore, compared to civilians, veterans also may be protected against metabolic syndrome because they may have higher recommended levels of physical activity and cardiovascular fitness inversely associated with individual metabolic syndrome risk factors. This highlights the complex relationship between military service and metabolic syndrome that warrants further research. Lastly, metabolic syndrome is a group of risk factors associated with an increased risk of chronic morbidities such as cardiovascular

disease, type 2 diabetes mellitus, and select cancers in the U.S.[62-65]. A brief review comparing the risk for these chronic morbidities between civilians and veterans is presented below.

Cardiovascular Disease

Results from a nationally representative U.S. sample reported that veterans were at an increased risk of reporting ever receiving a provider diagnosed myocardial infarction or heart attack, angina or coronary heart disease, and/or stroke compared to civilians (OR=1.37; 1.29-1.46)[231]. Similar to other risk factors and chronic morbidities discussed in the review, the role of combat exposure and psychological distress appear to be important factors when elucidating the association between military service and cardiovascular disease. For example, after controlling for smoking status, alcohol consumption, and body mass index, the risk (HR=1.27; 1.17-1.52) of an ICD-8 diagnosis of arterial disease (e.g. peripheral vascular diseases) among World War II and Korean War veterans increased as a function of PTSD symptom burden[249]. Another study utilizing a large sample of World War II Prisoners of War (POWs) reported that POWs with PTSD were at significant risk of ever being diagnosed with circulatory disease (OR=1.58; 1.43-1.74), hypertension (OR=1.25; 1.16-1.35), or chronic heart disorder (OR=1.19; 1.11-1.29) compared to POWs without PTSD[250]. Similarly, veterans enrolled in the Vietnam Era Twin Study with symptoms of depression experienced an increased risk of a variety of cardiovascular diseases such as hypertension and angina compared to veterans with no symptoms of depression[251].

Evidence also indicates that prior military service may confer a more subtle level of risk. For example, results from a sample of veterans participating in the Atherosclerosis Risk in Communities (ARIC) study found a null association between combat-exposure or veteran status and prevalence rate ratios of cardiovascular heart disease or ischemic stroke[252]. However, another study utilizing the same sample reported significant risk difference (RD=12.82; 0.75-24.89) of subclinical atherosclerosis measured by carotid intima-media thickness (C-IMT)[253]. This finding potentially highlights more subtle subclinical differences based on combat exposure and veteran status.

The literature generally supports military service, specifically combat-related service[252-254], as a risk factor for cardiovascular disease. PTSD[249,250,255,256], general anxiety disorder and depression[251,257] are associated with an increased risk of cardiovascular risk factors among active-duty service members and veterans, which may explain some of these reported differences. However, the specific pathophysiologic or behavioral changes that causally link psychiatric morbidities such as PTSD and subsequent cardiac risk factors and disease are unknown[258,259]. Future research needs to address these gaps with a specific emphasis on how unique military exposures such as combat affect the risk of cardiovascular risk factors and disease in comparison to civilians that lack these exposures[260].

Type 2 Diabetes Mellitus

Results from a nationally representative sample reported that active-duty service members (OR=0.67; 0.52-0.86) but not veterans (OR=1.02; 0.97-1.08) were protected

against ever receiving a provider diagnosis of type 2 diabetes mellitus (T2DM)[231]. Furthermore, another study of OEF/OIF service members reported that deployment with or without combat was not a risk of incident T2DM[261]. Lastly, data from the 2000 BRFSS reported that a higher prevalence of reporting ever smoking was the only significant ($p \leq 0.05$) difference in health behaviors between veteran (70%) and non-veteran (60%) participants with T2DM[262]. Again, there is a need for future research to examine health behaviors and exposures increasing the risk for T2DM among the military population.

Cancer

It remains unclear if prior military service is a risk factor for cancer. There is evidence that prior military service confers both protection and risk for incidence of a variety of different cancers compared to the civilian population[263-265]. This section of the review will compare the incidence of the five leading cancers types[266] among men in the civilian population (prostate, lung and bronchus, colorectal, urinary bladder, and melanoma of the skin) to the incidence among active-duty service members and veterans.

Yamane et al.[265] compared standardized incidence rates of different cancer types between Air Force members and civilians from 1989-2002. The military data was from the Automated Central Tumor Registry (ACTUR) and the civilian data came from the Surveillance, Epidemiology, and End Results Program (SEER) from the National Cancer Institute (NCI). Male Air Force service members were at an increased risk of incident prostate cancer (IRR=1.44; 1.21-1.69) and protected against incident testicular cancer

(IRR=0.68; 0.61-0.76), colorectal cancer (IRR=0.52; 0.43-0.63), and urinary bladder cancer (0.46; 0.33-0.61). Despite an increased incidence of smoking among military service members, lung and bronchus cancer was not one of the top ten types of incident cancer among Air Force service members. In fact, the top three cancer types were melanoma (20.4%), testicular (17.8%), and prostate (7.2%), which accounted for approximately half of all incident cancers. Another study[267] using a similar methodology across all service branches explored the risk of melanoma in greater detail, and reported that compared to civilians active-duty personnel experienced protective effects earlier in life (20-44 years) and an increased risk of melanoma later in life (≥45 years).

A similar study used the same two sources of data from 1990-2004, but expanded the ACUTR sample to all military branches and restricted the military sample to only active-duty military personnel aged 20 to 59 years[264]. This study supported Yamane and colleagues findings of increased risk of incident prostate cancer among both white (IRR=2.12; 1.95-2.30) and black (IRR=2.09; 1.77-2.43) male service members. Moreover, white (IRR=0.58; 0.51-0.66) and black male (IRR=0.35; 0.26-.045) service members were protected against incident lung cancer. However, only white service members were significantly protected against colorectal cancer (IRR=0.83; 0.75-0.91) and neither race was significantly protected against testicular cancer. Contrary to the previous two studies, data from an older cohort of male veterans within the VA from 1973-1977 found the cumulative risk of prostate cancer (RR=1.09; 0.93-1.25) was not significantly higher compared to civilians[263]. In addition, this study reported a significant risk of lung and bronchus cancer (RR=1.76; 1.55-1.95).

Lastly, there are different patterns of cancer incidence comparing military service members to civilians; however, accurately identifying these differences and elucidating differential health behaviors and exposures related to these differences remain unclear. For example, the evidence that military service increases the risk of lung and bronchus cancer is mixed despite research supporting military service members are at an increased risk of ever and heavy cigarette smoking.

CONCLUSION

Although U.S. involvement in the longest two wars in its history is ending at the time of writing this dissertation, concern for the health and well-being of service members will remain for many years to come. The initial focus will be on meeting their short-term needs for treatment and rehabilitation of both the physical and psychological wounds of war, including PTSD and concussion/mTBI, in order to aid their successful return to military or civilian life. However, few published studies have investigated the effectiveness of current approaches to treating and managing the symptoms that sometimes persist after concussion/mTBI, which is very often accompanied by PTSD. Research from previous conflicts indicates that significant resources will be needed to treat and manage these and other adverse effects from these wounds long after military service ends.

Apart from the micro-level effects of injuries, evidence of the impact of military service on veterans' health at a macro-level seems to be mixed. Findings from one study that used data from the National Health Interview Survey (2007-2010) showed that veterans in

select older age groups were more likely than civilians with no prior military service to have chronic diseases and report psychological distress associated with metabolic syndrome[268]. However, these veterans were also more likely than their civilian counterparts to have access to health care. Thus, this study suggests that military service may affect long-term health in both positive and negative ways but does not explain how or why prior military service leads to these differences. More studies with better methodology are needed to further elucidate these important relationships.

The studies proposed in this dissertation will help to fill these gaps in the literature in the following two ways:

(1) The micro-level description and evaluation of patients requiring treatment and rehabilitation for persistent psychological and post-concussive symptoms attributed to concussion/mTBI will elucidate which service members require these services and specific factors potentially important for the long-term management of these symptoms. This research is important because sustaining a concussion/mTBI and exposure to psychological trauma is associated with long-term physical, psychological, and social impairment. Therefore, the early identification and appropriate treatment and rehabilitation of these patients will potentially curb these long-term effects across the life-course.

(2) The macro-level comparison between older men with and without prior military service will highlight potential positive and negative sociodemographic factors, health behaviors, neuropsychiatric outcomes, and specific clinical variables associated with

military service important in understanding differential health outcomes contributing to metabolic syndrome. Lastly, these results will help the design and implementation of future health promotion interventions aimed at reducing the chronic disease burden among veterans.

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JOURNAL ARTICLE 1

Title of Journal Article: Description and Factors Associated with Persistent Post-Concussive and Post-Traumatic Stress Disorder Symptom Change among Military Service Members with Mild Traumatic Brain Injury Completing Treatment at San Antonio Military Medical Center 2008-2013

Name of Journal Proposed for Article Submission: Journal of Head Trauma Rehabilitation

INTRODUCTION

Since 2000, more than three-fourths of the estimated 294,000 traumatic brain injuries (TBIs) diagnosed among service members were classified as a concussion or mild TBI (mTBI)[1]. The symptoms of concussion typically resolve within 3 months[2]. However, a small yet significant proportion of service members will experience persistent post-concussive symptoms (PPCS). These symptoms, which include chronic daily headaches[3] and sleep disturbance[4-6] continue beyond three months post-injury and sometimes for years. It remains unclear if PPCS are due to physiologic changes caused by injury to the brain[2,7,8], related to the psychological effects of exposure to war-related trauma[9], or a combination. Post-traumatic stress disorder (PTSD), one of the most common effects of exposure to war trauma, has many of the symptoms attributed to mTBI[10], which makes differentiating the etiology of war-related mTBI difficult. Although war-related mTBI has received the greatest attention because of the current conflicts, the U.S. Department of Defense estimates that only about

20% of TBIs sustained by service members occur in the war theater. Therefore, all mTBIs that occur among US service members are of concern

The need for treatment for persistent mTBI symptoms has also been increasingly recognized during the current conflicts [11]. Published research has identified factors related to self-report of initial symptom severity, including comorbidities (e.g. PTSD[12,13], depression[14,15], chronic pain[16]), severity of other physical injuries sustained[17,18], injury etiology[19,20], combat stress[21], misattribution of symptoms[22-24], pre-injury personality characteristics[25], and potential compensatory litigation[26-28] that are associated with initial self-reported persistent post-concussive symptom (PPCS) severity. However, whether treatment for PPCS in the military mTBI population is effective and how these and other factors influence symptom resolution in response to treatment is not known.

Therefore, the primary aims of the current study are to (1) describe the military mTBI patient population, (2) examine the change in self-reported persistent post-concussive and PTSD symptoms, and (3) explore potential demographic-, injury-, and rehabilitation-related factors associated with symptom change among U.S. military service members and veterans diagnosed with mTBI completing treatment at the San Antonio Medical Military Center (SAMMC) Traumatic Brain Injury Clinic from 2008-2013.

METHODS

Study Design

This is a one group, pre-experimental, pre- to post-treatment study of persistent post-concussive and post-traumatic stress symptom change among service members and veterans completing mTBI rehabilitation at SAMMC.

Data Source

Patients were referred by their primary care manager to the SAMMC TBI clinic from 2008-2013. As part of standard operating procedures, all individuals referred to the clinic completed self-report symptom questionnaires on a computer kiosk prior to their initial encounter with physical medicine and rehabilitation (PM&R) personnel (e.g. Physician, Physician Assistant, and Nurse Practitioner). Next, the assigned PM&R personnel decided if the (1) patient had a TBI, (2) if so, the severity of the TBI, and (3) if any treatment was required.

Lastly, a "standard" Stabilization Treatment Track program designed by PM&R personnel uses a diverse combination of therapeutic techniques targeted to the individual (Table 1-2) based on the patients' post-traumatic stress and persistent post-concussive symptoms. The Stabilization Treatment Track program was designed and administered at SAMMC, and was designed specifically for mTBI patients with common PPCS described in Table 1-2.

Only patients with a diagnosed mTBI who completed the Stabilization Treatment Track program were included in the analyses. Of the 2,502 TBI patients evaluated at SAMMC from 2008-2013, 989 (39.5%) patients sustained a mTBI and were administered the Stabilization Treatment Track program (Figure 1-2). A further 10 patients were excluded due to an unknown or missing treatment track transition at SAMMC. Burn and amputation patients (n=74) were excluded because compared to mTBI patients without concomitant burns or amputations; these patients require a unique treatment plan to meet there therapeutic needs. Lastly, 648 patients were excluded because they were missing initial (pre-treatment) and/or discharge (post-treatment) assessments (NSI and PCL-M) necessary for pre- to post treatment symptom evaluation. Therefore, the final analytic sample consisted of 257 mTBI patients completing treatment and rehabilitation due to PPCS and PTSD symptoms attributed to mTBI.

Dependent Variables

Persistent Post-concussive Symptoms (PPCS)

PPCS were assessed with the Neurobehavioral Symptom Inventory (NSI)[29]. The NSI (Appendix B) is a 22-item self-report inventory of common post-concussive symptoms. Based on a recent factor analysis of the NSI using three different military samples[30], the following three domain specific symptom clusters were identified: cognitive (range: 0-16), affective (range: 0-28), and somatic/sensory (range: 0-44). Global PPCS refers to the total rating of self-reported symptoms across all three-symptom clusters (range: 0-88). Pre- and

post-treatment NSI scores were analyzed (1) globally across all symptom clusters and (2) for each of the three symptom clusters.

Pre-and post-treatment individual PPCS were also dichotomized based on patient responses for each individual question on the NSI. Patients reporting "moderate" to "very severe" symptom complaints were considered to have reported impairment for that symptom and categorized as "impaired." Patients reporting "none" to "mild" symptom complaints were considered to have no reported impairment for that symptom and categorized as "not impaired."

A recent psychometric study reported that the NSI had high internal consistency and moderate external validity among a sample of OEF/OIF veterans[31]. The study reported high internal consistency (α=0.95) for the global post-concussive symptom rating and for the cognitive (α=0.92), affective (α=0.91), and somatic/sensory (α=0.88) subscale post-concussive domains. In addition, the NSI was positively associated with probable TBI diagnosis ($r=0.41$; $p<0.001$). However, the association was attenuated ($r=0.24$; $p<0.001$) after adjustment for probable post-traumatic stress disorder (PTSD), depression, and general anxiety disorder. Therefore, the association between NSI score and TBI diagnosis was strongly influenced by PTSD, depression, and general anxiety disorder symptomology.

Persistent Post-Traumatic Stress Disorder Symptoms

Persistent PTSD symptoms were assessed with the PTSD Checklist-Military version (PCL-M)[32]. The PCL-M (Appendix C) is a 17-item self-rated interval rating scale that asks about symptoms specific to stressful military experiences. The 17-items on the PCL-M capture one of three distinct symptom clusters representing B (re-experiencing; range: 5-25), C (avoidance and numbing; range: 7-35), and D (hyperarousal; range: 5-25) item diagnostic criteria for PTSD in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[33]. Global persistent PTSD symptoms refer to the total rating of self-reported symptoms across all three-symptom clusters (range: 17-85). Pre-treatment and post-treatment PCL-M scores were analyzed (1) globally across all symptom clusters and (2) for each of the three symptom clusters.

Pre-treatment and post-treatment individual persistent PTSD symptoms were also dichotomized into two categories based on patient responses to each individual question on the PCL-M. Patients reporting a "moderately" to "extremely" high frequency of symptom complaints were considered to have reported impairment for that symptom and categorized as "impaired". Patients reporting a "not at all" to "a little bit" frequency of symptom complaints were considered to have no reported impairment for that symptom and categorized as "not impaired."

The PCL-M generally has strong reliability and validity. The two to three day test-retest reliability among a sample of 123 male Vietnam veterans reported a Cronbach's alpha

(α) of 0.96[34]. Further, the internal consistency was high for the total symptom severity score (α=0.97), B item symptom criteria (α=0.93), C item symptom criteria (α=0.92), D item symptom criteria (α=0.92), and item specific symptom scores (α=0.62-0.87). In addition, the study reported strong convergent validity between the PCL-M and a variety of other assessments including the Mississippi Scale for Combat-Related PTSD (r=0.85-0.93, p-value unknown). A more recent study supported these findings of strong convergent validity between the Impact of Event Scale-Revised and the PCL-M (r=0.84, p<0.001) among a different sample of Vietnam veterans[35].

Independent Variables

Demographic Variables

The continuous demographic variable was age (years) at pre-treatment evaluation. The categorical demographic variables were sex and enlisted rank. Rank data were collected using the following response options: junior enlisted soldiers (E1-E4), non-commissioned officers (E5-E9) and officers (Commissioned or Warrant). These data were further dichotomized as (1) enlisted soldiers or (2) non-commissioned and commissioned or warrant officers for analysis of covariance (ANCOVA) analyses. Age was dichotomized based on the sample median (i.e., ≤29 years or >29 years) for ANCOVA. There were no available data on race/ethnicity, education, marital status, or military branch from patient electronic medical records.

Injury-related Variables

The continuous injury-related variables were the total number of self-reported TBIs and number of deployments. The categorical injury-related variables in this study were as follows: Number of self-reported TBIs (single/multiple), Number of self-reported deployments (single/multiple), PTSD at pre-treatment evaluation (yes/no), TBI mechanism (blast/non-blast), and geographic location of injury (Continental United States, Outside Continental United States, OEF, OIF). The methodology used to diagnose PTSD in this study required that patients rated at least (1) 1 B item (questions 1-5), (2) 3 C item (questions 6-12) and (3) 2 D item (questions 13-17) symptoms as "moderately" symptomatic or above (responses 3 through 5) and (4) reported a global PCL-M score ≥ 50[36]. Geographic location of injury (Continental United States/Outside Continental United States and OEF/OIF) was dichotomized for ANCOVA analyses.

Rehabilitation Variables

The continuous rehabilitation-related variables in this study were the time from the most recent self-reported mTBI to pre-treatment evaluation (months) and length of rehabilitation stay (days). The categorical rehabilitation-related variables in this study were total number of consults (single/multiple) and rehabilitation treatment history (standard transition/repeated rehabilitation). Time from mTBI to treatment evaluation and length of rehabilitation stay were dichotomized based on the median (i.e., ≤ 5 months or >5 months and ≤ 50 days or >50 days, respectively) for ANCOVA.

Patients were grouped into two categories of treatment and rehab history based on the expert recommendations from clinicians at SAMMC TBI Clinic. The "Standard Rehabilitation Transition" group followed one of two rehabilitation transition paths. This group either received only one mTBI consultation and one complete Stabilization Treatment Track program or completed more than one consult naturally transitioning into or out of the Stabilization Treatment Track program. For example, a patient may have initially been treated as an inpatient at SAMMC following the first consultation and naturally transitioned into the mTBI Stabilization Treatment Track program after a recommended second consultation at the TBI clinic due to persistent mTBI related symptoms. The "Repeated Rehabilitation Transition" group followed a more complex rehabilitation transition requiring 2 to 5 consults and repeated treatment for lingering persistent symptoms that did not resolve during completion of their first Stabilization Treatment Track program.

Statistical Methods

Measures of central tendency (mean) and dispersion (standard deviation) were reported for continuous demographic-, injury-, and rehabilitation-related variables, and the number and proportion of categorical variables are reported for the study patients. The NSI and PCL-M interval rating scale summed global and domain specific scores, were considered to be normally distributed under the assumption of the central limit theorem where $n \geq 30$[37]. To evaluate differences between included and excluded patients in the study, Student's t-test was used to test for significant differences ($p<0.05$) of continuous variables and the Chi-square test was used to test for significant differences of categorical variables, respectively.

Primary Hypothesis

The primary hypothesis was that patients would report a significant reduction in global and domain specific post concussive and PTSD symptoms following rehabilitation at the SAMMC. Paired t-tests were performed to test for mean differences in PPCS change (post-treatment evaluation minus (-) pre-treatment evaluation) assessed by the NSI. The test-statistic, p-value, and Cohen's d were reported for the (1) overall symptom score and (2) domain specific symptom cluster group score (i.e. somatic/sensory, affective, and cognitive). Four different comparisons were performed for this family of tests; therefore, the test specific Bonferroni type 1 error level adjustment for the paired t-tests was $p<0.0125$ to conserve the family-wise error rate of 0.05.

Paired t-tests were also performed to test for mean differences in PTSD symptom change (post-treatment evaluation minus (-) pre-treatment evaluation) assessed by the PCL-M among patients. The test-statistic, p-value, and Cohen's d were reported for the (1) overall symptom score and (2) domain specific symptom cluster group score (i.e. DSM-IV-TR B, C, and D item symptom criteria for PTSD). Four different comparisons were performed for this family of tests; therefore, the test specific Bonferroni type 1 error level adjustment for the paired t-tests was $p<0.0125$ to conserve the family-wise error rate of 0.05.

Secondary Hypotheses

(1) Patients reported a reduction in the proportion of moderate to very severe individual post concussive (NSI score range 2-4) and PTSD (PCL-M score range 3-5) symptom impairment.

(2) Compared to patients with only mTBI at pre-treatment evaluation, patients with comorbid mTBI and PTSD reported a greater global and domain specific PPCS burden.

(3) Discharge PCL-M and NSI scores differed by the following independent variables: age, TBI mechanism, PTSD diagnosis, time from injury to treatment evaluation, length of rehabilitation stay, and rehabilitation treatment history after adjustment for pre-treatment PCL-M and NSI scores, respectively.

There were 47 multiple comparisons assessing PPCS with NSI scores among these secondary hypotheses. Therefore, the test specific Bonferroni type 1 error level adjustment to account for multiple comparisons was $p<0.001$. In addition, there were 34 multiple comparisons assessing persistent PTSD symptoms with PCL-M scores among these secondary hypotheses. Therefore, the test specific Bonferroni type 1 error level adjustment to account for multiple comparisons was also $p<0.001$. There was no consideration of a priori family-wise set type 1 error level for these tests because they are all secondary endpoints.

McNemar's tests were performed to test for differences in the proportion of patients with PPCS impairment pre-treatment to the proportion of patients with PPCS impairment

post-treatment for each of the 22 individual questions on the NSI. McNemar's tests were also performed to test for differences in the proportion of patiens with persistent PTSD impairment pre-treatment to the proportion of patients with symptom impairment post-treatment for each of the 17 individual questions on the PCL-M.

Independent group t-tests were performed to test for differences in PPCS assessed by the NSI (1) pre-treatment and (2) post-treatment between patients with mTBI only and patients with comorbid mTBI and PTSD. The test-statistic and p-value were reported for the (1) overall symptom score and (2) domain specific scores (i.e. somatic/sensory, affective, and cognitive). Equality of variances were assessed with an F-test to determine if the Satterwaite (unequal variances) or Pooled t-test (equal variances) as appropriate.

Analysis of covariance was performed to explore if reported least square mean post-treatment NSI and PCL-M scores were different across individual dichotomous demographic-, injury-, and rehabilitation-related independent variables after adjusting for pre-treatment NSI and PCL-M scores. The model assumption of normality of residuals was assessed with the Kolmogorov-Smirnov test. Homogeneity of regression slopes was assessed with an interaction term and if the p-value for the interaction term was ≤ 0.10 then regression slopes were not considered homogenous and the interaction term was retained in the model. Otherwise, the interaction term was not included. Least-square means were reported for varying pre-treatment NSI and PCL-M scores for models identified with an interaction term. There was evidence of a violation of the homogeneity of variance assumption for both the

NSI and PCL-M ANCOVA models. The necessary transformations were identified to improve the homogeneity of variance and ANCOVA models were re-run with the transformations. However, the estimated least square means estimates only varied slightly from the untransformed ANCOVA models and the interpretation of results did not change. Therefore, the untransformed models were reported due to the robustness of ANCOVA against homogeneity of variance violations[38] and to improve the interpretation of results. All statistical analyses were generated on available data using SAS/STAT software, version 9.2, of SAS System for Windows (SAS Institute, Cary, NC).

Study Power

The sample (n=257) was adequately powered (80%) to perform the proposed paired t-tests for global NSI and PCL-M symptom change with Bonferonni correction (α=0.0125) based on data from Walters et al.[39], which was the only study identified assessing pre- to post persistent PTSD (PCL-S) and post-concussive (NSI) symptom change following treatment among patients at a military hospital. The PCL-S and NSI treatment effect size from the Walters et al.[39] study was d=1.18 and d=0.64, respectively.

Human Subjects, Animal Subjects, or Safety Considerations

The Brooke Army Medical Center (BAMC) and University of Texas School of Public Health Institutional Review Board (HSC-SPH-14-0126) approved this secondary data analysis.

RESULTS

Patients excluded from the analyses reported a greater proportion of multiple TBIs (73.5% v. 61.5%; p=0.003), fewer blast-related mTBIs (54.1% v. 61.9%, p=0.03), and a longer time from injury to initial treatment evaluation (21.8 months v. 16.3 months; p=0.003) (Table 2-2). Fewer excluded patients than included patients had 2+ consults (30.7% v 37.4% respectively, borderline significance, p=0.05).

Study patients were predominantly male (89.1%), non-commissioned or commissioned/warrant officers (58.7%), and their mean age was 30 (s.d.= 8.3) years old. Further, the majority of patients reported multiple TBIs (61.5%), multiple deployments (53.9%), a blast-related mechanism of mTBI (61.5%), and sustaining their most recent mTBI during OEF/OIF (77.8%). Approximately one-third of patients met the criteria for a diagnosis of PTSD at pre-treatment evaluation. The mean time from injury to treatment evaluation was over 1 year (16.3 months) and the average length of treatment stay was approximately 2 months (70.2 days). In addition, the majority of patients had one consult (62.7%) and followed a standard treatment track transition (84.4%).

Patients reported a statistically significant ($p<0.0001$) reduction in global and domain specific (i.e. affective, cognitive, somatic/sensory) PPCS (Table 3-2). Moreover, the effect size for global PPCS reduction was medium (d=0.72), and the effect size for domain specific symptom reductions were also medium (d=0.59-0.68). Patients also reported a statistically significant ($p<0.0001$) reduction in global and domain specific (i.e. re-experiencing,

avoidance and numbing, hyperarousal) persistent PTSD symptoms (Table 4-2). Furthermore, the effect size for global persistent PTSD symptom reduction was small (d=0.34), and the effect sizes for domain specific symptom reductions were small to medium (d=0.25-0.48).

Patients reported a significant reduction ($p<0.001$) in all of the individual PPCS and a significant reduction in all but one of the affective (i.e. feeling sad or depressed) and somatic/sensory (i.e. change in taste and/or smell) symptoms (Table 5-2). Regarding persistent PTSD symptoms (Table 6-2), patients reported a significant reduction ($p<0.001$) in all of the individual persistent hyperarousal symptoms, all but two of the individual persistent re-experiencing symptoms (i.e. flashbacks and psychological reactivity), and a significant reduction in only one of the individual persistent avoidance and numbing symptoms (i.e. foreshortened future).

Compared to patients with only mTBI, patients with comorbid mTBI and PTSD at pre-treatment evaluation reported a statistically significant ($p<0.0001$) increase in global and domain specific (i.e. affective, cognitive, somatic/sensory) PPCS at both the pre-treatment and at the post-treatment evaluation (Table 7-2).

Based on the ANCOVA models (Table 8-2), the only demographic-, injury-, or rehabilitation-related variable with an estimated least square mean NSI post-treatment score that was statistically significant ($p<0.001$) was for patients meeting the diagnosis criteria for PTSD at pre-treatment evaluation compared to patients that did not meet the criteria for

PTSD at pre-treatment evaluation (27.9 v. 21.7; p=0.0009). None of the variables of interest for the ANCOVA models predicting PCL-M score at post-treatment evaluation were statistically significant. TBI mechanism (Blast v. Non-blast) was identified as a potential effect modifier based on a significant ($p<0.10$) interaction term for both the NSI (p=0.003) and PCL-M (p=0.03) ANCOVA models (Table 9-2). The estimated least square mean post-treatment NSI and PCL-M score increased disproportionately for Non-blast patients compared to Blast patients as the pre-treatment NSI and PCL-M scores increased.

DISCUSSION

Our study showed that military patients with chronic mTBI symptoms who completed multidisciplinary treatment reported not only a reduction in persistent post-concussive symptoms but also PTSD symptom resolution. PTSD was the only variable found to significantly influence persistent post-concussive symptom resolution. Previous studies have examined the acute and persistent post concussive and PTSD symptom burden attributed to mTBI among service members using cross-sectional post-deployment surveys[40-42], longitudinal surveys of recruited service members[43,44], post-deployment trauma registries[45], and patient records from military hospitals, Veterans Affairs (VA) Medical Centers, and outpatient clinics[13,31,46,47]. Fewer studies[39] have (1) described the patient population requiring treatment and rehabilitation for persistent post concussive and PTSD symptoms, (2) examined how these persistent symptoms change pre- to post-treatment, or (3) explored potential demographic-, injury-, and rehabilitation-related variables associated with persistent symptom change. To our knowledge, the current study was the first to address all three of

these gaps in the literature by investigating these associations in a large patient population at a major U.S. military hospital.

We found that the multidisciplinary treatment regimen administered at SAMMC was effective in reducing chronic symptoms attributed to mTBI. Walter et al.[39] was the only other study identified that reported pre- to post-treatment persistent post-concussive and PTSD symptom change. In this study, 28 veterans with comorbid mild, moderate, and severe TBI and diagnosed PTSD completed an adapted 8-week Cognitive Behavioral Therapy program following evaluation at a VA Medical Center. As in our study, Walter et al. reported that their therapy program reduced global PPCS assessed by the NSI, and global persistent PTSD symptoms assessed by both the Clinician-Administered PTSD scale and PTSD Checklist-Stressor specific version. However, unlike our study, Walter et al. did not evaluate domain-specific symptom change or individual level symptom change. Further, because they included only patients with comorbid TBI and PTSD, they were unable to show as we did the pattern of symptom resolution for patients with mTBI alone, including that the pre-treatment symptom burden was lower for mTBI-only patients but that they also reported post-treatment symptom resolution.

After adjusting for pre-treatment NSI score, PTSD was the only demographic-, injury-, or rehabilitation-related variable that was significantly associated with PPCS resolution. Again, results from the current study mirror results from Walter et al[39] who found that PTSD symptoms were associated with both pre-treatment PPCS and pre- to post-

treatment resolution of PPCS. Many of the symptoms of PPCS are the same as those for PTSD, including dizziness, memory problems, and irritability. This is likely due to the fact that several of the areas of the brain that are vulnerable to mTBI are also involved in PTSD[48] which may explain why numerous studies have found that service members with PTSD report significantly greater PPCS.[12,13,40,42,49]. Results from 55,000 comprehensive TBI evaluations of patients at VA Medical Centers indicated clinicians attributed 23% of patient PPCS reporting to PSTD or another behavioral health condition alone, while 61% was attributed to a combination of TBI and a behavioral health condition[46]. Thus, PPCS attributed to mTBI likely are at least partially if not entirely due to PTSD and/or other comorbid outcomes such as depression or chronic pain[14-16,50]. This potential multifactorial etiology of persistent symptoms may also help explain why the multidisciplinary treatment program at SAMMC, which specifically addresses these overlapping symptoms was successful in resolving both persistent post-concussive and PTSD symptoms. However, a variety of pre-, peri-, and post-mTBI factors[51] such as pre-mTBI patient personality characteristics[25], symptom exaggeration in the context of potential compensatory litigation[26-28,52], and misattribution of all negative symptoms experienced to a recent trauma[22,23] may also influence symptom resolution and were not available to be investigated in this study. Future studies aimed at confirming our findings should include more detailed information about these factors.

Although 80% of diagnosed TBIs in the U.S. military occur outside the deployed setting, the majority of mTBI patients in our study were young men reporting multiple

deployments to Iraq and Afghanistan. This patient profile reemphasizes the importance of examining deployment related factors such as psychological trauma[9,10], combat stress[21], severity of comorbid injuries[17], and injury etiology[19,20] that may contribute to the greater need for treatment of persistent symptoms attributed to mTBI among service members deployed to the combat theater.

TBI mechanism (Blast v. Non-blast) was identified as a potential effect modifier in both persistent PTSD and PPCS resolution. Patients with greater pre-treatment persistent symptoms and a blast-related mechanism of injury reported greater symptom resolution post-treatment compared to patients with greater pre-treatment persistent symptoms and a non-blast related mechanism of injury. No previous studies specifically investigated the association between blast mechanism and persistent symptom resolution; however, our finding is in contrast with other studies that explored the association between initial persistent symptom burden and blast mechanism and have found no significant difference[53-56]. Thus, future studies are warranted to establish the true association between blast mechanism and persistent symptom resolution.

There are limitations to the current study. First, this was a pre-experimental study (e.g. unblinded, non-randomized, and without a control group) and therefore does not allow for the conclusion that persistent symptom resolution was caused by the treatment and rehabilitation program. However, implementing improved study design features must be weighed against the ethical considerations of withholding treatment from patients and

therefore make the implementation of stronger study design features impractical. Second, a large number of patients were excluded primarily because of missing post-treatment assessment data. We hypothesize that the majority of these assessments were missing because the patients spontaneously stopped treatment because their symptoms had resolved. If so, then the effect on our results for the effectiveness of the treatment would be biased toward the null and the treatment may have been more effective than our results indicate. However, excluded patients reported sustaining a greater number of TBIs[57,58] and a longer time from injury to treatment evaluation[47] indicating that attrition of these patients may have been related to more severe persistent symptoms and a lack of responsiveness to the treatment. Future studies should attempt to quantify differences between these two groups of patients. We also excluded the small number of burn and amputation patients from our study. Future studies with larger populations of patients with serious comorbid injuries should investigate how the presence of these other injuries might influence symptom resolution. Third, this study was a secondary analysis of retrospective data originally collected for clinical purposes and not designed for research. As a result, some important variables of interest (e.g. education, pre-injury characteristics, social support, effort, symptom exaggeration, external incentives) were not collected. Prospective studies on this topic should include these factors. Finally, our study found that the SAMMC multidisciplinary treatment program was effective in reducing persistent symptoms; however, evaluation of the effectiveness of specific elements of the program was not possible due to the lack of detailed information. Future studies using a rigorous methodology with valid and reliable measures

are needed to strengthen the evidence regarding specific aspects of this rehab treatment approach[59].

Conversely, a major strength of the study is the focus on evaluating the effectiveness of multidisciplinary treatment for persistent post-concussive symptoms and the fact that it is the first of its kind. Because SAMMC is one of the largest military medical centers, the results may be applicable to other large military medical centers and VA hospitals that have similar patient complexity and staff competency.

CONCLUSION

The results from this study suggest that the multidisciplinary treatment and rehabilitation approach implemented at SAMMC TBI Clinic is effective in reducing self-reported persistent post concussive and PTSD symptoms. Research from other military treatment facilities is needed to confirm our findings. We also showed the importance of collecting and analyzing clinical data in providing information about treatment effectiveness. Efforts to improve the quality and completeness of clinic data collection will go a long way toward establishing a research culture in an applied clinical setting that can provide quality scientific evidence to improve clinical practice, inform clinical practice guidelines, and ultimately provide patients with the most effective and innovative treatment[60].

Table 1-2. Common mTBI Symptoms and Multidisciplinary Treatment Program at San Antonio Military Medical Center 2008-2013

Symptom	Provider	Treatment	Setting
Dizziness	Occupational Therapist	Vestibular Rehab	Individual
	Physical Therapist	Musculoskeletal Therapy	Individual
Headaches	Physical Therapist	Pharmacotherapy	Individual
	Medical Personnel	Musculoskeletal Intervention	Individual
PTSD/Anxiety	Psychologist	Exposure Therapy	Individual
		Cognitive Behavioral Therapy	Individual
		Relaxation Therapy	Individual
		Mindfulness Therapy	Individual
	Psychologist Medical Personnel	Pharmacotherapy	Individual
Depression	Psychologist	Cognitive Behavioral Therapy	Individual
	Psychologist Medical Personnel	Pharmacotherapy	Individual
Cognitive Impairment	Speech Language Pathologist Occupational Therapist	Cognitive Rehab	Individual Group
Sleep Disturbance	Occupational Therapist	Psychoeducation	Individual Group
	Psychologist Medical Personnel	Pharmacotherapy	Individual Group

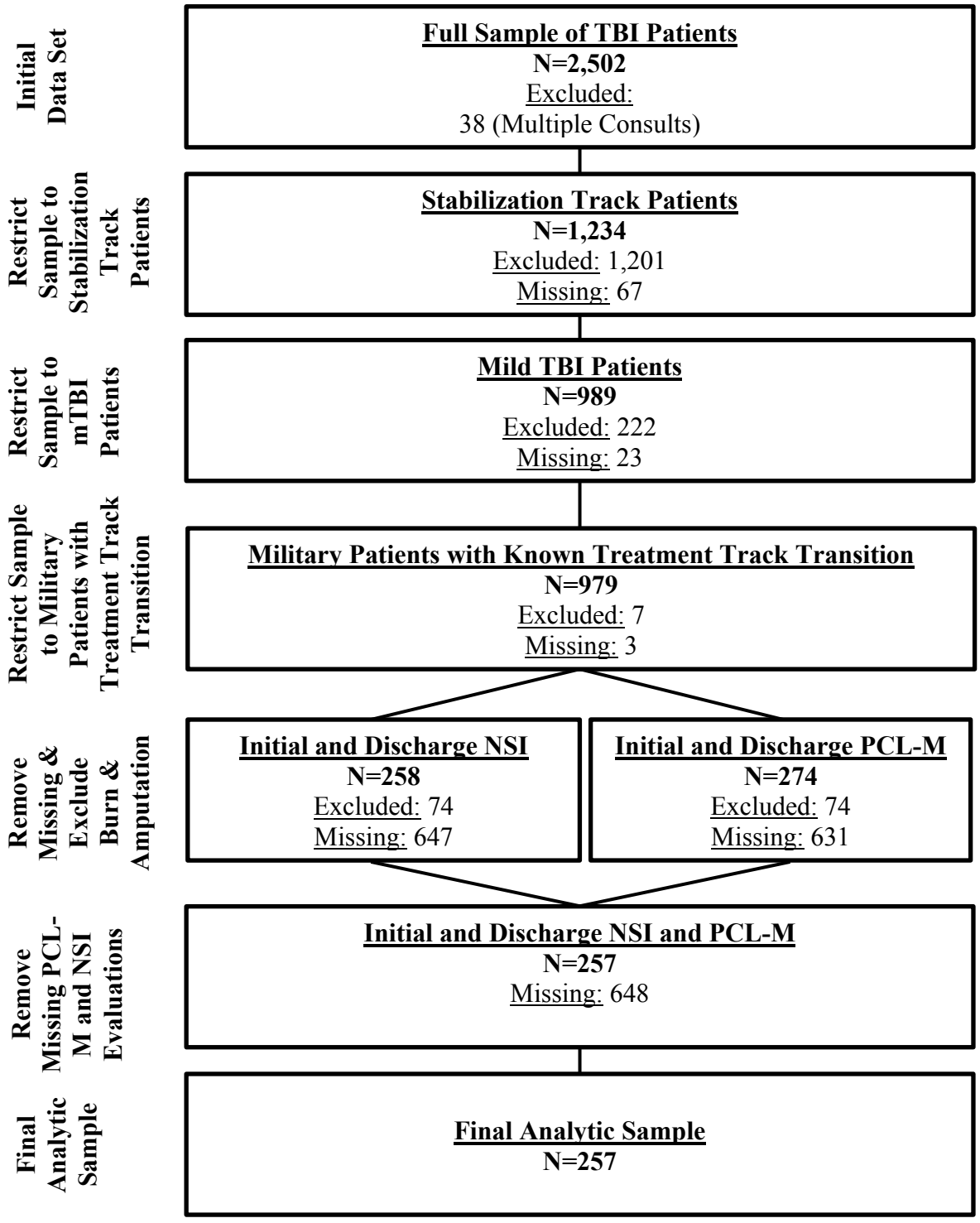

Figure 1-2. Flow diagram of data management to obtain final analytic sample of mTBI Patients Completing Treatment at San Antonio Military Medical Center 2008-2013

Table 2-2. Description of San Antonio Military Medical Center Traumatic Brain Injury Clinic Stabilization Track Patients with Mild Traumatic Brain Injury at Initial Pre-Treatment Evaluation 2008-2013

	Included Patients[a.] (n =257)	Excluded Patients[b.] (n =648)	p-value[c.]
Demographics			
Age at Injury[d.] (mean, s.d.)	30.5 (8.3)	30.0 (8.2)	0.33
Gender (n, %)			
Male	229 (89.1)	594 (91.7)	0.23
Female	28 (10.9)	54 (8.3)	
Enlisted Rank (n, %)			
Junior Enlisted (E1-E4)	106 (41.3)	259 (40.0)	0.12
Non-Commissioned Officers (E5-E9)	131 (51.0)	308 (47.5)	
Officers (Commissioned or Warrant)	20 (7.7)	81 (12.5)	
Injury-related			
Number of Self-Reported TBIs[e.] (n, %)			***0.003***
Single	81 (38.5)	86 (26.5)	
Multiple	129 (61.5)	239 (73.5)	
Number of Self-Reported Deployments (n, %)			0.96
None/Single	118 (46.1)	197 (45.9)	
Multiple	138 (53.9)	232 (54.1)	
Injury Year (n, %)			0.15
1995-2009	153 (59.5)	352 (54.3)	
2010-2013	104 (40.5)	296 (45.7)	
Initial Post-Traumatic Stress Disorder (n, %)			0.83
Yes	88 (34.2)	223 (35.0)	
No	169 (65.8)	414 (65.0)	
TBI Mechanism (n, %)			***0.03***
Blast	159 (61.9)	346 (54.1)	
Non-Blast	98 (38.1)	294 (45.9)	
Geographic Location of Injury (n, %)			0.09
Continental United States	46 (17.9)	94 (19.2)	
Outside Continental United States	11 (4.3)	23 (4.7)	
Operation Iraqi Freedom	108 (42.0)	161 (32.9)	

Operation Enduring Freedom	92 (35.8)	212 (43.3)	
Rehabilitation-Related (mean, s.d.)			
Time from Injury to Treatment Evaluation[f.]	16.3 (24.0)	21.8 (27.5)	***0.003***
Length of Stay[g.]	70.2 (69.3)	60.5 (67.0)	0.06
Total Number of Consults (n, %)			0.05
1	161 (62.7)	449 (69.3)	
≥2	96 (37.4)	199 (30.7)	
Rehabilitation Treatment History (n, %)			0.81
Standard Rehabilitation Transition[h.]	217 (84.4)	543 (83.8)	
Repeated Rehabilitation[i.]	40 (15.6)	105 (16.2)	

[a.]The analytic sample comprised of patients with initial and discharge Neurobehavioral Symptom Inventory and Post-Traumatic Stress Disorder Checklist-Military Version; [b.]Patients excluded from analysis; [c.]Student's t-test was used to test for significant differences (***p<0.05***) of continuous variables and the Chi-square test was used to test for significant differences of categorical variables; [d.]Age reported in years; [e.] TBIs:Traumatic Brain Injuries; [f.]Time reported in months (days/30); [g.]Length reported in days; [h.]Patients following a standard Rehabiltiation progression(i.e. Standard Rehabilitation without transition to another rehabilitation program); [i.]Patients transitioning into another rehabilitation program due to persistent symptoms.

Table 3-2. San Antonio Military Medical Center Traumatic Brain Injury Clinic Stabilization Track Patients Neurobehavioral Symptom Inventory Global and Domain Specific Symptom Cluster Scores 2008-2013 (n=257)

	Mean Pre-Treatment NSI Score	Mean Post-Treatment NSI Score	Mean Difference	Paired t-test	p-value[a.]	Standardized Mean Difference (Cohen's d)
Global Symptoms (0-88)	35.0	23.8	11.2	15.21	***<0.0001***	0.72
Domain Specific Symptom Clusters[b.]						
Affective (0-28)	13.8	10.1	3.7	12.05	***<0.0001***	0.59
Cognitive (0-16)	7.9	5.3	2.6	12.04	***<0.0001***	0.68
Somatic/Sensory (0-44)	13.4	8.6	4.8	13.94	***<0.0001***	0.68

[a.]Bonferroni significance adjustment for domain specific symptom clusters ***p<0.0125***; [b.]Organized by Caplan et al.'s suggested symptom grouping.

Table 4-2. San Antonio Military Medical Center Traumatic Brain Injury Clinic Stabilization Track Patients Post-Traumatic Stress Disorder Syndrome Checklist-Military Version Global and DSM-IV Symptom Criteria Scores 2008-2013 (n=257)

	Mean Pre-Treatment NSI Score	Mean Post-Treatment NSI Score	Mean Difference	Paired t-test	p-value[a.]	Standardized Mean Difference (Cohen's d)
Global Symptoms (17-85)	43.2	37.7	5.5	8.14	***<0.0001***	0.34
Domain Specific Symptom Clusters[b.]						
Re-experiencing (B symptoms; 5-25)	12.3	10.9	1.4	5.79	***<0.0001***	0.25
Avoidance and Numbing (C Symptoms; 7-35)	16.0	14.3	1.7	5.81	***<0.0001***	0.25
Hyperarousal (D symptoms; 5-25)	14.9	12.5	2.4	10.18	***<0.0001***	0.48

[a.] Bonferroni significance adjustment is ***p<0.0125***; [b.] Organized by Diagnostic and Statistical Manual 4th Edition symptom grouping.

Table 5-2. Proportion of San Antonio Military Medical Center Traumatic Brain Injury Clinic Stabilization Track Patients with Persistent Post Concussive Impairment 2008-2013 (n=257)

	Proportion Pre-Treatment	Proportion Post-Treatment	Proportion of Discordant Pairs[a.]	McNemar's Test Statistic	p-value[b.]
Domain Specific Symptom Clusters[c.]					
Affective					
Headaches	67.3	46.7	27.2 (6.6)	32.3	***<0.0001***
Fatigue, loss of energy, getting tired easily	69.7	48.6	28.8 (7.8)	31.0	***<0.0001***
Difficulty falling or staying asleep	81.7	63.4	23.4 (5.1)	30.3	***<0.0001***
Feeling anxious or tense	64.6	43.6	24.5 (3.5)	40.5	***<0.0001***
Feeling depressed or sad	40.1	31.9	15.2 (7.0)	7.7	0.005
Irritability, easily annoyed	72.4	49.0	26.1 (2.7)	48.6	***<0.0001***
Poor frustration tolerance, feeling easily overwhelmed by things	59.1	36.6	26.5 (3.9)	43.1	***<0.0001***
Cognitive					
Poor concentration, can't pay attention, easily distracted	72.8	50.2	26.9 (4.3)	42.1	***<0.0001***
Forgetfulness, can't remember things	81.7	51.8	32.7 (2.7)	65.2	***<0.0001***
Difficulty making decisions	49.4	29.2	26.5 (6.2)	32.2	***<0.0001***
Slowed thinking, difficulty getting organized, can't finish things	56.0	33.9	25.3 (3.1)	44.5	***<0.0001***
Somatic/Sensory					
Feeling Dizzy	34.6	14.4	23.7 (3.5)	38.6	***<0.0001***
Loss of Balance	37.0	13.6	26.5 (3.1)	47.4	***<0.0001***
Poor Coordination, clumsy	35.0	14.8	23.7 (3.5)	38.6	***<0.0001***
Nausea	21.0	10.9	14.4 (4.3)	14.1	***0.0002***

Vision problems, blurring, trouble seeing	37.7	19.8	23.4 (5.5)	28.6	***<0.0001***
Sensitivity to light	41.6	25.7	19.1 (3.1)	29.5	***<0.0001***
Hearing difficulty	45.9	35.4	14.0 (3.5)	16.2	***<0.0001***
Sensitivity to noise	50.6	31.9	22.6 (3.9)	33.9	***<0.0001***
Numbness or tingling on parts of my body	54.9	40.1	20.6 (5.8)	21.2	***<0.0001***
Change in taste and/or smell	15.2	8.6	10.5 (3.9)	7.8	0.005
Loss of appetite or increased appetite	44.8	30.7	20.2 (6.2)	19.1	***<0.0001***

[a.] Proportion of patients with "Moderate" to "Very Severe" symptoms complaints at initial evaluation and "None" to "Mild" complaints at discharge evaluation compared to (proportion of patients with "None" to "Mild" symptoms complaints at initial evaluation and "Moderate" to "Very Severe" complaints at discharge evaluation); [b.] Bonferroni significance adjustment for domain specific symptom clusters ***p<0.001***; [c.] Organized by Caplan et al.'s suggested symptom grouping.

Table 6-2. Proportion of San Antonio Military Medical Center Traumatic Brain Injury Clinic Stabilization Track Patients with Persistent Post Traumatic Stress Disorder Symptom Impairment 2008-2013 (n=257)

	Proportion Pre-Treatment	Proportion Post-Treatment	Proportion of Discordant Pairs[a.]	McNemar's Test Statistic	p-value[b.]
Domain Specific Symptom Clusters[c.]					
Re-experiencing (B symptoms)					
B1: Intrusive Memories	56.0	38.9	20.6 (3.5)	31.2	***<0.0001***
B2: Nightmares	49.4	38.1	16.7 (5.5)	14.8	***0.0001***
B3: Flashbacks	25.7	22.6	10.1 (7.0)	1.5	0.22
B4: Psychological Disturbance	47.1	31.3	22.6 (6.6)	22.4	***<0.0001***
B5: Psychological Reactivity	42.4	35.8	13.2 (6.6)	5.7	0.02
Avoidance and Numbing (C Symptoms)					
C1: Thoughts/Feelings	45.9	37.7	16.0 (7.8)	7.2	0.007
C2: Activities/Places/People	38.1	31.9	14.4 (8.2)	4.4	0.04
C3: Trauma-Related Amnesia	35.4	26.9	14.8 (6.2)	9.0	0.003
C4: Diminished Interest	42.4	33.1	16.7 (7.4)	9.3	0.002
C5: Detachment	43.2	34.6	15.2 (6.6)	8.6	0.003
C6: Restricted Affect	33.5	31.5	10.1 (8.2)	0.5	0.47
C7: Foreshortened Future	24.9	15.2	15.2 (5.5)	11.8	***0.0006***
Hyperarousal (D symptoms)					
D1: Sleeping difficulty	78.6	60.7	23.7 (5.8)	27.8	***<0.0001***
D2: Irritability/Anger	54.1	34.6	24.1 (4.7)	33.8	***<0.0001***
D3: Difficulty Concentrating	69.3	44.8	30.0 (5.5)	43.6	***<0.0001***
D4: Hypervigilance	54.5	42.4	19.5 (7.4)	13.9	***0.0002***
D5: Exaggerated Startle	49.4	37.4	17.5 (5.5)	16.3	***<0.0001***

[a.] Proportion of patients reporting "Moderately" to "Extremely" high frequency of symptoms complaints at initial evaluation and "Not at All" to "Little Bit" frequency of symptom complaints at discharge evaluation compared to (proportion of patients reporting "Not at All" to "Little Bit" high frequency of symptoms complaints at initial evaluation and "Moderately" to "Extremely" frequency of symptom complaints at discharge evaluation); [b.] Bonferroni significance adjustment for domain specific symptom clusters ***p<0.001***; [c.] Organized by Diagnostic and Statistical Manual 4th Edition symptom grouping.

Table 7-2. Neurobehavioral Symptom Inventory Global and Domain Specific Symptom Cluster Scores for San Antonio Military Medical Center Traumatic Brain Injury Clinic mTBI Stabilization Track Patients Stratified by Pre-Treatment PTSD diagnosis 2008-2013 (n=257)

			Pre-Treatment Evaluation		
	mTBI& PTSD[a.] (n=88)	mTBI[b.] (n=169)	Δ[c.]	t-test	p-value[d.]
Global Symptoms (0-88)	48.7	27.9	20.8	14.2	***<0.0001***
Domain Specific Symptom Clusters[f.]					
Affective (0-28)	19.5	10.8	8.7	16.5	***<0.0001***
Cognitive (0-16)	10.6	6.4	4.2	9.3	***<0.0001***
Somatic/Sensory (0-44)	18.6	10.7	7.9	9.7	***<0.0001***
			Post-Treatment Evaluation		
	mTBI& PTSD[a.] (n=88)	mTBI[b.] (n=169)	Δ[e.]	t-test	p-value[d.]
Global Symptoms (0-88)	36.2	17.4	18.8	10.2	***<0.0001***
Domain Specific Symptom Clusters[f.]					
Affective (0-28)	15.0	7.5	7.5	9.9	***<0.0001***
Cognitive (0-16)	7.8	3.9	3.9	8.6	***<0.0001***
Somatic/Sensory (0-44)	13.4	6.1	7.3	8.3	***<0.0001***

[a.]Patients with mTBI and PTSD at initial evaluation; [b.]Patients with mTBI only; [c.]Mean Difference at Pre-Treatment Evaluation; [d.]Bonferroni significance adjustment is ***p<0.001***; [e.]Mean Difference at Post-Treatment Evaluation; [f.]Organized by Caplan et al.'s suggested symptom grouping.

Table 8-2. Analysis of Covariance[a.] of San Antonio Military Medical Center Traumatic Brain Injury Clinic Stabilization Track Patients Global Post-Concussive and Post Traumatic Stress Disorder Symptoms 2008-2013 (n=257)

	Neurobehavioral Symptom Inventory		
Covariates	**Adjusted Mean[b.] (95% CI)**	**Mean Difference[c.] (95% CI)**	**p-value[d.]**
Demographics			
Age at Initial Evaluation		1.4 (-4.2, -1.4)	0.32
≤29 years	23.2 (21.3, 25.1)		
>29 years	24.6 (22.6, 26.5)		
Sex		-1.1 (-5.5, 3.3)	0.62
Male	23.7 (22.3, 25.2)		
Female	24.8 (20.7, 25.2)		
Enlisted Rank		-1.6 (-4.4, 1.3)	0.28
Junior Enlisted	22.9 (20.8, 25.1)		
NCO/Officer	24.5 (22.7, 26.3)		
Injury-related			
Injury Year		0.7 (-2.0, 3.5)	0.59
1995-2009	24.1 (22.4, 25.9)		
2010-2013	23.4 (21.2, 25.5)		
Number of self-reported TBIs[e.]		-0.5 (-3.6, 2.5)	0.73
None/Single	23.5 (21.1, 25.9)		
Multiple	24.1 (22.2, 26.0)		
Number of Deployments		0.6 (-2.2, 3.4)	0.68
Single	24.2 (22.2, 26.2)		
Multiple	23.6 (21.7, 25.5)		
PTSD at Initial Evaluation		6.2 (2.6, 9.9)	***0.0009***

Yes	27.9 (25.2, 30.7)		
No	21.7 (19.9, 23.5)		
TBI Mechanism[f.,g.]		0.9 (-1.9, 3.6)	0.54
Blast	24.2 (22.2, 25.9)		
Non-Blast	23.4 (21.2, 25.6)		
Geographic Location of Injury		1.9 (-1.4, 5.2)	0.25
OEF/OIF	24.3 (22.7, 25.8)		
CONUS/OCONUS	22.4 (19.5, 25.2)		
Rehabilitation-Related			
Time from Injury to Treatment Evaluation		-2.1 (-4.9, 0.7)	0.14
≤5 months	22.8 (20.8, 24.7)		
>5 months	24.9 (22.9, 26.8)		
Length of Stay		-3.8 (-1.1, -6.6)	0.006
≤50 days	22.0 (20.1, 23.9)		
>50 days	25.8 (23.9, 27.7)		
Total Number of Consults		0.2 (-2.6, 3.1)	0.87
Single	23.9 (22.2, 25.7)		
Multiple	23.7 (21.5, 25.9)		
Rehab Treatment History[h.]		-2.4 (-6.1, 1.4)	0.22
Standard	23.5 (22.0, 25.0)		
Repeated	25.8 (22.4, 29.3)		

	Post-Traumatic Stress Disorder Checklist-Military Version		
Covariates	**Adjusted Mean[b.] (95% CI)**	**Mean Difference[c.] (95% CI)**	**p-value[d.]**
Demographics			

Age at Initial Evaluation		-1.4 (-3.9, 1.2)	0.30
≤29 years	37.0 (35.2, 38.8)		
>29 years	38.4 (36.5, 40.2)		
Sex		0.4 (-3.7, 4.6)	0.83
Male	37.7 (36.4, 41.2)		
Female	37.2 (33.4, 39.1)		
Enlisted Rank		-1.4 (-4.0, 1.2)	0.07
Junior Enlisted	36.9 (34.8, 38.9)		
NCO/Officer	38.3 (36.6, 39.9)		
Injury-related			
Injury Year		-1.7 (-4.3, 1.0)	0.21
1995-2009	37.0 (35.3, 38.7)		
2010-2013	38.7 (36.6, 40.7)		
Number of self-reported TBIs[e.]		-0.7 (-2.2, 3.6)	0.65
Single	37.9 (35.6, 40.2)		
Multiple	37.2 (35.4, 39.0)		
Number of Deployments		0.2 (-2.4, 2.9)	0.86
Single	37.9 (35.8, 39.9)		
Multiple	37.6 (36.0, 39.3)		
TBI Mechanism[f.,g.]		0.1 (-2.8, 2.5)	0.92
Blast	37.8 (36.3, 39.5)		
Non-Blast	37.7 (35.7, 39.8)		
Geographic Location of Injury		1.1 (-2.0, 4.2)	0.48
OEF/OIF	37.9 (36.5, 39.4)		
CONUS/OCONUS	36.8 (34.1, 39.5)		
Rehabilitation-Related			
Time from Injury to Treatment Evaluation		-0.4 (-3.0, 2.3)	0.78

≤5 months	37.5 (35.6, 39.3)		
>5 months	37.9 (36.0, 39.7)		
Length of Stay		-2.2 (-4.8, 0.4)	0.10
≤50 days	36.6 (34.8, 38.4)		
>50 days	38.8 (37.0, 40.7)		
Total Number of Consults		0.1 (-2.5, 2.8)	0.91
Single	37.7 (36.1, 39.3)		
Multiple	37.6 (35.5, 39.7)		
Rehab Treatment History[h.]		-0.8 (-4.4, 2.7)	0.64
Standard	37.5 (36.1, 38.9)		
Repeated	38.4 (35.1, 41.6)		

[a.] Model: $Y(Global\ Discharge\ Evaluation\ Score) = \beta_\theta + \beta_1(Global\ Initial\ Evaluation\ Score) + \beta_2(Covariate)$; [b.] Least Square Mean and 95% Confidence Interval of Least Square Mean; [c.] Difference between Least Square Means and 95% Confidence Interval of Difference Between Least Square Means; [d.] p-value for difference between Least Square Means and Bonferroni significance adjustment is ***p<0.001***; [e.] TBI: Traumatic Brain Injury; [f.] Significant interaction found between variable of interest and pre-treatment NSI evaluation score (see Table 9-2); [g.] Significant interaction found between variable of interest and pre-treatment PCL-M evaluation score; [h.] Patients following a standard Rehabilitation progression(i.e. Standard Rehabilitation without transition to another rehabilitation program) and patients transitioning into repeated rehabilitation programs due to persistent symptom.

Table 9-2. Analysis of Covariance[a.] Effect Modifiers of San Antonio Military Medical Center Traumatic Brain Injury Clinic Stabilization Track Patients Global Post-Concussive and Post Traumatic Stress Disorder Symptoms 2008-2013 (n=257)

	Neurobehavioral Symptom Inventory		
Covariates	**Adjusted Mean[b.] (95% CI)**	**Mean Difference[c.] (95% CI)**	**p-value[d.]**
TBI Mechanism			
Blast & Initial NSI Score = 55	37.1 (34.3, 40.0)	-3.1 (-7.6, 1.5)	0.18
Non-blast & Initial NSI Score = 55	40.2 (36.6, 43.8)		
Blast & Initial NSI Score = 65	43.6 (39.8, 47.4)	-5.0 (-11.1, 1.1)	0.11
Non-blast & Initial NSI Score = 65	48.6 (43.8, 53.4)		
Blast & Initial NSI Score = 75	50.1 (45.3, 54.9)	-7.0 (-14.7, 0.8)	0.08
Non-blast & Initial NSI Score = 75	57.1 (51.0, 63.1)		

	Post-Traumatic Stress Disorder Checklist-Military Version		
Covariates	**Adjusted Mean[b.] (95% CI)**	**Mean Difference[c.] (95% CI)**	**p-value[d.]**
TBI Mechanism			
Blast & Initial PCL-M Score = 55	46.1 (44.2, 48.1)	-1.9 (-5.3, 1.3)	0.24
Non-blast & Initial PCL-M Score = 55	48.0 (45.4, 50.8)		
Blast & Initial PCL-M Score = 65	53.1 (50.5, 55.8)	-3.8 (-8.3, 0.7)	0.10
Non-blast & Initial PCL-M Score = 65	56.9 (53.3, 60.5)		
Blast & Initial PCL-M Score = 75	60.1 (56.6, 63.7)	-5.6 (-11.5, 0.3)	0.06
Non-blast Initial PCL-M Score = 75	65.7 (61.1, 70.4)		

[a.] Model: $Y(Global\ Discharge\ Evaluation\ Score) = \beta_0 + \beta_1(Global\ Initial\ Evaluation\ Score) + \beta_2(Covariate) + \beta_3(Interaction)$; [b.] Least Square Mean and 95% Confidence Interval of Least Square Mean; [c.] Difference between Least Square Means and 95% Confidence Interval of Difference Between Least Square Means; [d.] p-value for difference between Least Square Means, Bonferroni significance adjustment is ***p<0.001.***

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JOURNAL ARTICLE 2

Title of Journal Article: Prediction Equations of Persistent Post-Concussive and Post-Traumatic Stress Disorder Symptom Change among Military Service Members with Mild Traumatic Brain Injury Completing Treatment and Rehabilitation at San Antonio Military Medical Center 2008-2013

Name of Journal Proposed for Article Submission: Journal of Head Trauma Rehabilitation

INTRODUCTION

Advances in antiseptic and neurosurgical techniques, protective military equipment, rapid air evacuation of wounded soldiers, and adoption of policies supporting the use of these new techniques have all increased the survival from traumatic brain injuries (TBIs) that were often fatal during earlier American conflicts such as the Civil War[1,2]. Because of the increased survivability following a TBI, comprehensive interdisciplinary treatment programs such as the one at Brooke General Hospital at Fort Sam Houston; San Antonio, Texas[1] and other post-acute rehabilitation programs[3] were first established during World War II in an effort to improve the outcomes of more severely injured service members.

Prognostic models that predict the outcome of these more severe TBIs at admission to hospital have greatly helped doctors and patients make decisions about early medical treatment[4]. Similarly, prediction equations that could identify, at enrollment into rehabilitation, the types of patients most likely to benefit would help clinicians make better

decisions about who to enroll and what types of later treatments might facilitate recovery and facilitate their reintegration into their work and social environments post-injury. A focus on less severe or mild TBI (mTBI) could be especially useful for the military because of the high incidence of mTBI[5] during the period of the conflicts in Iraq and Afghanistan. As a result, facilitating recovery from persistent post-concussive symptoms (PPCS) and related post-traumatic stress disorder symptoms associated with these injuries has been a major focus of treatment and rehabilitation during this time.

Research exploring prediction equations using potential clinical factors associated with persistent post-concussive and PTSD symptom change within the military population is lacking. Beginning to identify prediction equations using clinical factors associated with symptom resolution based on scientific evidence and clinical expertise may help clinicians to effectively develop treatment and rehabilitation plans that successfully manage patient symptoms. Therefore, the purpose of this study was to develop prediction equations of (1) global post-concussive and post-traumatic symptom impairment post-treatment and (2) clinically meaningful post-traumatic stress symptom treatment response among U.S. military service members and veterans with a diagnosed mTBI completing a pre- and post-treatment clinical evaluation at the San Antonio Medical Military Center (SAMMC) TBI Clinic from 2008-2013.

METHODS

Study Design

Patient records were used for a retrospective, one group, pre-experimental pre- to post-treatment study design to identify factors associated with persistent post-concussive and post-traumatic stress symptom resolution among service members and veterans completing mTBI rehabilitation at SAMMC.

Data Source

Patients were referred by their primary care manager to the SAMMC TBI clinic from 2008-2013. As part of standard operating procedures, all individuals referred to the clinic completed self-report symptom questionnaires on a computer kiosk prior to their initial encounter with physical medicine and rehabilitation (PM&R) personnel (e.g. Physician, Physician Assistant, and Nurse Practitioner). Next, the assigned PM&R personnel decided if the (1) patient had a TBI, (2) if so, the severity of the TBI, and (3) if any treatment was required.

Lastly, a "standard" Stabilization Treatment Track program designed by PM&R personnel uses a diverse combination of therapeutic techniques targeted to the individual (Table 1-3) based on the patients' post-traumatic stress and persistent post-concussive symptoms. The Stabilization Treatment Track program was designed and administered at SAMMC, and was designed specifically for mTBI patients with common PPCS described in Table 1-3.

Only patients with a diagnosed mTBI who completed the Stabilization Treatment Track program were included in the analyses. Of the 2,502 TBI patients evaluated at SAMMC from 2008-2013, 989 (39.5%) patients sustained a mTBI and were administered the Stabilization Treatment Track program (Figure 1-3). A further 10 patients were excluded due to an unknown or missing treatment track transition at SAMMC. Burn and amputation patients (n=74) were excluded because compared to mTBI patients without concomitant burns or amputations; these patients require a unique treatment plan to meet there therapeutic needs. Lastly, 648 patients were excluded because they were missing initial (pre-treatment) and/or discharge (post-treatment) assessments (NSI and PCL-M) necessary for pre- to post treatment symptom evaluation. Therefore, the final analytic sample consisted of 257 mTBI patients completing treatment and rehabilitation due to PPCS and PTSD symptoms attributed to mTBI.

Outcome Variables

Outcome 1: Persistent Post Concussive Symptom Resolution

PPCS were assessed with the Neurobehavioral Symptom Inventory (NSI)[6]. The NSI (Appendix B) is a 22-item self-report inventory of common post-concussive symptoms. Based on a recent factor analysis from three different military samples[7], three domain specific symptom clusters (i.e. cognitive, affective, and somatic/sensory) were analyzed in the military sample for this study. Global symptoms refer to the total rating of post-concussive symptoms reported across all three-symptom clusters and scores range from 0 to

88 on the NSI. The outcome for PPCS resolution was post-treatment global NSI score, which is a measure of post-treatment PPCS impairment.

A recent psychometric study reported that the NSI had high internal consistency and moderate external validity among a sample of OEF/OIF veterans[8]. The study reported high internal consistency (α=0.95) for the global post-concussive symptom rating and for the cognitive (α=0.92), affective (α=0.91), and somatic/sensory (α=0.88) subscale post-concussive domains. In addition, the NSI was positively associated with probable TBI diagnosis ($r=0.41$; $p<0.001$). However, the association was attenuated ($r=0.24$; $p<0.001$) after adjustment for probable post-traumatic stress disorder (PTSD), depression, and general anxiety disorder. Therefore, the association between NSI score and TBI diagnosis was strongly influenced by PTSD, depression, and general anxiety disorder symptomology.

Outcome 2: Persistent Post-Traumatic Stress Disorder Symptom Resolution

Persistent PTSD symptoms were assessed with the PTSD Checklist-Military version (PCL-M)[9]. The PCL-M (Appendix C) is a 17-item self-rated interval rating scale that asks about symptoms specific to stressful military experiences. The 17-items on the PCL-M capture one of three distinct symptom clusters representing B (re-experiencing; questions 1-5), C (avoidance and numbing; questions 6-12), and D (hyperarousal; questions 13-17) item diagnostic criteria for PTSD in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[10]. Patient global symptom severity scores ranging from 17 to 85 were

calculated by summing scores across all 17-items. The outcome for persistent PTSD symptom resolution was post-treatment global PCL-M score, which is a measure of post-treatment persistent PTSD symptom impairment.

The PCL-M generally has strong reliability and validity. The two to three day test-retest reliability among a sample of 123 male Vietnam veterans reported a Cronbach's alpha (α) of 0.96[11]. Further, the internal consistency was high for the total symptom severity score (α=0.97), B item symptom criteria (α=0.93), C item symptom criteria (α=0.92), D item symptom criteria (α=0.92), and item specific symptom scores (α=0.62-0.87). In addition, the study reported strong convergent validity between the PCL-M and a variety of other assessments including the Mississippi Scale for Combat-Related PTSD (r=0.85-0.93, p-value unknown). A more recent study supported these findings of strong convergent validity between the Impact of Event Scale-Revised and the PCL-M (r=0.84, $p<0.001$) among a different sample of Vietnam veterans[12].

Outcome 3: Clinically Meaningful Persistent PTSD Treatment Response

The National Center for PTSD[13,14] recommends that a 10-point change in reported symptoms is the minimum threshold indicating clinically meaningful symptom resolution. Therefore, a dichotomous variable was created by categorizing patients with clinically meaningful treatment response (pre-treatment PCL-M – post-treatment PCL-M $\geq$10) and patients without clinically meaningful symptom resolution (pre-treatment PCL-M – post-

treatment PCL-M <10). The outcome for the prediction equations with outcome 3 was a clinically meaningful persistent PTSD treatment response (yes/no).

Predictor Variables

Predictor variables were chosen based on the following three criteria: (1) expert clinical consensus of predictive importance of a given variable; (2) literature support for the importance of a given variable; and (3) the variable was collected or available for abstraction from electronic medical records. Based on these criteria, six variables were selected to form the basis of model construction for all three outcomes of interest.

Global pre-treatment NSI and PCL-M scores were selected and scaled to 5-point increments to improve interpretation of parameter estimates. Age at injury in years was included in all full models. Age was also scaled to 5 year increments to improve interpretation of parameter estimates. Pre-treatment PTSD diagnosis was included in models with outcome 1 as the dependent variable. The methodology used to diagnose PTSD in this study required that patients rated at least (1) 1 B item (questions 1-5), (2) 3 C item (questions 6-12) and (3) 2 D item (questions 13-17) symptoms as "moderately" symptomatic or above (responses 3 through 5) and (4) reported a global PCL-M score ≥ 50[15]. If the patient did not meet these requirements then they were not diagnosed with pre-treatment PTSD. Mild TBI mechanism of injury (blast/non-blast) and an interaction term of mTBI mechanism with pre-treatment NSI (outcome 1) and pre-treatment PCL-M (outcome 2 and 3) score also met the criteria for selection as predictor variables. Compared to a non-blast mechanism of injury, a

blast-related mTBI was used as a proxy for exposure to higher levels of psychological trauma and combat stress[16-18] in the war theater resulting in an increased pre-treatment persistent symptom burden. Further, there is evidence that acute PTSD symptoms following trauma may increase over time[19-22] and impair post trauma symptom resolution[20,23]. Therefore, we hypothesized that patients with persistent post concussive and PTSD symptoms may initially report significantly more impairment and experience poorer symptom resolution compared to non-blast patients. Lastly, time from sustained mTBI to pre-treatment evaluation (≤5 months/>5 months) was the final variable that met the criteria for selection as a predictor variable.

Statistical Methods

Measures of central tendency (mean) and dispersion (standard deviation) were reported for continuous demographic-, injury-, and rehabilitation-related variables. The number and proportion of categorical variables were reported for the study patients. Continuous variables, including the NSI and PCL-M interval rating scale summed global scores, were considered normal under the assumption of the central limit theorem where n ≥30[24]. To evaluate differences between participants included in the study and participants excluded, Student's t-test was used to test for significant differences ($p<0.05$) of continuous variables and the Chi-square test was used to test for significant differences of categorical variables, respectively.

Primary Hypotheses

Post-treatment NSI score was regressed on pre-treatment NSI score in model 1. Model 2 represents post-treatment NSI score regressed on pre-treatment NSI score, age at injury, pre-treatment PTSD diagnosis, mTBI mechanism, mTBI mechanism and pre-treatment NSI interaction term, and time from injury to treatment evaluation. Model 1 and 2 were compared with a partial F-test to evaluate the variability explained of post-treatment PPCS. The first hypothesis was that model 2 explained more variability in post-treatment NSI scores compared to model 1.

Post-treatment PCL-M score was regressed on pre-treatment PCL-M score in model 3. Model 4 represents post-treatment PCL-M score regressed on pre-treatment PCL-M score, age at injury, mTBI mechanism, mTBI mechanism and pre-treatment PCL-M interaction term, and time from injury to treatment evaluation. Model 3 and 4 were compared with a partial F-test to evaluate the variability explained of post-treatment persistent PTSD symptoms. The first hypothesis was that model 4 explained more variability in post-treatment PCL-M scores compared to model 3.

Secondary Hypothesis

Clinically meaningful persistent PTSD treatment response was regressed on pre-treatment PCL-M score in model 5. Model 6 represents clinically meaningful persistent PTSD treatment response regressed on pre-treatment PCL-M score, age at injury, mTBI mechanism, mTBI mechanism and pre-treatment PCL-M interaction term, and time from

injury to treatment evaluation. Model 5 and 6 were compared with a partial likelihood ratio test to evaluate the variability explained of clinically meaningful persistent PTSD treatment response. The first hypothesis was that model 6 explained more variability in clinically meaningful persistent PTSD treatment response compared to model 5.

Model Specification

All models were assessed to ensure that all model assumptions of normality, linearity, and homoscedasticity were met. Linear regression model residuals were normal and homoscedastic based on analysis of descriptive plots. Further, multicollinearity between predictors was assessed with multivariate linear regression tolerance testing and a variable tolerance threshold of 0.5 for predictors not used in an interaction term.

Model Estimation

This study presents maximum likelihood parameter estimates for all linear regression (models 1-4) and logistic regression models (models 5-6). This study also reports a uniform heuristic shrinkage estimate[25] for regression coefficients in the logistic regression models (models 5 and 6) because this technique is recommended for models with an event per variable value that is less than 20[26] to improve goodness of fit with small samples.

Model Performance

The partial F-test was performed to determine if the full linear regression models (models 2 and 4) provided a statistically significant difference on the fit of post-treatment

NSI and PCL-M scores compared to the reduced models (models 1 and 3). The Likelihood ratio test was performed to determine if model 6 provided a statistically significant difference on the fit of persistent PTSD symptom treatment response compared to model 5. The adjusted R-squared goodness of fit statistics for linear regression models and corrected Akaike information criterion (AICC) were also reported (models 1-4). Discriminative ability of the logistic regression model (models 5 and 6) were assessed by the area under the curve (AUC) summary measure based on Receiver Operator Characteristic (ROC) curves.

Model Validation

Internal validation of the prediction equations was performed by using a bootstrapping re-sampling technique[27,28] where participants are drawn at random from the original sample with replacement. The bootstrapping technique in this study used 1000 individual bootstrap replicates (each with n=257). The mean parameter estimates with 95% confidence intervals for each predictor and mean model fit statistics with 95% confidence intervals were calculated across each replicate sample.

Sample Size Calculation and/or Study Power

A ratio of events per variable (EPV) method was used to ensure adequate power to estimate prediction equation models 1-6. Evidence from simulation models supports 10 events per predicative variable as the minimum needed for model estimation[29].

Human Subjects, Animal Subjects, or Safety Considerations

The Brooke Army Medical Center (BAMC) and University of Texas School of Public Health (HSC-SPH-14-0126) Institutional Review Board approved this retrospective study.

RESULTS

Patients excluded from the analyses reported a greater proportion of multiple TBIs (73.5% v. 61.5%; p=0.003), fewer blast-related mTBIs (54.1% v. 61.9%, p=0.03), and a longer time from injury to initial treatment evaluation (21.8 months v. 16.3 months; p=0.003) (Table 2-3). Fewer excluded patients than included patients had 2+ consults (30.7% v 37.4% respectively, borderline significance, p=0.05).

Study patients were predominantly male (89.1%), non-commissioned or commissioned/warrant officers (58.7%), and their mean age was 30 (s.d. = 8.3) years old. Further, the majority of patients reported multiple TBIs (61.5%), multiple deployments (53.9%), a blast-related mechanism of mTBI (61.5%), and sustaining their most recent mTBI during OEF/OIF (77.8%). Approximately one-third of patients met the criteria for a diagnosis of PTSD at pre-treatment evaluation. The mean time from injury to treatment evaluation was over 1 year (16.3 months) and the average length of treatment stay was approximately 2 months (70.2 days). In addition, the majority of patients had one consult (62.7%) and followed a standard treatment track transition (84.4%).

Model 2 with post-treatment NSI score as the outcome explained more variability than model 1 ($F\text{-test}_{5,250}=4.1$; p=0.001) (Table 3-3). However, model 4 with post-treatment PCL-M score as the outcome did not explain more variability than model 3 ($F\text{-test}_{4,251}=1.1$; p=0.17) (Table 4-3). Model 6 with clinically meaningful persistent PTSD treatment response as the outcome ($\chi^2(4, n=257)=1.0$; p=0.91) was not more discriminative than model 5 (Table 5-3). For all three prediction equations, the mean parameter estimates across the 1000 bootstrap replicates were similar to the parameter estimates from the original sample. However, bootstrap parameter estimate and their 95% confidence intervals for two of the predictor variables included zero for models 2, 4, and 6 (i.e. age at injury and time from treatment to evaluation) indicating that we did not observe a meaningful association with persistent PTSD or PPCS post-treatment scores. Further, the bootstrap parameter estimate and their 95% confidence intervals for the mTBI mechanism interaction term included zero or a clinically insignificant estimate in models 2, 4, and 6 that also indicates we did not observe a meaningful association with persistent PTSD or PPCS post-treatment scores for this predictor variable.

The adjusted R-squared values for models 2 and 4 were 0.53 and 0.59, respectively. The average adjusted R-squared values and 95% confidence intervals for models 2 and 4 across the 1000 bootstrap replicates were 0.54 (0.46, 0.62) and 0.60 (0.52, 0.68), respectively. The AUC value for model 6 with clinically meaningful persistent PTSD treatment response as the outcome was 0.75. The average AUC values and 95% confidence intervals across the 1000 bootstrap replicates was 0.76 (0.70, 0.82).

DISCUSSION

Prediction equations of treatment response among patients with persistent post concussive and PTSD symptoms revealed that pre-treatment symptom burden and diagnosis of PTSD were the only important factors identified from among the six demographic-, injury-, and rehabilitation-related factors that were studied. The literature evaluating factors predicting successful symptom resolution following mTBI treatment is limited. However, studies of this type can provide extremely useful information that can be used to identify and target treatment to the type of patient most likely to respond, as well as indicating for which type of patient symptom resolution is less likely. Using a sample of U.S. service members completing treatment and rehabilitation for persistent symptoms attributed to mTBI, the current study addressed this gap in the literature by presenting prediction equations of persistent post concussive and PTSD symptom resolution and PTSD treatment response. To our knowledge, this was the first study to explore predictive equations of persistent post concussive and PTSD symptom resolution attributed to mTBI using a wide range of factors of interest.

With regard to post-treatment PPCS burden, we found that pre-treatment NSI (PPCS symptom burden) score and PTSD diagnosis were the most meaningful predictors. The literature evaluating predictive factors of successful symptom resolution following concussion/mTBI treatment is limited. However, the finding that pre-treatment level of PPCS and PTSD diagnosis were the most clinically meaningful factors in prediction equations of post-treatment PPCS burden is consistent with previous research among civilian hospital

patients with mTBI[30,31] and a retrospective analysis of male veterans from the Vietnam Experience Study[32]. Ponsford et al.[31] found that pre-injury psychiatric diagnosis and anxiety symptoms present one week post-injury were associated with higher post concussive symptom scores but mTBI diagnosis was not associated at 3 months post- injury. Stulemeijer et al.[30] found that acute self-report of a lack of severe post-concussive symptoms and no acute post-traumatic stress post-injury were associated with greater odds of reporting "low" PPCS, defined as no more than a mild impairment that did not interfere with daily activities. As in our study, these previous studies found that pre-treatment comorbid psychiatric variables were important predictive factors associated with PPCS resolution, and thus may be less likely to resolve with mTBI treatment. This may explain why based on the bootstrap estimates and 95% confidence intervals, pre-treatment NSI score and a diagnosis of PTSD at pre-treatment evaluation were the most stable and clinically meaningful variables associated with post-treatment PPCS scores. The other variables of interest, including the TBI mechanism interaction, may be due to sampling error and have no true population level effect because the bootstrap estimate 95% confidence intervals included zero.

With regard to post-treatment persistent PTSD symptom burden and PTSD symptom treatment response, we found that pre-treatment PCL-M (PTSD symptom) score was the only meaningful predictor. Although the impact of demographic-, injury-, and rehabilitation-related factors on persistent PTSD symptom resolution has not been fully explored, it is not surprising that these factors did not significantly improve prediction equations of persistent PTSD symptom resolution and treatment response. The literature suggests that other pre-

trauma (e.g. unit cohesion, education, prior trauma, prior psychiatric history), peri-trauma (e.g. combat exposure) and post-trauma factors (e.g. trauma severity, post-trauma life stress, and lack of social support)[33-38] not available in the current analyses are likely to be among the most important influences on persistence and resolution of PTSD symptoms. Future studies need to include these factors to improve future prediction equations. The lack of these important factors in our study may explain why based on the bootstrap estimates and 95% confidence intervals, pre-treatment PCL-M score was the most stable and clinically meaningful variables associated with post-treatment PPCS scores. The other variables of interest, including the TBI mechanism interaction, may have no true population level effect because the bootstrap estimate 95% confidence intervals included zero or a range of values that are not likely to be clinically meaningful.

The current study has several limitations. First, the pre-specified models in this study were internally validated but future studies should use a larger sample of patients in order to develop predictive models that can be externally validated to ensure their generalizability. Second, approximately 72% of potential 905 patients were excluded from analysis because they did not complete a pre-treatment (7%) or post-treatment (65%) evaluation of persistent symptoms, which could limit the validity of results. Third, this study was a secondary data analysis based on data from patient medical records so other predictor variables of interest (e.g. depression[39,40], chronic pain[41], severity of other physical injuries sustained[42,43], pre-injury personality characteristics[44]) could not be included in the current models. Furthermore, some available predictors of interest could not be used due to a limited sample size (i.e. sex

and CT/MRI results) or concerns over the validity of self-reported data (i.e. number of previous TBIs sustained). Lastly, the NSI was designed as an assessment of global post concussive symptoms and no valid, reliable, or clinically meaningful cut-point for PPCS resolution have been established. Therefore, prediction equation models of PPCS treatment response could not be developed.

Strengths of the study include the innovative approach that involved assessing clinical predictors of persistent symptom resolution among a sizeable patient population completing treatment and rehabilitation at a major U.S. military TBI Clinic. Moreover, the study used a rigorous methodology with an event per variable ratio that was greater than 10 to improve validity of results. The prediction models for PTSD used a clinically meaningful outcome of treatment response. Lastly, SAMMC is one of the largest military medical treatment facilities (MTFs) with results applicable to other large MTFs and VA hospitals based on patient complexity and staff competency.

CONCLUSION

Identifying clinical predictors of symptom resolution is challenging because the etiology is a complex mix of psychogenic and/or physiogenic[23,45,46] factors and other influences such as social support. Although mTBI clinic data provides an available resource for developing these models, the lack of information for some key variables may limit their usefulness. Regardless of the true etiology, clinicians and medical personnel are responsible for providing patients with the most effective and innovative treatment to manage these

persistent symptoms. Future studies need to measure and evaluate pre-, peri-, and post-injury factors to improve future prediction equations of persistent symptom resolution and facilitate improvements in targeting of treatment to those patients with the greatest potential to benefit from them.

Table 1-3. Common mTBI Symptoms and Multidisciplinary Treatment Program at San Antonio Military Medical Center 2008-2013

Symptom	Provider	Treatment	Setting
Dizziness	Occupational Therapist	Vestibular Rehab	Individual
	Physical Therapist	Musculoskeletal Therapy	Individual
Headaches	Physical Therapist	Pharmacotherapy	Individual
	Medical Personnel	Musculoskeletal Intervention	Individual
PTSD/Anxiety	Psychologist	Exposure Therapy	Individual
		Cognitive Behavioral Therapy	Individual
		Relaxation Therapy	Individual
		Mindfulness Therapy	Individual
	Psychologist Medical Personnel	Pharmacotherapy	Individual
Depression	Psychologist	Cognitive Behavioral Therapy	Individual
	Psychologist Medical Personnel	Pharmacotherapy	Individual
Cognitive Impairment	Speech Language Pathologist Occupational Therapist	Cognitive Rehab	Individual Group
Sleep Disturbance	Occupational Therapist	Psychoeducation	Individual Group
	Psychologist Medical Personnel	Pharmacotherapy	Individual Group

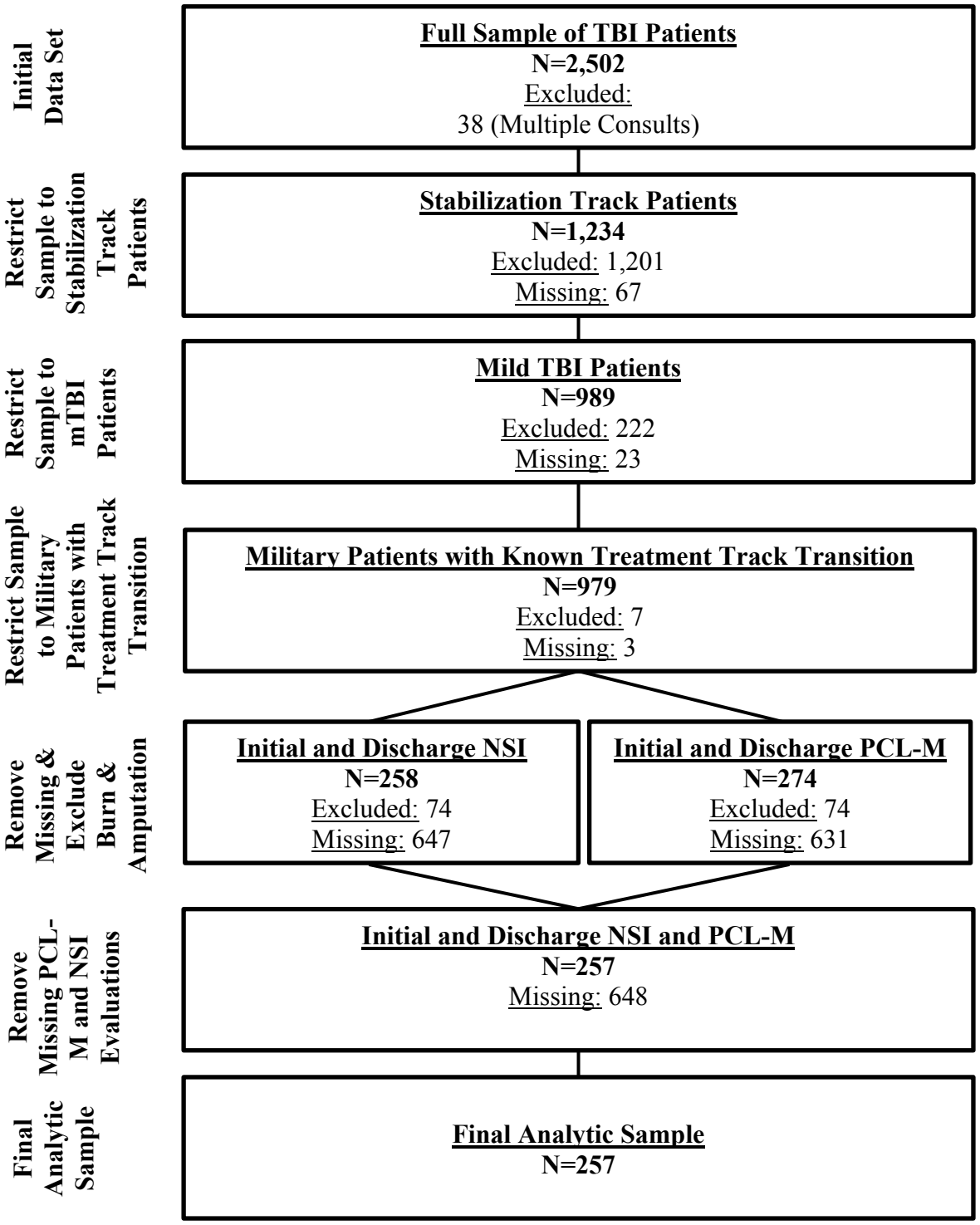

Figure 1-3. Flow diagram of data management to obtain final analytic sample of mTBI Patients Completing Treatment at San Antonio Military Medical Center 2008-2013

Table 2-3. Description of San Antonio Military Medical Center Traumatic Brain Injury Clinic Stabilization Track Patients with Mild Traumatic Brain Injury at Initial Pre-Treatment Evaluation 2008-2013

	Included Patients[a.] (n =257)	Excluded Patients[b.] (n =648)	p-value[c.]
Demographics			
Age at Injury[d.] (mean, s.d.)	30.5 (8.3)	30.0 (8.2)	0.33
Gender (n, %)			
Male	229 (89.1)	594 (91.7)	0.23
Female	28 (10.9)	54 (8.3)	
Enlisted Rank (n, %)			
Junior Enlisted (E1-E4)	106 (41.3)	259 (40.0)	0.12
Non-Commissioned Officers (E5-E9)	131 (51.0)	308 (47.5)	
Officers (Commissioned or Warrant)	20 (7.7)	81 (12.5)	
Injury-related			
Number of Self-Reported TBIs[e.] (n, %)			***0.003***
Single	81 (38.5)	86 (26.5)	
Multiple	129 (61.5)	239 (73.5)	
Number of Self-Reported Deployments (n, %)			0.96
None/Single	118 (46.1)	197 (45.9)	
Multiple	138 (53.9)	232 (54.1)	
Injury Year (n, %)			0.15
1995-2009	153 (59.5)	352 (54.3)	
2010-2013	104 (40.5)	296 (45.7)	
Initial Post-Traumatic Stress Disorder (n, %)			0.83
Yes	88 (34.2)	223 (35.0)	
No	169 (65.8)	414 (65.0)	
TBI Mechanism (n, %)			***0.03***
Blast	159 (61.9)	346 (54.1)	
Non-Blast	98 (38.1)	294 (45.9)	
Geographic Location of Injury (n, %)			0.09
Continental United States	46 (17.9)	94 (19.2)	
Outside Continental United States	11 (4.3)	23 (4.7)	
Operation Iraqi Freedom	108 (42.0)	161 (32.9)	

Operation Enduring Freedom	92 (35.8)	212 (43.3)	
Rehabilitation-Related (mean, s.d.)			
Time from Injury to Treatment Evaluation[f.]	16.3 (24.0)	21.8 (27.5)	***0.003***
Length of Stay[g.]	70.2 (69.3)	60.5 (67.0)	0.06
Total Number of Consults (n, %)			0.05
1	161 (62.7)	449 (69.3)	
≥2	96 (37.4)	199 (30.7)	
Rehabilitation Treatment History (n, %)			0.81
Standard Rehabilitation Transition[h.]	217 (84.4)	543 (83.8)	
Repeated Rehabilitation[i.]	40 (15.6)	105 (16.2)	

[a.]The analytic sample comprised of patients with initial and discharge Neurobehavioral Symptom Inventory and Post-Traumatic Stress Disorder Checklist-Military Version; [b.]Patients excluded from analysis; [c.]Student's t-test was used to test for significant differences (***p<0.05***) of continuous variables and the Chi-square test was used to test for significant differences of categorical variables; [d.]Age reported in years; [e.] TBIs:Traumatic Brain Injuries; [f.]Time reported in months (days/30); [g.]Length reported in days; [h.]Patients following a standard Rehabiltiation progression(i.e. Standard Rehabilitation without transition to another rehabilitation program); [i.]Patients transitioning into another rehabilitation program due to persistent symptoms.

Table 3-3. Linear Regression Parameter Estimates for Prediction Equations of Neurobehavioral Symptom Inventory Scores Post-treatment Among Stabilization Track Patients with Mild Traumatic Brain Injury at San Antonio Military Medical Center 2008-2013 (n=257)

	Model 1			Model 2		
Predictor Variables	Parameter Estimates (S.E.[a.])	p-value	Bootstrap Parameter Estimate (95% CI)	Parameter Estimates (S.E.)	p-value	Bootstrap Parameter Estimate (95% CI)
Intercept	-1.7 (1.72)	0.33	-1.7 (-4.2, 0.9)	-7.8 (3.6)	0.03	-7.9 (-14.1, -1.4)
Pre-Treatment NSI[b.] Score	3.6 (0.2)	<0.0001	3.6 (3.2, 4.1)	3.5 (0.4)	<0.0001	3.5 (2.7, 4.3)
Age at Injury[c.]				0.6 (0.5)	0.16	0.6 (-0.2, 1.6)
Pre-Treatment PTSD Diagnosis				5.8 (1.8)	0.002	5.8 (1.6, 9.6)
mTBI[d.] Mechanism				7.6 (3.4)	0.03	7.6 (2.3, 12.8)
mTBI Mechanism*Pre-Treatment NSI Score				-0.9 (0.4)	0.04	-0.9 (-1.7, 0.01)
Time from Injury to Treatment Evaluation				1.7 (1.4)	0.22	1.7 (-1.1, 4.4)
Model Fit Statistics						
Adjusted R-squared	*0.51*		*0.51 (0.43, 0.58)*	*0.53*		*0.54 (0.46, 0.62)*
AICC	*1496.5*		*1492.1 (1439.5, 1542.9)*	*1487.0*		*1479.6 (1429.2, 1530.1)*
			Partial F-Test (5, 250) = 4.1; p =0.001			

[a.]S.E.: Standard Error; [b.]NSI: Neurobehavioral Symptom Inventory and variable scaled to 5 NSI points; [c.]Age reported in years and variable scaled to 5 years; [d.]mTBI:mild Traumatic Brain Injury

Table 4-3. Linear Regression Parameter Estimates for Prediction Equations of Post-Traumatic Stress Disorder Checklist-Military Version Scores Post-treatment Among Stabilization Track Patients with Mild Traumatic Brain Injury at San Antonio Military Medical Center 2008-2013 (n=257)

	Model 3			Model 4		
Predictor Variables	Parameter Estimates (S.E.[a.])	p-value	Bootstrap Parameter Estimate (95% CI)	Parameter Estimates (S.E.)	p-value	Bootstrap Parameter Estimate (95% CI)
Intercept	4.1 (1.9)	0.03	4.1 (1.0, 7.1)	-3.2 (3.6)	0.38	-3.3 (-9.7, 2.8)
Pre-Treatment PCL-M[b.] Score	3.9 (0.2)	<0.0001	3.9 (3.5, 4.3)	4.3 (0.3)	<0.0001	4.3 (3.8, 4.9)
Age at Injury[c.]				0.5 (0.4)	0.26	0.5 (-0.4, 1.4)
mTBI[d.] Mechanism				8.2 (3.8)	0.03	8.2 (1.9, 14.7)
mTBI Mechanism*Pre-Treatment PCL-M Score				-0.9 (0.4)	0.03	-0.9 (-1.7, -0.1)
Time from Injury to Treatment Evaluation				0.5 (1.3)	0.73	0.5 (-2.0, 3.0)
Model Fit Statistics						
Adjusted R-squared	*0.59*		*0.59 (0.50, 0.67)*	*0.59*		*0.60 (0.52, 0.68)*
AICC	*1465.0*		*1460.1 (1400.7, 1515.6)*	*1466.9*		*1461.1 (1404.8, 1512.3)*
			Partial F-Test (4, 251) = 1.1; p =0.17			

[a.]S.E.: Standard Error; [b.] PCL-M:Post-Traumatic Stress Disorder Checklist-Military Version and variable scaled to 5 PCL-M points; [c.]Age reported in years and variable scaled to 5 years; [d.]mTBI:mild Traumatic Brain Injury

Table 5-3. Logistic Regression Parameter Estimates for Prediction Equations of Post-Traumatic Stress Disorder Symptom Treatment Response Among Stabilization Track Patients with Mild Traumatic Brain Injury at San Antonio Military Medical Center 2008-2013 (n=257)

	Model 5			Model 6		
Predictor Variables	Parameter Estimates[a.] (S.E.[b.])	p-value	Bootstrap Parameter Estimate (95% CI)	Parameter Estimates (S.E.)	p-value	Bootstrap Parameter Estimate (95% CI)
Intercept	-3.5 (0.5)	<0.0001	-3.6 (-4.4, -2.8)	-3.6 (1.0)	0.0002	-3.7 (-5.5, -2.0)
Pre-Treatment PCL-M[c.] Score	0.3 (0.1)	<0.0001	0.3 (0.2, 0.4)	0.3 (0.1)	0.0003	0.3 (0.2, 0.4)
Age at Injury[d.]				0.01 (0.1)	0.94	0.0001 (-0.2, 0.2)
mTBI[e.] Mechanism				-0.1 (1.0)	0.64	-0.1 (-1.8, 1.5)
mTBI Mechanism*Pre-Treatment PCL-M Score				0.02 (0.1)	0.93	0.02 (-0.2, 0.2)
Time from Injury to Treatment Evaluation				0.2 (0.1)	0.88	0.2 (-0.5, 0.9)
Model Fit Statistics						
Area Under the Curve	*0.75*		*0.75 (0.69, 0.81)*	*0.75*		*0.76 (0.70, 0.82)*
			Likelihood Ratio Test (χ^2=1.0; d.f. =4); p =0.91			

[a.] To calculate the shrinkage parameter estimate multiply the parameter estimate by the shrinkage estimator (γ=0.87); [b.]S.E.: Standard Error; [c.] PCL-M: Post-Traumatic Stress Disorder Checklist-Military Version and variable scaled to 5 PCL-M points; [d.]Age reported in years and variable scaled to 5 years; [e.]mTBI:mild Traumatic Brain Injury

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JOURNAL ARTICLE 3

Title of Journal Article: The Association Between U.S. Military Service Status and Metabolic Syndrome: Secondary Data Analysis of The Cooper Center Longitudinal Study 1970-2013

Name of Journal Proposed for Article Submission: American Journal of Preventive Medicine

INTRODUCTION

The United States (U.S.) Armed Forces was solidified as a national and occupational institution during the first part of the 20th century[1]. This institution requires that military service members exhibit self-sacrifice and willingness to serve their country, yet at the same time promotes physical activity[2] and provides benefits, such as specialized training and monetary compensation in return for meeting service obligations. However, these obligations also confer deployment-related occupational risks during times of war such as physical injuries and prolonged exposure to combat-related stress. Moreover, service obligations also result in other risks such as family disruption to facilitate geographic mobility[3], injuries from physical training[4,5], and exposure to negative health behavior norms such as smoking[6-8]. Therefore, military service is associated with both protective and risk factors that have the potential to alter a veteran's physical, psychological, and social health long after completion of service obligations or military retirement[9-13].

Metabolic syndrome is a group of risk factors associated with an increased risk of cardiovascular disease, type 2 diabetes mellitus, select cancers, and all-cause mortality in the U.S.[14-17] that has gained clinical attention over the last 25 years[15]. Similar to the civilian population[18], metabolic syndrome is a growing public health concern among U.S. veterans given the noteworthy estimated prevalence (>20%) and current obesity epidemic[19]. Metabolic syndrome is associated with several sociodemographic factors (e.g. older age, low household income, low educational attainment)[20-22], health behaviors (e.g. smoking, physical inactivity)[20,23] and neuropsychiatric outcomes (e.g. depression, generalized anxiety disorder, post-traumatic stress disorder (PTSD))[24-26]. Military service may be both a risk and protective factor for these sociodemographic characteristics, health behaviors and neuropsychiatric outcomes[11,27]. Concerning sociodemographic factors, the military provides an economic and social support system that may promote economic independence, stable family formation, educational opportunities, and responsible membership in communities[28-30]. Conversely, prior military service may increase the risk of criminality, marital difficulties, and impede economic achievement[11]. In addition, prior military service is associated with negative health behaviors (e.g. smoking)[31-33], positive health behaviors (e.g. physical activity)[2,33,34], and neuropsychiatric outcomes (e.g. anxiety disorders, depressive disorders, and PTSD) [33,35], which are risk and protective factors for metabolic syndrome. Moreover, military service often begins late in adolescence or early in adulthood and evidence suggests that adoption of these health behaviors (i.e. smoking[36-38] and physical activity[39-41]) during these critical developmental periods are predictive of these behaviors across the life-course. Therefore, adoption of these behaviors may persist long-term for service members influencing the

lifetime risk of metabolic syndrome. The same is true for veterans with combat exposure that may experience long-term psychological impairment associated with chronic anxiety and/or PTSD[42-48]. However, combat exposure may also increase resilience that can mitigate the negative psychological and physical effects of such exposure[49,50]. This differential effect of combat exposure demonstrates one example of how the overall long-term impact of prior military service on an individual's metabolic risk profile is complicated and currently unclear[51]. Therefore, understanding the distribution of occupational risk and protective factors among former military service members is important to understanding how these factors influence the association between military service and metabolic syndrome.

The purpose of this study was to compare the prevalence of metabolic syndrome among men reporting and not reporting prior military service, and to explore the role of sociodemographic factors, health behaviors, neuropsychiatric health, and clinical factors that may be associated with metabolic syndrome using a large sample from the Cooper Center Longitudinal Study (CCLS).

METHODS

Study Design

This study was a cross-sectional analysis of data collected during comprehensive medical evaluations of participants in the Cooper Center Longitudinal Study (CCLS) from 1970-2013. Participants signed an informed consent and approved the use of their data for

research. The data collection protocols and informed consent are reviewed and approved annually by The Cooper Institute's Institutional Review Board.

Data Source and Study Participants

The CCLS is a prospective cohort study of men and women who came to the Cooper Clinic (Dallas, Texas) for a preventive medical visit and agreed to enroll in the study. The CCLS is a fee for service preventive medical clinic with participants that are generally well educated, non-Hispanic white, and from middle to upper socioeconomic strata. Participants for this study were men and that had at least one visit to the Cooper Clinic (1970–2013). Women (n=25,684) and unemployed (n=97) participants were excluded due the small sample of participants in these categories indicating prior military service. If participants had more than one evaluation, then only data from the earliest evaluation visit was included to be consistent with participants that only had one initial visit and no subsequent visits.

Clinical Examination

Clinical examinations of participants were completed after a 12-hour fast and were conducted by trained clinical personnel according to the Cooper Clinic's standardized manual of operations. The specific details of the examination are described elsewhere[52]. Definitions and a brief description of assessment methodology for clinical variables relevant to this study are described below (see independent variable section).

Data Management

Military specific information (i.e. length of service in years, service branch, military retirement) relevant to participants with prior military service was not abstracted from the CCLS Medical History Questionnaire into the CCLS database as part of standard protocol. Therefore, this information was abstracted from electronic medical records and entered into the CCLS database. IRB approval for the abstraction was obtained through The University of Texas Health Science Center (HSC-GEN-12-0789). There were 1,250 CCLS participants indicating that they had a history of prior military service eligible for abstraction. Data on branch of service, retirement status from the military, and length of military service were abstracted into the CCLS database.

A participant did not meet the definition of military service if the reported branch of service was public health service or junior high/high school Reserve Officer's Training Corp (ROTC). The guidelines used for abstraction of military related demographic variables are listed in Table 1-4. In cases of conflicting medical records (i.e., one record states military service and another record indicates no prior service or service in a different military branch), data were abstracted from the most recent record. A continuous sampling plan methodology was employed as a measure of quality control[53]. Three errors were identified with a sampling interval of 10 records. Thus, the proportion of incorrect data was 0.002 and the relative gain in record quality after a visual record verification with this continuous sampling plan was 10%.

Dependent Variables

Metabolic Syndrome

Diagnosis of metabolic syndrome was based on criteria from the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III)[54]. The NCEP ATP III requires three or more of the following five criteria for a diagnosis of metabolic syndrome in men: (1) waist circumference ≥102 cm (2) triglyceride level ≥150 mg/dL, (3) high density lipoprotein cholesterol (HDL-C) <40 mg/dL (4) blood pressure ≥ 130/85 mmHg or treatment with antihypertensive medications, and (5) fasting glucose ≥100 mg/dL or treatment with diabetic medications[54,55]. Medication history was not available for this study; therefore, only the examination (e.g., waist circumference and blood pressure) or laboratory data (e.g., triglycerides, HDL-C, and fasting glucose levels) were used to determine if each criterion was met or not met. Participants were classified as meeting or not meeting the criteria for metabolic syndrome.

Individual Metabolic Syndrome Risk Factors

The six individual metabolic syndrome risk factors (i.e. waist circumference≥102 cm, triglyceride level≥150 dg/mL, high density lipoprotein cholesterol<40 mg/dL, systolic blood pressure≥130 mmHg, diastolic blood pressure≥85 mmHg, fasting glucose≥100 mg/dL) were also individually modeled as dichotomous dependent variables (met/not met). Participants were classified as meeting or not meeting the criteria for each individual metabolic syndrome risk factor.

Tension and Anxiety

Participant responses to the tension and anxiety scale on the CCLS Medical History Question were used to categorize participants' tension and anxiety level at first visit to the Cooper Clinic. Participants that reported "moderate tension," "high tension", or "very tense" were classified as having high tension and anxiety. Participants that reported "no tension" or "slight tension" were classified as having no tension and anxiety. This variable was also modeled as a confounder of interest in the other full regression models.

Prior Military Service Status

Prior military service status (yes/no) was also modeled as a dependent variable to explore the association between prior military service status regressed on independent variables of interest.

Independent Variables

All of the sociodemographic, health promoting, health compromising, neuropsychiatric health, and clinical variables are described in Table 2-4. Age was collapsed in these categories (20-39 years, 40-49 years, 50-59 years, ≥60 years) for use in the full regression models. All non-clinical variables used in this study were self-reported via the CCLS Medical Health Questionnaire. Cardiorespiratory fitness was determined using a symptom-limited graded maximal treadmill exercise test using a modified Balke protocol[52] to estimate maximal aerobic capacity (VO_2max). With this protocol, the treadmill speed is set at 3.3 miles per hour (mph) until minute 25 and then increased by 0.2 mph each additional

minute. Treadmill incline is set to 0% for the first minute and then increased by 2% after the first minute, followed by 1% increases each additional minute. Participants are encouraged to give maximal effort. The test is terminated at the physician's discretion or volitional exhaustion. Maximal metabolic equivalents (METs; 1 MET = 3.5 ml oxygen uptake · kg body mass-1 · min-1), a valid estimate of measured VO_2max, is determined via the final treadmill speed and grade[56,57]. Cardiovascular fitness was categorized as low (<10 METS), moderate (≥10-12.5METS), and high fitness (≥12.5 METS) based on sample tertiles of VO_2.

Body mass index (BMI) is calculated as weight in kilograms divided by height in meters squared. Height was obtained via stadiometer and weight via calibrated balance scale. BMI scores were categorized as normal (≤24.9 kg/m^2), overweight (>24.9-≤29.9 kg/m^2) and obese (≥30 kg/m^2) based on the Centers for Disease Control and Prevention standard weight status categories for adults[58]. Waist circumference was measured at the level of the umbilicus with a plastic anthropometric tape. Skinfold measurements at seven sites or underwater weighing measurements were used to estimate percent body fat. The American Heart Association protocol was followed to obtain a seated resting blood pressure with a mercury sphygmomanometer[59]. Standards from the U.S. Centers for Disease Control and Prevention Lipid Standardization Program[52,60] were followed to obtain serum cholesterol and triglycerides, HDL-C, and glucose from participant fasting venous blood using automated techniques at the Cooper Clinic Laboratory. History of high blood pressure, blood

cholesterol, and blood triglycerides were self-reported variables obtained from the participants' first visit on the CCLS Medical Health Questionnaire.

Statistical Methods

The mean and standard deviation of continuous variables and the number and proportion of categorical variables were stratified by prior military service status to describe sociodemographic factors, health promoting behaviors, health compromising behaviors, neuropsychiatric health outcomes, and clinical factors among CCLS participants. The generalized linear regression modeling strategy for assessing confounding with no interaction between metabolic syndrome related dependent variables (i.e. metabolic syndrome and individual metabolic syndrome risk factors) and the primary exposure of interest (i.e. prior military service status) followed three steps[61]. First, variables for the proposed full model included variables that based on evidence from the literature and recommendations from expert clinicians. Second, the proposed full model was run and the prevalence ratio for prior military service was recorded. Third, subsets of the full model were run by systematically removing independent variables from the full model individually. This process continued until all eligible subsets were identified and compared to the prevalence ratio for prior military history in the proposed full regression model. If the removal of a variable resulted in a change in the prior military service prevalence ratio of 5% or more, then the variable was retained in the model as a confounder. The final model identified confounders that provided the largest gain in precision over the proposed full model. Table 3-4 lists the variables selected for the full regression model. The full model with waist circumference as the

dependent variable did not include BMI as a confounder of interest because BMI is highly correlated with the outcome of interest. Generalized linear regression log binomial models were performed by regressing the prevalence of metabolic syndrome on prior military history (exposure of interest) and potential confounders of interest to calculate prevalence ratios. Prevalence ratios were reported instead of prevalence odds ratios because prevalence ratios are more conservative, consistent, and interpretable for non-rare (prevalence >10%) disease outcomes[62-64].

A third generalized linear regression model explored the association of the tension and anxiety dependent variable regressed on all of the independent variables of interest including prior military status. An unadjusted model with prior military service as the sole predictor and an adjusted model with all independent variables of interest were reported. An adjusted logistic regression model was performed regressing prior military service status on all the independent variables of interest. A logistic regression model rather than generalized linear regression model was performed for this dependent variable because the prevalence of prior military service in this sample was small (1.9%), and prevalence odds ratios approximate prevalence ratios for low prevalence outcomes (<10%)[62-64].

Primary Hypothesis: Metabolic Syndrome

After adjusting for confounders of interest, we hypothesized that participants with prior military service had a higher prevalence of metabolic syndrome compared to participants with no military service. The Wald Chi-Square test was performed to determine

if the regression coefficient for the dichotomous prior military service exposure variable was significantly associated with the outcome. The type 1 error level for the Wald Chi-Square test was $p<0.05$ to determine if the regression coefficient for the dichotomous prior military service exposure variable was significantly associated with the outcome.

Secondary Hypothesis: Individual Metabolic Syndrome Risk Factors

After adjusting for confounders of interest, we hypothesized that participants with prior military service had a higher prevalence of the individual metabolic syndrome risk factor criteria modeled individually than participants with no prior military service. The Wald Chi-Square test was performed to determine if the regression coefficient for the dichotomous prior military service exposure variable was significantly associated with the outcome. The type 1 error level for the Wald Chi-Square test was $p<0.008$ to determine if the regression coefficient for the dichotomous prior military service exposure variable was significantly associated with the outcome and to conserve the family-wise error rate of 0.05.

Secondary Hypothesis: Tension and Anxiety

We hypothesized that participants with prior military service reported a higher adjusted prevalence of high tension and anxiety compared to participants with no military service. The Wald Chi-Square test was performed to determine if the regression coefficient for the dichotomous prior military service exposure variable was significantly associated with the outcome. The type 1 error level for the Wald Chi-Square test was $p<0.05$ to

determine if the regression coefficient for the dichotomous prior military service exposure variable was significantly associated with the outcome.

Secondary Hypothesis: Prior Military Service Status

We hypothesized that the adjusted odds of prior military service for independent variables of interest (i.e. age, smoking history, history of depression, tension and anxiety, cardiovascular fitness, and BMI) were significantly associated with the outcome. The Wald Chi-Square test was performed to determine if the regression coefficients were significantly associated with the outcome. There were eleven multiple comparisons for this family of tests; therefore, the type 1 error level for the Wald Chi-Square test was $p<0.004$ to determine if the regression coefficients were significantly associated with the outcome and to conserve the family-wise error rate of 0.05.

Human Subjects, Animal Subjects, or Safety Considerations

The Cooper Clinic and University of Texas School of Public Health (HSC-SPH-14-0126) Institutional Review Board approved this cross-sectional study.

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RESULTS

The sample of participants with prior military service was 1,250 and the number of civilian men in the CCLS database was 64,220 (Table 4-4). Participants reporting prior service were older (mean: 55 years v. 44 years) than civilians. Both prior service members and civilians were predominantly white (>93%), married (>85%), employed (>94%), and

college educated (>74%). The largest proportion of participants with prior military service reported serving in the Army (48%) and 6 years was the average length of service.

Regarding health promoting behaviors, participants with prior military service reported a higher number of years of regular or lifetime exercise (22.9 years v. 18.2 years) (Table 5-4). Furthermore, participants with prior service reported a lower prevalence of the following health compromising behaviors: history of excessive alcohol use (6.8% v. 14.1%), currently smoking (11.5% v. 17.1%), and recreational drug use (8.1% v. 16.5%). There were not meaningful differences in the prevalence of participants reporting a history of depression, anxiety, and suicidal thoughts. However, participants with prior military service reported a lower prevalence of high tension and anxiety (20.4% v. 27.6%).

Participants with prior service reported a similar level of cardiovascular fitness (11.2 METs v. 11.4 METs), BMI (27.4 v. 27.0), and other clinical variables of interest. They reported a higher prevalence of a history of hypertension (20.8% v. 16.9%), hyperlipidemia (29.8% v. 17.4%), and high blood triglycerides (14.3% v. 9.7%). The results for the following variables of interest, also shown in Table 5-4, should be interpreted with caution due to missing values that exceed 5%: total years of exercise, history of excessive alcohol use, history of recreational drug use, tension and anxiety, HDL-C, LDL-C, percent fat, and waist circumference.

Compared to men with no prior military service, the unadjusted prevalence of metabolic syndrome was higher for men reporting prior military service (PR= 1.05, 0.94-1.18) compared to men with no prior military service but was not statistically significant (Table 6-4). Older age, former smoking status, history of depression, being overweight/obese, and low fitness were identified as factors associated with a higher prevalence of metabolic syndrome in the full regression model. Conversely, after adjustment for age, BMI, and cardiovascular fitness, the prevalence of metabolic syndrome was lower for participants reporting prior military service compared to participants not reporting prior service (PR=0.90, 0.82-0.99). Age, cardiovascular fitness, and BMI were identified as confounders of the association between prior military service and metabolic syndrome in the final adjusted model.

After adjusting for age and cardiovascular fitness, prior military service was associated with a higher prevalence (PR=1.24, 1.11-1.38) of abdominal obesity (waist circumference ≥102 cm) compared to participants with no prior military service in the final adjusted model (Table 7-4). Yet, after adjusting for age, prior military service was also associated with a lower prevalence of high levels of blood triglycerides (PR=0.86, 0.78-0.96) and low levels of HDL-C (PR = 0.68, 0.62-0.74) in the final adjusted model. Military service was not associated with high systolic blood pressure, high diastolic blood pressure, or high blood glucose. After controlling for confounders of interest, the full tension and anxiety model indicated that prior military service was associated with a lower prevalence of reporting high tension and anxiety (PR=0.86, 0.77-0.96) (Table 8-4). Prior military service

members reported a higher odds of older age (>60 years) (OR=9.57, 7.72-11.86), moderate (OR=1.62, 1.39-1.89) and high (OR=1.72, 1.44-2.07) cardiovascular fitness, overweight BMI (OR=1.33, 1.16-1.52), and obese BMI (OR=1.72, 1.44-2.07) compared to civilians (Table 9-4). Lastly, prior military service members reported a lower prevalence of current smoking (OR=0.75, 0.63-0.91) and high tension and anxiety (OR=0.80, 0.69-0.93), but no statistically significant association with a history of depression or former smoking status.

DISCUSSION

Compared to civilians, evidence indicates that veterans may have a greater risk of health compromising behaviors and neuropsychiatric outcomes (e.g. smoking, self-reported depressive and anxiety disorders)[33] associated with an increased risk of metabolic syndrome; yet, may also be more likely to report health promoting behaviors and clinical factors protective (e.g. physical activity, less obesity)[2,33] of metabolic syndrome. Despite these important differences, there is currently not a clear understanding of specific clinical factors, neuropsychiatric health outcomes, health promoting and health compromising behaviors that are associated with metabolic syndrome among veterans. This study fills this gap by exploring the association between prior military service and metabolic syndrome while controlling for confounders of interest.

The current study has three key findings. First, sociodemographic variables were similar between participants; thus, not supporting a differential impact of prior military

service on employment, educational attainment, or marital status[11,28,30]. Moreover, participants with prior military service reported an average of five more years of regular exercise; however, those reporting prior military services were also approximately 7 years older that their civilian counterparts. Despite the inability to comment on specific physical activity characteristics (i.e., activity type, frequency, intensity, and duration), these results support prior research that physical activity patterns are similar among civilians and veterans post-service[2,33,34,65]. Those reporting prior military service also reported a lower prevalence of health compromising behaviors (i.e. smoking, excessive alcohol use, and recreational drug use) and a similar neuropsychiatric history (i.e. history of depression, anxiety, and suicidal thoughts) than men with no prior military service. In fact, prior service members reported a lower prevalence of high tension and anxiety.

These results are contrary to prior research with evidence indicating that military service is a risk factor for these health compromising behaviors and neuropsychiatric outcomes[31-33,44,66]. Therefore, it could be hypothesized that prior military service and probable traumatic combat exposure may have instilled resiliency in this sub-group of participants in the CCLS[67-69]. For example, a recent study reported that 70% of older (≥60 years) veterans reporting a high number of lifetime traumas were psychologically resilient later in life[67]. This resilient group of veterans were more likely to have higher levels of educational attainment, emotional stability, social connectedness such as social support, and a positive perception of the military's impact on their life. This conclusion is further supported by the fact that this sample consisted of participants that predominantly attained a

high level of education and affluent economic status. Moreover, participants with prior military service were protected against reporting a lower prevalence of high tension and anxiety, which is also consistent with the resiliency theory.

Second, after adjusting for confounders of interest, prior military service was associated with a lower prevalence of meeting the criteria for metabolic syndrome. Participants indicating prior military service had higher odds of being overweight and obese, which is a risk factor for metabolic syndrome[70,71]; yet, also had higher odds of moderate and high physical fitness, which is a protective factor for metabolic syndrome[72-75]. While preventing a loss of fitness and an increase in adiposity have both been identified as independent risk factors important to reducing the risk of developing metabolic syndrome, the true relationship between fitness, adiposity, and metabolic syndrome is complicated. For example, a recent prospective study reported that the increased risk of metabolic syndrome associated with an increase in fat gain was attenuated by the improvement or maintenance of cardiovascular fitness[76]. However, the increased risk of metabolic syndrome associated with a loss of cardiovascular fitness was also attenuated by the maintenance or loss of fat. Therefore, despite the fact that participants with prior military service had an increased odds of being overweight and obese compared to participants with no prior military service, it is plausible that the independent risk of metabolic syndrome from higher levels of adiposity was attenuated by higher levels of cardiovascular fitness for prior military service members. Lastly, evidence from one study indicates that whether veterans are more likely to have increased adiposity compared to non-veterans is dependent on the measure used (i.e. self-

report BMI, direct-measure BMI, waist circumference, waist-stature ratio, or percent body fat by DXA)[77]. This study reported that a higher proportion of veterans were in the highest categories of waist circumference (≥102 cm) but a lower proportion of veterans were in the highest category of percent body fat by DXA (≥35%).

Third, after adjusting for age, prior military service was associated with a higher prevalence of one metabolic syndrome risk factor (i.e. waist circumference ≥102 cm) and lower prevalence of two others (i.e. triglycerides ≥150 mg/dL and HDL-C < 40 mg/dL). Results from the Millennium Cohort found an increase in weight gain following service in the U.S. military and may explain the difference in abdominal obesity reported in this study[78]. There are two plausible explanations for the protective effect of military service regarding triglyceride and HDL-C levels. First, service members were more physically fit and cardiovascular fitness is associated with a decrease in triglyceride levels and an increase in HDL-C levels[75,79,80]. However, after adjusting for age, cardiovascular fitness and other potential confounders of interest (e.g. smoking status[81] and tension and anxiety[82]), cardiovascular fitness did not significantly confound the association between prior military service and triglycerides or HDL-C. A second, more likely explanation, was that participants with prior military service reported a higher prevalence of a history of hyperlipidemia and high blood triglycerides. Although medication use data were not available in the CCLS, it is plausible that this group of older service members were disproportionately using lipid-lowering medications, which would inflate the estimated prevalence ratios and bias the association away from the null.

There are limitations to the current study. First, the external validity of this study is limited because the sample predominantly consists of well-educated, affluent, white men. However, this was true of both participants with and without prior military service; therefore, differential effects from these sociodemographic factors are unlikely. Second, dietary intake is an important health promoting behavior to consider when evaluating the association between prior military service and metabolic syndrome, but adequate dietary data were not available[73]. Third, physical activity was not explored as a confounder but is moderately associated with cardiovascular fitness[83]. Fourth, as previously mentioned, information regarding medication history was not available for this study. Therefore, it is plausible that a higher proportion of participants with prior military service were on medications that would qualify them for a positive metabolic syndrome diagnosis, especially because these participants reported a high prevalence of a history of hyperlipidemia, high blood triglycerides, and hypertension. Fifth, the tension and anxiety scale in the CCLS is not a validated measure and warrants cautious interpretation of results. Lastly, this was as secondary analysis so other variables of interest such as military rank, combat exposure, and job occupation were not available in this data set.

The study also had several strengths. This study explored the association between prior military service and metabolic syndrome using a large sample with a diverse array of health promoting, health compromising, neuropsychiatric health and clinical variables. Second, this study used sound methodological analysis reporting prevalence ratios rather than odds ratios for a non-rare disease outcome. Lastly, this study abstracted data regarding

military service into a well-known prospective cohort for the first time, which allowed for an innovative examination of factors that impact long-term health useful for both civilians and individuals with prior military service.

CONCLUSION

In summary, exposure to a unique occupational environment during military service has the potential to alter the health trajectory of individuals who serve because service typically begins in early adulthood; a critical stage when long-term behavior patterns are established as men transition from adolescence to adulthood[36,40]. Evidence from the current study indicates a protective association between prior military service and metabolic syndrome, which previous studies have identified as a group of risk factors associated with cardiovascular disease, type 2 diabetes mellitus, and select cancers. Participants with prior military service were less likely to report current/former smoking status, low cardiovascular fitness, or high tension and anxiety. Therefore, this study supports a resiliency theory that suggests military service may increase resiliency among a subset of veterans post-service resulting in better educational attainment, employment opportunities, social stability, and health promoting decisions. However, the results of the current study suggest that prior military service also was associated with a higher prevalence of central obesity in later life. These findings support health promotion strategies focused on weight reduction through dietary modification[84,85] and increased physical activity[2,34] in order to reduce risk of metabolic syndrome and/or type 2 diabetes mellitus in older veterans. Furthermore, future

studies are needed to improve the external validity of results and better understand the association between factors associated with service and metabolic syndrome such as sociodemographic characteristics (i.e. race/ethnicity, education, income), health behaviors (i.e. smoking), neuropsychiatric outcomes (i.e. PTSD, depression, anxiety), combat exposure, and military occupation representative of the general veteran population.

Table 1-4. Military Demographic Abstraction Definitions and Guidelines

Variable	Self-Reported Description
Service Branch	
Army	Army/National Guard/Reserves/Corps of Engineers/Finance Corps
Marine Corp	Marine Corps/Reserves
Navy	Navy/Reserves
Air Force	Air Force/Air National Guard/Reserves
Coast Guard	Coast Guard
Other	Multiple Service Branches Reported (e.g. Navy and Army)
Length of Service	
Description	Number of reported years of service
	Years at U.S. service academy included
	Both active duty and reserve time included
Retirement	
Description	Retirement status at the time of first visit (Yes/No)
	Retirement from military was changed from "Yes" to "No" if dates of service were < 20 years indicating discharge from military other than retirement or if occupational data clearly indicated that the participant was not in the military for an extended period of time.

Table 2-4. Independent Variables

	Description and Response Categories
Sociodemographic	
Age (years)	Continuous variable
Employment Status	Categorical Variable Employed Retired
Race	Categorical Variable White Other
Marital Status	Categorical Variable Single/Widowed Married Divorced
Education	Categorical Variable College Degree or Higher Less than College Degree
Service Branch (Prior Service Only)	Categorical Variable Army Navy Air Force Marine Corps/Other
Years of Service (Prior Service Only)	Continuous variable
Retired from Military(Prior Service Only)	Categorical Variable Yes No
Health Promoting Behaviors	
Total Years of Regular Exercise	Continuous variable
Health Compromising Behaviors	
History of Excessive Alcohol Use	Categorical Variable Yes No
Smoking History	Categorical Variable

	Description and Response Categories
	Never Past Current
History of Recreational Drug Use	Categorical Variable Yes No
Neuropsychiatric Health	
History of Depression	Categorical Variable Yes No
History of Anxiety	Categorical Variable Yes No
Tension and Anxiety Scale	Categorical Variable Moderate/Very Tense No/Slight Tension
History of Suicidal Thoughts	Categorical Variable Yes No
Clinical Variables	
Cardiorespiratory Fitness ($ml \cdot kg^{-1} \cdot min^{-1}$)	Continuous variable
BMI (kg/m^2)	Continuous variable
Percent Body Fat	Continuous variable
Waist Circumference (cm)	Continuous variable
Glucose (mg/dL)	Continuous variable
Total Cholesterol (mg/dL)	Continuous variable
HDL-C (mg/dL)	Continuous variable
Triglycerides (mg/dL)	Continuous variable

	Description and Response Categories
Systolic Blood Pressure (mm Hg)	Continuous variable
Diastolic Blood Pressure (mm Hg)	Continuous variable
History of High Blood Pressure	Categorical Variable Yes No
History of High Blood Cholesterol	Categorical Variable Yes No
History of High Blood Triglycerides	Categorical Variable Yes No

Table 3-4. Variables of Interest in the Full Regression Model

Sociodemographic
Age
20-39
40-49
50-59
≥60
Health Compromising Behaviors
Smoking History
Never
Current
Former
Neuropsychiatric Health
History of Depression
Yes
No
Tension and Anxiety Scale
Moderate to Very High Tension
No to Slight Tension
Clinical Variables
Cardiorespiratory Fitnes
Low Fitness (<10 METs)
Moderate Fitness (≥10-12.5 METs)
High Fitness (≥12.5 METs)
BMI
Normal (≤24.9 kg/m^2)
Overweight (25.0- ≤29.9 kg/m^2)
Obese (≥30 kg/m^2)

Table 4-4. Description of Cooper Clinic Longitudinal Study Sample 1970-2013

	Prior Military Service (n =1,250)	No Prior Military Service (n =64,220)
Sociodemographic		
Age (mean, s.d.[a.])	51.3 (10.7)	44.7 (9.9)
Age Category		
20-39	176 (14.1)	19,838 (30.9)
40-49	382 (30.6)	25,038 (39.0)
50-59	396 (31.7)	14,461 (22.5)
≥60	296 (23.7)	4,883 (7.6)
Employment Status (n, %)		
Employed	734 (94.2)	22,018 (98.1)
Retired	45 (5.8)	423 (1.9)
Race (n, %)		
White	1,157 (95.8)	27,146 (93.8)
Other	51 (4.2)	1,789 (6.2)
Marital Status(n, %)		
Single/Widowed	54 (5.5)	2,757 (7.7)
Married	884 (89.5)	31,089 (86.6)
Divorced	50 (5.1)	2,062 (5.7)
Education (n, %)		
≥College degree	926 (74.3)	22,371 (77.1)
<College degree	320 (25.7)	6,660 (22.0)
Service Branch[c.] (n,%)		
Army	575 (48.2)	
Air Force	247 (20.7)	

Navy	227 (19.0)	
Marine Corps/Other	144 (12.1)	
Years of Service[b.] (mean, s.d.)	6.4 (6.6)	
Retired Military[b.] (n, %)		
Yes	101 (8.2)	
No	1,130 (91.8)	

[a.]s.d.: standard deviation; [b.]Among Participants with prior military service.

Table 5-4. Description of First Visit Reported Health Behaviors, Neuropsychiatric Health and Clinical Factors 1970-2013

	Prior Military History (n =1,250)	No Prior Military Service (n =64,220)
Health Promoting Behaviors		
Total Years of Regular Exercise (mean, s.d.[a.])	22.9 (15.7)	18.2 (13.4)
Health Compromising Behaviors		
History of Excessive Alcohol Use (n, %)		
Yes	65 (6.8)	5,260 (14.1)
No	889 (93.2)	32,162 (85.9)
Smoking History (n, %)		
Never	992 (79.4)	47,420 (73.8)
Current	144 (11.5)	10,946 (17.1)
Former	114 (9.1)	5,584 (9.1)
History of Recreational Drug Use (n, %)		
Yes	56 (8.1)	2,884 (16.5)
No	638 (91.9)	14,650 (83.6)
Neuropsychiatric Health		
History of Depression (n, %)		
Yes	85 (6.8)	3,318 (5.2)
No	1,165 (93.2)	60,902 (94.8)
History of Anxiety (n, %)		
Yes	86 (6.9)	4,489 (7.0)
No	1,164 (93.1)	59,731 (93.0)
Tension and Anxiety Scale (n, %)		
High Tension and Anxiety	238 (20.4)	15,931 (27.6)
No Tension and Anxiety	930 (79.6)	41,852 (72.4)

History of Suicidal Thoughts (n, %)		
Yes	17 (1.4)	585 (0.9)
No	1,233 (98.6)	63,635 (99.1)
Clinical Variables (mean, s.d.)		
VO^2 Max ($ml \cdot kg^{-1} \cdot min^{-1}$)	11.2 (2.4)	11.4 (2.5)
VO^2 Max Category ($ml \cdot kg^{-1} \cdot min^{-1}$)		
Low Fitness (<10 METs [b.])	375 (30.0)	19,167 (29.9)
Moderate Fitness (≥10-12.5 METs)	483 (38.6)	23,399 (36.4)
High Fitness (≥12.5 METs)	392 (31.4)	21,643 (33.7)
Stress Test (minutes)	17.2 (5.0)	17.4 (5.1)
BMI (kg/m2)	27.4 (3.9)	27.0 (4.1)
BMI Category (n, %)		
Normal (≤24.9)	388 (31.0)	25,002 (38.9)
Overweight (25.0- ≤29.9)	606 (48.5)	28,325 (44.1)
Obese (≥30)	256 (20.5)	10,893 (17.0)
Percent Body Fat	22.6 (5.4)	21.8 (5.9)
Waist Circumference (cm)	95.0 (11.7)	93.5 (15.7)
Glucose (mg/dL)	100.1 (14.6)	100.6 (20.1)
Total Cholesterol (mg/dL)	198.1 (38.0)	206.5 (40.5)
HDL-C (mg/dL)	48.5 (12.7)	46.4 (12.2)
LDL-C (mg/dL)	124.0 (33.0)	131.4 ()
Triglycerides (mg/dL)	129.5 (132.2)	140.4 (119.1)
Systolic Blood Pressure (mm Hg)	124.1 (14.7)	122.5 (13.7)
Diastolic Blood Pressure (mm Hg)	82.0 (9.6)	81.8 (9.7)
History of Hypertension (n, %)		
Yes	260 (20.8)	10, 856 (16.9)
No	990 (79.2)	53,364 (83.1)
History of Hyperlipedmia (n, %)		

Yes	372 (29.8)	11,165 (17.4)
No	878 (70.2)	53,055 (82.6)
History of High Blood Triglycerides (n, %)		
Yes	179 (14.3)	6,208 (9.7)
No	1,071 (85.7)	58,012 (90.3)

[a.]s.d.: standard deviation; [b.]METs: Metabolic Equivalent of Tasks

Table 6-4. Crude and Adjusted Prevalence Ratios of Metabolic Syndrome 1970-2013

	Unadjusted Regression Model (95%CI[a].)
Prior Military Service	
No	Reference
Yes	1.05 (0.94, 1.18)
	Full Regression Model (95% CI)
Prior Military Service	
No	Reference
Yes	0.90 (0.82, 1.00)
Sociodemographic	
Age (Years)	
20-39	Reference
40-49	1.14 (1.10, 1.19)
50-59	1.24 (1.19, 1.29)
≥60	1.28 (1.22, 1.35)
Health Compromising Behaviors	
Smoking History	
Never	Reference
Current	1.04 (1.00, 1.07)
Former	1.34 (1.29, 1.39)
Neuropsychiatric Health	
Tension and Anxiety Scale	
No Tension and Anxiety	Reference
High Tension and Anxiety	1.02 (0.98, 1.04)
History of Depression	
No	Reference
Yes	1.10 (1.05, 1.15)
Clinical Variables	
VO^2 Max ($ml \cdot kg^{-1} \cdot min^{-1}$)	
Low Fitness (<10 METs[b.])	Reference
Moderate Fitness (≥10-12.5 METs)	0.83 (0.80, 0.85)
High Fitness (≥12.5 METs)	0.42 (0.40, 0.45)
BMI (kg/m^2)	
Normal (≤24.9)	
Overweight (25.0- ≤29.9)	3.58 (3.35, 3.83)
Obese (≥30)	8.41 (7.86, 9.00)
	Final Adjusted Regression Model (95% CI)
Prior Military Service	
No	Reference
Yes	0.90 (0.81, 0.99)*
Sociodemographic	

Age (Years)	
20-39	Reference
40-49	1.15 (1.10, 1.20)
50-59	1.30 (1.24, 1.35)
≥60	1.35 (1.28, 1.42)
Clinical Variables	
VO^2 Max ($ml \bullet kg^{-1} \bullet min^{-1}$)	
Low Fitness (<10 METs)	Reference
Moderate Fitness (≥10-12.5 METs)	0.83 (0.81, 0.86)
High Fitness (≥12.5 METs)	0.44 (0.41, 0.46)
BMI (kg/m^2)	
Normal (≤24.9)	Reference
Overweight (25.0- ≤29.9)	3.85 (3.6, 4.11)
Obese (≥30)	9.27 (8.67, 9.90)

[a.]CI: Confidence Interval; [b.]METs: Metabolic Equivalent of Tasks; *$p<0.05$ for prior military service exposure of interest

Table 7-4. Adjusted Prevalence Ratios and 95% Confidence Intervals of Meeting Individual Metabolic Syndrome Risk Factors 1970-2013

	Waist Circumference[a.]	Triglycerides[b.]	HDL-C[c.]	Resting SBP[d.]	Resting DBP[e.]	Glucose[f.]
			Full Regression Models			
Prior Military Service						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.19	0.91	0.73	0.99	0.97	0.96
	(1.06, 1.34)	(0.83, 1.00)	(0.67, 0.80)	(0.92, 1.07)	(0.90, 1.04)	(0.91, 1.03)
			Final Adjusted Regression Models			
Prior Military Service						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.24*	0.86*	0.68*	0.97	0.97	0.96
	(1.11, 1.38)	(0.78, 0.94)	(0.62, 0.74)	(0.90, 1.05)	(0.90, 1.05)	(0.90, 1.03)
Sociodemographic						
Age (Years)						
20-39	Reference	Reference	Reference	Reference	Reference	Reference
40-49	1.17	1.27	0.91	1.17	1.38	1.32
	(1.12, 1.23)	(1.23, 1.31)	(0.89, 0.93)	(1.13, 1.21)	(1.34, 1.42)	(1.28, 1.36)
50-59	1.22	1.38	0.85	1.74	1.64	1.68
	(1.16, 1.28)	(1.33, 1.43)	(0.83, 0.87)	(1.69, 1.81)	(1.59, 1.69)	(1.63, 1.73)
≥60	1.02	1.18	0.81	2.35	1.49	1.84
	(0.95, 1.09)	(1.12, 1.24)	(0.79, 0.84)	(2.26, 2.44)	(1.43, 1.56)	(1.77, 1.91)
Clinical Variables						
VO^2 Max ($ml \cdot kg^{-1} \cdot min^{-1}$)						

Low Fitness (<10 METs[g.])	Reference	
Moderate Fitness (≥10-12.5 METs)	0.45 (0.43, 0.46)	
High Fitness (≥12.5 METs)	0.09 (0.08, 0.10)	

[a.]Waist circumference ≥102 cm; [b.]Triglyceride level ≥150 mg/dL; [c.]HDL-C: High Density Lipoprotein-Cholesterol <40 mg/dL; [d.]Resting SBP: Resting Systolic Blood Pressure ≥ 130 mmHg; [e.]Resting DBP: Resting Diastolic Blood Pressure ≥ 85 mmHg; [f.]Fasting glucose ≥100 mg/dL; *p<0.008 for prior military service exposure of interest; [g.]METs: Metabolic Equivalent of Tasks

Table 8-4. Crude and Adjusted Prevalence Ratios and 95% Confidence Intervals of High Tension and Anxiety 1970-2013

	Unadjusted Regression Model
Prior Military Service	
No	Reference
Yes	0.74 (0.66, 0.83)
	Adjusted Regression Model
Prior Military Service	
No	Reference
Yes	0.86 (0.77, 0.96)*
Sociodemographic	
Age (Years)	
20-39	Reference
40-49	0.86 (0.83, 0.88)
50-59	0.69 (0.67, 0.72)
≥60	0.46 (0.43, 0.49)
Health Compromising Behaviors	
Smoking History	
Never	Reference
Current	1.16 (1.13, 1.20)
Former	1.08 (1.03, 1.13)
Neuropsychiatric Health	
History of Depression	
No	Reference
Yes	1.98 (1.91, 2.05)
Clinical Variables	
VO^2 Max ($ml \cdot kg^{-1} \cdot min^{-1}$)	
Low Fitness (<10 METs[b.])	Reference
Moderate Fitness (≥10-12.5 METs)	0.87 (0.84, 0.90)
High Fitness (≥12.5 METs)	0.77 (0.74, 0.80)
BMI (kg/m^2)	
Normal (≤24.9)	Reference
Overweight (25.0- ≤29.9)	0.99 (0.96, 1.02)
Obese (≥30)	0.90 (0.86, 0.94)

[a.] METs: Metabolic Equivalent of Tasks; *p<0.05 for prior military service exposure of interest.

Table 9-4. Adjusted Prevalence Odds Ratios and 95% Confidence Intervals of Reporting Prior Military Service 1970-2013

	Adjusted Regression Model
Sociodemographic	
Age (Years)	
20-39	Reference
40-49	1.84 (1.52, 2.22)*
50-59	3.63 (2.99, 4.40)*
≥60	9.57 (7.72, 11.86)*
Health Compromising Behaviors	
Smoking History	
Never	Reference
Current	0.75 (0.63, 0.91)*
Former	0.79 (0.65, 0.97)
Neuropsychiatric Health	
History of Depression	
No	Reference
Yes	1.24 (0.98, 1.56)
Tension and Anxiety Scale	
No Tension and Anxiety	Reference
High Tension and Anxiety	0.80 (0.69, 0.93)*
Clinical Variables	
VO^2 Max ($ml \cdot kg^{-1} \cdot min^{-1}$)	
Low Fitness (<10 METs[a.])	Reference
Moderate Fitness (≥10-12.5 METs)	1.62 (1.39, 1.89)*
High Fitness (≥12.5 METs)	2.10 (1.76, 2.51)*
BMI (kg/m^2)	
Normal (≤24.9)	Reference
Overweight (25.0- ≤29.9)	1.33 (1.16, 1.52)*
Obese (≥30)	1.72 (1.44, 2.07)*

[a.]METs: Metabolic Equivalent of Tasks; *p<0.004

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OVERALL CONCLUSION

This dissertation used a life-course perspective[1] to explore occupational risk and protective factors of U.S. military service that can alter the long-term health trajectory of service members after separation and transition to a different occupation or military retirement. Compared to civilian occupations, military service is unique because it requires the adoption of institutional norms and values such as self-sacrifice and service to country[2]. These requirements include both deployment-related (e.g. physical injury and psychological trauma during combat) and non-deployment related exposures (e.g. adoption of health promoting and compromising behaviors).

The first two journal articles explored the longer-term impact of mild traumatic brain injury (mTBI) or concussion and the effectiveness of multidisciplinary treatment for persistent post-concussive symptoms (PPCS) obtained at a large stateside military treatment facility. Because mTBI commonly co-occurs with post-traumatic stress disorder (PTSD) in this population, the effect of PTSD on the effectiveness of treatment was also investigated. Although many of the symptoms of PPCS, such as headache, are common among individuals without mTBI, inability to carry out one's daily routine because of them is what leads individuals to seek treatment.

Although guidelines for treating service members and veterans with PPCS have been in use since 2009[3], some studies of patients seen at VA hospitals have been published[4], but

no studies of service members treated in an military treatment facility had been reported in the literature. Our finding that the multidisciplinary treatment approach implemented at SAMMC was effective in reducing patient self-reported persistent post-concussive and PTSD symptoms provides important evidence of the usefulness of these methods. The finding that PPCS burden and PTSD diagnosis were the only meaningful predictors of post-treatment PPCS supports the importance of a treatment program that also addresses psychogenic factors such as PTSD[3].

Additional studies are needed to confirm the generalizability of these findings. A larger sample of patients is needed to explore the relationship of other variables not available in the current studies (e.g. female sex, multiple TBIs, compensation, effort, depression, social support) and symptom resolution. Treatment strategies and implementation vary from clinic to clinic and hospital to hospital. However, hospitals and TBI clinics need the tools and guidance necessary to develop a research culture[5] so that different treatment programs can be compared and specific treatment(s) effective in managing different symptom clusters can be identified. The studies reported here were made possible by the availability of data from unique clinic database and the desire of the TBI clinic director, a physician, to support this research to better understand the needs of her patients. In addition to the publishable research findings, practical suggestions for improving the quality and completeness of the clinic data from these studies are helping to inform ongoing efforts to implement a DOD-wide behavioral health clinic database that will include TBI.

The third study in this dissertation explored broader macro-level military service occupational factors potentially associated with metabolic syndrome, defined as a metabolic profile that is associated with an increased risk of cardiovascular disease, type 2 diabetes mellitus, and select cancers. The finding that prior military service was protective for metabolic syndrome is intriguing yet challenging to explain given the risk factor profile of our study sample. Of note, the sample of participants with prior military service were predominantly well educated and affluent men. In addition, unlike some previous studies comparing civilians to veterans[6-8], men with prior military service were healthier reporting a lower prevalence of both smoking and high tension and anxiety, and greater cardiovascular fitness. Thus, results from this study may support the resiliency theory among a sub-group of veterans for whom military service has a positive impact on education, employment, and health. However, prior military service was also associated with an increased prevalence of abdominal obesity, which is a risk factor for metabolic syndrome.

Future studies need to utilize a large and diverse sample of participants to determine the true association between health behaviors (e.g. smoking and physical activity) and outcomes (e.g. depression and PTSD) historically associated with military service and metabolic syndrome. Further, variables related to diet, medication history, and military occupation also need to be explored as potential confounders associated with metabolic syndrome and prior military service. Lastly, a prospective study that estimates the incidence of metabolic syndrome and individual metabolic syndrome risk factors while adjusting for

pre-service and post-service factors will be most useful for determining the best timing of interventions targeted specifically to veterans with the goal of changing health behaviors and positively altering their health trajectory.

In summary, by 2040, there will be an estimated 14.5 million living veterans in the United States[9]. Many of these veterans will require treatment and rehabilitation services to manage the chronic physical, psychological, and social outcomes associated with their service and the costs will be high, perhaps reaching $1 trillion dollars over the next 40 years[10] for direct medical care alone. As we near the end of the current conflicts, rigorous scientific efforts should continue to focus improving their long-term physical, mental, and social health Veterans and ensure their role as healthy and vital members of communities across the country.

OVERALL CONCLUSION REFERENCES

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APPENDICES

Appendix A: Biomechanics and Pathophysiology of mTBI

Biomechanics of Mild Traumatic Brain Injury

There are unique biomechanical properties that describe the external force necessary to cause a TBI, specifically concussion/mTBI[1]. The external force transfers energy to the brain tissue resulting in potential neuronal damage or death associated with acute and persistent neuropsychological symptoms (e.g. loss or alteration of consciousness, attention, concentration, memory, and cognition)[2].

Biomechanical Forces of Head Trauma

The two broad categories of mechanical forces associated with TBIs are contact and inertial forces[1]. Contact forces encompass the forces caused by direct contact of an object striking the head and only occur during impact loading. Inertial forces encompass the forces of acceleration during impact loading and acceleration loading, which are forces generated by impulsive head motions during trauma not caused by contact forces. Primary injury from contact forces may result in both proximal injury at the site of impact (e.g. skull fracture) and distal injury from stress waves away from the site of impact. However, the brain is relatively tolerant to focal contact forces that result in structural lesions such as linear or depressed skull fractures. Therefore, head injuries from contact forces are more common with moderate to severe TBIs, and the strongest evidence for the cause of concussions/MTBIs is due to inertial forces during the moment of impact.

The two components of inertial forces that occur during a head trauma are linear and rotational acceleration. Evidence from experimental studies with human cadaver skulls support a positive correlation between the external force of a linear acceleration and the subsequent internal response on the brain measured as a change in intracranial pressure[3,4]. Further experimental research from animal studies supports a correlation between increased levels of brain pressure and neurological dysfunction[5,6]. However, brain tissue is more likely to deform from nonlinear shear forces during rotational acceleration due to the physical properties of the brain compared to linear forces[7,8]. In addition, it is difficult to induce unconsciousness without rotational acceleration to the head[9] providing further support for shear forces from rotational acceleration as a distinct biomechanical cause of concussions/mTBIs.

Transfer of Biomechanical Forces to the Brain

If enough force is generated by the head trauma, then these external forces are transferred by pressure and shear forces internally to the brain tissue[1]. Brain tissue deformation caused by intracranial pressure from external linear acceleration forces during impact and inertial loading are relatively small compared to the deformation of tissue caused by shear forces experienced during rotational acceleration[10-12]. Further, univariate predictive models based on simulated head to head football collisions reported that maximum shear stress in the midbrain of the brainstem was the best predictor of concussion/mTBI (Wald

Statistic=8.11; p=0.01)[12]. Interesting, this supports one prevailing theory that the acceleration and deceleration forces that cause TBI result in shearing forces exerted on the brain tissue, which ultimately results in damage to neurons and blood vessels primarily residing in the brainstem responsible for alertness, awareness, and consciousness[13,14]. Thus, explaining why even concussion/mTBI causes an alteration or loss of consciousness. However, there is also strong evidence supporting damage to neurons in the grey to white matter junction of the cerebral cortex[15,16] following a TBI. This evidence suggests that damage to these more peripheral neurons, potentially responsible for activation of specific regions of the brainstem[17], suppress cells in this region of the brain due to lack of sufficient input[18,19]. In fact, there is evidence for traumatic axonal injury in the following locations of the brain: gray to white matter junction in the frontotemporal region, white matter of internal capsule, deep gray matter, upper brainstem, and corpus callossum[20,21].

The direction of the rotational acceleration also may play a critical role in subsequent impairment of the sustained head injury. For example, a hallmark experimental study by Gennarelli and colleagues[22] initiated non-impact traumatically induced coma on 45 primates and reported differences in length of coma, degree of traumatic axonal injuries and neurological impairment dependent on where the direction of rotational acceleration was applied. Coronal or laterally applied rotational acceleration caused the greatest neurological disability, traumatic axonal injury, and coma lasting longer than 6 hours. Horizontal and

sagittally applied rotational acceleration has the potential to cause a similar level of brain damage but requires a higher magnitude of force.

It is important to highlight that a concussion/mTBI results in shearing forces on the brain tissue but not primary shearing or tearing of the axons (primary axotomy), which is a common misconception and important distinction[2,23]. Rather, the external forces transferred to the brain during trauma cause the axons to twist and stretch potentially causing a neurometabolic cascade leading to the tearing of the axon (secondary axotomy) and cell death over time[24]. However, cell death is rare and the majority of damaged axons will recover from concussion/mTBI[2]. Therefore, current evidence supports that the deficits experienced following a concussion/mTBI are due primarily to cellular abnormalities that damage but do not kill neurons.

Blast-related Forces and Transfer of Blast-related Forces to Brain Tissue

The specific biomechanical influence of blasts and subsequent concussion/mTBI is especially important for military service members and veterans because blasts are the most common mechanism of injury related to TBI during the recent conflicts in Iraq and Afghanistan[25,26]. This is primarily due to the high incidence of improvised explosive devices (IEDs) used by enemy combatants in the war theater.

A solid or liquid explosive is converted into a gas resulting in 4 sequential changes to atmospheric pressure and the blast wind during an explosive event (e.g. mortar shells, rocket propelled grenades, IEDs) [20,27,28]. First, there is normal atmospheric pressure before the shock front. Second, the maximal high pressure wave (1st positive phase) follows the initial blast with wind flowing away from the explosion. Third, a drop in atmospheric pressure follows with a reversed blast wind blowing back towards the initial explosion. Fourth, a second lower intensity high pressure wave occurs (2nd positive phase) before the atmospheric pressure returns to normal and the wind subsides.

A blast force can transfer potentially damaging forces to brain tissue via a variety of mechanisms[27,28]. The three most common mechanisms include direct atmospheric forces of the primary blast wave (primary injury), forces caused by the blast wave propelling objects (e.g. shrapnel, rocks) to contact the head (secondary injury), and forces to the head caused by the blast throwing a soldier to the ground, against a solid object, or a structural collapse onto the soldier (tertiary injury). Quaternary injury involving burns and inhalation of toxic inhalants is also possible but not pertinent to TBI unless the quaternary injury results in a subsequent head trauma (e.g. the soldier sustains a concussion/mTBI after a fall due to inhalation of a noxious toxin).

Pathophysiology of Mild Traumatic Brain Injury

Macro-level Abnormalities

Structural Brain Lesions

Individuals meeting all the criteria of concussion/mTBI with additional visible intracranial abnormalities (e.g. bleeding, bruising, or swelling of the brain) are often classified as complicated concussion/mTBI and individuals without such abnormalities are classified as uncomplicated concussion/mTBI. One reason for the distinction is evidence supporting poorer performance on neuropsychological tests within the first days to weeks[29-31] and even months[32] after the initial injury when comparing complicated mTBI cases to uncomplicated cases. However, the evidence is mixed with studies also reporting no significant neurocognitive differences, especially recent studies examining neuropsychological deficits in the weeks to months following the injury[33,34].

A review of the literature reported that the estimated prevalence of emergency room mTBI patients with computer tomography abnormalities identified on the same day of injury was as high as 20%[2]. Another comprehensive review of the literature performed by the World Health Organization Collaborating Centre Task Force on Mild Traumatic Brain Injury reported that the prevalence of computer tomography abnormalities was 5% for hospital patients with a GCS score of 15 and 30% for patients with a GCS score of 13. It is important to note experts believe the true prevalence of structural lesions is significantly lower[2] due to the high proportion of individuals sustaining an mTBI and either seek no medical attention or are treated at a doctor's office or clinic and therefore not accounted for in the current literature due to selection bias[35,36]. Therefore, the majority of concussions/mTBIs and

subsequent acute and chronic outcomes are not characterized by these macroscopic abnormalities.

Cellular Abnormalities

The current evidence describing the pathophysiology after a concussion/mTBI at the cellular level includes the following: ion flux, hypometabolism, reduction in cerebral blood flow, and debilitated neurotransmission[2,23,37,38].

Neurometabolic Cascade

The complete picture of the neurometabolic pathway following a concussion/mTBI is unclear, but a general understanding of the molecular pathophysiology has emerged[2,23,37,38]. First, numerous action potentials are generated following a depolarization of neurons caused by the release of potassium ions outside the cell resulting from the stretching and twisting of neuronal cell membranes and axons caused by the external forces applied during a head trauma. Second, high levels of the excitatory neurotransmitters, specifically glutamate, are released with continued ion flux of potassium ions outside the cell and sodium and calcium ions inside the cell following these action potentials. This excitatory period is followed by a spreading neuronal suppression, which may be associated with classic concussion/mTBI symptoms. Third, glucose hypometabolism begins to provide the necessary amount of adenosine triphosphate (ATP) to the sodium potassium pump attempting to maintain ionic balance and homeostasis within the cell that has been perturbed. In this hypometabolic state

glycolysis results in lactate accumulation and calcium ion accumulation inside the mitochondria which may impair oxidative metabolism causing the cell to further rely on anaerobic glycolysis for ATP production. Fourth, this disruption of oxidative metabolism can impair neuronal functioning or cause cell death via the accumulation of calcium ions in the mitochondria, which ultimately activates the calpain enzyme signaling cell apoptosis.

Following the initial increase in glucose from glycolyisis there is a decrease in the local cerebral metabolic rate of glucose, which is a measure of the amount of glucose utilized per minute per 100 milligrams of brain tissue. The specific mechanism that induces this decreased rate of glucose utilization is unknown. Further, it is unclear if this mechanism serves as a protection against further injury or makes the brain tissue more vulnerable. Another unclear response following trauma is the decreased levels of intracellular magnesium ions. The decrease in magnesium ions may further depress glycolysis and oxidative metabolism or allow greater influx of calcium ions by leaving more N-methyl-D-aspartate (NMDA) receptors open, which are blocked by magnesium ions absent necessary action potentials.

Traumatic Axonal Injury

There is also a proposed pathophysiology for injury specific to the axon following concussion/mTBI[37,38]. First, disruption of the axon membrane increases cell membrane permeability and causes calcium ion influx following trauma induced axonal stretching and

twisting. Second, neurofilament compaction occurs which may result in neurofilament instability or collapse. Third, the calcium ion accumulation may lead to microtubule disassembly and accumulation of axonally transported organelles. Fourth, the accumulation of organelles may result in axonal swelling and secondary axotomy. Of note, the pathophysiology describing how a primary blast wave causes a TBI, especially a concussion/mTBI remains unclear, but follow a similar neurometabolic cascade that results in traumatic axonal injury from inertial loading is one proposed mechanism of interest[26,28,39].

Cerebral Blood Flow

There is also decreased cerebral blood flow experienced during hypometabolism within the neuron at sub-ischaemic levels[37,38,40]. The triphasic response reported with severe TBI[41] beginning with an initial decrease in cerebral blood flow (0-1 days), then an increase in blood flow (1-3 days), and lastly another decrease in blood flow (4-15 days) may also be similar in mTBI, but there is no definitive evidence. The effect of concussion/mTBI on cerebrovascular reactivity and cerebral oxygenation are currently not well understood[40].

Altered Neurotransmitter Brain Activation

There are numerous proposed post-concussion/mTBI excitatory neurotransmitter alterations associated with neurocognitive deficits following concussion/mTBI[37,38]. For example, evidence of impaired long-term potentiation of NMDA channels associated with learning. Definitive mechanisms of impaired activation have yet to be established.

APPENDIX A REFERENCES

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Appendix B: Neurobehavioral Symptom Inventory

Neurobehavioral Symptom Inventory (NSI)

Please rate the following symptoms with regard to how much they have disturbed you IN THE LAST 2 Weeks.
The purpose of this inventory is to track symptoms over time. Please do not attempt to score.

0 = None – Rarely if ever present; not a problem at all

1 = Mild – Occasionally present, but it does not disrupt my activities; I can usually continue what I'm doing; doesn't really concern me.

2 = Moderate – Often present, occasionally disrupts my activities; I can usually continue what I'm doing with some effort; I feel somewhat concerned.

3 = Severe – Frequently present and disrupts activities; I can only do things that are fairly simple or take little effort; I feel I need help.

4 = Very Severe – Almost always present and I have been unable to perform at work, school or home due to this problem; I probably cannot function without help.

Symptoms	**0**	**1**	**2**	**3**	**4**
Feeling Dizzy	O	O	O	O	O
Loss of balance	O	O	O	O	O
Poor coordination, clumsy	O	O	O	O	O
Headaches	O	O	O	O	O
Nausea	O	O	O	O	O
Vision problems, blurring, trouble seeing	O	O	O	O	O
Sensitivity to light	O	O	O	O	O
Hearing difficulty	O	O	O	O	O
Sensitivity to noise	O	O	O	O	O
Numbness or tingling on parts of my body	O	O	O	O	O
Change in taste and/or smell	O	O	O	O	O
Loss of appetite or increased appetite	O	O	O	O	O
Poor concentration, can't pay attention, easily distracted	O	O	O	O	O
Forgetfulness, can't remember things	O	O	O	O	O
Difficulty making decisions	O	O	O	O	O
Slowed thinking, difficulty getting organized, can't finish things	O	O	O	O	O
Fatigue, loss of energy, getting tired easily	O	O	O	O	O
Difficulty falling or staying asleep	O	O	O	O	O
Feeling anxious or tense	O	O	O	O	O
Feeling depressed or sad	O	O	O	O	O
Irritability, easily annoyed	O	O	O	O	O
Poor frustration tolerance, feeling easily overwhelmed by things	O	O	O	O	O

Appendix C: Post-Traumatic Stress Disorder Checklist-Military Version

PTSD CheckList – Military Version (PCL-M)

Patient's Name: _____ **Date:** _____

SSN:_____ **Service:**_____**Rank:**_____

Instruction to patient: **Below is a list of problems and complaints that veterans sometimes have in response to stressful military experiences. Please read each one carefully, put an "X" in the box to indicate how much you have been bothered by that problem *in the last month*.**

		Frequency:				
No.	**Problem or Complaint:**	**Not at all (1)**	**A little bit (2)**	**Moderately (3)**	**Quite a bit (4)**	**Extremely (5)**
1.	Repeated, disturbing *memories, thoughts,* or *images* of a stressful military experience?					
2.	Repeated, disturbing *dreams* of a stressful military experience?					
3.	Suddenly *acting* or *feeling* as if a stressful military experience *were happening again* (as if you were reliving it)?					
4.	Feeling very upset when something reminded you of a stressful military experience?					
5.	Having *physical reactions* (e.g., heart pounding, trouble breathing, or sweating) when *something reminded* you of a stressful military experience?					
6.	Avoid *thinking about* or *talking* about a stressful military experience or avoid *having feelings* related to it?					
7.	Avoid *activities* or *talking about* a stressful military experience or avoid *having feelings* related to it?					
8.	Trouble *remembering important parts* of a stressful military experience?					
9.	Loss of *interest* in things that you used to enjoy?					
10.	Feeling *distant* or *cut off* from other people?					
11.	Feeling *emotionally numb* or being unable to have loving feelings for those close to you?					
12.	Feeling as if your *future* will somehow be *cut short*?					
13.	Trouble *falling* or *staying* asleep?					
14.	Feeling *irritable* or having *angry outbursts*?					
15.	Having *difficulty* concentrating?					
16.	Being "*super alert*" or watchful on guard?					
17.	Feeling *jumpy* or easily startled?					

PCL-M for DSM-IV (11/1/94)

Weathers, F.W., Huska, J.A., Keane, T.M. PCL-M for DSM-IV. Boston; National Center for PTSD – Behavioral Science Division, 1991.

Appendix D: Glossary of Terms

Acute Post Concussion Symptoms: physical, cognitive, and behavioral/emotional post-concussion/mTBI related symptoms occurring within the first 30 days following a sustained concussion/mTBI.

Behavioral/Emotional Post Concussion Symptoms: subset of post-concussion symptoms (e.g. depression, anxiety, and agitation) caused by a complex pathophysiologic cascade of events following damage to the brain sustained during a concussion/mTBI.

Chronic Traumatic Encephalopathy (CTE): a progressive neurodegenerative disease reportedly due to a single or repetitive closed brain injury; also known as dementia pugilistica.

Cognitive Post Concussion Symptoms: subset of post-concussion symptoms (e.g. deficits in attention, memory, and concentration) caused by a complex pathophysiologic cascade of events following damage to the brain sustained during a concussion/mTBI.

Concussion/mild Traumatic Brain Injury (mTBI): the least severe TBI characterized by an alteration of consciousness and post-traumatic amnesia lasting for less than twenty-four hours, and while a loss of consciousness is not required; if a loss of consciousness does occur

then it should not last longer than 30 minutes. Persons with a concussion/mTBI typically have an initial Glasgow Coma Scale score ranging from 13 to 15.

External Cause: the nature of how an injury occurred (e.g., motor vehicle crash or fall)

Functional and Social Disability: a wide range of deficits associated with concussion/mTBI related to employment, social relationships, independent living, recreation and quality of life.

Functional Somatization: the primary manifestation of medically unknown physical symptoms with no known pathology not following psychological distress such as anxiety or depression.

Incidence of concussions/mTBI: the number of new concussion/mTBI events within a specified time interval (e.g., annual) with symptoms that may or may not persist long-term.

Late On-Set Stress Symptomology (LOSS): exposure to traumatic combat related experience(s) with no functional impairment or chronic stress disorder in adulthood but an increase in stress symptomology late in life as the thoughts, memories, and feelings of the trauma are contemplated.

Life-course perspective: the understanding of how chronological age, relationships, common life transitions (e.g. military service), and social change shape people's lives from birth to death (e.g. long-term health outcomes).

Persistent Post Concussion Symptoms (PPCS): physical, cognitive, and behavioral/emotional post-concussion/mTBI related symptoms that do not resolve within the first 3 months following a sustained concussion/mTBI.

Physical Post Concussion Symptoms: subset of post-concussion symptoms (e.g. sensitivity to light and hearing loss) caused by a complex pathophysiologic cascade of events following damage to the brain sustained during a concussion/mTBI.

Physiogenic etiology: persistent post-concussive symptoms with a physical origin rather than psychogenic origin; therefore, these symptoms are attributed to the complex pathophysiologic cascade of events following damage to the brain sustained during a concussion/mTBI.

Post-Traumatic Stress Disorder (PTSD): a mental disorder, caused by a traumatic event, that leads to re-experiencing (e.g.flashbacks) and avoidance of memories of the event, combined with hyperarrousal (e.g., insomnia and exaggerated startle response).

Post-Traumatic Stress Disorder Symptoms: physical, cognitive/mental, emotional, and behavioral symptoms caused by exposure to traumatic event(s). Many of these symptoms overlap with Persistent Post-Concussion Symptoms.

Presenting Somatization: the secondary manifestation of medically unknown physical symptoms following psychological distress such as anxiety or depression.

Prevalence of disability from concussion/mTBI: the number or percent of individuals who have had one or more concussion/mTBIs and are living with persistent symptoms.

Prevalence of a history of concussion/mTBI: the number or percent of individuals who have "ever" experienced at least one concussion/mTBI regardless of whether they have persisting symptoms or related disability.

Prior Military Service: the branch specific requirement for the number of days of military service to be classified as having previous service in the military.

Psychogenic etiology: persistent post-concussive symptoms with a psychological origin rather than physiogenic origin; therefore, these symptoms are attributed to causes other than the physical damage to the brain following a concussion/mTBI such as PTSD and depression.

Somatic Post Concussion Symptoms: the manifestation of physical symptoms such as headaches, nausea, and joint pain with an unknown medical pathology (i.e. not attributed to concussion/mTBI) usually attributed to psychological distress.

Traumatic Brain Injury (TBI): an alteration in brain function, or other evidence of brain pathology, caused by an external force.

Veteran: completion of full active duty military service obligation or early honorable discharge.