

MILD TRAUMATIC BRAIN INJURY, SLEEP, AND CARDIOVASCULAR
DISEASE:
AN ANALYSIS OF MILITARY HEALTH SYSTEM DATA

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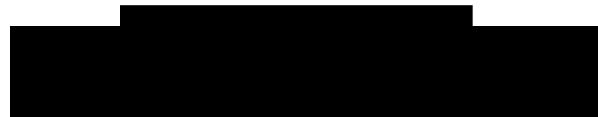
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ABSTRACT

Title of Dissertation: “Mild traumatic brain injury, sleep, and cardiovascular disease: An analysis of Military Health System data”

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Dissertation directed by: Dr. David S. Krantz, PhD, Medical and Clinical Psychology

Background. Mild traumatic brain injury (mTBI) and Post-Traumatic Stress Disorder (PTSD) are important health consequences associated with military service. mTBI and PTSD share similar symptomology and sequelae, and together with comorbid sleep conditions, increase risk of coronary heart disease (CHD).

Study Purpose. To assess the independent influences of mTBI, PTSD, and sleep disorders on long-term CHD risk.

Methods. This study compared 68,705 mTBI and 128,252 matched non-mTBI control patients by analyzing encounter-level data within the Military Healthcare System (MHS) between 2007-2019. Patients were followed up from study entry to one of the following occurred: CHD, death, disenrollment from the MHS, or end of the study. The primary study outcome was CHD as indicated by ICD codes. Cox proportional hazard models with time-varying covariates examined the relationship of mTBI, PTSD, and/or sleep problems to CHD incidence.

Results. mTBI was associated with increased rates of multiple comorbid health conditions, including sleep problems (OR=3.95, 95% CI: 3.87-4.03, $p<0.001$), PTSD

(OR=6.49, CI: 6.30-6.69, $p<0.001$), and obesity (OR=1.50, 1.45-1.54, $p<0.001$), and with increased mortality during the study period. However, contrary to hypothesis, Cox regressions revealed that mTBI was associated with reduced incidence of CHD after adjusting for sleep disorders and PTSD (HR=0.322, CI: 0.271-0.383, $p<0.001$). Sleep disorders were independently associated with increased CHD after controlling for mTBI and PTSD (HR=2.037, CI: 1.727-2.402, $p<0.001$). PTSD was also associated with CHD in univariate analyses, but its effect was lessened by the presence of mTBI and/or sleep disorders (HR=1.365, CI: 1.076-1.730, $p<0.05$).

Conclusion. The present study provides evidence that mTBI is associated with greater mortality and comorbidities (e.g., sleep disorders, etc.) which themselves are risk factors for CHD. However, contrary to prior research, mTBI was associated with reduced CHD incidence in this younger sample of MHS patients. Explanations for these findings may include the relatively young age of this population and procedures used for matching cases and controls in the study. It is suggested the mTBI is a systemic disorder initiating a disease process leading to poor physical and mental health even after the initial neurological insult resolves.

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CHAPTER 1: Introduction

OVERVIEW

Military service members experience unique occupational stressors. These stressors increase the risks of certain diseases or conditions, such as Post-Traumatic Stress Disorder (PTSD), mild traumatic brain injury (mTBI), and sleep problems. The high incidence of blast-related injury in Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) has increased attention to study mTBI and PTSD (289). Post-Traumatic Stress Disorder is a psychiatric condition associated with exposure to a traumatic event, such as witnessing death of a friend or suffering combat injury (10). Post-Traumatic Stress Disorder is highly comorbid with TBI, which occurs when external force upon the head is severe enough to cause damage to the brain (147). Among the sequelae shared by both mTBI and PTSD are sleep problems, such as insomnia and sleep apnea. These shared symptoms further confound the effects of mTBI, PTSD, and their outcomes.

More recently, sleep disturbances in the military have garnered more attention as they pertain to mTBI and PTSD (208). It is well-documented that service members who deployed tend to have greater rates of PTSD, mTBI, and sleep disturbances compared to civilians due to the occupational demands and hazards in the military. Moreover, past literature also indicated an association between PTSD, mTBI, and sleep problems with a variety of poorer physical health outcomes, with growing evidence of a link between the aforementioned and cardiovascular health. However, there is a dearth of research on these comorbidities and their impact on long-term cardiovascular health, especially among

military personnel. Therefore, further study is needed of the comorbidity of mTBI, PTSD, and sleep problems among military service members and their relationships to long-term physical health outcomes, with a focus on the risk for cardiovascular disease (CVD).

OVERVIEW OF TRAUMATIC BRAIN INJURY

Definition and Diagnostic Criteria

Traumatic brain injury occurs as a result of external force from physical trauma incidents, such as the impact of falls or motor vehicle accident, that are strong enough to damage the brain and its function (22). Traumatic brain injury is further described by the degrees of severity at the time of injury: mild, moderate, or severe. Mild traumatic brain injury (mTBI) is defined as 1) an external injury to the brain; 2) confusion, disorientation, or loss of consciousness (LOC) for 30 minutes or less; 3) Glasgow Coma Scale score (GCS) of 13 to 15; and 4) posttraumatic amnesia for less than 24 hours. Moderate TBI involves 1) LOC between 30 minutes and 24 hours, 2) GCS of 9 to 12, and 3) posttraumatic amnesia between one and seven days. Severe TBI extends the severity from moderate TBI, usually implicated with GCS between 3 to 8, LOC greater than 24 hours, posttraumatic amnesia greater than seven days, and worse cognitive impairment, leading to poor prognosis (53; 195; 252).

Epidemiology and Risk Factors for Traumatic Brain Injury

An estimated 1.7 million people from the general public sustain traumatic brain injury in the United States each year (22). 5.3 million individuals are living with a disability due to TBI (44), with 52,000 individuals dying due to their injuries annually.

Incidence rates of TBI varies across age groups, with rates highest among young adults and older adults. Although the mechanism of injury may be impacted by a range of risk factors, such as lifestyles and activities, males are overall more likely to experience TBI compared to females across all age groups (93). Among emergency visits, Black racial group has the highest rate of TBI reported rate, followed by white racial group and American Indian (93).

Pathophysiologic Effects of Traumatic Brain Injury

It has been suggested that (320) there are two principal mechanisms of injury involved in TBI: “(a) focal brain damage due to contact injury types resulting in contusion, laceration, and intracranial hemorrhage and (b) diffuse brain damage due to acceleration/deceleration injury types resulting in diffuse axonal injury or brain swelling” (320). Subsequently, TBI leads to several stages of pathophysiology, including: 1) damage to cerebral blood flow (e.g., hypo/hyperperfusion, cerebral vasospasms), 2) cerebral metabolic dysfunction, 3) oxidative stress, and 4) inflammation (for a detailed review, see Werner and Engelhard (320)). Several symptoms are associated with TBI. These are generally categorized into three clusters: somatic, cognitive, and affective symptoms (147; 233). Somatic symptoms include sleep problems, sensitivity to sound and light, headache, and nausea. Cognitive symptoms include problems with concentration, mental fog, decreased processing speed, and attention and memory difficulties. Affective symptoms include irritability, anxiety, depression, and emotional lability (147; 233). These symptoms often interact and exacerbate each other in a dysfunctional feedback loop, resulting in the maintenance of symptoms and impacting functional outcome even after medical signs have resolved (149).

Comorbidities Associated with Mild Traumatic Brain Injury

In addition, Masel and Dewitt (191) postulated TBI as a chronic disease process that impacts multiple organ systems, either as disease causative and/or accelerative factor rather than a singular, isolated event or injury (44). As such, the TBI-induced disease process is believed to be widespread, affecting physical, cognitive, and behavioral domains of human functioning. Masel and Dewitt (191) reviewed the literature and examined hypotheses linking multiple comorbidities with TBI. Some of the conditions include higher post-trauma morbidity of sleep disorders (193; 327), neurodegenerative diseases (e.g., Alzheimer's disease; see Lye et al. (180) for a review), neuroendocrine disorders (e.g., gonadotropin deficiency) (5), musculoskeletal dysfunctions (85), metabolic dysfunction (15; 16), and so on.

For example, by analyzing archival data from rehabilitation patients, Holcomb et al. (131) reported that rehabilitation patients with TBI reported higher ear, nose, and throat (ENT) problems, hypertensive symptoms, and musculoskeletal injuries, although the authors reported that the sample in the analysis reported feeling healthier than other rehabilitation populations, such as those who sustained stroke and orthopedic injury. The increased rate of other comorbidities in mTBI patients was further corroborated in other studies (54; 104; 219; 325). Moreover, the comorbidities were found to be sex and age dependent, such that older populations with TBI exhibit significantly more comorbidities, especially among older females (54). Additionally, mTBI was found to have an impact on cardiovascular pathology and is associated with increased cardiovascular mortality (7) and a significant reduction in long-term survival (41).

Pathophysiologic Mechanisms Associated with Mild Traumatic Brain Injury

Dash and colleagues (72) reviewed the biomolecular mechanisms through which TBI impacts physical health. Primary results of TBI are typically mechanical damage that deform grey and white matters by distorting cell membranes and disrupting release of intracellular contents. Pertaining to physical health, there is a secondary injury effect associated with mTBI which is a sequela of a cascade of events that worsen physical function and promotes further cell death in neuronal and vascular structures. This secondary damage could occur days, weeks, or even months after the TBI symptoms have resolved. Possible pathophysiological effects of these processes include increased inflammation, altered homeostasis, breakdown of the blood-brain barrier, hypertension, cell death, ischemia, and other indirect system damage (e.g., migration of immunocompetent cells such as polymorphonuclear neutrophil, which would lead to morphological damage to peripheral organs) (72; 204).

Esterov and colleague (89) reviewed mTBI and its impact on the autonomic nervous system (ANS). Corroborating the evidence presented above, the authors concluded that systemic complications after mTBI are likely due to large catecholamine release and inflammatory responses to the primary insult. In turn, it is thought that the cascade of stress responses associated with mTBI increases sympathetic activity and subsequently suppresses the immune system through a dynamic and complex interactions involving neural and non-neural modulations of peripheral immune responses and signaling mechanisms (151). This cascade of responses may lead to the development of a host of conditions, such as endocrine abnormalities, changes in heart rate variability, psychiatric disorders, gastrointestinal problems, and more (89).

Interestingly, one study reported that severity of initial TBI and cardiovascular autonomic dysregulation are correlated (128). These researchers studied adult patients who had suffered a mTBI, adult patients who suffered a moderate or severe TBI, and healthy individuals as control. Individuals were assessed for their autonomic functions (e.g., electrocardiographic RR intervals, blood pressures, respiratory frequency, baroreflex activation, and heart rate variability in various orthostatic positions). Evaluation of medical records, physical and neurological status, and TBI severity was also conducted. This study demonstrated that the individuals who experienced moderate to severe TBI were more likely to experience increased sympathetic and decreased parasympathetic cardiovascular autonomic modulation at rest when compared to healthy individuals and mTBI patients. Additionally, patients with more severe TBI experienced greater compromised baroreflex function upon orthostatic challenge, suggesting the greater severity of the initial injury was a factor in patients' inability to mount sympathetic activation and to withdraw parasympathetic modulation upon baroreflex unloading. These effects lingered even after months to years after the initial injury. Thus, the study investigators concluded that patients with moderate and severe, compared to mild TBI are more prone to greater autonomic dysfunction (128).

Although there has been extensive research on TBI and impaired physical health (71), the focus of most of this research has not been on TBI with mild severity. Given that 75-90% of TBI are classified as mild (233), it is surprising that the literature on the relationship between mTBI and physical health is lacking. Nevertheless, some of the evidence identified the associations between mTBI with cardiovascular complications and autonomic dysfunctions. These associations will be reviewed in the section on CVD.

Traumatic Brain Injury and Post-Traumatic Stress Disorder: Comorbidity and Mechanisms

Post-Traumatic Stress Disorder and TBI are commonly comorbid due to the traumatic nature of brain injuries, although the nature and etiology of the comorbidity has been in debate (44). Some researchers have argued that PTSD could not develop following a TBI because of post-TBI impaired consciousness. The altered or loss of consciousness would, in turn disrupt memory formation of the traumatic experience, one of the important elements in diagnosis (44). However, emerging evidence suggests that PTSD does develop in a significant number of individuals after individuals sustaining a TBI (44). Interestingly, some evidence indicates that development of PTSD is even possible among those with moderate and severe TBI, despite having suffered amnesia so significant that they could not recall the traumatic experience.

Several models have been posited to explain the mechanism of PTSD development after TBI. These include fear conditioning, memory reconstruction, and post-amnesia resolution (44). A fear conditioning model of the relationship of PTSD to TBI draws findings from psychology and postulates that trauma induces sympathetic arousal and release of neurochemicals norepinephrine and epinephrine, resulting in the overconsolidation (i.e., excessive strengthening of memory after its initial acquisition) of trauma memories (57). As such, when exposed to stimuli associated with the trauma (e.g., showing a picture of a car to a motor vehicle accident survivor), an automatic physiologic fear response activates, resulting in bodily changes, such as increased heart rate, that are symptoms of PTSD.

A memory reconstruction model is another mechanism proposed to explain the presence of trauma-related memories after trauma (43). The model suggests that

individuals who have sustained TBI recreate traumatic memories vicariously (e.g., via police reports, images from the scene, medical records, second-hand account, etc.), despite posttraumatic amnesia. Case reports have shown that the reconstructed memories could be so intrusive and compelling that the experience of recalling these memories is similar to recalling of the actual trauma, thus leading to PTSD (45). Alternatively, a post-amnesia resolution explanation explains PTSD as being developed as a result of experiences secondary to the trauma. Although individuals may not recall the trauma, the experience post-trauma (e.g., being in an ambulance, receiving treatment, hospitalization, witnessing blood, and providing a police record), may by itself be traumatic. Subsequent PTSD may then develop as a result of having experienced these events (44).

Thus, the notion that PTSD can develop after TBI is supported by the growing body of research on PTSD as a sequela of TBI (107; 200; 217). The high rate of comorbidity (130) of the two conditions has led researchers to suggest that these are overlapping disorders. Indeed, Bryant (44) discusses the overlapping symptoms and etiologies of TBI and PTSD that lead to frequent confusion between the two disorders. There is further evidence that PTSD and TBI may interface on biological (e.g., structural, endocrine, and neurochemical change) and genetic levels, thereby resulting in similar pathophysiological symptom profiles (72; 150). For example, recent imaging studies (251) have also found that the loci of injury correlated with an mTBI overlap with areas of abnormal cerebral activity in the frontal and medial temporal lobes found in PTSD. Despite these similarities, however, evidence suggests that the co-occurrence of PTSD and TBI may have different outcomes from when each occurs by itself (44). Evidence for this assertion is reviewed below. Thus, the task of delineating the effects of TBI and

PTSD is necessary, although difficult, to improve our understanding of the nature of their effects on human health (217).

Traumatic Brain Injury in the Military

Unlike in the general population, TBI in the military can often occur without witnesses and go without treatment or assessment, especially in combat environments (e.g., exposure to improvised explosive devices) necessitated quick responses with minimal time to rest, recover, or wound care (165). With increased awareness, more efforts have been put in place to surveil and monitor (17) and improve treatment and assessment of TBI in the military (88). Nearly 15% of deployed soldiers reported injury that resulted in loss of consciousness and altered mental status (130). One report found that more than 33,000 Active Duty (AD) service members (SMs) from all services (including active reserve components of the National Guard) sustained TBI in 2011 (22), making TBI one of the most survived types of injury in the OEF/OIF conflicts, second only to orthopedic injuries (311). As stated above, mTBI is the most common form of TBI, with an incidence rate that may exceed 300 per 100,000 in the general population (32), and researchers believe that the incidence of TBI is likely much higher in the military setting (56; 130). In 2003, an estimated expenditure of \$16.7 billion was spent on mTBI alone, suggesting the burden mTBI places on the healthcare system (323). Consequently, mTBI is a major concern in the military as service members are more likely to be in hazardous environments and hence are prone to head injuries.

Estimates indicate that 10 to 20% of military personnel who deployed may have suffered a mTBI during deployment (74). Another study reported that nearly 1 in 4 service members were determined to have experienced TBI during post-deployment

assessment (297). However, these numbers may be underestimated due to a myriad of reasons, including stigma and reporting issues associated with mental health problems in the military (260). This is in contrast with the general population, where compensable nature of the condition can lead to symptom exaggeration or malingering (335). The downplaying of potential problems associated with TBI in the military may result in reduced effectiveness in combat, reduced readiness, increased healthcare costs, and poor quality of life for service members (203).

OVERVIEW OF CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) is a range of conditions that affect the heart and blood vessels, including coronary heart disease (CHD), hypertension, stroke, and peripheral artery disease (241). Cardiovascular disease is the leading cause of death in the U.S., with 80 million Americans having at least one type of CVD (241), and CVD accounting for 25% of U.S. deaths annually (271).

Arteriosclerotic cardiovascular disease (ASCVD) is one of the major CVDs. It is a broad term for heart and vascular conditions resulting from arteriosclerosis, the narrowing of arteries due to fatty deposits called plaques (241). In the coronary arteries, the development of atherosclerosis can lead to myocardial ischemia, or inadequate blood flow to the heart muscle (myocardium). Myocardial ischemia may be accompanied by chest pain, which is a condition called angina pectoris. Eventually, arterial plaque can become unstable and rupture, leading to the death of cardiac tissue (myocardial infarction; MI) or heart attack (157; 303). Behavioral factors such as poor diet, lack of physical activity, and smoking are some of the leading causes of CVD, and these factors are often compounded by psychosocial (e.g., education, socioeconomic status, etc.) and

physiological variables (e.g., age, gender, genetic predisposition, comorbidities, etc.) (157).

Cardiovascular Disease in the Military

As with the general population, SMs and veterans are also afflicted by CVD more than any other chronic disease, and the prevalence of risk factors for CVD in the military, such as obesity, smoking, and hypertension, has continued to rise in recent years (271). However, when compared with civilian populations, military service has also been associated with positive health outcomes and lower mortality rates due to a “healthy soldier effect,” a term coined for the physical fitness and other health requirements for military service resulting in a self-selection of healthier individuals in the military (129).

Regarding comparisons of civilian and military populations, one study compared cardiovascular health in the military to the general population: AD U.S. Army personnel generally had better cardiovascular health metrics based on the American Heart Association guidelines (178; 271), which measure several health and behavioral risk factors pertaining to cardiovascular disease such as physical activity, body mass index (BMI), and diet scores. Further, U.S. Army personnel smoke at the same rate as the general population. While self-selection and physical requirements reduce the rate of obesity and diabetes in the military, SMs had higher risks of hypertension compared to civilians of similar age (55% vs 30%), which could be explained by military-specific occupational stressors (e.g., combat deployment, inconsistent diet, and irregular sleep schedules, etc.). The effects were observed even when controlling for sex, race/ethnicity, and age, but the authors were not able to control for other measures of social disadvantage (271).

Hinojosa (129) compared military veterans and non-veterans in the National Health Interview Survey (NHIS) with respect to self-report of cardiovascular conditions, such as hypertension, coronary heart disease, stroke, and heart attack. The author found that a national sample of veterans and nonveterans differed according to age by CVD conditions, number of comorbid CVD conditions, and CVD counts. Specifically, younger veterans had a higher rate of CVD morbidity than their nonveteran counterparts. The increased morbidity risk for veterans was evident around age 35. However, the nonveterans risk of CVD morbidity increased over time, and at age 70, nonveteran individuals reported more CVD conditions than veteran population. The cross-over interaction was observed likely due to earlier onset of CVD morbidities and comorbidities in veterans, which may have caused higher CVD-related mortality among veterans. Although mortality data were not reported in the study, the author suggested that fewer older veterans survived into older ages in the survey and were more likely to experience death due to CVD conditions. The author concluded that the “healthy soldier effect” may not be as strong of a protective factor for CVD conditions among veterans, especially after military service, as was previously thought. Hinojosa (129) further suggested that the overall poorer cardiovascular health in this study may be caused by an increase in other risk factors for CVD among Iraq and Afghanistan veterans, such as socioeconomic situations in the current era, compared to World War II, Korean War, and Vietnam War, and the evolving nature of military conflicts (282). Despite the limitations associated with the methodology of the Hinojosa’s study (129), such as use of self-report and survey data and the cross-sectional nature of the data, the finding of the association between military service and poorer cardiovascular health at younger ages raises

questions about the nature of the protective nature of military status and its association with cardiovascular health.

Standard Risk Factors for Cardiovascular Disease

Research has identified several so-called standard risk factors for CVD (3; 157; 241; 339), which can be further classified into modifiable or non-modifiable risk factors. Modifiable risk factors include elevated blood pressure, elevated low density lipoprotein (LDL) cholesterol, obesity, and behaviors such as smoking, excessive alcohol consumption, other substance use, physical inactivity, and high cholesterol diet (76; 241; 339). These risk factors are deemed “modifiable” as individuals have the potential to lower the risks of CVD by changing behaviors associated with these risk factors. For example, cigarette smokers have CHD death rates 1.7-3 times higher than those of nonsmokers, and death rates increased exponentially as smoking increases (241). Moreover, nonsmokers demonstrate increased risk of CHD when exposed to passive smoke at work or at home, linking exposure to environmental tobacco smoke (i.e., passive smoking or secondhand smoke) with increased risk of CVD (148). Thus, individuals can reduce their risks for CVD by reducing and eliminating use of cigarette and exposure to cigarette smoke (330). Similarly, managing other modifiable risk factors have been shown to reduce risk of CVD. In contrast, nonmodifiable risk factors are generally risk factors that cannot be controlled. These are usually population-attributable risks. Old age, male sex, race, ethnicity, and family history of CVD are some of the risks that cannot be modified directly. The literature on standard risk factors for CVD and the biological processes involved with these risk factors, is vast and beyond the scope of the

current paper. See Anderson et al. (13), D'Agostino et al. (70), and Goff et al. (113) for detailed discussion.

Psychosocial Risk Factors for Cardiovascular Disease

Research in the past 30 years has advanced knowledge considerably on the role of psychosocial risk factors in CVD. A variety of psychosocial factors have been linked with early development of atherosclerosis. These factors include individual characteristics such as depression and hostility/anger, social characteristics such as low social support and low socioeconomic status, and environmental characteristics such as exposure to psychological or psychosocial stress (227; 291). Of note, human studies have associated personality traits (77; 141), chronic stress (81; 246), depression (124; 339), anger and hostility (19; 153; 206), and anxiety (86; 244; 318) with the development and/or progression of CHD.

Stress, Anger, and Cardiovascular Disease

Studies have indicated that exposure to acute and chronic stress may promote the atherosclerotic process and precipitate acute coronary syndromes such as myocardial infarction, ischemia, and sudden cardiac death (291). In addition, stress-related disorders such as PTSD have been associated with CVD incidence in an increasing number of studies (6; 84; 152; 310); see review in later sections of this proposal). One set of animal model studies illustrates the role of social factors in the atherosclerotic process (145). In a study using cynomolgus monkeys, Kaplan et al. (145) demonstrated that monkeys placed in stressful situation had more extensive atherosclerosis than monkeys in stable environment, even after controlling for serum cholesterol, triglycerides, and blood

pressure. Additionally, when placed in an unstable social environment where group membership changed, more aggressive albeit normolipidemic animals experienced greater atherosclerosis compared to their nonaggressive counterparts (186). In several large studies, those with high levels of depression, anger, or cynical hostility had an increased risk of CVD, including nonfatal infarction and coronary death (26).

Both chronic stress and acute stress have been linked to the development of CHD and to the triggering of acute cardiovascular events (e.g., myocardial ischemia, myocardial infarction, malignant arrhythmia) in patients with CHD (114; 156; 158). For example, research found that stress associated with 9/11 attacks was associated with tachyarrhythmias in patients with implantable cardioverter defibrillators (ICDs) prior to the attacks (290). Moreover, literature on stress-induced transient myocardial ischemia suggests that mental stress can stimulate transient reversible ischemia (e.g., ventricular wall motion abnormalities) and acute coronary artery vasoconstriction (334). Although these symptoms are typically secondary to CHD, they can be induced in healthy individuals through everyday stress (122) and can lead to further cardiovascular morbidity and mortality (21; 270). A recent study also found that anger, both as an emotional state and as a personality trait, increased the risk for myocardial ischemia among patients with a history of myocardial ischemia when they were mentally, but not when physically, stressed (230). For a detailed review, please see Dimsdale (81) and Steptoe and Kivimaki (291).

Depression, Anxiety, and Cardiovascular Disease

Depression and anxiety are relatively common among patients with CVD, especially those with heart failure (HF) (255) and myocardial infarction (MI) (52). In a

meta-analysis of 12 studies (total $N = 3,485$), Tully and Cosh (309) found that Generalized Anxiety Disorder (GAD) has a 11-14% prevalence in CHD samples and the prevalence of Major Depressive Disorder (MDD) in CHD samples is similar or larger in magnitude (15%) (300).

The literature on depression, anxiety, and CVD has focused on the role of depression and anxiety as risk factors for CVD etiology as well as prognosis. For example, Nicholson et al. (212) reviewed 54 observational studies (total $N = 146,538$) with 6,362 CHD events to determine the effect of depression on CHD etiology and prognosis. They observed that clinically assessed depression, as opposed to depression defined by symptom scales, was associated with higher risk for future CHD and that the more severe the depression the higher the risk of CHD. A more recent meta-analysis corroborates with these findings, suggesting that depression significantly increased risk of incident CHD by 30% even after adjusted for potential confounders, such as lifestyle factors and demographic characteristics (106). However, the presence of depressive symptoms, even in the absence of a formal MDD diagnosis, also is predictive of poor prognosis in CHD patients (196). Studies have also suggested that the presence of CHD symptoms, such as chronic angina (chest pain), may lead to depression (286). Depression is also a predictor of poor prognosis in CHD patients and may accelerate the atherosclerotic process (49). In a meta-analysis of prognostic studies published between 2003 and 2005 ($N = 16$), more studies confirmed the link between depression as a prognostic factor of CHD than not (101). Another meta-analysis ($N = 19$) (199) on the prognostic association of depression following MI found that post-MI depression was associated with 1.6-2.7 fold increased risk of impaired outcomes, such as all-cause

mortality, cardiac mortality, and cardiac events, further strengthening the link between depression and poor cardiovascular outcome.

Anxiety is also a significant risk factor for poor prognosis in CHD patients. For example, Martens et al. (188) conducted a prospective cohort study of outpatients with stable CHD and GAD. They assessed the association of GAD and cardiovascular events among these patients while controlling for a myriad of potential mediators, including cortisol, C-reactive protein (CRP) levels, heart rate variability, smoking, medication nonadherence, and physical inactivity. The authors found that GAD was associated with 74% greater rate of cardiovascular events even after adjusted for the potential mediators. The finding confirms prior work that investigated the prognostic importance of GAD in patients with stable CHD (100). It also suggests that further research is needed to determine potential mediators of these associations.

Researchers have also focused on depression and anxiety's associations with other CHD risk factors such as smoking and diet, and comorbidities, such as diabetes mellitus (DM), and metabolic syndrome (253; 339). For example, Ruo et al. (253) analyzed psychosocial factors and health outcomes in patients with CHD. These researchers found that patients with CHD with depression were more likely to have a history of MI, DM, smoking, stress, and lower social support. Additionally, patients with depression also had a higher BMI and lower exercise capacities. In another study, Bonnet et al. (39) studied 1,612 patients referred for outpatient evaluation for cardiovascular disease, and the authors found that anxiety and depression were associated with unhealthy diet, such as higher cholesterol intake as well as higher caloric intake. Further, patients with anxiety and/or depression are more likely to have a sedentary lifestyle and to smoke (339).

A wide range of potential pathophysiological mechanisms were proposed to explain the impact of depression and anxiety on heart health, including hyperactivation of HPA axis and cortisol (228; 250; 302), which subsequently leads to autonomic nervous system (ANS) dysfunction (e.g., heart rate variability), inflammation, platelet dysfunction, etc., which are factors that may promote atherogenesis and acceleration of atherosclerosis (see below for a review) (50; 51; 302). In addition, as noted above, depression and anxiety are also associated with poor health habits and other known CVD risk factors (39; 318). However, researchers have criticized the oversimplification of linear models that assume that risk factors act independently. An alternate, multi-factor model, posits that cardiac outcomes are a result of a confluence of various risk factors operating in a “perfect storm,” activating critical pathophysiological processes that lead to cardiac events (46).

An exhaustive review of the literature on depression, anxiety, and CVD is beyond the scope of this proposal. For a detailed review, please see Carney & Freedland (50), Carney et al. (51), Chauvet-Gelinier et al. (58), Emdin et al. (86), Hare et al. (124), and Thurston et al. (302). It is also important to note that, to date, no study was conducted to investigate the associations of depression, anxiety, and CVD in the military.

Other Psychosocial Risk Factors and Cardiovascular Disease

The association between social factors, such as low socioeconomic status (SES) and poor social networks and low social support, and CHD risk is also well documented (144; 157; 301). Socioeconomic status is conceptualized as a set of measures and conditions, such as education, income, and employment, that may affect a wide range of health risks and outcomes (187). A large body of data indicates an inverse, linear

relationship between socioeconomic status and cardiovascular as well as overall health (4). Low SES, measured in terms of low income and education levels, appears to be associated with greater risk for CHD, even after adjusting for covariates, such as age, race, and gender (176). Although there is no single pathway that could explain the link between social disadvantage and adverse health outcomes (29; 176), the presence of multiple forms of psychosocial disadvantages and risk factors may multiply the risk of CHD.

Pathophysiologic Mechanisms Linking Psychosocial Risk Factors and Cardiovascular Disease

Evidence suggests that psychosocial factors such as depression and stress affect several physiological systems that may promote the development of CVD. For example, stress increases sympathetic nervous system activity and blood pressure leads to an increase in catecholamines, activates the hypothalamic-pituitary-adrenocortical (HPA) axis, and thereby promotes inflammatory responses that subsequently increase the risks for CVD (50; 157). For example, a brief period of mental stress has been found to cause transient dysfunction in the endothelium (the inner layer of arteries) in young, healthy individuals with no apparent risks for CVD (109). Hemodynamic turbulence secondary to psychological stress promotes endothelial injury, particular at branch points, and is thought to be a critical first step in atherosclerosis (249). Subsequently, damaged endothelium release growth factors that stimulate atherogenesis, promotes the movement of lipoproteins from the artery wall, as well as increasing platelet activity (274). Other factors that may contribute to endothelial injury include elevated levels of catecholamines and other hormones, such as cortisol, leading abnormality in vasoconstriction, modifying macrophage activity, and inflammatory response (274). In one study, men with

depression had higher levels of inflammatory markers, such as serum CRP and interleukin (IL)-6 (243). Depression, even after adjusted for these marker, was still associated with subsequent development of CHD (243).

As stated above, psychosocial factors may also promote increased levels of lifestyle risk factors associated atherosclerosis (39). Psychosocial factors are correlated with poor diet (39), substance use (166; 324), and hypertension (339), and may be most evident among those who with depression (101) and those who experience prolonged exposure to stress (e.g., PTSD) (66; 84).

Impact of Traumatic Brain Injury on Cardiovascular Health

Emerging evidence suggests that TBI has several possible impacts on cardiovascular health. One primary mechanism involves inflammatory processes. In comparative literature, mild blast TBI in mice produced similar effects as chronic stress in elevating biomarkers related to atherosclerotic plaque development and vascular dysfunctions (e.g., endothelin, brain-derived neurotrophic factor, etc.) (132; 179).

Gregory and Smith (118) proposed similar pathophysiologic processes initiated by TBI in humans (174), which include neuroinflammatory and neurogenic catecholamine responses that affect the cardiovascular and pulmonary systems post-injury that may lead to cardiac injury and associated complications (e.g., cardiac events, mortality).

Specifically, these authors propose that TBI and subarachnoid hemorrhage (SAH) induce a systemic catecholamine storm, damaging the insula and hypothalamus, and leads to intense inflammatory and sympathetic nervous responses that may have adverse effects on the heart (61; 211). Through a complex interaction between the brain and the immune and autonomic nervous systems (174; 211), increased inflammatory responses are likely

the cause of a series of cardiovascular complications, including left ventricular (LV) dysfunction, cardiac arrhythmias, hypertension, hypotension, and release of biomarkers of cardiac injury (120; 211).

Another set of studies suggest that TBI is associated with increased levels of neuroendocrine and metabolic measures that promote increased cardiovascular risk. In one study, Ahmadi et al. (7) investigated SMs from OEF and Iraqi Freedom for cardiovascular complications (e.g., rate of hypertension, hypercholesterolemia, and coronary artery calcification [CAC]), and examined the cardiovascular event-free survival rate. This study reported that participants who sustained TBI have a higher rate of hypercholesterolemia, hypertension, and CAC and that they have a lower event-free survival rates (74.1% vs. 89.5% in those without a history of TBI). These investigators demonstrated that mTBI is associated with severity of coronary atherosclerosis, as measured by CAC, and also with increased cardiovascular mortality. In addition, a positive correlation was found between mTBI and severity of CAC with the highest mortality rate observed in mTBI subjects with PTSD and increased CAC level (7). Ahmadi and colleagues (7) posited that mTBI-related oxidative stress injury as well as endothelial dysfunction in the blood-brain barrier and vasculature may be the underlying mechanisms for the effects of mTBI on coronary atherosclerosis. In a related study, researchers found abnormal cardiac autonomic physiological changes (e.g., respiratory sinus arrhythmia, heart rate variability) among active duty SMs following exposure to mTBI and proposed using electrophysiologic cardiac responses as a screening tool to confirm mTBI diagnosis in forward deployed settings (254).

These findings corroborate those of other studies (e.g., Hilz et al.) (128) that support the role of mTBI in initiating a series of dysfunctional physiological processes, such as oxidative stress, endothelial dysfunction, and ANS dysfunction, which result in cardiac complications. Moreover, Ahmadi et al. (7) hypothesized that mTBI-related oxidative stress injury and endothelial dysfunction persist even after post-concussive symptoms are resolved. This may suggest that these effects are independent of mTBI symptoms and, more importantly, that mTBI may have a long-term systemic impact on cardiovascular health – please see Sabet et al. for a detailed review of the systemic effects of TBI (257).

Beyond studies exploring the biomarkers and pathophysiological mechanisms underlying TBI (326) and its association with cardiovascular risks noted above, studies directly linking TBI, specifically mTBI, with rates of CVD are sparse, and present literature has mixed results. Previous studies found minimal evidence for the association between TBI and rates of CVD. For example, one prospective observational study found that patients with moderate-severe TBI admitted to intensive care unit at a hospital presented with elevated troponin and echocardiogram abnormalities, but these patients were not at greater risk for CVD (266).

In contrast, a recent case-control cohort study assessed a hospital-based patient registry from an academic medical center to explore if TBI was linked with higher incidence rates of cardiometabolic disorders, which include hypertension, diabetes, and ischemic strokes (138). The study included 4351 patients with mild or moderate-to-severe TBI with no prior comorbidities matched with a frequency-matched non-TBI patients and found that those with mTBI were 2.5 times as likely to be diagnosed with hypertension,

1.9 times as likely to be diagnosed with diabetes, and 2.2 times as likely to have ischemic stroke after TBI exposure. Similar findings for those with moderate-severe TBI were found, where their risk was increased 2.4 times for hypertension, 1.9 times for diabetes, and 3.6 times for ischemic stroke when compared to their non-TBI counterparts. Notably, these rates were significantly elevated among those in age 18 to 40 years (e.g., 5.9 times and 3.9 times more likely for hypertension for mTBI and moderate-severe TBI, respectively). Of note, the study also found TBI status, regardless of severity, was associated with increased other comorbidities, such as psychiatric, endocrine, and neurological conditions.

Pertaining to the associations between TBI and CVD rates among military populations, one recent study found that older veterans (mean age = 67) with TBI across the severity spectrum (80% mTBI) were more likely (36%) to have a CVD diagnosis, such as heart failure, atrial fibrillation, ischemic stroke, and CHD, than their non-TBI counterparts (24%) (155). Older veterans with TBI were also found to have increased cardiovascular risk factors, including greater reports of tobacco use and hypertension. As such, current literature suggests that TBI of varying degree of severity is likely associated with increased risk of poor long-term cardiovascular health.

Mild Traumatic Brain Injury and Depression

It is important to note that mTBI is associated with depression and may also contribute to increased cardiovascular risk by way of this association (38; 138; 169; 288). As stated above, depression is a strong independent risk factor for CVD. In animal models of concussive injury, laboratory induced mTBI was shown to increase depression-like behaviors among rats, such as decreased motor responsiveness, decreased learning,

and social withdrawal (24). The increase in depression-like behaviors was only slightly worsened by repeated injuries, suggesting the significance of a single injury may have in increasing the risk for depression. Similar findings of mTBI and depression were observed among human studies, but the findings are less consistent (247; 273).

The incidence of depression associated with TBI reported in the literature is highly varied (between 14% and 77%) (273). Similar to the incidence rate, the prevalence rate of depression post-TBI is also relatively varied (between 7% to 60%) (168; 239; 288). However, epidemiologic studies of depression and mTBI are difficult to compare due to differences in population, methodology, and approaches in assessments and measurements (288). Nevertheless, there is a consensus among researchers that mTBI is the “forerunner to a host of neuropsychiatric disorders,” including depression (288).

The causal relationships between mTBI and depression are complex and are thought to involve neural and behavioral underpinnings, psychosocial predispositions, antecedent mental health problems (239; 288). Nonetheless, mTBI and subsequently depression likely increase the risks of a range of physical and psychological conditions through a common mechanistic pathway that was described above, involving physiologic factors, such neuroinflammation and stress-related oxidative damage (38; 288), and behavioral factors, such as poor diet and smoking (39). These mechanisms, as mentioned above, have significant impact on cardiovascular health (50; 124; 128).

OVERVIEW OF SLEEP PROBLEMS AND DISORDERS

Definition and Diagnostic Criteria

The human body has adapted to the day-night cycle such that it anticipates periods of activity and rest, and deviations from such rhythms can result in functional detriments (94). Further, severe deviations are likely to result in sleep-wake disorders, which are commonly conceptualized as a range of medical conditions resulting from problems with the quality, timing, and amount of sleep. Sleep problems are common, and an estimated 50 to 70 million Americans suffer from some form of chronic sleep problems (137). Common sleep complaints include not being able to sleep (insomnia), sleeping too much (hypersomnia), difficulties with breathing while asleep (sleep apnea), sleeping issues related to day-night cycle (circadian rhythm disorder), excessive daytime sleepiness (narcolepsy), and excessive movement during sleep (parasomnia) (261). The primary consequence of most of these conditions is sleep loss, and sleep loss, in turn, adversely affects various aspects of human functioning.

Studies have shown that after a total night of sleep deprivation would lead to a decrease in performance equivalent to a blood alcohol level of 0.07% (91), and several large population-based prospective studies linked sleeping five hours or less with increased mortality risk from all causes by about 15 percent results in premature death in rats (161; 225; 295). Given the significant and observable impact of sleep on human performance and on everyday life, sleep and sleep problems has continued to receive substantial research attention during the past three decades (94).

The following sections of this dissertation will provide an overview of commonly known sleep problems and their consequences. Specifically, this review will consider insomnia, hypersomnia and narcolepsy, sleep apnea, circadian rhythm disorder, and parasomnias as well as their consequences.

Insomnia

Insomnia – the difficulty falling asleep or maintaining sleep – is the most common sleep problem (137). Insomnia affects at least 10% of American adults (12; 99) with some studies citing up to 40% prevalence rate in other populations (184). Associated symptoms of insomnia include excessive daytime sleepiness and difficulty with concentration. Prevalence of insomnia is higher among women than men and in older vs. younger individuals, with gender and age being two main risk factors (172). In a population-based study, women were shown to be twice as likely to be affected by insomnia (99). Other risk factors include family history of insomnia, stressful lifestyles, psychiatric comorbidities such as anxiety and depression, and shift work (172)

The causes of insomnia are not well understood but are generally thought to be complex and multifactorial, involving biological, psychological, social, and environmental factors (119; 216; 313). Experts in the field believe that stress plays a leading role in insomnia, triggering the hypothalamic-pituitary axis (HPA) that leads to a host of deleterious consequences. For example, Vgontzas et al (313) examined 24-hour sleep parameters and patterns of adrenocorticotrophic hormone (ACTH) activities of young adults with chronic insomnia and compared them with those of control group. They found that young adults with chronic insomnia averaged higher levels of ACTH and cortisol over a 24-hour period compared to their control counterparts, and the authors concluded that hyperarousal (i.e., HPA activation; increased anxiety, elevated whole-body metabolic rate, etc.) is a key characteristic of chronic insomnia. This contrasts with the opposite response where healthy control experienced acute sleep loss, where the primary consequences were fatigue, exhaustion, and sleepiness.

Cognitive factors associated with stress, such as worry and anxiety, perpetuate the HPA response through the process of behavioral conditioning (223). Additionally, insomnia has a high rate of psychiatric comorbidity, with studies indicating people with insomnia were 10 times more likely to have depression and 17 times more likely to have anxiety compared to normal sleepers (296), but the causal relationships among these comorbidities remain unclear (137; 172). Insomnia has thought to be a symptom of other psychiatric conditions, but these conditions might both be a manifestation of the same and overlapping disturbances (55; 99; 216). One study found that nearly half of the study participants had past or current mental disorders (such as affective disorder), and that insomnia appeared in 56 to 80 per cent of participants experiencing relapse into one or more mental disorders. This finding suggests that insomnia symptoms are likely a part of psychopathological progression of other mental disorders (216). Lastly, environmental factors, including light exposure and unstable sleep schedule, also contributes to insomnia and other sleep problems (119; 223; 340)

Hypersomnia and Narcolepsy

Idiopathic hypersomnia and narcolepsy occur when an individual experiences excessive daytime sleepiness that cannot be explained by other sleep or medical conditions (262). This excessive daytime sleepiness often results in irresistible urge to sleep (i.e., sleep attacks) and unintended napping that provides brief relief from the sleepiness. In severe cases, individuals with excessive daytime sleepiness may feel intense and acute sleepiness while performing an action that they continue to complete the action in an automatic fashion while being unaware of the situation. Due to the sleepiness, they often do not recall their actions during these instances. Cataplexy, sleep

paralysis, hypnagogic/hypnopompic hallucinations, and REM behavior disorder are also common symptoms of narcolepsy (73; 127; 137). In terms of prevalence, narcolepsy with cataplexy is relatively rare and affects approximately 0.02-0.05% of North American and European population, and the rate fluctuates significantly across other countries, ranging as low as 0.002% in Israel to as high as 0.16% in Japan (136; 201). Few studies have investigated the prevalence of narcolepsy without cataplexy, but it is estimated that 2-4% of the population met criteria for the condition (136). Similarly, little is known about the prevalence of hypersomnia, with a few reports on patients seen in neurologic sleep centers suggesting a rate of about 1% (73).

Like other sleep disorders, little is known about the etiology and risk factors for narcolepsy and hypersomnia (137). However, studies suggest both conditions share similar risk factors, including genetic predispositions (e.g., presence of haplotype HLA-DQB1*0602, decreased hypocretin-producing hypothalamic neurons) (201), dysregulation in neurochemical system in the brain (e.g., reduced cerebral spinal fluid histamine levels (73; 142), and neurophysiological abnormalities, particularly in circadian rhythms and in arousal systems that result in alteration to sleep microstructure (e.g., altered dynamics of slow-wave sleep) (73; 231).

Sleep Apnea

Sleep apnea is another common sleep disorders. Sleep apnea is a spectrum of disorders caused by paused breathing during sleep (137; 226). In obstructive sleep apnea (OSA), repeated episodes of collapse or partial collapse in the pharyngeal airway occur and results in the obstruction of breathing tract (117). Apneas reduce blood oxygen saturation (hypoxemia) and increase sleep arousal (e.g., gasping for air, cortical and

brainstem arousal, and sympathetic nervous system activation, etc.), thereby interrupting sleep continuity and reducing sleep quality (137). Sleep arousal due to sleep apnea also triggers pathophysiological changes that extend into wakeful states during the day. For instance, people with OSA have higher sympathetic activity (276) and heightened chemoreflex sensitivity (209) compared to those without OSA. Moreover, these effects have downstream detrimental consequences on vascular tone, inflammatory response, and endocrine changes, among others (198). As discussed below, these physiological effects are significant contributors to the development of hypertension, stroke, and CVD, and emerging research further suggests that OSA is related to a range of long-term health effects (198).

Based on a population-based study of middle-aged workforce (338), OSA impacts an estimated 4-24% of men and 2-9% of women in the US. Age is a risk factor for OSA, with prevalence increasing with age. Specifically, prevalence of OSA among individuals 65-90 years of age is three times higher than in middle-aged adults (11; 160) while OSA only impacts about 2% of children population (245). However, these numbers may not reflect the actual severity of OSA due to underreporting and failure to recognize the symptoms (336; 337). Additionally, male gender (269), obesity (33), family history (121), physiologic and anatomical abnormalities to cranial facial structure (117), lesions of the autonomic nervous system (205; 245), and race (especially racial minorities in the U.S.) (37; 240), are also risk factors for OSA.

Another type of sleep apnea, central sleep apnea (CSA) – cessation of breathing during sleep as a result of disturbance in the brain's respiratory center – has been studied less and has a less clear etiology (137). There are multiple subtypes of CSA, such as sleep

transition apnea, narcotic-induced central apnea, Cheyne-Stokes breathing, complex sleep apnea, and idiopathic central apnea (i.e., primary CSA) (see Malhotra et al. (185) for a detailed review). Whereas OSA is a result of abnormality in the pharyngeal airway, CSA is believed to be caused by ventilatory instability or depression of the brainstem respiratory centers or chemoreceptors (181). The ventilatory instability may be due to a faulty negative feedback loop in the ventilatory system that involves peripheral and central chemoreceptors, intrapulmonary vagal receptors, respiratory control centers in the brain stem, and the respiratory muscles. This dysfunctional feedback loop would cause symptoms whereby baseline respiration is delayed or disrupted, and this phenomenon is seen as central to the pathogenesis of CSA (181). Furthermore, the mechanism responsible for OSA symptoms can also be seen among some individuals with CSA and can confound the nature of the symptoms (185). CSA is relatively uncommon, is thought to have a prevalence of less than 1% in the general population (34), and accounts for 5-10% of patients with sleep breathing disorders. Similar to OSA, male and elderly individuals are at the highest risks for CSA.

Circadian Rhythm Sleep Disorder

Chronic disruption and changes to the circadian clock results in circadian rhythm sleep disorders (CRSD), which then results in insomnia, excessive sleepiness (1). Impairment of social, occupational, and other functions is one of the requirements to meet a diagnosis of circadian rhythm disorder (2). Circadian rhythm sleep disorders can be further subcategorized into nine different types based on International Classification of Sleep Disorders criteria (9; 262): delayed sleep phase type, advanced sleep phase type, non-entrained sleep-wake type, irregular sleep-wake type, shift work type, and jet lag

type. The following review will focus on the two most common types of CRSD: delayed sleep phase type and advanced sleep phase.

Delayed Sleep Phase Syndrome

Delayed sleep phase type CRSD is characterized by a sleep onset and wake times that are delayed by 3-6 hours relative to typical sleep-wake times (1). Although total sleep duration may be normal, individuals who experience delayed sleep phase experience difficulties with initiating sleep before 2:00 to 6:00 am and prefer to wake up between 10:00 am to 1:00 pm. Little is known about the effects of delayed sleep phase disorder, but evidence suggests that those with delayed sleep phase reported poorer job performance, increased marital problems, financial difficulty, increased daytime irritability, poor school performance, and mental disturbances (2). While the exact prevalence of delayed sleep phase type in the general population is unknown, it appears to be more prevalent in adolescents and young adults (3.3% to 7%) than middle-aged adults (0.7%) (1). Multiple risk factors for delayed sleep type have been proposed, including environmental (e.g., extended exposure to light in extreme latitudes) behavioral (e.g., chronic late bedtimes and rise times), biological (e.g., alterations to endogenous circadian system), physiological (e.g., dysregulation of melatonin) and genetic (e.g., polymorphisms in circadian genes, such as human PER2) factors (137).

Advanced Sleep Phase Syndrome

In contrast to delayed sleep phase type, advanced sleep phase type is characterized by involuntary sleep and wake time that are 3 hours earlier than conventional sleep-wake time, and the shift in sleep-wake time results in impairment in

social and occupational functioning (1). The exact prevalence of advanced sleep phase type is unknown, but it is estimated to affect up to one percent of middle-aged adults (14) and the rate is higher among adolescents (3.3%) (275). Little is known about its etiology, but several mechanisms similar to delayed sleep phase syndrome have been proposed, where biological, environmental, and genetic factors are posited to contribute to the condition (1).

Parasomnia

Parasomnias refer to a range of conditions that are characterized by unpleasant or undesirable behaviors or experiences that occur during sleep, especially during transitions of sleep phases (312). Parasomnias are categorized into primary and secondary parasomnias (137). Primary parasomnias are disorders of the sleep state whereas secondary parasomnias occur as a part of the dysfunctions in other body systems during sleep (137). Primary insomnias are further categorized based on the sleep state from which they arise: non-rapid eye movement sleep (NREM) and rapid eye movement sleep (REM). Of the primary parasomnias, disorders of arousal, such as sleepwalking, confusional arousals, are the most common type of parasomnia, estimated to affect up to four percent of the adult population (215). Activities resulting from parasomnias can cause excessive daytime sleepiness and, in some cases, serious injuries and disruptions (135; 183). The literature on parasomnias is vast and beyond the scope of this paper. For an extensive review, please see Howell (134) and Fleetham and Fleming (97).

Pathophysiologic Mechanisms Accounting for Effects of Sleep Problems on Physical Health

Because of the number and heterogeneity in symptomatology and pathophysiology of over 100 sleep disorders, a comprehensive overview of sleep problems and their impact on long-term physical health is beyond the scope of this dissertation. Nevertheless, as previously described, sleep problems typically manifest in three ways: 1) sleep deprivation, either due to poor sleep quality or insufficient amount of sleep; 2) inability to maintain sleep; and 3) events (e.g., apneic episodes or parasomnia activation) that may occur during sleep (194). This section will focus on sleep deprivation, which is one of the most common consequences of sleep problems.

Although individual sleep needs may differ depending on age and other factors, adults generally experience sleep deprivation when they have six hours or less sleep (25). The main symptom of sleep deprivation is excessive daytime sleepiness and may include other symptoms such as depressed mood and cognitive deficiencies. Given the role of sleep in human functioning, chronic sleep deprivation results in serious consequences for health and performance. Some of the common physical conditions associated with sleep insufficiency are immunosuppression, stroke, increased cardiometabolic diseases (e.g., overweight/obesity, hypercholesterolemia, etc.), and increased cardiovascular, cancer, and all-cause mortality (8; 60; 116; 137; 194). Additionally, insufficient sleep is correlated with poor renal function and increased risk for renal disease (60). More recently, sleep issues were found to simultaneously contribute or worsen other physical and psychiatric conditions and also present as a symptom of other psychiatric conditions, such as PTSD (10) and TBI (63). This is especially true for combat veterans, because they are often subjected to occupational stressors affecting their sleep (8).

Association between Mild Traumatic Brain Injury and Sleep Problems

Disrupted sleep is one of the most common comorbid symptoms of TBI, and it has been suggested that mTBI can precipitate a wide range of sleep disorders (315). Based on a meta-analytic review, the prevalence of sleep problems after TBI ranges from 30% to 84% (27). This report confirmed prior findings that TBI is frequently accompanied by sleep complaints (31). Therefore, it is not surprising that sleep deprivation shares various similar physical sequelae as TBI due to sleep dysfunction being a core symptom of a variety of physical disorders.

The types of sleep disturbances that occur following mTBI may depend on the type of injury and the brain region where the injury to sleep regulation occur (314; 315). For instance, hypersomnia post-TBI is linked with insults to the brain regions responsible for the maintenance of wakefulness, which include brainstem reticular formation, posterior hypothalamus, and the third brain ventricle. A high incidence of sleep-disordered breathing occurs after whiplash injuries, where the impact is strongest around the frontal cortex and the occipital cortex. Common sleep complaints associated with disrupted post-head injury include difficulties initiating and maintaining sleep, circadian rhythm sleep disorder, concomitant daytime sleepiness, narcolepsy, pleiosomnia (i.e., increased sleep need), abnormal behaviors during sleep (e.g., limb movements, somniloquy, enuresis, and somnambulism), and sleep apnea. Other ancillary symptoms are also common: headache, pain, and impaired cognitive functions (e.g., decreased concentration, memory, and attention) (314).

Although research has shown TBI-related sleep problems may change or improve over time without treatment (especially among those who sustained moderate to severe TBI), the subjective experience of sleep problems continues to be elevated in TBI

patients when compared with control groups, even after recovery over time (27).

Surprisingly, sleep complaints are more disruptive among those who experience mTBI, compared to severe TBI (31; 62; 95; 182; 229). Researchers have postulated that associations between less severe forms of TBI and sleep disruptions may be due to one or several of the following: 1) an over-endorsement of sleep complaints among those with mTBI, 2) decreased awareness about the severity of their sleep complaints among those with more severe TBI, 3) neurobiological differences in head injuries, as well as 4) relative experience of the individuals depending on the severity of the injury (315)

Although much remains to be learned about the relationship between brain injury and sleep disorders, researchers have suggested that the mechanism of brain injury and the nature of the injury may play a major role in the development of sleep disorders among those with TBI (63). Evidence suggests that blunt head traumas were more likely to result in poor sleep quality and a higher rate of sleep apnea whereas blast trauma injuries were linked with higher rates of insomnia (63). Further, brain traumas that cause damage to the white matter may lead to impaired axonal transmission of neurotransmitters that are crucial in regulating sleep-wake cycle (210; 268). In contrast, damage to the suprachiasmatic nuclei is associated with disrupted production of melatonin, a hormone linked with circadian rhythm regulation, in the pineal gland (210; 268). Injury in the HPA axis may result in decreased levels of wake-promoting neurotransmitters (e.g., hypocretin and histamine) and consequently lead to hypersomnia (28; 258). Despite evidence suggesting these pathophysiological explanations, more research is needed to better understand the relationships between the types of brain injury and specific types of sleep disorders. Based on the current understanding, researchers

have proposed that TBI and sleep problems share similar pathophysiologic mechanism. Inflammatory responses, chronic activation of sympathetic nervous system, and negative changes to hypothalamic hormones are some of the major causes leading to the adverse outcomes among individuals who experience TBI and poor sleep (48).

Sleep Problems in the Military

Combat veterans often experience irregular sleep schedules, exposure to austere environments, combat stress, elevated injury rates, and deployment-related stressors (e.g., post-deployment psychosocial reintegration) (8). Consequently, it is not surprising that the prevalence of sleep-related disorders is elevated among veterans compared to the general population (207). Additionally, studies have shown that the incidence and prevalence of sleep-related diagnoses in veterans have been increasing since 2000 and that the total number of sleep disorder diagnoses in the Veteran Health Administration (VHA) increased nearly 6-fold from 2000 (~0.9%) to 2010 (~5.8%) (8). Researchers are uncertain whether this change represents a true increase in prevalence of sleep disorders or it is a result of increased benefits in medical coverage for sleep disorders, such as greater access to medical devices for sleep problems, increased awareness about sleep disorders, influx in certified sleep physicians VHA system (to better recognize sleep disorders), and updates to sleep disorder diagnoses, or a combination of factors (8). Nevertheless, the exponential increase in sleep disorder diagnoses pose a significant issue for military health as the presence of sleep disorders increases a multitude of health risks (208), exacerbates comorbid physical and mental disorders (10), and ultimately can endanger SMs, and compromise the success of military missions. Therefore, sleep-related disorders among service members constitute an important issue for the military.

Sleep disorders have received increased scholarly attention in recent years and, subsequently, the methodology of sleep research, particularly with regard to objective measurements, has improved (94). However, most research on sleep disorders in the military has not used objective measures to assess of sleep disorders and has relied on subjective self-report measures, which limited the generalizability and accuracy of the findings. Mysliwiec and colleagues (208) conducted one of the first systematic investigations of sleep disorders among a large cohort of service members with objective measures. Through an analysis of polysomnography data and medical records, they reported that 88.2% of service members who underwent post-deployment sleep evaluation were diagnosed with a sleep disorder. Of these, 62.7% met the criteria for OSA, 63.6% met the criteria for insomnia, and 38.2% met both the criteria for OSA and insomnia. Even with these elevated rates, Mysliwiec et al. (208) warned that these statistics may have underestimated the actual rate of sleep disorders due to underreporting of symptoms among service members.

The comorbidity of sleep disorders with TBI is very high both among both military TBI survivors and civilians with TBI (63). Collen et al. (63) reported that among military members who survived combat-related TBI, nearly all (97.4%) admitted having at least one sleep complaint. Hypersomnia (85.2%), sleep fragmentation (54.3%), OSA (34.5%), and insomnia (55.2%) are some of the most common sleep complaints reported. In another retrospective cross-sectional analysis of military polysomnography testing – a type of multi-parametric diagnostic tool for sleep issues – OSA was the most frequent diagnosis (51.2%), followed by insomnia (24.7%) and behaviorally induced insufficient sleep syndrome (BISS; 8.9%). The key findings from both studies highlight an elevated

rate of sleep disorders and sleep-related symptoms in the military, as compared to civilian, population. These sleep complaints adversely affect daily functioning and impede recovery among TBI survivors, ultimately leading to poorer physical and mental health outcomes (27). These findings also highlight the need to further the understanding of sleep issues among military members in relation to other comorbidities, particularly PTSD and mTBI.

Impact of Sleep Problems on Cardiovascular Health

Although it has been long known that sleep plays an important role in the restoration of the human body, its role in regulation of cardiovascular homeostasis (308) has received increased attention only in recent years (328). It follows then that irregularities in sleep, such as irregular circadian rhythm, sleep loss or disrupted sleep, and disordered breathing during sleep, may affect health (64), including cardiovascular health and outcomes (98; 140; 162; 164; 238; 281; 304; 306; 308)

One of the ways that sleep impacts cardiovascular health is related to the circadian rhythm's role in regulating cardiac function (69). It is known that cardiac sympathetic activity is the highest, and parasympathetic activity lowest, during the day, and the opposite is observed at night, where parasympathetic activity is more pronounced and sympathetic activity is subdued (103). Evidence suggests that factors related to cardiovascular health, such as endothelial function, vascular tone (218), and coagulation and platelet activity (307), also fluctuate with states of wakefulness and sleep stages. When circadian timing for sleep is disrupted, as evident among shift workers (82), cardiovascular health is thought to be impacted as well. Indeed, some studies indicated that chronic irregularity in circadian rhythm and its sequelae have been associated with a

wide array of cardiac dysfunctions (20; 47; 192). The pathophysiological mechanisms explaining the impact of irregular circadian rhythm on cardiovascular health are not well understood, but current understanding points to several mediating factors that may lead to poor cardiovascular outcomes. Evidence indicates that disrupted circadian rhythm, and subsequently poor sleep, can lead to several detrimental consequences associated with increased risks for poor cardiovascular health. These detrimental consequences include cell death due to oxidative stress (90), leukocytosis and reduced plasma hypocretin, which in turn facilitates atherosclerosis (192), dysfunctions in vascular tone (222), abnormal endothelin level (220), increased sympathetic nervous activity in the heart (279), and/or activation of the inflammatory process which leads to elevated CRP, IL6, and TNF- α (90; 220; 279).

Similarly, suboptimal sleep duration, whether it is insufficient or excessive, has been shown to impact cardiovascular health. In a meta-analysis, researchers found a curvilinear relationship between self-reported sleep duration and cardiovascular outcomes, where sleeping 9 hours or more increased risk for all-cause mortality (risk ratios: 1.14-1.47) while sleeping 6 hours or less increased risk for cardiovascular disease and stroke mortality (risk ratio: 1.44) (164). Divergence from the recommended 7 to 8 hours of sleep (214) also increased incident CVD (164). The underlying pathophysiology associating sleep duration and CVD is not well understood. In addition to previously mentioned mechanisms linking poor sleep with cardiovascular outcomes (e.g., endothelial dysfunction) (23), current literature suggests that short sleep duration leads to imbalance in a range of hormone levels, including higher levels of leptin, ghrelin, and cortisol (280; 294). Leptin and ghrelin are linked with appetite and caloric intake, and

elevated levels of leptin and ghrelin may increase risk of obesity, DM, and subsequently CVD (278-280). Both short (< 6 hours) and long (> 8 hours) sleep duration were significantly correlated with factors associated with poor cardiovascular health, such as psychiatric conditions (depression, anxiety), high BMI, and low physical activity level (162; 292), which may further explain how sleep duration may lead to increased risk for CVD.

Disordered breathing related to sleep (e.g., OSA) is another area that received significant attention for its relationship with CVD (140; 238; 281; 304) . As mentioned above, sleep loss is a primary feature of OSA and therefore results in detrimental effects on the cardiovascular system. Further, OSA is also characterized by cessation of respiratory airflow, causing significant hemodynamic and neuroendocrine effects in the human body, and a profound decrease in oxygen saturation, which in severe cases would lead to hypoxemia. These autonomic and hemodynamic effects may explain the occurrence of acute episodes of nocturnal ST-segment depression in individuals, whether or not these individuals had a prior history of CHD (329). The effects are thought to be facilitated by a range of factors associated with OSA, including increased whole blood viscosity, decreased fibrinolytic activity, activation of the diving reflex (i.e., sympathetic vasoconstriction, vagal activation of the heart, bradyarrhythmia, etc.) (277; 329). Thus, untreated OSA leads to a higher risk of cardiovascular mortality (105; 267; 329). Indeed, studies suggest that individuals with OSA had an increased risk for sudden cardiac death during the sleeping hours (with a relative risk of 2.57) than the general population (105).

Although no single direct mechanism is thought to moderate the relationship between OSA and CVD, emerging evidence points toward several secondary effects of

OSA that may explain the causal relationship (267). Research has identified OSA's association with adiposity and leptin resistance, and this is thought to increase cardiovascular risk indirectly by leading to obesity-induced cardiometabolic dysfunctions (e.g., metabolic syndrome, insulin resistance, and glucose intolerance) (267). Other evidence suggests OSA's role in chronic arterial hypertension, although the pathophysiological mechanism is likely complex and involves multiple contributing factors, such as enhanced sympathetic activity, impaired baroreflex, endothelial dysfunction, increased endothelin (which leads increase blood pressure and potentially hypertension), and decreased nitric oxide (267; 328). Lastly, OSA is implicated in arteriosclerosis, as suggested by elevated markers of systemic arteriosclerosis, such as calcified carotid artery, atheroma, and increased carotid wall thickness. These effects have been found to be independent of age, gender, race, body mass index, hypertension, smoking habits, lipid levels, and diabetes, indicating OSA's probable role in the causal mechanisms related to arteriosclerosis (328). As stated previously, the pathophysiologic mechanisms are complex and involve multiple factors (e.g., oxidative stress, sympathetic activation, endothelial dysfunction), but the most important factor is OSA and its association with inflammation. Inflammatory markers, such as CRP, play a pivotal role in the initiation and progression of atherogenic processes (274). OSA is thought to increase these inflammatory markers, along with increased serum amyloid A, various adhesion molecules, and increased expression of these molecules on leukocytes and endothelial cells (105). As such, the systemic inflammatory process is central to the development of arteriosclerosis, and thereby may serve as intermediary mechanisms contributing to cardiovascular disease, along with other factors described previously.

Impact of Post-Traumatic Stress Disorder on Cardiovascular Health

Post-traumatic stress disorder is one of the most common psychological disorders among service members (130). The high prevalence of PTSD in military populations is in large part due to the traumatic and stressful nature of war and operational deployment, especially when service members are exposed to enemy fire, deploy for multiple combat tours, and/or experience other deployment-related stressors (68; 331). Among Vietnam veterans, as high as 30.9% of men and 26.9% of women were estimated to have experience PTSD based on clinical interview (242). About 12% of Gulf War veterans assessed scored 50 or above and met the PTSD criteria based on their responses on PTSD Checklist (242). The rate is similar among veterans who deployed during Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF), with a prevalence rate of 13.8% (242). When compared to a national rate of 7%, veterans are at least twice as likely as civilians to experience PTSD (242).

Traumatic stress has also been shown to substantially impact physical health. Schnurr (264) reviewed physical health outcomes associated with traumatic events. Evidence indicates that individuals who are exposed to traumatic events are likely to report poor health, increased morbidity, elevated utilization of medical services, and have an increased mortality rate (87; 264). Additionally, PTSD was found to be a stronger factor than mere trauma exposure in predicting poor physical health outcomes among those who developed PTSD (283). The increased risk of physical morbidity associated with PTSD is further aggravated by PTSD symptom severity, comorbidity of other psychiatric disorders, and PTSD chronicity (213). Some researchers (213; 264; 283) have concluded that, similar to TBI, neurochemical changes in the brain play a role in the

adverse effects of PTSD on physical health. Moreover, biological (e.g., altered HPA activity), behavioral (e.g., poor health habits), and psychological (e.g., depression) correlates of PTSD have also been theorized to explain the mechanism behind PTSD's impact on physical health. However, few studies have investigated the exact variance as explained by these factors, and existing literature, particularly on the associations between biological factors and PTSD, is mixed and inconclusive (197; 221).

Nevertheless, the current literature strongly suggests that PTSD may lead to poorer physical health outcomes. Asnaani et al. (18) examined the predictive strength of PTSD symptoms for physical and mental health outcomes. Based on a regression model, they reported that PTSD symptoms were predictive of poor self-reported physical health, accounting for 40% of the overall variance in physical health. Among the PTSD symptoms, re-experiencing symptoms were the strongest predictors of self-reported physical health, physical functioning, and bodily pain. In a meta-analysis (219), PTSD diagnosis and symptoms related to PTSD were found to be strongly associated with broad general health outcomes, such as general health symptoms (as a summary score of overall health), general medical conditions (presence or absence of a disease), quality of living, pain, and cardiorespiratory and gastrointestinal conditions and complaints. In another study, PTSD was associated with musculoskeletal disorders, especially arthritis (236). Levine et al. (171) reported an increased incidence of various health conditions, such as cardiometabolic diseases (e.g., obesity, diabetes), impaired immunity, rheumatoid arthritis, psoriasis, thyroid disease, fibromyalgia, and osteoarthritis, among individuals with PTSD. These findings and others (40) suggest that PTSD is an important factor in long-term physical health.

In light of the associations between PTSD and physical health, an increasing body of evidence has linked PTSD to poorer cardiovascular outcomes (6; 83; 84; 171) even after controlling for associated psychological comorbidities, such as depression (310). Comprehensive reviews of the links between PTSD and cardiovascular risk have been provided by Bedi and Arora (30), Coughlin (66), Edmondson et al. (83), Edmondson et al. (84), Koenen et al. (154), Levine et al. (171), and Schnurr (265). These reviews and meta-analyses report that, when compared to people without PTSD, individuals with PTSD have heightened risk of subsequent cardiac events, such as incident CHD (Hazard Ratio [HR], unadjusted for depression = 1.55; HR adjusted for depression = 1.27) (84); incident stroke or transient ischemic attack (Relative Risk [RR] = 2.36); and recurrent MI, unstable angina, or mortality (RR = 2.0) (84). Previous studies were done with US samples, with a focus on predominantly male veteran samples, but recent studies with European (115) and female (293) populations corroborated results of prior literature.

The two pathways commonly identified to explain the associations between PTSD and CVD have either a physiological or a behavioral emphasis (154). Interestingly, there is considerable overlap between mechanisms proposed for the effects of TBI and PTSD on CVD. Physiologically, it has been suggested that both heightened sympathetic activation associated with PTSD and increased markers of inflammatory mechanisms related to PTSD account for the associations of PTSD with cardiovascular risk (84). The pathophysiologic mechanisms proposed to explain associations between PTSD and CVD risk are similar to the one that explains TBI's association with poor physical health (150). For instance, PTSD symptoms have been associated with an array of inflammatory biomarkers (e.g., IL-1 β , IL-6, TNF- α , interferon γ , and CRP) (84; 112; 175; 224; 283;

284), and these biomarkers are also commonly associated with TBI (89; 190). As reviewed above, these biomarkers are indicative of systemic inflammation and are parameters of CVD risk (110). There is also evidence suggesting that CVD risks are associated with disrupted regulation of stress hormone by the HPA axis and resulting deleterious physiological consequences, such as hypercoagulability, immune dysfunction, and endothelial damage (319). Similar to TBI (234), PTSD has also been found to disrupt ANS regulation, exaggerating basal activity, and increasing demand on various organ systems, particularly the cardiovascular system (42). Behaviorally, PTSD is associated with a range of health behaviors or behavior-related conditions that are detrimental to cardiovascular health (154), including smoking (102), physical inactivity (59), poor diet (123), insomnia (167; 170), and medication non-adherence (163). By themselves, these behavioral risk factors are thought to mediate, but not fully account for, the PTSD-CVD relationship by increasing risks for other CVD risks (154).

SUMMARY, RATIONALE, AND CONCEPTUAL MODEL

Post-Traumatic Stress Disorder, mTBI, and sleep disorders are conditions commonly associated with each other. Based on this research, it is known that mTBI and PTSD share many features and are difficult to distinguish from one another. Further, both mTBI and PTSD have been found to interface on physiological, biological, and genetic levels (289). Notably, sleep disturbances are considered to be one of the core symptoms of mTBI and PTSD (189). As discussed above, current view holds that the stress response, dysregulation of the ANS, and immune and inflammatory factors play important roles in the development and/or maintenance of sequelae associated with mTBI, PTSD, and sleep problems. Behavioral factors, such as smoking, drinking, poor

diet, and reduced medical adherence can also be antecedents and consequences, both directly and indirectly, of PTSD, sleep disorders, and mTBI. Consequently, biological, as well as behavioral, responses likely play important roles in the relationship between mTBI, PTSD, and sleep problems and physical health (see conceptual model below, Figure 1).

Although sleep disorders have long been understood as a symptom of mTBI and PTSD, it was not until in the past decades that more research has focused on these disorders and their relationships as they pertain to the military population. With evidence suggesting that sleep as an impactful factor in recovery and treatment outcome among veterans (111), it is important that more research be conducted to better understand how these conditions affect SMs, particularly the impact of sleep problems in long-term physical health among SMs with mTBI. However, our understanding about these conditions is still limited, and there has been a debate about the nature of the role of sleep in the physical and mental health consequences of mTBI (189; 208).

With respect to mTBI, as proposed by Masel and Dewitt (191), future studies need to consider and conceptualize TBI as a the beginning of a complex disease process – a systemic disorder and not just an event – such that a brain injury should be thought of a start of a complex, multi-faceted disease process which has a downstream systemic impact in the body, leading to the development of various conditions including PTSD and sleep problems (257). Notably, all three conditions (mTBI, PTSD, sleep disorders) have a high comorbidity rate (111) and share common physiological and behavioral consequences which can lead to a cascade of negative effects in multiple organ systems, as reviewed above. Much remains unclear, however, about the underlying mechanisms

shared by the disorders in explaining their effects on physical health, as well as the extent to which there are independent effects of each disorder on cardiovascular health. Investigating the associations, overlap, and independent contributions of these conditions to CVD will better our understandings about these conditions. Therefore, the present study examines the independent effects of each disorder on cardiovascular health.

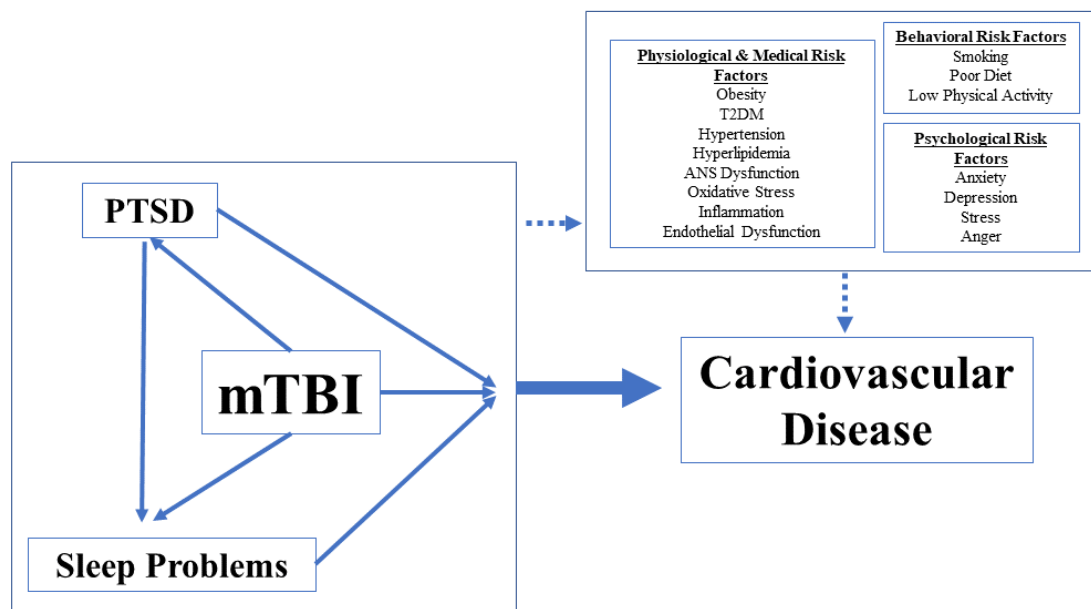


Figure 1. Conceptual model explaining the associations between TBI, PTSD, sleep problems and CVD. Physiological, medical, behavioral, and psychological risk factors are hypothesized as pathophysiologic mechanisms but are not measured in the present study.

The conceptual model guiding the proposed study is provided in Figure 1. In this model, it is proposed that the overlapping diagnoses of mTBI, sleep disorders, and PTSD affect a common set of pathophysiologic and behavioral factors that predispose to the development of CVD. In the present study, TBI is conceptualized as a factor increasing the likelihood of PTSD and sleep problems. Further, PTSD is thought to worsen sleep problems. However, TBI, PTSD, and sleep problems share various direct and indirect

pathways which have been hypothesized to increase CVD risk. These pathways, not directly assessed in this study, include psychological, physiological and medical variables, as well as behavioral risk factors.

STUDY AIMS AND HYPOTHESES

Aim 1. To determine the longitudinal associations between mTBI and risk of negative cardiovascular outcomes among patients with mTBI within the military health systems.

Hypothesis 1. Patients with mTBI will have a higher rate of one or more cardiovascular diagnoses compared to patients without mTBI.

Aim 2. To determine the longitudinal associations between sleep disorders and cardiovascular outcomes among patients with mTBI within the military health systems.

Hypothesis 2. Patients with mTBI and sleep disorder diagnoses will have a higher rate of negative cardiovascular outcomes compared to patients with mTBI and without a sleep disorder diagnosis.

Aim 3. To determine the longitudinal associations between PTSD and cardiovascular outcomes among patients with mTBI within the military health systems.

Hypothesis 3.1. Patients with mTBI and PTSD diagnoses will have a higher rate of negative cardiovascular outcomes compared to patients with mTBI or PTSD diagnosis or patients without mTBI or PTSD.

Hypothesis 3.2. Patients with mTBI or PTSD diagnosis will have a higher rate of negative cardiovascular outcomes compared to patients without mTBI or PTSD.

Aim 4. To determine if the relationships between mTBI, sleep disorders, and CHD are independent of the association with PTSD with CHD.

Hypothesis 4. Relationships between mTBI, sleep disorders, and CHD will be independent of contributions of PTSD to CHD.

CHAPTER 2: Methods

STUDY DESIGN

The study was a case-control cohort study of clinical data from SMs in the Military Health System (MHS). The overall study purpose was to determine the predictive relationships of mTBI, sleep disorders, and PTSD for CHD. Covariates of interest in the study included demographic characteristics, including race, age, sex, and branch of service.

DATA SOURCES AND STUDY POPULATION

The study utilized military healthcare data from the MHS, which serves over 9.6 million beneficiaries, including AD personnel, military retirees, and their dependents (202). A core repository for the MHS clinical data is the Military Health System Data Repository (MDR). Within the MDR, the Comprehensive Ambulatory Provider Encounter Record (CAPER) database captures ambulatory outpatient clinical data collected from the MHS's Composite Health Care System (CHCS) and Armed Forces Health Longitudinal Technology Application (AHLTA) (79). Both CHCS and AHLTA are the primary platforms used to record clinical encounters in the MHS, and they provide direct care outpatient encounter records to MDR by interfacing with CAPER.

To obtain the data for the study, the Clinical and Research Informatics Department of National Intrepid Center of Excellence (NICoE), Bethesda, MD, extracted the dataset from MHS for this study. Encounter-level administrative and clinical data from electronic health records of SMs for the duration of the baseline period (1 January

2007 to 31 December 2007) and the study period (1 January 2008 to 31 December 2019) were abstracted from CAPER. Specifically, encounter-level metadata from these records was extracted, which include International Classification of Diseases (ICD) diagnostic codes, dates of diagnosis, procedural terminology codes, and demographics (age, race, gender, and branch of service). Administrative information such as the dates of first and last clinical encounters in MHS was also gathered. No identifiable information was collected. Clinical diagnoses were only considered present if the ICD codes associated with the diagnosis were recorded in at least two outpatient encounters. This criterion was used in previous studies conducted with large healthcare system and has shown to enhance diagnostic accuracy (248; 272; 305). The ICD Ninth Revision - Clinical Modification (ICD-9-CM), ICD Tenth Revision (ICD-10), and Current Procedural Terminology (CPT) codes of diagnoses of interest for inclusion and exclusion criteria (PTSD, TBI, sleep disorders, CVD, etc.) were identified and categorized based on existing taxonomy (i.e., ICD) and in consultations with medical experts for relevance to the study hypotheses. For example, Acute Myocardial Infarction (ICD-9-CM Code: 410) and Angina Pectoris (ICD-9-CM Code: 413) are considered subtypes of Atherosclerotic Cardiovascular Disease and were categorized as such.

Selection of Study Participants

Data available for analysis covered the study period from 1 January 2007 to 31 December 2019. Study participants selected from the database included individuals with algorithm-confirmed diagnosis mTBI (i.e., two or more TBI diagnoses) during the study period and a control group of individuals who enrolled into the MHS in fiscal year 2007 who did not have a diagnosis of mTBI over the study period. Patients with mTBI, CVD,

and other conditions of interest prior to study period were excluded. The mTBI cohort was then matched in 1:2 ratio using propensity scoring method to a control group based on age, sex, race, and branch of service – see more below.

The index date used in the study was defined as the date of the initial mTBI diagnosis (see below). The follow-up period began the day after the index date, and ended either when: (1) an outcome event, defined as a positive diagnosis of a CHD (for specific definitions, see below); (2) when the patient exited the MHS, which is determined to be the date of last encounter in the database, if before the study end date (31 Dec 2019); (3) at the end of the study period (31 Dec 2019); or (4) if the patient died while in the database, determined by the presence of a ICD-9-CM (798) or ICD-10 (R99) diagnostic code for death. Once these criteria were applied, data for that individual will be censored from further consideration.

Inclusion and Exclusion Criteria and Selection of Control Sample

To be eligible, all patients needed to be enrolled in MHS, be at least 18 years of age at index date, and have no prior diagnoses consistent with the diagnoses of CVD, PTSD, TBI, and other diagnoses of interests as defined in this study. As noted above, patients were excluded if they had one or more diagnoses of cancer, history of cardiac surgery, cardiovascular congenital anomalies, HIV, or other disqualifying conditions (see Table 1) prior or during the study period.

Selection of Controls (Non-Traumatic Brain Injury cases)

Control participants were selected only from 2007 cohort from the MHS database, compared to mTBI group that was selected from 2007 to 2019. To be sampled for

control, participants were determined to be free of diagnoses of interests prior to study entry. Additionally, they had to be free of mTBI diagnoses over the duration of their inclusion in the study period. After mTBI cases were identified using the same exclusion criteria described above, each mTBI case was randomly matched to a non-TBI case from the 2007 cohort based on race, sex, age, and branch of service using propensity score matching with 1:2 ratio (see Figure 1 for details).

STUDY MEASURES

Using the algorithms utilized in similar studies (248; 272; 305) to enhance diagnostic accuracy, criteria for a positive diagnosis requires two or more outpatient encounters with the same ICD code category. Unless otherwise specified, each ICD code included all the subcodes under the diagnosis (e.g., I20.X would include I20.1 to I20.9).

Identifying and Determination of Traumatic Brain Injury

Following the surveillance case definition established by Armed Forces Health Surveillance Branch (AFHSB) (17), mTBI is defined as the presence of one or more ICD-9-CM and ICD-10 diagnoses of mild brain injuries, which include superficial injury of head, open wound of head, fracture of skull and facial bones, dislocation and sprain of joints and ligaments of head, injury of cranial nerve, injury of eye and orbit, intracranial injury, crushing injury of head, avulsion and traumatic amputation of part of head, other unspecified head injuries, and/or post-concussion syndrome that are Mild in severity (see Table 2). For enhanced diagnostic accuracy, two medical encounters with a diagnosis of mTBI were used as the criterion for confirmed mTBI diagnosis for the purpose of present analyses. Therefore, the first of the two medical encounters with a diagnosis of mTBI was the primary index event. mTBI cases were selected from any point during the study

period (1 Jan 2007 – 31 Dec 2019), in contrast with control group that was selected from cohort year 2007 only.

Table 1. Other Diagnoses Excluded from the Study Sample

Entity Description	ICD-9-CM	ICD-10
AIDS/HIV	042.x–044.x	B20
Congenital cardiovascular anomalies	745.x, 746.x, 747.x	Q20. X, Q21.X, Q22.x, Q23.X, Q24.X, Q25.XX, Q26.X, Q27.X, Q28.X, Q30.X, Q31.X, Q32.X, Q33.X, Q34.X
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	140.x–172.x, 174.x–195.8, 196.x–199.x, 200.x–208.x, 238.6	C81-C96
All subcodes of substance use-related sleep disorders		F10.XXX (Alcohol), F13.XXX (Opioid, Other sedatives), F14.XXX (Cocaine), F15.XXX (Other stimulant), F19.XXX (Other psychoactive substance)
All subcodes for Insomnia not due to a substance or known physiological condition		F51.0X
Psychoses and conditions with psychotic features	293.8, 295.x, 296.04, 296.14, 296.44, 296.54, 297.x, 298.x	F20.89, F23, F28, F29, F30.13, F30.2, F31.2, F31.5, F31.64
Acute Stress Disorders and related conditions	308.X	F43.X
Other anxiety disorders	300, 300.4, 300.9	
Other sleep disorders with no known condition or unspecified		F51.8, F51.9
Other conditions or disorders	Sickle cell (282.6), cerebral palsy (343), spina bifida (741), Genetic/Chromosomal disorders (758.X), hydrocephalus (742.3), microcephalus (742.1), encephalocele (742.0), severe mental retardation (318.x), cystic fibrosis (277.XX)	Sickle Cell (D57.XXX), Cystic Fibrosis (E84.X), Intellectual Disabilities (F70-F79), Cerebral Palsy (G80.X), Hydrocephalus (G91.X), Kyphoscoliotic Heart Disease (I271), Eisenmenger's Syndrome (I27.83), Moyamoya Disease (I67.5), Q05.9, Q90.9, G91.X, Q02, Q03, Q01, Q01.1, Q01.2, Q01.8, Q01.9

To determine the severity of TBI, the study will utilize the TBI severity data derived from the encounter-metadata associated with a TBI diagnosis. The TBI diagnoses are categorized into five levels of severity in the database: Mild, Moderate, Severe, Penetrating, and Unclassified. For the purposes of this study, only cases with Mild TBI diagnoses were included.

Table 2. Diagnostic Codes for Traumatic Brain Injury

Entity Description	ICD-9-CM	ICD-10
Traumatic brain injury (excluding Moderate and Severe cases)	800 to 804, 850 to 854, 310.2	S00, S01, S02, S03, S04, S05, S06, S07, S08, S09, F07.81

Identifying and Determination of Cardiovascular Disease

For this study, incidence of cardiovascular disease (CVD) diagnoses was assessed with an emphasis on CHD as the primary outcome. CHD was defined as the presence of ICD-9-CM or ICD-10 diagnoses of nonfatal myocardial infarction, angina, other ischemic heart diseases. Because of the difficulty to distinguish ischemic stroke from hemorrhagic or other causes of stroke caused by brain trauma, ischemic stroke will not be included as an endpoint in the study (see Table 3).

Table 3. Diagnoses of Atherosclerotic Cardiovascular Disease.

Entity Description	ICD-9-CM	ICD-10
Nonfatal Myocardial Infarction	410.XX-412	I21.X, I22.X, I23.X
Angina	413	I20.X
Coronary atherosclerosis	414.XX	
Other Ischemic Heart Diseases		I24.X, I25.X

Definition of Sleep Disorders

Sleep disorders are a set of ICD-9-CM or ICD-10 sleep-related diagnoses, which include insomnia, hypersomnia, circadian rhythm sleep disorder, narcolepsy, parasomnia, disordered breathing sleep conditions, narcolepsy, parasomnia, sleep related movement disorders, and other sleep disorders (see Table 4).

Table 4. Diagnoses for Sleep Disorders

Entity Description	ICD-9-CM	ICD-10
Sleep disorders	307.4X (Nonorganic sleep disorders) 327.1X (Hypersomnia) 327.2X (Disordered breathing sleep conditions) 373.3X (Circadian Rhythm Sleep Disorder) 327.4X (Parasomnia) 327.5X (Other sleep related movement disorders) 327.8 (Other organic sleep disorders) 780.5 (Sleep disturbances) 780.51-780.52 (Insomnia) 780.53-780.54 (Hypersomnia) 780.5X (Other sleep disorders)	F51.XX, G47.0X (Insomnia) G47.1X (Hypersomnia) G47.2 (Circadian Rhythm Sleep Disorder) G47.3X (Disordered breathing sleep conditions) G47.4 (Narcolepsy) G47.5X (Parasomnia) G47.6X (Other sleep related movement disorders) G47.8-G47.9 (Other sleep disorders) Z72.82X (Insufficient sleep syndrome sleep deprivation)

Definition of Post-Traumatic Stress Disorder

Post-Traumatic Stress Disorder is defined as ICD-9-CM or ICD-10 diagnoses as listed in Table 5.

Table 5. Diagnoses of Depression, Anxiety, and Posttraumatic Stress Disorder

Entity Description	ICD-9-CM	ICD-10
Post-Traumatic Stress Disorder	309.81	F43.1x

Other Comorbidities for Secondary Analyses

Other factors used in the study analyses were selected based on study relevance and on prior research (3). These include demographic data (age, sex, race/ethnicity, and

branch of service) and comorbidities as ascertained by ICD-based diagnostic codes. As reviewed above, several additional medical disorders or health conditions are considered to be risk factors for CHD and have been found to be associated with mTBI and PTSD as well. Table 6 lists these disorders, conditions, or risk factors, which include hyperlipidemia, hypertension, DM, obesity, depression, anxiety, and substance use disorders or related conditions.

Table 6. Medical Disorders or Conditions Associated with Atherosclerotic Cardiovascular Disease

Entity Description	ICD-9-CM	ICD-10
Hyperlipidemia	272.X	E78.X
Hypertension	401.X	I10.x, I15.8, I15.9, I16.0, I16.1, I16.9
Diabetes Mellitus	250.XX	E10.X-E11.X
Obesity	278.XX	E66, E66.0X, E66.1, E66.2, E66.3, E66.8, E66.9
Anxiety	300.02, 300.09	F41.1, F41.3, F41.8, F41.9
Depression	296.XX, 311	F32.X
Substance Use Conditions and Disorders	Tobacco: 305.1X, 649.0X, 99406, 99407, V15.82 Alcohol: 291.X, 303.XX, 305.XX, 357.5, 425.5, 535.3X, 571.X, 980.X, V11.3 Opioid: 304.0X, 305.5X Sedative, hypnotic, and anxiolytic: 304.1X, 305.4X Cocaine: 304.2X, 305.6X Cannabis: 304.3X, 305.2X Other stimulants: 304.4X, 305.7X Hallucinogen: 304.5X, 305.3X Other drugs and substance-use related conditions: 292.XX, 304.6, 304.7X-304.9X, 305.8X, 305.9X, V65.42X	Tobacco & Nicotine: Z72.0, F17.2X Alcohol: F10.XX, Z71.41 Opioid: F11.XX Cannabis: F12.XX Sedative, hypnotic, and anxiolytic: F13.XX Cocaine: F14.XX Other stimulants: F15.XX Hallucinogen: F16.XX Inhalant: F18.XX Other psychoactive substance: F19.XX

EXPLORATORY ANALYSES

Although the primary focus of this study is on atherosclerotic cardiovascular disorders, exploratory analyses using hypertension as a study endpoint were conducted since essential hypertension is also thought to be related to increased sympathetic nervous system activity and autonomic nervous system dysfunction and to coronary endothelial dysfunction. A second reason for these exploratory analyses was that sleep disorders (particularly OSA) have been demonstrated to be an important predictor of the later development of hypertension. These analyses would provide data as to whether mTBI was an antecedent of essential hypertension as well as early manifestations of signs and symptoms associated with CHD.

STATISTICAL ANALYSIS

Analyses were conducted using the statistical software R with base package (237) and additional packages, including but not limited to, the following: “dplyr” (322), “tidyverse” (321), “powerSurvEpi” (235), “survival” (299), “survminer” (146), “summarytools” (65), “finalfit” (125), and “TrialSize” (341). Due to the massive amount of data, duplicates in the datasets were first eliminated before joining the different data files (in comma-separated values format [*.csv]). Then, mTBI patients with only one or less mTBI encounters were excluded. Due to discrepant coding in race data in various data files, a recode procedure was conducted to match the race data for consistent coding (e.g., “A” for Asian Pacific Islander throughout). Then, missing or incomplete data were discarded to facilitate propensity score matching procedure. After matching, the matched dataset was evaluated and assessed for discrepant data or outliers (see Overview of Sample Selection Process for further details). Then, preliminary and primary analyses, as discussed below, were conducted to address aims and hypotheses.

Statistical significance was determined by a 2-sided P of < 0.05 . Follow-up time for each patient was considered separately for each outcome category, and depending on whether individuals are classified as mTBI cases or controls, the follow-up time ended on the date of the first CHD event, the date of data censoring (i.e., death, last MHS encounter in the database), or the last day of study data inclusion (31 December 2019), whichever occurred first.

For preliminary analyses, demographic and clinical data were examined according to CHD outcome and mTBI status using t-test and logistic regressions. Survival curves were generated using Kaplan-Meier methods. The Kaplan-Meier survival curves were compared using a log-rank test to determine if the two groups (mTBI vs. non-mTBI) differ significantly (143; 146; 299). For primary analyses, the associations between mTBI and CHD will be tested using Cox Proportional Hazards (PH) regression with time-varying covariates (67; 342) with a 95% Confidence Interval (CI). A series of models was generated and tested sequentially by fitting the demographic characteristics and predictors – see Table 7 for the list of models.

For the purpose of this study, mTBI is treated as time-fixed variable, that is, the effect of mTBI status is not hypothesized to have a significant interaction with time. Patients are categorized based on their mTBI status during the study period. For any patients with mTBI, they are grouped into mTBI and vice versa for those without mTBI. Hence, patient's mTBI status does not change in the study. Likewise, baseline demographic variables such as age and sex are also treated as time-fixed covariates. In contrast, comorbid conditions, such as PTSD and sleep disorders, are treated as time-varying covariate: time-to-event for these conditions are thought to be dependent on

exposure to mTBI and subsequently would affect time to exposure of outcome of interest (e.g., CHD). Once a patient was exposed to these conditions at any given point in the study, they are censored for said conditions and treated as having the condition for the rest of the study period.

To test if the models meet the proportional hazards assumption, the “cox.zph()” function in the “survival” package (298; 299; 342) was utilized, which would generate a significant value for each coefficients as well as the overall model if proportional hazards assumption violating the assumptions (i.e., significant correlation between survival time and scaled Schoenfeld residuals). Should the proportional hazards assumption violation were detected, time-fixed variables would be treated as time-varying covariates as the first statistical accommodation to address the violation (96; 298). If further accommodation were needed to address the violation, a step function would be used to stratify the study period into separate time intervals to explore the result (96; 298).

Table 7. Predictors and Regression Models for Analysis

Model	Factors for CHD Outcome
Model 1	mTBI
Model 2	mTBI + Demographic
Model 3	mTBI + Sleep Disorder+ mTBI x Sleep Disorder + Demographic
Model 4	mTBI + PTSD + mTBI x PTSD + Demographic
Model 5	mTBI + PTSD + Sleep + Demographic

Power Analysis

Sample size calculations and power analysis for a Cox PH model with time-dependent covariates requires pre-specification of significance level, desired power, estimated effect at baseline, baseline survival distribution, censoring distribution, and the variation of the time-dependent covariates over time (317). These parameters were not

readily available due to a lack of existing literature providing estimation for the data and population used in this study. Moreover, due to the technical and computational complexity involved in the calculation, a power analysis specifically for a Cox PH model with time-dependent covariates was beyond the scope of this paper.

Therefore, power for the study was estimated using a power analysis for a Cox PH for 2-sided equality test (with no assumptions of time-variance). The power analysis was conducted with “TrialSize” in R (341), with the following parameters: significance level $\alpha = 0.05$, power $1 - \beta = 0.99$, log hazard ratio $B = \log(1.5)$, proportion of cases in mTBI group $p1 = 0.33$ (1:2 ratio matching), and the estimated probability of observing an event $d = 0.0035$ (0.35%). The estimated probability was generated based on the preliminary count of CHD cases in the mTBI group and is slightly lower than but within the margins of error for the estimates of the current prevalence rate of CHD for population age 20-39 (0.5-1.0%) (316).

This power analysis indicated that the study was very highly powered. The required sample size to reach a power of 0.99 was 144,412. The final sample size in the study is $N = 196,957$ (see Results section for more details). Based on this information, the study was expected to meet the power level required to detect the effects.

CHAPTER 3: Results

OVERVIEW OF SAMPLE SELECTION PROCESS

Determining the final sample of individuals included in the study was based on a process consisting of several phases designed to identify the initial sample of mTBI and control cases and then to define the final sample.

Phase I consisted of initial determination of mTBI cases. Phase II consisted of initial determination of control cases. Matching TBI cases with control cases occurred in Phase III. Lastly, in Phase IV, the matched sample was evaluated for outliers and discrepant data, producing the sample for analysis. These steps are described in detail in the following sections (see Figure 2).

Phase I: Initial Determination of Mild Traumatic Brain Injury Cases in the MHS Database

To determine the initial sample of mTBI cases, a total of 436,228 records of patient clinical encounters from years 2007-2019 with TBI-related diagnoses were identified. Of these, 127,151 cases were removed due to duplicate records in the criteria (patients with two or more TBI-related records). Additionally, 19,585 Moderate, 340 Penetrating, 348 Severe, and 27,447 Unclassified cases, for a total of 47,720 individuals were removed for not meeting the “Mild” severity of TBI, as described in the Methods section. Those meeting exclusion criteria (e.g., records with cancer or HIV diagnoses) were then excluded ($n = 9,454$). The initial sample of mTBI cases prior to elimination of

outliers and discrepant cases consisted of an $n = 84,889$. Further, 167,014 cases were removed for failing to meet data selection.

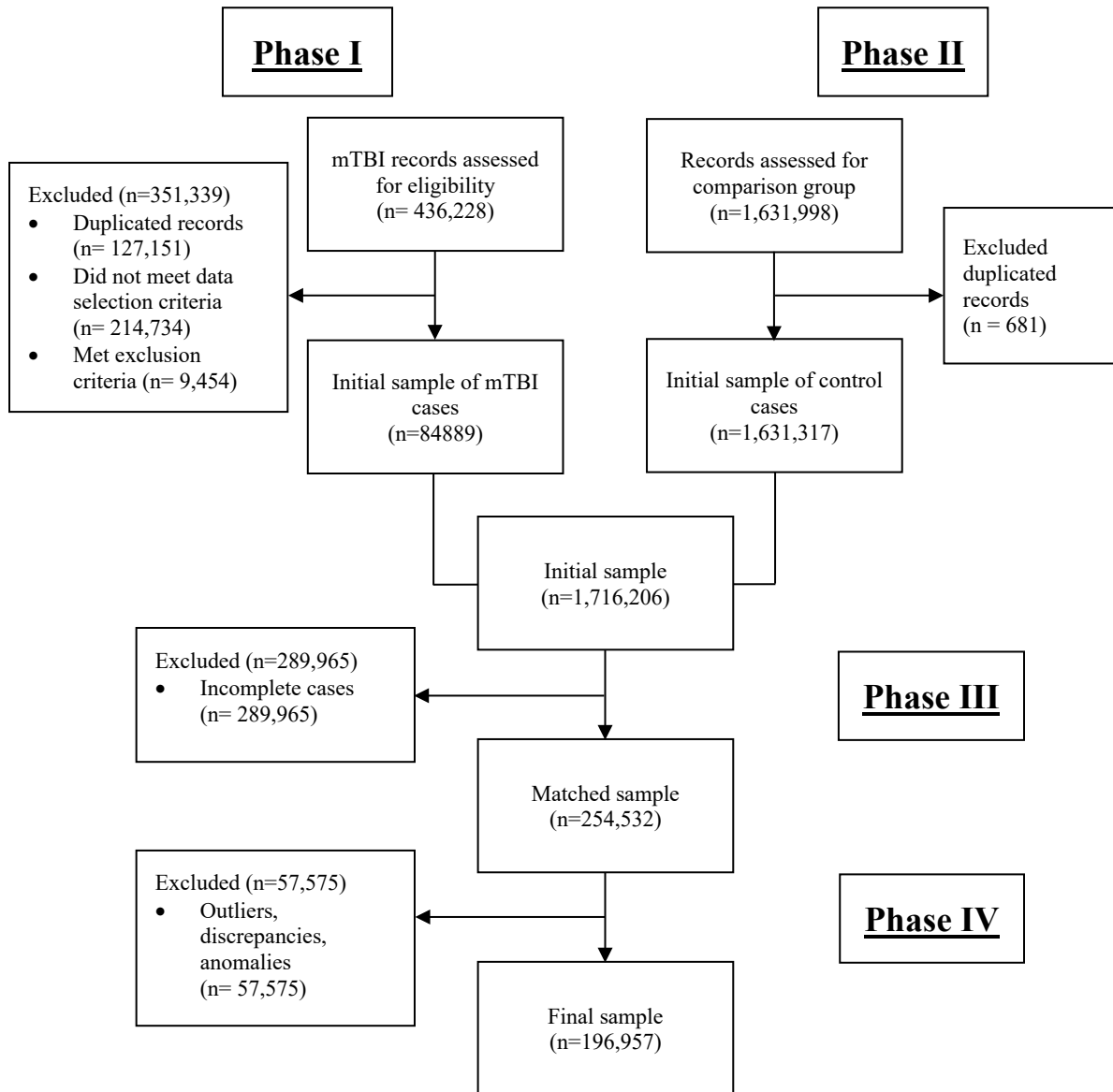


Figure 2. Consort diagram for the sampling and matching process.

Phase II: Initial Determination of Control Cases in the MHS Database

Control cases were defined as individuals without TBI-related encounters in their health records. Control cases were extracted from the 2007 cohort in the MHS dataset, i.e., those who entered or utilized MHS in year 2007. They were further defined based on

their TBI status prospectively (i.e., not having any TBI-related encounters) between 2007-2019 – cases with any TBI-related encounters between 2007-2019 were excluded. This resulted an initial list of 1,631,998 control cases. It is worth mentioning that, during Phase II of the sample selection process, control cases were identified based solely on the absence of TBI encounters. As such, clinical data were not readily available for these individuals at this stage. This is relevant as we were not able to determine if the control cases would meet inclusion and/or exclusion criteria for the study during Phase II. Clinical data for control group were obtained in Phase III, as described below.

Phase III: Matching the TBI Cases and Control Cases Determined in Phase I and Phase II

In Phase III, the initial lists of mTBI and Control group subjects, obtained in Phase I and Phase II respectively, were merged for the purposes of sample matching. This was done using the propensity scoring method (PSM) based on the demographic variables described in the Methods section, with 2 Control cases for each mTBI case. Before the matching procedure was conducted, the n for mTBI cases was 84,899 and n for control cases was 1,631,998, for a combined n = 1,716,887. Additional duplicated cases (n = 681) were identified and excluded, resulting in a refined list of n = 1,716,206. As PSM matching procedure requires complete cases in all matching variables, a total of 289,965 incomplete cases were excluded, yielding a sample of 1,426,241 (n = 84,844 TBI cases, n = 1,341,397 control cases) before matching. After matching, the process generated a matched sample of n = 254,532 (TBI n = 84,844, control n = 169,688). Clinical data for the matched control cases were obtained at this stage.

Phase IV: Evaluating and Eliminating Outliers and Discrepant Data from the Matched Sample in Phase III

In Phase IV, the matched sample (n = 254,532) was further examined for outliers, discrepancies, and other data anomalies. Note that a case may meet multiple conditions that warranted its exclusion. Criteria for exclusion included:

1. Control cases that met exclusion criteria, as outlined in Methods section (n = 24987).
2. Patients whose records indicated that they were in the MHS database for less than 120 days were excluded (n = 17,054). The duration of time used to determine the amount of time individuals' records were in the system was the difference between the first and last dates in CHCS, which were used to determine the dates of entry and exit of the CHCS, respectively.
3. Presence of illogical, "negative time" of diagnosis from a statistical perspective, as defined as having a diagnosis before the start of study or before entering the MHS database based on first dates in CHCS (n = 7718)
4. Presence of one or more mTBI diagnosis before the start of study (n = 2619)
5. Presence of one or more CHD diagnoses before mTBI (n = 133)
6. Age less than 18, which meets the exclusion criteria (n = 5352)
7. Age 100 or above, a condition which is extremely rare in the military sample (n = 2)

Together, 57,575 cases were excluded (Table 8), yielding a sample of n = 196,957 for the final analysis (Table 9).

CHARACTERISTICS OF THE FINAL SAMPLE USED IN MAIN ANALYSES

After all phases of sample selection, the final identified sample for the main analyses has a sample size of N = 196,957. Demographic characteristics at study entry of

the sample are presented in Table 9. With some exceptions, the sample characteristics are mostly consistent with the demographics trends and profiles of the AD military community from 2000 to 2020 (78).

Table 8. Demographics of Cases Excluded Due to Discrepancies, Anomalies, or Being Outliers.

		Duration in the study < 120 days	Negative Outcome Time	TBI before Study	CHD before TBI	Age < 18	Age > 100
Age	Mean (SD)	22.2 (6.9)	30.4 (10)	30.7 (7.8)	45.6 (8.0)	16.1 (3.4)	111
Sex	Male	15649 (91.8%)	6868 (89.0%)	2457 (93.8%)	128 (96.2%)	5081 (94.9%)	1 (50.0%)
	Female	1405 (8.2%)	850 (11.0%)	162 (6.2%)	5 (3.8%)	271 (5.1%)	1 (50.0%)
Race	American Indian/Alaskan Native	24 (0.1%)	38 (0.5%)	33 (1.3%)	1 (0.8%)	5 (0.1%)	0
	Asian or Pacific Islander	340 (2.0%)	463 (6.0%)	228 (8.7%)	8 (6.0%)	76 (1.4%)	0
	Black, not Hispanic	1200 (7.1%)	1126 (14.6%)	235 (9.0%)	29 (21.8%)	159 (3.0%)	0
	White, not Hispanic	3881 (23.0%)	3941 (51.2%)	1299 (49.6%)	84 (63.2%)	942 (17.6%)	1 (50%)
	Hispanic	28 (0.2%)	227 (2.9%)	208 (7.9%)	7 (5.3%)	99 (0.1%)	0
	Others	1 (0.0%)	5 (0.1%)	0	0	5 (0.1%)	
	Unknown	11553 (68.5%)	1918 (24.9%)	616 (23.5%)	4 (3.0%)	4066 (76.0%)	1 (50.0%)
Service Branch	Army	12141 (71.2%)	4697 (60.9%)	1860 (71.0%)	104 (78.2%)	4816 (90.0%)	0
	Coast Guard	31 (0.2%)	57 (0.7%)	21 (0.8%)	1 (0.8%)	8 (0.1%)	0
	Air Force	1004 (5.9%)	1273 (16.5%)	186 (7.1%)	9 (6.8%)	136 (2.5%)	0
	Marine Corps	1396 (8.2%)	590 (7.6%)	346 (13.2%)	10 (7.5%)	233 (4.4%)	0
	Navy	1590 (9.4%)	980 (12.7%)	189 (7.2%)	9 (6.8%)	134 (2.5%)	0
	Unknown	892 (5.2%)	121 (1.6%)	17 (0.6%)	0	25 (0.5%)	2 (100.0%)
Total		17054	7718	2619	133	5352	2

Note: Numbers correspond to N (%) or Mean (SD).

Table 9. Demographic Characteristics of the Sample.

		mTBI group	Control	Total	p-levels and significance of differences between mTBI cases and controls
Age	Mean (SD)	28.0 (8.3)	24.8 (8.1)	25.9 (8.3)	p<0.001
Sex	Male	60313 (87.8%)	113384 (88.4%)	173697 (88.2%)	p<0.001
	Female	8392 (12.2%)	14868 (11.6%)	23260 (11.8%)	
Race	American Indian/Alaskan Native	760 (1.1%)	453 (0.4%)	1213 (0.6%)	p<0.001
	Asian or Pacific Islander	3568 (5.2%)	4870 (3.8%)	8438 (4.3%)	
	Black, not Hispanic	8354 (12.2%)	15130 (11.8%)	23484 (11.9%)	
	White, not Hispanic	35930 (52.3%)	50746 (39.6%)	86676 (44.0%)	
	Hispanic	7099 (3.3%)	2397 (1.9%)	9496 (4.8%)	
	Other	--	276 (0.2%)	276 (0.2%)	
	Unknown	12994 (18.9%)	54380 (42.4%)	67374 (34.2%)	
Service Branch	Army	45108 (65.7%)	83139 (64.8%)	128247 (65.1%)	p<0.001
	Coast Guard	489 (0.7%)	621 (0.5%)	1110 (0.6%)	
	Air Force	6895 (10.0%)	16489 (12.9%)	23384 (11.9%)	
	Marine Corps	9376 (13.6%)	8312 (6.5%)	17688 (8.9%)	
	Navy	6445 (9.4%)	17302 (13.5%)	23747 (12.1%)	
	Unknown	392 (0.6%)	2389 (1.9%)	2781 (1.4%)	
Total		68705 (34.9%)	128252 (65.1%)	196957 (100%)	

Note: Numbers presented as N (%) or mean (SD).

*Due to changes in the codes used to report Other ethnicity, reliable data on Other ethnicity for mTBI group could not be determined from the data available.

mTBI Cases

There are 68,705 mTBI cases in the study, averaging 5,285 cases per year (range: 2857-7541 cases) – see Table 10. The median time to mTBI exposure was 2771 days in the study.

Table 10. Year-by-Year Frequency of mTBI Cases in the Study

Year	'07	'08	'09	'10	'11	'12	'13	'14	'15	'16	'17	'18	'19
Cases	2857	4176	4366	4436	5258	5321	3690	5014	5081	6986	6733	7246	7541

Age and Sex

The sample was mostly male (87.8%) with mean age of 28.0 (SD=8.3) years. This is comparative to the AD forces where male SMs accounted for approximately 84.4% to 85.2% with 64.2% to 66.4% reporting 30 years or younger from 2000-2020. Further analysis conducted found that the difference in age was present in Phase 3 of sample selection process. One explanation for the difference is due to sampling procedure: we selected mTBI cases from all the years whereas control was from 2007. Given the variables considered in the matching process (age, sex, branch of service, and race) as well as the matching criteria selected for propensity scoring method matching (nearest neighbor), mTBI cases were likely matched best to their younger counterparts despite the algorithm to reduce differences in age. Although the difference is pronounced statistically (Cohen's $d = \sim 0.39$), for the purpose of CHD risk, mean ages 28.0 (mTBI) and 24.8 (Control) are considered clinically within the same age group and should not differ dramatically.

Race

For those who provided information on race and ethnicity, White, not Hispanic was the most represented group (44.0%), followed by Black, not Hispanic (11.9%), Asian

or Pacific Islander (4.3%), Native American or Alaskan Native (0.6%), and Others (0.2%). Approximately 34.2% of the participants did not indicate their race or the information was missing from the database. The percentages of racial groups in the present study were relatively inconsistent with the surveillance from 2000-2020 due to a large proportion of Unknown data. From 2000-2020 (78), a majority of SMs identified as White (68.9%), followed by Black or African American (17.2%), Asian (4.8%), Other/Unknown (3.9%), Multi-Racial (3.0%), Native Hawaiian or Other Pacific Islander (1.2%), and American Indian or Alaska Native (1.1%). Of note, data surveillance noted inconsistency in reporting of racial data among service branches. For instance, Army did not report “Multi-Racial” in the surveillance data. Thus, it is important to note that there were several concerns with race as coded in the present dataset. Specifically, non-report of race information or differences in responses for race for some subjects in the database were observed. Therefore, there were several versions of codes to document race data over the study period, and the race data may therefore be not reliable.

Branch of Service

Army made up the majority of the sample (65.1%), followed by Navy (12.1%), Air Force (11.9%), Marine Corps (8.9%), and Coast Guard (0.6%). There were 1.4% of the cases reported Unknown branch of service. The percentages for branch of service were not consistent with the proportion of branch of service in the larger forces. From 2000-2020 (78), Army was the largest service branch, comprising 36.1% of the total AD force, followed by Navy (25.6%), Air Force (24.7%), and Marine Corps (13.6%) in 2020 (data on Coast Guards not assessed in surveillance data for AD forces).

In part due to these factors, after the initial matching process, there remained differences between mTBI and control cases in demographic characteristics. However, these differences are more likely to be accounted for by the large sample sizes, which may result in increased statistical sensitivity to small effects which would result in statistical significance. Those demographic variables differing between mTBI and control cases will be used as covariates in later analyses. However, due to anomalies in the race and branch of service data as noted above, they were not included as covariates in subsequent analyses. While preliminary analyses indicated that race and branch of service were significant predictors, due to unreliability of the information, interpretation about the significance cannot be made conclusively. Moreover, both branch of service and race did not significantly impact the results of the analyses. As such, in the analyses discussed in section below (Analysis by Hypothesis), those analyses were completed without race and branch of service as demographic covariates.

ANALYSES OF COMORBID DIAGNOSES

There were many comorbid diagnoses present in mTBI cases and the presence of these comorbidities in mTBI cases and controls are presented in Table 11 (frequency table) and Table 12 (logistic regression table). In the univariable analyses (Table 12), those with mTBI were more likely than their counterparts to have comorbid diagnoses in their records, including sleep disorders (OR = 3.95, $p < 0.001$), substance use disorder (OR = 1.47, $p < 0.001$), hypercholesterolemia (OR = 1.09, $p < 0.001$), hypertension (OR = 1.11, $p < 0.001$), PTSD (OR = 6.49, $p < 0.001$), obesity (OR = 1.50, $p < 0.001$), depression (OR = 2.25, $p < 0.001$), and anxiety disorders (OR = 4.85, $p < 0.001$). Contrarily, those with mTBI were less likely to be diagnosed with diabetes (OR = 0.76, $p < 0.001$) and CHD (OR =

Table 11. Frequency Table of Comorbid Diagnoses Present in of TBI Cases and Controls, with Corresponding Demographic Variables

Presence of Comorbid Diagnoses	mTBI (n=68,705) N (%)	Controls (n=128,252) N (%)	Age Mean (SD)	Male N (%)
Sleep Disorder	35025 (51.0%)	26773 (20.8%)	29.8 (8.9)	54825 (88.8%)
Substance Use Disorder	27525 (40.1%)	40179 (31.3%)	25.5 (7.6)	62327 (92.1%)
Hypercholesterolemia	7269 (10.6%)	12562 (9.8%)	36.2 (8.7)	18109 (91.3%)
Hypertension	8073 (11.8%)	13743 (10.7%)	33.5 (9.6)	19595 (89.8%)
PTSD	17317 (25.2%)	6329 (4.9%)	30.0 (8.5)	21708 (91.8%)
Obesity	8595 (12.5%)	11178 (8.7%)	29.4 (8.8)	15893 (80.4%)
Diabetes	586 (0.9%)	1438 (1.1%)	38.1 (8.3)	1785 (88.2%)
Depression	13191 (19.2%)	12242 (9.6%)	27.7 (8.4)	21101 (83.0%)
Anxiety	8584 (12.5%)	3668 (2.9%)	30.3 (8.5)	9814 (80.1%)
CHD	203 (0.3%)	545 (0.4%)	40.3 (9.0)	707 (94.5%)
Death During Study	34 (0.00%)	18 (0.00%)	29.1 (8.6)	43 (82.7%)

Table 12. Logistic Regression for Comparisons of Health Conditions between mTBI and Control groups with Odd Ratios, 95% Confidence Intervals, and P-values of 0.05 for Significance Testing

Health Conditions		Control N (%)	TBI N (%)	OR (CI, p-value) (univariable)	OR (CI, p-value) (multivariable)
Sleep	Without	101519 (75.1)	33680 (24.9)	-	-
	With	26733 (43.3)	35025 (56.7)	3.95 (3.87-4.03, p<0.001)	3.02 (2.95-3.09, p<0.001)
Substance Use Disorder	Without	88073 (68.1)	41180 (31.9)	-	-
	With	40179 (59.3)	27525 (40.7)	1.47 (1.44-1.49, p<0.001)	1.07 (1.05-1.09, p<0.001)
Hypercholesterolemia	Without	115690 (65.3)	61436 (34.7)	-	-
	With	12562 (63.3)	7269 (36.7)	1.09 (1.06-1.12, p<0.001)	0.68 (0.66-0.71, p<0.001)
Hypertension	Without	114509 (65.4)	60632 (34.6)	-	-
	With	13743 (63.0)	8073 (37.0)	1.11 (1.08-1.14, p<0.001)	0.69 (0.67-0.72, p<0.001)
PTSD	Without	121923 (70.3)	51388 (29.7)	-	-
	With	6329 (26.8)	17317 (73.2)	6.49 (6.30-6.69, p<0.001)	4.11 (3.97-4.25, p<0.001)
Obesity	Without	117074 (66.1)	60110 (33.9)	-	-
	With	11178 (56.5)	8595 (43.5)	1.50 (1.45-1.54, p<0.001)	1.04 (1.00-1.08, p=0.029)
Diabetes	Without	126814 (65.1)	68119 (34.9)	-	-
	With	1438 (71.0)	586 (29.0)	0.76 (0.69-0.83, p<0.001)	0.59 (0.52-0.65, p<0.001)
Depression	Without	116010 (67.6)	55514 (32.4)	-	-
	With	12242 (48.1)	13191 (51.9)	2.25 (2.19-2.31, p<0.001)	0.98 (0.95-1.01, p=0.184)
Anxiety	Without	124584 (67.5)	60121 (32.5)	-	-
	With	3668 (29.9)	8584 (70.1)	4.85 (4.66-5.05, p<0.001)	2.66 (2.55-2.78, p<0.001)
Coronary Heart Disease	Without	127707 (65.1)	68502 (34.9)	-	-
	With	545 (72.9)	203 (27.1)	0.69 (0.59-0.81, p<0.001)	0.60 (0.50-0.71, p<0.001)
Death During Study	Without	128234 (65.1)	68671 (34.9)	-	-
	With	18 (34.6)	34 (65.4)	3.53 (2.02-6.38, p<0.001)	1.67 (0.90-3.17, p=0.109)

0.69, $p < 0.001$). The prevalence of CHD and diabetes among those with mTBI (CHD = 0.3%, diabetes = 0.9%) was similar to those without (CHD = 0.4%, diabetes = 1.1%). Additionally, it can also be seen in Tables 11 and 12 that while death rates were low in both groups, there were more deaths among mTBI patients during the course of the study, and that patients with mTBI had a 3.53 times higher mortality rate in this study.

KAPLAN-MEIER SURVIVAL CURVES AND LOG-RANK TEST FOR SURVIVAL CURVES COMPARISON

As a convention of survival analysis, a Kaplan-Meier survival plot (35) was generated for visual comparison of survival probabilities between mTBI and Control groups (see Figure 3). In this case, survival probability is defined as the likelihood of not having a CHD diagnosis during the study period, i.e., the group that survives better is less likely to have CHD diagnosis. Based on visual inspection, those without mTBI (solid line, below) are more likely to experience CHD than those in mTBI group (dotted line, above) consistently over time.

A log-rank test (Table 13) (36) comparing the two survival curves indicated a significant difference in terms of probability of CHD diagnosis between the mTBI and Control groups (Chi-Square = 19.2, $df = 1$, $p < 0.001$). Of note, a log-rank test is a test of significance done for pre-analysis and cannot provide an estimate of the magnitude of the difference between the groups or a confidence interval. For these estimates and confidence intervals, please see Data Analysis by Study Hypothesis section below.

Table 13. Log-Rank Test Comparing the Kaplan-Maier Survival Curves between mTBI and Control Groups

	N	Observed (O)	Expected (E)	$(O-E)^2/E$	$(O-E)^2/V$
Control	128252	545	488	6.65	19.2
mTBI	68705	203	260	12.49	19.2

Chi-Square = 19.2, $df = 1$, $p < 0.001$

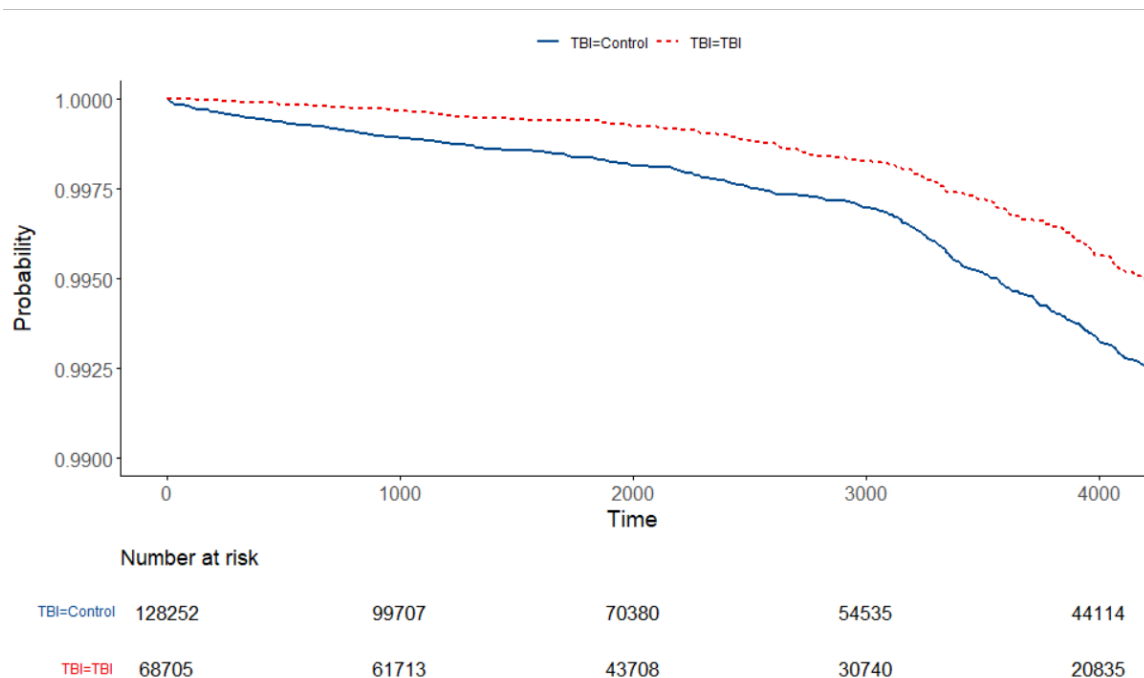


Figure 3. Kaplan-Meier survival plot comparing survival probability (Y-axis) mTBI (dotted line) vs. Control groups (solid line) of being free of a CHD diagnosis during the study period (X-axis, 1 Jan 2007 to 31 Dec 2019).

DATA ANALYSIS BY STUDY HYPOTHESIS

Hypothesis 1

In Hypothesis 1, it was predicted that patients with mTBI will have a higher rate of one or more cardiovascular diagnoses compared to patients without mTBI. As proposed in the Methods, the initial strategy for analyzing relationships of mTBI to CHD was using the pre-selected case-control sample utilizing mTBI as a time-fixed variable. To test this hypothesis, hierarchical Cox Proportional Hazard (PH) regressions were created. First, a univariate Cox PH regression with mTBI as the only predictor (and no other covariates) was conducted. Second, a Cox PH with demographic variables, including age and sex, was conducted to detect the effects of baseline characteristics on outcome. Afterwards, a Cox PH with demographic variables and mTBI as a predictor was

conducted. The primary outcome variable for all the Cox PH above was incidence of CHD (as described in Methods).

Table 14. Associations between Demographic Variables, mTBI and CHD Outcome

Variable	Univariable Analysis HR (95% CI, p-value)	Multivariable Analysis HR (95% CI, p-value)
Age	1.130 (1.122-1.138, p<0.001)	1.137 (1.129-1.145, p<0.001)
Sex (Male)	2.738 (1.998-3.751, p<0.001)	3.287 (2.397-4.506, p<0.001)
TBI	0.698 (0.594-0.821, p<0.001)	0.387 (0.329-0.455, p<0.001)

In the univariate Cox PH where mTBI was the sole predictor and the occurrence of CHD the primary outcome (Univariable Analysis, Table 14), the Hazard Ratio (HR) for mTBI was HR = 0.698 (95% CI: 0.594-0.821, p<0.001). This result indicating reduced rate of CHD diagnosis for mTBI compared to Controls was unexpected, since it suggested that patients with mTBI was at 30.2% (i.e., $1 - [\text{HR for mTBI}] \times 100\%$) lower risk of CHD over the course of the study relative to those without mTBI. In another univariable analyses (Table 14), baseline demographics of age and sex were investigated. Age was statistically significant in predicting CHD diagnosis (HR = 1.130, 95% CI: 1.122-1.138, p<0.001): the risk for CHD increases 13.0% for every year older. Male sex was also a significant predictor of CHD, such that male participants were 2.738 more likely than female participants to have CHD over the course of the study period (HR = 2.738, 95% CI: 1.998-3.751, p<0.001).

When the analysis was repeated with mTBI and adjusted for demographic covariates (Multivariable Analysis, Table 14), the HR indicating the negative association between mTBI and CHD increased in strength, specifically from 30.2% to 61.3% (HR = 0.387, 95% CI: 0.329-0.455, p<0.001). Older age (HR = 1.137, 95% CI: 1.129-1.145, p<0.001) and male sex (HR = 3.287, 95% CI: 2.397-4.506, p<0.001) remained significant

predictors of increased chance of CHD diagnosis in these analyses. Figure 4 presents a forest plot of the HR for mTBI and demographic variables.

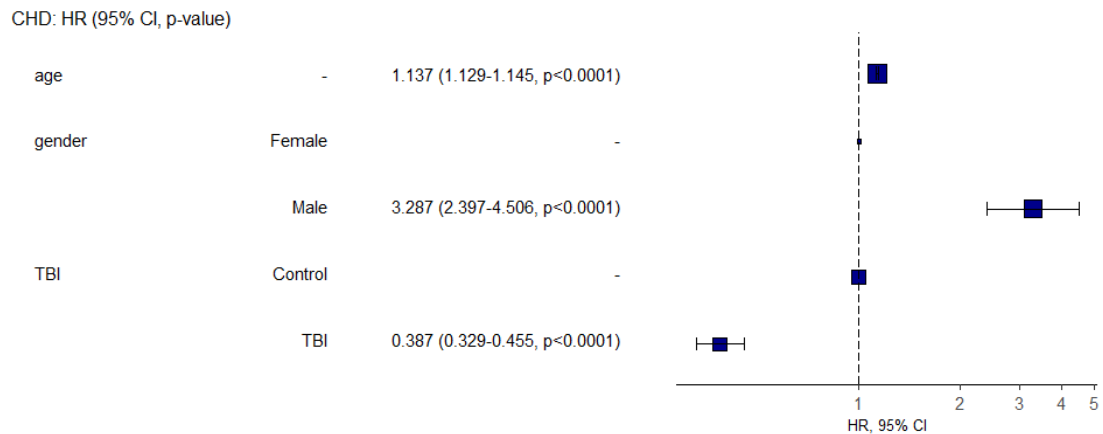


Figure 4. Forest plot of the hazard ratios of the associations between demographic variables, mTBI and CHD outcome.

Hypothesis 2

To determine the relationships between sleep disorders and cardiovascular outcomes among patients with mTBI within the MHS, Hypothesis 2 predicted that patients with mTBI and sleep disorder diagnoses will have a higher rate of negative cardiovascular outcomes compared to patients with mTBI and without a sleep disorder were treated as time-fixed variable in these analyses. The primary predictors were mTBI status, sleep disorder status, and the interaction term for mTBI and sleep disorder status. In practical terms, this creates a 2 x 2 comparison (with/without mTBI vs. with/without Sleep Disorder; Table 15). The primary outcome was incidence of CHD. Demographic variables were included as covariates in the analyses.

In this analysis, the HR for those with mTBI only was HR = 0.279 (95% CI: 0.214-0.364, p<0.001) and HR for those with sleep disorders only was HR = 1.951 (95% CI: 1.626 -2.340, p<0.001). The interaction effect of mTBI and sleep disorder is statistically significant, HR = 1.423 (95% CI: 1.012-2.001, p<0.05). As such, HR for

those with mTBI and sleep disorders is calculated by multiplying the HR of the joint effect of mTBI and Sleep Disorder (HR = 1.423) with the HR of mTBI only (HR = 0.279), which resulted in HR = 0.397 for those with both mTBI and sleep disorders (80; 133). Those with mTBI only were 0.743 times less likely (i.e., $1 - \text{HR for mTBI}$) to have CHD relative to those without mTBI or sleep disorder. In contrast, those with sleep disorders only were 1.951 times more likely to have CHD than those without mTBI or sleep disorders. For those with both mTBI and sleep disorders, the individuals were 0.397 times as likely to have CHD than those with none of the conditions. As with results from Hypothesis 1, mTBI unexpectedly mitigated the CHD risk whereas the presence of sleep disorders increases the risk. Figure 5 presents a forest plot of the HR for mTBI and sleep disorders.

Table 15. Associations between mTBI, Sleep Disorder, and Both mTBI and Sleep Disorder with Demographic Covariates and CHD Outcome.

Variable	Multivariable Analysis HR (95% CI, p-value)
Age	1.133 (1.125-1.141, p<0.001)
Sex (Male)	3.236 (2.360-4.436, p<0.001)
mTBI only	0.279 (0.214-0.364, p<0.001)
Sleep Disorder only	1.951 (1.626-2.340, p<0.001)
Interaction of mTBI and Sleep Disorder	1.423 (1.012-2.001, p<0.05)

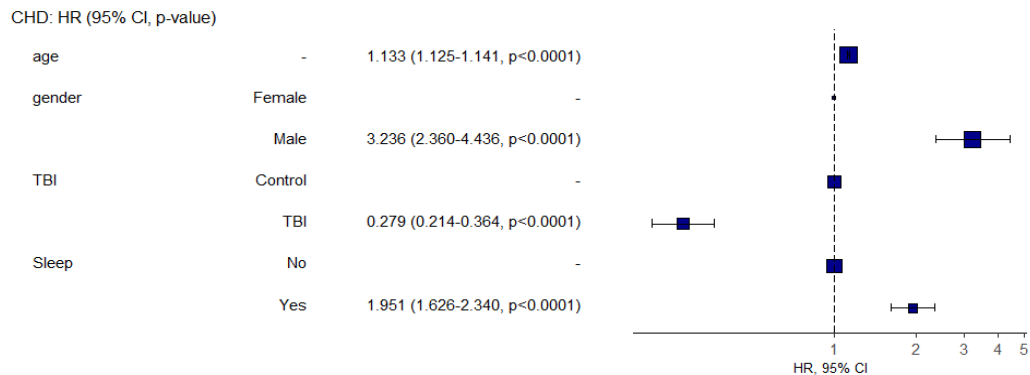


Figure 5. Forest plot of the hazard ratios of the associations between mTBI and sleep disorders with demographic covariates and CHD outcome.

Hypothesis 3

To determine the associations between PTSD and cardiovascular outcomes among patients with mTBI, Hypothesis 3 predicted that patients with both mTBI and PTSD diagnoses will have a higher rate of negative cardiovascular outcomes compared to patients with mTBI only, PTSD only, or without mTBI or PTSD. Similar to the analysis in Hypothesis 2, the analysis to test Hypothesis 3 was a Cox PH regression with PTSD as a time-varying covariate. All other predictors/covariates (i.e., mTBI, age, and sex) were treated as time-fixed variables. The primary predictors were the presence of both mTBI and PTSD, mTBI only, and PTSD only status, and as before, the primary outcome is CHD diagnosis. Demographic variables (sex and age) were covariates in the analysis.

Table 16. Associations between mTBI, PTSD, and presence of both mTBI and PTSD with Demographic Covariates and CHD Outcome.

Variable	Multivariable Analysis HR (95% CI, p-value)
Age	1.137 (1.129-1.145, p<0.001)
Sex (Male)	3.255 (2.374-4.462, p<0.001)
mTBI only	0.317 (0.262-0.385, p<0.001)
PTSD only	1.276 (0.846-1.925, p=0.245)
Interaction Effects of mTBI and PTSD	1.676 (1.016-2.765, p<0.05)

In this analysis (Table 16), the HR for mTBI was HR = 0.317 (95% CI: 0.262-0.385, p<0.001) and the HR for PTSD was HR = 1.276 (95% CI: 0.846-1.925, p=0.245). The interaction effect of mTBI and PTSD was statistically significant, HR = 1.676 (95% CI: 1.016-2.765, p <0.05). As such, the HR for those with mTBI and PTSD is calculated by multiplying the HR of the joint effect of mTBI and PTSD (HR = 1.676) with the HR of mTBI only (HR = 0.317), which resulted in HR = 0.531 for those with both mTBI and PTSD (80; 133). Thus, those with mTBI only were 0.683 times (i.e., 1 – HR for mTBI) as likely to get diagnosed with CHD when compared to those without mTBI or PTSD. In

contrast, those with PTSD were 1.276 times more likely to have CHD when than those without mTBI and PTSD, although the effect was not statistically significant ($p=0.245$). Those with mTBI and PTSD were 0.531 times as likely to have CHD relative to those without mTBI and PTSD. Figure 6 presents a forest plot of the HR for mTBI and PTSD.

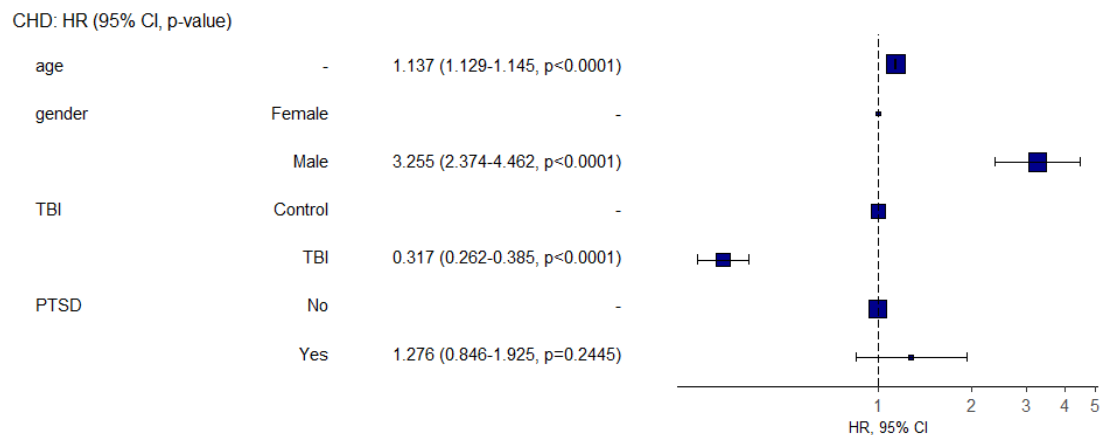


Figure 6. Forest plot of the hazard ratio of the associations between mTBI and PTSD with demographic covariates and CHD outcome.

Hypothesis 4

To determine if the relationships between mTBI and CHD as well as sleep disorder and CHD are independent of the association with PTSD with CHD, we predict in Hypothesis 4 that the effect of mTBI and sleep disorders on CHD will be independent of contributions of PTSD to CHD. The hypothesis was tested using Cox PH regression with PTSD and sleep disorder as time-varying covariates. All other predictors/covariates i.e., mTBI, age, and sex) were treated as time-fixed variable. The primary predictors were mTBI, sleep disorders, and PTSD diagnoses. The primary outcome was CHD diagnosis. Demographic variables (age and sex) were covariates.

The multivariable analysis once again yielded a small HR for mTBI, HR = 0.322 (95% CI: 0.271-0.383, p<0.001). In contrast, the HR for sleep disorder was HR = 2.037 (95% CI: 1.727-2.402, p<0.001) whereas the HR for PTSD was HR = 1.365 (95% CI: 1.087 – 1.740, p<0.01). After adjusted for sleep disorder and PTSD status, those with mTBI were 68.8% as likely to have CHD compared to those without mTBI. After adjusting for mTBI and PTSD, those with sleep disorders were 2.037 times more likely to have CHD than those without sleep disorders. Similarly, those with PTSD were 1.365 times more likely to have CHD than those without PTSD, after adjusting for mTBI and sleep disorder statuses. The results suggest that the effects of mTBI, PTSD, and sleep disorders on CHD outcome were independent of each other. Figure 7 presents a forest plot of these results.

Table 17. Associations between mTBI, PTSD, Sleep Disorder with Demographic Covariates and CHD Outcome.

Variable	Univariable Analysis HR (95% CI, p-value)	Multivariable Analysis HR (95% CI, p-value)
Age	1.130 (1.122-1.138, p<0.001)	1.133 (1.125-1.141, p<0.001)
Sex (Male)	2.738 (1.998-3.751, p<0.001)	3.232 (2.357-4.431, p<0.001)
mTBI	0.698 (0.594-0.821, p<0.001)	0.322 (0.271-0.383, p<0.001)
PTSD	1.600 (1.287-1.989, p<0.001)	1.365 (1.076-1.730, p<0.05)
Sleep Disorder	3.017 (2.578-3.531, p<0.001)	2.037 (1.727-2.402, p<0.001)

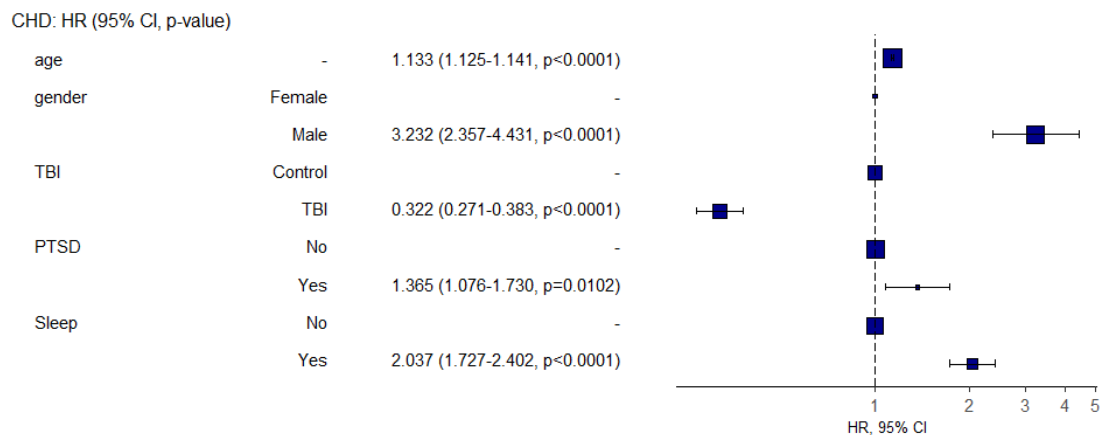


Figure 7. Forest plot of the hazard ratios of the associations between mTBI and PTSD with demographic covariates and CHD outcome.

Testing the Proportional Hazard Assumption for the Analyses

Inherent in a standard model of Cox PH regression, the individual predictors and the model are expected to meet the assumption of proportional hazard. As such, the model above (Table 18) was tested to evaluate if the individual predictors and the overall model met the assumption of proportional hazard. This is accomplished by evaluating the proportionality of hazards using the Schoenfeld residuals test (298; 332). Schoenfeld Residuals test is used to test the independent relationship between scaled residuals and time, and a significant Schoenfeld residuals test (i.e., $p < 0.05$, a non-zero slope on the graph) suggests a violation of the proportional hazard assumption. In the case of a significant Schoenfeld residual test, the standard model of Cox PH regression is flexible and able to accommodate the violation of proportional hazard assumption by coding a variable as a time-varying variable, which will be discussed below.

Table 18. Schoenfeld Residuals Test to Evaluate Proportional Hazards Assumption of a Cox Regression in Initial Model with mTBI as a Time-fixed Predictor

	Chi Square	df	P-value
Age	3.583	1	0.058
Sex	0.799	1	0.371
mTBI	5.350	1	0.021*
PTSD	0.015	1	0.902
Sleep Disorder	7.336	1	0.001*
Model	19.874	5	0.001*

Note: * indicates $p < 0.05$

As shown in Table 18, mTBI and sleep disorder as individual predictors were significant ($p < 0.05$) in the test of proportional hazards assumption, which indicates that the predictors violated the proportional hazards across time assumption. To address the violation of this assumption, mTBI was treated as a time-varying predictor in the models for Hypotheses 1 through 4, and these analyses repeated with the goal of accommodating the overall model to meet required assumptions (Table 19-22). As sleep disorder was

already treated as a time-varying predictor, no additional statistical correction was applied to this variable. As can be seen in the results presented in the next sections, results differed between analyses utilizing mTBI as a time-fixed vs. time varying variable.

SUPPLEMENTARY ANALYSES: MTBI AS TIME-VARYING PREDICTOR

Hypothesis 1

In the univariable analysis presented in Table 19 for Hypothesis 1, mTBI as a time-varying predictor was associated with a 1.336 times increased probability for CHD (CI = 1.111-1.607, $p < 0.01$). This is in contrast to the reduced likelihood associated with mTBI when it was treated as a time-fixed variable. However, in the time-varying analysis of mTBI, its effect was no longer statistically significant (HR = 1.028, $p = 0.773$, CI= 0.852-1.240, $p=0.773$) when demographic variables were adjusted in the model.

Table 19. Associations between mTBI as a Time-varying Predictor with Demographic Covariates and CHD as the Outcome.

Variable	Univariable Analysis HR (95% CI, p-value)	Multivariable Analysis HR (95% CI, p-value)
Age	1.130 (1.122-1.138, $p < 0.001$)	1.131 (1.123-1.139, $p < 0.001$)
Sex (male)	2.738 (1.998-3.751, $p < 0.001$)	2.850 (2.080-3.906, $p < 0.001$)
mTBI*	1.336 (1.111-1.607, $p < 0.01$)	1.028 (0.852-1.240, $p=0.773$)

Note. mTBI* = mTBI as a time-varying predictor

Hypothesis 2

When sleep disorder status was considered (model from Hypothesis 2) (Table 20), however, mTBI's effects on CHD risk was positive, such that those with mTBI only were 1.631 times more likely to have CHD than those with no mTBI or sleep disorder (CI: 1.198-2.221, $p < 0.01$). Similarly, those with sleep disorders were 2.181 times more likely to have CHD compared to those with neither mTBI nor sleep disorders (CI: 1.825-2.607,

p<0.001). For those with both mTBI and sleep disorders, they were 35.4% less likely to experience CHD compared to those without either condition (HR for mTBI x HR for interaction effects = 1.631 x 0.396 = 0.646), consistent with previous results that indicated the strong inverse association between mTBI and CHD diagnosis.

Table 20. Associations between mTBI as a Time-varying Predictor and Sleep Disorder with Demographic Covariates and CHD Outcome.

Variable	Multivariable Analysis HR (95% CI, p-value)
Age	1.127 (1.119-1.136, p<0.001)
Sex	2.820 (2.057-3.864, p<0.001)
mTBI* only	1.631 (1.198-2.221, p<0.01)
Sleep Disorder only	2.181 (1.825-2.607, p<0.001)
Interaction Effects of mTBI* and Sleep Disorder	0.396 (0.271-0.580, p<0.001)

Note. mTBI* = mTBI as a time-varying predictor

Hypothesis 3

For the associations of mTBI, PTSD, and CHD in Hypothesis 3 (Table 21), when mTBI was treated as a time-varying predictor, there were no statistically significant differences observed between those with mTBI alone (HR = 1.049, CI: 0.837-1.315, p=0.679) and PTSD alone (HR = 1.242, 0.892-1.729, p=0.200). The interaction effects between mTBI and PTSD was insignificant (HR = 0.798, CI: 0.501-1.270, p=0.340).

Table 21. Associations between mTBI as a Time-varying Predictor and PTSD with Demographic Covariates and CHD Outcome.

Variable	Multivariable Analysis HR (95% CI, p-value)
Age	1.131 (1.123-1.139, p<0.001)
Sex (Male)	2.843 (2.075-3.897, p<0.001)
mTBI* only	1.049 (0.837-1.315, p=0.679)
PTSD only	1.242 (0.892-1.729, p=0.200)
Interaction Effects of mTBI* and PTSD	0.798 (0.501-1.270, p=0.340)

Note. mTBI* = mTBI as a time-varying predictor

Hypothesis 4

For the model tested in Hypothesis 4, in the univariable analysis with mTBI as a time-varying predictor, mTBI was a significant predictor of CHD such that those with mTBI was 1.336 times more likely than those without mTBI to contract CHD ($p < 0.01$). However, when adjusted for age, sex, and other conditions (sleep disorder and PTSD), mTBI reversed in its effect, such that those with mTBI were less likely to have CHD than those without mTBI, by a factor of 0.871, although the effect was not significant ($p = 0.184$). This nonsignificant and negative association between mTBI and CHD outcome is similar to ones observed in earlier analyses where mTBI was treated a time-fixed predictor, suggesting that mTBI, whether as a time-varying or time-fixed predictor, was not a reliable predictor of hazards for CHD in this study.

Table 22. Associations between mTBI as a Time-varying Predictor, Sleep, and PTSD with Demographic Covariates and CHD Outcome.

Variable	Univariable Analysis HR (95% CI, p-value)	Multivariable Analysis HR (95% CI, p-value)
Age	1.130 (1.122-1.138, $p < 0.001$)	1.127 (1.119-1.135, $p < 0.001$)
Sex (Male)	2.738 (1.998-3.751, $p < 0.001$)	2.814 (2.053-3.857, $p < 0.001$)
mTBI*	1.336 (1.111-1.607, $p < 0.01$)	0.871 (0.710-1.068, $p = 0.184$)
Sleep	3.017 (2.578-3.531, $p < 0.001$)	1.869 (1.578-2.213, $p < 0.001$)
PTSD	1.600 (1.287-1.989, $p < 0.001$)	0.914 (0.719-1.161, $p = 0.461$)

Note. mTBI* = mTBI as a time-varying predictor

Retesting of Proportional Hazard Assumption for the Analyses with mTBI as a Time-Varying Predictor

Nevertheless, after the model was fitted with mTBI as a time-varying predictor, the extended model was re-evaluated with Schoenfeld residual test to see if mTBI and the overall model meets the assumptions of proportional hazard (Table 23). As can be seen in Table 23, fitting mTBI as a time-varying covariate in the model still did not resolve the violation of proportional hazard assumption ($p < 0.05$). It is the practice under such circumstances (298; 342) to utilize a step function, stratify the data, and generate

different coefficients over different time intervals to generate a coefficient for each time intervals for variables that violated the proportional hazard assumption. Based on visual inspection of the Schoenfeld residual plot (Figure 8) (298; 342), the data were arbitrarily divided into three time epochs, 1-2750 days (tgroup = 1), 2750-3750 days (tgroup = 2), and 3750-4380 days (tgroup = 3). After the data were stratified, the model was reanalyzed and retested for violation of proportional hazard assumption.

Table 23. Test of the Proportional Hazards Assumption of a Cox Regression in Initial Model with mTBI as a Time-Varying Predictor

	Chi Square	df	P
Age	7.932	1	0.005*
Sex	0.788	1	0.375
mTBI (Time-Varying)	17.471	1	0.001*
PTSD	0.190	1	0.663
Sleep	14.440	1	0.001*
Model	34.320	5	0.001*

Note: * indicates $p < 0.05$

From the Schoenfeld residual test (Table 24), a fit to the stratified data show that the revised model no longer violates the proportional hazard assumption as indicated by p-value greater than 0.05 ($p = 0.55$). However, mTBI as an individual predictor continues to violate the proportional hazard assumption ($p < 0.05$). After stratifying the data (Table 25), the effects of sleep and mTBI are time-dependent across the study period, e.g., there were significant interaction between the diagnoses and time, making these results uninterpretable due to violation of proportional hazard assumption.

Nonetheless, several observations can be made from Table 25: there was a linear trend of increased hazard for CHD for those who were diagnosed with mTBI at the later time in the study (tgroup = 3) than earlier (tgroup = 1). In contrast, a parabolic relationship between sleep and time was observed, such that those diagnosed with a sleep

disorder halfway through the study period had less hazard for CHD than those diagnosed with sleep earlier or later in the study (Table 25).

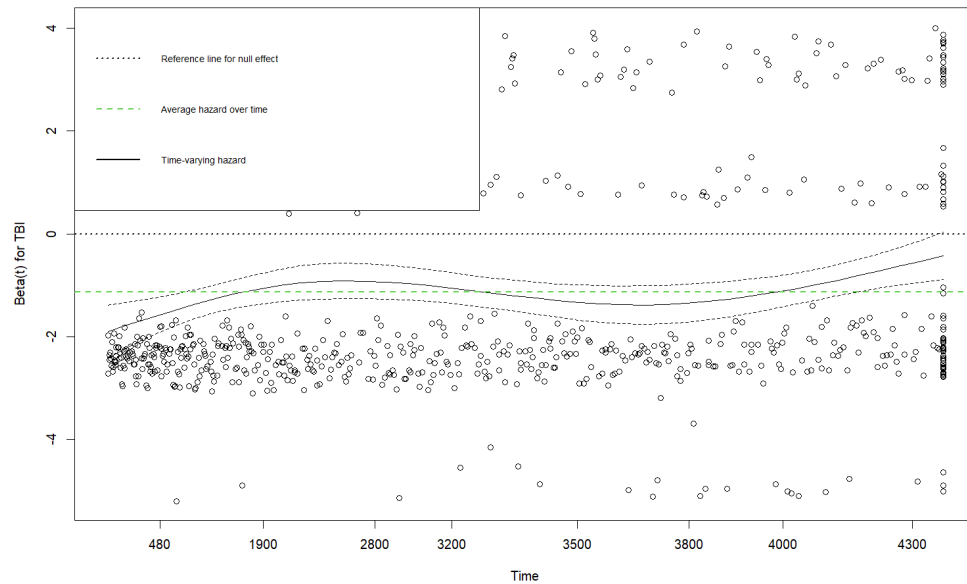


Figure 8. Plot of Schoenfeld residuals evaluating the proportional hazard assumption of a Cox Regression model fit. A non-zero slope (i.e., non-horizontal) results indicates time-varying effect of mTBI as a predictor, which suggests violation of proportional hazard assumption.

Table 24. Schoenfeld Residual Test to Evaluate the Proportional Hazards Assumption of a Cox Regression After Step Function

	Chi Square	df	P
Age	3.52	1	0.061
Sex	1.06	1	0.304
mTBI (stratified)	8.16	3	0.043*
PTSD	0.14	1	0.709
Sleep (stratified)	2.91	3	0.405
Model	16.63	9	0.055

EXPLORATORY ANALYSES: HYPERTENSION AS OUTCOME

An exploratory analysis (Table 26) was conducted to evaluate the effects of mTBI, sleep, and PTSD with hypertension as the outcome variable (instead of CHD as in Table 16). For those with mTBI, their risk for hypertension is lowered by a factor of

0.365 compared to those without mTBI (CI: 0.616-0.653, $p<0.001$) when adjusted sleep disorder and PTSD statuses. In contrast, those with PTSD were 1.731 times for as likely as those without PTSD to have hypertension (CI: 1.648-1.819, $p<0.01$) whereas those with sleep were 1.927 as likely as those without sleep disorders to have hypertension (CI: 1.860-1.996, $p<0.001$), after adjusting other covariates in the model.

Table 25. Hazard Ratios of Predictors in the Stratified Model

Variable	HR	95% CI	P
Age	1.133	1.125-1.141	<0.001
Male	3.247	2.368-4.451	<0.001
PTSD	1.337	1.052-1.698	0.017
mTBI * tgroup=1	0.277	0.211-0.364	<0.001
mTBI * tgroup=2	0.300	0.219-0.411	<0.001
mTBI * tgroup=3	0.445	0.330-0.599	<0.001
Sleep * tgroup=1	3.039	2.346-3.937	<0.001
Sleep * tgroup=2	1.480	1.124-1.949	0.005
Sleep * tgroup=3	1.739	1.301-2.325	<0.001

Note: tgroup=1 is from 1-2750 days, tgroup=2 is from 2750-3750 days, tgroup=3 is from 3750-4380 days

Table 26. Associations between mTBI, Sleep, and PTSD with Demographic Covariates and Hypertension Outcome.

Variable	Univariable Analysis HR (95% CI, p-value)	Multivariable Analysis HR (95% CI, p-value)
Age	1.077 (1.076-1.079, $p<0.001$)	1.078 (1.077-1.079, $p<0.001$)
Sex (Male)	1.321 (1.264-1.380, $p<0.001$)	1.445 (1.383-1.510, $p<0.001$)
mTBI	1.018 (0.990-1.047, $p=0.201$)	0.635 (0.616-0.653, $p<0.001$)
PTSD	2.339 (2.236-2.448, $p<0.001$)	1.731 (1.648-1.819, $p<0.001$)
Sleep Disorder	2.540 (2.458-2.624, $p<0.001$)	1.927 (1.860-1.996, $p<0.001$)

CHAPTER 4: Discussion

GENERAL SUMMARY RESULTS

The purpose of this study was to determine the relationship of mTBI to cardiovascular risk and to determine the role of associated conditions of sleep disorders and PTSD in this relationship. Results indicated a complex set of findings. Initial analyses utilizing Cox Proportional Hazard (PH) regressions suggested that surprisingly and contrary to the study hypotheses, mTBI had a significant negative relationship to CHD, such that those with mTBI diagnoses were less likely to be diagnosed with CHD over the course of the study. The negative relationship between of mTBI and CHD was opposite to what has been found in the literature, as reviewed in the Introduction, which implicates brain injuries of varied severity with significant health deteriorations (7; 38; 71; 138; 191; 234). In contrast, in the present study, the presence of sleep disorders was associated with elevated risks for CHD, independent of other predictors and covariates, and the combination of sleep disorders and mTBI was also associated with increased CHD incidence despite the negative association between mTBI only with CHD. By itself, PTSD was predictive of CHD risk in univariable analyses, but the effect of PTSD on CHD risk became nonsignificant when adjusted for mTBI status. Nevertheless, CHD incidence was higher among those with both mTBI and PTSD when compared to those with only PTSD or mTBI alone.

Cross-sectional analyses indicated that mTBI is associated with increased risk for a range of other physical and mental health conditions, such as substance use disorder, hypercholesterolemia, hypertension, obesity, diabetes, depression, and anxiety disorders (Table 11). In addition, mTBI was also associated with increased mortality over the

course of the study (OR = 3.53, $p < 0.001$; Table 11). Despite these findings, taken together, these results lead to the general conclusion that although mTBI was associated with increased general morbidity and mortality, mTBI alone was not associated with elevated risk of CHD incidence in this study, and that any elevated risks for CHD appear to be associated with comorbid conditions that are commonly found in those with mTBI, including sleep disorders and PTSD. Specifically, those with mTBI were 67.8% as likely as those without mTBI to have CHD after adjusting for PTSD and sleep disorder status. In contrast, those with PTSD and Sleep Disorder were 1.365 times and 2.037 times as likely to have CHD after adjusting for mTBI.

In the following sections, the study findings will be discussed with reference to each of the study hypotheses, interpreted in terms of the existing literature, and possible explanations offered. In addition, this discussion will focus on the conceptual model of the study, where mTBI is theorized as an initial event that promotes a disease process associated with many comorbidities, and the role of sleep disorders in these relationships.

DISCUSSION OF RESULTS BY AIMS AND HYPOTHESES

Aim 1

Hypothesis 1 proposed that patients with mTBI will have a higher rate of one or more cardiovascular diagnoses over the course of the study compared to patients without mTBI. As noted above, various analyses indicated that the opposite was true when the effects of mTBI were considered in the absence other conditions such as sleep disorders and PTSD; specifically, those with mTBI were less likely to be diagnosed with CHD over the course of the study. These results were surprising and not consistent with prior

research findings indicating that mTBI is associated with multiple poor health and quality of life outcomes, including biomarkers for arteriosclerotic cardiovascular disease (7).

In prior studies, TBI has been associated with higher prevalence of disorders (e.g., sleep disorders (193; 327), neurodegenerative diseases (180), neuroendocrine disorders (5), musculoskeletal dysfunctions (85), metabolic dysfunction (15; 16), etc., as well as higher reported health complaints and musculoskeletal injuries. Previous surveys of cardiovascular conditions and risk factors prevalence (e.g., hypertension, CHD, stroke, heart attack) among veterans vs. nonveterans also found that military veterans had a higher rate of CVD morbidity than their nonveteran counterparts, and these effects are more prominent among younger veterans, with increased morbidity risk for veterans evident around age 35 (129). Of note, the mean age of participants at baseline in the current study was 24.8 and the study period was 13 years, which would theoretically allow us to surveil the early signs of CHD among our sample.

As a whole, the present study results corroborate prior findings that individuals with mTBI demonstrate higher prevalence of comorbidities, many of which are CHD risk factors. Specifically, those with mTBI in the present data had high rates of various conditions, such as sleep disorder (OR = 3.95), substance use disorder (OR = 1.47), hypertension (OR = 1.11), PTSD (OR = 6.47), obesity (OR = 1.50), depression (OR = 2.25), and anxiety disorders (OR = 4.85). Lastly, in the current study, finding those with mTBI have 3.53 times higher mortality rate than those without (OR = 3.53, $P < 0.001$), even though the effect dissipated when comorbid conditions were controlled for (OR = 1.67, $p = 0.109$).

Thus, present study provides additional confirmation that exposure of TBI is associated with secondary injury effects that worsen physical function that may last even after resolution of TBI symptoms. The mechanisms for these effects were discussed in the Introduction (128) and include autonomic nervous system (ANS) dysfunctions, changes in heart variability, increased inflammation, altered homeostasis, breakdown of the blood-brain barrier, hypertension, cell death, ischemia, and other indirect system damage (e.g., morphological damage to peripheral organs) (72; 204).

Possible Explanations for Reduced CHD Among Individuals with mTBI

Nevertheless, despite the unexpected finding, it is important to explore and explain Hypothesis I study findings of decreased incidence of CHD in mTBI in prospective analyses. Taking the mTBI results at their face value, one explanation for this finding is that mTBI was assessed in the study in terms of diagnoses from medical visits for this condition, and the possibility that those with mTBI in the military health system (MHS) may be more likely to have increased healthcare utilization compared to those outside the MHS. Such increased healthcare utilization might result in increased likelihood of diagnoses among participants with mTBI but also in increased detection of CHD risk factors. In one study investigating service members with mTBI in 2012, those with a mTBI diagnosis was almost twice as likely to receive complex and “persistent care”, which is defined as mTBI-related treatment for longer than three months after the initial mTBI diagnosis (92). As such, conditions commonly impacting cardiovascular risks are more likely to be detected and subsequently treated among those with mTBI and thereby reducing the overall risk for poor cardiovascular health. This increased healthcare utilization, in turn, might have resulted in higher rates of diagnoses of comorbid

conditions. If increased healthcare utilization also resulted in treatment for these conditions, that might have reduced cardiovascular risk in treated individuals.

Another explanation for the current findings for lower CHD diagnoses in the mTBI group might be the higher mortality we observed among those diagnosed with mTBI compared to those without in the present study. This would suggest the possibility that a percentage of those with mTBI may not live long enough to develop chronic diseases such as CHD or that those with undiagnosed CHD in the mTBI group were more likely to die without a CHD diagnosis. Yet, the number of deaths in the mTBI group (n=34) and in the control group (n = 18) were comparatively small when compared to the overall sample size (n = 196,957) and thereby unlikely to drastically impact the overall outcomes of the analyses even when death was taken into consideration.

Relatedly, those with mTBI may stay in the MHS for less time due to reasons such as lost to follow-up, leaving active service, etc. This is important considering cardiovascular conditions are more likely to develop at later stages in life. Referencing an alternate definition of hazard ratio (285), a person with a higher hazard is more likely to reach endpoint (e.g., exposure to incident of interest, death, lost to follow-up, etc.) earlier when compared to a person with lower hazard. Thus, bias is likely introduced when one group naturally “survives” longer in the study and thereby appeared to have increased risk simply for longer survival time in the study. To that end, a supplementary analysis was conducted to investigate the time in study between the mTBI and control group in cohort of year 2007. The analysis found that, mTBI group has median time in the MHS of 2036 days vs. 2333 days for control group ($F=87.32$, $p<0.001$), supporting the assertion that those with mTBI were less likely to stay in the MHS. This explains that those with

mTBI has a shorter overall time in the study compared to those without mTBI. As such, any effects that mTBI might have on cardiovascular health at the later stages in life were not detected. This is salient considering that mTBI cases in the present study represent only the subset of individuals who were medically diagnosed with mTBI in outpatient settings and not those individuals who may have had 1) mTBI that was not treated or formally diagnosed within MHS, 2) in inpatient settings and VA, or 3) those who sought care out-of-network. It is speculated that those with mTBI, if followed after leaving the MHS and entering into the VA healthcare system, are likely to exhibit higher risk for CHD.

In addition to the above explanations, the unexpected findings regarding Hypothesis 1 warranted a closer examination of the statistical issues that may have affected results for Hypothesis I. To test study hypotheses with mTBI as a predictor, a series of models were created in order to investigate the effects of the predictors on the study outcome of CHD. Following previous examples (248), factors theorized to have time-varying elements (i.e., variables that change over the course of the study) were introduced into the models (e.g., sleep, PTSD), generating statistical models with both time-fixed predictors (e.g., age, gender) and time-varying predictors (e.g., sleep, PTSD) that impacted the hazard for CHD differently depending on when one acquires these conditions. In these analyses, however, mTBI was treated as a time-fixed variable and was determined by whether individuals developed mTBI at any point during the study. Therefore, statistical conventions dictates that the models be tested to see if they meet the assumptions for the proportional hazard and, if not, to apply appropriate accommodations, such as 1) inputting mTBI as a time-varying covariate and retest the

assumptions of proportional hazards and 2) stratified the data in different time group through a process called step function. The steps taken for this study are discussed below, but in-depth details of these statistical corrections are beyond the scope of this paper and, as such, readers are referred to review Therneau et al. (298) and Zhang et al. (342) for in-depth discussions.

With regard to the test of assumption of proportional hazards (i.e., test of Schoenfeld residuals), the model used for this test included mTBI, PTSD, and sleep disorder as the primary predictors and age and gender as demographic covariates (Table 16). The test will show if individual predictors and covariates as well as the overall model (i.e., combined effects of all the predictors and covariates) meet the assumption. The results of the test show that both mTBI and sleep disorder appeared to have violated the assumptions for having small p-value of less than 0.05. Additionally, the overall model also violated the assumption for the same reason. To assess for potential areas for statistical accommodation to address the violation, individual predictors that violated the assumption, i.e., mTBI and sleep disorder, were evaluated: since sleep disorder was already coded as a time-varying predictor, it was not expected to meet the assumption, which left mTBI as possible and likely explanation for the model not meeting the assumptions. As stated before, one of the first steps to correct the model was to input mTBI as a time-varying predictor. However, even after mTBI was entered as a time-varying predictor, the model did not improve as expected: the associations between CHD and mTBI as a time-varying predictor remained not positive (e.g., statistical nonsignificant), against hypothesized outcome, when other predictors were controlled for.

A final accommodation, which is to stratify the data using a step function, was employed to ensure individual predictors and the model meet the proportional hazard assumption. To that end, the model was stratified into three groups based on predetermined time-intervals (i.e., time-group) where time-varying effects were likely observed (see Figure 6). Similar to previous correction, the individual predictors and the overall models were assessed to see if they met the assumption of proportional hazard when the effects were assessed at predetermined time-intervals. Although the overall model (with mTBI as time-varying predictor) met the assumption of proportional hazard, mTBI as an individual predictor continued to violate the assumptions for having a significant $p < 0.05$. Therefore, because of these statistical issues and with minimal to no improvement to the model even after applying several corrective measures, interpretations of the effects attributable to mTBI in this study should be made cautiously as their statistical validity may be questionable. Nevertheless, comparison between the model with mTBI as a time-fixed variable vs. time-varying variable indicated mTBI alone was either having a negative relationship with CHD risk (time-fixed variable) or insufficient to impact CHD risk (time-varying variable) while other factors, such as age, gender, and sleep disorder, retained their predictive effects on CHD risk. These issues will be further discussed under Hypotheses 2, 3 and 4.

Hypothesis 1 Summary

In summary, regarding Hypothesis 1, mTBI alone was insufficient in predicting diagnosed coronary heart disease or hypertension. As will be described for the other study hypotheses, this result lends further support of the results that mTBI did not directly influence the incidence of CHD diagnoses but instead does so indirectly through

increasing risks for associated comorbid conditions, such as sleep disorders. Similar results were obtained in separate analyses and models where the effects of mTBI, sleep, and PTSD on hypertension were assessed, such that mTBI remained a nonsignificant predictor whereas sleep and PTSD were strongly associated with increased risk for hypertension. This points towards the fact that mTBI indirectly increases the likelihood of CHD by elevating risks for comorbid conditions that are more strongly associated with CHD, even among a generally healthier and younger population such as the military population.

Aim 2

For Aim 2, we hypothesized that patients with mTBI and sleep disorder diagnoses will have a higher rate of negative cardiovascular outcomes compared to patients with mTBI and without a sleep disorder diagnosis. In the analysis investigating the relationships between sleep and mTBI with CHD, the findings supported this hypothesis. Exposure to sleep disorder alone nearly doubled the likelihood for CHD ($HR = 1.951$). Those with both mTBI and sleep disorder diagnoses ($HR = 0.397$) have a higher rate of CHD compared to those with mTBI only ($HR = 0.279$). Previous literature provides strong evidence for the effect of sleep on cardiovascular health. There are indications that both acute and chronic difficulties with sleep, even if the severity was below clinical disorder level, have a significant negative impact on cardiovascular health. Some of the common physical conditions associated with sleep insufficiency are immunosuppression, stroke, increased cardiometabolic diseases, and increased cardiovascular, cancer, and all-cause mortality (8; 60; 116; 137; 194). Consistent with previous findings, the current findings confirms that sleep issues were found to contribute or worsen other physical and

psychiatric conditions and also present as a symptom of other psychiatric conditions, such as PTSD (10) and TBI (63).

In contrast, as discussed above, the presence of mTBI presented as a significant factor associated with reduced incidence of diagnosed CHD. Among those with both sleep disorders and mTBI diagnoses, the effects of sleep disorder on CHD risk were countered by the effects of exposure to mTBI (HR = 0.397). Similarly, despite the fact that mTBI was associated with multiple comorbidities – many of which are CHD risk factors – the relationship of mTBI to reduced CHD incidence was unexpected and not consistent with existing literature: to date, there is no evidence to suggest that mTBI is linked with reduced CHD incidence. It is important to note that disrupted sleep is one of the most common comorbid symptoms of TBI, and it has been suggested that mTBI can precipitate a wide range of sleep disorders (315). As previously stated, the prevalence of sleep problems after TBI ranges from 30% to 84% (27; 31) in the general populations and the statistics for military members varied depending on the sleep complaints: Collen et al. (63) reported that among military members who survived combat-related TBI, nearly all (97.4%) admitted having at least one sleep complaint. Hypersomnia (85.2%), sleep fragmentation (54.3%), OSA (34.5%), and insomnia (55.2%) are some of the most common sleep complaints reported. In another retrospective cross-sectional analysis of military polysomnography testing – a type of multi-parametric diagnostic tool for sleep issues – OSA was the most frequent diagnosis (51.2%), followed by insomnia (24.7%) and behaviorally induced insufficient sleep syndrome (BISS; 8.9%). The key findings from both studies highlight an elevated rate of sleep disorders and sleep-related symptoms in the military, as compared to civilian, population. Our current finding

suggests that approximately 56.7% of those who suffered from mTBI also reported a wide range of sleep disorders, comparable to the general findings of previous data on sleep problems among military members.

Previous research suggests that the subjective experience of sleep problems continues to be elevated in TBI patients even after recovery over time (27). As noted previously in this dissertation, sleep complaints are more disruptive among those who experience mTBI compared to those with severe TBI (31; 62; 95; 182; 229). Researchers have postulated that associations between less severe forms of TBI and sleep disruptions may be due an over-endorsement of sleep complaints among those with mTBI (315). And when considering the likely causal effect of mTBI on the presence of sleep disorder among military population (i.e., mTBI preceding poor sleep), it is possible that the decreased risk of CHD among those with both mTBI and sleep disorders ($HR = 0.397$), relative to those with sleep disorders alone ($HR = 1.951$) is related to the relationship between exposure to mTBI and increased healthcare utilization in the military setting, as discussed above, and thereby allowing for early interventions to address and mitigate the negative effects of sleep disorders.

Sleep Disorders and CHD

The significant positive relationship between sleep disorder and CHD risk in current finding is expected. A large number of studies have discussed that irregularities in sleep, such as irregular circadian rhythm, sleep loss or disrupted sleep, and disordered breathing during sleep, may affect health (64), including cardiovascular health and outcomes (98; 140; 162; 164; 238; 281; 304; 306; 308). Many mechanisms have been proposed regarding how sleep affects cardiovascular health, including circadian rhythm's

role in regulating cardiac function (69; 103), such as endothelial function, vascular tone (218), and coagulation and platelet activity (307). As pointed in Introduction, despite the attention given to these associations, the pathophysiological mechanisms explaining the impact of irregular circadian rhythm on cardiovascular health are still not well understood. Stipulations on several mediating factors that may lead to poor cardiovascular outcomes were discussed, such as sleep-related cell death due to oxidative stress (90), leukocytosis and reduced plasma hypocretin, which in turn facilitates atherosclerosis (192), dysfunctions in vascular tone (222), abnormal endothelin level (220), increased sympathetic nervous activity in the heart (279), and/or activation of the inflammatory process which leads to elevated CRP, IL6, and TNF- α (90; 220; 279). The type of sleep disorders may have unique pathophysiologic mechanisms that may further contribute to sleep-related cardiovascular risks. For instance, disordered breathing related to sleep, such as cessation of respiratory airflow due to OSA, can cause significant hemodynamic and neuroendocrine effects in the human body as well as a profound decrease in oxygen saturation, which in severe cases would lead to hypoxemia, which is associated with severe cardiovascular complications (329). Considering untreated OSA leads to a higher risk of cardiovascular mortality (105; 267; 329) as well as an increased risk for sudden cardiac death (105), the higher rate of sleep disorders among those with mTBI in current study is likely contributing to the higher mortality rate among them.

Aim 3

For Aim 3, we attempt to determine the longitudinal associations between PTSD and cardiovascular outcomes among patients with mTBI within the military health systems. We hypothesized that patients with mTBI and PTSD diagnoses will have a

higher rate of negative cardiovascular outcomes compared to patients with mTBI or PTSD diagnosis or patients without mTBI or PTSD.

As such, the impact of comorbidity mTBI and PTSD was investigated in comparison with those with mTBI or PTSD alone and those without either condition. Consistent with above findings, mTBI continued to be associated with decreased likelihood for CHD diagnoses (HR = 0.317). For those with PTSD only, the risk for CHD was elevated (HR = 1.276), but the effect was not statistically significant. The risk of CHD is lower for those with both mTBI and PTSD than those without either condition (HR = 0.531. This finding is contradicting with previous literature, which suggests that PTSD increases the risk for negative cardiovascular outcome (264). Previous research also indicates that individuals who are exposed to traumatic events are likely to report poor health, increased morbidity, elevated utilization of medical services, and have an increased mortality rate (87; 264). Given strong evidence suggesting PTSD impact on physical health, we hypothesized PTSD to have a significant impact on CHD risk. However, our finding indicated otherwise. Notably, it is surprising that those with both mTBI and PTSD have increased risk for poor cardiovascular outcomes, considering that mTBI was expected to ameliorate the risk of CHD based on observations noted in above sections (e.g., mTBI decreased effects of sleep disorder on CHD risk).

It is likely that an interaction between the comorbidity of mTBI and PTSD impacts health in a way that cannot be accounted for by each condition alone. Previous researchers noted the difficulties distinguishing between the effects of mTBI and PTSD on health due to high comorbidity among these conditions (44). In current study, having mTBI or PTSD alone was insufficient in increasing the risk of CHD. But the presence of

both appeared to significantly increase the risk of CHD. It is noteworthy to mention the synergistic effects of mTBI and PTSD comorbidity have been observed in other studies, specifically on cognitive performance and executive functioning (259), although researchers were not clear on the mechanisms underlying the interactions between mTBI and PTSD. However, there is evidence that PTSD and TBI may impact on biological (e.g., structural, endocrine, and neurochemical change) and genetic levels, thereby resulting in similar pathophysiological symptom profiles (72; 150). Some researchers (213; 264; 283) have concluded that, similar to TBI, similar neurochemical changes in the brain play a role in the adverse effects of PTSD on physical health. Moreover, biological (e.g., altered HPA activity), behavioral (e.g., poor health habits), and psychological (e.g., depression) correlates of PTSD have also been theorized to explain the mechanism behind PTSD's impact on physical health. These biological, behavioral, and psychological factors are also common among those with mTBI (191). However, few studies have investigated the exact variance as explained by these factors, and existing literature, particularly on the associations between biological factors and PTSD, is mixed and inconclusive (197; 221). Although the exact mechanisms are not explored in the current study, the results show that the presence of mTBI or PTSD was not enough to elevate cardiovascular risk. Additionally, the comorbidity of mTBI and PTSD may have synergistic effects on negative cardiovascular risk, likely due to similar pathophysiologic mechanisms as both mTBI and PTSD can be considered systemic disorders that increase risk factors for CHD (159; 191; 256; 257).

Aim 4

In Aim 4, we attempted to determine if the relationships between mTBI, sleep disorders, and CHD are independent of the association with PTSD with CHD. We hypothesized that the relationships between mTBI, sleep disorders, and CHD will be independent of contributions of PTSD to CHD.

In regression models with PTSD and mTBI above, presence of PTSD alone elevated CHD risk but the effect was not statistically significant. This finding was not consistent with other findings in the literature regarding the association between PTSD and cardiovascular health (30; 66; 265; 319). Nevertheless, the model that included mTBI, sleep disorder, and PTSD as predictors of CHD outcome yielded a different result. In this model, PTSD (HR = 1.365) and sleep disorders (HR = 2.037) were each significant predictor of increased CHD. Consistent with previous models, mTBI was associated with decreased risk of CHD (HR = 0.322). The finding confirms the hypothesis that the relationships between mTBI and sleep disorders are independent of the contribution of PTSD to CHD risk. Moreover, the reversal of statistically insignificant (after adjusted for mTBI) to significant finding for the effects of PTSD to CHD risk was likely a result of adjusting for sleep disorder in the multivariable analysis. This suggests that presence of sleep disorder in association of PTSD plays a large role in the relationship between PTSD and cardiovascular health. This is similar to findings from a previous study (263) whereby the effects of PTSD on negative cardiovascular health were attenuated and better explained by comorbid conditions such as sleep disorder, substance use disorder, anxiety disorders, and depression. It is likely that PTSD alone is insufficient in elevating CHD risk. Rather, the relationship between PTSD and CHD outcome is likely mediated by a range of comorbid conditions, such as sleep disorders. One way to

conceptualize the relationship between PTSD and comorbid conditions on cardiovascular risks is through the “systemic disorder model” (159). In this model, PTSD as a diagnosis is considered a “tip of the iceberg” for a wide range of systemic changes and biological dysregulation intrinsic to PTSD. Therefore, comorbid diagnoses, such as sleep disorders, are not considered as separate and independent risk factors but rather pathophysiological conditions that contribute towards poor cardiovascular health as a part of PTSD psychopathologic mechanisms. As demonstrated in current findings, PTSD became a statistically significant predictor after sleep disorder was controlled for, which suggests moderating effects by sleep disorder to the associations between PTSD and CHD risk. However, the impact of sleep disorder remains independent of PTSD. This suggests that in addition to being a part of PTSD’s pathophysiologic mechanisms, sleep disorder itself is an independent risk factor for poor cardiovascular outcome.

STRENGTHS OF THIS STUDY

The study has several notable strengths, including large sample size necessary to detect effects of interest and sophisticated methodology to ensure accuracy and reliability of findings. Given the small probability of CHD in a military population, which tends to be healthier and younger, a large sample size enables the detection of effects that would otherwise been elusive to survey in a small sample size. Additionally, multiple safeguard procedures were utilized to address common problems with large datasets containing medical records. These problems range from changes in coding policy and procedures (e.g., from ICD-9 to ICD-10, insurance reimbursement criteria) to human errors in data maintenance. For instance, the study utilized empirically validated algorithm to increase diagnostic accuracy commonly used in analysis of big datasets (i.e., two or more

outpatient encounter) (248). Further, the use of diagnostic information (made by healthcare professional) has an advantage over other measures, such as self-report questionnaires, that may subject to subjective biases.

Another strength of the study was the sample and dataset representative of the MHS at a time during combat operations with mTBI as a signature injury. The study highlighted the impact of mTBI on physical health among the military population who served during the height of military operations. The sample and dataset were relevant and provided necessary and valid information to investigate the association between mTBI and physical health in the military population.

Relatedly, with some exceptions, the sample was largely matching the larger military forces. Notably, the study included all branch of service and inclusive of all races in the military, despite the limitations on Hispanics group as discussed above. As such, conclusions made based on the current study are relevant to the military population in general. To that end, while a “clean” dataset free of any error is ideal, the likelihood of acquiring dataset with perfect fidelity and accuracy is very low, especially considering the size of the MHS database. Nevertheless, the process of reducing systemic error in the data involved consultation with experts in respective fields as well as referencing previous literature and latest guidance and convention for empirically supported methods to analyze the data.

LIMITATIONS OF THIS STUDY

There are several limitations to the study, conceptually and methodologically. As shown in 2020 statistics, most CHD cases occur in age 45 and above (177). The mean age in our study population was 25.9, which is far from the age where CHD are commonly

seen. As such, even if a participant remained in the study until the end of study period, it is likely that participant will be undiagnosed despite meeting criteria for CHD (i.e., false negative), as common cardiovascular preventive practices was not recommended until above age 45 (113). It is possible that a higher amount of false negative cases exists in the study and went undetected.

Another shortcoming of the study was the evolving nature of mTBI definition in the literature. The mTBI cases used in the study is based on DoD case definition established by Armed Forces Health Surveillance Branch (AFHSB) in Aug 2008. The case definition has changed and updated five times since its inception. Majority of the changes were addition or removal of specific diagnoses; however, the most significant change that occurred with the case definition was the incorporation of ICD-10 codes, which allowed surveillance of multiple TBI events as well as matching comparable ICD-9 codes to ICD-10. Since our study utilized both ICD-9 and ICD-10 codes based on the most updated surveillance code (most recent 2019; study was conducted in 2020-2021), it is unlikely that the change in mTBI case definition affected our study results.

Moreover, although diagnostic information can be more reliable than self-reported symptoms, the reliance on diagnostic information (ICD and CPT codes) can be problematic as diagnostic accuracy may vary, especially when the diagnoses were made by healthcare providers from different expertise or specialty. For example, a PTSD diagnosis is most reliable when made by mental health provider, who is trained in conducting psychiatric or psychological evaluation. Contrarily, a PTSD diagnosis made by a dermatologist may be questionable. As stated above, the definition for both mTBI and PTSD for the study are highly sensitive to operational case definitions, and providers

in MHS are often challenged by distinct and evolving coding guidance (92). Further, the dataset in the study only covered care provided at outpatient setting. Data from inpatient care and civilian purchased care network are not included. Lastly, mTBI is often underdiagnosed (232): if service members were not given the appropriate diagnostic code for mTBI they were not captured in the study. In present study, these factors were not formally evaluated and controlled for. In anticipation of these concerns, previous literature with similar dataset recommended two outpatient diagnosis for the same condition as a way to confirm a diagnosis. The above recommendation purportedly increased diagnostic accuracy up to 90% (248). While imperfect, it is within acceptable margins of error, especially considering the benefit of using a large dataset as well as safeguard procedures to ensure external validity.

Another issue with the study is missing or discrepant data. A few variables were deemed inappropriate for analysis due to a large amount of missing data or simply having multiple entries with contradicting information. For example, a portion of the racial information was coded with four race options (e.g., without Hispanic) whereas others were coded with five race options (e.g., with Hispanic). Attempts were made to reconcile the discrepancy, but there remains a significant portion of the racial information uninterpretable, rendering the removal of race as a covariate from the analysis. There were other similar discrepancies and outliers in the datasets, as discussed extensively in the Results sections, including those with same entry and exit dates out of the MHS, improbably diagnosis date (e.g., being diagnosed before officially entered into the MHS), etc. The removal of these data amounted to approximately 23% of dataset being discarded, which is larger than the conventional 10-15% acceptable range. Discarding

such large amount of data may biased the sample, particularly when systematic bias (e.g., coding of race information) may be present. These issues may be mitigated by the overall large sample size.

Lastly, the study had several sources of bias which is due to limitations associated with sampling and matching process. As discussed in Methods section, the control group was derived from cohort year 2007 only whereas the mTBI group was sampled from the study period (2007-2019). The decision to select the control cases from cohort year 2007 was due to the massive numbers of potential control cases over the span of the study (approximately 20 million). In the process of reducing possible control cases, it is likely that cohort effect was introduced in the sampling process. Notably, if cases were able to matched year of entry by year, Cox regression with time varying covariates would be a more appropriate strategy and allows for better accommodations for statistical violations. Nevertheless, longitudinal nature of the study, propensity scoring method used to match the samples based on key demographic characteristics, and the large samples for both mTBI and the control group should help mitigate these biases.

IMPLICATIONS OF THE STUDY

Previous study investigated the relationship between mTBI and the biomarkers of CHD (7), but no study to date has evaluated mTBI and its effect on CHD longitudinally among the military population. The present study also evaluated the significance of PTSD and sleep disorders in the associations between mTBI and CHD. In corroboration with previous findings (191), mTBI acts as a start-point for a deterioration of physical health and disease process even after recovery from the initial insult, paralleling the effects observed in TBI cases with greater severity which have extensively been studied

(191). This finding is notable for mTBI accounts approximately 90% of all TBI in the military in 2007-2008 (88). Present study confirms previous findings of high associations of mTBI with increased rates of various disorders, such as sleep disorders and substance use disorder. Thus, the study provides strong support to not delay the delivery of much needed care to address comorbid conditions associated with mTBI and subsequently to poorer physical health. This information should inform clinical care whereby assessment and treatment of mTBI and its symptoms should go beyond the conventional standard of care of treating acute symptoms to address the systemic impact of the primary insult on the body (287).

Moreover, the study indicates the important role of sleep disorder as the primary driver of poor cardiovascular health among military service members independent of the effects of mTBI and PTSD. There are mounting evidence suggesting poor sleep is prospectively linked to both the risk for and clinical course of cardiovascular diseases. Several pathophysiologic mechanisms linked with pathogenesis of cardiovascular diseases were proposed, to include endocrine dysregulation, increased inflammation, and autonomic imbalance, which are common symptoms of sleep deprivation (139). Considering sleep disruption is a common symptom of mTBI, it is not a surprise that the ultimate effects of mTBI are detrimental to the presence of multiple cardiovascular risk factors, comorbidities, and increased total mortality. In contrast, based on existing literature, PTSD is hypothesized to have a more established impact on cardiovascular risk (6; 30; 66; 84; 248; 265; 310).

Recent studies provided a new way of conceptualization PTSD's role in poor cardiovascular outcome: PTSD is a systemic disorder, with various intrinsic

pathophysiologic conditions such as sleep disruption and elevated stress, that is highly associated with and predictive of poor cardiovascular outcomes but do not necessarily or insufficient by itself to cause them (159; 263). The current study lends support to the aforementioned as indicated by the observed synergistic effects of mTBI and PTSD comorbidities as well as moderating effects of sleep disorders on the influence of PTSD on cardiovascular risks.

IMPLICATIONS FOR FUTURE RESEARCH

The study is to date the first to explore the longitudinal impact of mTBI on cardiovascular health in associations of common comorbidities, such as PTSD and sleep disorders, on cardiovascular outcome among military service members. There are several implications for future study based on this study, namely improving data quality and integrity for increased research capacity, utilizing data-driven machine learning research method, and enhancing future studies by incorporating risk factors that studied in this paper as well as additional data beyond diagnostic codes.

As previously discussed, there were several notable concerns pertaining to the MHS data including diagnostic coding and fidelity. For instance, some ICD-9 codes were not directly translated to ICD-10 codes whereas some ICD-10 codes capture some conditions not previously measured in ICD-9. It is no surprise since healthcare is an evolving field with new data and findings. However, relating to longitudinal research, it poses significant challenge for research due to inconsistencies in measurement and assessment for which due diligence to address these matters had to be made a priori. Moreover, the inconsistencies in administrative data (e.g., date of entry into the military, demographic data, etc.) introduced further potential errors when analyzing MHS data,

which severely limits interpretation of some findings, especially considering the importance of social determinants of health risks and outcomes (126). The issue may be related to the lack of interconnectedness of data, such as inpatient vs. outpatient data, medical vs. military records, which deterred surveillance and research in the military. Creating interoperable databases and database management system that allow extraction of high-quality data will facilitate and encourage meaningful clinical research in the military.

One limitation of current analytical and statistical strategies is the inability to incorporate a dataset as rich as MHS that necessitates capabilities for high computing power to analyze the data. To accommodate this limitation, future research should consider data-driven approach in analyzing a large and rich database such as MHS. Notably, advances made in machine learning in the psychological science allow more accurate prediction of risk factors of an outcome of interest (333). The methods of data-driven approach, such as machine learning, is beyond the scope of this study, but briefly, the underlying principles of data-driven approaches revolve around making atheoretical prediction first and foremost based on as many prognostic factors as available to analyze. Historically, psychological research focus on limited set of risk factors (e.g., current study) and often relying on parametric statistical methods to test hypothesis circumscribed a priori based on a theory-driven conceptual model. In a nutshell, data-driven approaches attempt to find an algorithm that resulted in data observed whereas traditional approaches explore the data to fit theoretical driven model in hope to find the true estimates. While the traditional approach is useful in some situations, such as in randomized controlled trials to accurately identify treatment efficacy, data-driven

approaches has several advantages over traditional, hypothesis-driven approaches, including minimizing the effects of overfitting in a model (i.e., the tendency in statistical model to fit sample-specific noise as if it were a signal), p-hacking or data-contingent analysis (i.e., the practice of selecting analytical procedures based on the quality of the results), increase interpretability of findings, and answering predictive questions without preoccupations with identifying underlying causal mechanisms (108; 333). With the rise of technological advances on big data analysis, it is now feasible to analyze data using state-of-the-art, computationally intense methods to design and optimize accurate prediction.

Referencing the study conceptual model, future studies utilizing aforementioned methodologies should consider incorporating likely psychological, behavioral, physiological, and medical, variables in the prediction model to assess the predictive strengths of these variables that were previously hypothesized to influence the relationship between mTBI and CVD. For instance, obesity and hypercholesteremia are conditions that are commonly associated with poor heart health. Additionally, data on lifestyle factors, such as physical exercises, smoking, alcohol use, and diet, were not readily available in the current data set, and these factors are known to be associated with cardiovascular health (173). Given that these variables were not directly assessed in current study, future studies should consider measuring these factors. Of note, biomedical information such as BMI (a proxy of obesity) and lipid levels (proxy of hypercholesteremia) is data that exist in the MHS. Other lifestyle information can be captured by common screening practices in military healthcare system through self-report measures, such as Insomnia Severity Index and Alcohol Use Disorders Identification Test

(AUDIT) for alcohol use (75). Such information can improve our accuracy when determining the presence of diagnoses as well as allowing greater statistical control for enhanced prediction of CVD risks, e.g., assessing changes in lipid levels associated with mTBI and subsequent risk of CVD. These research efforts should guide policy in the military, particularly in sleep-related issues given the present finding.

CONCLUSION

The study is consistent with the theory that mTBI initiates a disease process that has a lasting impact of physical and mental health even after the resolution of the initial injury. Although mTBI was not directly associated with poorer cardiovascular outcome in this study, it is associated with a range of comorbid conditions, such as sleep disorders and PTSD, risk factors for poor heart health, such as hypercholesterolemia, and greater mortality rate. Clinical care for patients with mTBI should take this into consideration to mitigated chronic impact of mTBI. Future research should investigate and delineate the physiological, psychological, medical, and behavioral components of the pathophysiological mechanisms involved in the disease process.

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APPENDIX: Sample R Syntax For Select Statistical Procedures

```
#####Syntax for Propensity Score Matching#####
library(MatchIt)
match<-matchit(TBI ~ age + gender + race + sponservagg, data = data.psm,
method="nearest", ratio=2)
#won't work because data.psm has missing data

#assess missing data
install.packages("mice")
install.packages("naniar")
library(mice)
library(naniar)
missing.data = aggr(data.psm, col=mdc(3:6), numbers=TRUE, sortVars=TRUE,
labels=names(data.psm), cex.axis=.9, gap=2, ylab=c("Proportion of missingness",
"Missingness Pattern"))

#remove missing data
data.psm.completecases<-data.psm.debug[complete.cases(data.psm.debug), ]
match.1to2<-matchit(TBI ~ age + gender + race + sponservagg, data =
data.psm.completecases, method="nearest", ratio=2)
plot(match, type = 'jitter', interactive = FALSE)

#save as data frame
df.match.1to2.new<-match.data(match.1to2, distance= "pscore")

#use this line to save data frame if you don't want psm data
##df.match<-match.data(match, distance= "pscore")[1:ncol(data.psm.completecases)]

##exporting df.match.1to2.new
write.csv(df.match.1to2.new, "matched control 1to2.new.csv")

#####Syntax for Log-Rank Test#####
library(survival)
logrank<-survdiff(Surv(OutcomeTime, Outcome) ~ TBI, data=analysis.data)

#####Syntax for Cox PH Regressions#####
#tmerge() to restructure the dataset
library(survival)
datatime<-tmerge(data1=analysis.data1, data2=analysis.data2, id=PTID,
Outcome=event(OutcomeTime, Outcome),
Sleep=tdc(TimeSleep),
PTSD=tdc(TimePTSD),
TBItdc=tdc(TimeTBI)) ##creating TBI as a time-varying covariate

##Time-fixed models
```

```

model.TBIonly<-coxph(Surv(tstart, tstop, Outcome) ~ TBI
                    + cluster(PTID), datatime)
summary(model.TBIonly)

model.0<-coxph(Surv(tstart, tstop, Outcome) ~ age+gender
              + cluster(PTID), datatime)
summary(model.0)

model.1<-coxph(Surv(tstart, tstop, Outcome) ~ age+gender+TBI
              + cluster(PTID), datatime)
summary(model.1)

model.2<-coxph(Surv(tstart, tstop, Outcome) ~ age+gender+TBI+Sleep+TBI*Sleep
              + cluster(PTID), datatime)
summary(model.2)

model.3<-coxph(Surv(tstart, tstop, Outcome) ~ age+gender+TBI+PTSD+TBI*PTSD
              + cluster(PTID), datatime)
summary(model.3)

model.4<-coxph(Surv(tstart, tstop, Outcome) ~ age+gender+TBI+Sleep+PTSD
              + cluster(PTID), datatime)
summary(model.4)

##Time-varying model
model.TBItdc<-coxph(Surv(tstart, tstop, Outcome) ~ age+gender+TBItdc+Sleep+PTSD
                  + cluster(PTID), datatime)
summary(model.TBItdc)

#####Example of Double-Checking/QA using “finalfit” package #####
library(finalfit)
library(tidyverse)

##supplementary analysis to have TBI as time-dependent covariate (TBItdc)
####make sure that variable is coded as categorical if it's not already
#datatime$TBItdc <- factor(datatime$TBItdc, levels=c(0, 1), labels=c("No", "Yes"))
TBItdc_D = "Surv(tstart, tstop, Outcome)"
TBItdc_E = c("TBItdc", "age", "gender")

datatime %>%
  finalfit(TBItdc_D,TBItdc_E, dependent_label_prefix = "", digits = c(3,3,4)) ->TBItdc

datatime %>%
  hr_plot(TBItdc_D,TBItdc_E, dependent_label = "CHD",

```

```

      table_text_size=4, title_text_size=12, digits = c(3,3,4),
      plot_opts=list(xlab("HR, 95% CI"), theme(axis.title = element_text(size=10)))) ->
HR_TBItdc

```

```

TBItdc_E_all = c("TBItdc", "age", "gender", "Sleep", "PTSD")

```

```

datetime %>%
  finalfit(TBItdc_D, TBItdc_E_all, dependent_label_prefix = "", digits = c(3,3,4)) -
> TBItdc_all

```

```

datetime %>%
  hr_plot(TBItdc_D, TBItdc_E_all, dependent_label = "CHD",
    table_text_size=4, title_text_size=12, digits = c(3,3,4),
    plot_opts=list(xlab("HR, 95% CI"), theme(axis.title = element_text(size=10)))) ->
HR_TBItdc_all

```

```

save(datetime,
      TBItdc_D, TBItdc_E,
      TBItdc_E_all, TBItdc,
      HR_TBItdc, TBItdc_all,
      HR_TBItdc_all,
      TBItdc_E_all_interaction,
      file="TBI as tdc.rda")

```

###Sample Codes of Generating Tables and Plots Using Knitr####

```

##Create rmd file in R and input the following

```

```

---
title: "Sample"
author: "Keen Seong Liew"
date: "2/17/2022"
output:
  word_document: default
---

```

```

````{r setup, include=FALSE}
Load data into global environment.
library(finalfit)
library(tidyverse)
library(knitr)
load("final tables and plots.rda") ##file with your dataframe, lists, and variables
````

```

```

#### Desc Table OR Clinical
````{r OR_clinical, echo=FALSE, results='asis'}
knitr::kable(OR_clinical, row.names=FALSE, align=c("l", "l", "r", "r", "r", "r"))

```

```

'''

Model Table TBI Univariate
```{r table_uni, echo=FALSE, results='asis'}
knitr::kable(table_uni, row.names=FALSE, align=c("l", "l", "r", "r", "r", "r"))
```

Model Table Demo
```{r table_demo, echo=FALSE, results='asis'}
knitr::kable(table_demo, row.names=FALSE, align=c("l", "l", "r", "r", "r", "r"))
```

HR Plot Demo
```{r , echo = FALSE, results='asis',fig.width=10}
datetime %>%
  hr_plot(dependent_demo,explanatory_demo, dependent_label = "CHD",
    table_text_size=4, title_text_size=12, digits = c(3,3,4),
    plot_opts=list(xlab("HR, 95% CI"), theme(axis.title = element_text(size=10))))
```

```