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14. ABSTRACT
The purpose of this study was to determine the agreement between the Centers for Disease Control and Prevention (CDC) definition and the clinical judgment of a board-certified neurologist based upon medical records review, and to utilize a historical prospective design in a large, well documented United States Air Force (USAF) population to determine possible performance and health decrements among USAF service members who have been diagnosed with mild traumatic brain injury (mTBI). The scope of this study includes all active duty USAF men and women who served for six or more months during October 1, 2001 through September 30, 2008. The study included 518,893 Airmen with 5,065 (or almost 1%) who meet the CDC definition of mTBI. The results of this study are important in understanding the possible adverse performance and health decrements associated with mTBI.

15. SUBJECT TERMS
Military personnel, Brain injury, Epidemiology, Neurologic disorders, Mental disorders, Social functioning, Addiction-related, Substance use

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INTRODUCTION:

Mild traumatic brain injury (mTBI) is often dismissed as a condition that dissipates, not requiring further follow-up, however there has yet to be a comprehensive study to validate the subsequent effects from mTBI that may affect United States Air Force (USAF) Airmen performance. Airmen and other military personnel with mTBI may suffer from physiological and psychological health disorders that compromise their mission readiness. A retrospective cohort study among male and female USAF enlisted and officer personnel (Airmen) was conducted to determine 1) the reliability and validity of using the CDC's ICD-9-CM codes (Administrative Data Definition) to identify individuals with an mTBI according to the CDC's Clinical Record Data Definition from medical records located at Wright-Patterson Medical Center (WPMC), 2) the short- and long-term adverse health outcomes associated with mTBI, and 3) the risk for subsequent mishaps post-mTBI.

BODY:

Background

Blast injuries are common occurrences for troops serving in the current conflicts in Iraq and Afghanistan [6]. Damage to cranial structures may account for up to 50% of these blast injuries and can involve the brain or other parts of the Central Nervous System (CNS) [6-9]. These types of injuries are generally termed traumatic brain injury (TBI), and are now a frequent diagnosis among battle-injured US service members [6, 9]. Depending on the level of severity, TBI may be associated with short-term sequelae such as headache, irritability and memory problems in mild TBI (mTBI) to coma or death in severe cases. Trauma to the brain may also cause long-term mechanical and biochemical damage that may lead to neurological diseases [9-13], psychiatric diseases [14, 15], or an increased likelihood of disability [16]. While there are several national civilian initiatives tracking the sequelae of moderate and severe TBI, less is known about mTBI and its potential impact on civilian and military populations. The objective of this research effort focuses on the varied psychiatric/mental, neurologic, and substance use/addiction-related outcomes of mTBI utilizing the vast resources of a well-documented military population.

Psychiatric/Mental Outcomes

Psychiatric sequelae of TBI appear to be significant in military populations, yet few studies have evaluated psychiatric outcomes in military populations with TBI. A recent survey concluded that "After returning from deployments to Iraq or Afghanistan, service members experience relatively high rates of mental disorders such as depression, anxiety, substance abuse, and post-traumatic stress disorder (PTSD)" [12]. In their survey of those re-deployed in Iraq or Afghanistan from 2001 to 2006, 12.2% experienced more than one mental health diagnosis. These disorders are often long-term and place a large burden on the patient and health care system. Notably, Hoge et al., surveyed 2,525 US Army soldiers 3-4 months following a one-year deployment to Iraq [10]. In this study, 4.9% and 10.3% of participants, respectively, reported injuries with loss of consciousness and injuries with altered mental status. Although soldiers with mTBI, reported poorer general health, more missed workdays and medical visits, and a high number of somatic and postconcussive symptoms than were soldiers with other injuries, only headache remained significantly associated with mTBI after adjustment for PTSD and depression.

Depression represents a significant problem following combat deployment [13], yet the relationship over time of mTBI and depression has not been delineated. Studies have reported a prevalence of major depression or depressive symptoms using Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria ranging from 24% to 59% in TBI populations [14-16]. Other studies using non-TBI controls appear to confirm these results [17, 18]. Moreover, when compared with controls, TBI patients with more medical and neurologic outcomes were shown to have higher rates of depressive symptoms [18]. Significantly, the American Neuropsychiatric Association Committee on Research has recommended additional study of the incidence, prevalence and course of depression using standardized, validated criteria [19]. They also suggest more research to describe the long-term psychosocial, functional and physical impact of depression after TBI.

Similar to depression, the relations of PTSD and anxiety disorders to mTBI has not been studied in a large cohort analyzed prospectively to characterize the time relationship between these conditions. PTSD has been regarded as one of the signature conditions of the conflicts in Iraq and Afghanistan. As noted in the MSMR 2007 Survey [12], medical encounters for PTSD at initial and subsequent visits ranked among the highest reported diagnoses of 39.3% in mental health settings and 22.2% in non-mental health settings. Multiple studies have shown the prevalence of PTSD symptoms to be from 11% to 17% in TBI populations between 6 and 12 months after the initial injury [20-22]. When considering PTSD as part of a broader anxiety syndrome, the prevalence of anxiety disorders across TBI is between 24% to 29% of cases [23, 24]. However, in well controlled studies where patients with TBI were compared with those who experienced trauma to a site other than the brain, no differences in PTSD rates were found [25-27]. Yet, the background prevalence of PTSD in non-TBI populations may be as high as 6.8% in the community and 39% in motor vehicle accident victims [28, 29]. The ANPA Committee on Research made note of the consistent limitation of small sample sizes in the current research on TBI and PTSD [19]. Moreover, given the frequency of anxiety disorders and the paucity of studies investigating the full range of these disorders in a single population, current research on anxiety disorders and TBI should include PTSD and other anxiety disorders.

Co-morbidity of anxiety and depression remain to be elucidated following mTBI. Anxiety and depressive disorders have been shown to occur together 33% to 35% of the time [30]. Studies show that approximately 44% of PTSD patients also have depression up to 4 months after the trauma [31]. The few studies that have focused on the subject have found concomitant mood and anxiety disorders to be common following TBI [31, 32]. Given the high prevalence of debilitating co-morbidity, investigation of these diagnoses in mTBI groups remains a significant gap in current literature.

The long term consequences of mTBI on sleep architecture and sleep disorders has not been delineated in a prospective study of military populations. Various studies show that sleep disturbances may occur in 30-70% of TBI patients [33]. Difficulty falling asleep or maintaining sleep is likely to exacerbate other symptoms of TBI especially pain, cognitive deficits and mood disorders. In one study, 80% of TBI patients reported changes to their sleep versus 23% of controls [34]. This study also found that more nighttime awakenings and longer sleep onset latency were reported more frequently by patients with mild injuries. In another study, 15 out of 42 mTBI patients with complaints of insomnia had circadian rhythm sleep disturbances versus 7-10% of the standard population reporting to a sleep clinic for insomnia [35]. A study across 3 university hospitals found abnormal sleep studies in 46% of TBI patients, of which 23% had obstructive sleep apnea (OSA), 11% posttraumatic hypersomnia, 7% periodic limb movements in sleep (PLMS) and 6% narcolepsy [36]. There is a need for increased knowledge about the incidence of sleep disorders among individuals with mTBI to allow improvement in the rehabilitation of these patients.

Persistent headaches may discriminate between a mild blow to the head and mTBI [37]. Studies report incidence of headaches following mTBI from 34-90% [38], and one study reported an 18-33% incidence of headaches lasting beyond one year following injury [39]. Evans further observed that the prevalence and duration of headaches were greater in those sustaining mTBI than in those with more severe injuries [38]. Chronic headaches lasting beyond 6 months may be permanent and highly disabling [39].

Neurological Outcomes

The role of head trauma and the development of neurological diseases continues to undergo intense study. Current research suggests that head trauma significantly increases the risk of neuronal changes in the brain [7, 40], as yet few studies have examined the potential association between mTBI and neurodegenerative disease in the military, particularly Alzheimer's Disease and Parkinson's Disease. Long term effects resulting in cognitive decline may increase the risk of developing neurodegenerative diseases such as Alzheimer's disease (AD) [7] and Parkinson's disease (PD) [41]. Neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) have been linked to military service [42, 43], although there have been few studies to support this observation. Also of interest, AD has become the most common neurodegenerative disease with an estimated 20 million cases worldwide and 4 million cases in the US with an estimated 13.5 million prevalent cases domestically by the year 2040 [11, 44]. While multiple studies have investigated the pathologic features of TBI [4, 5, 8, 40], few studies have examined the long term risk of AD and PD in mTBI cases. Several studies have found that neurological disorders after TBI may include the other serious disorders of dementia and place an individual at increased risk for Alzheimer's disease [4, 45] or dystonia [46, 47]. Thus, understanding the relations between TBI and neurological disease is necessary to address the needs of active duty service members, veterans and their families [48, 49].

The association between mTBI and convulsive disorders has not been established. In studies of military personnel, 32-52% of TBI cases experienced late post traumatic seizures [46, 50]. One study found seizure onset was delayed after TBI [51], and another study found an increased excess risk of seizures after mTBI of 1.95 that was marginally significant (95% confidence interval 1.0 – 2.2) [52]. Moreover, in cases of severe TBI, increased risk of late post traumatic seizures may exist up to twenty years post-TBI [50].

Endocrine Outcomes

The association between moderate to severe TBI and endocrine dysfunction is well documented in numerous studies [53-60], however, the associations with mTBI is not established. Previous studies have screened patients for endocrine abnormalities from the time between their initial injury to one year post-injury [59, 60]. Abnormalities reported include: gonadotropin deficiency, adrenal insufficiency, hypopituitarism, hypothyroidism, growth-hormone deficiency and posterior pituitary dysfunction [53, 54, 56-60].

Growth Hormone Deficiency (GHD) may be a significant link between TBI and Diabetes. GHD has been observed in 17 to 37% of TBI cases in prospective studies up to one year of follow-up [54, 60]. GHD produces a state nearly identical to metabolic syndrome [61, 62]. In both the GHD state and metabolic syndrome, two of the most common findings are abdominal obesity and insulin resistance [61, 62]. Increased abdominal obesity and insulin resistance are two known major risk factors for development of Type 2 Diabetes Mellitus (DM) [62, 63]. The potential association between GHD and subsequent development of DM warrants further examination given the morbidities associated with DM. This study will compare the risk of DM in those with and without an mTBI in the study population. Although this examination of a possible association between mTBI and DM will not yield a result that would establish a direct causal relationship, it may provide evidence of the need for further controlled studies on this association.

Diabetes Insipidus (DI) occurring in the context of moderate to severe TBI is well established in the literature [53, 64]. However, studies focusing on the incidence of DI in mTBI has not been established. Exploration of the potential for increased incidence of DI after an mTBI is needed to consider strategies to minimize associated morbidities and further the understanding of mild brain injuries and their effect on the hypothalamo-pituitary-adrenal axis.

Symptoms of Thyroid-Stimulating Hormone (TSH) Deficiency overlap with those seen in PTSD and Post Concussion Syndrome. Thyroid-stimulating Hormone (TSH) deficiency is another common endocrine abnormality seen in up to 22% of patients after a moderate to severe TBI [54, 60]. TSH deficiency leads to central hypothyroidism which can result in fatigue, apathy, decreased strength and cognitive dysfunction, symptoms commonly observed in PTSD [54]. Recognizing a possible association between mTBI and TSH deficiency is one focus of this study.

Subsequent Risk For Injury

The long term impact of mTBI on US service members' risk for subsequent mishaps post-mTBI has not been established. Although it is important to describe long-term medical sequelae associated with mTBI, it is as important to look at other indicators associated with the public health burden of TBI, including risk for further injury. These are important topics that have received little attention within the military, although one report estimated that at least 5.3 million Americans had long-term or lifelong need for help to perform activities of daily living as a result of a TBI [65] It has also been estimated that TBI causes $642 million in lost wages, $96 million in lost income taxes, and $353 million in increased public assistance [66]. Using historical prospective methods, this study will assess the risk of subsequent injury among those with mTBI compared to another group with injuries of similar severity, but without involvement of the head.

1. Wright-Patterson Medical Center (WPMC) Validation Sub-Study of CDC's Administrative Data Definition of mTBI

Methods

Medical records for male and female US Air Force enlisted and officer personnel (Airmen) stationed at Wright-Patterson AFB (WPAFB) were reviewed to determine the feasibility for using the Centers for Disease Control and Prevention (CDC) Administrative Data Definition of mild Traumatic Brain Injury (mTBI) for Surveillance or Research [67]. Electronic outpatient medical diagnoses consistent with the CDC mTBI definition were compared to a similar number of electronic outpatient medical record diagnoses consisting of other head injuries that did not meet the CDC mTBI definition. Medical record information was copied, de-identified and given to a board certified neurologist who reviewed the blinded documents for evidence to support a diagnosis consistent with mTBI. The kappa statistic [68] was then used to determine the agreement between the electronic International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM codes [69] that were consistent with the CDC mTBI definition and evidence consistent with an mTBI in the medical record, as determined by the neurologist.

CDC's Clinical Record Data Definition was used as the basis for establishing true disease [67]. According to the CDC's Clinical Record Data Definition, a case of mTBI is defined as having any one of the following characteristics appearing in a medical record:

- Any period of transient confusion, disorientation, or impaired consciousness
- Any period of dysfunction of memory around the time of injury
- Observed signs of other neurological or neuropsychological dysfunction, including:
    - Seizures acutely following head injury
    - Symptoms including headache, dizziness, irritability, fatigue, or poor

concentration when identified soon after injury

- Any period of loss of consciousness lasting 30 minutes or less
- Glasgow Coma Scale score between 13 and 15 assigned at the time of first medical evaluation
- Abbreviated Injury Severity Scale score of 2 for the head region

The Centers' for Disease Control and Prevention (CDC's) Administrative Data Definition of mTBI for Surveillance or Research is comprised of a listing of International Classification of Diseases, 9th Revision, Clinical Modifications (ICD-9-CM) codes (Table 1).

Table 1. CDC Administrative Data Definition of mTBI for Surveillance or Research

Title	**ICD-9-CM Codes**
Fracture of the Skull	
Closed without mention of intracranial injury	800.0, 800.00, 800.01, 800.02, 800.06, 800.09
Open without mention of intracranial injury	800.5, 800.50, 800.51, 800.52, 800.56, 800.59
Fracture of base of skull	801.0, 801.00, 801.01, 801.02, 801.06, 801.09
Open without mention of intracranial injury	801.5, 801.50, 801.51, 801.52, 801.56, 801.59
Closed without mention of intracranial injury	803.0, 803.00, 803.01, 803.02, 803.06, 803.09
Open without mention of intracranial injury	803.5, 803.50, 803.51, 803.52, 803.56, 803.59
Closed without mention of intracranial injury	804.0, 804.00, 804.01, 804.02, 804.06, 804.09
Open without mention of intracranial injury	804.5, 804.50, 804.51, 804.52, 804.56, 804.59
Intracranial Injury, Excluding those with Skull Fracture	
With no loss of consciousness	850.0, 850.00, 850.01, 850.02, 850.06, 850.09
With brief loss of consciousness	850.1, 850.10, 850.11, 850.12, 850.16, 850.19
With loss of consciousness of unspecified duration	850.5, 850.50, 850.51, 850.52, 850.56, 850.59
Concussion, unspecified	850.9, 850.90, 850.91, 850.92, 850.96, 850.99
Without mention of open intracranial injury	854.0, 854.01, 854.02, 854.06, 854.09
Certain Traumatic Complications and Unspecified Injuries	
Head injury unspecified	959.01*

*Based on this study, this code was removed from consideration.

This study was conducted in accordance with all applicable federal regulations governing the protection of human subjects in research as approved by Air Force Research Laboratory/Wright Site Institutional Review Board (Protocol F-WR-2009-0066-H).

Population and Data Sources

Electronic data were obtained through data use agreements with the Defense Manpower Data Center (DMDC) and TRICARE Management Activity (TMA). US Air Force (USAF) personnel data were obtained from DMDC and used to identify Airmen currently stationed at Wright-Patterson Air Force Base (WPAFB). These data were linked with electronic medical records maintained by TMA's Military Health System (MHS). These combined data were used to identify a study population whose paper medical records were currently located at Wright-

Patterson Medical Center (WPMC). Copies of de-identified records were obtained from WPMC, and only ICD-9-CM diagnoses found in the medical records on the date of an individual's original visit were used, follow-up visits were not considered.

Record Validation Methods

A preliminary assessment of 30 records was performed by a flight surgeon with the Vulnerability Analysis Branch of the Air Force Research Laboratory, WPAFB and a board-certified staff neurologist assigned to the 88th Medical Group (88 MDOS), WPAFB. Findings from the preliminary assessment identified ICD-9-CM code 959.01 as having poor agreement for a diagnosis of mTBI and were removed as possible mTBI codes from all analyses in the primary assessment.

Researchers identified two mTBI-related injury groups for this study. The first group contained medical records coded consistent with the CDC's ICD-9-CM definition of mTBI [67] and planned to be used to identify mTBI cases for all phases of this study. Individuals included in the control group were those who had sustained an injury to the head identified as "head trauma without mild traumatic brain injury". A final total of 60 WPMC medical records met requirements and were available (Table 2). A board-certified neurologist blindly reviewed these 60 records to determine if the medical encounter met criteria for an mTBI diagnosis.

Statistical Analyses

For both the preliminary and final assessments, Cohen's kappa statistic [70] was used to assess agreement between the neurologist's judgment of whether or not the medical encounter met the CDC's Clinical Record Data Definition and the CDC's definition comprised of ICD-9-CM codes for mTBI. The specific negative agreement (NA) and the specific positive agreement (PA) of these measures were calculated using standard formulas [70] which are closely analogous to sensitivity and specificity [71]. All statistical analyses were conducted using SAS® (Version 9.2, SAS Institute, Inc., Cary, North Carolina).

Results

Records were not considered for analysis if they were documented as 959.01, were unreadable, incomplete, or were follow-ups to the original visit. Entry criteria to the study were fulfilled by 60 Airmen whose original paper medical records were located at WPMC. Of these available records, 26 had been coded in electronic data as having the CDC's ICD-9-CM definition of mTBI and 34 medical records had been coded as having an injury to the head identified as "head trauma without mild traumatic brain injury". In univariate analysis, Airmen coded with having suffered "head trauma without mTBI" were more likely to be male, born prior to 1976, white, enlisted, operational career field, and have high school or less education when compared to the mTBI group (Table 2). Using Pearson's Chi-square test, no demographic or military characteristics between the two groups displayed statistically significant differences at $\alpha = 0.05$.

Data showed that a moderate level of agreement was achieved with a Cohen's Kappa statistic of $k = 0.51$. This kappa was statistically significant with a 95% confidence interval of (0.29 – 0.72). Table 3 documents the concordance between neurologist review and specific ICD-9-CM codes. When calculated separately, specific negative agreement (NA) was superior to specific positive agreement (PA). These proportions were PA = 0.68 (95% CI, 0.52 - 0.84) and NA = 0.82 (95% CI, 0.72 - 0.91), implying that between electronic data and neurologist review, agreement was higher when identifying records not coded as mTBI.

Table 2. Demographic and Military Characteristics

Characteristic*	CDC mTBI n (%)	Other head injury n (%)
Gender		
Female	8 (30.77)	6 (17.65)
Male	18 (69.23)	28 (82.35)
Race/Ethnicity		
White (non-Hispanic)	18 (69.23)	26 (76.47)
Black (non-Hispanic)	2 (7.69)	5 (14.71)
Asian or Pacific Islander	0 (0.00)	1 (2.94)
Other/Unknown	6 (23.08)	2 (5.88)
Birth Year		
Before 1965	1 (3.85)	6 (17.65)
1966 – 1975	7 (26.92)	10 (29.41)
After 1976	17 (65.38)	16 (47.06)
Unknown	1 (3.85)	2 (5.88)
Marital Status		
Married	10 (38.46)	18 (52.94)
Not Married	12 (46.15)	14 (41.18)
Unknown	4 (15.38)	2 (5.88)
Education		
High School or Less	11 (42.31)	16 (47.06)
Some College/Bachelor's	8 (30.77)	13 (38.24)
Advanced Degree	2 (7.69)	2 (5.88)
Unknown	5 (19.23)	3 (8.82)
Rank		
Enlisted	15 (57.69)	24 (70.59)
Officer	11 (42.31)	10 (29.41)
Career Field		
Operations	2 (7.69)	5 (14.71)
Logistics/Maintenance	2 (7.69)	5 (14.71)
Support	2 (7.69)	4 (11.76)
Medical	8 (30.77)	12 (35.29)
Professional/Acquisitions/Finance	7 (26.92)	3 (8.82)
Other/Unknown	5 (19.23)	5 (14.71)

Abbreviations: CDC, Centers for Disease Control and Prevention; mTBI, mild traumatic brain injury.
*Differences were not statistically significant (Pearson chi-square test of association, $\alpha = 0.05$).

The results of the neurologist review of the 60 records (using a response of "yes" or "no") to assess the agreement of the CDC's ICD-9-CM codes [69] to identify an mTBI according to the

CDC's Clinical Record Data Definition is provided in Table 3. As seen in Table 3, most of the disagreement occurs for ICD-9-CM codes 850.0 and 850.9.

However, electronic coding of mTBI symptomatology was not always consistent with paper medical record documentation, raising possible inconsistencies regarding what coding recommendations are being followed. According to the CDC, to be classified as an mTBI, an individual must experience one or more of the following: post-traumatic amnesia (PTA), loss of consciousness (LOC) lasting under 30 minutes, or a mental status change such as being noticeably "dazed", "disoriented", or "slow to respond". Examination of de-identified medical records showed that out of the 26 records coded as having an mTBI in electronic data, six of these records (23%) had no indications of PTA, LOC or mental status change, meaning they would not meet the CDC Administrative Data Definition of mTBI.

Table 3. Concordance between Neurologist and Outpatient ICD-9-CM Codes

	Concordance (Neurologist / ICD-9-CM)			
ICD-9-CM Code	+/+ n (%)*	+/- n (%)*	-/+ n (%)*	-/- n (%)*
Meets CDC mTBI criteria				
850.0‡	4 (40.0%)	0 (0.0%)	6 (60.0%)	0 (0.0%)
850.1‡	2 (100 %)	0 (0.0%)	0 (0.0%)	0 (0.0%)
850.11‡	1 (100 %)	0 (0.0%)	0 (0.0%)	0 (0.0%)
850.5‡	5 (83.3%)	0 (0.0%)	1 (16.7%)	0 (0.0%)
850.9‡	2 (33.3%)	0 (0.0%)	4 (67.7%)	0 (0.0%)
854.09†	1 (100 %)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Meets head injury without mTBI criteria				
802.0†	0 (0.0%)	2 (16.7%)	0 (0.0%)	10 (83.3%)
802.6†	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100 %)
802.8†	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100 %)
850.2‡	0 (0.0%)	1 (100 %)	0 (0.0%)	0 (0.0%)
853.00†	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100 %)
873.0†	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (100 %)
Total	15 (25.0%)	3 (5.0%)	11 (18.3%)	31 (51.7%)

*Row percent.

2. Adverse Medical and Mental Health Outcomes of US Air Force Airmen Following Mild Traumatic Brain Injury

Methods

A retrospective cohort study among male and female US Air Force enlisted and officer personnel (Airmen) was conducted to determine any long-term adverse health outcomes associated with mTBI. This study utilized the Centers for Disease Control and Prevention (CDC) Administrative Data Definition of mTBI for Surveillance or Research [67], which is comprised of a listing of International Classification of Diseases, 9th Revision, Clinical Modification [68] (ICD-9-CM) codes considered by an expert panel to be indicative of mTBI. ICD-9-CM diagnoses for mTBI found in electronic health records were used to identify mTBI cases. Cases of mTBI were compared to similar Airmen without mTBI to determine the association between mTBI and subsequent medical outcomes associated with mental, neurological/post-concussion syndrome, and substance use/impulse control/addiction-related disorders. This study was conducted in accordance with all applicable federal regulations governing the protection of human subjects in research as approved by Air Force Research Laboratory/Wright Site Institutional Review Board (Protocol F-WR-2009-0066-H).

Population and Data Sources

Electronic personnel data were obtained from the Defense Manpower Data Center (DMDC). Demographic and military specific information collected included gender, birth date, highest achieved education level, marital status, race/ethnicity, military rank, deployment records, primary career field, and a personal identifier (Table 4).

Electronic medical record data, to include hospitalization and outpatient records, were obtained from the Military Health System, which is maintained by the TRICARE Management Activity and then matched to study participants' demographic and military specific data by personal identifiers. Datasets developed for this study were evaluated for post-mTBI diagnoses of the specified disorders (Table 5).

For this analysis, Airmen on active duty for at least 180 days between October 1, 2001 and September 30, 2008 were selected. To increase the probability of only including incident cases, individuals with a history of mTBI or other head injuries two years prior to entering the study were removed from consideration, resulting in 518,958 Airmen who met eligibility criteria.

Two non-mTBI comparison groups were used. The first comparison group included the entire study population without an mTBI during the study period, and with no previous history of mTBI, or other head injuries, within the two years prior to study entry. The second comparison group included a non-mTBI injured group, which was a sub-set of the original comparison group; also without an mTBI or other head injuries two years prior to entering the study. To reduce medical surveillance bias, the Substance Use/Addiction-Related Disorders are only compared to the injury cohort. Individuals included in the injury comparison group were those who had sustained an injury to the torso, spinal cord, abdomen, pelvis, digestive tract, or genitourinary tract (ICD-9-CM 805-810, 860-870, 900-905, 922-923, 926-927, and 933-959).

Table 4. Active Duty US Air Force Airmen Demographics 10/1/2001 – 9/30/2008*

Characteristic	CDC mTBI Definition n = 5,065 No.	(%)	Injury Comparison n = 44,733 No.	(%)	Full Comparison n = 513,893 No.	(%)
Gender						
Male	4,158	(82.09)	33,674	(75.28)	409,076	(79.60)
Female	907	(17.91)	11,059	(24.72)	104,817	(20.40)
Race/Ethnicity						
White (non-Hispanic)	3,802	(75.06)	32,772	(73.26)	369,788	(71.96)
Black (non-Hispanic)	588	(11.61)	6,162	(13.78)	78,522	(15.28)
Asian and Pacific Islander	126	(2.49)	1,269	(2.84)	14,811	(2.88)
Hispanic	329	(6.50)	2,604	(5.82)	27,702	(5.39)
Native American	35	(0.69)	368	(0.82)	3,177	(0.62)
Other/Unknown	185	(3.65)	1,558	(3.48)	19,893	(3.87)
Birth year						
Before 1965	340	(6.71)	6,259	(13.99)	89,223	(17.36)
1966-1975	795	(15.70)	10,020	(22.40)	109,131	(21.24)
1976 or later	3,930	(77.59)	28,454	(63.61)	315,539	(61.40)
Marital Status						
Currently married	1,481	(29.24)	18,588	(41.55)	221,192	(43.04)
Never married	3,418	(67.48)	24,228	(54.16)	271,182	(52.77)
No longer married	166	(3.28)	1,917	(4.29)	21,519	(4.19)
Education						
High School or less	4,536	(89.56)	36,277	(81.10)	381,900	(74.32)
Some College/ Bachelor's	364	(7.19)	5,614	(12.55)	86,775	(16.89)
Advanced degree	150	(2.96)	2,699	(6.03)	42,304	(8.23)
Unknown	15	(0.30)	143	(0.32)	2,914	(0.57)
Rank						
Enlisted	4,814	(95.04)	40,307	(90.11)	434,196	(84.49)
Officer	251	(4.96)	4,426	(9.89)	79,697	(15.51)
Deployed						
Never	2,526	(49.87)	22,163	(49.55)	287,340	(55.91)
Once	1,400	(27.64)	12,274	(27.44)	129,080	(25.12)
Twice	661	(13.05)	5,971	(13.35)	56,985	(11.09)
More than twice	478	(9.44)	4,325	(9.67)	40,488	(7.88)
Career Field						
Operations	774	(15.28)	8,196	(18.32)	101,729	(19.80)
Logistics/Maintenance	1,940	(38.30)	14,724	(32.92)	157,834	(30.71)
Support	1,466	(28.94)	12,596	(28.16)	141,039	(27.45)
Medical	381	(7.52)	4,116	(9.20)	46,382	(9.03)
Professional/Acquisitions/ Finance	112	(2.21)	1,350	(3.02)	19,698	(3.83)
Other/ Unknown	392	(7.74)	3,751	(8.39)	47,211	(9.19)

Abbreviations: US, United States; CDC, Center for Disease Control and Prevention; mTBI, mild traumatic brain injury.

* Airmen included were on active duty for six or more months during this time period.

All differences were tested with the Pearson chi-square test of association and are statistically significant at $\alpha = 0.05$.

Medical Outcome Methods

A list of ICD-9-CM codes for medical outcomes of interest was identified for each population member (Table 5). Participants with a previous history of a specified outcome were eliminated from the analysis of that outcome, to ensure proper temporal relationship. After investigation of population characteristics, Cox proportional hazards analyses were performed to assess the significance of associations between mTBI and the specified health outcomes while adjusting for variables in the model and accounting for differences in person-time contributed by study members.

Each of the ICD-9-CM categories was investigated separately to calculate hazard ratios among those with a diagnosis in each category. For each individual, person-time began on either October 1, 2001, the date they entered active duty, or the date at which they were diagnosed with mTBI or injury, whichever occurred later. Person-time ended when they left active duty, developed the outcome of interest, or at the end of the study (September 30, 2008), whichever occurred first. If an individual suffered an mTBI or other head injury following a bodily injury, person-time ended the day before the subsequent event. All Cox proportional hazards models were adjusted for gender, marital status, race/ethnicity, date of birth category, deployment status, education level, rank, and career field. In addition, the neurological disorders were adjusted for PTSD and depression because of the comorbidity of these outcomes with post-concussion syndrome (PCS). No significant interactions or multicollinearity were detected among any independent variables in these models.

To study the association between mTBI and the outcomes of interest, post exposure time was divided into three time periods: 2-30 days, 31-179 days, and 180 days or more. We then identified the time interval in which the outcome of interest was first identified in the electronic data and conducted stratified analyses based upon the three time intervals. To clarify, the first occurrence of each outcome was used; therefore individuals in the subsequent categories were not previously diagnosed with that outcome in the preceding category(s). Individuals who left the study during the first two time periods were removed from analysis for the succeeding time period(s). Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to compare the risk of the specified outcomes between the mTBI populations and the two non-mTBI populations in the case of the mental and neurological system disorders but only with the injury cohort for the substance use/addiction-related disorders.

Statistical Analyses

Descriptive demographic and military specific data were analyzed using frequency distributions and Pearson's Chi-Squared tests to determine statistical significance and univariate differences. Cox proportional hazards models were used in the multivariate analysis. All statistical analyses were conducted using SAS® (Version 9.2, SAS Institute, Inc., Cary, North Carolina).

Table 5. ICD-9-CM codes used in analysis

Description	**Code**
Post-concussion syndrome	310.2
Cognitive Disorders	
Memory loss and amnesia	294.0, 437.7, 780.93
Cognitive disorder NOS	294.9
ADD/ADHD	314.00, 314.01
Schizophrenia and other psychotic disorders	293.81, 293.82, 295.10-295.45, 295.60-295.75, 295.90-295.95, 297.1, 297.3, 298.8, 298.9
Sleep disorders	307.41-307.42, 307.45, 307.46-307.47, 347.00-347.01, 780.59
Mood Disorders	
Unipolar Depression	296.30-296.36, 300.4, 311
Unspecified/episodic mood disorders	293.83, 296.90-296.99
Bipolar and cyclothymic disorders	296.00-296.06, 296.40-296.89, 301.13
Anxiety Disorders	
General anxiety or anxiety NOS	293.84, 300.00-300.09
Panic/Phobic disorders	300.20-300.29
Obsessive-compulsive disorders	300.3, 301.4
Acute stress disorder	308.3
Post-traumatic stress disorder (PTSD)	309.81
Adjustment reactions	309.0, 309.1, 309.24, 309.28, 309.3, 309.4, 309.82-309.9
Diseases of the Nervous System and Sense Organs	
Epilepsy and recurrent seizures	345.00-345.51, 345.70-345.91
Headaches	307.81, 784.0
Migraines	346.00-346.91
Vertigo/dizziness	386.10-386.11, 438.85, 780.4
Peripheral neuropathies	337.0, 337.1
Pain Disorders	
Acute	338.11, 338.19
Chronic	338.21, 338.29
Chronic pain syndrome	338.4
Generalized pain	780.96
Substance Use Disorders/Addiction-Related	
Alcohol dependence	303.90
Drug dependence	304.00-304.93
Nondependent abuse of drugs (*includes alcohol*)	305.20-305.83
Nicotine dependence	305.10-305.13
Opioid dependence/abuse	304.00-304.03, 305.50-305.53
Caffeine-related disorders	305.90-305.93
Amphetamine dependence/abuse	304.40-304.43, 305.70-305.73
Impulse Control Disorders	
Impulse control disorder, unspecified	312.30
Pathological gambling disorder	312.31
Intermittent explosive disorder	312.34

Univariate Results

This study included a total of 518,958 active duty Airmen of which 5,065 (or just under 1%) suffered from an mTBI as defined by the CDC's Administrative Data Definition. Along with the mTBI group, there were two comparison groups: 1) the full comparison cohort (513,893) and 2) the injury comparison cohort (44,733). In the univariate analysis, the mTBI group was more likely to be male, white, born after 1975, never married, high school or less education level, enlisted, and worked in the logistics/maintenance career field (Table 2). Moreover, except for gender, the proportions are more similar between the mTBI group and the injury group than the mTBI and the full cohort group. All demographic and military characteristics displayed statistically significant differences of $p < 0.001$ using Pearson's Chi-square test (Table 4).

Multivariate Results – Mental Disorders

There were several mental disorder outcomes within the first 30 days post exposure time in which the percentages of the outcomes within the full cohort were not sufficient to generate a hazard ratio (HR) or 95% confidence interval (CI). However, Airmen with an mTBI were at increased risk for all the remaining outcomes that were sufficient to generate a HR and 95% CI when compared to the full cohort across all three time periods. The smallest HR being for "adjustment reaction" in which Airmen with an mTBI were 1.5 times more likely to be diagnosed with this outcome than Airmen from the full cohort at more than 180 days (Table 6, Figure 1). The largest HR being for "unipolar depression" in which Airmen with an mTBI were over 315 times more likely (large CI may indicate estimate somewhat unstable) to be diagnosed with this outcome than Airmen from the full cohort during the first 30 days post exposure (Table 6, Figure 1). These results indicate that the outcomes were not merely short-term, temporary disorders, but lasting past 180 days post mTBI when compared to the full cohort.

Our attempt at a more equivalent comparison group, led to the injury cohort. Although more comparable, there were still a number of statistically significant HRs in the within 30 days, between 30-180 days, and ≥180 days post mTBI exposure periods. The most notable of these are the "cognitive disorder not otherwise specified" which is still more than 10 times more likely for Airmen in the mTBI group when compared to Airmen in the injury cohort group (Table 6, Figure 2). In addition, "memory loss and amnesia", "unipolar depression", "bipolar and cyclothymic disorders", and "PTSD" are still significant past 180 days post exposure time. Again suggesting that the effects of mTBI on mental disorders are not just short term problems, but lasting 6 months and longer.

Table 6. Mental Disorders Hazard Ratios by Time Period

Category*	mTBI n = 5,065 n (%)	Full Cohort n = 513,893 HR (95% CI)	Injury Cohort n = 44,733 HR (95% CI)
1-30 days post exposure			
Cognitive Disorders			
Memory loss and amnesia	37 (0.73)	§	55.88 (23.34 – 133.78)†
Cognitive disorder NOS	25 (0.49)	§	85.17 (25.39 – 285.69)†
ADD/ADHD	6 (0.12)	13.24 (5.59 – 31.35)†	2.00 (1.21 – 3.33)†
Schizophrenia	6 (0.12)	§	7.08 (2.35 – 21.31)†
Mood Disorders			
Unipolar Depression	70 (1.38)	315.27 (77.10 – 1289.14)†	2.03 (1.56 – 2.64)†
Unspecified/episodic mood disorders	7 (0.14)	§	3.76 (1.50 – 9.41)†
Bipolar and cyclothymic disorders	5 (0.10)	§	2.36 (0.86 – 6.46)
Anxiety Disorders			
General anxiety or anxiety NOS	26 (0.51)	112.45 (26.50 – 477.19)†	1.88 (1.23 – 2.89)†
Panic/Phobic disorders	2 (0.04)	§	1.10 (0.25 – 4.88)
Obsessive-compulsive disorders	0 (0.00)	§	§
Acute Stress disorder	8 (0.16)	29.28 (13.27 – 64.62)†	7.02 (2.69 – 18.34)†
PTSD	6 (0.12)	§	2.86 (1.76 – 4.63)†
Adjustment reaction	50 (0.99)	6.05 (4.54 – 8.05)†	1.65 (1.21 – 2.24)†
31 - 179 days post exposure			
Cognitive Disorders			
Memory loss and amnesia	32 (0.63)	175.74 (101.96 – 302.93)†	12.30 (7.17 – 21.11)†
Cognitive disorder NOS	38 (0.75)	§	29.84 (15.12 – 58.92)†
ADD/ADHD	16 (0.32)	4.43 (2.68 – 7.32)†	1.13 (0.72 – 1.78)
Schizophrenia	15 (0.30)	72.86 (16.44 – 322.91)†	4.46 (2.35 – 8.46)†
Mood Disorders			
Unipolar Depression	146 (2.88)	17.69 (13.42 – 23.32)†	1.70 (1.42 – 2.03)†
Unspecified/episodic mood disorders	11 (0.22)	52.86 (11.47 – 243.50)†	1.82 (0.94 – 3.52)
Bipolar and cyclothymic disorders	12 (0.24)	26.41 (8.43 – 82.70)†	1.54 (0.83 – 2.88)
Anxiety Disorders			
General anxiety or anxiety NOS	60 (1.18)	12.87 (8.66 – 19.14)†	1.22 (0.93 – 1.60)
Panic/Phobic disorders	8 (0.16)	24.81 (6.50 – 94.75)†	1.31 (0.62 – 2.76)
Obsessive-compulsive disorders	1 (0.02)	9.74 (0.61 – 156.34)	0.35 (0.05 – 2.60)
Acute Stress disorder	11 (0.22)	4.55 (2.48 – 8.33)†	2.15 (1.11 – 4.17)†
PTSD	28 (0.55)	26.66 (12.87 – 55.21)†	2.65 (1.82 – 3.88)†
Adjustment reaction	152 (0.30)	3.09 (2.63 – 3.64)†	1.51 (1.27 – 1.80)†
≥ 180 days post exposure			
Cognitive Disorders			
Memory loss and amnesia	49 (0.97)	8.91 (6.68 – 11.89)†	4.00 (2.85 – 5.63)†
Cognitive disorder NOS	31 (0.61)	14.96 (9.13 – 24.52)†	10.75 (6.39 – 18.09)†
ADD/ADHD	46 (0.89)	1.65 (1.24 – 2.21)†	1.16 (0.86 – 1.58)
Schizophrenia	14 (0.28)	2.46 (1.39 – 4.34)†	1.58 (0.89 – 2.82)
Mood Disorders			
Unipolar Depression	312 (6.16)	2.07 (1.84 – 2.32)†	1.21 (1.07 – 1.36)†
Unspecified/episodic mood disorders	29 (0.57)	2.29 (1.55 – 3.40)†	1.33 (0.90 – 1.98)
Bipolar and cyclothymic disorders	40 (0.79)	2.73 (1.95 – 3.82)†	1.57 (1.12 – 2.21)†

Anxiety Disorders			
General anxiety or anxiety NOS	228 (4.50)	2.24 (1.95 – 2.57)†	1.12 (0.97 – 1.28)
Panic/Phobic disorders	24 (0.47)	1.69 (1.11 – 2.58)†	0.90 (0.59 – 1.37)
Obsessive-compulsive disorders	17 (0.34)	3.20 (1.89 – 5.40)†	1.68 (0.99 – 2.84)
Acute Stress disorder	27 (0.53)	2.22 (1.52 – 3.25)†	1.40 (0.93 – 2.11)
PTSD	59 (1.16)	2.76 (2.10 – 3.65)†	1.35 (1.03 – 1.76)†
Adjustment reaction	333 (6.57)	1.50 (1.35 – 1.67)†	1.11 (0.99 – 1.24)

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; NOS, not otherwise specified; ADD, Attention deficit disorder; ADHD, attention deficit hyperactivity disorder; NOS, not otherwise specified; PTSD, post-traumatic stress disorder.

* Adjusted for gender, marital status, race/ethnicity, birth year, deployment, education, rank, and career field.

† Differences are statistically significant at α = 0.05.

§ Percentage of outcome in comparison population was not sufficient to generate a hazard ratio with a 95% confidence interval.

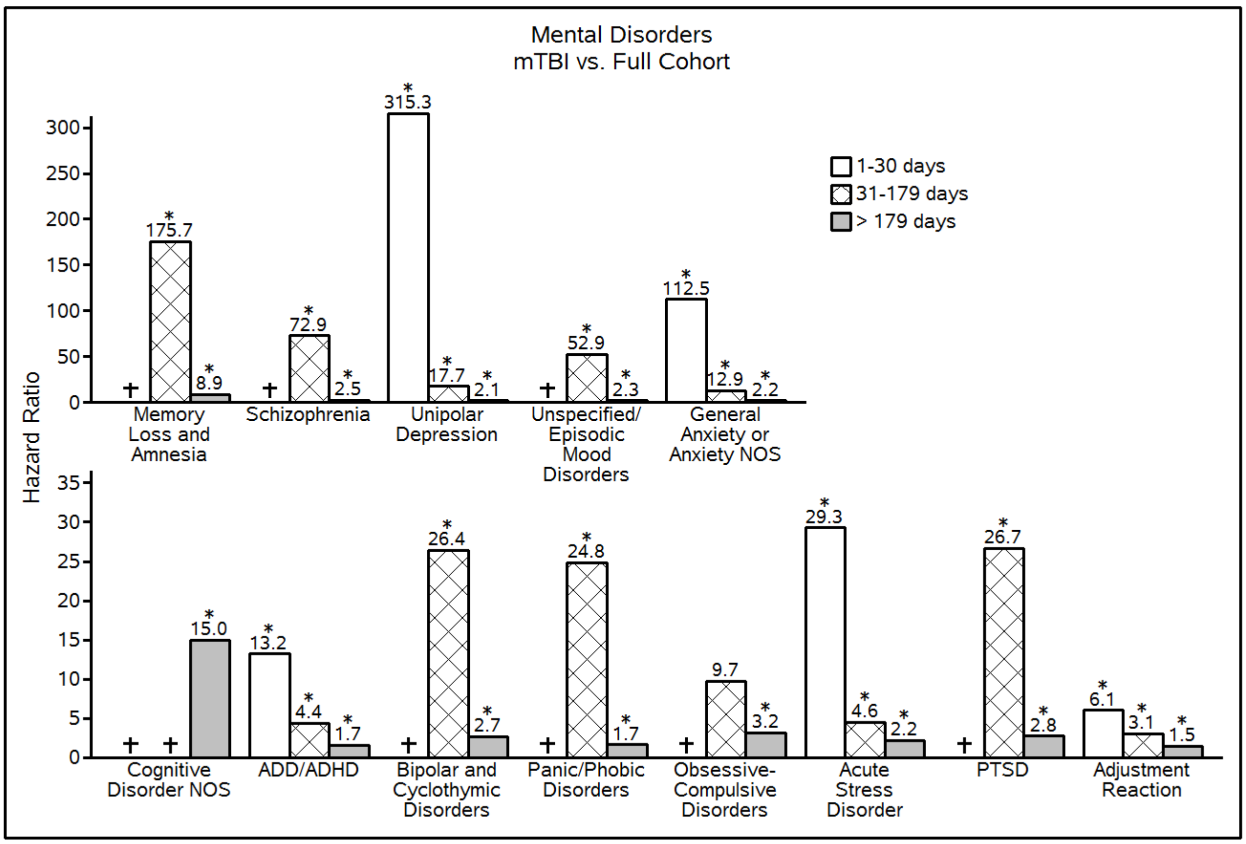

Figure 1. Plot of Adjusted Hazard Ratios for Mental Disorders (mTBI vs. Full Cohort)

Adjusted for gender, marital status, race/ethnicity, birth year, deployment, education, rank, and career field.

* Statistically significant at α = 0.05 level.

† Percentage of outcome in comparison population was not sufficient to generate a hazard ratio with a 95% confidence interval.

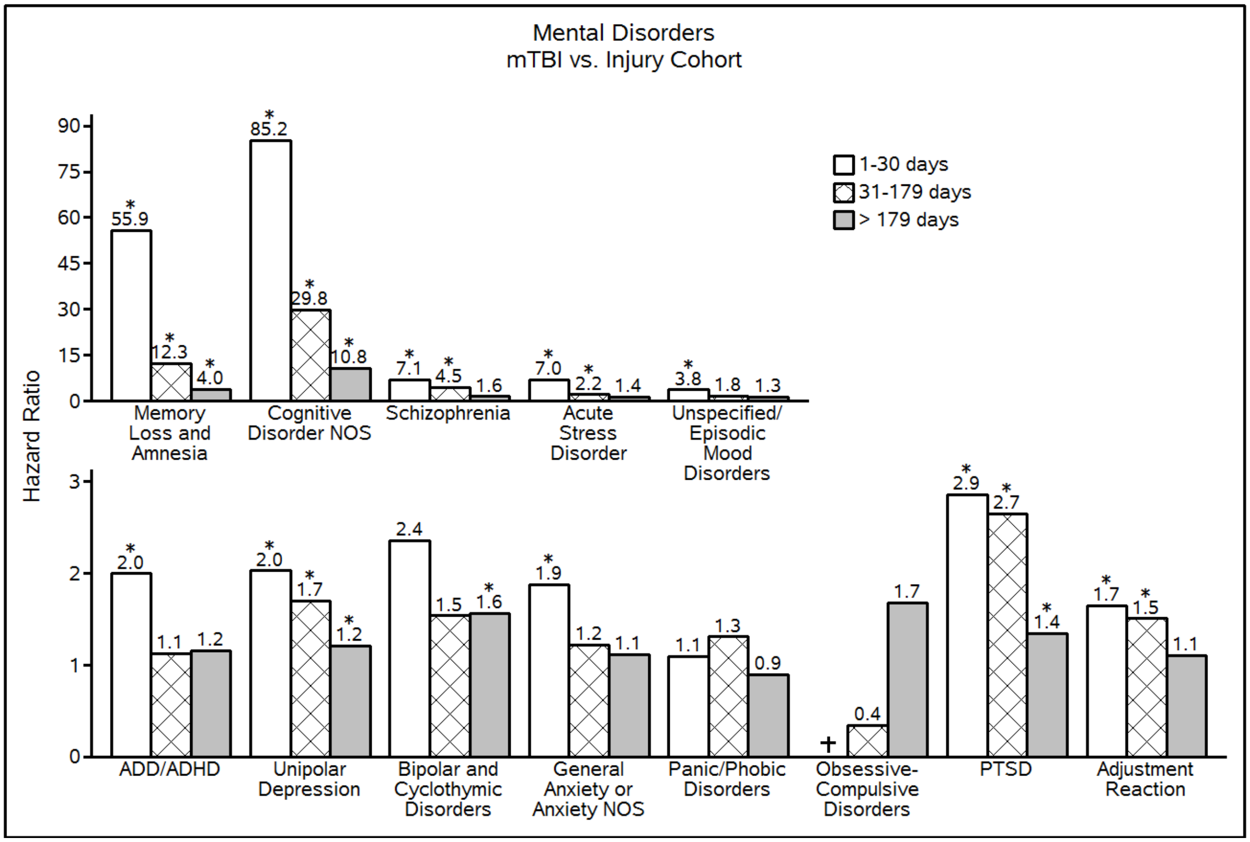

Figure 2. Plot of Adjusted Hazard Ratios for Mental Disorders (mTBI vs. Injury Cohort)
Adjusted for gender, marital status, race/ethnicity, birth year, deployment, education, rank, and career field.
* Statistically significant at $\alpha = 0.05$ level.
† Percentage of outcome in comparison population was not sufficient to generate a hazard ratio with a 95% confidence interval.

Multivariate Results – Neurological System Disorders

As with the mental disorders, there were neurological system disorder outcomes that when assessed within the full cohort and within the first 30 days post exposure, were not sufficient in number to generate a Hazard Ratio (HR) or 95% Confidence Interval (CI). Although, mTBI diagnosed Airmen were at increased risk for all the remaining outcomes that were sufficient to generate a HR and 95% CI when compared to Airmen from the full cohort across all three time periods. The smallest HR being for “headaches” in which Airmen with an mTBI were 1.65 times more likely to be diagnosed with this outcome than Airmen from the full cohort at more than 180 days time period (Table 7, Figure 3). The largest HR being for “post-concussion syndrome (PCS)” in which mTBI diagnosed Airmen were almost 310 times more likely (large CI may indicate estimate somewhat unstable) to be diagnosed with PCS than Airmen from the full cohort group between 30 days and 180 days post exposure (Table 7, Figure 3). These results indicate that the outcomes were not merely short-term, temporary disorders, but lasting past 180 days post mTBI when compared with the full cohort.

We once again made use of the more comparable injury cohort group. Although more comparable, there were still a number of statistically significant HRs in the within 30 days, between 30-180 days, and ≥180 days post mTBI. The most notable of these are the PCS and PCS-related (sleep disorders, cognitive disorder NOS and memory loss and amnesia) outcomes, all of which are still significant past 180 days post exposure time. Again suggesting that the effects of mTBI on neurological disorders are not just short term problems, but lasting 6 months and longer. It is notable that pain disorder HRs are significant in time periods greater than 30 days after exposure when compared to the injury control group. Conversely, headaches and migraines have HRs that decrease over subsequent time periods and after 6 months are not significantly different than the injury control group. These results suggest that while mTBI increases the risk of post concussive symptoms like memory loss, cognitive disorders, sleep disorders, and pain disorders more than 6 months after injury, the symptom most commonly associated with head injury, headaches, was not increased compared to non-head injured controls.

Comparing the HRs for the neurological system disorders results between the full and injury cohorts yields some interesting results as well. As might be expected, pain disorders within 30 days after mTBI were very high compared to the full cohort but not increased compared to the injury controls. In each category the HRs are higher in the full cohort comparison and lower in the injury control comparison, supporting the hypothesis that injury stress, not brain injury, contribute to symptoms following mTBI. Although these results support the presence of non-brain injury associated factors contributing to neurological system disorders, mTBI clearly increases the risk of almost all of the PCS-related outcomes and epilepsy compared to injured controls. These results indicate that even with mild TBI, injury stress alone does not account for the post concussive neurological system disorders observed.

Table 7. Neurological System Disorders Hazard Ratios by Time Period

Category*	mTBI n = 5,065 n (%)	Full Cohort n = 513,893 HR (95% CI)	Injury Cohort n = 44,733 HR (95% CI)
1-30 days post exposure			
Post-Concussion Syndrome	239 (4.72)	§	549.19 (204.15 – 1477.40)†
Memory loss /amnesia	37 (0.73)	§	55.88 (23.34 – 133.78)†
Cognitive disorder NOS	25 (0.49)	§	85.17 (25.39 – 285.69)†
Sleep disorders	14 (0.28)	12.52 (7.10 – 22.07)†	2.02 (1.12 – 3.62)†
Neurologic Disorders			
Epilepsy/recurrent seizures	12 (0.24)	127.11 (53.10 – 304.26)†	38.49 (10.61 – 139.71)†
Headaches	241 (4.76)	21.27 (18.52 – 24.42)†	11.86 (9.84 – 14.30)†
Migraines	21 (0.41)	4.76 (3.06 – 7.39)†	1.82 (1.13 – 2.93)†
Vertigo/Dizziness	75 (1.48)	14.13 (11.06 – 18.04)†	8.36 (6.07 – 11.50)†
Pain Disorders	3 (0.06)	94.01 (18.72 – 472.06)†	1.78 (0.51 – 6.23)
31-179 days post exposure			
Post-Concussion Syndrome	67 (1.32)	309.42 (191.48 – 499.99)†	123.74 (49.70 – 308.09)†
Memory loss/ amnesia	32 (0.63)	175.74 (101.96 – 302.93)†	12.30 (7.17 – 21.11)†
Cognitive disorder NOS	38 (0.75)	201.02 (116.52 – 346.80)†	29.84 (15.12 – 58.92)†
Sleep disorders	26 (0.51)	3.19 (2.16 – 4.71)†	1.08 (0.72 – 1.63)
Neurologic Disorders			
Epilepsy/recurrent seizures	20 (0.39)	17.15 (10.67 – 27.56)†	8.00 (4.31 – 14.83)†
Headaches	142 (2.80)	2.92 (2.47 – 3.45)†	1.67 (1.40 – 2.00)†
Migraines	79 (1.56)	3.89 (3.10 – 4.87)†	1.78 (1.39 – 2.27)†
Vertigo/Dizziness	71 (1.40)	3.38 (2.67 – 4.28)†	1.88 (1.45 – 2.44)†
Pain Disorders	15 (0.30)	23.04 (13.11 – 40.48)†	2.77 (1.54 – 4.97)†
≥ 180 days post exposure			
Post-Concussion Syndrome	47 (0.93)	24.74 (18.09 – 33.84)†	18.21 (10.91 – 30.39)†
Memory loss/amnesia	49 (0.97)	8.91 (6.68 – 11.89)†	4.00 (2.85 – 5.63)†
Cognitive disorder NOS	31 (0.61)	17.79 (12.27 – 25.81)†	10.75 (6.39 – 18.09)†
Sleep disorders	162 (3.20)	2.49 (2.13 – 2.91)†	1.30 (1.10 – 1.53)†
Neurologic Disorders			
Epilepsy/recurrent seizures	25 (0.49)	4.52 (3.03 – 6.73)†	3.28 (2.06 – 5.25)†
Headaches	371 (7.32)	1.65 (1.49 – 1.83)†	1.11 (0.99 – 1.23)
Migraines	211 (4.17)	1.75 (1.53 – 2.00)†	1.13 (0.98 – 1.31)
Vertigo/Dizziness	187 (3.69)	1.69 (1.46 – 1.95)†	1.05 (0.90 – 1.22)
Pain Disorders	72 (1.42)	6.52 (5.15 – 8.25)†	1.44 (1.12 – 1.85)†

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; NOS, not otherwise specified; ADD, Attention deficit disorder; ADHD, attention deficit hyperactivity disorder; NOC, not otherwise classified; NEC, not elsewhere classified

* Adjusted for gender, marital status, race/ethnicity, birth year, deployment, education, rank, career field and coincidence with PTSD and depression.

† Differences are statistically significant at $\alpha = 0.05$.

§ Percentage of outcome in comparison population was not sufficient to generate a hazard ratio with a 95% confidence interval.

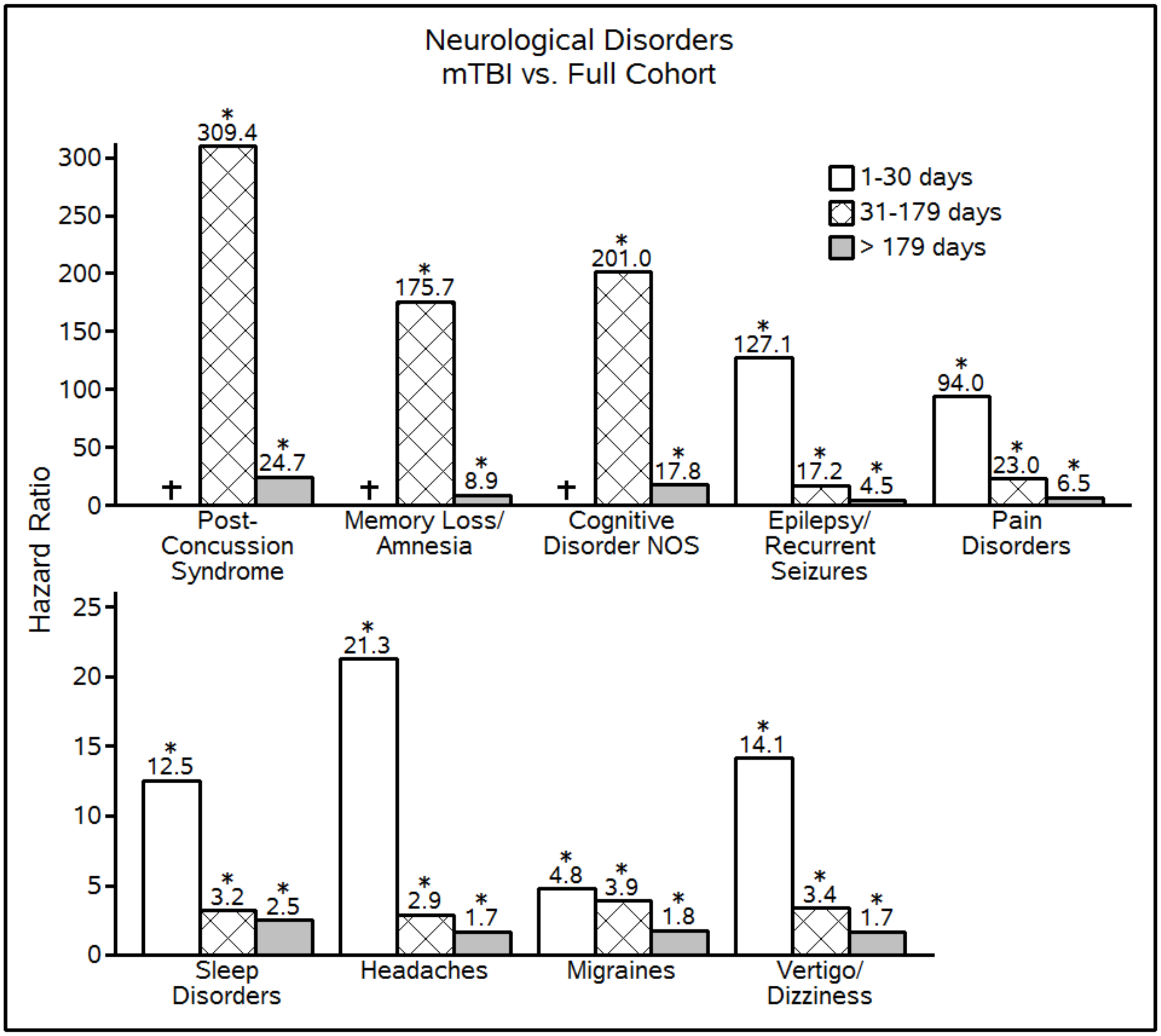

Figure 3. Plot of Adjusted Hazard Ratios for Neurological Disorders (mTBI vs. Full Cohort)
Adjusted for gender, marital status, race/ethnicity, birth year, deployment, education, rank, career field and coincidence with PTSD and depression.
* Statistically significant at α = 0.05 level.
† Percentage of outcome in comparison population was not sufficient to generate a hazard ratio with a 95% confidence interval.

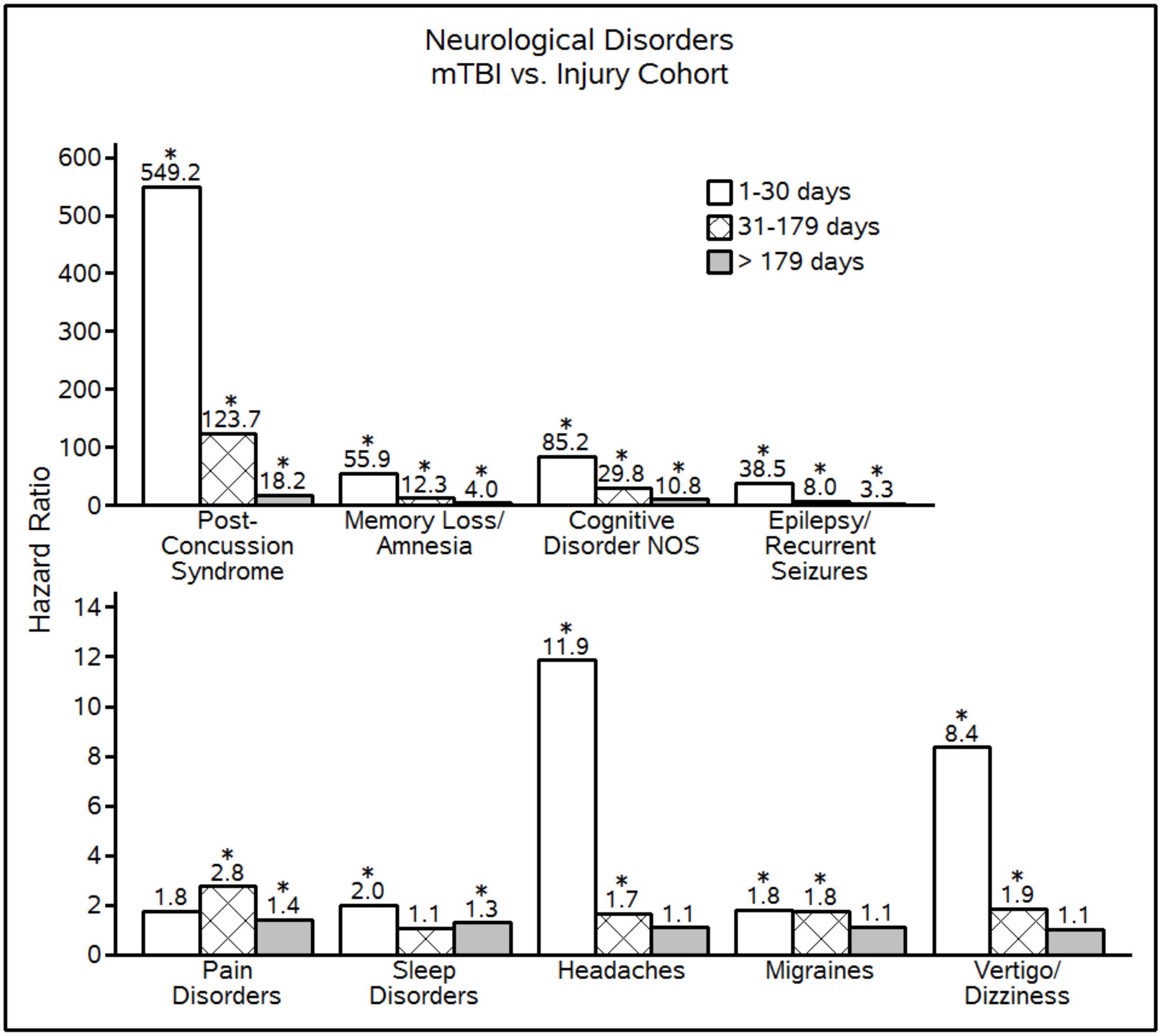

Figure 4. Plot of Adjusted Hazard Ratios for Neurological Disorders (mTBI vs. Injury Cohort)
Adjusted for gender, marital status, race/ethnicity, birth year, deployment, education, rank, career field and coincidence with PTSD and depression.
* Statistically significant at $\alpha = 0.05$ level.

Multivariate Results – Substance Use/Addiction-Related Disorders

As with the mental and neurological disorders, there were substance use/addition-related disorder outcomes that when assessed and within the first 180 days post exposure, were not sufficient in number to generate a hazard ratio (HR) or 95% confidence interval (CI). In general, frequencies of these outcomes are believed to be underreported. As previously mentioned, the mTBI group was only compared to the injury cohort group due to a medical surveillance bias. Most of the hazard ratios associated with the outcomes identified were not statistically significant past the first 30 days. Increased hazard ratios were seen for opioid dependence during the first two time periods. Airmen diagnosed with mTBI were also at increased risk for alcohol dependence when compared to Airmen from the injury cohort across all three time periods. These results indicate that alcohol dependence was not a disorder diagnosed only within a limited time period, but rather a disorder which continued to be diagnosed at all time periods beyond the index stressor, including beyond 6 months.

Table 8. Substance Use/Addiction-Related Disorders Hazard Ratios by Time Period

Category	mTBI n = 5,065 n (%)	Injury Cohort n = 44,733 HR (95% CI)
1 – 30 days post exposure		
Substance Use Disorder		
Alcohol Dependence	15 (0.30)	3.81 (2.04 – 7.12)†
Drug Dependence	4 (0.08)	8.63 (2.11 – 35.31)†
Nondependent abuse of drugs/alcohol	82 (1.62)	2.19 (1.71 – 2.80)†
Nicotine Dependence	69 (1.36)	2.08 (1.59 – 2.72)†
Opioid dependence, opioid abuse	3 (0.06)	7.57 (1.49 – 38.55)†
Caffeine-related disorders	4 (0.08)	4.13 (1.20 – 14.23)†
Amphetamine dependence/abuse	1 (0.02)	6.63 (0.41 – 107.24)
Pathological Gambling Disorder	0 (0.00)	§
31 – 179 days post exposure		
Substance Use Disorder		
Alcohol Dependence	42 (0.83)	2.94 (2.05 – 4.20)†
Drug Dependence	5 (0.10)	1.19 (0.46 – 3.06)
Nondependent abuse of drugs/alcohol	152 (3.00)	1.18 (0.99 – 1.40)
Nicotine Dependence	110 (2.17)	0.94 (0.77 – 1.15)
Opioid dependence, opioid abuse	4 (0.08)	4.33 (1.24 – 15.15)†
Caffeine-related disorders	7 (0.14)	1.90 (0.83 – 4.36)
Amphetamine dependence/abuse	0 (0.00)	§
Pathological Gambling Disorder	0 (0.00)	§
≥ 180 days post exposure		
Substance Use Disorder		
Alcohol Dependence	71 (1.40)	1.83 (1.41 – 2.37)†
Drug Dependence	23 (0.45)	1.51 (0.96 – 2.37)
Nondependent abuse of drugs/alcohol	534 (10.54)	1.03 (0.94 – 1.13)
Nicotine Dependence	513 (10.13)	1.02 (0.93 – 1.12)
Opioid dependence, opioid abuse	10 (0.20)	1.33 (0.68 – 2.62)
Caffeine-related disorders	22 (0.43)	1.40 (0.89 – 2.22)
Amphetamine dependence/abuse	1 (0.02)	0.86 (0.11 – 6.97)
Pathological Gambling Disorder	2 (0.04)	1.21 (0.27 – 5.49)

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval.
* Adjusted for gender, marital status, race/ethnicity, birth year, deployment, education, rank, and career field.
† Differences are statistically significant at $\alpha = 0.05$.
§ Percentage of outcome in comparison population was not sufficient to generate a hazard ratio with a 95% confidence interval.

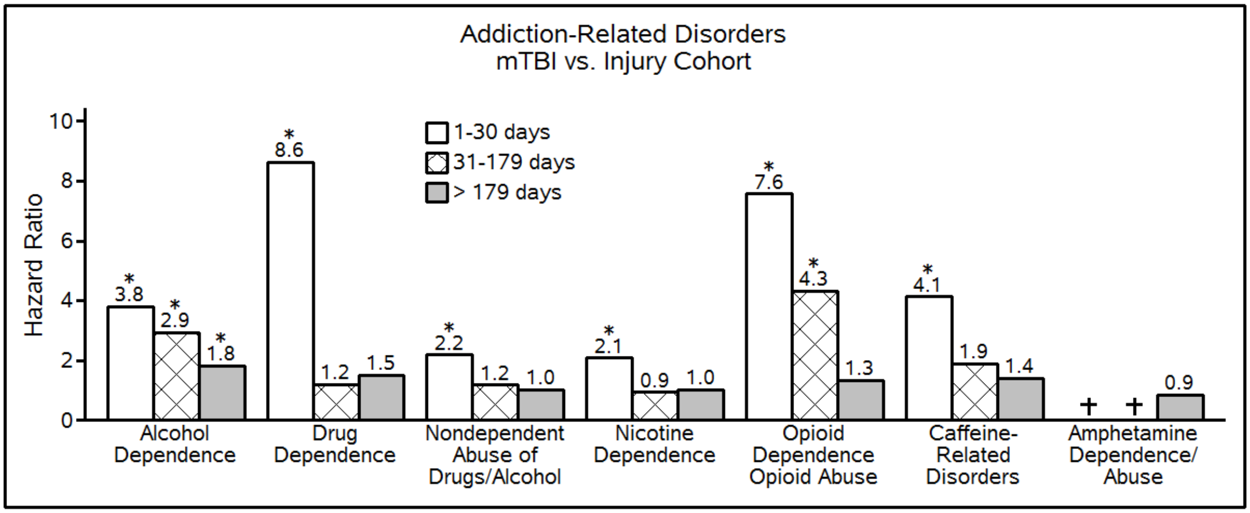

Figure 5. Plot of Adjusted HRs for Addiction-Related Disorders (mTBI vs. Injury Cohort)
Adjusted for gender, marital status, race/ethnicity, birth year, deployment, education, rank, and career field.
* Statistically significant at α = 0.05 level.
† Percentage of outcome in comparison population was not sufficient to generate a hazard ratio with a 95% confidence interval.

3. Subsequent Risk for Mishaps of US Air Force Airmen Following Mild Traumatic Brian Injury

Methods

A retrospective cohort study among male and female US Air Force enlisted and officer personnel (Airmen) was conducted to assess the association between being diagnosed with an mTBI and the risk of having a subsequent injury/safety mishap. This study utilized the Centers for Disease Control and Prevention (CDC) Administrative Data Definition of mTBI for Surveillance or Research [67], which is comprised of a listing of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes [69] considered by an expert panel to be indicative of mTBI. ICD-9-CM diagnoses for mTBI found in electronic medical records were used to identify mTBI cases for this study and were then analyzed to determine the association between mTBI and subsequent safety mishaps. This study was conducted in accordance with all applicable federal regulations governing the protection of human subjects in research as approved by Air Force Research Laboratory/Wright Site Institutional Review Board (Protocol F-WR-2009-0066-H).

Population and Data Sources

Electronic personnel data were obtained from the Defense Manpower Data Center (DMDC). Demographic and military specific information collected included gender, birth date, highest achieved education level, marital status, race/ethnicity, military rank, deployment records, primary career field, and a personal identifier. Table 4 provides the demographic characteristics for all Airmen included in the study.

Through a data use agreement, a listing of individuals with a documented safety mishap during the study period was developed using data from the Air Force Safety Automated System (AFSAS), the Air Force Safety Center's mishap reporting system, and then matched to study participants by personal identifiers. Table 9 provides the demographic characteristics for those with subsequent accidents from the mTBI and non-mTBI groups as indicated by instances within the AFSAS database.

For this analysis, Airmen on active duty for at least 180 days between October 1, 2001 and September 30, 2008 were selected. To increase the probability of only including incident cases, individuals with a history of mTBI or other head injury two years prior to entering the study were removed from consideration, resulting in 518,958 Airmen who met eligibility criteria, and were at risk of developing a new mTBI during the course of the study.

Two non-mTBI comparison groups were used. The first comparison group included the entire study population without an mTBI during the study period, and with no previous history of mTBI, or other head injuries, within the two years prior to study entry. The second comparison group included a non-mTBI injured group, which was a sub-set of the original comparison group; also without an mTBI or other head injuries two years prior to entering the study. Individuals included in the injury comparison group were those who had sustained an injury to the torso, spinal cord, abdomen, pelvis, digestive tract, or genitourinary tract (ICD-9-CM 805-810, 860-870, 900-905, 922-923, 926-927, and 933-959).

Subsequent Mishap Identification

For each individual, person-time began on either October 1, 2001, the date they entered active duty, or the date at which they were diagnosed with an mTBI or injury consistent with the reference category, whichever occurred later. Person-time ended when they left active duty, had a documentable mishap, the day before a subsequent mTBI or other head injury, or at the end of the study (September 30, 2008), whichever occurred first. Mishaps included were those occurring later than two days post-mTBI or injury, to ensure proper temporal relationship and exclude same-event diagnoses.

Statistical Analyses

Demographic and military specific data were analyzed using frequency distributions and Pearson's Chi-squared tests to determine univariate differences. After investigation of population characteristics, Cox proportional hazards analyses were performed to assess the significance of associations between mTBI and succeeding mishaps while adjusting for variables in the model and accounting for differences in person-time contributed by study members.

Table 9. Active Duty US Air Force Airmen Subsequent Mishap Demographics by mTBI status 10/1/2001 – 9/30/2008*

Characteristic	mTBI n = 327 No. (%)	No mTBI n = 16,648 No. (%)
Gender		
Male	280 (85.63)	14,205 (85.33)
Female	47 (14.37)	2,443 (14.67)
Race/Ethnicity†		
White (non-Hispanic)	261 (79.82)	12,044 (72.35)
Black (non-Hispanic)	25 (7.65)	2,414 (14.50)
Asian or Pacific Islander	8 (2.45)	441 (2.65)
Hispanic	18 (5.50)	1,044 (6.27)
Native American	4 (1.22)	119 (0.71)
Other/Unknown	11 (3.36)	586 (3.52)
Birth year†		
Before 1965	11 (3.36)	1,227 (7.37)
1966-1975	45 (13.76)	3,373 (20.26)
1976 or later	271 (82.87)	12,048 (72.37)
Marital Status†		
Currently married	88 (26.91)	6,099 (36.64)
Never married	230 (70.34)	9,953 (59.78)
No longer married	9 (2.75)	596 (3.58)
Education†		
High School or less	312 (95.41)	14,828 (89.07)
Some college/bachelor’s	11 (3.36)	1,371 (8.24)
Advanced degree	4 (1.22)	411 (2.47)
Unknown	0 (0.00)	38 (0.23)
Rank†		
Enlisted	321 (98.17)	15,787 (94.83)
Officer	6 (1.83)	861 (5.17)
Deployed		
Never	154 (47.09)	7,162 (43.02)
Once	84 (25.69)	4,802 (28.84)
Twice	50 (15.29)	2,611 (15.68)
More than twice	39 (11.93)	2,073 (12.45)
AFSC Category		
Operations	40 (12.23)	2,192 (13.17)
Logistics/Maintenance	162 (49.54)	7,566 (45.45)
Support	84 (25.69)	4,216 (25.32)
Medical	20 (6.12)	1,024 (6.15)
Professional/Acquisitions/Finance	4 (1.22)	311 (1.87)
Other/Unknown	17 (5.20)	1,339 (8.04)

Abbreviations: US, United States; mTBI, mild traumatic brain injury.
* Airmen included were on active duty for six or more months during this time period.
† Differences were tested with the Pearson chi-square test of association and are statistically significant at $\alpha = 0.05$.

Cox proportional hazards models were used in the multivariate analysis. All Cox proportional hazards models were adjusted for gender, marital status, race/ethnicity, date of birth category, deployment status, education level, rank, career field, previous mishap status, and injury severity. Previous mishap status was defined as having a documented mishap within two years prior to entering the study, and was adjusted for in the multivariable modeling. No significant interactions or multicollinearity were detected among any independent variables in these models.

Analyses assessed differences in post-mTBI mishap incidence rates, mishap severity, injury cause category, duty status (on or off duty), and body part injured. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to compare the risk of the specified outcomes between the mTBI population and the two non-mTBI populations. All statistical analyses were conducted using SAS® (Version 9.2, SAS Institute, Inc., Cary, North Carolina).

Results

Of the 518,958 Airmen who met study criteria, 5,065 were diagnosed with an mTBI, and 327 individuals had sustained both an mTBI and a subsequent safety mishap during the study period. In univariate analysis, Airmen coded with having suffered a subsequent mishap were more likely to be white (non-Hispanic), never married, enlisted, born during or after 1976, and have a high-school level of education (Table 9). Using Pearson's Chi-square test, gender, deployment status, or career field demographics did not display statistically significant differences at $\alpha = 0.05$.

Airmen with mTBI were at increased risk for subsequent mishaps for almost all categories when compared to the full cohort (Table 10). Increased risks were noted for subsequent mishaps involving motor vehicles, sports and recreation, industrial accidents, or for miscellaneous reasons. In addition to the type of mishap, when compared to the full cohort, Airmen suffering from mTBIs were more likely to have these subsequent mishaps when they were off-duty, were more likely to lose time at work, and were more likely to injure extremities such as their arms, legs, or head. Compared to the injured cohort, Airmen suffering from mTBIs were significantly less likely to have these subsequent mishaps on-duty and after two weeks post-mTBI, they were also less likely to lose time due to their subsequent mishap.

Hazard ratios also showed consistent significance (or insignificance) over the three time periods for both the full cohort and the injured cohort comparisons (Table 10). Most subsequent mishap categories that were significant when they occurred after two days post-mTBI or injury were still significant if they occurred over a month post-mTBI or injury. Likewise, most categories that were not statistically significant when they occurred after two days post-mTBI or injury were still not significant if they occurred over a month post-mTBI or injury.

These differences between the comparison populations may be attributed to individual characteristics such as seeking emergency care for injuries, risk-taking behaviors, occupations, and differential participation in sports activities.

Table 10. Hazard Ratios of Subsequent Injury over Time

Characteristics*	mTBI n = 5,065 n	Full Cohort n = 513,893 HR (95% CI)	Injury Cohort n = 44,733 HR (95% CI)
Mishaps occurring > 2 days post-mTBI			
Type of Mishap			
Private Vehicle	52	2.92 (2.19 – 3.87)†	1.31 (0.93 – 1.82)
Government Vehicle	0	§	§
Sports and Recreation	116	1.96 (1.62 – 2.38)†	1.01 (0.81 – 1.25)
Industrial	80	1.73 (1.34 – 2.22)†	0.86 (0.65 – 1.15)
Miscellaneous	59	2.16 (1.64 – 2.84)†	0.85 (0.63 – 1.15)
Duty Status			
On Duty	120	1.49 (1.22 – 1.81)†	0.74 (0.59 – 0.93)†
Off Duty	183	2.47 (2.13 – 2.88)†	1.13 (0.95 – 1.95)
Mishap Severity			
Lost Time Case	181	2.12 (1.83 – 2.46)†	1.04 (0.87 – 1.23)
Treated and Released	22	2.69 (1.71 – 4.22)†	1.69 (0.89 – 3.22)
No Lost Time	81	1.69 (1.34 – 2.14)†	0.77 (0.59 – 1.01)
Other	4	3.73 (1.03 – 13.56)†	§
Body Part Injured			
Extremities	88	2.01 (1.61 – 2.52)†	1.12 (0.87 – 1.45)
Head and Neck	24	1.60 (1.02 – 2.53)†	0.99 (0.59 – 1.66)
Spine	0	§	§
Torso	19	1.32 (0.81 – 2.17)	0.69 (0.40 – 1.18)
Unclassifiable	0	§	§
Mishaps occurring > 2 weeks post-mTBI			
Type of Mishap			
Private Vehicle	51	2.90 (2.18 – 3.86)†	1.32 (0.94 – 1.85)
Government Vehicle	0	§	§
Sports and Recreation	107	1.82 (1.49 – 2.23)†	0.93 (0.75 – 1.17)
Industrial	78	1.69 (1.31 – 2.18)†	0.87 (0.65 – 1.17)
Miscellaneous	57	2.11 (1.60 – 2.79)†	0.85 (0.62 – 1.15)
Duty Status			
On Duty	118	1.47 (1.20 – 1.80)†	0.72 (0.57 – 0.91)†
Off Duty	171	2.34 (2.01 – 2.74)†	1.09 (0.91 – 1.30)
Mishap Severity			
Lost Time Case	172	2.04 (1.75 – 2.37)†	1.01 (0.85 – 1.21)
Treated and Released	20	2.44 (1.52 – 3.92)†	1.40 (0.71 – 2.74)
No Lost Time	78	1.64 (1.29 – 2.08)†	0.74 (0.57 – 0.98)†
Other	4	7.71 (2.62 – 22.71)†	§
Body Part Injured			
Extremities	82	1.89 (1.50 – 2.38)†	1.05 (0.81 – 1.37)
Head and Neck	22	1.45 (0.90 – 2.35)	0.91 (0.53 – 1.55)
Spine	0	§	§
Torso	18	1.26 (0.76 – 2.10)	0.66 (0.38 – 1.15)
Unclassifiable	0	§	§

Mishaps occurring > 1 month post-mTBI			
Type of Mishap			
Private Vehicle	47	2.71 (2.01 – 3.65)†	1.26 (0.88 – 1.78)
Government Vehicle	0	§	§
Sports and Recreation	106	1.84 (1.50 – 2.25)†	0.95 (0.75 – 1.19)
Industrial	75	1.68 (1.30 – 2.17)†	0.86 (0.64 – 1.16)
Miscellaneous	57	2.15 (1.63 – 2.85)†	0.86 (0.63 – 1.18)
Duty Status			
On Duty	115	1.47 (1.20 – 1.80)†	0.75 (0.59 – 0.94)†
Off Duty	166	2.32 (1.98 – 2.72)†	1.08 (0.90 – 1.30)
Mishap Severity			
Lost Time Case	167	2.02 (1.73 – 2.35)†	1.01 (0.84 – 1.20)
Treated and Released	20	2.44 (1.52 – 3.92)†	1.40 (0.71 – 2.74)
No Lost Time	78	1.66 (1.31 – 2.10)†	0.75 (0.57 – 0.98)†
Other	3	5.73 (1.69 – 19.43)†	§
Body Part Injured			
Extremities	80	1.88 (1.48 – 2.38)†	1.88 (1.48 – 2.38)†
Head and Neck	20	1.39 (0.85 – 2.29)	1.39 (0.85 – 2.29)
Spine	0	§	§
Torso	17	1.20 (0.71 – 2.04)	1.20 (0.71 – 2.04)
Unclassifiable	0	§	§

Abbreviations: mTBI, mild traumatic brain injury; HR, Hazard Ratio; CI, Confidence Interval

* Adjusted for gender, marital status, race/ethnicity, birth year, deployment, education, rank, career field, duty status, previous mishap status, and injury severity.

† Differences are statistically significant at $\alpha = 0.05$.

§ Percentage of outcome in comparison population was not sufficient to generate a hazard ratio with a 95% confidence interval.

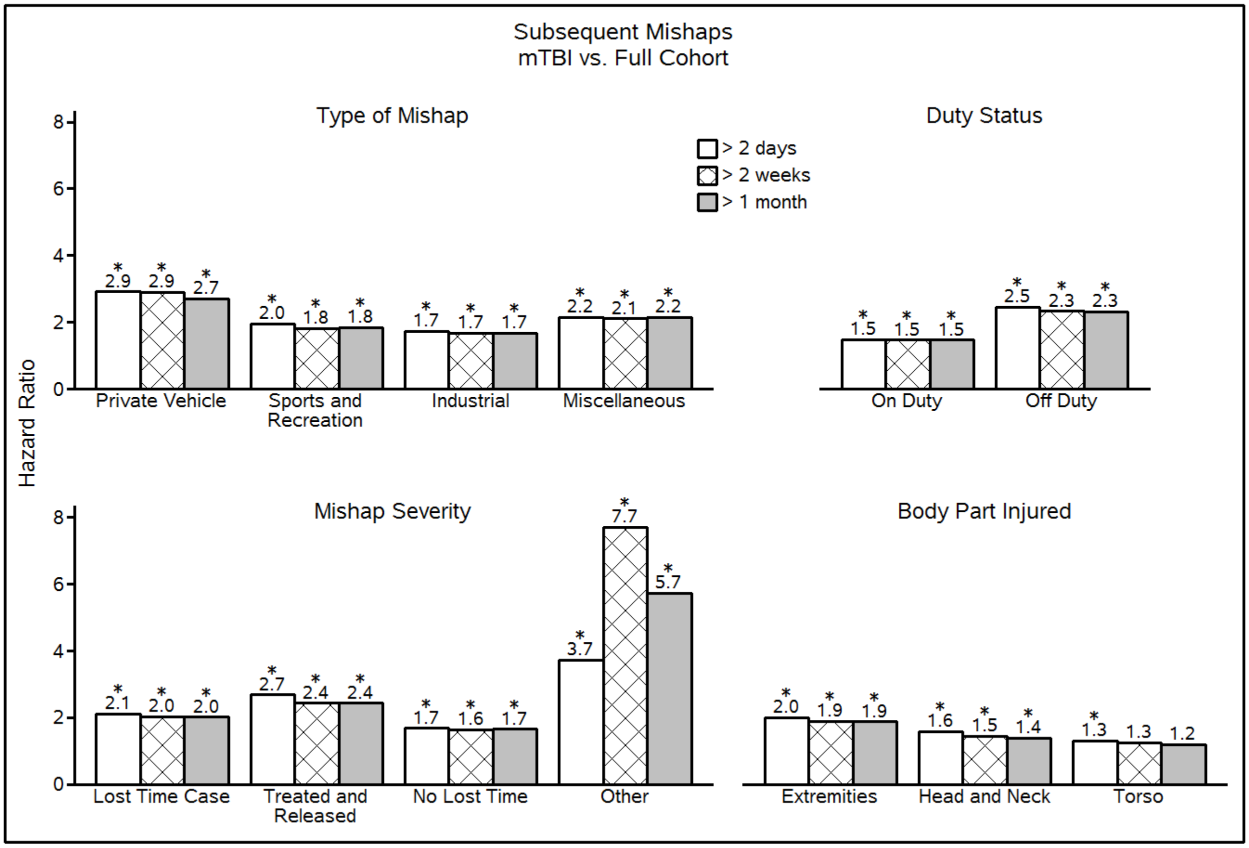

Figure 6. Plot of Adjusted Hazard Ratios for Subsequent Mishaps (mTBI vs. Full Cohort)
Adjusted for gender, marital status, race/ethnicity, birth year, deployment, education, rank, career field, duty status, previous mishap status, and injury severity.
* Statistically significant at $\alpha = 0.05$ level.

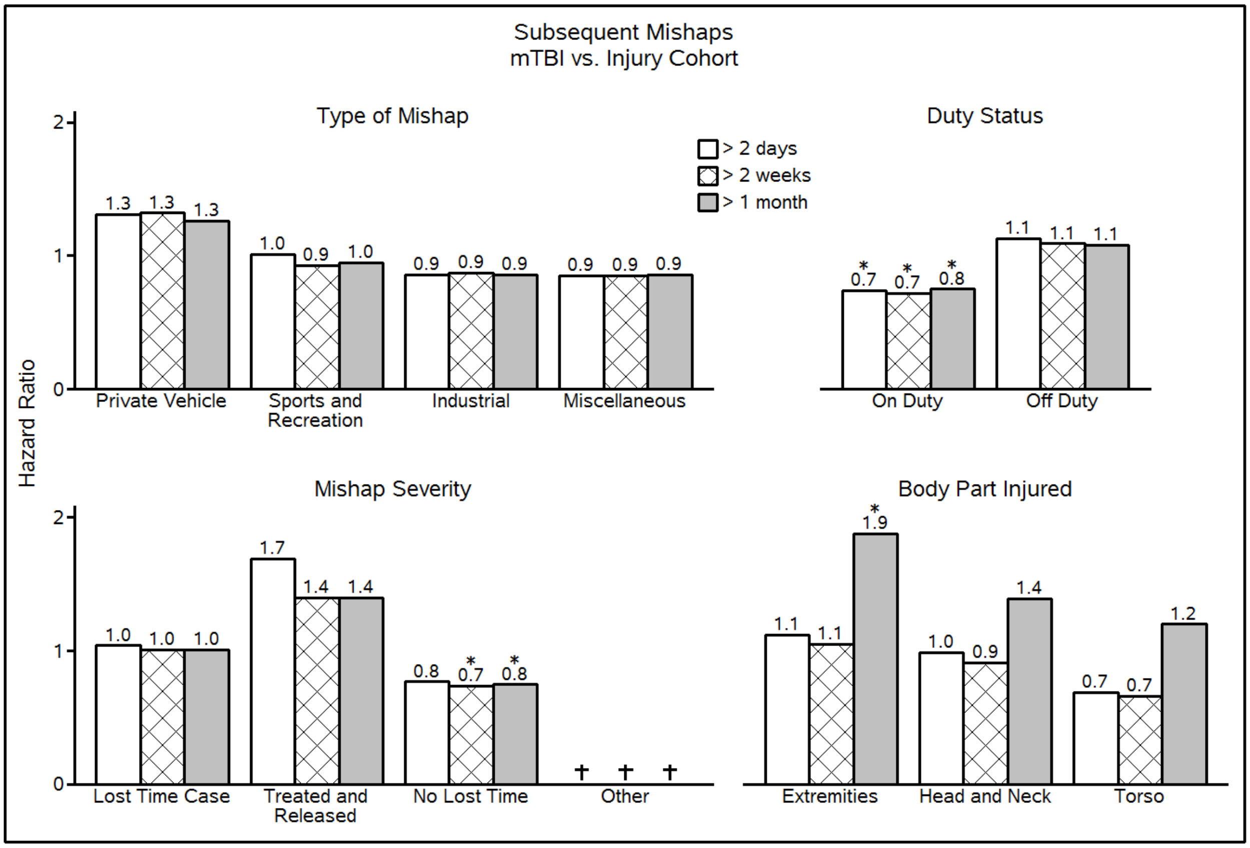

Figure 7. Plot of Adjusted Hazard Ratios for Subsequent Mishaps (mTBI vs. Injury Cohort)
Adjusted for gender, marital status, race/ethnicity, birth year, deployment, education, rank, career field, duty status, previous mishap status, and injury severity.
* Statistically significant at $\alpha = 0.05$ level.
† Percentage of outcome in comparison population was not sufficient to generate a hazard ratio with a 95% confidence interval.

KEY RESEARCH ACCOMPLISHMENTS:

- Verified the usefulness of using CDC's Administrative Data Definition of mTBI using electronic medical records. Although, an objective diagnostic aid for mTBI diagnosis, improved documentation for loss of consciousness and post-traumatic amnesia, and adjusted coding criteria limiting the use of 959.01 could improve its usefulness.

- This study was one of the first to utilize electronically-recorded data from a number of sources to better understand how mTBI may adversely impact warfighter performance.

- This study was also one of the first to utilize two different comparison populations and three different time periods to fully explore the short and long-term effects of mTBI.

- mTBI was associated with an increased risk for a number of mental, neurological, and addiction-related disorders. Furthermore, mTBI may significantly contribute to decreased warfighter performance among USAF Airmen due to the possible long-term effects of medical outcomes and increased risk of safety mishaps.

- Risks for subsequent mishaps for mTBI group may be attributed to individual characteristics such as seeking emergency care for injuries, risk-taking behaviors, occupations, and differential participation in sports activities. Suggesting that subsequent mishap risk is more likely due to the general increased risk for subsequent injury among those with an injury, rather than an increased risk associated specifically with an mTBI.

- Where previous research indicated that mTBI sequelae resolved quickly, this study suggests that a number of these outcomes had long-term effects, even 180 days or more post-mTBI.

- For endocrine disorders, there were some elevated hazard ratios within the first 30 days for the mTBI group compared to both the Full Cohort and Injury Cohort groups. However, they resolved with no significant differences noted after 30 days. Based on these results, endocrine disorders were no longer a main focus of this study.

REPORTABLE OUTCOMES:

- Poster presentation, 2009 Military Health Research Forum (Appendix 2)
- Poster presentation, 2010 Ohio State University's Injury Biomechanics Symposium (Appendix 3)
- Poster presentation, 2010 Force Health Protection Conference (Appendix 4)
- Abstract submissions, 2011 Armed Forces Public Health Conference (Appendix 5)
- Manuscripts in preparation for submission to peer reviewed journals: WPMC Validation, Mental Disorders, Neurological Disorders, Substance Use/Addiction-Related Disorders, and Subsequent Mishaps

CONCLUSION:

This study utilized electronic data to assemble a relatively large group of Airmen with incident mTBIs, and two comparison groups comprised of other bodily injuries and all Airmen without an mTBI. Analyses were then stratified by time periods (≤ 30 days, 31-179 days, and ≥180 days). Adding to the growing body of literature on the possible adverse health outcomes associated with mTBI, findings from this study suggest that a number of mental, neurological, and substance use disorders may have long-term associations with mTBI.

A unique strength of this study was the utilization of two comparison groups, a full cohort and a non-mTBI injury subset, which provided a more comprehensive examination of the effects of mTBI. Our mTBI population was a more cohesive/similar set of healthcare provider-diagnosed mTBI injuries versus other studies that included self-reports and a combination of mild, moderate, and severe TBI. The additional benefit of using healthcare provider-diagnosed mTBIs and health related outcomes is the fact that recall bias is not a possibility, in contrast to studies that use data from self-reports. Earlier studies have been limited by varied definitions of mTBI or concussion, limited follow-up after injury, small sample sizes, lack of control groups and failure to address all aspects of postconcussive recovery (i.e. neurological, symptomatic, cognitive, postural stability). By excluding those that had a previous diagnosis of mTBI or head-injury two years prior to the event of interest, this study also increased the probability of including only incident cases of mTBI. Finally, being able to adjust for diagnosed PTSD and depression, which of often are co-morbid with mTBI, was an additional strength.

Study findings should be interpreted within possible limitations. These include the accuracy of using ICD-9-CM codes to identify mTBI cases. The validation sub-study suggests that either health practitioners are failing to provide complete documentation of mTBIs in medical records, or may not be strictly following the CDC clinical guidelines for diagnosing mTBIs. If practitioners are more likely to code non-mTBI as mTBIs, this would lead to an over-estimate of the true number of mTBIs in this study. By design, this study does not evaluate causality or symptom persistence after diagnosis. Only the initial presentation after the incident mTBI event is considered and whether medical symptoms were exacerbated or caused by mTBI is unknown. We had, however, ruled out prior diagnoses of the dependent variables within the two year window prior to the event, increasing the likelihood that mTBI contributes to the sequelae. Outcomes of interest may also have been more striking due to increased medical surveillance if individuals with mTBI were more inclined to have follow-up medical care, however the use of an injured comparison group likely accounted for any such differences. Finally, studies support that only about half of those with mental disorders actually seek mental health care. Thus, mental disorders are likely under-reported in this study. The effect of any under-reporting on study findings is not clear and depends on whether or not under-reporting is differential with being an mTBI case, which remains unclear.

This study used administrative data, specifically ICD-9 diagnosis codes, to identify psychiatric conditions in US airmen. Whether codes are identified from in-patient or out-patient medical records has a marked effect on the rate of identification of these conditions [72]. Those who were not hospitalized and/or had few outpatient visits could have fewer diagnosis codes and consequently a lower likelihood of having a psychiatric condition. In addition, it is likely that ICD-9 codes underestimate the prevalence of the condition. Thus when compared to a "gold standard" ICD-9 codes tend to have low sensitivity and high specificity [73]; that is they correctly identify those who don't have the condition, but are nowhere as successful in identifying those with the condition. We believe the strategy of having injury and total comparison groups as well as examining prevalence at different time periods mitigates these limitations of ICD-9 codes.

The results of the validation sub-study of the CDC's Administrative Data Definition of mTBI indicated that identification of mTBI cases through electronic medical records were acceptable; however, an objective diagnostic aid for mTBI diagnosis, improved documentation for loss of consciousness and post-traumatic amnesia, and adjusted coding criteria limiting the use of 959.01 could improve its usefulness and acceptability in identifying cases of mTBI. With regard to the health related outcomes, it was clear from these results that a number of the health related outcomes in all the main categories examined (mental, neurological, and substance use/addiction-related disorders) were not resolved as quickly as previously assumed. Outcomes such as PCS, PCS-related, and PTSD had lasting effects, even 180 days or more post-mTBI. In addition, the results for alcohol dependence indicate that this disorder was not diagnosed only within a limited time period, but rather a disorder which continued to be diagnosed at all time periods beyond the index stressor, including beyond 6 months.

There is considerable evidence to suggest that mild traumatic brain injury should be considered separately from moderate and severe as its pattern of onset of sequelae may be different. Additionally, the significant hazard ratios observed here strongly indicate that a public health strategy should be considered to inform both clinicians and personnel responsible for aftercare of mTBI patients of the potential sequelae that may occur. Continued follow-up of mTBI patients is an important discussion that needs to be initiated in both civilian and military environments.

Although this study used a military population of USAF Airmen, in-theater medical encounters were more than likely not captured in this study and possibly not a good comparison of those exposed to combat and/or blast-related injuries. Therefore, these results are likely more generalizable to the general population. However, we recommend further studies to help validate the findings from this study.

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APPENDICES:

1: Statement of Work

2: Military Health Research Forum Poster

3: Ohio State University's Injury Biomechanics Symposium Poster

4: Force Health Protection Conference Poster

5: Armed Forces Public Health Conference Abstracts

SUPPORTING DATA:

All figures and/or tables are included within the text of the document.

Appendix 1. Statement of Work, Award No. 08-M-8089

Task	Month																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1. IRB approval	■	■	■	■	■	■																		
2. Annual report												■												
3. Final report																								■
1. Assemble cohort for review							■																	
2. Review records							■	■																
3. Perform analysis								■																
4. Draft report									■															
1. Data Acquisition							■																	
2. Preliminary analysis								■	■	■	■													
3. Final analysis												■	■	■	■									
4. Draft manuscript															■	■	■							
1. Data Acquisition							■	■	■	■	■													
2. Preliminary analysis												■	■	■	■									
3. Final analysis																■	■	■	■					
4. Draft manuscript																			■	■	■			
1. Data Acquisition												■	■	■										
2. Preliminary analysis															■	■	■	■						
3. Final analysis																			■	■	■	■		
4. Draft manuscript																						■	■	■

Appendix 2, MHRF Poster, Award No. 08-M-8089

Is Mild Traumatic Brain Injury Associated with Decreased Warfighter Performance?

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Abstract

Background: Traumatic brain Injury (TBI) is a concern for US military personnel serving in Iraq and Afghanistan. Additionally, US servicemen and women are at risk for TBI of varying levels of severity as a result of motor vehicle accidents, sports injuries, and other causes. The scientific literature is replete with descriptions of the long-term sequelae of moderate to severe TBI, but little is known regarding potential long-term adverse performance decrements associated with mild TBI (mTBI). The objectives of this study are to determine if mTBI is associated with a number of biological indicators that may adversely affect warfighter performance. This study is funded by the Defense Center of Excellence for Psychological Health and Traumatic Brain Injury

Methods: A historical prospective study will be conducted utilizing electronically-recorded demographic and military-specific data for all US Air Force (USAF) service members (Airmen) who served on active duty for six months or more during the time period of October 1, 2001 – September 30, 2008. A sub-study analysis will be performed on Airmen who suffered a reportable mishap utilizing data from the USAF Safety Center, and an additional sub-study will utilize Veteran's Health Administration (VHA) data. Airmen diagnosed with an mTBI will be identified using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes published by the Centers for Disease Control and Prevention (CDC) in a 2003 report to Congress. Outcomes include electronically recorded ICD-9-CM diagnoses of selected psychiatric, neurological, and endocrine disorders. A validation study will be conducted examining the accuracy of the CDC mTBi case definition against medical records. Cox proportional hazards modeling will be used to calculate hazard ratios while controlling for varying lengths of follow-up and potentially confounding variables.

Conclusions: TBI may significantly contribute to decreased warfighter performance among US Service men and women. This study will utilize electronically-recorded data from a cohort of active duty Airmen to provide a better understanding of possible outcomes associated with mTBI that may adversely affect warfighter performance.

Impact: A study of the underlying sequelae that may adversely affect the physiological component of warfighter performance will assist those conducting enhanced cognition research to understand the human response to mTBI as a stressor.

Background

- **mTBI is an important concern among US service members who are exposed to such hazards as blast injuries, sports injuries, and trauma associated with motor vehicle accidents**
- **It is believed that brain trauma may lead to long-term mechanical and biomechanical damage that can negatively impact the performance of US service members**
- **The US Military affords the opportunity to study potential long-term performance decrements associated with mTBI**

Objectives

- **To determine the agreement between the CDC administrative data definition of mTBI for surveillance or research and medical records review by a clinical neurologist**
- **To determine the relation between mTBI and select mental disorders, neurodegenerative conditions, and endocrine dysfunctions**
- **To determine the association between mTBI and measures of performance and social functionality**

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Methods

- **Compare Airmen with and without mTBI who served on active duty between Oct 1, 2001- Sep 30, 2008**
- **Exclude those with moderate & severe TBI along with those diagnosed with an mTBI and those with a diagnosis of the outcome of interest within 2 years prior to entrance into the study**
- **Data will be obtained from the Defense Manpower Data Center, the Military Health System, the Air Force Safety Automated System (AFSAS), and selected Department of Veterans Affairs databases**
- **Validate CDC administrative data definition of mTBI for surveillance and research against medical records review by a blinded neurologist co-investigator**
- **Primary study outcomes include:**
  - **Mental disorders: Cognitive disorders, psychotic disorders, mood disorders, anxiety disorders, substance use disorders, impulse control disorders, sleep disorders, adjustment reactions, headaches, fatigue**
  - **Neurological outcomes: Alzheimer's disease, epilepsy and seizure disorders, Parkinson's disease, amyotrophic lateral sclerosis**
  - **Endocrinological outcomes: type II diabetes mellitus, diabetes insipidus, thyroid disorders, adrenal disorders, pituitary disorders, sex hormone disorders**

Methods (cont.)

- **Ground safety sub-study will utilize data from the AFSAS and allow the use of an injured comparison group to study association between mTBI and mental disorders, and to additionally assess the risk for further injury during the follow-up period**
- **VA data will be used to study the relation between mTBI and disability, as well as conditions that may have long onset, such as selected dementias**
- **Statistical analyses:**
  - **Chi-square, and t-tests for univariate associations**
  - **Multivariable analyses utilize Cox proportional hazards modeling to adjust for possible confounding variables and differences in lengths of observation.**

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Discussion

- **Analyses are ongoing at this time**
- **mTBI may significantly contribute to decreased warfighter performance among US Service men and women.**
- **This study will be one of the first to utilize electronically-recorded data from a number of sources to better understand how mTBI may adversely impact warfighter performance**

Risk for Subsequent Mishaps among Airmen with Mild Traumatic Brain Injury

Casserly R. Whitehead, MPH[1]; Timothy S. Webb, MS, PhD[2]; Timothy S. Wells, DVM, MPH, PhD[2]; Suzanne H. Baktash, MPH[2]; Tracy J. Eicher, MD[3]; Clifford N. Otte, MPAS[2]; Sarah O. Fortuna, MD[2]; Russell K. Gore, MD[2]; Edward J. Boyko, MD, MPH[4]; Charles Maynard, PhD[4]; Bruce R. Burnham, DVM, MPH[5]; Philip Kemp, MS[5]

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Introduction

- Mild Traumatic Brain Injury (mTBI) results from trauma to the head, such as that occurring from motor vehicle or industrial accidents, or sports injuries
- United States Air Force members (Airmen) and other individuals with mTBI may suffer from cognitive deficits placing them at increased risk for subsequent mishaps

Background

- mTBI is an important concern among US service members who are exposed to such hazards as blast injuries, sports injuries, and trauma associated with motor vehicle accidents
- mTBI is often diagnosed among troops serving in Iraq and Afghanistan
- Even mild brain trauma may lead to long-term mechanical and biomechanical damage that can negatively impact performance
- The study objective was to determine if Airmen with mTBI were at greater risk for subsequent mishaps that may be indicative of decreased cognition as a result of the mTBI injury

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Methods

- This study included Airmen who had served on active duty for at least six months between Oct 1, 2001- Sep 30, 2008 and whose electronic personnel data was linked to medical and safety center data, also in electronic format
- Airmen were excluded if they had been diagnosed with an mTBI or an unspecified head injury within 2 years prior to entrance into the study
- Exposed individuals were Airmen with an ER-diagnosed mTBI during the study period
- Study outcomes were restricted to mishaps occurring more than two days post-mTBI or injury, to ensure proper temporal relationship and exclude same-event diagnoses
- Comparison groups included all other study members without a head injury, and an ER-diagnosed injured comparison group that was used to reduce possible biases associated with entry into the medical system as a result of an mTBI
- Statistical analyses included univariate methods to determine differences in demographic and military specific data, and Cox's proportional hazards modeling to calculate adjusted hazard ratios and 95% confidence intervals while controlling for varying lengths of follow-up

Results

- There were 522,080 Airmen who met study criteria, and 3,606 with an ER-diagnosed mTBI
- 100 individuals had sustained both an mTBI and a subsequent mishap during the study period
- Compared to those without mTBI, Airmen with an mTBI were more likely to be male, white (non-Hispanic), never married, enlisted, and born during or after 1976 (Table 1)

Results (cont.)

Table 1. Descriptive Data, Airmen with and without mTBI, 2001 - 2008

		Comparison group	
Characteristic*	mTBI n = 3,606	Full n = 518,474	ER-Injured n = 14,466
Gender			
Male	3,012 (83.5)	412,696 (79.6)	11,051 (76.4)
Female	594 (16.5)	105,778 (20.4)	3,415 (23.6)
Race/ethnicity			
White non-Hispanic	2,743 (76.1)	373,209 (72.0)	10,539 (72.9)
Black non-Hispanic	418 (11.6)	79,083 (15.3)	2,009 (13.9)
Other / unknown	445 (12.3)	66,182 (12.8)	1,918 (13.3)
Birth year			
Before 1965	197 (5.5)	89,653 (17.3)	1,528 (10.6)
1966 – 1975	540 (15.0)	110,111 (21.2)	2,906 (20.1)
1976 or later	2,869 (79.6)	318,710 (61.5)	10,032 (69.4)
Rank			
Enlisted	3,452 (95.7)	438,520 (84.6)	13,409 (92.7)
Officer	154 (4.3)	79,954 (15.4)	1,058 (7.3)
Marital Status			
Currently married	1,012 (28.1)	222,841 (43.0)	5,382 (37.2)
Never married	2,494 (69.2)	273,898 (52.8)	8,862 (58.9)
No longer married	100 (2.8)	21,735 (4.2)	559 (3.9)
Deployed			
Never	1,785 (49.5)	289,832 (55.9)	6,819 (47.1)
Once	1,047 (29.0)	130,320 (25.1)	4,095 (28.3)
Twice or more	774 (21.5)	98,322 (19.0)	3,552 (24.6)

*Differences were tested with the Pearson chi-square test of association; p-value ≤ 0.002 for all.

- Airmen with mTBI were at increased risk for subsequent mishaps when compared to the full cohort, but no significant differences were noted when compared to the ER-diagnosed injured cohort (Table 2)

Table 2. Hazard Ratios for Mishaps Among Airmen With and Without mTBI

Characteristic	mTBI n	Full cohort HR (95% CI)*	ER-Injured HR (95% CI)*
Type of mishap			
Private motor vehicle	15	1.56 (0.92, 2.66)	0.65 (0.32, 1.31)
Govt. motor vehicle	2	2.61 (0.64, 10.62)	-
Sports / recreation	45	1.81 (1.32, 2.49)	0.80 (0.54, 1.19)
Industrial	20	1.73 (1.00, 3.00)	0.33 (0.15, 0.73)
Other	18	1.66 (1.02, 2.73)	0.45 (0.24, 0.84)
Duty status			
On duty	26	1.62 (1.03, 2.55)	0.35 (0.18, 0.67)
Off duty	68	1.73 (1.35, 2.21)	0.69 (0.50, 0.94)
Mishap severity			
Lost time case	58	1.60 (1.24, 2.08)	0.75 (0.54, 1.04)
Treated / released	13	2.82 (1.54, 5.17)	2.33 (0.58, 9.41)
No lost time	16	1.28 (0.72, 2.28)	0.21 (0.08, 0.53)
Other	3	8.38 (2.24, 31.27)	-

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval

*Adjusted for gender, marital status, race/ethnicity, birth year, deployment, education, rank, career filed, duty status, previous mishap and injury severity

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Discussion

- This is one of the first large studies to utilize electronic data to calculate associations between mTBI and subsequent risk for mishap
- Airmen with mTBI appear to be at increased risk for subsequent mishaps compared to the full cohort
- The relations between mTBI, other significant injuries, and subsequent risk for mishap need further study to better understand causal pathways

Conclusion

- In a population with equal access to health care, risk for subsequent mishaps may be due to differences shared among those who seek emergency care for injuries:
  - Differential participation in sports activities
  - Risk-taking behaviors
  - Occupations
- Conflicting findings based upon comparison group suggest that increased risk for subsequent mishaps is likely not the result of decreased cognition, as may be expected among those with mTBI

This study was conducted in accordance with all applicable federal regulations governing the protection of human subjects in research as approved by Air Force Research Laboratory/Wright Site Institutional Review Board (Protocol F-WR-2009-0066-H)

Appendix 4, FHPC Poster, Award No. 08-M-8089

Sequelae of Mild Traumatic Brain Injury in a US Military Cohort

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Abstract

Military personnel are at risk for traumatic brain injury (TBI) as a result of combat and non-combat exposures. The sequelae of moderate to severe TBI is well described, but little is known regarding long-term performance decrements associated with mild TBI (mTBI). A historical prospective study was conducted utilizing electronically-recorded demographic and military-specific data for active duty US Air Force (USAF) members (Airmen) to study possible performance decrements associated with mTBI. Outcomes included electronically-recorded ICD-9-CM diagnoses of select mental, neurological, and endocrine disorders. Cox proportional hazards modeling was utilized to calculate hazard ratios while controlling for varying lengths of follow-up and potentially confounding variables. Airmen with mTBI were at increased risk for psychiatric, substance use, and neurological disorders compared to a similarly injured control group but without head injury. This study suggests that mTBI may contribute to decreased warfighter performance, and that US service members with mTBI may warrant additional medical follow-up.

Background

- mTBI is an important concern among US service members who are exposed to such hazards as blast injuries, sports injuries, and trauma associated with motor vehicle accidents
- Even mild brain trauma may lead to long-term mechanical and biomechanical damage that can negatively impact the performance of US service members
- The goal of this study was to determine if mTBI is associated with long-term health decrements that may adversely affect warfighter performance

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Methods

- This study was conducted utilizing electronically-recorded data for all Airmen who had served on active duty for at least six months between Oct 1, 2001- Sep 30, 2008
- Data was obtained from the Defense Manpower Data Center and the Military Health System and linked by personal identifiers
- Airmen were excluded if they had been diagnosed with an mTBI or an unspecified head injury within 2 years prior to entrance into the study
- Exposed individuals were Airmen with an emergency room (ER)-diagnosed mTBI during the study period
- The comparison population was a non-head injured group, of similar severity, diagnosed in the ER to minimize bias associated with healthcare seeking behavior
- Only individuals with incident cases were considered in the analysis for each outcome (within 2 years of study entry)
- To understand the relation between mTBI and onset of the outcomes of interest, post exposure time was divided into three time periods: 2-30 days, 31-179 days, and 180 days or more

Methods (cont.)

- The first occurrence of each outcome was used; individuals who left the study during the first two time periods were removed from analysis for the subsequent time period(s)
- Statistical analyses include:
  - Univariate methods used to determine differences in demographic and military specific data
  - Cox's proportional hazards modeling was used to calculate adjusted hazard ratios and 95% confidence intervals while controlling for varying lengths of follow-up

Results

- There were 18,086 Airmen who met study criteria
  - 3,609 Airmen had an ER-diagnosed mTBI
  - 14,477 comprised the referent group and had an ER-diagnosed injury to the torso, abdomen, pelvis, digestive tract, or genitourinary tract
- mTBI was associated with a number of mental disorders, neurological outcomes and performance problems 2-30 days post-mTBI, with the risk generally decreasing over time (Table 1)

Table 1. Select Medical Outcomes of Interest and their Hazard Ratios for Three Time Periods

Category	mTBI n	2-30 days post-exposure HR (95% CI)	mTBI n	31-179 days post-exposure HR (95% CI)	mTBI n	≥ 180 days post-exposure HR (95% CI)
Mental Disorders						
Cognitive	31	8.20 (4.32 – 15.54)	42	2.64 (1.76 – 3.94)	81	1.96 (1.50 – 2.57)
Mood	43	1.88 (1.30 – 2.71)	88	1.23 (0.97 – 1.57)	242	1.27 (1.10 – 1.47)
Anxiety	26	1.58 (1.00 – 2.49)	65	1.42 (1.07 – 1.88)	221	1.30 (1.12 – 1.52)
Substance Use	62	1.78 (1.31 – 2.42)	99	1.04 (0.83 – 1.30)	395	1.06 (0.94 – 1.18)
Adjustment Reactions	34	1.32 (0.89 – 1.96)	95	1.36 (1.07 – 1.72)	241	1.25 (1.08 – 1.45)
Neurological Outcomes	239	8.17 (6.55 – 10.19)	153	1.50 (1.25 – 1.81)	397	1.06 (0.95 – 1.18)
Epilepsy	11	22.73 (4.90 – 105.35)	15	8.49 (3.40 – 21.17)	12	3.45 (1.60 – 7.41)
Headaches	180	14.44 (10.84 – 19.23)	88	1.82 (1.43 – 2.33)	251	1.17 (1.02 – 1.35)
Vertigo/Dizziness	60	10.87 (6.76 – 17.47)	40	1.68 (1.16 – 2.43)	117	1.09 (0.89 – 1.34)
Pain Disorders	2	0.68 (0.15 – 3.13)	6	1.28 (0.50 – 3.23)	41	1.38 (0.97 – 1.98)
Endocrine Disorders	5	1.68 (0.61 – 4.67)	8	0.61 (0.29 – 1.28)	65	1.09 (0.83 – 1.43)
Performance Problems*	101	1.65 (1.30 – 2.10)	172	1.13 (0.95 – 1.34)	556	1.13 (1.02 – 1.24)

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval
Adjusted for gender, marital status, race/ethnicity, birth year, deployment, education, rank, and career field.
* Supplementary ICD-9-CM V-codes used to identify performance problems (mental, relational, and abuse/neglect)

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Results (cont.)

- Increased risk was still observed beyond six months for cognitive, mood, and anxiety mental disorders; epilepsy and headache neurological outcomes; and performance problems

Discussion

- This study is one of the first to utilize electronically-recorded data from a number of sources to better understand how mTBI may adversely effect warfighter performance
- An mTBI can have acute and chronic impacts on an individuals' health and mission readiness
- mTBI may significantly contribute to decreased warfighter performance among US Service men and women
- Additional analyses are planned to examine differences in promotion rates, healthcare utilization, and risk for subsequent mishaps among mTBI sufferers

Conclusion

- mTBI was associated with an increased risk for a number of mental disorders, neurological outcomes, and performance problems
- A study of the underlying sequelae that may adversely affect the physiological component of warfighter performance will assist those conducting enhanced cognition research to understand the human response to mTBI

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This study was conducted in accordance with all applicable federal regulations governing the protection of human subjects in research as approved by Air Force Research Laboratory/Wright Site Institutional Review Board (Protocol F-WR-2009-0066-H).

ACCURACY OF USING THE CDC ADMINISTRATIVE DATA DEFINITION OF MTBI IN CASE IDENTIFICATION

Introduction: United States Air Force (USAF) Airmen and other military personnel with mild traumatic brain injury (mTBI) may suffer from physiological and psychological health disorders that compromise their mission readiness. The Centers for Disease Control and Prevention's (CDC's) Administrative Data Definition of mTBI for Surveillance or Research is comprised of a listing of International Classification of Diseases, 9th Revision, Clinical Modifications (ICD-9-CM) codes. This study was conducted to determine the reliability and validity of using the CDC's ICD-9-CM codes to identify individuals with an mTBI according to the CDC's Clinical Record Data Definition.

Methods: Data obtained from the Defense Manpower Data Center (DMDC) and TRICARE Management Activity (TMA) were used to identify Airmen currently stationed at Wright-Patterson Air Force Base (WPAFB) and whose paper medical records were currently located at Wright-Patterson Medical Center (WPMC). The study group consisted of individuals whose medical records contained codes consistent with the CDC's ICD-9-CM definition of mTBI used to identify mTBI cases for this effort. Individuals included in the control group were those who had sustained an injury to the head identified as "head trauma without mild traumatic brain injury". A board-certified neurologist blindly reviewed these de-identified records to determine if the medical encounter met criteria for an mTBI diagnosis. Cohen's kappa statistic was used to assess agreement between the CDC's Clinical Record Data Definition and the CDC's definition comprised of ICD-9-CM codes.

Results: Findings identified ICD-9-CM code 959.01 as having poor agreement for a diagnosis of mTBI and those medical visits were removed from the study, leaving 60 records that met study criteria and were available for analyses. Electronic coding of mTBI symptomatology was not always consistent with paper medical record documentation, raising possible inconsistencies regarding what coding recommendations are being followed.

Conclusions: Though the kappa statistic was statistically significant with a moderate amount of agreement, a more robust significance was expected. An objective diagnostic aid for mTBI diagnosis, improved documentation for loss of consciousness and post-traumatic amnesia, and adjusted coding criteria limiting the use of 959.01 could improve agreement.

RISK FOR SUBSEQUENT MISHAPS AMONG AIRMEN WITH MILD TRAUMATIC BRAIN INJURY (MTBI)

Introduction: Mild Traumatic Brain Injury (mTBI) results from trauma to the head, such as that occurring from motor vehicle or industrial accidents, or sports injuries. Additionally, with increased use of improvised explosive devices, mTBI is often diagnosed among troops serving in Iraq and Afghanistan. United States Air Force (USAF) members (Airmen) and other military personnel with mTBI may suffer from cognitive deficits placing them at increased risk for mishaps.

Methods: Using a historical prospective cohort design, electronic data were assembled from the Defense Manpower Data Center, the Military Health System, and the Air Force Safety Automated System. Emergency room visit data were utilized to identify Airmen with mTBI and one of two comparison groups, consisting of injuries without involvement of the head, and the other control group consisting of all other study members without a diagnosis of a head injury. Cox's proportional hazards modeling was utilized to calculate adjusted hazard ratios and 95% confidence intervals while controlling for varying lengths of follow-up.

Results: There were 522,072 Airmen who met study criteria, and 3,609 with an Emergency Room-diagnosed mTBI. Compared to the injured control group, no differences were noted for subsequent mishaps involving motor vehicles, sports and recreation, industrial accidents, or for miscellaneous reasons. However, when compared to the other control group, Airmen with an mTBI were at increased risk for almost all categories.

Conclusions: These conflicting findings suggest that increased risk for subsequent mishaps is likely not the result of a cognitive deficit, as may be expected among those with mTBI, but rather due to differences shared among those who seek emergency care for injuries. These differences may include risk-taking behaviors, occupations, and differential participation in sports activities, among others.

MILITARY ATTRITION AND PROMOTION FOLLOWING MILD TRAUMATIC BRAIN INJURY (MTBI)

Introduction: Mild traumatic Brain Injury (mTBI) results from trauma to the head, such as that occurring from motor vehicle or industrial accidents, or sports injuries. With the increased use of improvised explosive devices, mTBI is often diagnosed among troops serving in Iraq and Afghanistan. United States Air Force (USAF) Airmen and other military personnel with mTBI may suffer from cognitive deficits placing them at increased risk for disability, affecting their length of military service and their opportunities for promotion.

Methods: Using a historical prospective cohort design, electronic data were assembled from the Defense Manpower Data Center and the Military Health System. This data was then utilized to identify Airmen with mTBI and one of two comparison groups, consisting of injuries without involvement of the head, and the other control group consisting of all other study members without a diagnosis of a head injury. Average time to promotion (in days) was computed for all three groups and compared with logistic regression to calculate adjusted odds ratios and 95% confidence intervals. Differences between groups' Interservice Separation Code (ISC) categories were tested with the Pearson chi-square test of association.

Results: There were 518,958 Airmen who met study criteria, and 5,065 with an mTBI. Differences between groups' ISC categories were significant as well as differences due to promotion and separation. Airmen with mTBI were at increased risk for separation when compared to the full cohort and at decreased risk for separation when compared to the injured cohort. Airmen with mTBI were also less likely to be promoted than the full cohort within the average time to promotion, but were promoted at a similar rate to the injured cohort.

Conclusions: These conflicting findings suggest an interaction, that any type of injury, whether mTBI or bodily, could contribute to attrition and lack of promotion and may not be attributable to a cognitive deficit. However, both mTBI and bodily injury significantly contributed to an individual's odds of separating from the military for non-routine reasons (i.e. disability, substance abuse, and misconduct).