Relationship Between Headache Characteristics and a Remote History of TBI in Veterans: A 10-Year Retrospective Chart Review

Author(s):
Colt Coffman, BS; Deborah Reyes, PhD; Mary Catherine Hess, NP; Alec M Giakas, BS, BA; Melinda Thiam, MD; Jason Jonathon Sico, MD, MHS, FAHA; Elizabeth Seng, PhD; William Renthal, MD, PhD; Charles Rhoades, MD; Guoshuai Cai, PhD; X. Michelle Androulakis, MD, MS, FAHS

Corresponding Author:
X. Michelle Androulakis, michelle.androulakis@uscmed.sc.edu

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
Affiliation Information for All Authors: 1 Department of Kinesiology, Michigan State University, East Lansing, MI, 48824, USA; 2. Department of Physical Medicine and Rehabilitation Services, Columbia VA Healthcare System, Columbia, SC, USA; 3. Department of Neurology, Columbia VA Healthcare System, Columbia, SC, USA; 4. University of South Carolina School of Medicine, Columbia, SC, USA; 5. Department of Psychiatry, Columbia VA Healthcare System, Columbia, SC, USA; 6. Yale School of Medicine, New Haven, CT, USA; 7. Headache Centers of Excellence Program, US Department of Veterans Affairs, West Haven, CT; 8. Montefiore Headache Center, Montefiore Medical Center, Bronx, NY, USA; 9. Department of Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; 10. Department of Neurobiology, Harvard Medical School, Boston, MA, USA; 11. Department of Environmental Health Science, Arnold School of Public Health, University of South Carolina, Columbia, SC, 29208, USA; 12. Headache Centers of Excellence Program, US Department of Veterans Affairs, Columbia, SC, USA

Equal Author Contribution:

Contributions:
Colt Coffman: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Deborah Reyes: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Mary Catherine Hess: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Alec M Giakas: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Melinda Thiam: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Jason Jonathon Sico: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Elizabeth Seng: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
William Renthal: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Charles Rhoades: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Guoshuai Cai: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data; Other
X. Michelle Androulakis: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Figure Count:
1

Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.
Abstract

Objective:
To examine the association between deployment-related Traumatic Brain Injury (TBI) severity, frequency, and other injury characteristics on headache outcomes in veterans evaluated at a Veterans Administration (VA) polytrauma support clinic.

Methods:
We conducted a retrospective chart review of 594 comprehensive TBI evaluations between 2011-2021. Diagnostic criteria were based upon the Department of Defense/VA Consensus-Based Classification of Closed TBI. Adjusted Odds Ratios and 95% Confidence Intervals were estimated for headache prevalence (logistic), severity (ordinal), and prevalence of migraine-like features (logistic) using multiple regression analysis. Regression models were adjusted for age, sex, race/ethnicity, time since injury, and mental health diagnoses.

Results:
TBI severity groups were classified as sub-concussive exposure (n= 189), mild (n= 377), moderate (n = 28), and severe TBI (n = 0). Increased headache severity was reported in veterans with mild TBI (AOR = 1.72 [1.15, 2.57] and moderate TBI (AOR=3.89 [1.64, 9.15]) as compared to those with sub-concussive exposure. A history of multiple mild TBI was associated with more severe headache (AOR = 2.47 [1.34, 4.59]) and migraine-like features (AOR = 5.95 [2.55, 13.77]). No differences were observed between blast and non-blast injuries; however, greater headache severity was reported in veterans with both primary and tertiary blast effects (AOR = 2.56 [1.47, 4.49]). Alterations of consciousness (AOC) and post-traumatic amnesia (PTA) longer than 30 minutes were associated with more severe headache (AORs = 3.37 [1.26, 9.17] and 5.40 [2.21, 13.42], respectively). The length of years between the onset of last TBI and the TBI evaluation was associated with headache severity (AOR = 1.09 [ 1.02, 1.17]) and prevalence of migraine-like features (AOR = 1.27[1.15, 1.40]). Lastly, helmet use is associated with less severe headache (AOR = 0.42 [ 0.23, 0.75]) and lower odds of migraine-like features (AOR = 0.45 [ 0.21, 0.98]).

**Discussion:**

Our data support the notion for a dose-response relationship between TBI severity and headache outcomes. A history of multiple mild TBI and longer duration of AOC and PTA are unique risk factors for poor headache outcomes in veterans. Furthermore, this study sheds light on the poor headache outcomes associated with sub-concussive exposure. Past TBI characteristics should be considered when developing headache management plans for veterans.

Keywords: Traumatic brain injury, deployment, headache, migraine, veterans
INTRODUCTION

Traumatic brain injury (TBI) is the “signature injury” among combat veterans returning from recent US military operations. Indeed, the Defense and Veterans Brain Injury Center reports 434,618 service members sustained TBI since the year 2000. Co-occurring TBI sequelae, post-traumatic stress disorder (PTSD), and chronic pain constitute a complex and prevalent clinical profile in veterans termed the “polytrauma triad”, which can perpetuate long-term functional disability following injury. Post-traumatic headache (PTH) is the most frequent manifestation of comorbid chronic pain within this population. The International Classification of Headache Disorders, 3rd edition, defines PTH as (1) a secondary headache disorder that develops, or (2) a primary headache disorder that becomes chronic or made significantly worse, in close temporal relation to a TBI. The most common clinical presentation of PTH is comparable to migraine (i.e., headache, nausea, photophobia, phonophobia); however, PTH is often refractory to conventional migraine therapies. An estimated 27 - 62% of veterans with sustained TBI experience persistent PTH (lasting longer than 3 months). Problematically, persistent PTH is associated with higher rates of disability, higher healthcare and societal costs, and poorer health outcomes in veterans.

While comorbid psychiatric conditions strongly influence chronic TBI symptomology, the extent to which TBI characteristics affect PTH is largely unknown. Studies have come to varied conclusions regarding the role in which TBI severity (i.e., mild, moderate, or severe) plays in headache occurrence and severity. Some analyses demonstrate null findings, whereas others suggest a direct or possible inverse relationship between TBI severity and headache outcomes. Further investigation into discrete measures correlated with TBI severity, such as loss/alteration of consciousness (LOC/AOC) and post-traumatic amnesia (PTA) duration, is warranted. Nonetheless, heterogeneous symptomatology within comparable TBI severities emphasizes the multidimensional etiology of PTH. Emerging evidence suggests there may be a cumulative effect of TBI on long-term sequelae, such as postural control deficits, psychiatric distress, neurocognitive dysfunction; however, it is unknown whether this relationship extends to post-injury headache. Blast exposure is the most common mechanism of injury during deployment. There is no published data on headache outcomes related to different types of injury mechanism in veterans. Blast-induced neurotrauma is complex as individuals are not only exposed to the primary blast wave but also possible secondary and tertiary effects (e.g., acoustic damage, penetrating debris, coup–countercoup injury). Moreover, blast proximity and personal protective equipment (PPE) also contribute to the variability in trauma received by an individual. Pre-clinical studies suggest that blast TBI may alter the integrity of cerebral vasculature and blood-brain barrier. As such, we hypothesize that blast-related TBI could be associated with poorer headache outcomes compared to blunt-trauma injury.

The aims of the present cross-sectional, retrospective chart-review were (1) to compare headache characteristics across TBI severity groups, (2) to examine the cumulative effect of TBI on headache outcomes, and (3) to evaluate injury characteristics (i.e., mechanism of injury, LOC/AOC, PTA, PPE) that may be associated with headache outcomes in veterans. Identifying unique TBI characteristics associated with post-injury headache severity and migraine-like features can help facilitate earlier and more individualized intervention for veterans at risk for persistent PTH.

METHODS

Data source: This study is a retrospective chart review of 594 Operation Iraqi Freedom/Operation Enduring Freedom/Operation New Dawn (OIF/OEF/OND) veterans who were administered a comprehensive TBI evaluation (CTBIE) at a local Southeastern Department of Veterans Affairs (VA) polytrauma support clinic. Data were extracted from electronic medical records of OEF/OIF/OND veterans evaluated between January 2011 and January 2021.
**Procedure:** All OIF/OEF/OND veterans are administered the VA Traumatic Brain Injury Screening Tool (VATBIST) by either the veteran’s case manager, primary care provider, or registered nurse at the time of their initial VA visit. A “positive” VATBIST requires the endorsement of at least 1 item for each of the 4 questions regarding: 1) An event that may have exposed the veteran to brain injury during OEF/OIF/OND deployment (i.e., Blast or Explosion, Vehicular accident/crash, Fragment or bullet wound above the shoulders, and/or Fall); (2) An alteration in consciousness or head injury immediately after that event (i.e., Losing consciousness/"knocked out", Being dazed, confused or “seeing stars”, Not remembering the event, Concussion, and/or Head injury); (3) The presence of new or worsened symptoms following the event (i.e., Memory problems or lapses, Balance problems or dizziness, Sensitivity to bright light, Irritability, Headaches, and/or Sleep problems); and (4) The continued presence of any of those symptoms in the week prior to the VATBIST.

Veterans with a “positive” VATBIST are referred to a trained physiatrist or specialty clinic for a CTBIE if the veteran agrees to further assessment and care of a potentially previously undiagnosed TBI. In regard to the present study, CTBIEs were administered by a trained physiatrist within the local polytrauma support clinic. The CTBIE confirms deployment-related TBI diagnoses and is the starting point to develop an interdisciplinary follow-up treatment plan. The physiatrist first collects relevant sociodemographic information and self-reported injury characteristics: mechanism(s) of injury (e.g., motor vehicle accident, blast, fall, blunt trauma), approximate blast effects and proximity (if applicable), years since most recent TBI, PPE use at the time of injury, and LOC, AOC, and PTA duration. The Neurobehavioral Symptom Inventory (NSI) was administered to each veteran to rate their symptoms in regard to the past 30 days. The NSI is a 22-item subjective assessment of post-concussive symptomatology rated on a 5-point Likert scale ranging from 0 (none; symptom is rarely ever present/not a problem at all) to 4 (very severe; symptom is almost always present/impairs performance at work, school, or home/individual probably cannot function without help). Finally, the physiatrist and multidisciplinary TBI team come to a conclusion regarding the TBI diagnoses, present/suspected/probable comorbid diagnoses were determined by trained clinicians (PTSD, depression, anxiety, etc.), and the degree in which these diagnoses are consistent with the veteran’s current clinical symptom presentation. A more detailed review of the VA TBI screening process is described by Donnelly et al. and Ruff et al.

**TBI diagnosis ascertainment:** A diagnosis of TBI was made only if the physiatrist believed that the reported deployment-related events fit criteria for TBI beyond reasonable doubt. TBI severity was ascertained using the Department of Defense/VA Consensus-Based Classification of Closed TBI Severity. Mild TBI is defined by a duration of LOC < 30 minutes, AOC < 24 hours, and/or PTA < 24 hours. Moderate TBI is defined by a duration of LOC > 30 minutes and < 24 hours, AOC > 24 hours, and/or PTA > 1 day but < 7 days. Severe TBI is defined by a duration of LOC > 24 hours and/or PTA > 7 days.

Those that did not meet the minimum criteria for mild TBI but had a “positive” VATBIST were categorized as the sub-concussive exposure group due to insufficient information to make a severity rating. For the purposes of the present study, veterans were grouped into three groups; sub-concussive exposure (n = 189), mild TBI (n = 377), and moderate TBI (n = 28) based upon their TBI severity using the aforementioned criteria. No veterans were identified as having a history of severe TBI.

**Outcome measures:** Outcome variables focused upon in the present study were measures of headache characteristics including headache prevalence, headache severity, and the prevalence of migraine-like features. Veterans who endorsed headaches in the 30 days prior to evaluation were classified as having headache. The prevalence of headache was coded as a binary variable (present/absent). Headache severity and prevalence of migraine-like symptoms were measured among those who endorsed headache. Headache severity was measured using the headache item from the NSI and was thus coded as an ordinal variable from 0 (“none”) to 4 (“very severe”). Veterans who reported...
headache and endorsed either nausea, sensitivity to light (photophobia), or sensitivity to noise (phonophobia) from respective items on the NSI, were used to define the presence of migraine-like features. The prevalence of migraine-like features was coded as a binary variable (present/absent).

**Statistical analysis:** All data analyses were performed in R Version 4.0 (R Core Team, 2019) using the “Rmimic” (version 1.0.3) R package. Chi-square ($\chi^2$) tests for categorical and ordinal variables and linear regression for continuous variables were used to compare key sociodemographic factors and post-concussive symptomatology across TBI severity groups. Logistic regression analyses were conducted to compare the prevalence of headache and headache with migraine-like features across TBI severity groups. Ordinal logistic regression analyses were conducted to compare headache severity across TBI severity groups. Only 28 veterans had a confirmed history of moderate TBI, thus this sample size was inadequate to achieve appropriate statistical power for analyzing headache differences in moderate TBI. Separate regression analyses for veterans with a history of mild TBI were conducted to examine the association between TBI frequency and headache characteristics: prevalence (logistic), severity (ordinal), and prevalence of migraine-like features (logistic). These models also included mechanism(s) of injury, blast effects (primary, secondary, or tertiary), approximate blast distance (feet), years since most recent TBI, helmet use at the time of injury (yes/no), LOC duration, AOC duration, and PTA duration to identify any injury characteristics that may be associated with post-injury headache characteristics. All regression analyses were adjusted for potential confounders based on conceptual importance and prior literature (i.e., biological sex [0 = male, 1 = female], age, race/ethnicity [0 = white, 1 = black, 2 = other, 3 = unknown], PTSD diagnosis [0 = no, 1 = yes], depression diagnosis [0 = no, 1 = yes], and anxiety diagnosis [0 = no, 1 = yes]). Effect sizes were calculated for regression models as odds ratios (OR)/adjusted odds ratio (AOR) with 95% Confidence Intervals (CI). An *a priori* familywise alpha level was set to $p = 0.05$. Bonferroni correction was applied to adjust for multiple comparisons when applicable.

**Standard Protocol Approvals, Registrations, and Patient Consents**

This study was approved by the Columbia VA Healthcare System Human Subjects Institutional Review Board. Participant consent was waived for this chart review study. All data were deidentified before conducting data cleaning.

**Data Availability**

Due to VA regulations and VHA ethics agreements, the analytic data sets used for this study are not permitted to leave the VA firewall without a Data Use Agreement. This limitation is consistent with other studies based on VA data. However, VA data are made freely available to researchers with an approved VA study protocol. For more information, please visit https://www.virec.research.va.gov or contact the VA Information Resource Center at VIReC@va.gov.

**RESULTS**

**Participants**

The current sample was predominantly male (92.8%) with a mean age of 34.41 ± 8.69 years old. Overall, 405 veterans had a confirmed history of TBI and were screened at an average of 6.29 ± 4.12 years since their most recent TBI. Demographic characteristics grouped by TBI severity can be found in Table 1. TBI severity groups were comparable with respect to sex, age, educational attainment, marital status, and PTSD and anxiety prevalence, however, differed significantly with respect to race/ethnicity and employment status. PTSD was diagnosed in 344 (56.2%) veterans. The prevalence of mental health diagnoses grouped by TBI severity can be found in Table 2. Veterans with sub-concussive exposure had a greater prevalence of depression than veterans with mild TBI (36.5% vs 25.7%; $p$-value = 0.008). The
distribution of veterans in this cohort with PTSD, confirmed mild/moderate TBI, and headache is shown in Figure 1.

Association between headache characteristics and TBI severity

The prevalence of headache, mean headache severity, and prevalence of migraine-like features for sub-concussive exposure, mild TBI, and moderate TBI groups can be found in Table 2. Unadjusted and adjusted (covariates including sex, age, race/ethnicity, PTSD, depression, and anxiety diagnoses) associations between headache characteristics and TBI severity can be found in Table 3. Veterans with a history of mild TBI were at higher odds of reporting more severe headache compared to veterans with sub-concussive exposure (AOR = 1.72; 95% CI = 1.15, 2.57; p-value = 0.008), however these groups did not differ in prevalence of headache or migraine like symptoms (p-values > 0.080). While veterans with a history of moderate TBI did not differ in headache prevalence compared to less severe injuries after adjustment for covariates and Bonferroni correction (p-values > 0.027), those with a history of moderate TBI had higher odds of reporting severe headache (AOR = 3.89; 95% CI = 1.64, 9.15; p-value = 0.002) and migraine-like features (AOR = 15.34; 95% CI = 1.99, 177.7; p-value = 0.009) than those with sub-concussive exposure. Furthermore, veterans with a history of moderate TBI had higher odds of endorsing migraine-like symptoms (AOR = 12.25; 95% CI = 1.63, 92.65; p-value = 0.015) compared to those with a history of mild TBI.

Association between headache characteristics and mild TBI frequency

Of the 377 veterans with a history of mild TBI, 71.6% had sustained a single mild TBI, 14.6% had sustained 2 mild TBIs, and 13.8% had sustained 3 or more TBIs. Descriptive statistics for headache prevalence, headache severity, and prevalence of migraine-like features with respect to mild TBI frequency can be found in Table 4. Associations between headache characteristics and TBI frequency with Bonferroni correction can be found in Table 5. No association was found between mild TBI frequency and headache prevalence. Veterans with a history of multiple mild TBI (≥ 2) had higher odds of reporting severe headache (AOR = 2.47; 95% CI = 1.34, 4.59; p-value = 0.004) and migraine-like features (AOR = 5.95; 95% CI = 2.55, 13.77; p-value < 0.001) compared to those with a single mild TBI. Veterans with a history of 2 mild TBIs did not statistically differ in headache severity from veterans with a history of ≥ 3 mild TBIs (AOR = 0.93; 95% CI = 0.37, 0.82; p-value = 0.883). Similarly, the prevalence of migraine-like features did not significantly differ between veterans with a history of 2 mild TBIs and ≥ 3 mild TBIs (84.9% vs 81.8%; p-value = 0.390).

Association between headache characteristics and injury characteristics

Blast exposure was the most common type of mechanism of injury among veterans with mild TBI (57.2%) followed by falls (16.8%), blunt trauma (16.5%), and motor vehicle accidents (9.5%). Improvised explosive device (IED)-blast exposure accounted for more TBIs than any other type of blast exposure (67.7%). Primary blast effects were experienced by 188 veterans with mild TBI, 66 veterans experienced secondary blast effects, and 113 veterans experienced tertiary blast effects. A combination of primary and tertiary blast effects was experienced by 95 veterans with mild TBI. Blast distances ranged from 0 to more than 50 feet away and the mode estimated blast distance was less than 10 feet away. Although the majority of veterans with a history of mild TBI did not experience LOC (63.4%) or PTA (74.8%) related to their injury or injuries, most experienced an AOC lasting less than 30 minutes (70.3%) and wore a helmet during the time of injury (69.2%). Descriptive statistics for headache prevalence, headache severity, and prevalence of migraine-like features among injury characteristics can be found in Table 4. Associations
between headache and injury characteristics can be found in Table 5. Longer number of years since the veteran’s most recent TBI was significantly associated with higher odds of more severe headache (AOR = 1.09; 95% CI = 1.02, 1.17; p-value = 0.009) and migraine-like features (AOR = 1.27; 95% CI = 1.15, 1.40; p-value = 0.001). Fall-related mild TBI was associated with lower odds of severe headache (AOR = 0.42; 95% CI = 0.19, 0.92; p-value = 0.031), however, associations were no longer significant after Bonferroni correction. No other mechanisms of injury were associated with headache characteristics. Interestingly, veterans who reported incurring both primary and tertiary blast effects had higher odds of reporting severe headache (AOR = 2.56; 95% CI = 1.47, 4.49; p-value < 0.001) compared to those that endorsed only single type of blast effect or no blast injury.

No associations between LOC duration and headache characteristics were observed. Compared to no AOC, AOC duration between 30 minutes and 24 hours following TBI was associated with higher odds of headache (AOR = 6.75; 95% CI = 2.08, 21.89; p-value = 0.001). Furthermore, AOC duration between 30 minutes to 24 hours was associated greater headache severity (AOR = 3.37; 95% CI = 1.26, 9.17; p-value = 0.016) compared to no AOC. No differences were observed between AOC duration less than 30 minutes and between 30 minutes to 24 hours. Similarly, PTA duration between 30 minutes and 24 hours following TBI was associated with greater headache severity compared to no PTA (AOR = 5.40; 95% CI = 2.21, 13.42; p-value < 0.001) and PTA duration less than 30 minutes (AOR = 5.04; 95% CI = 1.92, 13.50; p-value = 0.001). Helmet use at the time of injury was associated with lesser headache severity (AOR = 0.42; 95% CI = 0.23, 0.75; p-value = 0.003) and decreased odds of migraine-like features (AOR = 0.45; 95% CI = 0.21, 0.98; p-value = 0.043).

DISCUSSION

We conducted a retrospective, cross-sectional, multivariate analysis of OIF/OEF/OND veterans who were administered a CTBIE to investigate the association between headache characteristics and remote deployment-related TBI characteristics, while concurrently adjusting for age, sex, race/ethnicity, and comorbid mental health diagnoses. Our study found that veterans with a history of mild or moderate TBI who endorsed headache reported greater headache severity compared to veterans with sub-concussive exposure. Additionally, veterans with a history of moderate TBI had a greater prevalence of migraine-like features compared to veterans with a history of mild TBI or sub-concussive exposure. Veterans with a history of multiple mild TBIs had greater headache severity and odds of reporting migraine-like features than those with a single mild TBI. No differences were observed between mechanisms of injury; however, veterans who sustained both primary and tertiary blast effects did report greater headache severity. Furthermore, longer AOC and PTA duration following mild TBI was associated with poorer headache outcomes. In this cohort, earlier CTBIE in relation to the onset of TBI and helmet use at the time of injury were protective against migraine-like features and more severe headache. Lastly, we observed almost one third of veterans had overlapping symptoms of headache, PTSD, and TBI (mild and moderate), and notably, 1 in 5 veterans had overlapping symptoms of migraine-like headache, PTSD, and TBI. Overall, these findings suggest that several injury characteristics related to deployment-related TBI are independently associated with headache outcomes years after injury.

Consistent with existing literature, we found that veterans with a history of mild or moderate TBI had 1.72 and 3.89 times greater odds of more severe headache compared to veterans with sub-concussive exposure, respectively. While the prevalence of headache and migraine-like symptoms was similar between mild TBI and sub-concussive exposure groups, we identified moderate TBI as an independent risk factor for reporting headache with migraine-like features. The present findings provide contrary evidence to studies which suggest that individuals who sustain mild TBI are more likely to endorse headache than moderate TBI. Our findings further reflected a linear relationship between TBI severity and headache characteristics when using more discrete methodology for classifying TBI.
severity with LOC, AOC, and PTA duration. Notably, veterans who reported an AOC or PTA duration lasting 30 minutes to 24 hours were more likely to endorse headache and greater headache severity than veterans with none or shorter duration of AOC/PTA. To our knowledge, no prior studies have examined the relationship between AOC duration and headache. Bomyea et al. found that veterans with mild/moderate TBI and PTH were more likely to experience PTA than those without PTH, however, a number of prior studies showed no such association. The wide variety of TBI severity measures used in the existing literature (i.e., diagnostic TBI severity, presence/absence or duration of LOC, AOC, or PTA) may account for the incongruency in their findings. It has been suggested that categorizing LOC, AOC, or PTA to ascertain remote TBI severity may contribute to the misclassification of TBI injury severity.

Our novel findings demonstrate a cumulative effect of mild TBI on headache severity and prevalence of migraine-like features in veterans. Veterans with a history of ≥2 mild TBI are more than twice as likely to report severe headache and almost six times more likely to report migraine-like symptoms compared to those with a single mild TBI. Additional injury did not correspond to poorer headache outcomes in those with a history of 2 or more mild TBI. Wilk et al. 2012 observed that veterans with a history of multiple mild TBIs were more likely to report headache (OR = 4.0); however, only mild TBI with LOC was examined in that study. Nonetheless, the current literature suggests that an increasing frequency of mild TBI is neurologically detrimental. A cumulative effect of mild TBI has been observed for neurocognitive impairments, PTSD, depression, general pain, and suicidal behavior. It is hypothesized that multiple TBIs may incrementally compromise cerebral white matter integrity, which can produce potential long-term neurological dysfunction. Additional longitudinal research is needed to elucidate the pathophysiological mechanism(s) by which cumulative mild TBI increases the risk of PTH.

In this cohort, blast-related TBI was the most common mechanism of injury, which is consistent with prior findings. Prior evidence suggests that a difference between blast-related and non-blast TBI is indeterminant; however, most studies that report significant findings are in reference to post-traumatic symptoms. Similar to Wilk et al. 2010, we found no differences between blast and non-blast mild TBI in terms of headache outcomes when including veterans with/without LOC. Interestingly, we observed that veterans who reported incurring sequential primary (i.e., direct effect of the blast) and tertiary (i.e., hitting one’s head on the ground or other object) blast effects at the time of a mild TBI endorsed greater headache severity; possibly resulting from compounded neurotrauma. Inconsistencies in PPE may also partially account for the current findings. We observed that veterans who wore helmets during injury had a 58% decrease in odds of reporting severe headache and a 55% decrease in odds of migraine-like symptoms compared to those that did not wear a helmet. While helmet use did not differ between injury mechanisms, other forms of body armor were not accounted for. Advances in military PPE have certainly increased survival rates in combat theater; however, increased surface area of body armor may intensify blast wave effects. Future studies should continue to investigate the potential biomechanical differences between distinct mechanisms of injury to gain a better understanding of how to effectively protect against and manage the long-term sequela of TBI.

The present study has several strengths. First, we used a relatively large cohort that was representative of veterans with suspected TBI. Second, the VATBIST and CTBIE are both standardized methods used by the Department of Veterans Affairs which provided reliable demographic and health information from patient records to be controlled for in analyses. Several limitations that should be considered when interpreting the present findings. First, the true number of veterans with TBI may not be fully represented by our sample. For example, veterans who sustained TBI but whose symptoms resolved or failed to recall important TBI information would not have been identified by the VATBIST. Also, the CTBIE is a tool intended to capture previously undiagnosed traumatic brain injuries, and is not completed for veterans with known pre-existing diagnosis of traumatic brain injury. That is, a service member identified with a mild, moderate or severe TBI by the Department of Defense immediately after
deployment would not be referred to for a CTBIE. It is likely that majority of these patients are veterans with moderate / severe TBI injuries which required immediate medical intervention at that time. Given the focus of this paper is on mild TBI, we do not anticipate this affected the findings significantly. Additionally, the high percentage of veterans (31.8%) with sub-concussive exposure within our cohort may reflect the poor specificity of the VATBIST, a patient’s misattributing their symptoms to an origin event, or difficulty in distinguishing AOC from combat-induced emotional trauma. Second, the items included on the NSI are self-reported, non-specific to TBI and headache, and could be particularly influenced by psychiatric symptoms. Thus, the NSI is susceptible to bias and caution is warranted when this measure is given to patients with comorbid mental health disorders. We attempted to compensate for potential bias by adjusting for common comorbid mental health disorders. While the presence of migraine-like symptoms may be indicative of migraine-type headache, the NSI does not provide sufficient information to classify specific headache type. We suspect many veterans in this cohort are likely experiencing chronic post-traumatic headache; however, without establishing temporal relationship between headache and TBI onset, it is difficult to differentiate headache types. Finally, due to insufficient data, we failed to control for potential confounders including military branch/rank, number of deployments, use of prophylactic or rescue headache medication, and other post-traumatic symptoms. Replication analyses are needed to verify the current findings while accounting for these variables.

**Clinical Implications**

Our results suggest that clinicians may achieve greater precision for the prognosis of headache related to TBI by examining the duration of LOC, AOC, and PTA as semi-continuous variables rather than categorical criteria. Regardless of TBI diagnosis or severity, both headache with migraine-like features and psychiatric conditions were prevalent in the current cohort. These concurrent conditions pose a significant health burden for veterans and clinical challenges for healthcare providers. The overlapping nature of these conditions emphasizes a need for multidisciplinary care in veterans with a confirmed history of TBI and those with sub-concussive exposure within the VA polytrauma system of care. Diagnosis-based treatments may exclude veterans with sub-concussive exposure from more beneficial treatment options, despite sharing similar physiological pathways with chronic TBI symptoms. Focusing on a symptom-based approach to treatment may be more appropriate for veterans with multiple co-occurring post-concussive symptoms. For example, targeted treatments for autonomic dysfunction may help ameliorate shared symptom burden between several psychiatric conditions, migraine, and persistent TBI symptomology. Furthermore, we found that later administration of CTBIE was associated with a greater headache severity and prevalence of migraine-like features. This is consistent with prior research that suggests early diagnosis and intervention may be protective against poorer headache outcomes. Taken together with extant literature, we advocate for earlier TBI/headache intervention and similar integrative multidisciplinary headache care for veterans with and without a confirmed history of TBI.

The contents of this paper do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.
REFERENCES

1. Defense and Veterans Brain Injury Center. DoD TBI Worldwide Numbers. Military Health System. Accessed May 30, 2021. http://health.mil/About-MHS/OASDHA/Defense-Health-Agency/Research-and-Development/Traumatic-Brain-Injury-Center-of-Excellence/DOD-TBI-Worldwide-Numbers

2. Lew HL, Otis JD, Tun C, Kerns RD, Clark ME, Cifu DX. Prevalence of chronic pain, posttraumatic stress disorder, and persistent postconcussive symptoms in OIF/OEF veterans: Polytrauma clinical triad. J Rehabil Res Dev. 2009;46(6):697. doi:10.1682/JRRD.2009.01.0006

3. Pugh MJV, Finley EP, Copeland LA, et al. Complex Comorbidity Clusters in OEF/OIF Veterans: The Polytrauma Clinical Triad and Beyond. Med Care. 2014;52(2):172-181.

4. Lucas S, Hoffman JM, Bell KR, Dikmen S. A prospective study of prevalence and characterization of headache following mild traumatic brain injury. Cephalalgia. 2014;34(2):93-102. doi:10.1177/0333102413499645

5. Nampiaparampil DE. Prevalence of Chronic Pain After Traumatic Brain Injury: A Systematic Review. JAMA. 2008;300(6):711-719. doi:10.1001/jama.300.6.711

6. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211. doi:10.1177/0333102417738202

7. Metti A, Schwab K, Finkel A, et al. Posttraumatic vs nontraumatic headaches: A phenotypic analysis in a military population. Neurology. 2020;94(11):e1137-e1146. doi:10.1212/WNL.0000000000008935

8. Labastida-Ramirez A, Benemei S, Albanese M, et al. Persistent post-traumatic headache: a migrainous loop or not? The clinical evidence. J Headache Pain. 2020;21(1):55. doi:10.1186/s10194-020-01122-5

9. Ashina H, Iljazi A, Al-Khazali HM, et al. Persistent post-traumatic headache attributed to mild traumatic brain injury: Deep phenotyping and treatment patterns. Cephalalgia. 2020;40(6):554-564. doi:10.1177/0333102420909865

10. Theeler BJ, Flynn FG, Erickson JC. Headaches After Concussion in US Soldiers Returning From Iraq or Afghanistan. Headache J Head Face Pain. 2010;50(8):1262-1272. doi:https://doi.org/10.1111/j.1526-4610.2010.01700.x

11. Vanderploeg RD, Curtiss G, Luis CA, Salazar AM. Long-term morbidities following self-reported mild traumatic brain injury. J Clin Exp Neuropsychol. 2007;29(6):585-598. doi:10.1080/13803390600826587

12. Ashina H, Porreca F, Anderson T, et al. Post-traumatic headache: epidemiology and pathophysiological insights. Nat Rev Neurol. 2019;15(10):607-617. doi:10.1038/s41582-019-0243-8
13. Porter KE, Stein MB, Martis B, et al. Postconcussive symptoms (PCS) following combat-related traumatic brain injury (TBI) in Veterans with posttraumatic stress disorder (PTSD): Influence of TBI, PTSD, and depression on symptoms measured by the Neurobehavioral Symptom Inventory (NSI). *J Psychiatr Res.* 2018;102:8-13. doi:10.1016/j.jpsychires.2018.03.004

14. Verfaellie M, Lafleche G, Spiro III A, Bousquet K. Neuropsychological outcomes in OEF/OIF veterans with self-report of blast exposure: Associations with mental health, but not MTBI. *Neuropsychology.* 2014;28(3):337-346. doi:10.1037/neu0000027

15. Walker WC, Seel RT, Curtiss G, Warden DL. Headache After Moderate and Severe Traumatic Brain Injury: A Longitudinal Analysis. *Arch Phys Med Rehabil.* 2005;86(9):1793-1800. doi:10.1016/j.apmr.2004.12.042

16. Suri P, Stolzmann K, Iverson KM, et al. Associations Between Traumatic Brain Injury History and Future Headache Severity in Veterans: A Longitudinal Study. *Arch Phys Med Rehabil.* 2017;98(11):2118-2125.e1. doi:10.1016/j.apmr.2017.04.008

17. Couch JR, Stewart KE. Headache Prevalence at 4–11 Years After Deployment-Related Traumatic Brain Injury in Veterans of Iraq and Afghanistan Wars and Comparison to Controls: A Matched Case-Controlled Study. *Headache J Head Face Pain.* 2016;56(6):1004-1021. doi:https://doi.org/10.1111/head.12837

18. Bryan CJ, Hernandez AM. Predictors of Post-Traumatic Headache Severity Among Deployed Military Personnel. *Headache J Head Face Pain.* 2011;51(6):945-953. doi:https://doi.org/10.1111/j.1526-4610.2011.01887.x

19. Lucas S, Hoffman JM, Bell KR, Walker W, Dikmen S. Characterization of headache after traumatic brain injury. *Cephalalgia.* 2012;32(8):600-606. doi:10.1177/0333102412445224

20. Couch JR, Bearss C. Chronic Daily Headache in the Posttrauma Syndrome: Relation to Extent of Head Injury. *Headache J Head Face Pain.* 2001;41(6):559-564.

21. Maleki N, Finkel A, Cai G, et al. Post-traumatic Headache and Mild Traumatic Brain Injury: Brain Networks and Connectivity. *Curr Pain Headache Rep.* 2021;25(3):20. doi:10.1007/s11916-020-00935-y

22. Yumul JN, McKinlay A. Do Multiple Concussions Lead to Cumulative Cognitive Deficits? A Literature Review. *PM&R.* 2016;8(11):1097-1103. doi:https://doi.org/10.1016/j.pmrj.2016.05.005

23. Ruff RL, Riechers RG, Wang X-F, Piero T, Ruff SS. A case–control study examining whether neurological deficits and PTSD in combat veterans are related to episodes of mild TBI. *BMJ Open.* 2012;2(2):e000312. doi:10.1136/bmjopen-2011-000312

24. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild Traumatic Brain Injury in U.S. Soldiers Returning from Iraq. *N Engl J Med.* 2008;358(5):453-463. doi:10.1056/NEJMoA072972

25. Cernak I, Noble-Haeusslein LJ. Traumatic Brain Injury: An Overview of Pathobiology with Emphasis on Military Populations. *J Cereb Blood Flow Metab.* 2010;30(2):255-266. doi:10.1038/jcbfm.2009.203

26. Bryden DW, Tilghman JL, Hinds SR. Blast-Related Traumatic Brain Injury: Current Concepts and Research Considerations. *J Exp Neurosci.* 2019;13:1179069519872213. doi:10.1177/1179069519872213
27. Donnelly K, Donnelly J, Dunnam M, et al. Reliability, Sensitivity, and Specificity of the VA Traumatic Brain Injury Screening Tool. *J Head Trauma Rehabil.* 2011;26:439-453. doi:10.1097/HTR.0b013e3182005de3

28. Levin HS, Mattis S, Ruff RM, et al. Neurobehavioral outcome following minor head injury: a three-center study. *J Neurosurg.* 1987;66(2):234-243. doi:10.3171/jns.1987.66.2.0234

29. Ruff R, Ruff S, Wang X-F. Headaches among Operation Iraqi Freedom/Operation Enduring Freedom veterans with mild traumatic brain injury associated with exposures to explosions. *J Rehabil Res Dev.* 2008;45:941-952. doi:10.1682/JRRD.2008.02.0028

30. Cifu DX, Bowles A, Hurley R, et al. Management of concussion/mild traumatic brain injury. *US Dep Veterans Aff US Dep Def Wash DC Manag ConcussionmTBI Work Group.* Published online 2009.

31. Pontifex MB. *Rmimic: An R Package That Mimic Outputs of Popular Commercial Statistics Software Packages with Effect Sizes and Confidence Intervals.* 2020. https://github.com/mattpontifex/Rmimic

32. Bomyea J, Lang AJ, Delano-Wood L, et al. Neuropsychiatric Predictors of Post-Injury Headache After Mild-Moderate Traumatic Brain Injury in Veterans. *Headache J Head Face Pain.* 2016;56(4):699-710. doi:https://doi.org/10.1111/head.12799

33. Ponsford JL, Spitz G, McKenzie D. Using Post-Traumatic Amnesia To Predict Outcome after Traumatic Brain Injury. *J Neurotrauma.* 2016;33(11):997-1004. doi:10.1089/neu.2015.4025

34. Wilk JE, Herrell RK, Wynn GH, Riviere LA, Hoge CW. Mild Traumatic Brain Injury (Concussion), Posttraumatic Stress Disorder, and Depression in U.S. Soldiers Involved in Combat Deployments: Association With Postdeployment Symptoms. *Psychosom Med.* 2012;74(3):249-257. doi:10.1097/PSY.0b013e318244c604

35. Lieb DA, Raiciulescu S, DeGraba T, Sours Rhodes C. Investigation of the Relationship Between Frequency of Blast Exposure, mTBI History, and Post-traumatic Stress Symptoms. *Mil Med.* 2021;(usab205). doi:10.1093/milmed/usab205

36. Seal KH, Bertenthal D, Samuelson K, Maguen S, Kumar S, Vasterling JJ. Association between mild traumatic brain injury and mental health problems and self-reported cognitive dysfunction in Iraq and Afghanistan Veterans. *J Rehabil Res Dev.* 2016;53(2):185-198. doi:10.1682/JRRD.2014.12.0301

37. Lindquist LK, Love HC, Elbogen EB. Traumatic Brain Injury in Iraq and Afghanistan Veterans: New Results From a National Random Sample Study. *J Neuropsychiatry Clin Neurosci.* 2017;29(3):254-259. doi:10.1176/appi.neuropsych.16050100

38. Bryan CJ, Clemans TA. Repetitive Traumatic Brain Injury, Psychological Symptoms, and Suicide Risk in a Clinical Sample of Deployed Military Personnel. *JAMA Psychiatry.* 2013;70(7):686. doi:10.1001/jamapsychiatry.2013.1093

39. Goswami R, Dufort P, Tartaglia MC, et al. Frontotemporal correlates of impulsivity and machine learning in retired professional athletes with a history of multiple concussions. *Brain Struct Funct.* 2016;221(4):1911-1925. doi:10.1007/s00429-015-1012-0

40. Ivanov I, Fernandez C, Mitsis EM, et al. Blast Exposure, White Matter Integrity, and Cognitive Function in Iraq and Afghanistan Combat Veterans. *Front Neurol.* 2017;8. doi:10.3389/fneur.2017.00127
41. Manners JL, Forsten RD, Kotwal RS, Elbin RJ, Collins MW, Kontos AP. Role of Pre-Morbid Factors and Exposure to Blast Mild Traumatic Brain Injury on Post-Traumatic Stress in United States Military Personnel. *J Neurotrauma*. 2016;33(19):1796-1801. doi:10.1089/neu.2015.4245

42. Ryan-Gonzalez C, Kimbrel NA, Meyer EC, et al. Differences in Post-Traumatic Stress Disorder Symptoms among Post-9/11 Veterans with Blast- and Non-Blast Mild Traumatic Brain Injury. *J Neurotrauma*. 2019;36(10):1584-1590. doi:10.1089/neu.2017.5590

43. Wilk JE, Thomas JL, McGurk DM, Riviere LA, Castro CA, Hoge CW. Mild Traumatic Brain Injury (Concussion) During Combat: Lack of Association of Blast Mechanism With Persistent Postconcussive Symptoms. *J Head Trauma Rehabil*. 2010;25(1):9-14. doi:10.1097/HTR.0b013e3181bd090f

44. Phillips YY, Mundie TG, Yelverton JT, Richmond DR. Cloth Ballistic Vest Alters Response to Blast: *J Trauma Inj Infect Crit Care*. 1988;28(Supplement):S149-S152. doi:10.1097/00005373-198801001-00030

45. Arcaya MC, Lowe SR, Asad AL, Subramanian SV, Waters MC, Rhodes J. Association of Posttraumatic Stress Disorder Symptoms With Migraine and Headache After a Natural Disaster. *Health Psychol Off J Div Health Psychol Am Psychol Assoc*. 2017;36(5):411-418. doi:10.1037/hea0000433

46. Howard L, Dumkrieger G, Chong CD, Ross K, Berisha V, Schwedt TJ. Symptoms of Autonomic Dysfunction Among Those With Persistent Posttraumatic Headache Attributed to Mild Traumatic Brain Injury: A Comparison to Migraine and Healthy Controls. *Headache J Head Face Pain*. 2018;58(9):1397-1407. doi:https://doi.org/10.1111/head.13396

47. Lagos L, Thompson J, Vaschillo E. A Preliminary Study: Heart Rate Variability Biofeedback for Treatment of Postconcussion Syndrome. *Biofeedback*. 2013;41(3):136-143. doi:10.5298/1081-5937-41.3.02

48. Tan G, Dao TK, Farmer L, Sutherland RJ, Gevirtz R. Heart Rate Variability (HRV) and Posttraumatic Stress Disorder (PTSD): A Pilot Study. *Appl Psychophysiol Biofeedback*. 2011;36(1):27-35. doi:10.1007/s10484-010-9141-y

49. Minen MT, Corner S, Berk T, et al. Heartrate variability biofeedback for migraine using a smartphone application and sensor: A randomized controlled trial. *Gen Hosp Psychiatry*. 2021;69:41-49. doi:10.1016/j.genhosppsych.2020.12.008

50. Scher AI, Midgette LA, Lipton RB. Risk Factors for Headache Chronification. *Headache J Head Face Pain*. 2008;48(1):16-25. doi:10.1111/j.1526-4610.2007.00970.x
**FIGURES AND TABLES**

**Figure 1.** Distribution of veterans with post-traumatic stress disorder (PTSD), confirmed traumatic brain injury (TBI), and headache/migraine-like features who presented for comprehensive TBI evaluation, 2011-2021.

![Venn Diagram showing the distribution of veterans with PTSD, confirmed TBI, headache, and migraine-like features.](image-url)
| Variable                            | Sub-concussive Exposure | Mild TBI | Moderate TBI | p-value |
|-------------------------------------|-------------------------|----------|--------------|---------|
| Total, N (%)                        | 189 (31.8%)             | 377 (63.5%) | 28 (4.7%) | 0.130   |
| Sex, N (%)                          |                         |          |              |         |
| Male                                | 179 (94.7%)             | 344 (91.2%) | 28 (100.0%) |         |
| Female                              | 10 (5.3%)               | 33 (8.8%)  | 0           |         |
| Age (20 – 71 years old)             |                         |          |              | 0.280   |
| Mean ± SD                           | 34.42 ± 9.21            | 34.22 ± 8.43 | 36.93 ± 8.54 |         |
| Race/Ethnicity, N (%)               |                         |          |              | 0.003†  |
| White                               | 92 (48.7%)              | 201 (53.3%) | 17 (60.7%) |         |
| Black                               | 65 (34.4%)              | 139 (36.9%) | 10 (35.7%) |         |
| Other *                             | 8 (4.2%)                | 23 (6.1%)  | 1 (3.6%)    |         |
| Unknown                             | 24 (12.7%)              | 14 (3.7%)  | 0           |         |
| Educational Attainment, N (%)       |                         |          |              | 0.900   |
| High School Diploma or less         | 125 (66.1%)             | 251 (66.6%) | 18 (64.3%) |         |
| Some College/Associate Degree       | 48 (25.4%)              | 102 (27.1%) | 8 (28.6%)  |         |
| Bachelor’s Degree or more           | 14 (7.4%)               | 21 (5.7%)  | 2 (7.1%)    |         |
| Unknown                             | 2 (1.1%)                | 3 (0.8%)   | 0           |         |
| Marital status, N (%)               |                         |          |              | 0.090   |
| Married or Partnered                | 99 (52.4%)              | 235 (62.3%) | 16 (57.1%) |         |
| Single/Separated/Divorced/Widowed   | 90 (47.6%)              | 142 (37.7%) | 12 (42.9%) |         |
| Employment status, N (%)            |                         |          |              | 0.047*  |
| Full-time                           | 82 (43.4%)              | 164 (43.5%) | 11 (39.3%) |         |
| Part-time                           | 8 (4.2%)                | 19 (5.1%)  | 2 (7.15%)   |         |
| Student                             | 26 (13.8%)              | 51 (13.5%) | 2 (7.15%)   |         |
| Unemployed                          | 73 (38.6%)              | 134 (35.5%) | 13 (46.4%) |         |
| Unknown                             | 0                      | 9 (2.4%)   | 0           |         |

Abbreviations: TBI, Traumatic Brain Injury; CTBIE, Comprehensive TBI Evaluation; SD, Standard Deviation
Tests for categorical variables were conducted using χ² tests. Tests for continuous variables were conducted using linear regression.
* Indicates statistical significance (p <= 0.05).
† Indicates statistical significance (p < 0.01).
* Asian, Native American, Hispanic/Latino, and Pacific Islander.
Table 2. Headache Characteristics and Mental Health Diagnoses Grouped by TBI Severity Among Veterans Who Were Administered a CTBIE, 2011-2021

| Variable                          | Sub-concussive Exposure | Mild TBI | Moderate TBI | p-value |
|-----------------------------------|-------------------------|----------|--------------|---------|
| Headache Prevalence, N (%)        | 139 (73.5%)             | 293 (77.7%) | 27 (96.4%) | 0.015*  |
| Headache Severity (0 – 4)         | Mean ± SD               | 2.04 ± 0.88 | 2.28 ± 0.81 | 2.63 ± 1.18 | < 0.001† |
| Prevalence of Migraine-like Features, N (%) * | 87 (62.6%) | 208 (71.0%) | 26 (96.3%) | < 0.001‡ |
| Photophobia                       | 74 (53.2%)              | 186 (63.5%) | 26 (96.3%) | < 0.001‡ |
| Phonophobia                        | 60 (43.2%)              | 165 (56.3%) | 24 (88.9%) | < 0.001‡ |
| Nausea                             | 47 (33.8%)              | 124 (42.3%) | 20 (74.1%) | < 0.001‡ |
| Mental Health Diagnosis, N (%)    |                         |          |              |         |
| PTSD                               | 113 (59.8%)             | 204 (54.1%) | 17 (60.7%) | 0.400   |
| Depression                         | 69 (36.5%)              | 97 (25.7%)  | 7 (25.0%)   | 0.028*  |
| Anxiety                            | 41 (21.7%)              | 53 (14.1%)  | 3 (10.7%)   | 0.053   |

Abbreviations: TBI, Traumatic Brain Injury; CTBIE, Comprehensive TBI Evaluation; SD, Standard Deviation
Tests for categorical and ordinal variables were conducted using χ² tests.
* Indicates statistical significance (p < 0.05).
† Indicates statistical significance (p < 0.01).
‡ Indicates statistical significance (p < 0.001).
a Endorsement of photophobia, phonophobia, or nausea among veterans with headache - Neurobehavioral Symptom Inventory.

Table 3. Association between Headache Characteristics and TBI Severity Among Veterans Who Were Administered a CTBIE, 2011-2021

| Variable                          | Mild TBI VS. Sub-concussive Exposure | Moderate TBI VS. Sub-concussive Exposure | Moderate TBI VS. Mild TBI |
|-----------------------------------|-------------------------------------|----------------------------------------|--------------------------|
| Headache Prevalence               |                                     |                                        |                          |
| OR [95% CI]                       | 1.25 [0.83, 1.90]                   | 9.71 [1.29, 72.88]                    | 7.74 [1.03, 58.48]       |
| AOR [95% CI] *                    | 1.28 [0.83, 1.97]                   | 9.91 [1.28, 75.82]                    | 7.74 [1.03, 58.48]       |
| Headache Severity                 |                                     |                                        |                          |
| OR [95% CI]                       | 1.81 [1.23, 2.68]                   | 4.05 [1.72, 9.43]                     | 2.23 [0.99, 4.99]        |
| AOR [95% CI] *                    | 1.72 [1.15, 2.57]                   | 3.89 [1.64, 9.15]                     | 2.26 [0.99, 5.09]        |
| Prevalence of Migraine-like Features b |                                    |                                        |                          |
| OR [95% CI]                       | 1.46 [0.95, 2.25]                   | 15.54 [2.06, 116.6]                   | 10.62 [1.41, 79.74]      |
| AOR [95% CI] *                    | 1.25 [0.80, 1.98]                   | 15.34 [1.99, 117.7]                   | 12.25 [1.63, 92.65]      |

Abbreviations: TBI, Traumatic Brain Injury; CTBIE, Comprehensive TBI Evaluation; OR, Odds Ratio; AOR, Adjusted Odds Ratio; CI, Confidence Interval
* Indicates statistical significance (p < 0.05).
† Indicates statistical significance (p < 0.001).
Boldface indicates statistical significance after Bonferroni correction for multiple comparisons (p-value < 0.0167, after correction for the 3 association tests between 3 TBI severity groups).
a Adjusted for sex, age, race/ethnicity, post-traumatic stress disorder, depression, and anxiety.
b Endorsement of photophobia, phonophobia, or nausea among veterans with headache - Neurobehavioral Symptom Inventory.
Table 4. Headache and Injury Characteristics Among Veterans with a Confirmed History of Deployment-related Mild TBI, 2011-2021

| Variable                  | Total N (%) | Headache Prevalence N (%) | Headache Severity Mean ± SD | Prevalence of Migraine-like Features a N (%) |
|---------------------------|-------------|---------------------------|----------------------------|---------------------------------------------|
| **Mild TBI Frequency**    |             |                           |                            |                                             |
| 1                         | 270 (71.6%) | 203 (75.2%)               | 2.25 ± 0.77                | 133 (65.5%)                                |
| 2                         | 55 (14.6%)  | 46 (83.6%)                | 2.43 ± 0.89                | 39 (84.9%)                                 |
| ≥3                        | 52 (13.8%)  | 44 (84.6%)                | 2.30 ± 0.90                | 36 (81.8%)                                 |
| **Mechanism of Injury**   |             |                           |                            |                                             |
| Motor Vehicle Accident    | 39 (10.3%)  | 31 (79.5%)                | 2.52 ± 0.77                | 24 (67.7%)                                 |
| Blast Exposure            | 235 (62.3%) | 182 (77.4%)               | 2.28 ± 0.80                | 124 (68.1%)                                |
| IED                       | 159 (42.2%) | 130 (81.7%)               | 2.29 ± 0.84                | 92 (70.8%)                                 |
| Mortar                    | 49 (13.0%)  | 36 (73.4%)                | 2.50 ± 0.85                | 31 (86.1%)                                 |
| RPG                       | 53 (14.1%)  | 41 (77.4%)                | 2.32 ± 0.76                | 29 (70.7%)                                 |
| Other                     | 36 (9.5%)   | 27 (75%)                  | 2.19 ± 0.83                | 18 (66.7%)                                 |
| Fall                      | 69 (18.3%)  | 56 (81.2%)                | 2.21 ± 0.89                | 46 (82.1%)                                 |
| Blunt Trauma              | 68 (18.0%)  | 52 (76.5%)                | 2.31 ± 0.88                | 39 (75.0%)                                 |
| **LOC**                   |             |                           |                            |                                             |
| No                        | 239 (63.4%) | 179 (74.5%)               | 2.27 ± 0.80                | 125 (69.8%)                                |
| Yes (< 5 min)             | 104 (27.6%) | 83 (79.8%)                | 2.24 ± 0.82                | 58 (69.9%)                                 |
| Yes (5 – 30 min)          | 34 (9.0%)   | 31 (91.2%)                | 2.45 ± 0.85                | 25 (80.6%)                                 |
| **AOC**                   |             |                           |                            |                                             |
| No                        | 37 (9.8%)   | 24 (64.9%)                | 2.04 ± 0.81                | 18 (75.0%)                                 |
| Yes (< 30 min)            | 265 (70.3%) | 200 (75.5%)               | 2.24 ± 0.79                | 132 (66.0%)                                |
| Yes (30 min – 24 hr)      | 75 (19.9%)  | 69 (92.0%)                | 2.51 ± 0.83                | 58 (84.1%)                                 |
| **PTA**                   |             |                           |                            |                                             |
| No                        | 282 (74.8%) | 213 (75.5%)               | 2.20 ± 0.75                | 137 (64.3%)                                |
| Yes (< 30 min)            | 66 (17.5%)  | 52 (78.8%)                | 2.31 ± 0.90                | 44 (84.6%)                                 |
| Yes (30 min – 24 hr)      | 29 (7.7%)   | 28 (96.6%)                | 2.89 ± 0.79                | 27 (96.4%)                                 |
| **Helmet Use**            |             |                           |                            |                                             |
| No                        | 116 (30.8%) | 92 (79.3%)                | 2.49 ± 0.80                | 71 (77.2%)                                 |
| Yes                       | 261 (69.2%) | 201 (77.0%)               | 2.21 ± 0.80                | 137 (68.2%)                                |

Abbreviations: TBI, Traumatic Brain Injury; SD, Standard Deviation; IED, Improvised explosive device; RPG, Rocket-propelled grenade; LOC, Loss of Consciousness; AOC, Alteration of Consciousness; PTA, Post-traumatic Amnesia; min, Minutes; hr, Hours

a Endorsement of photophobia, phonophobia, or nausea among veterans with headache - Neurobehavioral Symptom Inventory.
Table 5. Association between Headache and Injury Characteristics in Veterans with a Confirmed History of Deployment-related Mild TBI, 2011-2021

| Variable                        | Headache Prevalence                  | Headache Severity                     | Prevalence of Migraine-like Features a |
|--------------------------------|--------------------------------------|---------------------------------------|----------------------------------------|
|                                | AOR [95% CI]                         | p-value                               | AOR [95% CI]                           | p-value                               | AOR [95% CI]                           | p-value                               |
| Mild TBI Frequency             |                                      |                                       |                                        |                                        |                                       |                                        |
| 1                              | Reference                            | Reference                             | Reference                              |                                       |                                       |                                        |
| 2                              | 1.74 [0.74, 4.15]                    | 0.210                                 | 2.54 [1.22, 5.31]                      | **0.012‡**                             | 4.59 [1.68, 12.42]                     | **0.007‡**                             |
| ≥3                             | 2.61 [0.96, 7.10]                    | 0.058                                 | 2.38 [1.06, 5.32]                      | 0.035*                                 | 8.13 [2.67, 24.96]                     | **0.008‡**                             |
| Years Since Most Recent TBI    |                                       |                                       |                                        |                                        |                                       |                                        |
| Mechanism of Injury b          |                                      |                                       |                                        |                                        |                                       |                                        |
| Motor Vehicle Accident         | 0.76 [0.28, 2.01]                    | 0.580                                 | 2.01 [0.90, 4.49]                      | 0.087                                 | 1.53 [0.48, 4.89]                      | 0.470                                 |
| Blast Exposure                 | 0.80 [0.34, 1.90]                    | 0.610                                 | 0.89 [0.42, 1.92]                      | 0.773                                 | 0.66 [0.24, 1.79]                      | 0.410                                 |
| IED                            | 2.12 [0.91, 4.92]                    | 0.079                                 | 1.24 [0.61, 2.56]                      | 0.543                                 | 2.09 [0.76, 5.81]                      | 0.150                                 |
| Mortar                         | 0.71 [0.29, 1.74]                    | 0.450                                 | 2.09 [0.92, 4.77]                      | 0.076                                 | 3.47 [0.97, 12.35]                     | 0.057                                 |
| RPG                            | 0.88 [0.36, 2.18]                    | 0.800                                 | 0.84 [0.37, 1.88]                      | 0.675                                 | 1.09 [0.37, 3.22]                      | 0.900                                 |
| Other                          | 0.99 [0.36, 2.69]                    | 0.990                                 | 0.65 [0.27, 1.53]                      | 0.329                                 | 0.57 [0.17, 1.91]                      | 0.360                                 |
| Fall                           | 0.71 [0.26, 1.88]                    | 0.480                                 | 0.42 [0.19, 0.92]                      | 0.031*                                | 1.44 [0.46, 4.47]                      | 0.530                                 |
| Blunt Trauma                   | 0.71 [0.29, 1.75]                    | 0.450                                 | 0.62 [0.28, 1.36]                      | 0.234                                 | 0.78 [0.25, 2.33]                      | 0.660                                 |
| LOC                            |                                       |                                       |                                        |                                        |                                       |                                        |
| No (< 5 min)                  | 1.58 [0.83, 3.02]                    | 0.170                                 | 0.89 [0.51, 1.55]                      | 0.680                                 | 0.69 [0.33, 1.45]                      | 0.330                                 |
| Yes (5 – 30 min)              | 2.74 [0.72, 10.41]                   | 0.140                                 | 1.12 [0.52, 2.77]                      | 0.670                                 | 0.83 [0.25, 2.79]                      | 0.800                                 |
| AOC                            |                                       |                                       |                                        |                                        |                                       |                                        |
| No (< 30 min)                 | 2.36 [1.01, 5.49]                    | 0.046*                                | 2.46 [0.99, 6.20]                      | 0.055                                 | 0.60 [0.20, 1.84]                      | 0.380                                 |
| Yes (30 min – 24 hr)           | 6.75 [2.08, 21.89]                   | **0.001‡**                            | 3.37 [1.26, 9.17]                      | **0.016‡**                            | 1.23 [0.33, 4.59]                      | 0.800                                 |
| PTA                            |                                       |                                       |                                        |                                        |                                       |                                        |
| No (< 30 min)                 | 0.95 [0.44, 2.04]                    | 0.900                                 | 1.07 [0.55, 2.10]                      | 0.842                                 | 2.37 [0.92, 6.05]                      | 0.070                                 |
| Yes (30 min – 24 hr)           | 4.05 [0.48, 34.40]                   | 0.200                                 | 5.40 [2.21, 13.42]                     | <0.001†                               | 11.55 [1.17, 114.8]                    | 0.037*                                |
| Helmet Use                     |                                       |                                       |                                        |                                        |                                       |                                        |
| No                             | 0.89 [0.48, 1.67]                    | 0.700                                 | 0.42 [0.23, 0.75]                      | **0.003‡**                            | 0.45 [0.21, 0.98]                      | **0.043‡**                            |

Abbreviations: TBI, Traumatic Brain Injury; AOR, Adjusted Odds Ratio; CI, Confidence Interval; IED, Improvised explosive device; RPG, Rocket-propelled grenade; LOC, Loss of Consciousness; AOC, Alteration of Consciousness; PTA, Post-traumatic Amnesia; min, Minutes; hr, Hours

Note: Regression models were adjusted for sex, age, race/ethnicity, post-traumatic stress disorder, depression, anxiety, years since most recent TBI, and blast proximity (if applicable).

* Indicates statistical significance (p <= 0.05).

† Indicates statistical significance (p < 0.01).

Boldface indicates statistical significance after Bonferroni correction for multiple comparison (Mild TBI frequency, p-value < 0.0167, after correction for the 3 association tests between 3 TBI frequency groups; Mechanism of Injury, p-value < 0.0125, after correction for the 4 association tests between 4 mechanisms of injury; Blast type, p-value < 0.0125, after correction for the 4 association tests between 4 blast types; LOC/AOC/PTA, p-value < 0.0167, after correction for the 3 association tests between 3 duration groups).

a Endorsement of photophobia, phonophobia, or nausea among veterans with headache - Neurobehavioral Symptom Inventory.

b Reference: Any other mechanism of injury

Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.
Relationship Between Headache Characteristics and a Remote History of TBI in Veterans: A 10-Year Retrospective Chart Review
Colt Coffman, Deborah Reyes, Mary Catherine Hess, et al.
Neurology published online April 25, 2022
DOI 10.1212/WNL.0000000000200518

This information is current as of April 25, 2022

Updated Information & Services
including high resolution figures, can be found at:
http://n.neurology.org/content/early/2022/04/25/WNL.0000000000200518.full

Citations
This article has been cited by 2 HighWire-hosted articles:
http://n.neurology.org/content/early/2022/04/25/WNL.0000000000200518.full#otherarticles

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
All Clinical Neurology
http://n.neurology.org/cgi/collection/all_clinical_neurology
All Headache
http://n.neurology.org/cgi/collection/all_headache
All Pain
http://n.neurology.org/cgi/collection/all_pain
Brain trauma
http://n.neurology.org/cgi/collection/brain_trauma
Migraine
http://n.neurology.org/cgi/collection/migraine

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints
Information about ordering reprints can be found online:
http://n.neurology.org/subscribers/advertise

Neurology ® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.