Headache after Moderate-to-Severe Traumatic Brain Injury

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Abstract

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Background: Headache symptoms are a major contributor to chronic pain after moderate-to-severe traumatic brain injury (TBI). We investigated associations between headache symptoms after TBI and both psychological symptoms (depression and anxiety) and patient reported outcomes (satisfaction with life and loss of employment).

Methods: A cohort of 408 individuals with moderate-to-severe TBI was prospectively followed for headache symptoms through 5 years post-injury. Cox proportional hazards regression analyses were used to examine the association between time to headache resolution or development and measures of depressive symptoms (PHQ-9) at 1 year post-injury, anxiety (GAD-7) at 2 years post-injury, satisfaction with life (SWLS) at 5 years post-injury, and loss of employment by 5 years post-injury, adjusted for potential confounding variables identified a priori.

Results: Higher PHQ-9 and GAD-7 scores were associated with decreased rates of headache resolution (HR 0.93 and 0.95, respectively, per one point increase in score) and increased rates of headache development (HR 1.08 and 1.08, respectively, per on point increase in score). Higher SWLS scores were associated with increased rates of severe headache resolution (HR 1.04) and decreased rates of headache development (HR 0.96). Loss of employment was associated with increased rate of headache development (HR 3.14).

Conclusions: Greater symptoms of depression and anxiety after TBI were associated with headache supporting processes. The findings invite new investigation into depression and anxiety as risk factors for long-term headache after TBI and highlight the impact such headaches have on patient outcomes.

Introduction

Multiple studies have shown that headache is commonly observed initially after traumatic brain injuries (TBI) of all levels of severity (1). Two prospective cohort studies of individuals with moderate-to-severe TBI have observed 38% (2,3) of individuals to experience headache during the period of inpatient rehabilitation after injury. Such headache is of clinical significance, as it is the most commonly reported source of chronic pain by TBI patients (4). As a consequence of the strength of the association between headache and TBI and the presence of a clearly identifiable etiologic event, post-traumatic headache (PTHA) has been separately defined within the International Classification of Headache Disorders as a secondary headache syndrome (5). A close temporal relationship between trauma and headache onset (within 7 days) is a defining criterion of PTHA under this definition. Despite its classification as a secondary headache, the clinical presentation of headache after TBI varies sufficiently across patients such that TBI characteristics, the putative etiologic factor, poorly inform medical management of resultant headache. This variability further limits our understanding of the pathological mechanisms linking trauma to different presentations of headache after TBI (6).

Previous cohort studies of both military and civilian patient populations, which have followed headache symptoms for up to 5 years post-injury, have found that headache does not resolve in a significant proportion of individuals and remains a chronic contributor to overall morbidity after rehabilitation. Further, chronic headache may develop at a later time point in individuals who do not exhibit headache symptoms acutely post-injury. Such headaches are not included in the ICHD definition of PTHA, though findings that headaches occur at higher rates in this population suggest they are linked to ongoing TBI-related processes (3). In a cohort of active

military or veteran patients with moderate-to-severe TBI, 19% of all patients experienced chronic headache throughout 1 year post-injury (2). A further 17% developed headache after inpatient rehabilitation. In a cohort of patients with mild TBI, which has been suggested to have a greater association with the development of headache (7), 47% were observed to have chronic and 30% to have worsening headache trajectories over 1 year following injury, based on self-reported average headache pain level (8). In a prospective cohort of individuals with moderate-to-severe TBI, the prevalence of headache that was new or worse than any headache experienced before injury was 36% at 5 years post-injury (3). The incidence of developing such headache was estimated to be 20% over 4 years, between 1 and 5 years post-injury. These findings suggest that mechanisms underlying the development and maintenance of headache may remain active in a significant proportion of TBI patients through 5 years post injury. Because of this, the impact that long duration headache symptoms have on patient quality of life after TBI should be further investigated.

Some risk factors have been identified for the acute development of headache after TBI, such as female sex, previous history of headache, and severity of TBI (4,7,9,10). However, risk factors for chronic recurring headache symptoms after TBI or the late development of headache in the post-acute phase are unclear in the literature. Identification of such factors would likely be of etiologic and prognostic significance. There is some evidence that psychological factors, including post-traumatic depression and anxiety, are associated with chronic headache but not PTHA (2). This hypothesis is supported by the known association between the transition from acute to chronic pain and emotional distress (11). It would be of value to investigate the possibility of a shared pathological etiology between post-traumatic depression and anxiety and

the maintenance of headache after TBI or the propensity to develop headache at later time points after injury. The present study seeks to address these gaps in knowledge by investigating associations between symptoms of depression and anxiety and the rate of headache resolution and development through 5 years post-injury, using data from a large prospective cohort of individuals with moderate-to-severe TBI.

Methods

Study participants:

Data for this study was drawn from the TBI Model Systems (TBIMS) study, a prospective cohort study of the natural history of TBI-related outcomes after moderate-to-severe TBI. Seven of 16 participating TBIMS study centers additionally collected information about headache-related symptoms on all enrolled TBIMS participants during inpatient rehabilitation (baseline survey) and at 3, 6, 12, and 60 months after injury (follow-up surveys). The TBIMS participating study centers were: The Virginia Commonwealth TBI Model System, Moss TBI Model System, University of Washington TBI Model System, Mayo Clinic TBI Model System, Rocky Mountain Regional Brain Injury System, and North Texas TBI Model System. Enrollment occurred between October 2007 and July 2009.

The inclusion criteria for the TBIMS study consisted of the following: patients 1) experienced moderate to-severe TBI, as determined by either >24 hours of post-traumatic amnesia, >30 minutes of loss of consciousness following injury, a Glasgow Coma Scale assessment of <13 on

admission to the emergency department, or any observed intracranial abnormalities by neuroimaging; 2) had to be admitted to a TBIMS-affiliated hospital system emergency department within 72 hours of TBI; 3) received acute and inpatient rehabilitation care within the same hospital system; 4) were at least 16 years of age at the time of TBI; and 5) gave informed consent to participate in the study or have informed consent given by a legally authorized representative. All TBIMS participants who completed a baseline headache symptoms survey, completed at least one additional follow-up headache symptoms survey, and were followed through 5 years post-injury were included in this study.

Data collection:

All data were collected by trained study personnel using a structured interview. If a study participant was not capable of completing all or part of each interview independently, only those questions that could be reliably answered by a proxy respondent were assessed. Upon enrollment into the TBIMS study during inpatient rehabilitation, baseline demographic, injury-related, and medical history information were collected. This information included: age (at time of injury), sex, race and ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), education status (high school graduate, non-graduate), pre-injury employment status (employed, retired, unemployed), cause of injury (motor accident, violence, fall, sports injury, or other), Glasgow Coma Score on admission to the emergency department, length of post traumatic amnesia, and previous diagnosis of any mental health condition (yes/no).

Headache symptoms were assessed by participant self-report at the end of inpatient rehabilitation (baseline survey) and at 3, 6, 12 months, and 5 years post-injury (follow-up survey). For the baseline survey, study participants were asked whether they had a diagnosis of any headache prior to injury and whether they had experienced any symptoms of headache during their inpatient rehabilitation. They were further asked to characterize any extant headache by average pain level (0-10 scale, where greater scores indicate greater pain) and through a structured interview about headache symptoms, from which a derived variable for headache type (migraine, probable migraine, tension-type, cervicogenic, or unclassifiable) was produced according to International Classification of Headache Disorders-2 definitions. During the follow-up surveys, study participants were asked whether they had experienced any symptoms of headache in the 3 months preceding each survey. Extant headaches at each survey were characterized by headache type, pain level, frequency (daily, >1/week, 1/week, 1/month, or <1/month). A validated measure of headache impact on daily functioning, the Headache Impact Test (HIT-6) score, was also collected at each follow-up survey. A composite HIT-6 score (range 36-78, where greater scores indicate greater impact) of 50 or higher denote headaches with some impact to daily life (12).

Participants were asked about symptoms of depression at 1 year post-injury and anxiety at 2 years post-injury. These time points were selected for this study as they were the earliest time points post-injury that each assessment was made for the full study cohort. Depression symptoms were measured using the Patient Health Questionnaire (PHQ-9), a validated instrument for screening and monitoring depression symptom severity. A greater composite PHQ-9 score (range 0-27) indicates a greater severity of depression symptoms. PHQ-9 scores of 5, 10, and 20 represent mild, moderate, and severe depressive symptoms, respectively (13). Anxiety symptoms

were measured using the Generalized Anxiety Disorder 7-item scale (GAD-7). Composite GAD-7 scores (range 0-21, with greater scores indicating greater severity of symptoms) of 5, 10, and 15 represent mild, moderate, and severe generalized anxiety disorder symptoms. The PHQ-9 and GAD-7 scales assess distinct dimensions of functional impairment (14). Both PHQ-9 and GAD-7 scores were interpreted as continuous measures of depression and anxiety symptoms over their respective ranges.

Participants were asked about their employment status and perceived satisfaction with life at 5 years post-injury. Satisfaction with life was measured using the 5-item Satisfaction with Life Scale (SWLS). Composite SWLS scores (range 5-35) of 10, 20, and 30 represent an individual's self-assessment of life satisfaction as dissatisfied, neutral, and satisfied, respectively (15). A binary indicator of change in employment status from employed pre-injury to unemployed at 5 years post-injury was derived from each participant's pre-injury employment status (collected at baseline) and their employment status at 5 years post-injury. For this measure, those participants who reported at 5 years post-injury that they were retired as a consequence of their injury were considered unemployed, while those who reported they were retired for other reasons were not considered unemployed.

Data analysis:

The total study cohort was divided into two sub-cohorts on the basis of their headache symptoms during inpatient rehabilitation. The first sub-cohort included those who experienced headache during inpatient rehabilitation. Here, the outcome of interest was the resolution of headache. A

time to resolution of headache symptoms was calculated as the difference between the date of injury and the date of the first follow-up survey at which point a participant self-reported experiencing no headache. The second cohort included those who did not experience headache during inpatient rehabilitation. For this group, the outcome of interest was the development of headache. For each individual in this sub-cohort, a time to development of headache symptoms was calculated as the difference in time between the date of injury and the date of the first follow-up survey at which they reported experiencing any headache. For both sub-cohorts, in those instances where the outcome of interest (resolution or development of headache symptoms) was observed to have occurred for the first time after a missing assessment, the time to the outcome was assumed to have occurred at the midpoint between available assessments (e.g., for a participant who experienced headache during inpatient rehabilitation and at 3 months post-injury, had a missing assessment at 6 months, and no headache at 9 months, their time to resolution of headache symptoms would be calculated as 6 months). Those individuals who were lost to follow-up were considered censored immediately before the time of first missing follow-up survey after which all follow-up surveys were missing. Individuals were also considered censored if they were followed through 5 years without experiencing the outcome or if they died during follow up. A separate analysis was conducted in which outcomes were defined by the presence of severe headaches (average headache pain ≥ 4), rather than any headache.

Methods of survival analysis were used to analyze these time to event data. For each cohort member, the date of injury was considered their indexing date and the date at which they were discharged from inpatient rehabilitation was considered their entry date. For descriptive purposes, estimates of the probability of resolving or developing headache at each point in time

post-injury were produced for each relevant sub-cohort, by the Kaplan-Meier estimator. For inferential purposes, Cox proportional hazards regression analyses were used to examine the association between PHQ-9, GAD-7, SWLS, and change in employment status and time to resolution or development of headache. The Efron approximation for ties was chosen for estimating the partial likelihood during model fitting (16). Plots of Schoenfeld residuals for each exposure of interest were evaluated to test the assumption of proportional hazards. Separate models were fit for each exposure of interest. In these models, PHQ-9, GAD-7, and SWLS were treated as continuous variables, while change in employment status was treated as a binary measure. Models were adjusted for sex, age, length of post-traumatic amnesia (<1 day, 1-7 days, 8-28 days, ≥29 days), history of previous headache diagnosis, and history of mental health diagnosis and stratified by TBIMS site. Likelihood ratio tests comparing regression models containing a term for the exposure of interest to one where it is omitted were used to test the null hypothesis that individuals who differ in the exposure of interest do not differ in the hazard of developing or resolving headache, allowing for a type-1 error rate (α) of 0.05.

All statistical analyses were conducted in R (version 3.2.2, R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 452 individuals were recruited into the TBIMS study and followed for headache symptoms. Of those study participants, 408 completed at least one additional follow-up headache survey and were followed through 5 years post-injury, comprising the cohort for this study. 58

(14.2%) of all participants were lost to follow-up, contributing on average 8.8 months of follow-up time. 48 participants died during follow-up.

Demographic and headache characteristics:

Cohort demographics are presented in Table 1. Approximately half (47%) of the full cohort experienced any headache during inpatient rehabilitation. Qualitatively, individuals who experienced headache during rehabilitation differed from those that did not with respect to sex (36% female vs 23% female), prior history of headache diagnosis (23% vs 11%), and prior mental health diagnosis (30% vs 16%), but were comparable with respect to other baseline demographics and TBI characteristics. 124 individuals (30%) experienced severe headache (average pain score ≥ 4) during inpatient rehabilitation. In addition to differences with respect to sex, prior history of headache diagnosis, and prior mental health diagnosis, those with severe headache during inpatient rehabilitation also had shorter durations of post traumatic amnesia (mean 21.6 days) than those without severe headache (mean 31.5 days).

Headache characteristics at each survey date for each sub-cohort are presented in Table 2. Among individuals who experienced any headache during inpatient rehabilitation, >50% reported experiencing headache at each follow-up survey through 5 years post-injury. Only cervicogenic type headaches were observed to decrease consistently in prevalence within this sub-cohort. Headache frequency decreased over time. The average headache pain level remained constant through 1 year post-injury and decreased at 5 years post-injury.. Despite this, the average HIT-6 score remained high across all follow-up surveys, with no decreasing trend. The average HIT-6 score at 5 years post-injury among this group (57.3) suggests that headache

contributes a substantial impact to daily life. Among individuals who did not experience headache during patient rehabilitation, >30% reported headache at each subsequent longitudinal follow-up survey. Headache pain, but not frequency, tended to decrease over time. The average HIT-6 score among this group remained within the range suggesting some impact to daily life (50-55) throughout the 5 year follow-up period. A comparison of the two sub-cohorts shows that for those who reported headache during inpatient rehabilitation, headaches experienced at follow-up time points were, qualitatively, more painful, more frequent, and more impactful than those experienced by individuals that did not report any headache during rehabilitation. However, therwe was no difference in headache type between the two sub-cohorts.

Headache incidence:

The cumulative incidence of headache resolution post-injury among those who experienced headache during rehabilitation and the cumulative incidence of headache development among those who did not experience headache during rehabilitation are estimated in the Kaplan-Meier plots presented in Figure 1. Based on these estimates, we would expect the probability of resolving headache symptoms by 5 years post-injury to be 30.8% (95% CI: 25.5% - 38.6%) for any headache and 24.8% (95% CI: 17.9% - 34.5%) for severe headaches. Similarly, we would expect the probability of developing headache symptoms by 5 years post-injury to be 63.2% (95% CI: 55.5% - 69.6%) for any headache and 53.6% (95% CI: 46.6% - 59.7%) for severe headache. Due to the possibility for missed observations, given the sampling scheme of this study, these estimates are likely underestimates of the true cumulative incidence of headache resolution and development in this cohort.

Associations with depression and anxiety:

Symptoms of depression at 1 year post-injury and generalized anxiety disorder at 2 years post-injury were examined for their association with the rate of headache resolution or development by Cox proportional hazards regression analyses. Hazard ratios were estimated for these associations, adjusting for age, sex, length of post traumatic amnesia, prior headache and mental health diagnoses, and stratified by treatment site. For the sub-cohort of individuals who experienced headache during inpatient rehabilitation, hazard ratios for time to resolution of headache symptoms is given in Table 3. A hazard ratio >1 indicates an increased rate of headache resolution or a shorter time to headache resolution. From these analyses, we can estimate that each one point increase on the PHQ-9 scale is associated with a 7% decrease (95% CI: 4% - 11% decrease) in the hazard of resolving any headache and an 8% decrease (95% CI: 4% - 13% decrease) in the hazard of resolving a severe headache. Such estimates indicate, for example, a 43% difference in the hazard of resolving any headache between individuals with a 5 point difference in PHQ-9 scores (HR = 1/(0.93^5) = 1.43), indicating mild and moderate depressive symptoms, or a 297% difference in hazard between individuals with a 15 point difference in PHQ-9 scores, indicating mild and severe depressive symptoms. Adjusted hazard ratios for a one point difference in GAD-7 score were estimated to be similar in magnitude and direction to those obtained for PHQ-9 score. Higher GAD-7 and PHQ-9 scores were therefore associated with longer times to resolution of any headache or severe headache.

For the sub-cohort of individuals who did not experience headache during inpatient rehabilitation, hazard ratios for time to development of headache symptoms are given in Table 4. Hazard ratios >1 indicate an increased rate of headache development or a shorter time to headache development. Based on these analyses we estimate that each one point increase on PHQ-9 scale is associated with an 8% increase (95% CI: 4% - 11% increase) in the hazard of developing any headache and a 5% increase (95% CI: 2% - 14% increase) in the hazard of developing a severe headache. Adjusted hazard ratios for a one point difference in GAD-7 score were estimated to be similar in magnitude and direction to those obtained for PHQ-9 score. Higher GAD-7 and PHQ-9 scores were therefore associated with shorter times to development of any headache or severe headache. For both sub-cohorts, adjusted hazard ratios for PHQ-9 and GAD-7 scores were all found to be statistically significant by likelihood ratio tests ($P < 0.05$).

Associations with satisfaction with life and employment:

The impacts of differences in time to resolution or development of headache on life satisfaction and employment were also investigated by examining associations between SWLS scores and loss of employment at 5 years post-injury with rate of headache resolution or development by Cox proportional hazards regression analyses. Among the sub-cohort of those who experienced headache during inpatient rehabilitation, a significant association was only observed betweenSWLS and the hazard of resolving severe headache. Each 1 point increase in SWLS score was associated with a 4% increase (95% CI: <1% - 9% increase) in the rate of headache resolution ($P = 0.024$). This estimate suggests that shorter times to the resolution of severe

headache are associated with greater SWLS scores. No significant associations were observed between loss of employment and the resolution of headache symptoms.

Among the sub-cohort of those who did not experience headache during inpatient rehabilitation, longer times to the development of any headache or severe headache were found to be associated with greater SWLS scores. Each 1 point increase in SWLS score was associated with a 4% decrease (95% CI: 1% - 7% decrease) in the hazard of developing any headache or a 3% decrease (95% CI: <1% - 5%) in the hazard of developing severe headache. Individuals differing in SWLS by 10 points (the difference between a self-assessment of dissatisfied and neutral life satisfaction) would be estimated to differ in the hazard of developing any headache by 50% (1/(0.96^10) = 1.50). Loss of employment was estimated to be associated with an increased hazard of developing any headache (HR = 3.14) and severe headache (HR = 1.81).

Discussion

Previous prospective studies of headache after moderate-to-severe TBI have observed that symptoms of headache are common early after injury and may arise or persist after the acute phase of injury as a long-term contributor to chronic pain (2,3). Nearly half of this prospectively studied cohort developed any headache during inpatient rehabilitation following injury. Of those that did not experience headache symptoms acutely, a further 63% would be expected to do so over the course of 5 years post-injury. By stratifying on acute headache symptoms, we observed that those headaches that developed at a later time point were comparable in type to those that developed acutely, but less painful, less frequent, and less impactful, on average.

Some risk factors for the development of acute headache symptoms have been identified from these studies, such as sex, history of headache, and severity of headache. These same factors, however, have not been found to be informative as to whether a patient who develops headache acutely after injury will resolve their symptoms quickly or will go on to develop a chronic headache condition (3). Likewise, they are not informative as to which patients who do not experience acute headache symptoms will progress to develop headache at a later time point. For this reason, there is a need to separately evaluate risk factors for headache after TBI for their potential contribution to acute and chronic headache symptoms.

In this study, we examined symptoms of depression and generalized anxiety disorder as factors that may influence the maintenance or development of headache after inpatient rehabilitation for TBI, rather than for their association with acute headache symptoms. We observed that greater symptoms of depression at 1 year post-injury and generalized anxiety disorder at 2 years post-injury were associated with increased chronic headache symptoms. The estimated magnitudes of these associations are potentially clinically relevant. For example, among the sub-cohort of individuals who experienced headache symptoms during inpatient rehabilitation, 5, 10, and 15 point differences in PHQ-9 scores at 1 year post-injury, representing comparisons between individuals with no symptoms of depression and those of mild, moderate, and severe depression, were estimated to be associated with a 1.4-, 2.0-, and 4.3-fold decrease in the rate of headache resolution. Among the sub-cohort of those who did not experience headache symptoms during inpatient rehabilitation, the same PHQ-9 score differences were estimated to be associated with a 1.5-, 2.2-, and 4.7-fold increase in the rate of headache development. The estimates presented in

this study were adjusted for known risk factors of acute headache as well as pre-injury characteristics that may confound the observed associations, such as a history of previous mental health or headache diagnosis. That higher PHQ-9 and GAD-7 scores post-injury were associated with both a decrease in the rate of headache resolution and an increase in the rate of headache development in the separate sub-cohorts suggests that greater symptoms of depression and generalized anxiety disorder were overall associated with headache supporting processes, be it involved with the maintenance of early developing headache or the promotion of late developing headache.

There exist a number of different possible pathways between TBI and chronic headache that would be consistent with the findings of this study. First, the development of depression and anxiety after TBI may itself promote the development of headache. Second, a shared process may lead to the co-development of headache and psychological symptoms after TBI. Third, the development of headache may contribute to the development of psychological symptoms. Outside of the setting of TBI, cross-sectional and longitudinal studies have previously examined the association and temporal relationship between headache, particularly migraine, and psychological comorbidities, including both depression and generalized anxiety disorder (17). Findings from these studies have supported a bidirectional relationship between headache and depression, such that the presence of one increases the risk of incidence of the other (18). Similarly, anxiety disorders have been associated with the development of chronic migraine and the maintenance of migraine (19) and existent migraine has been associated with the development of generalized anxiety disorders, mediated by the development of chronic pain and limitations to daily life (20). Further, depression and anxiety may interact in their contribution to

the development of migraine (21). The findings from the present study would be consistent with either unidirectional or bidirectional causal relationships between headache and both psychological comorbidities. While it was not possible in this study to examine the temporal relationship between the development of depression and anxiety after TBI and the promotion of headache after TBI, as has been done in other settings, our findings highlight the need for diagnostic vigilance for these associated outcomes in patients with moderate-to-severe TBI, as each may be prognostic of the other. Studies designed to investigate the causal relationship between these outcomes in the setting of TBI would be a valuable future direction of research that may lead to better long-term management of TBI-related symptoms.

We also examined whether differences in long-term trends in headache symptoms were impactful on patient outcomes through 5 years post-injury. Among individuals who did not experience headache during inpatient rehabilitation, we observed that shorter times to development of headache were associated with lower satisfaction with life at 5 years post-injury and greater risk of loss of pre-injury employment by 5 years post-injury. The magnitude of these observed associations were large. For example, 10 and 20 point differences in SWLS scores at 5 years post-injury, representing comparisons between individuals with self-assessments of life satisfaction as satisfied with those that are neutral or dissatisfied, respectively, were estimated to be associated with 2.2- and 4.6-fold increases in the rate of headache development. These findings highlight the impact that late developing headache has on patient outcomes after moderate-to-severe TBI. In this study, it was not possible to stratify all individuals based on ICHD criteria for PTHA, as the ascertainment of acute headache symptoms was done with respect to the duration of inpatient rehabilitation, rather than a period covering 7 days after

injury. Nevertheless, those individuals who did not experience headache during inpatient rehabilitation, within whom a strong association was observed between headache development and 5 year outcomes, would not have met PTHA criteria. The observed associations with SWLS and loss of employment, coupled with the high cumulative incidence of headache over 5 years post-injury also observed among these individuals, highlight the importance of monitoring for headache symptoms among those who did not develop acute headache after injury.

This is the first study of headache after moderate-to-severe TBI which considered risk factors for the maintenance and late development of headache independently of those for acute headache. This approach has the advantage of allowing for the investigation of risk factors that can only arise after injury occurs, such as the psychological symptoms following TBI, which may have greater long-term prognostic value than pre-injury or baseline characteristics of an individual. These post-injury measures may provide valuable insights into the etiology of adverse outcomes. This study and the approach taken have some limitations which limit the interpretation of the findings. Characterization of the outcome as a time to event captures one salient dimension of an individual's experience with headache over the post-injury period, but may not fully describe it. This is particularly evident for those individuals who report intermittent symptoms of headache after injury. Imperfect ascertainment of the outcome of interest, due to the sampling scheme used, loss to follow up, and the reliance on self-report among a patient population that may have increased risk of recall bias, may also introduce bias into the study. We would expect that such bias, if present, would result in an underestimation of true cumulative incidence of headache resolution or development. Because such misclassification is not differential to the exposures of interest, we would expect that, on average, any introduced bias would attenuate observed

measures of relative risk from their true associations. Lastly, the cross-sectional ascertainment of the exposures of interest within these data prohibits investigation of the direction of causal relationships. Overall, however, these findings are drawn from one of the largest prospective cohort studies of headache after moderate-to-severe TBI conducted to date. The findings invite new investigation into depression and anxiety as risk factors for long-term headache after TBI and highlight the impact such headaches have on patient outcomes.

References:

1. Lane JC, Arciniegas DB. Post-traumatic Headache. Curr Treat Options Neurol. 2002 Jan;4(1):89–104.

2. Walker WC, Seel RT, Curtiss G, Warden DL. Headache after moderate and severe traumatic brain injury: a longitudinal analysis. Arch Phys Med Rehabil. 2005 Sep;86(9):1793–800.

3. Stacey A, Lucas S, Dikmen S, Temkin N, Bell KR, Brown A, et al. Natural History of Headache Five Years after Traumatic Brain Injury. J Neurotrauma. 2017 Jan 18;

4. Uomoto JM, Esselman PC. Traumatic brain injury and chronic pain: differential types and rates by head injury severity. Arch Phys Med Rehabil. 1993 Jan;74(1):61–4.

5. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia Int J Headache. 2013 Jul;33(9):629–808.

6. Lucas S, Hoffman JM, Bell KR, Walker W, Dikmen S. Characterization of headache after traumatic brain injury. Cephalalgia Int J Headache. 2012 Jun;32(8):600–6.

7. Couch JR, Bearss C. Chronic daily headache in the posttrauma syndrome: relation to extent of head injury. Headache. 2001 Jun;41(6):559–64.

8. Sawyer K, Bell KR, Ehde DM, Temkin N, Dikmen S, Williams RM, et al. Longitudinal Study of Headache Trajectories in the Year After Mild Traumatic Brain Injury: Relation to Posttraumatic Stress Disorder Symptoms. Arch Phys Med Rehabil. 2015 Nov;96(11):2000–6.

9. Walker WC, Marwitz JH, Wilk AR, Ketchum JM, Hoffman JM, Brown AW, et al. Prediction of headache severity (density and functional impact) after traumatic brain injury: A longitudinal multicenter study. Cephalalgia Int J Headache. 2013 Sep;33(12):998–1008.

10. Jensen OK, Nielsen FF. The influence of sex and pre-traumatic headache on the incidence and severity of headache after head injury. Cephalalgia Int J Headache. 1990 Dec;10(6):285–93.

11. Jacobsen L, Mariano A. General considerations of chronic pain. In: Loeser J, editor. Bonica's management of pain. Philadelphia: Lippincott Williams & Wilkins; 2001.

12. Kosinski M, Bayliss MS, Bjorner JB, Ware JE, Garber WH, Batenhorst A, et al. A six-item short-form survey for measuring headache impact: the HIT-6. Qual Life Res Int J Qual Life Asp Treat Care Rehabil. 2003 Dec;12(8):963–74.

13. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001 Sep;16(9):606–13.

14. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006 May 22;166(10):1092–7.

15. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction With Life Scale. J Pers Assess. 1985 Feb;49(1):71–5.

16. Efron B. The Efficiency of Cox's Likelihood Function for Censored Data. J Am Stat Assoc. 1977 Sep;72(359):557.

17. Hamelsky SW, Lipton RB. Psychiatric comorbidity of migraine. Headache. 2006 Oct;46(9):1327–33.

18. Breslau N, Davis GC, Schultz LR, Peterson EL. Joint 1994 Wolff Award Presentation. Migraine and major depression: a longitudinal study. Headache. 1994 Aug;34(7):387–93.

19. Smitherman TA, Penzien DB, Maizels M. Anxiety disorders and migraine intractability and progression. Curr Pain Headache Rep. 2008 Jun;12(3):224–9.

20. Fuller-Thomson E, Jayanthikumar J, Agbeyaka SK. Untangling the Association Between Migraine, Pain, and Anxiety: Examining Migraine and Generalized Anxiety Disorders in a Canadian Population Based Study. Headache. 2017 Mar;57(3):375–90.

21. Breslau N, Davis GC, Andreski P. Migraine, psychiatric disorders, and suicide attempts: an epidemiologic study of young adults. Psychiatry Res. 1991 Apr;37(1):11–23.

Table 1: Cohort demographics

	Total (N = 408)		Headache at baseline (N = 193)		No headache at baseline (N = 215)	
	n / Mean	**%[1] / SD**	**n / Mean**	**%[1] / SD**	**n / Mean**	**%[1] / SD**
Sex (Female)	118	29%	69	36%	49	23%
Age (Years)	42.4	19.5	41.0	17.7	43.6	21.0
Race/Ethnicity						
NH-White	302	74%	144	75%	158	73%
NH-Black	63	15%	26	13%	37	17%
Hispanic	25	6%	13	7%	12	6%
Other	18	4%	10	5%	8	4%
HS graduate	287	70%	134	69%	153	71%
Employment						
Employed	297	73%	140	73%	157	73%
Unemployed	63	15%	36	19%	27	13%
Retired	48	12%	17	9%	31	14%
Cause of Injury						
Motor accident	205	50%	85	44%	120	56%
Violence	38	9%	23	12%	15	7%
Fall	110	27%	53	27%	57	27%
Sports	31	8%	18	9%	13	6%
Other	24	6%	14	7%	10	5%
Glasgow Coma Score						
Mild (GCS: ≥13)	128	54%	59	54%	69	54%
Moderate (GCS: 9-12)	47	20%	23	21%	24	19%
Severe (GCS: 3-8)	62	26%	28	25%	34	27%
Observed Length of PTA						
<1 day	24	6%	12	6%	12	6%
1-7 days	74	18%	37	19%	37	17%
8-28 days	153	38%	72	38%	81	38%
>29 days	152	38%	70	36%	82	38%
Prior headache diagnosis	59	17%	38	23%	21	11%
Prior mental health diagnosis	92	23%	58	30%	34	16%
Length of inpatient rehabilitation (days)	47.2	35.9	45.6	35.1	48.6	36.5

1. Percent of non-missing values.

Table 2: Headache characteristics.

	Time post-injury									
Headache at baseline	**Rehabilitation**		**3 Months**		**6 Months**		**12 Months**		**5 Years**	
(N = 193)	**n / Mean**	**% / SD**	**n / Mean**	**% / SD**	**n / Mean**	**% / SD**	**n / Mean**	**% / SD**	**n / Mean**	**% / SD**
Any headache	193	100%	97	66%	90	57%	87	54%	82	57%
Headache type										
Migraine	48	30%	29	19%	29	18%	31	19%	32	22%
Probable migraine	36	22%	28	19%	23	14%	21	13%	22	15%
Tension	11	7%	14	9%	12	8%	19	12%	9	6%
Cervicogenic	12	7%	6	4%	3	2%	2	1%	1	1%
Unclassifiable	55	34%	20	13%	24	15%	14	9%	19	13%
Pain level	5.96	2.66	6.07	2.45	5.87	2.48	5.90	2.17	3.49	3.48
Frequency										
< 1/Month	-	-	10	7%	10	6%	10	6%	14	10%
1/Month	-	-	11	7%	21	13%	15	9%	21	15%
1/Week	-	-	19	13%	19	12%	21	16%	15	10%
1/Day	-	-	37	25%	16	10%	26	16%	23	16%
> 1/Day	-	-	20	14%	24	15%	15	9%	9	6%
HIT-6	-	-	55.5	12.8	57.9	12.4	57.2	11.2	57.3	11.2
No headache at baseline	**Rehabilitation**		**3 Months**		**6 Months**		**12 Months**		**5 Years**	
(N = 215)	**n / Mean**	**% / SD**	**n / Mean**	**% / SD**	**n / Mean**	**% / SD**	**n / Mean**	**% / SD**	**n / Mean**	**% / SD**
Any headache	0	0%	48	32%	55	32%	66	38%	54	36%
Headache type										
Migraine	-	-	13	9%	22	12%	17	10%	13	8%
Probable migraine	-	-	8	5%	7	4%	14	8%	15	10%
Tension type	-	-	12	8%	12	7%	11	6%	10	7%
Cervicogenic	-	-	2	1%	1	1%	4	2%	0	0%
Unclassifiable	-	-	13	9%	13	8%	20	11%	17	11%
Pain level	-	-	5.24	2.60	5.47	2.21	5.06	2.27	1.61	2.48
Frequency										
< 1/Month	-	-	14	9%	16	9%	23	13%	17	11%
1/Month	-	-	15	10%	14	8%	11	6%	16	11%
1/Week	-	-	6	4%	7	4%	16	9%	9	6%
1/Day	-	-	7	5%	15	9%	12	7%	9	6%
> 1/Day	-	-	6	4%	3	2%	4	2%	3	2%
HIT-6	-	-	52.4	14.0	53.9	12.9	53.7	12.1	52.0	9.8

Table 3: Factors associated with headache resolution

	Any headache			Severe headache		
Headache at baseline	**HR[1]**	**95% CI**	**P-value[2]**	**HR[1]**	**95% CI**	**P-value[2]**
PHQ-9, 1 year	0.93	0.89, 0.96	< 0.001	0.92	0.87, 0.96	< 0.001
GAD-7, 2 years	0.95	0.91, 1.00	0.032	0.92	0.87, 0.97	0.002
SWLS, 5 years	1.00	0.97, 1.04	0.790	1.04	1.00, 1.09	0.024
Loss of employment, 5 years	0.93	0.55, 1.56	0.776	0.83	0.43, 1.58	0.565

1. Hazard ratio for one point increase in PHQ-9, GAD-7, or SWLS scores, or between those who transitioned from employed to unemployed and those who did not for employment status. Hazard ratios are adjusted for age, sex, length of post traumatic amnesia, prior headache diagnosis, and prior mental health diagnosis and stratified by treatment site.
2. Based on likelihood ratio tests.

Table 4: Factors associated with headache development

	Any headache			Severe headache		
No headache at baseline	**HR[1]**	**95% CI**	**P-value[2]**	**HR[1]**	**95% CI**	**P-value[2]**
PHQ-9, 1 year	1.08	1.04, 1.11	< 0.001	1.05	1.02, 1.10	0.004
GAD-7, 2 years	1.08	1.02, 1.14	0.009	1.10	1.05, 1.16	< 0.001
SWLS, 5 years	0.96	0.93, 0.99	0.006	0.97	0.95, 1.00	< 0.001
Loss of employment, 5 years	3.14	1.77, 5.71	< 0.001	1.81	1.04, 3.15	0.040

1. Hazard ratio for one point increase in PHQ-9, GAD-7, or SWLS scores, or between those who transitioned from employed to unemployed and those who did not for employment status. Hazard ratios are adjusted for age, sex, length of post traumatic amnesia, prior headache diagnosis, and prior mental health diagnosis and stratified by treatment site.
2. Based on likelihood ratio tests.

Figure 1: Resolution and development of headache after TBI