Anxiety Trajectories the First 10 Years Following a Traumatic Brain Injury (TBI):

A TBI Model Systems Study

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This is the author's manuscript of the article published in final edited form as:

Neumann, D., Juengst, S. B., Bombardier, C. H., Finn, J. A., Miles, S. R., Zhang, Y., Kennedy, R., Rabinowitz, A. R., Thomas, A., & Dreer, L. E. (2022). Anxiety Trajectories the First 10 Years After a Traumatic Brain Injury (TBI): A TBI Model Systems Study. Archives of Physical Medicine and Rehabilitation, 103(11), 2105–2113. https://doi.org/10.1016/j.apmr.2022.07.002

We have no known conflict of interest to disclose.

The contents of this manuscript were developed under grants from the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR grant numbers: IU 90DRTB0002, NTX 90DPTB0013, UAB 90DPTB0015, Spaulding/Harvard 90DPTB0011, Moss 90DPTB0004 University of Washington 90DPTB008,). NIDILRR is a Center within the Administration for Community Living (ACL), Department of Health and Human Services (HHS). The contents of this manuscript do not necessarily represent the policy of NIDILRR, ACL, or HHS, and you should not assume endorsement by the Federal Government.

Dr. Finn's contributions to this manuscript are the result of work supported with resources and the use of facilities at the Minneapolis VA Health Care System, as well as the VA Polytrauma Rehabilitation Center Traumatic Brain Injury Model System, a funded collaboration between the Department of Veterans Affairs and the Department of HHS. The views, opinion, and/or findings contained in this article are those of the authors and should not be construed as an official position, policy, or decision of the US Department of Veterans Affairs or any other federal agency unless so designated by other official documentation.

Related conference presentation:

Neumann, D., Juengst, S.B., Bombardier, C.H., Finn, J.A., Miles, S., Zhang, Y., Kennedy, R.E., Rabinowitz, A.R., Thomas, A., Dreer, L.E. Trajectories and Predictors of Anxiety Over a Ten-year Duration after Traumatic BrainInjury: A TBIMS Study. ACRM 98th Annual Conference, Dallas, Texas (Virtual), September 26-29, 2021.

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ABSTRACT

Objective: Determine anxiety trajectories and predictors up to 10 years post-traumatic brain injury (TBI).

Design: Prospective longitudinal, observational study.

Setting: Inpatient rehabilitation centers.

Participants: 2,836 participants with moderate to severe TBI enrolled in the TBI Model Systems National Database who had ≥2 anxiety data collection points.

Main Outcome Measure: Generalized Anxiety Disorder-7 (GAD-7) at 1, 2, 5, and 10-year follow-ups.

Results: Linear mixed models showed higher GAD-7 scores were associated with Black race ($p<.001$), public insurance ($p<.001$), pre-injury mental health treatment ($p<.001$), 2 additional TBIs with loss of consciousness (LOC) ($p=.003$), violent injury ($p=.047$), and more years post-TBI ($p=.023$). An interaction between follow-up year and age was also related to GAD-7 scores ($p=.006$). A latent class mixed model identified three anxiety trajectories: low-stable (n=2,195), high-increasing (n=289), and high-decreasing (n=352). The high-increasing and high-decreasing groups had ≥mild GAD-7 scores up to 10 years. Compared to the low-stable group, the high-decreasing group was more likely to be Black (OR=2.25), have public insurance (OR=2.13), have had pre-injury mental health treatment (OR=1.77), and have had 2 prior TBIs (OR=3.16).

Conclusions: A substantial minority of participants had anxiety symptoms that either increased (10%) or decreased (13%) over 10 years, but never decreased below mild anxiety. Risk factors of anxiety included indicators of socioeconomic disadvantage (public insurance) and racial inequities (Black race) as well as having had pre-injury mental health treatment and two prior TBIs. Awareness of these risk factors may lead to identifying and proactively referring susceptible individuals to mental health services.

Key Words: Anxiety, brain injury, affect, rehabilitation, mental health

LIST OF ABBREVIATIONS:

AIC: Akaike's Information Criterion

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

GAD: Generalized Anxiety Disorder

LOC: Loss of Consciousness

PTA: Post-traumatic amnesia

TBI: Traumatic Brain Injury

TBIMS: Traumatic Brain Injury Model Systems

TFC: Time to Follow Commands

INTRODUCTION

Depression and anxiety are common, and often co-occurring, sequalae after traumatic brain injury (TBI).[1-5] However, much of the research to-date has focused on depression, leaving the post-injury course of anxiety and its antecedent factors largely unstudied, especially after moderate-to-severe TBI.[1-5] Post-TBI anxiety may represent a recurrence of a pre-TBI disorder or may result from neuropathophysiological damage, post-injury impairments (e.g. cognition, other emotional problems), anxiety related to the mechanism of injury or circumstances surrounding the injury in the form of post-traumatic stress, and/or life changes and challenges associated with TBI sequelae (e.g., loss of independence, uncertainty about future, unemployment).[6-10] Generalized anxiety in individuals with TBI has been associated with negative outcomes, including co-occurring issues with depression, problems socializing, occupational difficulties, lower quality of life, and even suicidality.[1,11-16] Generalized anxiety disorder (GAD) is one of the most common anxiety disorders,[17] defined as the presence of excessive anxiety/worry and somatic symptoms, causing significant distress or impairment to the individual.[18] In terms of the prevalence of GAD after TBI, a meta-analysis reported an average rate of 11% (range: 2-28%) when evaluated with a structured interview and 37% (range: 4-83%) when assessed with self-report measures.[6] Factors associated with anxiety after TBI include being female, being in middle adulthood, Black race, pre-injury unemployment, having a non-private insurance payor, lower education, prior mental health treatment, prior TBIs, and a more severe TBI.[4,6,19-21]

Past studies on the course of anxiety after TBI have produced conflicting results. A meta-analysis of cross-sectional studies that assessed anxiety at different times post-injury in studies of mild, moderate, and severe TBI reported that anxiety was highest 2 to 5 years post-injury (as opposed to earlier or later assessment time points).[6] However, a subsequent longitudinal study that examined rates of psychiatric disorders during the first five years after moderate to severe TBI found that anxiety disorders were most frequent the first year after TBI (44.1%).[7] Shorter-term longitudinal studies of anxiety have reported that after mild TBI the prevalence of anxiety significantly decreased from baseline (within 2 weeks of injury) to 12 months post-injury (42.2% to

29.3%) [22] and from baseline to two years after injury.[23] However, Ma and colleagues sought to examine clinically meaningful subgroups, and identified a group of participants who had clinically significant anxiety at both baseline and two years post-injury (43%) and another group who was asymptomatic of anxiety at both time points (57%), suggesting more stable anxiety over time.[23] Other authors examined anxiety trajectories in participants with severe TBI over a two-year period (n=129) and also identified two groups: one characterized by low and relatively stable anxiety (69.1%) and the other with consistently high anxiety at both time points (30.9%). [24]

In sum, much remains unknown about the long-term course of anxiety after moderate to severe TBI—particularly beyond the first 5 years post-injury—including the possible existence of clinically important subgroups that differ in the trajectory of symptoms. The current study sought to address these gaps by using latent class analysis to examine the presence of distinct anxiety trajectories across the first 10 years after TBI, and to identify demographic, preinjury, injury-related, and treatment factors associated with overall anxiety levels and class membership in different anxiety trajectory subgroups.

METHODS

Participants

The study sample was derived from participants who were enrolled in TBI Model Systems (TBIMS) national longitudinal database from April 2010 (when Generalized Anxiety Disorder-7 data collection began) through September 2020. Participants were assessed for baseline characteristics during inpatient rehabilitation and were administered the Generalized Anxiety Disorder-7 (GAD-7) at 1, 2, 5, and every 5 years after their TBI. Eligibility criteria for TBIMS participants are: (1) receive care at a trauma center affiliated with the TBIMS within 72 hours of TBI, (2) received inpatient rehabilitation treatment at a TBIMS site, and (3) ≥18 years old. Each TBIMS site received and maintained permission to conduct research from their local human subject review boards. A total of 9070 people consented to participate in the national database during this time period. For the current study, participants had to have ≥2 GAD-7 data points within the first 10 years post-TBI, which resulted in a sample of 2836 participants included in the current study. All excluded participants only

had one GAD-7 data point (1318 only had Year 1; 781 only had year 2; 2,766 only had Year 5, and 1369 only had year 10 data). Reasons participants would not have had ≥2 GAD-7 datapoints include: lost to follow-up, refused follow-up or variables, incarcerated, withdrew, expired/died, or were unable to provide self-report data. Additionally, TBIMS switched from GAD-7 to a different anxiety measure between October 2012 through September 2017, which also contributed to participants not having ≥2 datapoints during this period.

Measures

Generalized Anxiety Disorder – 7 item scale (GAD-7).[25] The GAD-7 is a self-report questionnaire of generalized anxiety symptom severity designed to map onto the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) symptom criteria for GAD. Participants described each symptom's frequency over the past two weeks using a 4-point rating scale, ranging from "not at all" to "nearly every day". Total GAD-7 scores (range 0-21) of less than 5 indicate minimal anxiety, 5 to 9 indicate mild anxiety, 10 to 14 indicate moderate anxiety, and scores greater than 14 indicate severe anxiety.

Sociodemographic variables at injury. Sociodemographic variables were collected at the time of enrollment into the TBIMS study and included age; race (i.e., White, Black, Native American, Asian/Pacific Islander, Hispanic Origin, Other and Unknown); marital status at injury (single, married, divorced, separated, widowed, other), which was recoded into single, married, other; pre-injury education (number of completed years), with responses classified into "less than high school diploma", "high school diploma", "some college/associate's degree", and "bachelor's degree or more"; and primary pre-injury employment status (employed, student, or other for those retired, unemployed, volunteer workers, homemakers, or other employment status). Data on acute medical care payor was coded as private (i.e., private insurance, automotive insurance, worker's compensation, Tricare, HMO, and PPO), public (most government healthcare payments, e.g., Medicaid, State or County, Charity), Medicare, or other. Since insurance was used as a proxy for SES, Medicare—a prevalent insurance payor for individuals over 65 regardless of income- was separated out from other public forms of insurance.[26] Acute care payor (as opposed to Rehabilitation payor source) was selected due to precedence in other research examining outcomes in patients with TBI.[27]

Injury-related variables. Injury-related variables included cause of injury, time to follow commands, and number of TBIs with loss of consciousness (LOC) before the index TBI (i.e., the TBI that resulted in the hospitalization that qualified the individual for TBIMS participation). Time to follow commands was calculated based on number of days between the date of injury and the date the participant was able to follow simple motor commands in two successive assessments within a 24-hour period. The number of TBIs prior to the index injury was assessed via the Ohio State University-TBI Identification Method. [28,29]

TBI treatment variables. Treatment variables included days spent in acute medical care and days spent in rehabilitation.

Pre-injury behavioral health variables. Behavioral health variables included illicit drug use, binge drinking, mental health treatment. Pre-injury illicit drug use was coded dichotomously (yes/no) based on the reported use of illegal or non-prescription drugs during the year before the index TBI. Pre-injury binge drinking was coded dichotomously (yes/no) based on the reported number of alcoholic beverages during a single occasion the month before the index TBI (≥ 5 for males; ≥ 4 for females). Pre-injury mental health treatment was coded dichotomously (yes/no) based on participants reporting receipt of any type of treatment for "any mental health problems" (e.g., depression, anxiety).

Procedures

Upon consent, which occurred during inpatient rehabilitation or shortly after discharge, research staff extracted data from the medical record (i.e., birthdate, race/ethnicity, date of injury, cause of injury, time to follow commands, acute medical payor source, days spent in acute medical services, and days spent in rehabilitation services) and collected the remaining variables via self-report from a structured interview (i.e., marital status, education level, employment status, TBI history, illicit or non-prescription drug use, binge drinking, and mental health treatment). Participants completed the GAD-7 at follow-up assessments at 1, 2, 5, and 10 years post-injury via telephone, in-person interview, or mailed survey.

Data Analysis

Characteristics of participants were summarized using percentages for categorical variables and means and standard deviations for continuous variables. Linear mixed models were used to estimate change in GAD-7 scores over time.[30] For the overall group, we modeled the average rate of change across participants using a mixed model with a fixed intercept (baseline GAD-7 score) and slope (change in GAD-7 scores over time), as well as a random effect of time for each participant to model individual variation from the overall group. We then conducted latent class analysis to detect the presence of subgroups within the sample that differed in trajectory of GAD-7 scores over time. We constructed models with two to five groups, using Akaike's Information Criterion (AIC)[31] to determine the best fitting model. After determining the optimal number of groups, each participant was assigned to the group with the highest probability based on the latent class mixed model. We also calculated the means and standard errors for the GAD-7 scores of each of the groups at each of the observed time points. Models were estimated using the *lcmm* package [32] for the R statistical environment. [33] Multivariable logistic regression analysis was performed to examine the association between group classification and demographic/injury characteristics. Odds ratios and 95% confidence intervals were generated from the logistic regression models.

RESULTS

Half of the 2836 participants (51.8%) provided data at years 1 and 2, while 18.3% provided data at years 1, 2, and 10; 7.8% at years 2, 5, and 10; and 7.1% at years 2 and 10. Excluded (6234, 68.7%) and included participants did not significantly differ on most variables with a few exceptions (Supplemental Table 1). Relative to those who were excluded, those included were more likely to have ≥high school education (76.9% vs. 71.7%, respectively, p<.001) and had less severe TBI severity as measured by time to follow commands (19.1 days vs. 28.6 days, respectively, p=.001). Although some other comparisons were statistically significant (e.g. cause of injury), the differences were small. Demographic, injury, and GAD-7 information for the current sample is presented in Table 1.

----------INSERT TABLE 1----------

Linear mixed effect model results are summarized in Table 2. Higher GAD-7 baseline scores were associated significantly with Black race (compared to White), having public insurance (compared to private), premorbid mental health problems, experiencing 2 additional TBIs with LOC (compared to no prior TBI with LOC), and having had a violent TBI (compared to vehicle-related injuries). GAD-7 scores were found to increase with longer follow-up time. A small, yet significant interaction between follow-up year and age was also identified, suggesting younger participants were more likely to have increases in anxiety over time compared to older participants.

----------INSERT TABLE 2----------

Using latent class mixed model analysis, three groups were identified based on GAD-7 trajectories: low-stable (n = 2195, 77.4%), high-increasing (n = 289, 10.2%), and high-decreasing (n = 352, 12.4%). Patterns of completion for GAD-7 assessments at different combinations of time points (e.g., years 1 and 2; years 1, 2, and 10; years 5 and 10) were not significantly different among the three trajectories (p=.265), indicating trajectories did not depend on completion rates. Percentage of GAD-7 data missingness was also similar at each follow-up time point among the three trajectory groups. We assessed the stability of trajectory group assignments by examining the differences in the probabilities for the highest and next highest group assignment across all participants. The mean difference was 92.6% for participants assigned to the low-stable group, 55.4% for high-increasing group, and 72.5% high-decreasing group, indicating negligible ambiguity in assigning participants to a single group. Differences in demographic, injury, and GAD-7 scores by group trajectory can be seen in Table 1.

----------INSERT FIGURE 1----------

Figure 1 provides the GAD-7 mean values and number of data points for each of the three groups at each of the follow-up time points. Mean GAD-7 scores for the high-increasing group starts at 7.02 (SD=4.23) at year 1 and increases to 15.15 (SD=3.29) at year 10, while the mean GAD-7 scores for the high-decreasing group starts from 14.61 (SD=4.18) at year 1 and decreases to 5.94 (SD=4.00) at year 10. These groups were named “high-increasing” and “high-decreasing” because their anxiety levels were greater than minimal. Mean

GAD-7 scores for the low-stable group stay around 2, significantly lower than both the increasing and decreasing group.

Multivariate logistic regression analyses were carried out to identify characteristics that were associated with GAD-7 trajectory assignments. First, we examined factors that were associated with the group that started with high-increasing GAD-7 scores vs. the low-stable GAD-7 group (Table 3, left). After adjusting for other characteristics, those who identified as Native Americans or Other race were more likely to be in the high-increasing GAD-7 groups compared to those who identified as White-- though the sample size was quite small (N=13 Native Americans and N=29 Other race in total sample). Next we examined factors that were associated with the group that started with high-decreasing GAD-7 scores vs. the low-stable GAD-7 group (Table 3, middle). Compared to Whites, those who identified as Black were more likely to be in the high-decreasing GAD-7 group. Participants with public insurance were more likely to be in the high-decreasing group compared to those with private insurance. Participants with a mental health treatment history were also more likely to be in the high-decreasing group compared to those without. Those with 2 prior TBIs with LOC before index injury were more likely to be in the high-decreasing group compared with those without any TBI before the index one. Lastly, we examined which characteristics differed between the high-increasing and high-decreasing GAD-7 groups (Table 3, right). No significant factors were identified, except "Other" race being more likely to experience increase in GAD-7 scores compared to Whites, though again the sample size was quite small (N=10 race being other in high-increasing and high-decreasing groups).

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DISCUSSION

This was the first study that longitudinally examined anxiety up to 10 years post moderate-to-severe TBI. Baseline anxiety in the entire sample (not taking trajectory into consideration) was related to several socio-demographic factors (i.e., Black race, having public insurance) and injury related characteristics (i.e., having mental health treatment prior to index TBI, two prior TBIs with LOC, violent cause of TBI). These relationships are consistent with findings from prior research.[4,34] In addition, we also observed an interaction with age and

time post-injury, suggesting that younger individuals were more likely to experience an increase in their anxiety over time.

Several reasons should be considered when trying understand why Black race and public insurance were associated with worse anxiety outcomes. Some research examining anxiety in the general population shows that increased anxiety symptom distress in Blacks is associated with perceived discrimination, racial injustices, and internalized racism.[35-37] These factors might partially explain why we found higher anxiety symptom burden among our participants who identified as Black. Research in non-TBI populations also indicates that attitudes and stigma regarding mental health treatment are more negative for Blacks than Whites, which likely prevents utilization of mental health services.[38,39] The fact that greater anxiety was not observed in other traditionally minoritized groups (e.g., Hispanics) in our sample could potentially be due to either the smaller sample sizes or the possibility that these findings are specific to the unique inequities and anti-Black discrimination experienced by the Black community. Our findings regarding public insurance (e.g. Medicaid) might be an indicator that socioeconomic status (SES) is relevant to anxiety outcomes after TBI. Public health insurance is often considered a reasonable proxy for lower SES, especially since eligibility for Medicaid is largely based on low income.[26,40] Studies show that socioeconomic disadvantages and/or lack of access to quality healthcare services and service providers are risk factors for worse health outcomes,[26,41-44] which may explain the relationship we see with public insurance and more severe anxiety symptoms. Future qualitative studies examining the reasons for our findings are warranted in addition to the use of more precise measurements of SES.[45]

Pre-TBI mental health treatment is believed to be an indicator of premorbid psychiatric complaints[4] and as such, may reflect genetic risk factors, early life trauma, poor problem-solving skills, lowered social support, family dysfunction, and/or socioeconomic disadvantages associated with increased risk of psychiatric symptoms, particularly anxiety. In terms of the relationship of anxiety outcomes with cause or mechanism of injury, it is possible that individuals may experience post-traumatic stress that contributes to heightened anxiety symptoms in different ways depending upon type of injury. It is possible that survivors of a violence-related TBI would be likely to have more anxiety (compared to a motor vehicle accident) potentially due to the violent

nature of the event and possible subsequent posttraumatic stress, and/or pre-morbid factors with regards to their safety in social situations or in their neighborhoods. Future studies are warranted to tease out reasons and differences in anxiety symptom presentation among survivors of different mechanisms of injury. The fact that we found 2 TBIs with LOC to be related to higher anxiety is consistent with other work showing multiple TBI's to be related to worse outcomes.[46] The fact that 3 TBIs with LOC did not reach significance is likely due to the small number of participants who had that many TBIs. Our findings that younger individuals with initial anxiety were more likely to experience an increase in their anxiety over time more than older individuals with initial anxiety highlights the potential need for long-term anxiety surveillance, particularly for patients whose TBI occurred at an earlier stage in life. There may be developmental milestones that may contribute to greater anxiety (e.g,. just starting a career; starting a family). This finding also implies that older age was a protective factor for anxiety, which is consistent not only with prior work in TBI samples, but also studies in the general population. Stress and anxiety are most prevalent in middle age, when family and work demands tend to be highest, and dissipate as individuals reach retirement age and may have fewer responsibilities and may be more financially secure.[47]

When examining anxiety trajectories, we identified three classes: low-stable, high-increasing, and high-decreasing. Most individuals in the sample had low (minimal) anxiety that was stable over time (77%) with fewer experiencing initial higher anxiety that increased from mild to severe anxiety (10%) or decreased from severe to mild anxiety (13%) as time progressed post-injury. It is important to note that both the high-increasing and high-decreasing anxiety groups had ≥mild anxiety throughout the 10 year trajectory, which is similar to the prevalence (21%) of clinically significant anxiety found in prior research in the TBIMS National Data Base at one-year post injury.[4] The fact that we found subgroups with low-stable anxiety versus elevated anxiety (that never lowered beyond mild) is also consistent with prior work, as described earlier.[23,24]

When determining factors associated with group trajectory classification, we found that Black race, public insurance, prior mental health, and having had two TBIs had increased odds (relative to those who were White, had private insurance, no history of mental health treatment, or no prior TBI) of belonging to the high-

decreasing anxiety group than the low-stable group. Although anxiety in this group decreases from borderline severe anxiety to the low-end of mild anxiety, which is meaningful, it is important to note that even 10 years later, some anxiety symptoms are still present. In contrast, no major factors dictated who was at greater risk for being in the high-increasing group (vs low-stable or vs high-decreasing groups). Although Native American and Other race was significant when comparing high-increasing vs low-stable, and Other race was significant when comparing high-increasing vs high-decreasing, these findings need to be interpreted cautiously due to the small number of subjects in the categories. No other demographic or clinical characteristics were associated with greater risk for being in the high-increasing group (vs low-stable or vs high-decreasing groups). It seems likely that belonging to the high-increasing group, wherein anxiety increased from mild to severe over time, may be more related to proximal situational factors and life stressors not examined in this study, which should be considered in future work.

Clinical Implications/Application

The current results show that a substantial percentage of survivors of a moderate-severe TBI continue to report significant problems with anxiety up to 10 years post-TBI, supporting the conceptualization of TBI as a chronic condition that may require a variety services beyond traditional rehabilitation decades after the initial injury.[48] If a patient presents with one or more risk factors (e.g. Black race, has public insurance, premorbid mental health treatment, younger age, etc.) providers can use brief screeners, such as the GAD-7, to assess for early detection or treatment need. For those who screen positive for anxiety, evidence-based cognitive behavioral therapies (CBT) have shown some promise in reducing anxiety after TBI and can be provided in a variety of settings.[49]

Study Limitations

While this study yields important findings regarding the evolution of anxiety during the first 10 years after TBI, it is acknowledged that there are limitations that warrant cautious interpretation and further investigation before more definitive conclusions can be made. One study limitation was only being able to include 31.3% of the TBIMS sample in the analyses, as we required all participants to have at least two GAD-7

assessments in order to examine longitudinal changes in anxiety. However, there were only minor differences between our sample and the excluded TBIMS participants, which increased the confidence in our findings. There were also fewer participants at longer-term follow-up points (e.g., 10 years) compared to 1 and 2 year follow-ups, which makes it difficult to determine the true trajectory of change. That said, it is important to keep in mind that among the three trajectories, patterns of GAD-7 completion did not signficiantly differ, signifying that trajectories were not reliant on completion rates. We were also unable to determine if an excluded participant dropped out of the study completely or simply missed a follow up appointment. However, since all three groups (stable, high-increasing, or high-decreasing) had similar percentages of participants at each assessment period, it suggests that participants were not dropping out due to anxiety. If dropouts were due to anxiety, the two groups with higher anxiety (increasing and decreasing) would be expected to have higher percentages of dropout. Some of the variable categories would benefit from larger samples (e.g., Native American). When apprpropriate, future studies should consider collapsing small categories with others *a priori* (e.g, 3 prior TBIs into $\geq$ 2 prior TBIs with LOC) to increase power. Finally, this study did not capture data on proximal life stressors which could contribute to anxiety (e.g. changes in relationships, employment, functional status, socioeconomic status, and other social determinants of health), which should be assessed in future studies in participants with and without TBI to get a better understanding of the impact of environmental and sociological factors on anxiety outcomes.

CONCLUSION

This is the first study to examine how anxiety symptoms change over 10 years post-moderate or severe TBI. Fortunately, the vast majority of those who sustained a TBI experienced minimal anxiety and remained stable after injury. However, two smaller subgroups had substantial anxiety. Survivors who were Black, had a mental health treatment history, had public health insurance, and two prior TBIs with LOC were more likely to be in one of the two elevated anxiety groups. It is notable that preinjury risk factors and sociodemographic characteristics appear to represent enduring risk factors for elevated anxiety, not only in the immediate aftermath, but also years after TBI. We recommend screening TBI survivors with our identified risk factors for

anxiety and arranging for appropriate mental health services for those in need. Reducing anxiety after TBI has the potential to also decrease depression, occupational difficulties, and suicidality.[11] Future research should examine proximal variables and stressors that may be related to current anxiety symptoms.

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Figure 1 Figure Legend: GAD-7 Scores Per Group at 1,2,5, and 10 years Post-injury.
Note: Numbers above the lines indicate the GAD-7 means scores for that follow-up year. Numbers below the line represent the sample size that that follow-up year.