



Original Contribution

Traumatic Brain Injury and Attempted Suicide Among Veterans of the Wars in Iraq and Afghanistan

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Studies of the association between traumatic brain injury (TBI) and suicide attempt have yielded conflicting results. Furthermore, no studies have examined the possible mediating role of common comorbid psychiatric conditions in this association. This study used Veterans Affairs registry data to evaluate the associations between deployment-related TBI, psychiatric diagnoses, and attempted suicide among 273,591 veterans deployed in support of Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn, and who received care from the Department of Veterans Affairs during 2007–2012. We performed Cox proportional hazards regression analyses, adjusting for demographic characteristics. Mediation analyses were conducted to quantify the impact of psychiatric conditions (posttraumatic stress disorder, depression, anxiety, and substance abuse) on this association. The sample was predominantly male (84%); mean age = 28.7 years. Veterans with TBI (16%) were more likely to attempt suicide than those without (0.54% vs. 0.14%): adjusted hazards ratio = 3.76, 95% confidence interval: 3.15, 4.49. This association was attenuated in mediation analyses (adjusted hazards ratio = 1.25, 95% confidence interval: 1.07, 1.46), with 83% of the association of TBI with attempted suicide mediated by co-occurring psychiatric conditions and with posttraumatic stress disorder having the largest impact. These results suggest that veterans with these conditions should be closely monitored for suicidal behavior.

attempted suicide; cohort studies; traumatic brain injury; veterans

Abbreviations: ICD-9, *International Classification of Diseases, Ninth Revision*; mTBI, mild traumatic brain injury; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; OND, Operation New Dawn; PTSD, posttraumatic stress disorder; TBI, traumatic brain injury; VA, Department of Veterans Affairs.

Mild traumatic brain injury (mTBI) is considered one of the signature injuries of the wars in Iraq and Afghanistan (1), with as many as 23% of US veterans who served in these conflicts reporting at least one mTBI during their military service (2–5). Among veterans of these wars (Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND)), psychiatric conditions are more common among those with traumatic brain injury (TBI) than among those without TBI—the insurgency warfare nature of these conflicts set the stage for complex physical and psychological illness (6). A prospective cohort found that almost 80% of OEF/OIF/OND veterans with mTBI had current posttraumatic stress disorder

(PTSD), and approximately half had current depression (7). Further, observational studies in civilian (8–11) and veteran (9, 12–14) populations suggest that persons with TBI have an increased risk of attempted suicide. However, the results of these studies are mixed, and few have assessed the range of TBI or the impact of psychiatric comorbidity on the association with attempted suicide. The present study examined these associations in a large sample of OEF/OIF/OND veterans.

To date, 3 studies have assessed the association between TBI and attempted suicide among veterans (12–14), one of which focused specifically on OEF/OIF veterans (12). In a

cohort study of veterans attending a mental health clinic in a large Department of Veterans Affairs (VA) health-care system, Schneider et al. (14) found that a significantly higher proportion of those who screened positive for TBI had attempted suicide compared with those who screened negative. However, few suicide attempts were observed over the study period, and psychiatric comorbidity was not assessed. There was no association of mTBI with attempted suicide after adjustment for PTSD in a small cross-sectional study of OEF/OIF veterans (12). Similarly, TBI was not associated with risk of attempted suicide after adjustment for a history of PTSD in another small case-control study of veterans seeking mental health care in a large VA center (13). While these previous studies of the association between TBI and suicide attempt have adjusted for psychiatric comorbidity, to our knowledge, no investigators have examined whether psychiatric conditions mediate the association between TBI and attempted suicide in a population-based sample of veterans using prospective data.

The quantification of the impact of psychiatric comorbidity on the association between TBI and suicide attempt is important for targeted prevention efforts addressing suicidal behavior. Mediation analysis was previously employed to evaluate the impact of current PTSD and depression symptoms on the association between deployment-related TBI and suicidal ideation among OEF/OIF veterans (15). In the present study, we expand on that work by examining the mediating effects of these and other psychiatric conditions on the association between TBI and attempted suicide in a large prospective cohort of OEF/OIF/OND veterans receiving health care from the VA. We hypothesized that veterans with TBI would have a higher rate of attempted suicide than veterans without TBI, adjusting for demographic risk factors. Additionally, we hypothesized that this association would be mediated by co-occurring psychiatric conditions—the total number as well as each individual condition, including PTSD, mood disorder, anxiety disorder, and substance-use disorder.

METHODS

The sample was drawn from a national cohort of US veterans who were deployed in support of OEF/OIF/OND after September 11, 2001, who received health care from the VA between April 2007 and September 2012, and who were aged 18–40 years at the time they first accessed care at these facilities ($n = 518,427$). All OEF/OIF/OND veterans are eligible to use the VA system within 5 years of discharge from active military duty and even longer if they sustained deployment-related injuries or medical conditions. We excluded veterans with a diagnosis of bipolar disorder (*International Classification of Diseases, Ninth Revision* (ICD-9) codes 296.0, 296.1, and 296.4–296.8) and schizophrenia or related psychiatric disorder (ICD-9 codes 293.81, 293.82, 295, and 297–298)—except psychosis not otherwise specified due to trauma-related hallucinations—at any time during the study period ($n = 26,190$; 5%). These conditions are characterized by mood instability and irrational, disorganized behavior that could influence the assessment and prognosis of TBI (16). Finally, veterans with inconclusive TBI data were excluded ($n = 218,646$; 44%). The final sample included 273,591 veterans.

Data sources and variable definitions

All data came from national VA electronic medical records databases. These databases capture all health-care utilization occurring within the VA and a subset of care occurring at non-VA facilities that were reimbursed by the VA.

TBI exposure. Data for deployment-related TBI were collected from the VA primary TBI screen and comprehensive TBI evaluation. The VA primary TBI screen is a one-time, mandatory screening completed by all OEF/OIF/OND veterans entering the VA medical system starting in April 2007 (17). It consists of 4 questions to determine whether the veteran may have sustained a TBI during deployment. Veterans who answered affirmatively to all 4 questions on the primary screen were classified as “probable TBI” and referred for the comprehensive TBI evaluation. The comprehensive evaluation was administered by a trained interviewer (17), usually a physiatrist, and consists of questions about the mechanism (e.g., blast or blunt trauma) and severity of the injury, current neurobehavioral symptoms, and presence of suspected or probable psychiatric symptoms (e.g., PTSD, anxiety disorder, depression, and substance-use disorder). At the end of the evaluation, the clinician confirms or rules out a TBI diagnosis.

For the present study, TBI was defined as a confirmed TBI diagnosis from the VA comprehensive TBI evaluation. Veterans were categorized as not experiencing TBI during deployment if they did not report any head injury during deployment on the VA primary TBI screen. We also evaluated the severity and mechanism of injury among veterans with a confirmed TBI diagnosis. TBI severity ranged from mild to severe and was based on self-reported duration of loss of consciousness, alteration of consciousness, and posttraumatic amnesia. Mild TBI was defined as a period of self-reported loss of consciousness ≤ 30 minutes, posttraumatic amnesia ≤ 24 hours, or alteration of consciousness ≤ 24 hours following a credible injury mechanism (e.g., blast, motor vehicle accident, etc.) (18, 19).

Attempted suicide outcome. Nonfatal, attempted suicide was captured using ICD-9 injury E codes (E950–E959) recorded in emergency room visits or inpatient hospital admissions within the VA or non-VA facilities that were reimbursed by the VA. Suicide attempt diagnoses recorded in VA outpatient clinic visits were previously reviewed and deemed to have inadequate validity (Massachusetts Veterans Epidemiology Research and Information Center, VA Boston Healthcare System, unpublished data); therefore we limited our analyses to the first attempted suicide that resulted in an emergency room visit or hospitalization during the study period.

Covariates. Demographic and clinical covariates included sex, race (white, black, other, unknown/missing), age, marital status (single, married, or divorced/separated/other), and psychiatric conditions. We considered a psychiatric condition to be present if the veteran had at least 2 outpatient or 1 inpatient ICD-9 diagnosis code at any time during the study period (i.e., between primary TBI screen and first attempted suicide or other censoring event, described in the Analyses section below). The psychiatric conditions included PTSD (ICD-9 code 309.81), mood disorder (ICD-9 codes 296.2, 296.3, 293.83, 300.4, and 311), anxiety disorder (ICD-9 codes 293.84, 300, 308, 313.0, 313.1, 313.21, 313.22, 313.3, 313.82, and 313.83), and substance-use disorder (ICD-9 codes 291, 292, 303, 304, 305.00–305.03, and 305.2–305.9).

A veteran could have more than 1 specific psychiatric condition (e.g., generalized anxiety disorder and social phobia) within the diagnostic categories of anxiety, mood, and substance-use disorders.

Analyses

The incident rate, rate ratio, and 95% confidence intervals for attempted suicide were computed, comparing veterans with and without TBI. A veteran started to contribute person-time following the primary TBI screen and continued to contribute time until the date of the first suicide attempt, death, discontinuation of continual care at VA (which was defined as at least 1 outpatient clinic visit every 18 months following the primary TBI screen), or the end of the study period (September 30, 2012—the end of the last full fiscal year for which data were available at the time of the study). All rates were reported per 10,000 person-years. Cox proportional hazards regression was performed to estimate the hazard ratio for the association between TBI and attempted suicide association in unadjusted models and models adjusted for demographic characteristics. The proportional hazards assumption was examined using Kaplan-Meier curves and by testing the time-dependent covariates in the Cox model.

Mediation analyses were conducted to determine the direct and indirect associations between TBI and attempted suicide while quantifying the impact of comorbid psychiatric conditions. We did not include multiple psychiatric conditions as mediators in the same model because they were strongly correlated and thus violate the assumption of independent causal pathways for the weighted survival analysis approach (20, 21). Instead, to quantify the impact of multiple psychiatric conditions, we created an ordinal variable that reflected the co-occurrence of these diagnoses as the mediator (e.g., no psychiatric conditions, only 1 psychiatric condition present, and 2 or more psychiatric conditions present). As an exploratory analysis, we assessed the impact of each psychiatric diagnosis on the association between TBI and attempted suicide, conducting separate mediation analyses for each psychiatric diagnosis. We calculated the inverse probability weights using logistic regression, with the mediator as the outcome and TBI as the exposure, adjusting for the baseline demographic confounders: age, sex, race, and marital status. We computed the direct and indirect associations of TBI with attempted suicide, adjusting for covariates, using a weighted Cox proportional hazards model. Standard errors and 95% confidence intervals were computed using a robust sandwich covariance estimator. The proportion of the total effect that was explained by the presence of psychiatric conditions (i.e., the mediator), or simply percent mediated, was computed as the beta coefficient for the indirect effect divided by beta coefficient for the total effect (22). Finally, we conducted a sensitivity analysis to assess potential bias from unmeasured confounding of the mediator-outcome association (23).

SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina), was used for all analyses. This study was approved by the institutional review board at the VA Boston Healthcare system.

RESULTS

Of the 273,591 veterans who met the inclusion criteria, we identified 42,392 (16%) veterans with TBI and 231,199 veterans without TBI. The sample was predominately male (84%) and white (65%) and had an average age of 28.7 (standard deviation, 4.8) years. Demographic characteristics were similar among persons with and without TBI (Table 1). Among veterans with TBI, there was a higher proportion of each psychiatric condition than among those without TBI, ranging from 16% vs. 5% for substance-use disorder to 63% vs. 10% for PTSD.

Among the veterans with TBI, the majority had a mild TBI (88%), with the rest evenly distributed between moderate (6%) and severe (6%). Blasts were the most common mechanism of injury (74%), followed by other injuries (47%), motor vehicle accidents (40%), and falls (39%). Penetrating injury (e.g., bullet and fragment) occurred in only 7% of the TBIs.

Association between TBI and attempted suicide

Over the follow-up period, 545 attempted suicides occurred, with a higher proportion among veterans with TBI ($n = 227$, 0.54%) compared with those without TBI ($n = 318$, 0.14%). Veterans with TBI also had a higher unadjusted incidence rate of attempted suicide (21.89 attempted suicides per 10,000 person-years) than did veterans without TBI (5.56 attempted suicides per 10,000 person-years). The unadjusted rates of suicide attempt were similar across mechanism and severity of injury (Web Table 1, available at <https://academic.oup.com/aje>).

We confirmed that the proportional hazards assumption was met using Kaplan-Meier curves (Web Figure 1) and by testing the time-dependent covariates in the Cox model (data not shown). Veterans with TBI had an almost 4-fold higher risk of attempted suicide compared with those without TBI (unadjusted hazard ratio = 3.92, 95% confidence interval: 3.30, 4.64). The risk was slightly attenuated after adjusting for demographic characteristics (adjusted hazard ratio = 3.76, 95% confidence interval: 3.15, 4.49).

Mediation analyses

We observed an adjusted direct hazard ratio of 1.25 (95% confidence interval: 1.07, 1.46) for the association between TBI and attempted suicide in the mediation model accounting for the co-occurrence of psychiatric conditions (Table 2). The presence of co-occurring psychiatric conditions mediated 83% of the association of TBI with attempted suicide. In the mediation models evaluating individual psychiatric conditions, PTSD had the largest impact, mediating 73% of the association of TBI with attempted suicide. Mood disorder and substance-use disorder were weaker mediators, with approximately 50% of the association of TBI with attempted suicide mediated by each condition.

DISCUSSION

In this longitudinal, population-based study of OEF/OIF/OND veterans receiving care from the VA, veterans who sustained a deployment-related TBI had an increased risk of

Table 1. Baseline Characteristics According to Traumatic Brain Injury Status of Veterans of Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn Receiving Care From the Department of Veterans Affairs, Fiscal Years 2007–2012

Participant Characteristic	TBI (n = 42,392)		No TBI (n = 231,199)	
	No. of Participants	%	No. of Participants	%
Demographic factors				
Age ^a	28.2 (4.5)		28.7 (4.8)	
Male sex	40,413	95.3	189,849	82.1
Race				
White	31,357	74.0	146,599	63.4
Black	3,981	9.4	35,615	15.4
Other	2,178	5.1	10,874	4.7
Unknown/missing	4,876	11.5	38,111	16.5
Marital status				
Single	13,585	32.0	95,197	41.2
Married	18,909	44.6	88,585	38.3
Divorced/separated/other	9,898	23.4	47,417	20.5
Psychiatric conditions				
PTSD	26,781	63.2	22,365	9.7
Mood disorder	13,068	30.8	27,362	11.8
Anxiety disorder	7,326	17.3	17,728	7.7
Substance-use disorder ^b	6,749	15.9	11,000	4.8
Alcohol	5,631	13.3	8,894	3.9
Other	2,739	6.5	4,462	1.9
No. of co-occurring psychiatric conditions ^c				
0	9,078	21.4	167,202	72.3
1	13,234	31.2	33,553	14.5
2	11,377	26.8	20,120	8.7
≥3	8,703	20.6	10,324	4.5

Abbreviations: PTSD, posttraumatic stress disorder; TBI, traumatic brain injury.

^a Age is presented as mean (standard deviation).

^b Includes substance abuse and dependence disorders.

^c Calculated as the total number of psychiatric conditions (PTSD, mood disorder, anxiety disorder, and substance-use disorder) during the study period.

attempted suicide compared with those without a TBI, thus supporting our first hypothesis. In support of our second hypothesis, the mediation analyses indicated that much of this association operated through psychiatric comorbidity; 83% of the association of TBI with attempted suicide was mediated by the number of psychiatric conditions. Further, in mediation analyses of individual diagnoses, PTSD had the largest impact on the association between TBI and suicide attempts; PTSD mediated 73% of the association of TBI with attempted suicide.

Our observation of a 25% higher rate of attempted suicide among veterans with TBI in the mediation model is consistent with the 27% higher risk observed in a previous study of civilian patients with a history of mild TBI who were hospitalized for a major depressive episode (8). By contrast, our finding that PTSD substantially attenuated but did not completely account for the impact of TBI on attempted suicide differs

from previous studies that found no association between TBI and attempted suicide after accounting for PTSD. There are several possible reasons for these inconsistencies. First, our study employed a longitudinal design that could evaluate the mediation by psychiatric conditions. The mediation model quantifies the impact of the important comorbid psychiatric conditions on the association, which could not be achieved in previous studies that adjusted for psychiatric conditions as confounders (12, 13). The definition of TBI and the base population may also explain the inconsistencies; our study used a standardized measure to evaluate deployment-related TBI among a national cohort of OEF/OIF/OND veterans. In comparison, the previous study identified a history of TBI recorded in the medical records among a subset of veterans, from all service eras, seen at a single VA medical center (14). In summary, the methods used in our study support our finding of an association between TBI and suicide attempt.

Table 2. Direct and Indirect Association of Traumatic Brain Injury With Attempted Suicide, With Psychiatric Conditions as Mediators, Among Veterans of Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn Receiving Care from the Department of Veterans Affairs, Fiscal Years 2007–2012

Covariate ^a	Co-occurrence ^b			Psychiatric Condition as Mediator											
				PTSD			Mood Disorder			Anxiety Disorder			Substance-Use Disorder		
	HR	95% CI	PM (%)	HR	95% CI	PM (%)	HR	95% CI	PM (%)	HR	95% CI	PM (%)	HR	95% CI	PM (%)
TBI vs. no TBI	1.25	1.07, 1.46		1.41	1.19, 1.68		2.01	1.75, 2.32		2.92	2.56, 3.45		1.88	1.63, 2.17	
Psychiatric condition	2.98	2.59, 3.43	82.5	2.62	2.23, 3.07	72.7	1.88	1.65, 2.14	47.6	1.30	1.15, 1.48	20.0	1.98	1.73, 2.25	51.4

Abbreviations: CI, confidence interval; HR, hazard ratio; PM, percent mediated; PTSD, posttraumatic stress disorder; TBI, traumatic brain injury.

^a Analyses adjusted for age, sex, race (white vs. other), and marital status (single, married, or divorced/separated/other).

^b Ordinal measure of the co-occurrence of the psychiatric diagnoses as the mediator (e.g., no psychiatric conditions, only 1 psychiatric condition present, or 2 or more psychiatric conditions present).

The mechanism through which TBI may have a direct influence on suicide attempt after accounting for psychiatric diagnoses is unclear. Among civilians, the majority of symptoms associated with mTBI resolve within a month of the injury, and individuals return to preinjury level of functioning (24, 25). Further, among deployed US Army soldiers, there were limited lasting neuropsychological consequences from mTBI (26). It is therefore possible that the association we observed was attributable to a strong association between the more severe forms of TBI and suicide attempt. Our dose-response analyses showed no meaningful differences in associations by TBI severity; however, these analyses were limited by a small subsample with moderate or severe TBI who made a suicide attempt. Future studies can expand upon this work by examining additional mechanisms through which TBI and suicide attempt are associated as well as examining these associations in larger samples of these potentially higher-risk subgroups.

This study had several limitations that should be considered when interpreting our results. First, it was limited to OEF/OIF/OND veterans who received care in the VA health-care system. All OEF/OIF/OND veterans are eligible to use the VA system within 5 years of discharge from active military duty and even longer if they sustained a deployment-related injury or medical condition. Nevertheless, only 58% of OEF/OIF/OND veterans have obtained VA health care (27). OEF/OIF/OND veterans who receive care from the VA closely resemble the demographic characteristics of the National Health Study for a New Generation of US Veterans (28). However, veterans who receive care from the VA have lower socioeconomic status (29) and more psychiatric symptoms, including more chronic and severe PTSD (30). Thus, our study sample may not be representative of US veterans who did not use VA services during our study period.

In addition, our results may not be generalizable to veterans from other service eras due to the differences in prevalence of deployment-related TBI across periods of service. Compared with previous wars, the OEF/OIF/OND conflicts were characterized by insurgency warfare with prevalent exposure to blast injuries caused by explosive devices,

including landmines, rockets, and improvised explosive devices. A substantial number of OEF/OIF/OND veterans have survived injuries that would have been fatal in previous wars due to improvements in medicine and protective gear (31–35). Consequently, deployment-related TBI is considered one of the signature injuries among OEF/OIF/OND veterans (1).

Furthermore, in the present study we focused on suicide attempts that resulted in an emergency room visit or inpatient hospitalization because validation work has shown these diagnoses to be the most valid in VA data (Massachusetts Veterans Epidemiology Research and Information Center, VA Boston Healthcare System, unpublished data). Therefore, our results may not be generalizable to patients who received only outpatient care following a suicide attempt or those who made a suicide attempt that is not severe enough to warrant medical attention. Future studies should examine the association between TBI and attempted suicide for patients receiving outpatient care only following the attempt.

Additionally, this study was unable to adjust for predeployment covariates that may be confounders, particularly psychiatric conditions, because medical records prior to and during military service were unavailable. There may also be unmeasured mediator-outcome confounding, particularly by the other psychiatric conditions, when evaluating the individual psychiatric mediation models (20, 21). The causal structure of TBI and psychiatric diagnoses in predicting suicide attempt is complex, and many of the relevant psychiatric diagnoses are highly correlated. A constraint of the weighted proportional hazards approach currently available is that it does not allow strongly correlated variables in the same model, which limits our ability to evaluate this confounding via traditional regression-based methods. Therefore, we conducted a sensitivity analysis to evaluate the impact of this confounding on our associations of interest. Results suggested that moderate to substantial confounding of the psychiatric diagnosis–suicide attempt associations would be required to explain away these associations (relative risk due to unmeasured mediator-outcome confounding ranging from 1.92 to 5.41). Although this analysis provided additional important contextual information for our results and

highlights considerations for the definitions of these variables in future research, taken together our results consistently provide evidence that psychiatric disorders largely account for observed associations between TBI and suicide attempt in this sample. As methods for mediation analyses continue to evolve, future research will need to replicate our findings with adjustment for highly correlated variables.

It is possible that our results may have been influenced by various forms of systematic error. The VA primary TBI screen assessed only OEF/OIF/OND deployment-related TBI, and veterans classified as not having TBI may have experienced a TBI prior to or after their deployment. Given the prospective nature of the data, this misclassification would be nondifferential with regard to later suicide attempts, resulting in bias toward the null. Additionally, we assumed that all the psychiatric conditions diagnosed at the VA occurred after the deployment-related TBI exposure, even if the condition was diagnosed the same day as the TBI evaluations. Moreover, psychiatric mediators may be underreported, although we do not expect a large proportion to be misclassified because all participants received regular VA care and had the opportunity to receive a diagnosis if the condition was present. Selection bias due to censoring may be of concern when interpreting our results because veterans who were censored at the time of discontinuing VA care may differ from others who continue care. However, we found that a comparable percentage of veterans with and without TBI were censored due to discontinuation of continuous care (7.7% vs. 11.2%, respectively). Further, we do not believe that selection bias from the inclusion criteria was a concern for this study, which includes all OEF/OIF/OND veterans who received care at the VA, including the mandatory VA TBI screen, from April 2007 through September 2012.

Nonetheless, this study had several strengths, including a prospective study design, large sample size, specific definition of attempted suicide, and standardized measures to assess TBI, including the full range of TBI severity. In addition, to our knowledge, this was the first study to evaluate the impact of psychiatric mediators on the association between TBI and attempted suicide.

In conclusion, the results of this study suggest that OEF/OIF/OND veterans who received health care at the VA and who had a deployment-related TBI are at increased risk of attempted suicide. Moreover, our results suggest that psychiatric comorbidity serves as an important mechanism through which TBI influences suicidal behavior and also an important target for suicide intervention and prevention efforts. Thus, veterans who receive care at the VA and who have TBI and comorbid psychiatric conditions, especially PTSD, are a particularly vulnerable group that should be closely monitored for suicidal behavior. Future research should be directed at identifying the risk factors that account for the residual increase in suicidal behavior with TBI. In addition, future studies should explore other mechanisms of this association, including the possible biological interaction of TBI and psychiatric conditions and the effect of lifetime psychiatric comorbidity.

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