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Traumatic Brain Injury and Long-Term Risk of Stroke Among U.S. Military Veterans

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Abstract

Background: Traumatic brain injury (TBI) is associated with significant morbidity, but the association of TBI with long-term stroke risk in diverse populations remains less clear. Our objective was to examine the long-term associations of TBI with stroke and to investigate potential differences by age, sex, race/ethnicity, and time since TBI diagnosis.

Methods: Retrospective cohort study of U.S. military veterans aged 18+ years receiving healthcare in the VHA system between 10/1/2002 and 9/30/2019. Veterans with TBI were matched 1:1 to veterans without TBI on age, sex, race/ethnicity, and index date, yielding 306,796 veterans with TBI and 306,796 veterans without TBI included in the study. In primary analyses, Fine-Gray proportional hazards models adjusted for sociodemographics and medical/psychiatric comorbidities were used to estimate the association between TBI and stroke risk, accounting for the competing risk of mortality.

Results: Participants were a mean age of 50 years, 9% were female, and 25% were of non-White race/ethnicity. Overall, 4.7% of veterans developed a stroke over a median follow-up of 5.2 years. Veterans with TBI had 1.69 times (95%CI=1.64-1.73) increased risk of any

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DISCLOSURES

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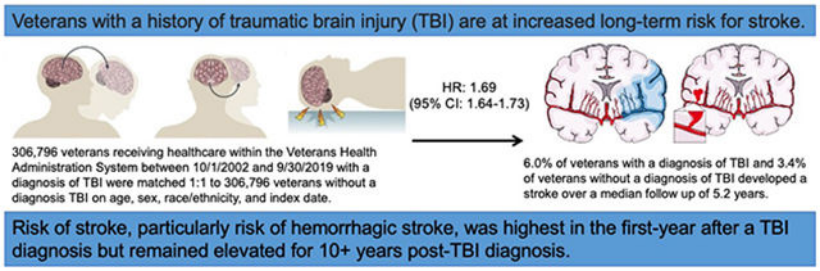
stroke (ischemic or hemorrhagic) compared to veterans without TBI. This increased risk was highest in the first-year post-TBI diagnosis (HR=2.16, 95%CI=2.03-2.29) but remained elevated for 10+ years. Similar patterns were observed for secondary outcomes, with associations of TBI with hemorrhagic stroke (HR=3.92, 95%CI=3.59-4.29) being stronger than with ischemic stroke (HR=1.56, 95%CI=1.52-1.61). Veterans with both mild (HR=1.47, 95%CI=1.43-1.52) and moderate/severe/penetrating injury (HR=2.02, 95%CI=1.96-2.09) had increased risk of stroke compared to veterans without TBI. Associations of TBI with stroke were stronger among older compared to younger individuals (p-interaction-by-age<0.001) and were weaker among Black veterans compared to other race/ethnicities (p-interaction-by-race<0.001).

Conclusions: Veterans with prior TBI are at increased long-term risk for stroke, suggesting they may be an important population to target for primary stroke prevention measures.

Graphical Abstract



INTRODUCTION

Traumatic brain injury (TBI) is common and is associated with significant morbidity among survivors.[1,2] Military veterans have a higher prevalence of lifetime history of TBI (up to 56%) compared to civilians and therefore represent an enriched population in which to study the long-term sequelae of TBI.[3] Much of the prior research on TBI has focused on shorter-term injury recovery-related outcomes (i.e., functional outcomes occurring within 1 year of injury),[4,5] with fewer studies focused on associations with longer-term neurologic consequences.

Traumatic cerebral microvascular injury is an increasingly recognized endophenotype of TBI and there is emerging evidence that resulting persistent microvascular dysfunction after TBI may lead to later neurologic disease, including dementia and stroke.[6] Indeed, there have been several prior studies investigating associations of TBI with stroke risk.[7-16] The majority of these prior studies are limited by racial/ethnic homogeneity[9-13]. Many of these prior studies also did not investigate associations of TBI with both ischemic and hemorrhagic stroke risk.[7-16] The long-term risk of stroke after TBI remains unclear, particularly in populations comprised of diverse race/ethnicity groups. Information on these outcomes is important to better understand risk, burden, and possible mechanisms.

The overall objective of the present study was to examine the long-term associations of TBI and TBI severity with stroke risk (overall, and separately for ischemic and hemorrhagic stroke types) in a sample of U.S. military veterans receiving healthcare in the Veterans Health Administration (VHA) system. We additionally sought to investigate potential

differences in associations of TBI with stroke risk by age, sex, race/ethnicity, and time since TBI diagnosis.

METHODS

Data Availability

The study data are derived from VHA electronic health records; please contact the authors for information regarding the process of accessing this data.

Study Design and Study Population

We conducted a retrospective cohort study of U.S. military veterans aged 18 years or older using data from two nationwide VHA system databases: 1) the inpatient and outpatient visits database (National Patient Care Databases) and 2) the Vital Status File. Of the 2,045,903 veterans with at least one VHA system visit between October 1, 2002 and September 30, 2019, we excluded 74,287 with history of stroke at their first VHA system visit and 171,149 with no follow-up visit in the VHA system, leaving 1,800,167 veterans (of whom 357,158 had a TBI diagnosis and 1,443,009 did not have a TBI diagnosis). We defined the index date for entry into follow-up as the first TBI diagnosis date for individuals who sustained a TBI. For individuals that did not have a TBI diagnosis, the index date for entry into follow-up was defined as a randomly selected healthcare encounter visit date occurring within 1 year of the matched individual's index TBI diagnosis date. All eligible individuals were required to have had at least one visit in the VHA system within the 2 years prior to the index date in order to define prevalent medical comorbidities. We performed 1:1 matching of veterans with a TBI diagnosis to veterans without a TBI diagnosis on age (±3 years), sex (self-identified male versus female), race/ethnicity (self-identified non-Hispanic White versus non-Hispanic Black versus Hispanic versus other), and index date (±1 year), resulting in 306,796 veterans with a TBI diagnosis and 306,796 veterans without a TBI diagnosis included in our analytic population (Supplemental Figure 1).

Standard Protocol Approvals

This study was approved by the Institutional Review Boards at the University of California, San Francisco, the San Francisco Veterans Affairs Medical Center, and the US Army Medical Research and Materiel Command Human Research Protection Office. Informed consent was waived because de-identified archival data was used. This manuscript follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.[17]

Traumatic Brain Injury

TBI diagnosis and TBI severity (mild versus moderate, severe, or penetrating injury) were defined using the Defense and Veterans Brain Injury Center list of International Classification of Disease, Ninth and Tenth Revisions (ICD-9 and ICD-10) Codes for TBI surveillance.[18]

Stroke

Incident stroke events were ICD-9 and ICD-10 code defined in accordance with the Department of Veterans Affairs Infrastructure for Clinical Intelligence project phenotype library definition.[19] ICD codes used to define ischemic stroke and hemorrhagic stroke are shown in Supplemental Table 1. Our primary outcome was the composite outcome of any stroke (defined as ischemic stroke plus hemorrhagic stroke). Secondary outcomes considered ischemic stroke and hemorrhagic stroke separately.

Covariates

Information on age, sex, and race/ethnicity was collected from VHA inpatient or outpatient files. Zip codes and 2012 US Census data were used to categorize each veteran's address into median annual income and education categories. Income was categorized as living in a zip code with median annual income <$25,930 (lowest tertile) versus ≥$25,930 (middle and highest tertiles). Education was categorized as ≤25% versus >25% of residents in zip code with bachelor's degree or higher education. Current smoking, medical comorbidities (hypertension, hyperlipidemia, diabetes, atrial fibrillation, and coronary artery disease [comprised of myocardial infarction, cardiac arrest, coronary arteriosclerosis, or coronary artery bypass grafting procedure codes]), and psychiatric comorbidities (post-traumatic stress disorder and depression) were defined using ICD-9 and 10 codes from encounters occurring during the 2-year period prior to the index date.

Statistical Analyses

Baseline characteristics were presented by TBI status using means and standard deviations (SDs) or medians and 25^{th}-75^{th} percentiles for continuous variables and using numbers and percentages for categorical variables. Characteristics were compared between groups using standardized mean differences to allow for comparison of the magnitude of group differences between variables. A standardized mean difference of greater than 0.1 or less than −0.1 was considered a meaningful difference.[20,21] We used Kaplan Meier analyses to calculate the cumulative incidence of stroke by TBI status. We first conducted Cox proportional hazards models to estimate the hazard ratios and 95% confidence intervals (CIs) for the associations of TBI with stroke risk using years since 30-days post-index date as the timescale and the end of follow up defined as the date of first stroke (defined as any stroke for primary analyses, and as either ischemic or hemorrhagic stroke in secondary analyses), date of death, or date of last VHA system visit occurring prior to September 30, 2019. A lag of 30-days post-index date was performed to reduce the possible influence of misdiagnosis of head injury as strokes in the immediate post-injury time-period. In our main analyses, we used Fine-Grey proportional hazards models to account for the competing risk of death.[22] We used Schoenfeld residuals and complementary log-log plots to confirm that the proportional hazards assumption was met.[23] Statistical models were adjusted for demographics, medical comorbidities and psychiatric comorbidities. We performed formal testing for multiplicative interaction by age group, sex, and race/ethnicity and present stratified results if there was evidence of interaction. In secondary analyses, we investigated the risk of stroke by TBI severity and by time since TBI diagnosis. In sensitivity analyses, we added index date as a covariate and performed analyses accounting for the variation

between matched pairs[24] (using a shared-frailty Cox proportional hazards model both without and with the use of methods described by Wolber et al.[25,26] to account for the competing risk of mortality).

A two-sided p-value <0.05 was considered statistically significant. SAS version 9.4 and STATA/MP version 16.1 were used for all analyses.

RESULTS

Baseline characteristics of included veterans by TBI status are shown in Table 1. Overall participants were a mean age of 50 years, 9% were female, and 25% were of non-White race/ethnicity. Veterans with a TBI were more likely than veterans without a TBI to be current smokers (19% versus 13%), have hypertension (38% versus 31%), have hyperlipidemia (34% versus 29%), and have atrial fibrillation (4% versus 2%). Veterans with TBI were much more likely than veterans without TBI to have comorbid post-traumatic stress disorder (36% versus 10%) and depression (36% versus 16%).

Overall, 4.7% of veterans developed a stroke over a median follow up of 5.2 years (25th percentile: 2.4 years, 75th percentile: 8.8 years). A total of 18,435 stroke events occurred over 1,787,238 person-years (PYs) of follow-up among veterans with TBI (unadjusted incidence rate [IR] per 1,000 PYs: 10.3, 95% CI: 10.0-10.7) compared to 10,297 stroke events occurring over 1,811,490 PYs of follow-up among veterans without TBI (unadjusted IR per 1,000 PYs: 5.7, 95% CI 5.4-6.0) (Table 2). Cumulative incidence was consistently increased among veterans with TBI compared to veterans without TBI for the primary outcome of any stroke as well as for the secondary individual outcomes of ischemic stroke and hemorrhagic stroke (all log-rank p-values <0.001) (Figure 1). Veterans with TBI had 1.80 times (95% CI: 1.76-1.85) increased risk of any stroke compared to veterans without TBI in adjusted Cox proportional hazards models. After accounting for the competing risk of death in adjusted Fine-Gray proportional hazards models, veterans with TBI had 1.69 times (95% CI: 1.64-1.73) increased risk of any stroke compared to veterans without TBI. Similar patterns were observed for the secondary individual outcomes of ischemic stroke and hemorrhagic stroke, with associations of TBI with hemorrhagic stroke being stronger than associations of TBI with ischemic stroke. In sensitivity analyses, adding index date as a covariate (Supplemental Table 2) and accounting for the variation between matched pairs (Supplemental Table 3), results were similar to our main statistical models.

Associations of TBI with our primary composite outcome of any stroke were stronger among older individuals (aged 65+ years, adjusted HR: 1.94, 95% CI: 1.86-2.03) compared to younger individuals (aged 45-64 years, HR: 1.54, 95% CI: 1.49-1.60; aged 18-44 years, HR 1.68, 95% CI: 1.54, 1.83) (p-interaction-by-age <0.001) and were weaker among non-Hispanic Black individuals (HR: 1.42, 95% CI: 1.35-1.50) as compared to other race/ethnicities (non-Hispanic White individuals, HR: 1.74, 95% CI: 1.69-1.79; Hispanic individuals, HR: 1.84, 95% CI: 1.58-2.14; other race/ethnicity, HR: 1.73, 95% CI: 1.40-2.13) (p-interaction-by-race/ethnicity <0.001) (Table 2, Table 3). Similar patterns were seen by both age and race/ethnicity for associations of TBI with ischemic stroke and hemorrhagic

stroke (all p-interaction <0.001). There was no evidence for effect modification by sex in the associations of TBI with stroke.

In secondary analyses, veterans with moderate, severe, or penetrating injury had 2.02 times (95% CI: 1.96-2.09) increased risk and veterans with mild injury had 1.47 times (95% CI: 1.43-1.52) increased risk of the composite outcome of any stroke compared to veterans without TBI (Table 4). Similar patterns were observed for associations of TBI severity with the secondary individual outcomes of ischemic stroke and hemorrhagic stroke. In secondary analyses stratified by time since TBI, the highest risk of the composite outcome of any stroke occurred in the first-year post injury (HR: 2.16, 95% CI: 2.03-2.29), but risk remained elevated for 10+ years (Figure 2). Similar patterns were observed for the secondary individual outcomes of ischemic stroke and hemorrhagic stroke.

DISCUSSION

In this cohort of 613,592 U.S. military veterans with and without a diagnosed TBI receiving healthcare in the VHA system, TBI was consistently associated with long-term risk of stroke. We observed the strongest associations of TBI with hemorrhagic stroke and with stroke events occurring within the first year after TBI, but this risk remained elevated for 10+ years. Associations of TBI with stroke risk were stronger among older (i.e., aged 65+ years) individuals and were weaker among individuals of self-identified non-Hispanic Black race/ethnicity.

Our findings extend the prior literature[7-16] on this topic in several important ways, including accounting for the competing risk of death in statistical models, a racially/ethnically diverse population of adults across the age-spectrum, and by the inclusion of a robust investigation into potential differences in observed associations by age, sex, race/ethnicity, and time since TBI diagnosis. Similar to several prior studies[7,9,15] we found that the risk of hemorrhagic stroke was greater than the risk of ischemic stroke, particularly in the first year after TBI and particularly among individuals with greater TBI severity. In contrast to one prior study which found stronger associations of TBI with odds of ischemic stroke among younger (<50 years) compared to older (≥50 years)[8] and one study which found no difference in associations of TBI with any stroke risk by age[12], we found stronger associations of TBI with stroke risk among older (≥65 years) compared to younger (<65 years) veterans. Observed differences may be attributable to differences in study population, head injury severity/mechanism, or other factors; future studies including investigation for interaction by age in the association of TBI with stroke risk are warranted for clarification of which subgroups may be at higher risk for post-TBI strokes. Similar to a prior study, we found no difference in associations of TBI with stroke risk by sex.[12] In contrast to prior studies which were largely performed in Taiwan,[9-13] our population allowed for investigation into potential differences in the association of TBI with stroke risk by race/ethnicity. Indeed, we found that associations of TBI with stroke risk were weaker among Black veterans as compared to other race/ethnicity groups. Racial disparities in stroke incidence and mortality are well documented, with Black individuals having both higher incidence and mortality compared to White individuals[27,28]. Given the higher baseline risk of stroke in Black compared to in White individuals, it is possible that the additional contribution of TBI to

stroke risk is less among Black as compared to among White individuals. Alternatively, the weaker associations observed among Black veterans in our study may be due to possible underdiagnosis of stroke using ICD codes, which may be related to differential access to health care and/or socioeconomic disadvantages among racial/ethnic minorities. Indeed, a greater proportion Black compared to White individuals lived in zip codes with lower median income and lower percentage of college educated residents, but our cohort included only veterans with access to healthcare, which may have mitigated some of these traditional barriers to care; additional research is needed on racial/ethnic differences in associations of TBI with neurological outcomes.

There are several potential mechanisms that may underly the observed association of TBI with stroke. Cerebral microvascular injury leading to persistent microvascular dysfunction after TBI is one mechanism hypothesized to link TBI with stroke and other neurologic sequelae including dementia.[6,29] This hypothesis is supported by animal models showing increased vulnerability to cerebral ischemia after TBI via induced vascular dysfunction, which leads to worsened stroke outcomes secondary to impaired reperfusion.[30] Trauma-induced coagulopathy (either hypocoagulable or hypercoagulable states) and blunt cerebrovascular injury (traumatic dissections) have also been hypothesized to contribute to stroke risk. [31,32] However, trauma-induced coagulopathy is most evident within 24 hours of injury and the risk remains for approximately 5 days post-injury and typically resolves within 14 days of injury.[33] Similarly, the risk of stroke associated with blunt cerebrovascular injury is typically within the first 4 weeks post-injury[34]. Trauma-induced coagulopathy and blunt cerebrovascular injury are therefore unlikely mechanisms underlying the observed long-term associations in our cohort where we specifically excluded stroke events occurring within 30-days of TBI in order to decrease the possible influence of misdiagnosis of TBI-related sequelae as strokes in the acute post-injury time period. Alternatively, it is possible that individuals with TBI are at higher risk for stroke as a result of a higher prevalence of comorbid vascular risk factors due to disability and resultant decreased physical activity secondary to the TBI. Indeed, in our cohort, veterans with a TBI diagnosis had higher prevalence of hyperlipidemia, hypertension, and atrial fibrillation compared to veterans without a TBI diagnosis. However, even after accounting for these factors in our statistical models, the elevated risk of stroke associated with TBI remained. As we have shown, the risk for stroke changes over time, and it is possible that different mechanisms are responsible earlier versus later after TBI; more work is needed to elucidate mechanisms underlying the observed associations of TBI with stroke risk.

Our results should be interpreted in the context of study limitations and strengths. First, our study was performed in a cohort of U.S. military veterans receiving healthcare within the VHA system. Consequently, we do not capture either TBI or stroke events if veterans received care outside of the VHA system. The magnitude of bias attributable to non-captured events is unknown, however, among veterans receiving healthcare within the VHA system, the median number of primary care encounters per year is three.[35] Therefore, the bias is more likely to be a delay in stroke diagnosis whereby a stroke event not treated at the VHA may be captured at the subsequent VHA primary care encounter rather than being an entirely missed stroke diagnosis. Veterans who receive non-VHA healthcare tend to be younger, have higher levels of education, and have alternative sources of healthcare

coverage compared to veterans who receive healthcare within the VHA system,[36,37] thus the generalizability of our results to populations beyond veterans receiving healthcare in the VHA system needs to be confirmed. Second, our TBI and stroke definitions are ICD-code based, and therefore we do not have specific details regarding history of prior remote TBIs, injury mechanism or TBI or stroke treatment. Further, our TBI definition captures all TBI diagnoses occurring within the VHA system between October 1, 2002 and September 30, 2019 and we are unable to determine if the TBI diagnosis is indicative of a prevalent or an incident injury. However, the ICD-code based definition for TBI is consistent with what is used by the Defense and Veterans Brain Injury Center for TBI surveillance[18] and has been previously validated, with sensitivity of 70%, specificity of 82%, and positive predictive value of 85%.[38] Similarly, the stroke definitions used are defined in accordance with the DaVINCI project phenotype library definition[19] and the use of ICD codes to identify acute stroke events has been shown to have greater than 82% sensitivity, greater than 95% specificity, and greater than 81% positive predictive value.[39] Since all of our TBI cases were identified via ICD codes, it is possible that our results may not generalize to more mild TBIs which do not necessitate medical care. Although we ascertained comorbidity status in the two years prior to the TBI index date, it is possible that some of the medical comorbidities herein may be a result of the TBI diagnosis, rather than prevalent at the time of TBI, particularly for individuals with milder TBIs who may have had a delayed diagnosis of TBI. It is also possible that acute TBI-related sequelae may have been misdiagnosed as strokes, but we implemented a lag of 30-days post-index date in order to reduce this possible influence of misdiagnosis of head-injury sequelae as strokes. We also reduced the possible influence of the competing risk of mortality by using Fine-Gray proportional hazards model in our main analyses. Additionally, our population was comprised of only 9% women and further study in populations with a greater proportion of women is warranted, but we were able to robustly investigate potential differences in associations between TBI and stroke risk across the age spectrum and by race/ethnicity group. Finally, the possibility of residual confounding remains due to the retrospective cohort design of our study. In particular, our study is subject to the possibility of residual confounding by socioeconomic status as a result of the coarseness of the education and income variables available.

In conclusion, this study provides strong inferential evidence supporting the association of TBI with long-term risk for stroke. Risk of stroke, particularly risk of hemorrhagic stroke and particularly among individuals with TBIs of greater injury severity, was highest in the first-year post-injury, but the risk remained elevated for 10+ years. This observed long-term increased risk of stroke after TBI suggests that scrupulous attention to vascular risk factor modification and to other primary stroke prevention strategies among individuals with prior TBI may be important.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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NON-STANDARD ABBREVIATIONS AND ACRONYMS

CI	Confidence interval
HR	Hazard ratio
ICD-9	International Classification of Disease, Ninth Revision
ICD-10	International Classification of Disease, Tenth Revision
IR	Incidence rate
PYs	Person-years
SD	Standard deviation
TBI	Traumatic brain injury
VHA	Veterans Health Administration

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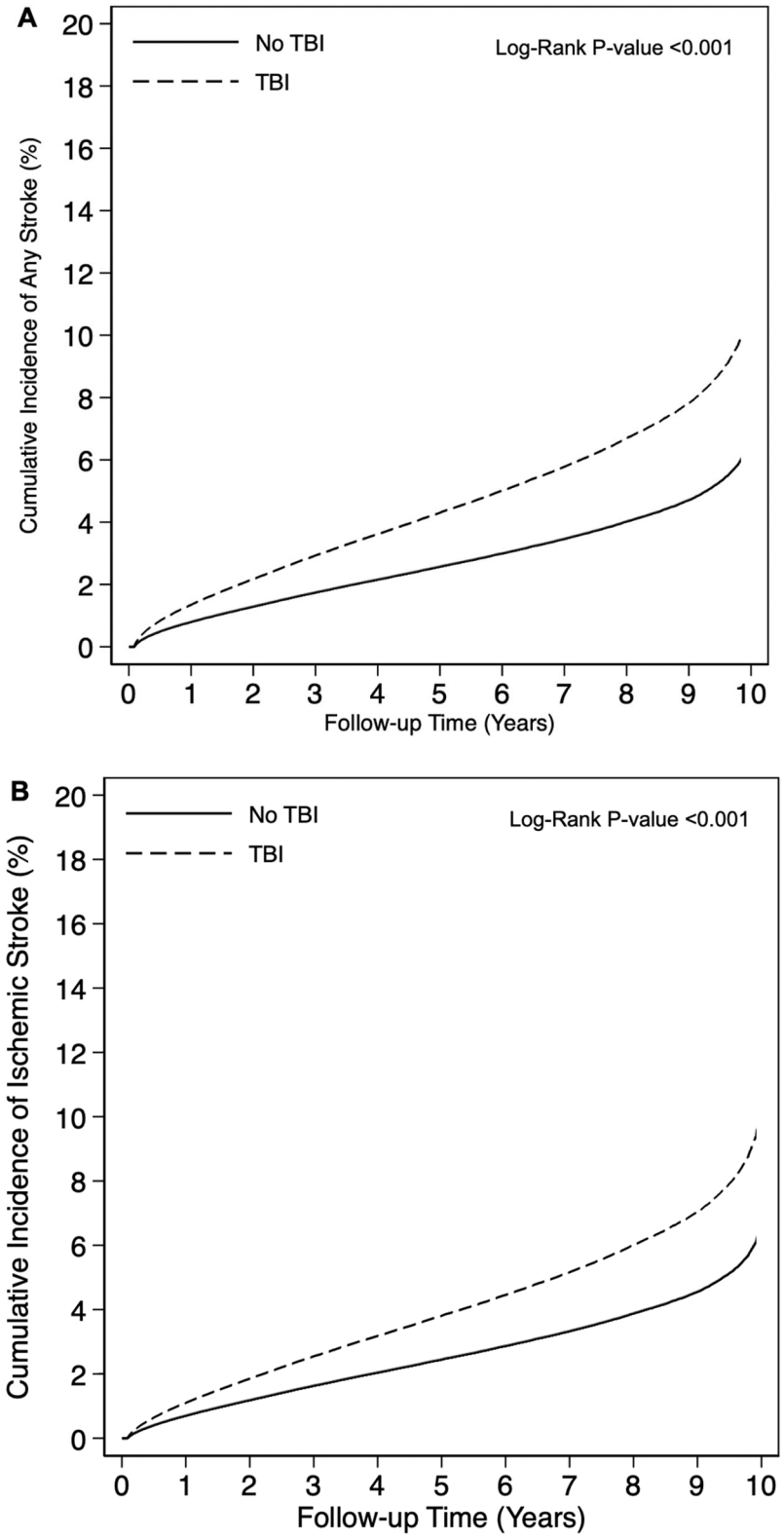


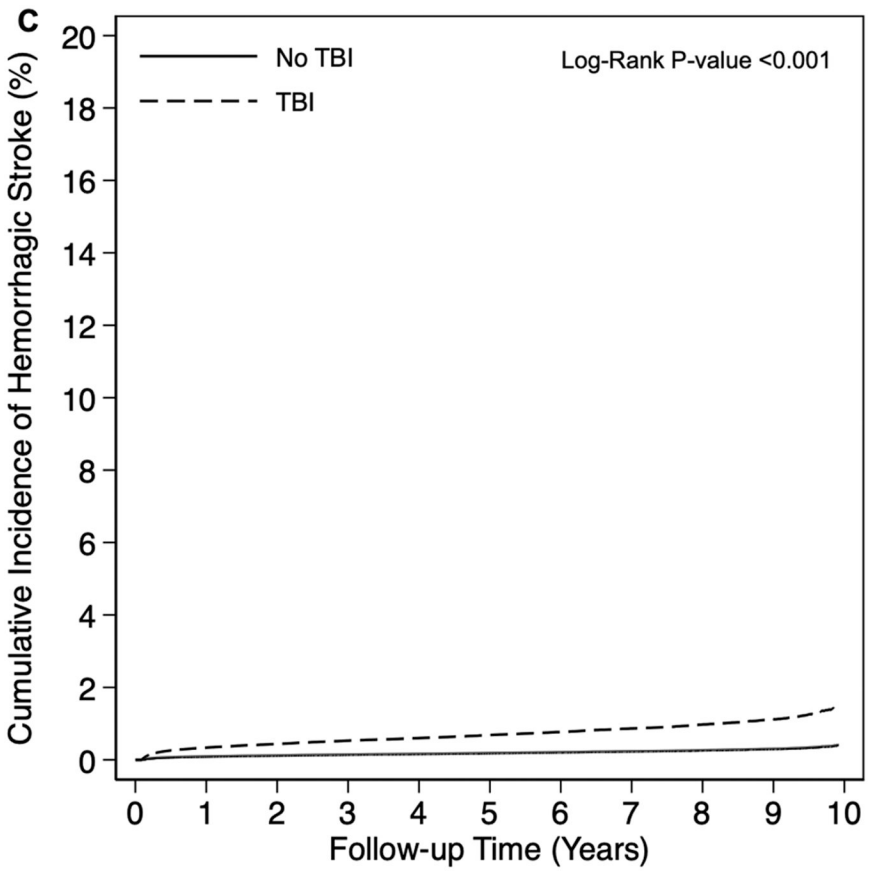
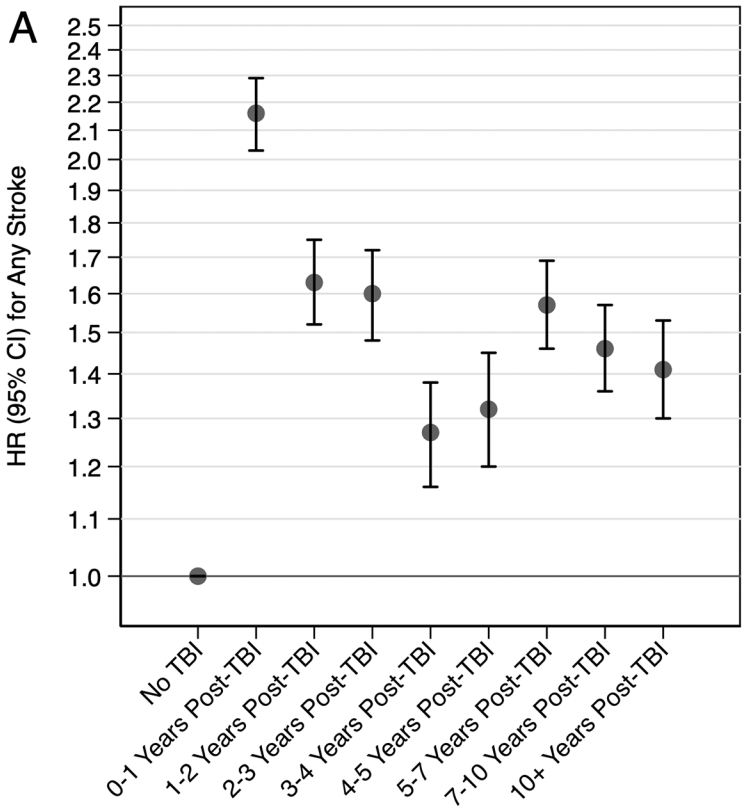
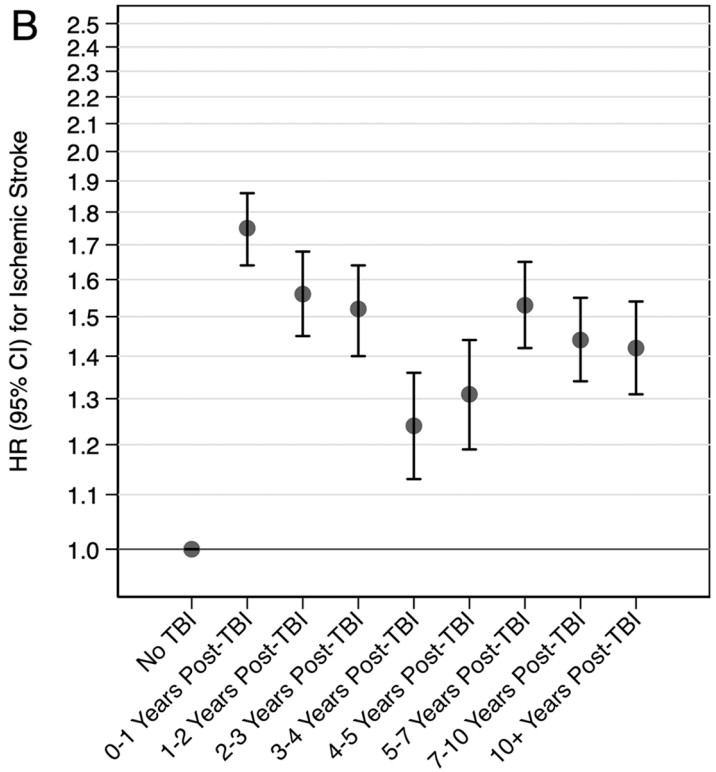


Figure 1.

Cumulative Incidence of Stroke by Traumatic Brain Injury Status (A: Any Stroke, B: Ischemic Stroke, C: Hemorrhagic Stroke).





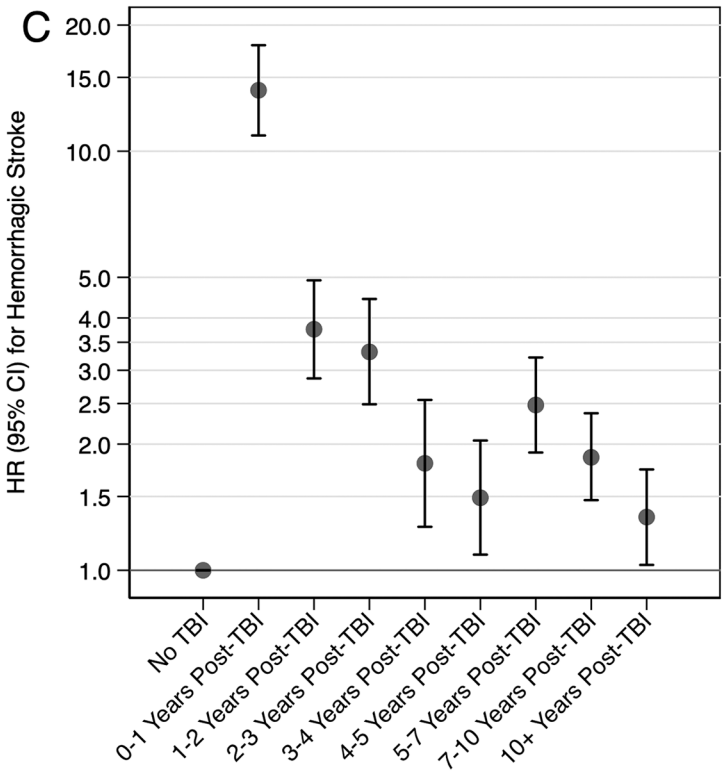


Figure 2. Adjusted* Risk of Stroke Stratified by Time Since TBI (A: Any Stroke, B: Ischemic Stroke, C: Hemorrhagic Stroke).

*Fine-Gray proportional hazards model adjusted for demographics (age, sex, race/ethnicity, income, education, and current smoking), medical comorbidities (hypertension, hyperlipidemia, diabetes, coronary artery disease, and atrial fibrillation) and psychiatric comorbidities (post-traumatic stress disorder and depression).

Table 1.

Baseline Characteristics of U.S. Veterans With and Without TBI.

	Veterans Without TBI (n=306,796)	Veterans With TBI (n=306,796)	SMD
Demographics			
Age (years), mean (SD)	50.4 (17.6)	50.2 (17.6)	−0.012
Age category, n (%)			−0.010
18-44 years	129,887 (42.3)	130,909 (42.6)	
45-64 years	111,583 (36.3)	111,742 (36.4)	
65+ years	65,326 (21.2)	64,145 (20.9)	
Female, n (%)	27,866 (9.0)	27,866 (9.0)	−0.001
Race/ethnicity, n (%)			<0.001
Non-Hispanic White	230,179 (75.0)	230,179 (75.0)	
Non-Hispanic Black	56,609 (18.4)	56,609 (18.4)	
Hispanic	9,925 (3.2)	9,925 (3.2)	
Other *	10,083 (3.2)	10,083 (3.2)	
Median annual income in zip code <$25,930, n (%)	97,708 (31.8)	98,026 (31.9)	0.004
>25% of residents in zip code college educated, n (%)	153,638 (50.0)	155,741 (50.7)	0.020
Current smoking, n (%)	38,456 (12.5)	57,087 (18.6)	0.168
Index year, median (25^{th}-75^{th} percentile)	2012 (2008-2015)	2012 (2009-2015)	0.006
Follow-up time, median (25^{th}-75^{th} percentile)	5.23 (2.35-8.78)	5.18 (2.35-8.71)	−0.021
Medical Comorbidities			
Hypertension, n (%)	94,700 (30.8)	115,945 (37.7)	0.145
Hyperlipidemia, n (%)	89,413 (29.1)	105,547 (34.4)	0.112
Diabetes, n (%)	36,557 (11.9)	46,088 (15.0)	0.090
Atrial fibrillation, n (%)	6,789 (2.2)	13,256 (4.3)	0.118
Coronary artery disease, n (%)	19,055 (6.2)	24,836 (8.1)	0.072
Psychiatric Comorbidities			
Post-traumatic stress disorder, n (%)	32,479 (10.5)	111,178 (36.2)	0.635
Depression, n (%)	48,040 (15.6)	111,669 (36.4)	0.486

Abbreviations: SMD, standardized mean difference

* Other race/ethnicities includes: American Indian or Alaska Native, Asian, and Native Hawaiian

A standardized mean difference of greater than 0.1 or less than −0.1 was considered a meaningful difference.

Table 2.

Risk of Stroke by TBI Status.

	Veterans Without TBI	Veterans With TBI
Any Stroke		
No. Events/No. PYs	10,297/1,811,490	18,435/1,787,238
Unadjusted Incidence Rate per 1,000 PYs (95% CI)	5.7 (5.4-6.0)	10.3 (10.0-10.7)
Adjusted * Cox proportional hazards model, HR (95% CI)	1 (Reference)	1.80 (1.76-1.85)
Adjusted * Fine-Gray proportional hazards model, HR (95% CI)	1 (Reference)	1.69 (1.64-1.73) **†
Ischemic Stroke		
No. Events/No. PYs	9,924/1,812,455	16,645/1,795,283
Unadjusted Incidence Rate per 1,000 PYs (95% CI)	5.5 (5.2-5.7)	9.3 (8.9-9.6)
Adjusted * Cox proportional hazards model, HR (95% CI)	1 (Reference)	1.68 (1.63-1.72)
Adjusted * Fine-Gray proportional hazards model, HR (95% CI)	1 (Reference)	1.56 (1.52-1.61) **†
Hemorrhagic Stroke		
No. Events/No. PYs	660/1,848,365	2,603/1,851,144
Unadjusted Incidence Rate per 1,000 PYs (95% CI)	0.4 (0.3-0.4)	1.4 (1.3-1.5)
Adjusted * Cox proportional hazards model, HR (95% CI)	1 (Reference)	3.92 (3.59-4.29)
Adjusted * Fine-Gray proportional hazards model, HR (95% CI)	1 (Reference)	3.73 (3.40-4.08) **†

*Model adjusted for demographics (age, sex, race/ethnicity, income, education, and current smoking), medical comorbidities (hypertension, hyperlipidemia, diabetes, coronary artery disease, and atrial fibrillation) and psychiatric comorbidities (post-traumatic stress disorder and depression).

**P-interaction by age <0.001

†P-Interaction by race/ethnicity <0.001

Table 3.

Adjusted* Risk of Stroke by TBI Status Stratified by Age and Race/Ethnicity.

	Veterans Without TBI		Veterans With TBI	
	No. Events/No. PYs	**HR (95% CI)**	**No. Events/No. PYs**	**HR (95% CI)**
Any Stroke				
Stratified by Age				
Age 18-44 years	1,002/733,018	1 (Reference)	1,687/778,267	1.68 (1.54-1.83)
Age 45-64 years	5,495/763,288	1 (Reference)	9,043/744,928	1.54 (1.49-1.60)
Age 65+ years	3,795/315,183	1 (Reference)	7,696/264,044	1.94 (1.86-2.03)
Stratified by Race/Ethnicity				
Non-Hispanic White	7,289/1,350,767	1 (Reference)	13,760/1,324,665	1.74 (1.69-1.79)
Non-Hispanic Black	2,518/352,689	1 (Reference)	3,756/351,792	1.42 (1.35-1.50)
Hispanic	309/55,856	1 (Reference)	598/57,000	1.84 (1.58-2.14)
Other	176/52,177	1 (Reference)	312/53,781	1.73 (1.40-2.13)
Ischemic Stroke				
Stratified by Age				
Age 18-44 years	930/733,201	1 (Reference)	1,461/779,535	1.55 (1.42-1.70)
Age 45-64 years	5,289/763,895	1 (Reference)	8,221/749,174	1.45 (1.40-1.50)
Age 65+ years	3,700/315,339	1 (Reference)	6,957/266,574	1.78 (1.71-1.86)
Stratified by Race/Ethnicity				
Non-Hispanic White	7,037/1,351,405	1 (Reference)	12,344/1,330,957	1.60 (1.55-1.65)
Non-Hispanic Black	2,420/352,959	1 (Reference)	3,481/353,191	1.36 (1.29-1.44)
Hispanic	296/55,890	1 (Reference)	538/57,188	1.70 (1.45-1.98)
Other	166/52,201	1 (Reference)	276/53,947	1.55 (1.25-1.94)
Hemorrhagic Stroke				
Stratified by Age				
Age 18-44 years	110/736,533	1 (Reference)	292/784,821	2.70 (2.12-3.44)
Age 45-64 years	385/784,829	1 (Reference)	1,245/781,098	3.00 (2.65-3.38)
Age 65+ years	165/328,003	1 (Reference)	1,063/285,224	6.21 (5.21-7.40)
Stratified by Race/Ethnicity				

	Veterans Without TBI		Veterans With TBI	
	No. Events/No. PYs	**HR (95% CI)**	**No. Events/No. PYs**	**HR (95% CI)**
Non-Hispanic White	420/1,376,949	1 (Reference)	1,976/1,371,638	4.32 (3.86-4.83)
Non-Hispanic Black	193/361,855	1 (Reference)	476/365,711	2.37 (1.98-2.82)
Hispanic	28/56,801	1 (Reference)	99/58,978	3.27 (2.10-5.08)
Other	19/52,760	1 (Reference)	49/54,816	2.59 (1.45-4.63)

*Fine-Gray proportional hazards model adjusted for demographics (age, gender, race, income, education, and current smoking), medical comorbidities (hypertension, hyperlipidemia, diabetes, and atrial fibrillation) and psychiatric comorbidities (post-traumatic stress disorder and depression).

Table 4.

Risk of Stroke by TBI Severity.

	Veterans Without TBI	Veterans With Mild TBI	Veterans With Moderate or Severe or Penetrating TBI
Any Stroke			
No. Events/No. PYs	10,297/1,811,490	6,744/791,250	8,767/607,738
Unadjusted Incidence Rate per 1,000 PYs (95% CI)	5.7 (5.4, 6.0)	8.5 (8.1, 9.0)	14.4 (13.7, 15.2)
Adjusted * Cox proportional hazards model, HR (95% CI)	1 (Reference)	1.59 (1.54-1.64)	2.18 (2.11-2.24)
Adjusted * Fine-Gray proportional hazards model, HR (95% CI)	1 (Reference)	1.47 (1.43-1.52)	2.02 (1.96-2.09)
Ischemic Stroke			
No. Events/No. PYs	9,924/1,812,455	6,323/792,827	7,585/613,534
Unadjusted Incidence Rate per 1,000 PYs (95% CI)	5.5 (5.2, 5.7)	8.0 (7.5, 8.4)	12.4 (11.7, 13.1)
Adjusted * Cox proportional hazards model, HR (95% CI)	1 (Reference)	1.55 (1.50-1.60)	1.92 (1.7-1.99)
Adjusted * Fine-Gray proportional hazards model, HR (95% CI)	1 (Reference)	1.43 (1.38-1.48)	1.78 (1.73-1.84)
Hemorrhagic Stroke			
No. Events/No. PYs	660/1,848,365	637/814,134	1,671/638,374
Unadjusted Incidence Rate per 1,000 PYs (95% CI)	0.4 (0.3, 0.4)	0.8 (0.6, 0.9)	2.6 (2.3, 2.9)
Adjusted * Cox proportional hazards model, HR (95% CI)	1 (Reference)	2.23 (1.99-2.50)	6.45 (5.87-7.09)
Adjusted * Fine-Gray proportional hazards model, HR (95% CI)	1 (Reference)	2.11 (1.88-2.36)	6.14 (5.58-6.76)

* Model adjusted for demographics (age, sex, race/ethnicity, income, education, and current smoking), medical comorbidities (hypertension, hyperlipidemia, diabetes, coronary artery disease, and atrial fibrillation) and psychiatric comorbidities (post-traumatic stress disorder and depression).