Traumatic brain injury may be an independent risk factor for stroke

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ABSTRACT

Objective: To explore whether traumatic brain injury (TBI) may be a risk factor for subsequent ischemic stroke.

Methods: Patients with any emergency department visit or hospitalization for TBI (exposed group) or non-TBI trauma (control) based on statewide emergency department and inpatient databases in California from 2005 to 2009 were included in a retrospective cohort. TBI was defined using the Centers for Disease Control definition. Our primary outcome was subsequent hospitalization for acute ischemic stroke. The association between TBI and stroke was estimated using Cox proportional hazards modeling adjusting for demographics, vascular risk factors, comorbidities, trauma severity, and trauma mechanism.

Results: The cohort included a total of 1,173,353 trauma subjects, 436,630 (37%) with TBI. The patients with TBI were slightly younger than the controls (mean age 49.2 vs 50.3 years), less likely to be female (46.8% vs 49.3%), and had a higher mean injury severity score (4.6 vs 4.1). Subsequent stroke was identified in 1.1% of the TBI group and 0.9% of the control group over a median follow-up period of 28 months (interquartile range 14–44). After adjustment, TBI was independently associated with subsequent ischemic stroke (hazard ratio 1.31, 95% confidence interval 1.25–1.36).

Conclusions: In this large cohort, TBI is associated with ischemic stroke, independent of other major predictors. *Neurology*® **2013;81:33–39**

GLOSSARY

CI = confidence interval; **ED** = emergency department; **HCUP** = Healthcare Cost and Utilization Project; **HR** = hazard ratio; **ICD-9-CM** = *International Classification of Diseases*, ninth revision, Clinical Modification; **OR** = odds ratio; **SEDD** = State Emergency Department Databases; **SID** = State Inpatient Databases; **TBI** = traumatic brain injury.

Ischemic stroke and traumatic brain injury (TBI) are common,[1,2] costly,[3,4] and leading causes of severe disability in adults.[1,5] In particular, both stroke and TBI are responsible for substantial disability in working-age adults—approximately 20% of strokes[6] and more than 40% of TBI[7] occur in adults younger than 65 years.

In the recent past, no specific stroke mechanism was identified for many strokes in the young.[8] Although the proportion of unexplained stroke may be decreasing based on more recent data,[9] a large proportion of stroke risk is unexplained by the frequently used stroke prediction models.[10] Identifying novel risk factors has the potential to improve stroke prevention and outcomes. TBI is a potential unrecognized stroke risk factor as trauma to the head and neck may increase stroke risk through vascular dissection,[11] microvascular injury, or abnormal coagulation.[12]

A recent observational study in Taiwan based on administrative data[13] suggested an association between TBI and all stroke types. However, the association was strongest for known components of TBI (subarachnoid and intracerebral hemorrhage), and a large proportion of stroke risk occurred in the first month. Therefore, it is possible that some events classified as incident stroke were merely sequelae of the TBI and that the magnitude of the observed association may have been overstated.

In the current study, we explored whether the findings in the Taiwanese study extend to a representative region in the United States while limiting to cases of ischemic stroke and accounting for additional confounders. In secondary analyses, we explored whether the TBI-stroke relationship differed by severity of trauma, subtype of TBI, and when excluding early recurrent stroke.

METHODS This retrospective cohort study was based on emergency department (ED) visits and inpatient discharges for the state of California from 2005 to 2009 from the State Inpatient Databases (SID),[14] State Emergency Department Databases (SEDD),[15] Healthcare Cost and Utilization Project (HCUP), and Agency for Healthcare Research and Quality. SID and SEDD capture all inpatient discharges and all ED visits that do not result in admission, respectively, within a given year. California was selected for this analysis because of its large population and because it allows for linkage of SEDD and SID records over multiple years using HCUP revisit files.[16] We compared TBI patients with non-TBI trauma patients (controls) while accounting for a variety of other variables that may confound the association between TBI and ischemic stroke.

Standard protocol approvals, registrations, and patient consents. The study protocol, which does not rely on human subjects, was deemed not regulated by the University of Michigan Institutional Review Board because it relied on private coded information that cannot be linked to specific individuals by the investigators.

Patient selection. Adults 18 years or older were entered into our cohort if they survived either an inpatient admission (SID) or an ED visit (SEDD) for TBI or trauma at any time from 2005 to 2009. TBI was defined using the Centers for Disease Control and Prevention criteria: *ICD-9-CM* 800.0–801.9, 803.0–804.9, 850.0–854.1, or 959.01 in any discharge diagnosis field.[17,18] Our TBI definition was designed to maximize differentiation of TBI and non-TBI trauma. Trauma is inherently a multisystem process, so limiting our diagnosis to only a subset of TBI claims (e.g., principal diagnoses only) would risk misclassifying patients with new TBI as non-TBI trauma. The non-TBI trauma group was composed of patients who had a fracture, excluding fractures of the head and neck: *ICD-9-CM* 807.0–807.9, 812–819.9, 822–822.9, or 823–827.9 in any position on the discharge record. If a patient had both TBI and non-TBI trauma codes or separate visits with both TBI and non-TBI trauma, they were classified as TBI. Individuals with a visit (ED or inpatient) with stroke (*ICD-9-CM* 433.x1, 434.x1, 436)[19] before TBI or trauma were excluded from the cohort. Similarly, if a patient had multiple TBI or non-TBI trauma visits, they were entered into the cohort with their first visit. In addition, given the known role of arterial dissection as a mediator of ischemic stroke risk in trauma patients, we excluded all patients with carotid (*ICD-9-CM* 433.21) or vertebral (433.24) dissection at the index visit (n = 66).

Outcome. Our primary outcome was any hospitalization with a discharge diagnosis of ischemic stroke: *ICD-9-CM* 433.x1, 434.x1, and 436 from 2005 to 2009.[19] This combination of diagnosis codes has been previously validated relative to medical record review and found to have a positive predictive value of 90% and sensitivity of 86%.[20] ED visits that did not result in admission for ischemic stroke were not included in the primary outcome because of concerns about the accuracy of coding.

Covariates. Our primary analysis adjusted for known and possible stroke predictors including demographics, vascular risk factors, comorbidities, trauma severity, and trauma mechanism. Age was divided into quartiles because of the known nonlinear relationship between age and stroke.[1] Vascular risk factors were defined using the HCUP single-level clinical classification system.[21] Comorbidities were defined based on diagnosis codes listed on the discharge record using the modified Charlson definition, and all Charlson comorbidities were included in our model.[22] Trauma severity was estimated with the Abbreviated Injury Scale (ICD/AIS)[23] using the software package ICDMAP-90[24]—a validated algorithm for assigning trauma severity using *ICD-9* codes.[25] Mechanism of trauma was accounted for by including major external cause of injury group codes (E codes), which describe the intent, mechanism, and circumstances of injuries independently of the anatomical location of an injury.[26,27]

Primary analysis. Demographics and baseline characteristics of the TBI and the non-TBI trauma groups were summarized using descriptive statistics. Subsequent stroke was compared by TBI status with Kaplan-Meier estimates and the log-rank test. We were unable to determine whether a patient died outside the context of a hospitalization and thus cases were not censored at death. Cumulative hazard of stroke was estimated at different time intervals using the Nelson-Aalen method and the differences in cumulative hazard were calculated. Confidence intervals (CIs) of the differences were estimated using bootstrapping.

Our primary adjusted analysis relied on Cox proportional hazards modeling.[28] We examined the association of TBI and stroke after adjusting for demographics, payer, vascular risk factors (hypertension, hyperlipidemia, diabetes, atrial fibrillation), all Charlson comorbidities, trauma severity, whether a patient had multiple visits for trauma/TBI, and trauma mechanism, while accounting for clustering at the hospital level. To explore how covariate groups (demographics, comorbidities, vascular risk factors, trauma severity, trauma mechanism) affected the TBI–ischemic stroke association, we also developed models in which covariate groups were added serially. Given the increased incidence of epilepsy in patients with TBI[29] and the potential for misdiagnosing seizure as stroke,[30] we included a covariate that represented whether a patient had any ED visit or admission for epilepsy (*ICD-9-CM* 345.x) or convulsions (780.3x).[31] The proportional hazards assumption central to Cox modeling was tested by visually inspecting plots of the cumulative hazards function and plots of Schoenfeld residuals and no violations of the proportional hazards assumption were found.[32]

Secondary analyses. We performed a series of post hoc secondary analyses to assess the robustness of the association between TBI and ischemic stroke that either added covariates to our primary analysis or stratified our primary analysis on covariates of interest. First, to determine whether there was a relationship between specific TBI types and ischemic stroke, we analyzed the risk of ischemic stroke for TBI subtypes identifiable by *ICD-9-CM* codes: skull fracture (800–801.9, 803–804.9), concussion (850–850.9), cerebral laceration/intracranial hemorrhage (851–853.9), other intracranial injury (854–854.9), and unspecified TBI (959.01).[33] Second, to assess whether the TBI–ischemic stroke association may differ depending on overall trauma severity, we repeated our primary analysis stratified over injury severity tertiles. In addition, to assess for possible missed early stroke diagnosis (i.e., stroke present at initial trauma/TBI presentation and not diagnosed at that time), we repeated our primary analysis excluding all ischemic stroke hospitalizations that occurred within 7, 30, or 60 days of trauma. Next, to characterize the relative temporal association between TBI and stroke, we repeated our

Table 1   Baseline patient characteristics

	No TBI (n = 736,723)	TBI (n = 436,630)
Demographics		
Age, y, mean (SD)	50.3 (20.1)	49.2 (22.4)
Female, n (%)	363,210 (49.3)	204,298 (46.8)
Race/ethnicity, n (%)		
White	426,587 (57.9)	251,095 (57.5)
African American	43,418 (5.9)	31,003 (7.1)
Hispanic	136,908 (18.6)	80,753 (18.5)
Asian	24,879 (3.4)	22,111 (5.1)
Other	104,931 (14.3)	51,668 (11.8)
Insurance, n (%)		
Medicare	190,409 (25.9)	120,571 (27.6)
Medicaid	72,680 (9.9)	43,502 (10.0)
Private	287,086 (39.0)	150,909 (34.6)
Self-pay	107,268 (14.6)	73,755 (16.9)
Other/missing	79,280 (10.8)	47,893 (11.0)
Vascular risk factors, n (%)		
Hypertension	125,752 (17.1)	75,438 (17.3)
Hyperlipidemia	41,206 (5.6)	20,873 (4.8)
Diabetes	59,141 (8.0)	31,897 (7.3)
Coronary artery disease	24,930 (3.4)	16,573 (3.8)
Peripheral vascular disease	6,151 (0.8)	3,045 (0.7)
Atrial fibrillation	14,702 (2.0)	12,359 (2.8)
Comorbidities,[a] n (%)		
Congestive heart failure	15,505 (2.1)	9,133 (2.1)
Dementia	5,061 (0.7)	5,504 (1.3)
Chronic obstructive pulmonary disease	34,775 (4.7)	17,129 (3.9)
Rheumatologic disease	4,915 (0.7)	2,092 (0.5)
Peptic ulcer disease	1,473 (0.2)	724 (0.2)
Mild liver disease	5,618 (0.8)	3,760 (0.9)
Renal disease	13,538 (1.8)	7,386 (1.7)
Cancer	5,064 (0.7)	3,385 (0.8)
Severe liver disease	849 (0.1)	627 (0.1)
Metastases	1,617 (0.2)	1,154 (0.3)
HIV/AIDS	490 (0.1)	330 (0.1)
Epilepsy[b]	7,997 (1.1)	14,798 (3.4)
History of multiple trauma/TBI[c]	103,090 (14.0)	69,863 (16.0)
Admission characteristics		
Admitted, n (%)	167,406 (22.7)	80,264 (18.4)
Injury severity,[d] mean (SD)	4.1 (3.6)	4.6 (10.1)

Abbreviation: TBI = traumatic brain injury.
[a] Defined using the modified Charlson definitions.
[b] Defined as *ICD-9-CM* 345.x or 780.3x.
[c] Defined as positive if a patient had multiple prior admissions or emergency department visits for trauma during the cohort.
[d] Assessed using the Abbreviated Injury Scale (ICD/AIS).

primary analysis by including only strokes that occurred in the first year after the index event and then again by excluding all strokes that occurred within the first year. We also explored the role of age on the TBI-stroke association by stratifying our analysis at age 50 years. In addition, to assess for alcohol and drug abuse/dependency as possible mediators of the relationship between TBI and ischemic stroke, we repeated our primary analysis adjusting for any alcohol/drug abuse diagnoses (*ICD-9-CM* 291–292.9, 303–304.9). Finally, to assess for the role of other potential stroke risk factors (e.g., vasculitis) and risk factors that are suboptimally measured (e.g., smoking[34]), we repeated our primary analysis and estimated the stroke-TBI association after adjusting for the following: hypercoagulable disorders, prior venous thromboembolism, obesity, vasculitis, arrhythmias other than atrial fibrillation, valvular disease, patent foramen ovale, and smoking.

RESULTS The study cohort included 1,173,353 total trauma subjects, 436,630 (37%) with TBI. The median duration of follow-up was 28 months (interquartile range 14–44), with a total of 11,229 (1%) ischemic strokes identified during this timeframe—1.1% in the TBI group and 0.9% in the non-TBI trauma group. The patients with TBI were slightly younger than controls (mean age 49.2 vs 50.3 years), less likely to be female (46.8% vs 49.3%), and had a higher mean injury severity score (4.6 vs 4.1). Further details of the study population are summarized in table 1.

Association between TBI and ischemic stroke hospitalization. Kaplan-Meier survival curves for survival free from ischemic stroke after TBI and non-TBI trauma are illustrated in the figure. The TBI group was more likely to be hospitalized for ischemic stroke than the non-TBI trauma group (log-rank test, $p < 0.01$). The difference between the unadjusted Nelson-Aaler cumulative hazard function in the TBI group compared with the non-TBI trauma group was 0.07% (0.06%–0.09%) at 90 days and 0.21% (0.18%–0.24%) at 2 years.

After adjustment for all covariates (table 2), TBI was associated with ischemic stroke hospitalization (hazard ratio [HR] = 1.31, 95% CI 1.25–1.36). This association only changed slightly when covariate groups were serially added: demographics only (HR = 1.34, 95% CI 1.28–1.39), addition of vascular risk factors (HR = 1.30, 95% CI 1.25–1.35), addition of comorbidities (HR 1.30, 95% CI 1.25–1.35), and addition of injury severity and trauma mechanism (HR = 1.31, 95% CI 1.25–1.36).

Secondary analyses. The association between TBI and ischemic stroke hospitalization was robust in that similar associations were observed under a variety of different modeling assumptions (table 3). All TBI subtypes had a similar magnitude of association with ischemic stroke, and when stroke hospitalization within 7, 30, 60, or 365 days of trauma was excluded from the outcome measure, the ischemic stroke–TBI association only modestly decreased (table 3). The

Figure Kaplan-Meier curves demonstrating the proportion of the cohort with stroke-free survival in traumatic brain injury (TBI) and non-TBI trauma patients
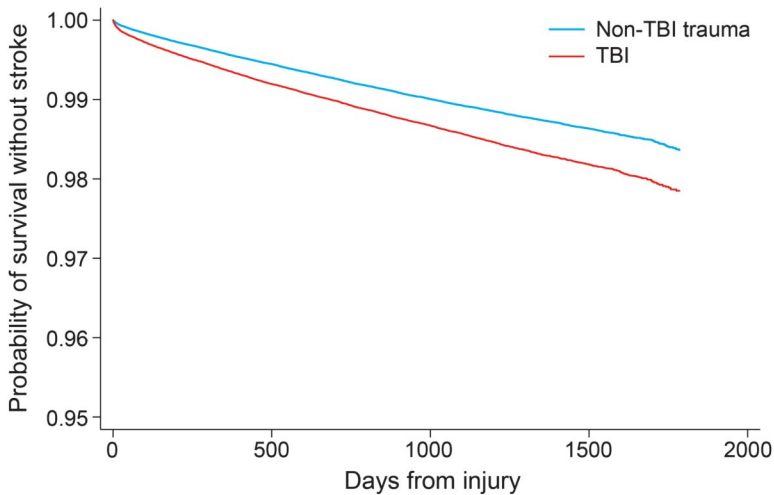
Note that these curves are presented to demonstrate the likely minimum difference in stroke risk between TBI and non-TBI trauma patients. The absolute risk estimates from this curve may be inaccurate because of lack of death censoring (see Discussion section). Log-rank test: $p < 0.00001$.

Table 2 Cox model output

	Hazard ratio (95% CI)[a]	p Value
Age, y, reference 18–32		
33–48	5.32 (4.26–6.64)	<0.01
49–66	16.3 (13.1–20.3)	<0.01
67+	37.3 (29.7–46.9)	<0.01
Female	0.98 (0.94–1.03)	0.48
Race/ethnicity, reference white		
African American	1.69 (1.56–1.83)	<0.01
Hispanic	1.08 (1.01–1.15)	0.03
Asian	0.88 (0.80–0.97)	0.01
Other	0.97 (0.90–1.04)	0.36
Vascular risk factors/comorbidities		
Hypertension	1.34 (1.28–1.40)	<0.01
Hyperlipidemia	0.91 (0.86–0.97)	<0.01
Diabetes	1.33 (1.26–1.40)	<0.01
Coronary artery disease	1.11 (1.04–1.23)	<0.01
Peripheral vascular disease	1.11 (1.00–1.23)	0.05
Atrial fibrillation	1.76 (1.65–1.88)	<0.01
Epilepsy	1.47 (1.34–1.61)	<0.01
Injury severity	1.00 (1.00–1.01)	0.60
TBI	1.31 (1.25–1.36)	<0.01

Abbreviations: CI = confidence interval; TBI = traumatic brain injury.
[a] Hazard ratio for major risk factors and TBI after also adjusting for payer, all Charlson comorbidities, injury mechanism (E codes), whether the patient had multiple events, and whether the patient was admitted.

age-stratified analysis was a secondary analysis in which the stroke-TBI association was most substantially altered, with a greater association observed in the population younger than 50 years (odds ratio [OR] 1.56, 95% CI 1.32–1.85) vs the population 50 years and older (OR 1.22, 95% CI 1.16–1.28).

DISCUSSION We found a robust association between TBI visits and subsequent hospitalization for ischemic stroke in California from 2005 to 2009, even after adjusting for a number of potential confounding variables. The magnitude of this association was substantial (HR 1.31) and was similar to the association between the leading stroke risk factor, hypertension (HR 1.34), and ischemic stroke. Given the higher prevalence of TBI in this trauma population, TBI was responsible for more ischemic stroke than hypertension. The TBI–ischemic stroke association persisted in secondary analyses after accounting for a variety of variables and assumptions that may alter the stroke-TBI relationship. Despite the robust association of TBI and ischemic stroke, the absolute ischemic stroke risk difference between TBI and non-TBI trauma patients in this low-risk cohort is small. Nonetheless, if further research definitively established TBI as a novel stroke risk factor, this would stimulate research to understand stroke pathophysiology after TBI and inform stroke prevention efforts in this young population with few vascular risk factors.

We found a similar association between ischemic stroke and TBI as in the prior Taiwanese study.[13] In our study, the association persisted after selecting non-TBI trauma controls that are likely more similar to the TBI population than the age- and sex-matched controls in the Taiwanese study. We also found that the ischemic stroke–TBI association was similarly unaffected by accounting for potential confounders such as trauma severity and trauma mechanism. Interestingly, we found that the difference in ischemic stroke risk between the TBI and non-TBI trauma groups was not just attributable to a high early risk in patients with TBI. The risk of stroke after TBI persisted even when excluding cases of stroke within 60 days of trauma. This finding differs somewhat from the prior Taiwanese study that found a large early recurrence rate and a more modest effect after 30 days. We also found that the TBI-stroke association was of considerably greater magnitude in the population younger than 50 years (OR 1.56) vs those 50 years and older (OR 1.22), suggesting that TBI may be uniquely important in younger patients.

If the association between TBI and ischemic stroke is causal, a number of potential pathways may explain this relationship. For example, TBI causes alterations in the coagulation cascade, which in turn may increase stroke risk.[12] However, given that these alterations last briefly, they likely explain at most a portion of the association found in this study. TBI is also known to cause vascular dissection—a well-described ischemic stroke mechanism.[35,36] Our analysis excluded dissection-mediated

Table 3 Secondary analyses[a]

	Hazard ratio (95% CI) for stroke after TBI
Baseline model	1.31 (1.25-1.36)
Baseline model limited to outcome of principal diagnosis of stroke	1.29 (1.23-1.35)
Excluding epilepsy rather than adjusting for epilepsy	1.31 (1.25-1.36)
Excluding all head/neck arterial injuries	1.29 (1.23-1.36)
Including alcohol and drug-related dependency	1.30 (1.25-1.36)
Including atypical stroke risk factors	1.29 (1.23-1.35)
Excluding stroke within 7 d	1.27 (1.22-1.33)
Excluding stroke within 30 d	1.25 (1.20-1.31)
Excluding stroke within 60 d	1.25 (1.20-1.31)
Excluding stroke within 1 y	1.24 (1.17-1.31)
Excluding stroke after 1 y	1.38 (1.31-1.46)
Stratified by trauma severity	
Tertile 1 (lowest severity)	1.10 (1.01-1.20)
Tertile 2	1.29 (1.16-1.43)
Tertile 3 (highest severity)	1.25 (1.16-1.35)
Stratified by age	
<50 y	1.56 (1.32-1.85)
≥50 y	1.22 (1.16-1.28)
Using TBI subtypes	
Skull fracture	1.21 (1.05-1.41)
Concussion	1.27 (1.17-1.37)
Intracranial bleeding	1.21 (1.12-1.31)
Other intracranial injury	1.38 (1.07-1.76)
Unspecified	1.33 (1.27-1.40)

Abbreviations: CI = confidence interval; TBI = traumatic brain injury.

[a] The top portion of the table shows the magnitude of the TBI-ischemic stroke association in our baseline model and in 5 additional models that accounted for possible confounders between the TBI-stroke association (misdiagnosis of epilepsy, alcohol/drug dependency, missed stroke diagnosis at the time of initial presentation, and atypical or poorly measured stroke risk factors [hypercoagulability, obesity, prior venous thromboembolism, vasculitis, any arrhythmia, endocarditis, any valvular abnormality, patent foramen ovale, and smoking]). The middle portion of the table shows the TBI-ischemic stroke association in analyses stratified by trauma severity. The bottom portion of the table demonstrates the association between TBI subtypes and ischemic stroke.

stroke; however, given the small number of dissections identified by claims, it is likely that some dissections were undetected. Dissection is unlikely, however, to explain the entire association given the relatively low long-term risk of ischemic stroke after dissection,[37] the high short-term recanalization rates after dissection,[38] and the fact that the risk difference between TBI and non-TBI trauma patients appears to continue to increase even years after the initial injury. Although other novel pathophysiologic pathways may have a role, it is also possible that patients with TBI may accrue conventional vascular risk factors at a faster rate than patients with non-TBI trauma because of a more sedentary lifestyle after TBI.

This study has a number of important limitations. First, inaccuracy in administrative diagnosis coding may affect both stroke and TBI diagnoses. For example, sequelae of TBI could lead to a misdiagnosis of ischemic stroke based on neuroimaging studies. If this was the case, we would have expected a stronger association between TBI and ischemic stroke in any position on the record compared with the association between TBI and ischemic stroke as the principal diagnosis because principal position diagnoses generally have a higher specificity.[39] However, we found a similar association between TBI and stroke regardless of the stroke's position on the claim, thus suggesting that the results are not attributable to diagnostic inaccuracy. Similarly, it is possible that patients presenting with focal neurologic symptoms after a seizure related to their TBI are misdiagnosed with stroke.[30] However, our primary analysis adjusted for patients with any epilepsy diagnosis and in secondary analyses we excluded these patients, but the TBI–ischemic stroke association was not substantially affected. Similar potential limitations exist for claims-based diagnosis of mild TBI, which is relatively specific but insensitive.[33] As a consequence, some of the patients in our non-TBI trauma control group likely had TBI. To the extent that this was the case, we would have expected the relationship between TBI and ischemic stroke to be biased toward the null. Similarly, because the control group may also be susceptible to an increased stroke risk relative to the general population (e.g., mediated through lack of mobility), it is possible that the reported association between TBI and stroke represents an underestimate. In addition, our estimates of the risk of ischemic stroke in both the TBI cases and controls are underestimates because we were unable to capture out-of-state stroke hospitalizations or to account for competing mortality. We do not expect, however, that either of these limitations would explain our primary findings. First, we were able to account for risk of mortality after trauma using the injury severity score. Second, TBI patients in general would be expected to have a higher mortality than non-TBI trauma patients[40]; therefore, failing to account for competing mortality would likely lead to underestimation of the true TBI–ischemic stroke association. As with all observational studies, unmeasured confounders (e.g., differences in baseline medications) may lead to biased estimates. Finally, this dataset enables only limited inferences about the possible mechanistic links between TBI and trauma given that many of clinical details (e.g., ischemic stroke subtype, localization, severity) are not measured.

TBI is associated with ischemic stroke, and further work is needed to assess whether it may be a novel stroke risk factor. Prospective cohort and/or population-based, cross-sectional studies are needed to confirm the association, explore potential mechanisms for the association

between TBI and ischemic stroke, and carefully characterize the clinical features of both TBI and subsequent stroke, including both TBI and stroke mechanism, size, and location.

AUTHOR CONTRIBUTIONS

STUDY FUNDING

DISCLOSURE

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