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Dementia risk after brain versus non-brain trauma: the role of age and severity

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Abstract

Importance—There is conflicting epidemiological evidence regarding the importance of traumatic brain injury (TBI) as a risk factor for dementia. Few prior studies have used non-TBI trauma (fracture) patients as controls and investigated the influence of age and TBI severity.

Objective—To quantify risk of dementia among adults with recent TBI compared to adults with fractures.

Design—Retrospective cohort study from January 2005 to December 2011 (follow-up 5 to 7 years).

Setting—California statewide administrative health database of emergency department (ED) and inpatient visits.

Participants—All patients aged ≥55 diagnosed with TBI or fracture in 2005–2006 without baseline dementia and who did not die during hospitalization (n=164,661).

Exposure—Mild versus moderate/severe TBI diagnosed using ICD-9 code Center for Disease Control (CDC) definitions. Fracture diagnosed using ICD-9 codes excluding fractures of head/neck.

Main outcomes—Incident ED/inpatient diagnosis of dementia (ICD-9 codes) ≥1 year after initial TBI or fracture. The association between TBI and risk of dementia was estimated using Cox proportional hazard models before and after adjusting for common dementia predictors and potential confounders. We also stratified by TBI severity and age-category (age 55–64, 65–74, 75–84, and 85+).

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Results—51,799 (31%) trauma patients had TBI. Of these, 4,361 (8.4%) developed dementia compared to 6,610 (5.9%) of fracture patients (p<0.001). TBI was associated with increased dementia risk (hazard ratio (HR) = 1.46; 95% confidence-interval (CI) 1.41–1.52). Adjustment for covariates had little impact except adjustment for age category (fully adjusted model HR=1.26; 95% CI 1.21–1.32). In stratified adjusted analyses moderate/severe TBI was associated with increased risk of dementia across all ages (age 55–64: HR = 1.72; 95% CI 1.40–2.10 vs. age 65–74: HR = 1.46; 95% CI 1.30–1.64), while mild TBI may be a more important risk factor with increasing age (age 55–64 HR = 1.11; 95% CI .80–1.53 vs. age 65–74 HR = 1.25; 95% CI 1.04–1.51) (age interaction p<0.0001).

Conclusions and Relevance—Among patients evaluated in ED or inpatient settings, moderate/severe TBI at age ≥55 or mild TBI at age ≥65 increases risk for developing dementia. Younger adults may be more resilient to effects of mild recent TBI than older adults.

INTRODUCTION

There is controversy regarding the causal link between a single TBI and risk of developing dementia. Several studies and meta-analyses have not found an association between TBI and risk of dementia.[1–5] Many prior studies have had notable limitations including recall bias due to self-reported diagnoses,[6–10] possible reverse causality[11] if patients with dementia have increased risk of TBI, possible confusion with post-concussive syndrome due to transient post-TBI cognitive symptoms,[12,13] or possible confounding if TBI patients are compared to healthy controls who may differ in many ways from patients prone to TBI.[13] Even among studies reporting a positive association between TBI and dementia, there is dramatic variability in the magnitude of reported risk, which may be due to differences in TBI severity, age of subjects, and follow-up period (with some being as short as two years) between studies.[2,14]

According to the Centers for Disease Control (CDC), Americans aged 55 and older account for more than 60% of all hospitalizations for TBI, with the highest rates of TBI-related ED, inpatient visits, and deaths occurring among those aged 75 and older (932 per 100,000 population).[15] This number is likely to be an underestimate of the population prevalence of TBI given that many patients with TBI never seek medical attention.[16] Thus, an improved understanding of the effects of a recent TBI sustained in middle-aged or older adulthood on the risk of development of dementia has important public health implications.

The primary goal of our study was to assess the effect of a single recent TBI on risk of dementia using a novel design that addresses some of the limitations of prior studies. Specifically, we sought to eliminate recall bias by using physician-generated diagnoses of TBI, to minimize reverse causality and misdiagnosis by excluding diagnoses of dementia within one year after TBI, and to minimize confounding by comparing TBI patients to patients with non-TBI trauma (NTT). Additionally, we investigated the role of TBI severity and patient age because we hypothesized that while a recent TBI of any severity would increase short-term risk of dementia across all ages, the risk would be greater with increasing TBI severity and increasing age due to increasing brain vulnerability.[17]

METHODS

Design and protocol approval

In this retrospective cohort study, data were derived from the State Inpatient Databases (SID)[18] and State Emergency Department Databases (SEDD)[19] for the state of California managed by the Healthcare Cost and Utilization Project (HCUP) and Agency for Healthcare Research and Quality. These data are available to researchers for a fee after completing a data use agreement. The SID and SEDD capture all inpatient and ED discharge diagnoses for participating states for each year. California was selected for analysis as it is the most populous state, data for each patient was linked by the HCUP to subsequent inpatient or ED visits prior to release to researchers in a de-identified fashion, and because linked data was available from 2005 to 2011. The study was approved by the University of California San Francisco Human Research Committee and the need for informed consent was waived due to the use of de-identified administrative data.

Patient selection

Adults ≥55 years old were included in the cohort if they were diagnosed with TBI or NTT during an inpatient or ED visit in 2005 or 2006, did not die during the hospitalization, and did not have a diagnosis of dementia in any discharge diagnosis field.

Exposure

TBI was defined using CDC criteria:[20,21] ICD-9-CM 800.0–801.9, 803.0–804.9, 850.0–854.1, or 959.01 in any discharge diagnosis field. Mild TBI was defined according to CDC criteria:[21] ICD-9-CM first four digits 800.0, 800.5, 801.0, 801.5, 803.0, 803.5, 804.0, 804.5, 850.0, 850.1, 850.5, and 850.9 (with a fifth digit of 0, 1, 2, 6, 9, or missing) or 854.0 (with a fifth digit of 1, 2, 6, 9, or missing). Moderate/severe TBI was defined as all non-mild TBI. NTT was defined as 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. Patients with both TBI and NTT during the same hospital visit were classified as TBI. We conservatively classified patients with multiple subsequent hospital visits based on their first visit only such that a patient who received an in-hospital diagnosis of leg fracture during hospital visit one but received an in-hospital diagnosis of TBI during hospital visit two, was classified as NTT.

Outcome

The primary outcome was a diagnosis of dementia made during a subsequent ED or inpatient hospitalization. Dementia was defined according to recommendations regarding validated ICD-9 codes for the diagnosis of dementia in an inpatient setting: ICD-9-CM 290.0–290.9, 331.0–331.2, or 294.1–294.11 (positive predictive value 60–96%, sensitivity 30–76%, specificity 95–100%)[22] The follow-up extended through the end of 2011, for a maximum follow-up of five to seven years from the initial hospital visit for trauma in 2005 or 2006. In order to minimize the chance of reverse-causality, misdiagnosis with a potentially resolving post-concussive syndrome,[12] or delirium from medications or other complications of recent trauma, patients were excluded if the diagnosis of dementia was made less than one year after the trauma.

Covariates

Information was collected on age, gender, race, comorbidities (depression,[23] delirium,[24] drug/alcohol disorders, and vascular risk factors including hypertension, hyperlipidemia, diabetes, coronary artery disease, peripheral vascular disease, and cerebrovascular disease), trauma mechanism, healthcare utilization, and trauma severity. Income quartile, calculated by the HCUP by matching each patient's ZIP code to annually updated demographic data provided by Claritas,[25] was included as a proxy for socio-economic status.[26] Comorbidities were based on ICD-9 discharge codes from the index visit for each patient. Vascular risk factors were generated using these HCUP single-level clinical classification system (ccs) codes:[27] hypertension 98 – 99, hyperlipidemia 53, diabetes 49 – 50, coronary artery disease 100 – 101, peripheral vascular disease 114, cerebrovascular disease 109 or 113. Other comorbidities were identified using the following ICD-9 codes: depression 296.2 – 296.36 or 311,[23] delirium 292.81 or 293.0 or 293.9, alcohol disorders/dependence 291 – 291.99 or 303 – 303.93, and drug disorders/dependence 292 – 292.99 or 304 – 304.99. Trauma mechanism was coded using major external cause of injury group codes (E codes)[28] and then divided into four categories: falls, vehicle accidents, assault, and other/unknown. Healthcare utilization data included total hospital visits and total trauma visits per patient during the follow-up period including the index visit, as well as the location of the index visit (ED or inpatient). Trauma severity was defined according to the new injury severity score (NISS),[29] a composite score that takes into account a patient's three most severe injuries regardless of anatomical location and has been shown to be an excellent predictor of mortality, particularly in patients with head/neck trauma.[30]

Data analysis

All statistical analyses were performed using STATA 13.1.[31] Summary statistics were generated for baseline characteristics and demographics of TBI and NTT groups and compared using t-test or chi-squared tests. We compared risk of developing dementia according to TBI status using Kaplan-Meier estimates. Patients were not censored at death as this information was not provided by the HCUP and de-identification precluded linkage to national death data. To evaluate the impact of potential confounders, we adjusted analyses using Cox proportional hazard modeling adjusting for all covariates listed above. In pre-planned analyses, to test for a "dose-response" and to investigate our theory regarding aging and brain vulnerability, we assessed for interaction between age and TBI severity and then performed further analyses stratified by TBI severity and age category (age 55–64, 65–74, 75–84, and 85+). Given our inability to censor at death, three additional post-hoc analyses were performed after excluding all dementia-free TBI and NTT patients who were not "seen alive" (did not have an ED or inpatient visit recorded in the database) within one year, six months, and 30 days of the end of the follow-up period. In order to test the robustness of our primary result and study design, we performed four additional post-hoc sensitivity analyses: 1) excluding patients with multiple trauma visits for TBI or NTT, 2) flipping patients into the TBI group if they sustained a TBI anytime during the follow-up period, 3) comparing patients with single versus multiple TBIs during the follow-up period, and 4) including patients with dementia diagnoses less than one year after the index visit.

RESULTS

After excluding patients with a dementia diagnosis less than one year after the initial trauma (n=4,187), the cohort included 164,661 trauma patients, of whom 51,799 (31%) had TBI. The median duration of follow-up was 6 years (interquartile range 0.4 – 0.5 years). A total of 10,971 (6.7%) patients were diagnosed with dementia during follow-up. Baseline patient characteristics are reported in Table 1. Compared to the TBI group, the NTT group was younger, had a higher proportion of women, less cerebrovascular disease, and the trauma mechanism was less commonly due to vehicle accidents or assault. The rate of falls was equivalent for TBI and NTT patients.

Those with TBI were more likely to be diagnosed with dementia compared to the NTT group (4,361, 8.4% versus 6,610, 5.9%, $p < 0.001$). Average time from trauma to dementia diagnosis was 3.2 years and was shorter in the TBI group compared to the NTT group (3.1 years versus 3.3 years, $p < 0.0001$).

In the unadjusted model, TBI was significantly associated with dementia diagnosis (hazard ratio (HR) = 1.46; 95% confidence interval (CI) 1.41–1.52). Individual adjustment for each covariate changed the HR by less than 10% except for age (model adjusted for age-category HR 1.25; 95% CI 1.20–1.30). Nonetheless, TBI remained significantly associated with dementia diagnosis in the final model adjusted for all covariates (HR = 1.26; 95% CI 1.21–1.32).

There was a significant interaction between TBI severity and age category (fully adjusted model, TBI severity*age category, $p<0.0001$) such that moderate/severe TBI was associated with increased dementia risk across all ages, while mild TBI became a relatively more important dementia predictor with increasing age (Table 2). There was, however, an unexpected attenuation of dementia risk after severe TBI with increasing age such that the trend toward a dose-response was reversed among the oldest old (aged 85 plus). Exclusion of all dementia-free patients that were not “seen alive” within one year of the end of the follow-up period resulted in the expected trend toward a dose response (Table 3 and Figure). Analyses excluding dementia-free patients not “seen alive” within six months or within 30 days of the end of follow-up produced similar results.

Further sensitivity analyses to test the robustness of our primary result produced similar findings. After excluding all patients with repeat trauma visits (either for TBI or NTT) during the follow-up period (n = 37,417), single TBI was associated with significantly increased risk of dementia compared to single NTT (fully adjusted HR 1.26; 95% CI 1.19–1.32). After excluding all NTT patients with subsequent TBI (n = 6,748) and then stratifying patients based on NTT versus single TBI versus >1 TBI during the follow-up period, the risk of dementia following single TBI was virtually equivalent to that reported in the primary analysis (fully adjusted HR = 1.25; 95% CI 1.20–1.31), but risk of dementia following >1 TBI was doubled (fully adjusted HR = 1.56; 95% CI 1.45–1.69). After re-categorizing all NTT patients with subsequent TBI during the follow-up period as TBI patients, TBI at any time during the follow-up period was associated with significantly increased risk of dementia compared to NTT without subsequent TBI (fully adjusted HR = 1.41; 95% CI

1.36–1.48). Lastly, when dementia diagnoses rendered less than one year after the index trauma were included, TBI was associated with an increased risk of dementia compared to NTT (HR = 1.37; 95% CI 1.32–1.42).

DISCUSSION

Among a large cohort of trauma patients evaluated in the ED or inpatient setting, we found an association between TBI sustained in middle-aged and older adulthood and the development of dementia. Stratification by age and TBI suggested that moderate or severe TBI was associated with risk of dementia in patients age 55 and older, while mild TBI was associated with risk of dementia among older patients.

Nearly all prior studies of TBI and dementia risk have compared TBI patients to the general population. This study design may account for the observation that some have found a marked attenuation of risk of post-TBI dementia after multivariate adjustment.[32] There may, however, be additional unique characteristics of TBI-prone patients that increase their risk of dementia and are unmeasured confounders in these studies (i.e. risk-taking behavior, poor judgment). Additional limitations of prior studies include possible reverse-causality, misdiagnosis due to a resolving post-concussive syndrome,[12] or misdiagnosis due to delirium from medications or other complications of recent trauma if dementia is diagnosed too soon after TBI. For example, a study of TBI and risk of Parkinson's disease reported that patients in the early stages of disease are more likely to fall and suffer a TBI in the months preceding the diagnosis of Parkinson's disease.[11] Similarly, a recent large population-based study that assessed dementia-free survival in patients with TBI compared to the general population found a three-fold increased risk for dementia following mild TBI.[13] The average time from TBI to dementia diagnosis, however, was just one year raising the possibility of reverse causality or misdiagnosis. Lastly, many studies reporting a lack of association between TBI and dementia have relied upon self-report[1,2,33] (raising concern for recall bias), have used a report of "head injury"[3–5] to approximate a history of TBI (raising concern for misdiagnosis), or have provided insufficient longitudinal follow-up.[2,14]

In our study, by comparing trauma patients with and without TBI,[34] we tried to account for potential unmeasured confounders and mitigated the possibility of reverse causality as it is unlikely that patients in an early stage of dementia would be more prone to suffer a traumatic brain than a traumatic limb injury. Other strengths of our study design were excluding dementia diagnoses less than one year after TBI and using validated ICD-9 code hospital-based diagnoses of TBI. Lastly, by conservatively classifying TBI and NTT based on the index visit only – an "intention-to-treat" model – we were able approximate risk of a single TBI. Given the lack of data about prior TBIs, we chose this model as our primary study design rather than a design that accounted for patients with multiple TBIs during the follow-up period, as such exclusion was considered arbitrary. Our additional post-hoc sensitivity analyses, however, in which we excluded patients with multiple traumas, stratified based on single versus multiple TBIs, or flipped NTT cases into the TBI group at any point during follow-up if they were diagnosed with TBI, all returned similar results and further confirmed the robustness and validity of our study design meant to quantify risk of a single recent TBI.

Major theories regarding the mechanism linking TBI and dementia include 1) the triggering of a progressive neurodegenerative cascade, 2) the acceleration of an established neurodegenerative cascade, and 3) a static brain injury that reduces cognitive reserve.[35,36] Given the relatively short duration of follow-up in this study (five to seven years), we are unable to comment on a possible role of TBI in triggering a de-novo neurodegenerative cascade, but our results could theoretically lend support to either of the other two proposed theories. Whether a person with TBI recovers cognitively or develops dementia, however, is likely dependent on multiple additional risk and protective factors ranging from genetics and medical comorbidities to environmental exposures and specific characteristics of the TBI itself. Furthermore, certain factors may combine with TBI synergistically to increase risk for neurodegenerative disease in a more than additive fashion.[37,38]

We found that moderate/severe TBI is a risk factor for developing dementia among adults age 55 and over, while mild TBI is a risk factor for adults age 65 and over. Increasing mortality after TBI with increasing age,[1,39,40] however, may mask the risk of dementia, particularly after moderate/severe TBI in the oldest-old population – a hypothesis supported by our analyses censoring patients that were not seen alive within one year, six months, or 30 days of the end of follow-up. Overall, the interaction with age and TBI severity suggests that younger patients may be more resilient to the effects of recent mild TBI or may take longer to manifest symptoms of dementia.

A limitation of this study is the use of retrospective inpatient and ED administrative health data. Sources of error may include misdiagnosis by the clinician or miscoding by the hospital billing staff. Specifically, inpatient ICD-9 diagnostic codes are relatively insensitive for the diagnosis of dementia.[22,41–43] Thus, while our study may underestimate dementia risk, this pattern should be equal between TBI and NTT patients and would not be expected to bias the magnitude of the association.

Additional limitations include the lack of data on family history, educational status, prior surgeries/illnesses, prior TBIs before the index visit, details of treatment during the index visit, relatively short duration of follow-up, inability to censor at death, lack of outpatient data, and the possibility that patients who present to the ED or are hospitalized for TBI may differ from those who do not seek medical attention.[16] By comparing TBI patients to NTT patients, we controlled for any additional deleterious systemic effects of trauma on the nervous system, such as an increase in peripheral inflammatory markers, that may further increase risk for dementia.[44] Lastly, as our goal was to assess risk of dementia after a recent TBI sustained in middle-aged or older adulthood, these data do not address the important issue of whether a single mild TBI sustained in adolescence or young-adulthood increases risk of dementia.

We found that mild TBI sustained at age 65 plus or moderate/severe TBI sustained at age 55 plus may significantly increase risk of developing dementia. Given the high rates of TBI in the population, primary prevention of TBI – which in this study was overwhelmingly (66%) due to falls – is critical. Impact of mild TBI sustained in middle age or earlier deserves further study over a longer period of follow-up. Additionally, further research is needed to

understand the mechanisms of post-TBI dementia in order to inform secondary preventative strategies.

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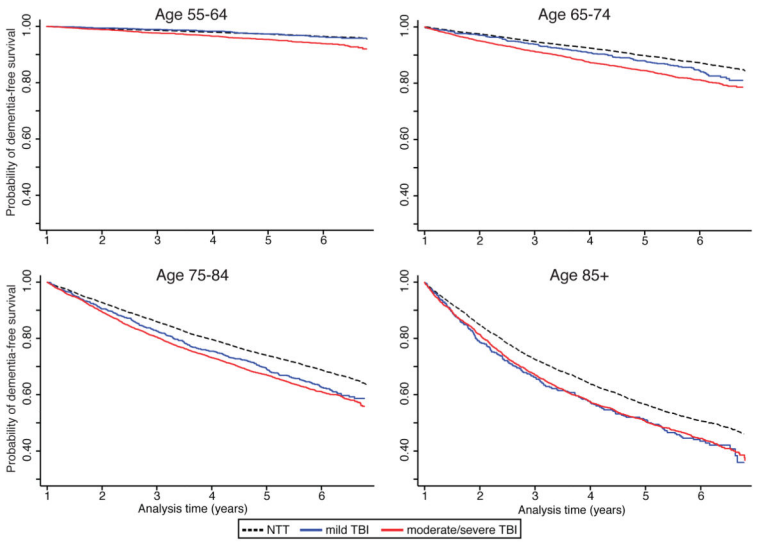

FIGURE. Kaplan-Meier plots for dementia-free survival after non-TBI trauma (NTT), mild TBI, or moderate/severe TBI

The association between TBI severity and risk of dementia stratified by age and excluding dementia-free patients not “seen alive” within one year of the end of follow-up. Sample sizes per Table 3.

Table 1

Baseline patient characteristics by Traumatic Brain Injury (TBI) status

Characteristics: mean (SD) or n (%)	Non-TBI Trauma (n=112,862)	TBI (n=51,799)	p-value
Age, y	70.8 (10.8)	73.2 (11.1)	<.0001
55–64	40,444 (35.8%)	14,697 (28.4%)	
65–74	27,991 (24.8%)	11,618 (22.4%)	
75–84	29,113 (25.8%)	15,603 (30.1%)	
85+	15,314 (13.6%)	9,881 (19.1%)	
Women	76,131 (69.1%)	29,057 (56.9%)	<.001
Race/ethnicity			<.001
White	75,467 (66.9%)	34,142 (65.9%)	
African American	3,820 (3.4%)	2,002 (3.9%)	
Hispanic	14,691 (13.0%)	6,225 (12.0%)	
Asian	4,148 (3.7%)	3,301 (6.4%)	
Other/Missing	14,736 (13.1%)	6,129 (11.8%)	
Median income quartile			<.001
1st (poorest)	25,613 (23.2%)	10,135 (20.1%)	
2nd	26,675 (24.2%)	12,055 (24.0%)	
3rd	29,663 (26.9%)	14,134 (28.1%)	
4th (wealthiest)	28,360 (25.7%)	14,015 (27.8%)	
ICD-9 comorbidities at index visit			
Hypertension	34,729 (30.8%)	17,997 (34.7%)	<.001
Hyperlipidemia	10,819 (9.6%)	4,889 (9.4%)	.344
Diabetes	15,382 (13.6%)	7,092 (13.7%)	.732
Coronary artery disease	8,972 (8.0%)	5,105 (9.9%)	<.001
Peripheral vascular disease	1,308 (1.2%)	581 (1.1%)	.509
Cerebrovascular disease	2,386 (2.1%)	1,973 (3.8%)	<.001
Depression	3,492 (3.1%)	1,606 (3.1%)	.944
Delirium	414 (0.37%)	224 (0.43%)	<.05
Drug disorder/dependence	437 (0.4%)	169 (0.3%)	.058
Alcohol disorder/dependence	1,237 (1.1%)	1,136 (2.2%)	<.001
Trauma Mechanism			<.001
Fall	74,986 (66.4%)	34,404 (66.4%)	
Vehicle accident	9,890 (8.8%)	7,454 (14.4%)	
Assault	815 (0.7%)	1,562 (3.0%)	
Other/missing	27,171 (24.1%)	8,379 (16.2%)	
Healthcare utilization			
Index visit location = ED	76,512 (67.8%)	35,269 (68.1%)	0.233
Total inpatient or ED visits	4.8 (6.2)	5.2 (7.0)	<.0001

Characteristics: mean (SD) or n (%)	Non-TBI Trauma (n=112,862)	TBI (n=51,799)	p-value
Total inpatient or ED visits for TBI/trauma	1.32 (0.70)	1.30 (0.72)	<.0001
New Injury Severity Score (NISS)	5.0 (3.7)	7.8 (5.9)	<.0001
TBI frequency			<.001
1 TBI anytime during study period	5,743 (5.1%)	44,440 (85.8%)	
>1 TBI anytime during study period	1,005 (0.89%)	7,359 (14.2%)	

Abbreviations: ED = emergency department, SD = standard deviation, y = years. Total inpatient or ED visits are mean per participant over follow-up period including index visit.

Table 2

Association between TBI and risk of dementia stratified by age and TBI severity

	HR (95% CI)	p-value
55–64 years, reference NTT (n=40,444)		
mild TBI (n=4,670)	1.11 (.80–1.53)	.546
moderate/severe TBI (n=10,027)	1.72 (1.40–2.10)	<.001
65–74 years, reference NTT (n=27,991)		
mild TBI (n=2,810)	1.25 (1.04–1.51)	<.05
moderate/severe TBI (n=8,808)	1.46 (1.30–1.64)	<.001
75–84 years, reference NTT (n=29,113)		
mild TBI (n=2,800)	1.21 (1.08–1.36)	<.005
moderate/severe TBI (n=12,803)	1.27 (1.19–1.36)	<.001
85+ years, reference NTT (n=15,314)		
mild TBI (n=1,443)	1.25 (1.09–1.44)	<.005
moderate/severe TBI (n=8,438)	1.14 (1.06–1.24)	<.005

Model adjusted for gender, race, income, comorbidities, trauma mechanism, healthcare utilization, and injury severity. Abbreviations: HR = hazard ratio, CI = confidence interval, NTT = non-TBI trauma.

Table 3

Association between TBI and risk of dementia stratified by age and TBI severity, excluding patients not “seen alive” within one year of end of follow-up

	HR (95% CI)	p-value
55–64 years, reference NTT (n=10,281)		
mild TBI (n=1,226)	1.08 (.77–1.49)	.665
moderate/severe TBI (n=2,769)	1.65 (1.35–2.02)	<.001
65–74 years, reference NTT (n=8,607)		
mild TBI (n=850)	1.22 (1.02–1.47)	<.05
moderate/severe TBI (n=2,750)	1.50 (1.33–1.68)	<.001
75–84 years, reference NTT (n=10,025)		
mild TBI (n=938)	1.26 (1.13–1.42)	<.001
moderate/severe TBI (n=4,347)	1.38 (1.29–1.47)	<.001
85+ years, reference NTT (n=4,218)		
mild TBI (n=422)	1.25 (1.09–1.44)	<.005
moderate/severe TBI (n=2,278)	1.31 (1.21–1.41)	<.001

Model adjusted for gender, race, income, comorbidities, trauma mechanism, healthcare utilization, and injury severity. Abbreviations: HR = hazard ratio, CI = confidence interval, NTT = non-TBI trauma.