RESEARCH ARTICLE

Associations Between Traumatic Brain Injury and Cognitive Decline Among Older Male Veterans

A Twin Study

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Abstract

Background and Objectives

Traumatic brain injuries (TBIs) are associated with increased risk of dementia, but whether lifetime TBI influences cognitive trajectories in later life is less clear. Cognitive interventions after TBI may improve cognitive trajectories and delay dementia. Because twins share many genes and environmental factors, we capitalize on the twin study design to examine the association between lifetime TBI and cognitive decline.

Methods

Participants were members of the National Academy of Sciences-National Research Council's Twin Registry of male veterans of World War II with self or proxy-reported history of TBI and with up to 4 observations over 12 years of the modified Telephone Interview for Cognitive Status (TICS-m). We used linear random-effects mixed models to analyze the association between TBI and TICS-m in the full sample and among co-twins discordant for TBI. Additional TBI predictor variables included number of TBIs, severity (loss of consciousness [LOC]), and age of first TBI (age <25 vs 25+ years [older age TBI]). Models were adjusted for age (centered at 70 years), age-squared, education, wave, twin pair, lifestyle behaviors, and medical conditions.

Results

Of 8,662 participants, 25% reported TBI. History of any TBI (β = −0.56, 95% CI −0.73 to −0.39), TBI with LOC (β = −0.51, 95% CI −0.71 to −0.31), and older age TBI (β = −0.66, 95% CI −0.90 to −0.42) were associated with lower TICS-m scores at 70 years. TBI with LOC (β = −0.03, 95% CI −0.05 to −0.001), more than one TBI (β = −0.05, 95% CI −0.09 to −0.002,), and older age TBI (β = −0.06, 95% CI −0.09 to −0.03) were associated with faster cognitive decline. Among monozygotic pairs discordant for TBI (589 pairs), history of any TBI (β = −0.55, 95% CI −0.91 to −0.19) and older age TBI (β = −0.74, 95% CI −1.22 to −0.26) were associated with lower TICS-m scores at 70 years. Those with more than one TBI (β = −0.13, 95% CI −0.23 to −0.03) and older age TBI (β = −0.07, 95% CI −0.13 to −0.002) showed greater cognitive decline compared with their co-twin without TBI.

Discussion

These findings support an association of the effect of TBI on cognitive score and the rapidity of cognitive decline in later life. The results in monozygotic pairs, who share all genes and many exposures, particularly in early life, provide additional evidence of a causal relationship between TBI and poorer late-life cognitive outcomes.

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Glossary

ApoE = Apolipoprotein epsilon; **LOC** = loss of consciousness; **MMSE** = Mini-Mental State Examination; **TBI** = traumatic brain injury; **TICS-m** = modified Telephone Interview for Cognitive Status.

Introduction

Approximately 64–74 million people worldwide are affected by traumatic brain injuries (TBIs) each year,[1,2] with the highest prevalence of TBIs occurring before 30 years[3] and again in those aged 70 years and older.[3,4] Substantial evidence supports an association between TBI across the life span and higher rates of Alzheimer disease and other dementias in later life.[3,5-12] This finding indicates that individuals with TBIs in earlier life who seem to have fully recovered from them may still be at increased risk of cognitive deficits and dementia later in life. Despite the extensive research on TBI and dementia, there is relatively little evidence on poorer cognitive outcomes in later life, especially cognitive decline, that do not meet the threshold for dementia.[13-15] Cognitive decline is common and often reflects the prodromal stages of a dementing process. Understanding the effect of lifetime TBI on the rate of cognitive decline in later life may help identify individuals who may benefit from early interventions that may slow cognitive decline and potentially delay or prevent the onset of dementia. Yet, the numerous prior studies evaluating TBI and cognition have been mostly cross-sectional or had short duration of follow-up after TBI, focused only on early or late-life TBIs, or did not examine cognition in later life when cognitive decline is most common.[16,17] To date, only one study has explored the association between lifetime history of TBI and 4-year cognitive trajectory among adults older than 50 years. The authors found lower baseline cognitive function among those with TBI compared with those without TBI, but no differences in slope of decline over the 4 years of follow-up.[18] A strength of our study is cognitive assessment follow-ups for more than a decade in later life.

Other factors across the life span have been reported to affect the risk of dementia and poor cognition later in life. Among these are social isolation, hearing loss, and physical inactivity.[19] Others, such as chronic cardiovascular and cerebrovascular conditions, are among the most researched and are consistently reported to have a detrimental influence on cognition in later life.[20,21] Yet, there are numerous other factors that are often unmeasurable but have a cumulative effect on the rate of cognitive decline in later life. These factors include both genetic and nongenetic factors, such as early-life socioeconomic status, quality of education, nutrition, and medical care.[22] Twin studies provide an ideal design to account for many of these factors because twins share many genetic and early-life exposures that cannot be reliably measured in the general population. Members of twin pairs typically share early-life experiences such as home environment and socioeconomic status. In addition, monozygotic (MZ) twins share 100% of their genes while dizygotic (DZ) twins share approximately half of their genes. Given this, twin studies allow for support of the causal nature of the relationship between TBI and cognition by accounting for within-pair differences in TBI exposure to evaluate its effect on cognitive function. Observed differences in genetically identical twin pairs (MZ twins) indicate environmental exposure differences vs if shared genetic factors are implicated, differences would be observed only among DZ twins.

We investigated the association between TBI and subsequent rate of cognitive decline in members of the National Academy of Sciences-National Research Center (NAS-NRC) Twin Registry of male World War II veterans. We examined the influence of a number of TBI-associated characteristics that have been reported to affect late-life cognitive outcomes, such as the number of TBIs, severity of the TBI (with or without loss of consciousness [LOC]), and age at the time of first TBI. We also controlled for several medical conditions that may also influence late-life cognition. Using the twin study design, we aimed to gain a better understanding of the association between TBI and rate of cognitive decline in later life.

Methods

Sample

Data were obtained from participants in the Duke Twins Study of Memory in Aging who were also members of the NAS-NRC Registry of World War II veteran male twins born between 1917 and 1927. The NAS-NRC Twin Registry was constructed in the mid-1950s using information from vital statistics offices in 42 states to identify White male twin pairs born in 1917–1927. The 54,000 pairs identified were estimated to represent 93% of the White male twin pairs born during this period in the United States. Birth certificates from these individuals were then matched to Department of Veterans Affairs files to determine veteran status, resulting in 15,924 pairs, which made up the original NAS-NRC Twin Registry.[23] Eligibility criteria for this study included cohort members with data on TBI and education and at least one modified Telephone Interview for Cognitive Status (TICS-m) score.

Standard Protocol Approvals, Registrations, and Patient Consents

All procedures were approved by the Duke University Medical Center Institutional Review Board, and verbal or written consent was obtained from participants or their legal representatives for data collected from 1990 onward.

Modified Telephone Interview for Cognitive Status

The original TICS instrument[24] and its modified[25] form provide a brief assessment of cognitive function that can be administered through telephone. The modified Telephone Interview for Cognitive Status (TICS-m) is modeled after the Mini-Mental State Examination (MMSE), but enhances its content with the inclusion of immediate and delayed recall of a 10-item word list and avoids the ceiling effect often seen with the MMSE.[26] It produces scores ranging from 0 to 50, is highly correlated with the MMSE,[25,27] and has high test-retest reliability.[27] The TICS-m has been shown to be sensitive to detecting change over time in studies evaluating cognitive performance in older adults.[27-31] Education-adjusted scores below 28 indicate suspect dementia.[28] In this study, the TICS-m was administered every 3–4 years beginning in 1990 as part of a screening and assessment protocol for dementia, as part of the Duke Twins Study. Participants completed up to 4 waves of cognitive screening, which represent a period of up to 12 years of cognitive follow-up.

Traumatic Brain Injury

For most of the participants, TBI data were collected directly from participants during telephone interviews at either Wave 3 (1996–1998) or Wave 4 (2000–2001) of the Duke Twins Study. For a subset of participants, information on TBI was collected during in-person or telephone interviews before the Wave 3 interviews, and for those who were unable to complete an interview, this information was obtained from a proxy informant. TBI data included (1) history of occurrence of TBI severe enough to require medical attention or cause LOC, (2) presence and duration of LOC, (3) number of TBIs, and (4) age(s) of TBI. We dichotomized TBI and LOC as yes/no.

Covariates/Demographics

Baseline age was defined as the age at their first TICS-m. For statistical modeling, we considered centered TICS-m age at 70 years for an individual; thus, TBI differences reflect TICS-m differences at 70 years. A squared-age term $(age\text{-}70)^2$ was added to allow for the accelerated-progression cognitive decline with older ages and to improve the model fit and reduce colinearity.[32] Years of education was collected at baseline TICS-m. Study wave was added to control for time in the study and TICS-m practice effects. A variable for twin pairs was included in the model to account for twins with a co-twin or singletons (without a co-twin). For a subset of twin pairs, zygosity was determined by DNA. For 87% of twins, it was determined from physical characteristics reported in military records, fingerprint records, by questionnaire, and (for a small sample) blood group testing.[33-35] This method of establishing zygosity has been estimated by cross-validation with DNA to be 97% accurate.[35] Apolipoprotein epsilon (*ApoE*) genotyping was determined from blood or buccal DNA using PCR amplification and a restriction isotyping method.[36] Because MZ twin pairs share the same genes, for 87 MZ twin pairs where DNA was not available for one twin, we assigned the *ApoE* genotype for the twin with DNA to the twin with no DNA. *ApoE* genotype was dichotomized into e4 allele carriers (*ApoE* 2/4, 3/4, 4/4) vs non–e4 carriers (*ApoE* 2/2, 2/3, 3/3).

Other covariates collected by questionnaire during the same interviews that the TBI information was collected include alcohol overuse (yes/no: defined as reporting a problem drinking more alcohol than he should or drinking 12 or more drinks per day at some time); smoking (current, past, or never smokers); and medical conditions categorized as follows: (a) cardiovascular and/or cerebrovascular disease (myocardial infarction or coronary thrombosis, coronary artery bypass graft, congestive heart failure, and/or stroke or transient ischemic attack); (b) cardiovascular risk (diabetes mellitus, hypertension, and/or hyperlipidemia); (c) neurologic conditions (Parkinson disease and/or seizure disorder); and (d) depression ("ever had a period of two weeks or more when, nearly every day you felt sad, blue or depressed, or unusually cross or irritable, or lost all interest and pleasure in things that you usually cared about or enjoyed?").

Statistical Analyses

Baseline descriptive statistics were calculated to characterize the overall study population and were stratified by TBI. We tested the longitudinal relationship between TBI (history of TBI, number of TBIs, LOC, and age of TBI) and cognitive score and change in score using random-effects linear mixed models. As implemented in this analysis, the model assumes a normal distribution of the residuals (error) of the outcome, linearity of response for the continuous predictors, homogeneity of variance of error across the predictor space, and that the variables randomly specified are not correlated. In the model we present, only 3 effects were considered random: (1) the intercept for the pair (allowing a different intercept for the pair when all continuous covariates are zero and all discrete variables are at the reference), (2) the intercept for the person within the pair (to distinguish difference that zero point between individuals within the pair), and (3) error of the residual. The 2 intercept estimates are typically ignored while the third term speaks of the precision of the model, that is, how well the model fits the prediction of the outcome. TBI was added in the models as a time-varying variable, which means that if a participant had a TBI during the assessment period, their status would change to reflect going from 'no TBI' to 'TBI'; this information was provided at the TICS-m assessment. We analyzed 2 models. Model 1 adjusts for age, age-squared, education, wave, and pair plus the interaction between age by TBI to measure difference in change in cognitive slope over time. Trajectory in all models was measured as interaction between main effect and time, calculated as age in years. Based on goodness-of-fit measures (model 1 AIC = 150,935.6 and BIC = 151,084.0 while model 2 AIC = 149,508.0 and BIC = 149,656.4), model 2 was determined to be the better fit model and included Model 1 variables plus alcohol abuse, smoking status, and medical conditions. A missing category was coded for all covariates with the purpose of not losing observations for a missing condition. We tested both models examining the association between TBI and TICS-m, followed by assessing the specificity of the TBI

Table 1 Sample Baseline Characteristics

	All (n = 8,662)	No TBI (n = 6,494)	TBI (n = 2,168)
Baseline TICS-m Score, mean ± SD	32.5 ± 5.0	32.5 ± 5.0	32.5 ± 4.9
Baseline TICS-m Age, mean ± SD	67.0 ± 3.0	66.9 ± 3.0	67.0 ± 2.9
Education, mean ± SD	13.2 ± 3.2	13.1 ± 3.2	13.4 ± 3.3
Age of first TBI (n = 2,120), mean ± SD			33.0 ± 23.3
Years between age of first TBI and baseline TICS (n = 2,120), mean ± SD			34.0 ± 23.1
Number of Head Injuries, % (n)			
One			78.9 (1710)
Two or More			18.7 (405)
Missing/DK			2.4 (53)
TBI with LOC, % (n)			
No			22.3 (484)
Yes			69.7 (1,510)
Missing/DK			8.0 (174)
TBI before 25 years, % (n)			
No			46.3 (1,003)
Yes			51.5 (1,117)
Missing			2.2 (48)
Alcohol Abuse, % (n)			
Yes	23.7 (2049)	21.6 (1,402)	29.8 (647)
No	75.0 (6,500)	77.1 (5,004)	69.0 (1,496)
Missing/DK	1.3 (113)	1.4 (88)	1.2 (25)
Smoking Status, % (n)			
Current smoker	8.0 (688)	7.8 (508)	8.3 (180)
Never smoked	28.0 (2,428)	27.7 (1798)	29.0 (630)
Past smoker	50.3 (4,357)	49.1 (3,187)	54.0 (1,170)
Missing/DK	13.7 (1,189)	15.4 (1,001)	8.7 (188)
All cardiovascular conditions			
Yes	32.1 (2,783)	30.6 (1986)	36.8 (797)
No	53.7 (4,646)	53.6 (3,482)	53.7 (1,164)
Missing	14.2 (1,233)	15.8 (1,026)	16.8 (207)
Cardiovascular risk			
Yes	61.4 (5,314)	60.1 (3,902)	65.1 (1,412)
No	24.8 (2,150)	24.5 (1,590)	25.8 (560)
Missing	13.8 (1,198)	15.4 (1,002)	9.0 (196)
Neurologic conditions			
Yes	3.4 (294)	2.7 (178)	5.4 (116)
No	83.6 (7,238)	82.6 (5,364)	86.4 (1874)
Missing	13.0 (1,130)	14.7 (952)	8.2 (178)
Depression			
Yes	20.5 (1777)	18.0 (1,168)	28.1 (609)
No	64.1 (555)	64.9 (4,214)	61.7 (1,338)
Missing	15.4 (1,333)	17.1(1,112)	10.2 (221)

Abbreviations: DK = do not know; LOC = loss of consciousness; TBI = traumatic brain injury; TICS-m = modified Telephone Interview for Cognitive Status. Cardiovascular and/or cerebrovascular conditions included myocardial infarction or coronary thrombosis, coronary artery bypass graft, congestive heart failure, and/or stroke or transient ischemic attack. Cardiovascular risk included diabetes mellitus, hypertension, and/or hyperlipidemia. Neurologic conditions included Parkinson disease and/or seizure disorder.

including severity of the TBI (with or without LOC), number of TBIs, and age at the time of first TBI as young (age younger than 25 years) vs not young (25 years and older).

We analyzed the full sample, which included singletons, because these individuals contribute to the estimation of the parameters of the cognitive function and thus increase the precision of the parameter estimates of the model and statistical power of the analyses. A sensitivity analysis was performed with complete pairs only to assess bias. We then conducted co-twin controlled analyses, which included just the complete pairs of twins with known zygosity (MZ vs DZ) who were discordant for TBI; thus, one twin is used as the matched control for the other twin. This approach allows the most control of confounding from genetics and early-life shared environmental factors. We first analyzed all the twin pairs and then repeated the analysis, stratified by zygosity. As a final step, for a subsample of twins with *ApoE* genotype, we ran both models stratified by *ApoE*-e4 carriers vs non–e4 carriers. All data analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC).

Data Availability

Deidentified individual-level data not provided in this article may be requested by any qualified investigator for purposes of replicating procedures and results.

Results

Our sample included 8,662 participants, of which 25% of twins endorsed having ever had a TBI. Detailed sample characteristics for the entire cohort are summarized in Table 1. Twins with and without TBI did not differ by age at baseline TICS-m (mean 67 years) or by baseline TICS-m

Table 2 Linear Mixed-Effect Regression Models Examining the Association Between Cognitive Function Measure by the Modified Telephone Interview for Cognitive Status and Traumatic Brain Injury Variables

	Model 1[a]		Model 2[b]	
	Estimated coefficient	95% CI	Estimated coefficient	95% CI
TICS-m level				
TBI (reference = no TBI), n = 8,662	−0.48	−0.66 to −0.30	−0.56	−0.73 to −0.39
Number of TBIs (reference = no TBI), n = 8,609				
One TBI	−0.28	−0.48 to −0.08	−0.39	−0.58 to −0.20
More than one TBI	0.05	−0.32 to 0.43	−0.21	−0.56 to 0.14
TBI with LOC (Reference = no TBI), n = 8,488	−0.44	−0.65 to −0.23	−0.51	−0.71 to −0.31
Age of First TBI (reference = no TBI), n = 8,614				
TBI at age <25	0.07	−0.17 to 0.31	−0.12	−0.34 to 0.11
TBI at age ≥25	−0.59	−0.84 to −0.34	−0.66	−0.90 to −0.42
TICS-m trajectory (per year)				
TBI (reference = no TBI), n = 8,662	−0.02	−0.05 to −0.001	−0.02	−0.05 to 0.001
Number of TBIs (reference = no TBI), n = 8,609				
One TBI	−0.02	−0.04 to 0.01	−0.02	−0.04 to 0.01
More than one TBI	−0.06	−0.10 to −0.01	−0.05	−0.09 to −0.002
TBI with LOC (Reference = no TBI), n = 8,488	−0.03	−0.05 to −0.002	−0.03	−0.05 to −0.001
Age of First TBI (reference = no TBI), n = 8,614				
TBI at age <25	0.001	−0.03 to 0.03	0.002	−0.03 to 0.03
TBI at age ≥25	−0.06	−0.09 to −0.03	−0.06	−0.09 to −0.03

Abbreviations: LOC = loss of consciousness; TBI = traumatic brain injury; TICS-m = modified Telephone Interview for Cognitive Status.
[a] Model 1 adjusts for age (centered at 70 years), age^2 (centered at 70 years), education, wave, singleton/twin pair, and TBI by time.
[b] Model 2 adjusts for age (centered at 70 years); age^2 (centered at 70 years); education; wave; singleton/twin pair; alcohol abuse; smoking status; and medical conditions (hypertension, cholesterolemia, myocardial infarction, coronary artery bypass graft, congestive heart failure, stroke/transient ischemic attack, diabetes, depression, Parkinson disease, and seizures at baseline) grouped as: cardiovascular disease risk factors, cardiovascular disease, neurologic conditions, depression, and TBI by time.

score (mean 32.5), but those with a TBI had slightly more education (3.6 more months) and reported more medical conditions than those without a TBI. There were no significant differences in education, alcohol, smoking, or any of the medical conditions within twin pairs. There were 1,474 singletons and 7,188 members of complete twin pairs (3,594 pairs). A total of 1,195 twin pairs were discordant for TBI and had known zygosity. A total of 1,392 twins had *ApoE* genotype: 425 e4 allele carriers (*ApoE* 2/4, 3/4, 4/4) vs 967 non–e4 carriers (*ApoE* 2/2, 2/3, 3/3). By zygosity, 248 MZ twins were *ApoE*-e4 carriers and 532 were non–e4 carriers while 177 DZ twins were carriers and 435 were non–e4 carriers.

Classical Cohort Study Design Results

Several modest but significant associations were observed between TBI and worse performance on the TICS-m (Table 2). After adjustment for age centered at 70 years, age-squared ((age-70)^2), education, wave, and twin pair, TBI was associated with lower TICS-m score and faster decline on the TICS-m across the study in Model 1 (TICS-m-$\beta_{(TBI)}$-0.48 [95% CI −0.66 to −0.30], slope $\beta_{(TBI*age)}$-0.02 [95% CI −0.05 to −0.001]). These results indicate that at 70 years, the twin who experienced a prior TBI scored 0.48 TICS-m points lower relative to his co-twin without TBI and his cognition declined faster (0.02 TICS-m points faster decline per year). Thus, over a 10-year period, the twin with a TBI would have declined 0.20 TICS-m points more than the co-twin without TBI. In Model 2, the effect sizes were similar but the slope did not reach statistical significance (TICS-m-$\beta_{(TBI)}$-0.56 [95% CI −0.73 to −0.39], slope $\beta_{(TBI*age)}$-0.02 [95% CI −0.05 to 0.001]).

Analyses of the number of TBIs showed that one TBI was associated with lower TICS-m scores in both models (model 1 TICS-m-$\beta_{(TBI)}$-0.28 [95% CI −0.48 to −0.08] model 2 TICS-m-$\beta_{(TBI)}$-0.39 [95% CI −0.58 to −0.20]), but the effect of additional TBIs was not associated with TICS-m level in either model (model 1 TICS-m-$\beta_{(TBI)}$0.05 [95% CI −0.32 to 0.43] model 2 TICS-m-$\beta_{(TBI)}$-0.21 [95% CI −0.56 to 0.14]).

Table 3 Linear Mixed-Effect Regression Models Examining the Association Between TBI and Cognitive Status Measured by the Modified Telephone Interview for Cognitive Status in Co-twin Control Sample Discordant for TBI

	Full sample		Monozygotic		Dizygotic	
	Estimated coefficient	95% CI	Estimated coefficient	95% CI	Estimated coefficient	95% CI
	Model 1[a]					
TICS-m level	n = 2,390		n = 1,178		n = 1,212	
TBI (reference = no TBI)	−0.64	−0.91 to −0.37	−0.61	−0.98 to −0.24	−0.67	−1.06 to −0.28
Number of TBIs (reference = no TBI)	n = 2,370		n = 1,170		n = 1,200	
One TBI	−0.34	−0.65 to −0.03	−0.44	−0.85 to −0.02	−0.24	−0.69 to 0.21
More than one TBI	−0.08	−0.61 to 0.44	−0.28	−1.02 to 0.46	0.06	−0.65 to 0.85
Age of First TBI (reference = no TBI)	n = 2,363		n = 1,162		n = 1,201	
TBI at age <25	0.02	−0.33 to 0.38	0.02	−0.47 to 0.50	0.05	−0.47 to 0.56
TBI at age ≥25	−0.66	−1.02 to −0.29	−0.82	−1.32 to −0.32	−0.51	−1.04 to 0.02
TICS-m trajectory (per year)						
TBI	−0.01	−0.05 to 0.03	−0.03	−0.08 to 0.02	0.01	−0.04 to 0.06
Number of TBIs (reference = no TBI)						
One TBI	−0.001	−0.04 to 0.04	−0.001	−0.06 to 0.05	−0.002	−0.06 to 0.05
More than one TBI	−0.04	−0.11 to 0.02	−0.14	−0.24 to −0.04	0.04	−0.05 to 0.13
Age of First TBI (reference = no TBI)						
TBI at age <25	0.03	−0.01 to 0.08	0.02	−0.04 to 0.09	0.04	−0.02 to 0.11
TBI at age ≥25	−0.05	−0.10 to −0.01	−0.07	−0.14 to −0.01	−0.03	−0.10 to 0.03
	Model 2[b]					
TICS-m level	n = 2,390		n = 1,178		n = 1,212	
TBI (reference = no TBI)	−0.59	−0.85 to −0.33	−0.55	−0.91 to −0.19	−0.65	−1.02 to −0.28
Number of TBIs (reference = no TBI)	n = 2,370		n = 1,170		n = 1,200	
One TBI	−0.31	−0.60 to −0.02	−0.37	−0.77 to 0.03	−0.27	−0.69 to 0.16
More than one	−0.23	−0.73 to 0.27	−0.49	−1.20 to 0.22	−0.03	−0.74 to 0.67
Age of First TBI (reference = no TBI)	n = 2,363		n = 1,162		n = 1,201	
TBI at age <25	−0.04	−0.37 to 0.30	−0.02	−0.49 to 0.44	−0.09	−0.58 to 0.39
TBI at age ≥25	−0.59	−0.94 to −0.24	−0.74	−1.22 to −0.26	−0.44	−0.98 to 0.05
TICS-m trajectory (per year)						
TBI	−0.01	−0.05 to 0.03	−0.03	−0.08 to 0.02	0.01	−0.04 to 0.06
Number of TBIs (reference = no TBI)						
One TBI	−0.002	−0.04 to 0.04	−0.003	−0.06 to 0.05	−0.005	−0.06 to 0.05
More than one TBI	−0.04	−0.10 to 0.03	−0.13	−0.23 to −0.03	0.04	−0.04 to 0.14

Continued

Table 3 Linear Mixed-Effect Regression Models Examining the Association Between TBI and Cognitive Status Measured by the Modified Telephone Interview for Cognitive Status in Co-twin Control Sample Discordant for TBI *(continued)*

	Full sample		Monozygotic		Dizygotic	
	Estimated coefficient	95% CI	Estimated coefficient	95% CI	Estimated coefficient	95% CI
Age of First TBI (reference = no TBI)						
TBI at age <25	0.03	−0.01 to 0.07	0.02	−0.05 to 0.08	0.04	−0.02 to 0.10
TBI at age ≥25	−0.05	−0.10 to −0.01	−0.07	−0.13 to −0.002	−0.03	−0.10 to 0.03

Abbreviations: LOC = loss of consciousness; TBI = traumatic brain injury; TICS-m = modified Telephone Interview for Cognitive Status.
[a] Model 1 adjusts for age (centered at 70 years), age^2 (centered at 70 years), education, wave, singleton/twin pair, and TBI by time.
[b] Model 2 adjusts for age (centered at 70 years); age^2 (centered at 70 years), education; wave; singleton/twin pair; alcohol abuse; smoking status; and medical conditions (hypertension, cholesterolemia, myocardial infarction, coronary artery bypass graft, congestive heart failure, stroke/transient ischemic attack, diabetes, depression, Parkinson disease, and seizures at baseline) grouped as: cardiovascular disease risk factors, cardiovascular disease, neurologic conditions, depression, and TBI by time.

However, having more than one TBI led to faster TICS-m decline in both models (model 1 TICS-m-$\beta_{(TBI*age)}$-0.06 [95% CI −0.10 to −0.01] model 2 TICS-m-$\beta_{(TBI\ TBI*age)}$-0.05 [95% CI −0.09 to −0.002]). Model 2 indicates that at 70 years, the twin who experienced more than one TBI declined 0.05 TICS-m points faster per year than his co-twin without TBI. Thus, over a 10-year period, the twin with more than one TBI would have declined half a TICS-m point more than the co-twin without TBI.

We assessed severity of TBI based on the presence vs absence of LOC. Both models showed TBI with LOC to be associated with lower TICS-m scores at 70 years and faster rate of TICS-m decline compared with no TBI (Table 2). Finally, in models assessing the association of cognition with age of TBI, those with TBI after 24 years had lower TICS-m scores at 70 years and faster rates of cognitive decline in both models (Table 2).

We conducted a post hoc sensitivity analysis to look at the effect of TBI excluding singletons from the full sample to assess for any possible bias (n = 7,188), and the results (Model 1 TICS-m-$\beta_{(TBI)}$-0.53 [95% CI −0.72 to −0.34], slope TICS-m-$\beta_{(TBI*age)}$-0.02 [95% CI −0.05 to 0.002]) differed a little from those reported on the full sample in Table 2 (model 1 TICS-m-$\beta_{(TBI)}$-0.48 [95% CI −0.66 to −0.30], slope TICS-m-$\beta_{(TBI*age)}$-0.02 [95% CI −0.05 to 0.001]).

Matched Co-Twin Control Sample

Among twin pairs discordant for TBI (Table 3), both models showed lower TICS-m scores at 70 years associated with (1) TBI (model 1 TICS-m-$\beta_{(TBI)}$-0.64 [95% CI −0.91 to −0.37], model 2 TICS-m-$\beta_{(TBI)}$-0.59 [95% CI −0.85 to −0.33]), (2) having only one reported TBI (model 1 TICS-m-$\beta_{(TBI)}$-0.34 [95% CI −0.65 to −0.03], model 2 TICS-m-$\beta_{(TBI)}$-0.31 [95% CI −0.60 to −0.02]), and (3) TBI at older age (model 1 TICS-m-$\beta_{(TBI\ age\ \geq 25)}$-0.66 [95% CI −1.02 to −0.29], model 2 TICS-m-$\beta_{(TBI\ age\ \geq 25)}$-0.59 [95% CI −0.94 to −0.24]). In addition, having a TBI at an older age vs younger age was associated with faster rate of TICS-m decline (both model 1 and model 2 TICS-m-$\beta_{(TBI\ age\ \geq 25)}$-0.05 [95% CI −0.10 to −0.01]). Thus, for example, in Model 2, in a twin pair, the twin who experienced a TBI after 24 years scored 0.59 TICS-m points lower at 70 years and his cognition declined faster (0.05 TICS-m points faster decline per year) relative to his non-TBI co-twin. Over a 10-year period, the co-twin with a TBI after 24 years would have declined half a point more on the TICS-m than the co-twin without TBI after accounting for covariates.

Stratification of these models by zygosity showed that most associations observed among the full group of TBI-discordant twins were strengthened for the MZ pairs. Notably, within MZ twin pairs discordant for TBI, twins with a TBI which occurred after 24 years scored lower relative to their co-twin at 70 years without TBI and their cognition declined faster (model 1 TICS-m-$\beta_{(TBI\ age\ \geq 25)}$-0.82 [95% CI −1.32 to −0.32], model 2 TICS-m-$\beta_{(TBI\ age\ \geq 25)}$-0.74 [95% CI −1.22 to −0.26]). In addition, among MZ pairs, twins with more than one TBI declined more rapidly than their co-twins without a TBI (model 1 TICS-m-$\beta_{(more\ than\ one\ TBI)}$-0.14 [95% CI −0.24 to −0.04], model 2 TICS-m-$\beta_{(more\ than\ one\ TBI)}$-0.13 [95% CI −0.23 to −0.03]). We further tested this last association in both models with a 3-way interaction (more than one TBI by age by zygosity), and in both models, the interactions were statistically significant (model 1 TICS-m-$\beta_{(more\ than\ one\ TBI*age*zyg\ =\ MZ)}$-0.003 [95% CI −0.08 to 0.07] and TICS-m-$\beta_{(more\ than\ one\ TBI*age*zyg\ =\ DZ)}$0.18 [95% CI 0.05–0.32] and model 2 TICS-m-$\beta_{(more\ than\ one\ TBI*age*zyg\ =\ MZ)}$0.004 [95% CI −0.07 to 0.08] and TICS-m-$\beta_{(more\ than\ one\ TBI*age*zyg\ =\ DZ)}$-0.18 [95% CI −0.31 to −0.05]). Among DZ discordant twin pairs, TBI was only associated with lower TICS-m levels at 70 years (model 1 TICS-m-$\beta_{(TBI)}$-0.67 [95% CI −1.06 to −0.28], model 2 TICS-m-$\beta_{(TBI)}$-0.65 [95% CI −1.02 to −0.28]).

Exploratory Analyses With *ApoE* e4 Allele

Sixteen percent of the study sample had *ApoE* genotype (n = 1,392). TICS-m scores in this sample were lower among *ApoE*-e4 carriers (mean TICS-m 31.6 [SD 5.4]) than non–e4 carriers (mean TICS-m 32.8 [SD 5.3]). The three-way

interaction (age by *ApoE*-e4 by TBI) in model 1 did not reach statistical significance (model 1 TICS-m $\beta_{(TBI*age*ApoE\text{-}e4)}$0.01 [95% CI −0.11 to 0.12]), but all lower level terms (2-way interactions) in the same model were statistically significant (model 1 TICS-m $\beta_{(age*ApoE\text{-}e4)}$-0.07 [95% CI −0.14 to −0.004] and TICS-m $\beta_{(TBI*ApoE\text{-}e4)}$1.52 [95% CI 0.58–2.46]). We then dropped the three-way interaction and kept the two-way interactions to determine whether the TBI effect was modified by age or *ApoE* status. Age by TBI (model 1 TICS-m $\beta_{(TBI*age)}$ −0.06 [95% CI −0.12 to −0.01]) and age by *ApoE*-e4 (model 1 $\beta_{(TBI*ApoE\text{-}e4)}$-0.07 [95% CI −0.12 to −0.004]) remained statistically significant. However, TBI by *ApoE*-e4 was not significant (model 1 TICS-m $\beta_{(TBI*ApoE\text{-}e4\ carriers)}$0.18 [95% CI −0.78 to 1.15] and TICS-m $\beta_{(TBI*ApoE\text{-}e4\ non\text{-}carriers)}$-0.26 [95% CI −1.10 to 0.58]). Overall, these interactions indicate that as male veterans age, those with TBI had lower TICS-m scores and declined faster if they were *ApoE*-e4 carriers relative to *ApoE*-e4 non-carriers.

Discussion

In this nationwide study of twins, we found that veterans who experienced at least one TBI in their lifetime generally had lower cognitive scores and faster rates of cognitive decline in later life, particularly among those with more severe TBI indicated by LOC and those who experienced TBI after 24 years. Although our results show modest effect sizes for TBI on cognition in later life, we note that the effect sizes reflect the contribution TBI has on cognitive function as compared with the co-twin without TBI (for pairs in which both twins were included in the analyses). This is the effect of TBI on cognition after accounting for sociodemographic and medical condition covariates and unidentified factors throughout the life span that are shared by the co-twins that may influence cognition. For instance, for a monozygotic twin pair, the co-twin who had a TBI after 24 years scored approximately 3 quarters of a TICS-m point (0.74 TICS-m points) lower than the twin without TBI at 70 years. In the example above, the twin with TBI is declining 0.07 points faster per year than his co-twin without TBI. Therefore, in 12 years of follow-up of this study, the co-twin with TBI would have steeper cognitive decline (0.84 TICS-m points) than his co-twin without TBI. Thus, the contribution of TBI on late-life cognition, in addition to the numerous other factors with a detrimental effect on cognition, may be sufficient to trigger an evaluation for cognitive impairment. These findings extend the results from prior research. One recent epidemiologic study of community adults older than 50 years measured cognition longitudinally in late life with a 4-year follow-up period and did not observe significant cognitive decline differences between those with and without TBI, regardless of TBI severity.[18] Our observed differences in rates of cognitive decline from the previous study may, in part, be because of adjustment of covariates and medical conditions known to influence cognitive trajectories (i.e., Parkinson disease, seizures, and depression). No other studies have repeatedly measured cognition in association with TBI for a period extending over a decade in later life.[16,17,22,37,38] We examined cognitive function longitudinally for up to 12 years, beginning an average of 34 years after TBI. This longer follow-up period and added control provided by the twin study design may have allowed us to detect differences in rates of decline.

The effect of specific risk factors of dementia varies by age.[19] Our finding that individuals with TBI at older ages had lower cognitive function and more rapid decline than those who had a TBI before 25 years suggests that age of exposure may also matter for cognitive decline in later life. Among the few studies exploring age effects of TBI, one reported a more rapid decline in processing speed but not in episodic memory for those 60 years and older who had a TBI during adulthood, compared with individuals who had a TBI during childhood.[39] This contrasts somewhat with our finding that global cognitive status, which included episodic memory, declined more rapidly after 60 years. One explanation for TBIs after early adulthood having a greater negative effect on late-life cognition is that the remyelination process is likely to be affected by TBI and becomes less efficient and occurs at a slower rate with age.[40]

Twin studies contribute uniquely to investigating associations between exposures and outcomes and add key information in building evidence for an association being due to causation.[41,42] Heterogeneity in cognitive reserve, genetic risk of neurodegenerative conditions, and underlying comorbidities complicate the degree to which we can predict risk of cognitive decline in late life attributable to a single factor such as TBI. However, the twin study design controls for many genes and shared early-life exposures, many of which have not been identified and cannot be reliably measured in other non-twin studies of late-life cognitive decline. Our study also controlled for many health conditions, alcohol overuse, and smoking, factors that negatively affect late-life cognition and could differ within twin pairs.[2,43] Most of our observed associations between TBI and worse cognition remained statistically significant after accounting for these additional factors, indicating the robustness of the results.

In the co-twin control analyses that used only twin pairs discordant for TBI, with each twin within the pair serving as his co-twin's matched control, TBI was most frequently associated with poorer cognitive outcomes in the MZ pairs. Notably, MZ twins with TBI after 25 years had a lower cognitive level and faster rate of decline than their co-twins without TBI. This finding suggests that in genetically identical individuals, TBI both lowers cognitive reserve (i.e., cognitive level) and quickens the pace of cognitive decline. Because MZ pairs share all of their genes and typically also share many early-life exposures, this finding suggests that the association between TBI and cognitive decline is likely not because of genetic confounding or the many early-life environmental exposures shared by co-twins. Thus, these findings strengthen the case for concluding that TBI contributes uniquely to late-life poorer cognitive outcomes beyond those observed in normal aging.

In a subsample with *ApoE* genotype, we found that *ApoE*-e4 carriers with TBI had lower cognitive scores and declined faster than non–e4 carriers, but we did not observe significant modification of the TBI effect by *ApoE* status. Evidence from other studies on the role of *ApoE*-e4 on cognitive outcomes has been mixed,[44,45] likely because of the study design differences, the small sample sizes of studies included, and the timing of cognitive assessments after TBI.

Our study has limitations. We relied on self or proxy report for the history of TBI, which may have resulted in some exposure misclassification, particularly for those with TBIs in early life. Our prior work[9] compared medical record documentation of TBI with self or proxy report decades later and showed that both individuals and their proxies tend to under-report lifetime history of TBI, with the less severe TBIs under-reported at a higher rate. However, this prior work did not indicate that under-reporting was more common among twins who later eventually developed dementia; thus, such under-reporting was unlikely to bias our results.[9] We note also that even studies using medical records to identify TBI may misclassify exposure to TBI because they are typically limited to relatively few years of the individual's total life span. Finally, the cohort consists exclusively of male veterans, primarily of White race born between 1917 and 1927, which means that the results may not be generalizable to female patients, other race and ethnic groups, or non-veteran populations, and our findings may be affected by secular trends in diagnosis and treatment of TBI and cognitive disorders.

Little is known about the interface between cognitive aging and the long-term effects of TBIs. Our twin study shows that TBIs, even decades before cognitive testing, led to lower cognitive levels and faster rates of cognitive decline in late life, regardless of shared genetics and early-life exposures and medical conditions. This association was stronger for those having a TBI at 25 years or later, suggesting that TBI both lowers cognitive reserve (level of cognition) and accelerates cognitive aging. Although many TBIs go unreported, there is a trend toward increased emergency department visits because of sports or recreational activities,[46,47] particularly among male patients aged 10–24 years or those 45 years or older.[47] These numbers combined with the estimated half million members of the military who suffered a TBI between 2000 and 2020[48,49] emphasize the potential long-term effect of TBIs in this population that cannot be overlooked.

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