SELF-REPORTED HEAD INJURY: ASSOCIATED RISK IN MILD COGNITIVE IMPAIRMENTAND PROGRESSION TO ALZHEIMER DISEASE

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by

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SELF-REPORTED HEAD INJURY: ASSOCIATED RISK IN MILD COGNITIVE IMPAIRMENT AND PROGRESSION TO ALZHEIMER DISEASE

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Traumatic brain injury (TBI) has been associated with a higher risk for and earlier onset of neurodegenerative disorders, including Alzheimer disease (AD), but its mechanistic link is not well understood. TBI has been hypothesized to activate a progressive neurodegenerative process, accelerate an already present neurodegenerative disorder, or disrupt neuronal/cognitive reserve and interact with aging. Although previous research has investigated the link between TBI and dementia, little is known if TBI is also associated with development of mild cognitive impairment (MCI), a prodromal phase of AD, and progression from

MCI to AD. This broad investigation consists of two studies devised to examine whether a history of TBI is a risk factor for MCI and progression from MCI to AD using a large, multicenter national database.

The aim of Study 1 was to determine if a history of TBI with LOC was associated with an increased risk for and earlier onset of MCI. Results revealed that a history of TBI was associated with a 1.35 fold higher risk for a diagnosis of MCI, even after adjusting for well-known factors linked to cognitive decline. A history of TBI was also linked to a nearly 2 year earlier age of MCI diagnosis. Thus, a TBI history does appear to be associated with an earlier diagnosis of MCI and may be a risk factor for MCI.

Study 2 was devised to investigate whether a history of TBI with LOC was associated with progression from MCI to AD. Results revealed that individuals with a history of TBI with LOC did *not* show faster progression from MCI to AD, higher annual rates of progression, or more rapid cognitive decline than those without a TBI history, suggesting that a history of TBI was not linked to progression from MCI to AD. This two-part investigation indicates that a history of TBI appears to be a risk factor for earlier development of MCI; however, once the neurodegenerative process for MCI to AD starts, a history of TBI appears unrelated to subsequent decline.

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LIST OF ABBREVIATIONS

Aβ	Amyloid-Beta Plaques
AD	Alzheimer's Disease
ADC	Alzheimer's Disease Center
ADRDA	Alzheimer's Disease and Related Disorders Association
Apoe4	Apolipoprotein E-e4
CAIDE	Cardiovascular Risk Factors, Aging, and Incidence of Dementia Risk Score
CDR	Clinical Dementia Rating Scale
CDR-SB	Clinical Dementia Rating Scale – Sum of Boxes Score
CI	Confidence Interval
CTE	Chronic Traumatic Encephalopathy
HR	Hazard Ratio
LR	Log Rank
MCI	Mild Cognitive Impairment
mLOC	Minutes Loss of Consciousness
NACC	The National Alzheimer's Coordinating Center
NFT	Neurofibrillary Tangles
NIA	National Institute of Aging
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
OR	Odds Ratio

ROC	Receiver Operating Characteristic
SD	Standard Deviation
TBI	Traumatic Brain Injury
TBI+	Subjects reporting a history of traumatic brain injury
TBI−	Subjects reporting no history of traumatic brain injury
UDS	Uniform Data Set

SECTION I

Introduction

Traumatic brain injury (TBI) is common (Faul, Xu, Wald, & Coronado, 2010), and has been associated with a higher risk for and earlier onset of neurodegenerative disorders, including Alzheimer disease (AD). While much of the evidence stems from more severe TBI (Barnes et al., 2014; Wang et al., 2012), evidence of a potential association between mild TBI and later life cognitive decline remains less clear (Plassman et al., 2000; Gardner et al., 2014). For instance, meta-analytic studies have found a history of TBI with loss of consciousness (LOC) to be associated with a higher likelihood for later developing AD (Fleminger, Oliver, Lovestone, Rabe-Hesketh, & Giora, 2003; Mortimer, French, Hutton, & Schuman, 1985), but not a history of any head trauma (Xu et al., 2015). Complicating this picture, a majority of studies have focused either on small samples carefully diagnosed with AD or large samples where diagnostic accuracy may be a concern (e.g., diagnosed outside specialized dementia clinics), likely restricting generalization of the findings.

The mechanistic link between TBI and later cognitive decline is unknown, but it has been hypothesized that TBI activates a progressive neurodegenerative process, accelerates an already present neurodegenerative disorder, or disrupts neuronal/cognitive reserve and interacts with aging (Gardner et al., 2014). Although previous research has investigated the link between TBI and dementia,

it is unclear whether TBI is also associated with mild cognitive impairment (MCI). MCI is often a prodromal phase of AD, where characteristic neuropathological changes are present but only subtle neurobehavioral deficits manifest. Thus, MCI is the earliest threshold for clinical manifestation of cognitive decline prior to AD onset, but little is known about whether TBI is associated with development of MCI, and no studies have examined whether TBI may be associated with progression from MCI to AD. Exploring these associations may shed light on what role TBI may play in later cognitive decline.

This broad investigation consists of two studies examining whether TBI is associated with a) earlier development of MCI, and b) progression from MCI to AD. Because the samples are derived from a large, multicenter national database where cognitive status is well-characterized with extensive standard diagnostic evaluations, this investigation overcomes a major limitation of many previous studies assessing the link between TBI and later cognitive decline. Also, this investigation accounts for many potential confounding variables linked to cognitive decline in the literature, such as Apoe4 and vascular factors, which few studies have explored. Therefore, the findings from this investigation could support an emerging literature that a history of TBI is a risk factor for later cognitive decline and yield insight in to what role TBI may play in the process.

SECTION II
Study I

Self-Reported Head Injury and Mild Cognitive Impairment: Increased Risk and Earlier Age of Diagnosis

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Abstract

This study examined whether a history of traumatic brain injury (TBI) is associated with increased risk and earlier onset of mild cognitive impairment (MCI). Subjects with MCI (n =1,981) and normal cognition (n=3,270) were obtained from the National Alzheimer's Coordinating Center database. TBI was categorized based on lifetime reported TBI with loss of consciousness (LOC) without chronic deficit. Logistic regression was used to examine TBI history as a predictor of MCI, adjusted for age, education, apolipoprotein E-e4, and a composite vascular risk score. ANCOVA was used to examine whether age at MCI diagnosis and estimated age of onset differed between those with (TBI+) and without (TBI−) a history of TBI. TBI history was a

significant predictor (p<.01) and associated with increased odds of MCI diagnosis in unadjusted (odds ratio=1.27) and adjusted models (odds ratio=1.34). MCI was diagnosed a mean of 2.3 years earlier (p<.001) in the TBI+ group, and a trend was observed (p=.05) for clinician-estimated age of onset, with TBI+ subjects having a mean onset 1.7 years earlier. This is the first report of a possible role for TBI as a risk factor in MCI, similar to research linking TBI with increased risk of dementia.

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INTRODUCTION

Each year, approximately 1.7 million persons sustain a traumatic brain injury (TBI) (Faul et al., 2010). While many survive the initial insult, cognitive, psychiatric, and physiological dysfunction often follows and may be transient or persistent, depending in part on severity of injury (US National Institutes of Health [NIH], 1998). Whether full recovery is achieved or not, sustaining a TBI has been implicated as a risk factor for later development of neurodegenerative disorders, including Alzheimer's Disease (AD) (Barnes et al., 2014; Smith, Johnson, & Stewart, 2013) with evidence demonstrating that risk increases with greater length of loss of consciousness (Fleminger et al., 2003; Guo et al., 2000) and severity (Plassman et al., 2000). In addition, repetitive mild TBIs have been controversially linked to chronic traumatic encephalopathy (CTE) (Randolph, 2014; Stein, Alvarez, & McKee, 2014), and while this link remains in question, recent evidence has shown that mild TBI may invoke a higher risk for dementia (Gardner et al., 2014).

The possible mechanism(s) associated with TBI in early or midlife and later development of AD remains unclear, but it is hypothesized that TBI activates a progressive neurodegenerative process (Johnson, Stewart, & Smith, 2010) which may interact with age and other factors over time. Nearly all severities of closed head injuries consist of damage to white matter tracts, i.e., diffuse axonal injury, which acutely disrupt biochemical and cytoskeletal functions that may

contribute to long-term damage to neurons and/or neuronal transmission (Johnson, Stewart, & Smith, 2013). As a consequence of diffuse axonal injury, amyloid precursor proteins are suspected of accumulating in the axon and forming amyloid-beta (Aβ) plaques (Johnson et al., 2013), while tau proteins aggregate into neurofibrillary tangles (NFT) (Abisambra & Scheff, 2014a), both believed to be involved in the pathogenesis of AD (Sivanandam & Thakur, 2012). Previous studies have found that within hours of acquiring a single, severe TBI, Aβ plaques are present in up to a third of severely injured patients, even children (Ikonomovic et al., 2004). It has also been noted that at autopsy, several years after the initial injury a significant proportion of TBI patients had Aβ plaques present that were fibrillary or a mixed diffuse/fibrillary pattern, unlike the predominantly diffuse plaques present in normal controls (Johnson, Stewart, & Smith, 2012). With respect to tau pathology, NFT appearance is seemingly delayed, as prior studies report that NFTs were not present within 4 weeks following a single, severe TBI (Smith, Graham, Murray, & Nicoll, 2003) but were present when patients were examined after at least 1 year post-injury (Johnson et al., 2012). Additionally, persons who had sustained even a single TBI in that sample showed more extensive NFTs and at a much earlier age relative to age-matched controls (Johnson et al., 2012). Such findings support the notion of TBI as a potential risk factor in the neurodegenerative process; however, a direct link to AD continues to be lacking as the long-term development of AD-like Aβ plaques remains to be

studied in humans and the interactive effects with normal aging are poorly understood.

Mild cognitive impairment (MCI) is often a prodromal stage of AD (Petersen, 2004). While previous research has explored the relationship between a history of TBI and AD (Abner et al., 2013; Fleminger et al., 2003; Gilbert et al., 2014), little is known about the potential impact of TBI on the development of MCI. For example, Guskiewicz et al. (2005) reported a relationship between MCI symptoms and a history of three or more concussions in a small sample (n = 22) of retired athletes. In addition, a recent finding showed that in a sample of individuals diagnosed with MCI (n = 141), those with a history of TBI and loss of consciousness (n = 22) showed greater amyloid deposition than those without, suggesting that TBI may be associated with AD-related neuropathology (Mielke et al., 2014). The odds ratio associated with a history of TBI in relation to AD was found to be 1.58 in a meta-analysis of 15 studies, suggesting an increased risk (Fleminger et al., 2002). Furthermore, an earlier age of onset has been observed in some studies of patients with dementia (Schofield et al., 1997), but these results have varied widely, ranging from 6 months to 8 years (Abner et al., 2013; Barnes et al., 2014; Nemetz et al., 1999). It is not known whether history of TBI conveys an increased risk for cognitive decline or an earlier age of onset in relation to MCI.

The current study sought to examine whether a history of TBI was a significant predictor of MCI diagnosis and was associated with increased risk for MCI. In addition, we assessed whether a reported history of TBI was linked with an earlier age of MCI diagnosis and clinician-estimated age of onset. Determining whether TBI is a risk factor for MCI and is associated with an earlier age of onset would support an emerging literature that remote TBI may be associated with later cognitive decline in some individuals.

METHOD

The National Alzheimer's Coordinating Center (NACC) has maintained a centralized database of demographic and clinical information pooled from National Institute of Aging (NIA) - funded Alzheimer's Disease Centers (ADC) across the U.S since September, 2005. For this study, the NACC Uniform Data Set (UDS) (Morris et al., 2006) was queried for subjects aged 50 years or older with initial and follow-up visits completed between September, 2005 and December, 2013. Subjects diagnosed with amnestic or non-amnestic MCI (n = 3308) were selected for examination. Subjects with normal cognition with three or more visits completed (n = 3270) were selected as a comparison group. Cognitive status and clinical diagnosis was determined by ADC clinicians using NINCDS/ADRDA guidelines. A clinical diagnosis of amnestic or non-amnestic MCI was made if there was impairment in memory or another cognitive domain (i.e., language, attention, executive function, visuospatial) and criteria for

dementia were not met. Normal cognition was defined as the absence of neuropsychological impairment and failure to meet published clinical criteria of MCI, dementia, or other neurological conditions. For the present study, age at initial ADC visit, education, sex, race, number of apolipoprotein E-e4 (APOE ε4) alleles, and clinician-estimated age of onset at the initial visit were examined.

The NACC database contains three questions related to TBI based on subject/informant interview. Subjects were asked if they ever sustained a TBI resulting in a) <5 minutes loss of consciousness (mLOC), b) ≥5 mLOC, and c) if they were left with a chronic deficit/dysfunction as a result of the injury. Each question was answered as absent, recent/active (defined as occurring within 1 year of visit or currently requiring treatment), remote/inactive (defined as occurring >1 year before visit and either having recovered from the injury or not requiring current treatment), or unknown. As the present study sought to examine the effect of a remote history of TBI on MCI diagnosis, only those individuals who reported either an absence of TBI history or a remote (defined as >1 year of visit) TBI with LOC and no chronic deficits were included.

In order to examine the potential influence of vascular risk factors, a history of the following conditions was obtained via self/informant report and coded as absent or present: heart attack, atrial fibrillation, angioplasty, cardiac bypass, pacemaker, congestive heart failure, stroke, transient ischemic attack, hypertension, hypercholesterolemia, and diabetes. Possessing multiple

cardiovascular or cerebrovascular conditions has been associated with increased risk for AD (Luchsinger et al., 2005), and as such, a composite vascular risk score was created from the above conditions to control for the potential influence in MCI. The number of above conditions was totaled to create a composite vascular risk score ranging from 0 to 11, with 11 indicating the highest risk.

STATISTICAL ANALYSIS

All analyses were conducted using IBM© SPSS Statistics V22 (IBM Corp, SPSS Statistics V22, Armonk, NY, 2013) with $p < .05$ as the cutoff for significance. Two logistic regression models were used to examine the utility of history of TBI as a predictor of a diagnosis of MCI (versus normal cognition). In the first model (unadjusted), TBI was the only predictor. A second, adjusted model included history of TBI and four other predictors linked to cognitive decline in the literature: age, years of education, number of Apoe4 alleles, and a composite vascular risk score. Hosmer-Lemeshow was used to examine the fit of the model to the data; the criterion of an acceptable fit was defined as $p > .20$ and a good fit as $p > .40$ instead of the standard cutoff of non-significance $p > .05$ (Tabachnick, Fidell, & Ostirland, 2001). Receiver operating characteristic (ROC) analyses were performed to compare the area under the curve for both models using the predicted scores from the logistic regression models. Using the ROC results, the best cut-score for group predictions was determined using a combination of criteria: sensitivity, specificity, accuracy, and maximum

perpendicular distance above the 45° line of equality (Hanley & McNeil, 1983). Two ANCOVAs, controlling for sex, were performed to examine if age at diagnosis of MCI and estimated age of cognitive decline onset were different between those with a self-reported history of TBI (TBI+) and those without (TBI−). Demographic characteristics, number of Apoe4 alleles, and vascular risk factors were compared between the TBI+ and TBI− groups using chi-square and independent samples t-tests.

Assumptions for all tests were reviewed, and unequal variances were observed between the TBI+ and TBI− groups when comparing age of MCI diagnosis. A Welch ANOVA was used with a Bonferroni correction of $p < .025$ in order to determine if unequal variances resulted in a Type I error.

RESULTS

The MCI cohort included 3,308 subjects that were 51% female, well educated ($M_{Educ} = 14.99$, SD = 3.32), had a mean age of 74.38 years (SD = 8.93), were 83% Caucasian, and possessed approximately two vascular-related conditions on average (Median = 1.00, SD = 1.71, range = 0-10). History of TBI with LOC was reported in 10% of those with MCI. Fifty-six percent of MCI subjects had no Apoe4 allele, 36% had only one Apoe4 allele, and 8% had two Apoe4 alleles. There were 3,270 normal cognition subjects who, like the MCI cohort, were 86% Caucasian, well educated ($M_{Educ} = 15.67$, SD = 2.78), and possessed approximately two vascular-related conditions on average (Median =

1.00, SD = 1.30, range = 0-8). The normal cognition subjects had a higher proportion of women (68%) and were slightly younger (mean age = 72.32 years, SD = 8.88) at the initial visit. History of TBI with LOC was reported in 8% of normal cognition subjects, 72% had no Apoe4 allele, 25% had only one Apoe4 allele, and 2% had two Apoe4 alleles. Demographic characteristics for the study samples can be found in Table 1.

Logistic regression for the unadjusted model showed that a history of TBI alone was a significant predictor for MCI diagnosis (Wald = 7.50, $p < .01$); a person with a history of TBI with LOC was 1.27 times (95% CI = 1.07-1.51) more likely to have a diagnosis of MCI than normal cognition. However, ROC analysis revealed that TBI history alone did not discriminate between the two groups, as the area under the ROC curve was .51 and non-significant ($p = .18$). In the second logistic regression model, age, education, number of Apoe4 alleles, composite vascular score, and history of TBI were all significant predictors of diagnosis ($p < .01$). In the adjusted model holding constant the effects of the other variables, a person with a history of TBI with LOC was 1.34 times (95% CI = 1.11-1.60; Wald = 9.84) more likely to be diagnosed with MCI than normal cognition. In terms of the other factors, older age, presence of Apoe4 alleles, and higher vascular risk scores were associated with greater risk for MCI, while higher education was protective. Odds ratios and 95% confidence intervals for

each logistic regression model can be found in Table 2. The Hosmer-Lemeshow statistic indicated that the adjusted model was an acceptable fit to the data (χ^2 p = .27). In addition, the area under the ROC curve was .67 and significantly (p < .001) discriminated MCI from normal cognition subjects. Using a cut score of .479, the model had a sensitivity of 64.6%, specificity of 60.3%, and an accuracy of 62.4%.

TBI+ and TBI− groups did not differ by race (p = .29), education (p = .86), average composite vascular risk score (p = .70), or number of Apoe4 alleles (p = .22) [see Table 3]. Because the TBI− group had a larger proportion of females (52%) than the TBI+ group (40%) (p < .001), sex was used as a covariate. Controlling for sex, the TBI+ group (M_{Age} = 72.32, SD = 9.84) was diagnosed with MCI on average 2.3 years earlier than the TBI− group (M_{Age} = 74.59, SD = 8.80; $F_{(1, 3305)}$ = 18.78, p <.001). Based on Levene's test ($F_{(1, 3305)}$ = 10.09, p < .001), the two groups had significantly unequal variances and a Welch's ANOVA was conducted to control for this discrepancy. Results from Welch's ANOVA showed that despite the unequal variances among the two groups, the TBI+ group was diagnosed with MCI significantly earlier than the TBI− group ($F_{(1, 374.343)}$ = 15.70, p < .001). Clinician-estimated age of cognitive decline was on average 1.7 years earlier for the TBI + group (M_{Age} = 68.11, SD = 12.20) compared to the TBI− group (M_{Age} = 69.82, SD = 13.57), although this was only a trend ($F_{(1, 3305)}$

= 3.85, p = .05). History of TBI demonstrated a small effect size for age of diagnosis (Cohen's d = .24) and a weak effect for estimated age of cognitive decline onset (Cohen's d = .14).

DISCUSSION

Self-reported TBI history alone was associated with increased odds of a diagnosis of MCI (1.27 odds ratio), but did not distinguish MCI subjects from those with normal cognition. However, when other risk factors were included, the adjusted relative risk for MCI remained increased (1.35 odds ratio) for persons with a history of TBI with LOC, and as a set, background risk factors discriminated cognitive status fairly accurately. Overall risk for MCI was greatest when individuals were older, less educated, Apoe4 carriers, had a history of TBI with LOC, and had several lifetime vascular conditions. The level of risk for MCI that was associated with a history of TBI was comparable to findings with respect to AD (Fleminger et al., 2003), indicating a similar risk for cognitive decline. Of those subjects diagnosed with MCI, a self-reported history of TBI with LOC was associated with a 2.3 year earlier age of diagnosis independent of demographic, Apoe4 status, and history of vascular factors. In addition, clinician-estimated age of cognitive decline was 1.7 years earlier for the TBI+ group, and while this was only a trend, the overall findings appear to provide support that a history of TBI with LOC can be associated with an earlier onset of MCI and may be a risk factor for MCI

Emerging literature has implicated “cognitive reserve” as an important component in the risk for cognitive decline with aging. Higher levels of education appear to delay cognitive decline by several years (Vemuri et al., 2014), and have also been shown to decrease the odds of dementia by approximately one-half (i.e., from 2.7 to 1.2) in Apoe4 carriers (Wang et al., 2012). The current findings suggest that a higher level of education may be similarly protective for cognitive decline associated with MCI. However, with respect to TBI as a risk factor, the TBI+ sample in the present study was relatively well educated (15 years) and diagnosed with MCI an average of 2.3 years earlier, indicating that, at the very least, “cognitive reserve” did not completely offset the associated risk with TBI. Based on previous findings, it is possible that the level of education in our sample may have delayed MCI onset and that an earlier onset of MCI may be observed in those with a history of TBI and relatively less education. To address this hypothesis, we categorized TBI+ and TBI− groups based on <12 years and >12 years of education. Two ANCOVAs with sex controlled were conducted as part of a preliminary analysis to determine whether an interaction between education and TBI had an effect on age of MCI diagnosis or estimated age of cognitive decline. Preliminary results revealed a non-significant interaction and weak effects for both age of diagnosis (p = .19; Cohen’s f = .01) and estimated age of cognitive decline (p = .12; Cohen’s f = .01). Further, less education was not associated with an earlier age of diagnosis (M difference$_{<12\ yearsEduc}$ = 1.6) or

estimated age of cognitive decline (M difference$_{<12\ yearsEduc}$ = 1.9) beyond 2 years. Therefore, it would seem that regardless of level of education, those with a history of TBI with LOC tended to have an approximately 2 year earlier onset of MCI.

Given that MCI is considered a prodromal phase of AD and dementia in general, and the TBI-related risk (e.g., odds ratios) for both MCI and AD are comparable, one would anticipate that TBI with LOC has a similar association with age of onset in both MCI and dementia. Along these lines, a recent investigation included a reasonably large dementia sample with a history of TBI (n = 196) and found that those with TBI developed dementia 2.1 years earlier than those without (Barnes et al., 2014), consistent with our findings in MCI. However, previous studies have been mixed, with some reporting no association between TBI and earlier dementia onset (Plassman et al., 2000; Rasmusson, Brandt, Martin, & Folstein, 1995), and others finding that those with a history of TBI developed dementia approximately 6 months (Abner et al., 2013; Sullivan, Petitti, & Barbaccia, 1987) or 8 years (Nemetz et al., 1999) earlier than those without. Methodological differences in the literature likely account for a great deal of the mixed findings, including limited cases, different criteria for TBI classification, reliance on medical records, variation in confounding factors, and dissimilar follow-up intervals. Although further investigation is needed, it would

appear that emerging literature supports an association between a history of TBI with LOC and a 2 year earlier expression of cognitive decline.

Several variables related to head injury appear to be important in the associated risk for MCI and dementia. In one small investigation, more severe TBI (i.e., extended LOC or posttraumatic amnesia >24 hours) was associated with a 4.5 time higher risk for AD, while moderate TBI (LOC or posttraumatic amnesia 30 minutes to 24 hours) was associated with a 2.3 fold increase in risk in one preliminary investigation (Plassman et al., 2000). In contrast, mild TBI (defined as LOC or posttraumatic amnesia < 30 minutes) was not related to an increased risk for AD in that study of 17 subjects with AD. However, a recent report utilizing a large (N = 51,799) TBI sample reported that a mild or moderate-to-severe TBI was associated with a higher risk for dementia, even after adjusting for several demographic and medical factors (Gardner et al., 2014). In addition, TBI occurring later in life (i.e., within 10 years of AD onset), has been found to be related to higher risk estimates and more rapid decline after dementia onset (Gilbert et al., 2014). Yet another related issue is that of repetitive TBI in relation to risk for cognitive decline later in life. Some studies have shown that MCI was more prevalent (24%) compared to the general population in retired football players who sustained an average of three or more mild TBIs during their career (Guskiewicz et al., 2005; Hart et al., 2013). Therefore, TBI severity, age at the time of injury, and repetitive injuries may be important components in the

associated risk of MCI.

It should be noted that the NACC data are not population - based and the present study was limited to subjects with complete data. Since many subjects in the NACC database were missing information for ApoE, generalizability may be limited. In addition, due to the limited data available regarding TBI details in the NACC database (i.e., based upon three questions), we were not able to examine potentially important variables such as TBI severity, age at the time of injury, or repetitive injuries. Even though this study attempted to examine the effect of remote TBI on MCI, it is possible that based on the definition for remote TBI, injuries could have occurred as recently as nearly one year prior to the initial visit. Since falls are one of the leading causes of TBI, particularly in an aging population (Faul et al., 2010), a number of TBIs in this sample could have been relatively more "recent" as opposed to occurring many years earlier, although we selected those with a history of TBI occurring >1 year earlier. Furthermore, while the majority of those with MCI and a history of TBI self-reported milder injuries (i.e., 66%; LOC < 5 minutes), TBI severity could not be assessed, as the cutoff of "LOC ≥ 5 minutes" (34%) has no upper boundary and may include a wide range of severity. Therefore, it is unknown how risk and age of onset may be affected by different levels of injury severity.

In summary, a self-reported history of TBI with LOC was associated with increased risk of MCI and approximately a 2.3 year earlier age of diagnosis.

These findings support emerging literature of TBI as a risk factor for cognitive decline later in life. This association deserves further investigation as much is still unknown. Future research should incorporate tools that more thoroughly assess TBI features (e.g. severity, age of injury, presence and duration of LOC, etc.) in order to identify which factors may be most associated with increased risk for or earlier onset of MCI.

Table 1

Demographics and Medical History of MCI and Normal Cognition Groups

	MCI (n=3308)	*Normal Cognition (n=3270)*
	M (SD)	*M (SD)*
Age	74.38 (8.93)	72.32 (8.88)
Education	14.99 (3.32)	15.67 (2.78)
Composite Vascular Risk Score	1.71 (1.43)	1.30 (1.25)
% Female	51	68
% Caucasian	83	86
% Apoe4 alleles		
0 ε4 alleles	56	72
1 ε4 allele	36	25
2 ε4 alleles	8	2
% History of TBI	10	8

Note. MCI = mild cognitive impairment; TBI = traumatic brain injury with loss of consciousness; Apoe4 = apolipoprotein E-e4.

Table 2

Odds Ratios and Confidence Intervals for Logistic Regression Models

	Odds Ratio	*95% CI*	*p-value*
Unadjusted Model			
TBI history*	1.27	1.07 – 1.51	.006*
Adjusted Model			
Age*	1.03	1.02 – 1.03	<.001*
Education*	0.94	0.92 - 0.95	<.001*
Composite vascular risk score*	1.21	1.17 – 1.26	<.001*
Apoe4 alleles			
1 ε4 allele*	1.97	1.76 – 2.20	<.001*
2 ε4 alleles*	5.51	4.18 – 7.25	<.001*
TBI history*	1.34	1.11 – 1.60	.002*

Note. * $p < .05$. *CI* = confidence interval; TBI = traumatic brain injury with loss of consciousness; Apoe4 = apolipoprotein E-e4.

Table 3

Demographics, Age of Diagnosis, and Age of Cognitive Decline in MCI Subjects With and Without TBI

	TBI+ (n=319)	*TBI− (n=2989)*	*p*
	M (SD)	*M (SD)*	
MCI Age of Diagnosis	72.32 (9.84)	74.60 (8.80)	<.001*
Age of Cognitive Decline	68.11 (12.20)	69.82 (13.57)	.05
Education	15.03 (3.58)	14.99 (3.29)	.86
Composite Vascular Risk Score	1.74 (1.43)	1.71 (1.43)	.70
% Female	40	52	<.001*
% Caucasian	86	82	.29
% Apoe4 alleles			.22
0 ε4 alleles	61	56	
1 ε4 allele	34	36	
2 ε4 alleles	6	8	

Note. * $p < .05$. TBI+ = subjects with history of traumatic brain injury (TBI) with loss of consciousness; TBI− = subjects without TBI; Apoe4 = apolipoprotein E-e4.

SECTION III
Study II

Traumatic Brain Injury History and Progression from Mild Cognitive Impairment to Alzheimer Disease

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Abstract

This study examined whether a history of traumatic brain injury (TBI) is associated with progression from mild cognitive impairment (MCI) to Alzheimer disease (AD). Data on subjects with MCI (n =2,719) were obtained from the National Alzheimer's Coordinating Center. TBI was categorized based on presence/absence of reported TBI with loss of consciousness (LOC) without chronic deficit occurring >1 year prior to diagnosis of MCI (TBI+/−). Survival analyses were used to determine if a history of TBI predicted progression from MCI to AD over the course of 9 years, adjusted for demographics, apolipoprotein E-e4 (Apoe4), a vascular risk score, and history of psychiatric factors. Random regression models were used to examine whether TBI history also predicted rate of decline on the Clinical Dementia Rating scale Sum of Boxes score (CDR-SB) among subjects who progress to AD. Across 9 years, TBI history was a

significant predictor but associated with *slower* progression from MCI to a diagnosis of AD in an unadjusted model (HR=0.77; 95% CI=0.61−0.97; p=.02). This association, however, diminished (p=.15) after adjustment for an earlier age of MCI diagnosis (2.6 years earlier for TBI+ subjects, p<.001). A history of TBI was a non-significant predictor for rate of decline on CDR-SB among subjects who progressed to AD (β=0.15, T=0.88, p=.38). A history of TBI with LOC was associated with an earlier age of diagnosis of MCI, but not progression to AD. These findings suggest TBI might reduce the threshold for onset of MCI and related conditions, but appears unrelated to subsequent decline.

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INTRODUCTION

Several lines of evidence suggest a history of traumatic brain injury (TBI) may be a risk factor for the later development of neurodegenerative disorders including Alzheimer Disease (AD)(Barnes et al., 2014; Fleminger et al., 2003; Guo et al., 2000; Mortimer et al., 1985; Plassman et al., 2000; Sivanandam & Thakur, 2012; van Duijn et al., 1992; Wang et al., 2012). The study by Plassman et al. (2000) provided some of the earliest and most convincing support for an association between remote TBI and the later development of AD. In that investigation, World War II veterans were examined if they had a documented TBI of any severity (n = 565) or a non-TBI medical condition (n = 1,242) during their military service approximately 40 years prior. Subjects were classified as having later developed AD, all-cause dementia, or experiencing normal aging according to standard clinical evaluations. Results showed that a remote history of moderate and severe TBI was associated with a 2- and 4- fold higher risk, respectively, for developing AD later in life, but not mild TBI (Plassman et al., 2000). In a meta-analysis of 15 case-control studies examining history of TBI with any loss of consciousness (LOC) as a risk factor for the later development of AD (n_{cases} = 1,986; $n_{controls}$ = 2,653), Fleminger et al. found that TBI with LOC was associated with an overall 1.6 higher risk (Fleminger et al., 2003).

More recent investigations have continued to provide support for an association between TBI and later cognitive disorders. However, a majority of the

evidence linking TBI to the development of AD stems from moderate-to-severe TBI, with evidence of the potential association between mild TBI and later life cognitive decline remaining less clear. For example, a retrospective analysis of medical records compared older veterans with a diagnosis of AD and all-cause dementia with a relatively recent (i.e., < 10 years) history of TBI of any severity (n = 1,229) to those with no TBI history (n =188,535) (Barnes et al., 2014). In that study, history of TBI was associated with an approximately 2- and 1.6- fold higher risk for developing AD or all-cause dementia, respectively, during a 9 year follow-up, although approximately 75% of TBIs appeared to be moderate-to-severe in nature. Similarly, another large-scale medical record review compared Taiwan citizens with a moderate-to-severe TBI (n = 44,925) to non-TBI cases (n = 224,625) matched at various age ranges (from 15 to ≥75 years). While a diagnosis of dementia was not restricted to older individuals, 91% of dementia cases were 50 years and older; those with a history of TBI had a 1.5- and 1.7- fold higher risk for developing AD and all-cause dementia, respectively, within 5 years of injury (Wang et al., 2012). However, it would appear that a reliance on medical record diagnostic codes outside of dementia clinics in both studies resulted in a limited proportion of AD cases (6% and 5% respectively) being identified from those with all-cause dementia, likely restricting generalizability of findings.

While there have been several reports of a link between TBI and later life cognitive disorders, not all have found an association. For example, a population-based investigation (n = 6,645) examined the risk of self-reported remote TBI on incidence of dementia and AD in older individuals from the Netherlands (Mehta et al., 1999). Subjects were classified as having later developed AD, all-cause dementia, or experiencing normal aging according to standard clinical evaluations nearly 2 years after an initial evaluation. In that investigation, a history of TBI with LOC, duration of LOC, time since injury, and multiple TBIs were not associated with an increased likelihood for developing AD or all-cause dementia. Further, another population-based study examined older individuals from Seattle, Washington, if they self-reported a history of TBI with LOC (n = 606) or no TBI history (n = 3,553) (Dams-O'Connor et al., 2013). Subjects were examined every 2 years, for an average of 7 years, for development of all-cause dementia or AD using standard clinical evaluations. Results showed a history of TBI with LOC was not linked to an increased risk for developing all-cause dementia or AD, regardless of the age at injury (i.e., injury ages <25, 25-54, 55-baseline). While the above studies and others (Lindsay et al., 2002) included well-characterized AD subjects, methodological factors such as different criteria for TBI classification and follow-up duration, may account for the mixed findings in the literature. Regardless, a history of moderate-to-severe TBI is considered an established risk factor for later cognitive decline and is now recognized as a risk

factor for AD by the Alzheimer's Association, behind age, family history, apolipoprotein E-e4 (Apoe4), and vascular factors (Alzheimer's Association, 2015).

Despite mounting evidence of an association between TBI and the later development of AD, the potential mechanism(s) underlying this risk remains poorly understood. This issue is particularly important since neurodegenerative dementias such as AD have an insidious onset, with growing evidence that this process develops over several decades. Classic AD pathology involves the accumulation of tau-related neurofibrillary tangles (NFT) and amyloid-β (Aβ) plaques, although these pathologies appear to represent distinct yet synergistic processes (Nelson, Braak, & Markesbery, 2009). NFTs first appear in the mesial temporal lobe and then progress to involve the inferior frontal region before coursing superiorly and posteriorly to include the entire frontal, parietal, and occipital regions as well (Braak & Braak, 1991; Nelson et al., 2009; Thal, Attems, & Ewers, 2014). Aβ plaques, on the other hand, initially occur in the neocortex, but then progress to the mesial temporal lobe, followed by the basal ganglia, brainstem, and cerebellum (Dietmar R Thal, Rüb, Orantes, & Braak, 2002; Dietmar Rudolf Thal et al., 2014). When the pathological burden surpasses a threshold, cognitive/behavioral impairments become clinically manifest (Nelson et al., 2009). It is well-known that TBI commonly affects frontal and temporal lobe structures/networks (Gentry, Godersky, & Thompson, 1988; Zappalà,

Thiebaut de Schotten, & Eslinger, 2012) via axonal and neuronal injury (Allen, Wu, & Bigler, 2011; Messé et al., 2011) and results in a cascade of abnormal neurochemical processes (Giza & Hovda, 2014). TBI may play a role in a neurodegenerative process by disrupting long-term neuronal functioning and connections, as some evidence indicates tau and Aβ accumulate as a result of TBI (Abisambra & Scheff, 2014; Ikonomovic et al., 2004; Johnson, Stewart, & Smith, 2010, 2012, 2013; Sivanandam & Thakur, 2012), and may serve as another central nervous system (CNS) risk factor such as Apoe4 (Liu, Kanekiyo, Xu, & Bu, 2013; Yu, Tan, & Hardy, 2014) and vascular conditions (Craft, 2009) or interact with such factors in genetically susceptible individuals (Mayeux et al., 1995).

Since TBI may contribute to the accumulation of tau and Aβ pathology found in AD, it is possible that TBI could hasten the threshold for clinical manifestation of later cognitive disorders in some individuals. The earliest threshold prior to AD onset where AD-related pathological changes occur and subtle neurobehavioral deficits manifest is known as mild cognitive impairment (MCI) (Forsberg et al., 2008; Pennanen et al., 2004; Wolf et al., 2004). MCI is often a transitional stage between normal aging and AD, and represents a period when neuropsychological impairment develops but everyday functioning is relatively preserved (Petersen, 2001). Approximately 10-15% of individuals with MCI go on to develop AD each year (Farias, Mungas, Reed, Harvey, & DeCarli,

2009), compared to 1-2% in the general population (Petersen et al., 1999). Thus, individuals who receive an MCI diagnosis are at high risk for progression and development of more significant cognitive decline as well as functional impairments. However, rates of progression vary widely in MCI, with some individuals advancing to AD within a year of MCI diagnosis, while others may not progress for many years (Petersen et al., 1999). Furthermore, some individuals diagnosed with MCI do not progress to AD or any dementia (Koepsell & Monsell, 2012; Tyas et al., 2007), and a subgroup of MCI patients shows a variable course, with up to 38% reverting to normal cognition over time (Koepsell & Monsell, 2012; Roberts et al., 2014). Given that TBI may accelerate the buildup of pathological burden in AD, individuals with a history of TBI may be more likely to progress from MCI to AD and at a faster rate.

Because of the variation in the clinical trajectory of MCI, much attention has been focused on the identification of factors related to progression from MCI to AD. Greater impairment in neuropsychological functioning at initial evaluation (Albert, Moss, Blacker, Tanzi, & McArdle, 2007; DeCarli et al., 2004; Manly et al., 2008; Morris et al., 2001; Tabert et al., 2006), presence of cerebral spinal fluid (CSF) AD biomarkers (phosphorylated tau, total tau, and the 42 amino-acid beta-amyloid protein) (Blom et al., 2009; Ewers et al., 2007; Hansson et al., 2006), and hippocampal atrophy (Apostolova et al., 2006; Devanand et al., 2012; Jack et al., 1999; Prestia et al., 2015; Yi et al., 2015) have been shown to predict those most

likely to progress to AD. However, these findings do not address why some individuals have an accelerated rate of progression whereas others do not. Emerging evidence suggests that this variation may be related to risk factors that play a role in the functioning of the CNS, similar to TBI. For example, the presence of Apoe4 and cerebrovascular conditions has been shown to be associated with higher risk for and faster progression from MCI to AD (Blom et al., 2009; Elias-Sonnenschein, Viechtbauer, Ramakers, Verhey, & Visser, 2011; Ettorre et al., 2012; Li et al., 2011). It is possible that other risk factors that affect the CNS, such as TBI, may also play a role in the rate of cognitive decline in MCI, though this is currently unknown.

Study 1 was a retrospective analysis of a large sample of subjects diagnosed with MCI from the National Alzheimer's Coordinating Center (NACC) dataset. NACC has maintained a combined database of clinical and sociodemographic information since September, 2005 from 34 past and present National Institute of Aging (NIA) - funded Alzheimer's Disease Centers (ADC) across the U.S (Morris et al., 2006). In that study, subjects with a remote (> 1 year prior to evaluation in an ADC) history of TBI with LOC had a 1.3 fold increased likelihood of an MCI diagnosis, supporting TBI as a risk factor for later-life cognitive decline. Furthermore, we found that a history of TBI with LOC was associated with an approximately two year earlier diagnosis of MCI (See Study 1; LoBue et al., 2016). When this finding is combined with results from previous

studies reporting an association between a history of TBI and earlier onset of AD (Nemetz et al., 1999; Sullivan, Petitti, & Barbaccia, 1987), an emerging literature supports the notion that TBI may accelerate the accumulation of pathological burden (e.g., NFT, Aβ) in MCI and AD, resulting in a reduced threshold for clinical manifestation of cognitive and functional impairment in these conditions. Because greater AD-related pathology has been associated with accelerated aging and greater cognitive impairment (Rodrigue et al., 2012), TBI may increase the risk for earlier onset of cognitive disorders and influence the course of decline.

The aim of this investigation was to examine whether a self-report history of TBI with LOC was associated with: a) an earlier onset of MCI, b) an increased risk for progression from MCI to AD, and c) faster progression from MCI to AD. It was hypothesized that, relative to those without a TBI history, individuals with a history of TBI with LOC would have an earlier age of MCI diagnosis, shorter time to progression from MCI to AD, higher annual rates of progression to AD, and greater decline as assessed on the Clinical Dementia Rating scale among subjects who progress to AD. Furthermore, given that the amnestic subtype of MCI has been found to progress to AD more frequently than the non-amnestic type (Albert et al., 2011; Vos et al., 2013), we expected the above associations to be heightened when only subjects with amnestic MCI were examined. These findings would support TBI as a risk factor for later cognitive decline and could yield insight into what role TBI may play in the process.

METHOD

This study was a retrospective analysis of the NACC Uniform Data Set (UDS) (Morris et al., 2006). Sociodemographic, medical, and clinical information were obtained for subjects with initial and final visits completed between September, 2005 and June, 2015. Selection criteria included subjects who were a) over age 50, b) diagnosed with MCI at their initial visit to an ADC, c) completed ≥ 2 visits, and d) remained MCI, reverted to normal cognition, or progressed to a diagnosis of AD during follow-up. Because AD typically manifests in individuals age 65 and older, examining individuals first diagnosed with MCI in this age range (i.e., ≥ 50) would provide insight into the association TBI may have on progression from MCI to AD in at-risk individuals. Cognitive status and clinical diagnosis were determined by ADC clinicians using established guidelines (McKhann et al., 1984; Petersen & Morris, 2005) along with a review of all available information, which typically included neuropsychological testing, neurological exam results, medical history, and psychosocial background. A clinical diagnosis of MCI was made if there was a cognitive complaint, evidence of cognitive impairment in one or more domains, everyday functioning was relatively intact, and criteria for dementia were not met (Petersen & Morris, 2005). If cognitive impairment included memory, the MCI diagnosis was defined as *amnestic type,* whereas if cognitive impairment was in any other non-memory cognitive domain (i.e., language, attention, executive function, or visuospatial

abilities), the MCI diagnosis was *non-amnestic* type. The diagnosis of AD was made according to NINCDS/ADRDA criteria and defined as *probable* or *possible* AD, while normal cognition was defined as a lack of neurocognitive impairment and failure to meet established clinical criteria of MCI, dementia, or other neurodegenerative conditions.

The NACC database contains three patient/informant-reported questions related to TBI as follows: a) whether subjects had ever sustained a TBI resulting in <5 minutes loss of consciousness (mLOC), b) ≥5 mLOC, and c) if there was a chronic deficit/dysfunction as a result of the injury. Each question is answered via subject/informant interview and coded as *absent*, *recent/active* (defined as occurring within 1 year of visit or currently requiring treatment), *remote/inactive* (defined as occurring >1 year of visit and either having recovered from the injury or no treatment is currently underway), or *unknown*. Age at TBI or time since injury is not collected by NACC. Therefore, the only way to examine the effect of a history of remote TBI was to select those subjects who were coded as having a TBI occurring more than 1 year prior to the initial visit (i.e., *remote/inactive).* Further, subjects reporting a history of TBI leading to a chronic deficit or a *recent/active* TBI at the initial visit or anytime thereafter were excluded in an attempt to remove the effect of acute cognitive decline directly attributable to a recent TBI. As such, this study only included individuals who reported a history

of TBI with LOC and no chronic deficits that occurred more than one year prior to the initial visit, or an absence of TBI history.

Measures

For the present study, the following sociodemographic variables were included in analyses because of their known link with later cognitive decline: age of MCI diagnosis, sex, race, education, and family history of dementia (i.e., a first-degree relative with a dementia diagnosis). In addition, because vascular risk factors have been associated with increased dementia risk (Luchsinger et al., 2005), the Cardiovascular Risk Factors, Aging and Incidence of Dementia (CAIDE) risk score was examined (Exalto et al., 2014). The CAIDE risk score has been shown to be a valid measure for predicting likelihood of developing dementia and was calculated by totaling weighted scores for age, education, sex, systolic blood pressure, body mass index, and presence/absence of hypercholesterolemia (i.e. reflective of total cholestrol $\geq$ 6.5 mmol/L). Genetic factors, such as presence of apolipoprotein E-e4 (Apoe4) alleles, and cigarette smoking history (number of years smoking cigarettes), have been linked to dementia risk as well (Boot et al., 2013) and were also examined.

Because psychiatric factors such as depression and heavy alcohol use have shown to be associated with increased risk for and earlier onset of dementia (Anttila et al., 2004; Harwood et al., 2010; Modrego & Ferrández, 2004; Rosenberg et al., 2013), and TBI is associated with later development of these

conditions (Rogers & Read, 2007), we examined their potential influence from available data. NACC contains some limited information about histories of depression and substance abuse. At the initial visit, subjects are asked two questions via subject/informant interview: if they ever 1) had a history of depression occurring >2 years prior and 2) had clinically significant impairment in occupational, social, or legal activities due to alcohol (i.e. alcohol abuse) or drug use (i.e., drug abuse). Episodes of depression were coded as *absent* or *present* and defined as consulting a clinician about depressed mood, being prescribed antidepressant medication, or receiving a mood disorder diagnosis (i.e., major depression, dysthymia, bipolar). The alcohol and drug abuse questions were coded similar to the TBI information, as *absent*, *recent/active*, *remote/inactive*, or *unknown*. To keep the timeline for other acquired risk factors consistent with the "remote" nature of TBI that we used, only remote/inactive histories of alcohol and drug abuse were examined.

Subjects in the NACC database are evaluated using the Clinical Dementia Rating (CDR) scale, a reliable (Cedarbaum et al., 2013; Morris et al., 1997; Rockwood, Strang, MacKnight, Downer, & Morris, 2000) and valid (Cedarbaum et al., 2013; Morris, 1997) semi-structured clinician interview rating scale for cognitive decline in 6 functional domains: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. Severity of impairment is rated for each domain as no impairment (0),

questionable impairment (0.5), mild (1), moderate (2), and severe (3), with the exception of the personal care domain which excludes a rating for questionable impairment. A Sum of Boxes score (CDR-SB) is computed by totaling severity ratings for all 6 domains. The CDR-SB is commonly used and is useful in staging dementia severity (Cedarbaum et al., 2013; Storandt, Grant, Miller, & Morris, 2006), and thus, CDR-SB for initial and follow-up visits were analyzed.

Statistical Analyses

Chi-square, independent samples t-tests, and nonparametric tests (Mann-Whitney U test) were used where appropriate to compare the TBI+ and TBI− groups on sociodemographic, clinical, and Apoe4 information at the time of MCI diagnosis. Only subjects with complete baseline data were included for analysis.

A Kaplan-Meier survival analysis was utilized to examine the ability of a history of TBI to predict progression from MCI to AD in an unadjusted model. A second, adjusted survival analysis used a Cox proportional hazard model that included age at MCI diagnosis, sex, race, education, family history of dementia, number of Apoe4 alleles, number of years smoking cigarettes, baseline CAIDE risk score, and histories of depression and alcohol abuse along with history of TBI. Covariates remained in the model if $p < 0.15$. Time to progression was calculated by taking the difference between the ages for diagnosis of MCI and AD. For subjects who did not progress to AD (i.e., remain MCI or revert to normal cognition), the time from age of MCI diagnosis to the last follow-up visit

was used instead. Survival rates from the two models were used to examine annual rates of progression to AD in those with a history of TBI (TBI+) compared to those without a history of TBI (TBI−). In a secondary analysis, an ANCOVA was performed, controlling for relevant demographic variables, to evaluate whether average time to progression to AD (as calculated above) differed between the TBI+ and TBI− groups.

Random regression models were used to assess whether a history of TBI is associated with rate of decline in CDR-SB scores over time among those who progressed to AD and completed ≥ 3 visits. Random regression models take into account unbalanced data occurring from subject drop-out and/or uneven follow-up intervals (Bernal-Rusiel et al., 2013), which is common in the NACC dataset. Because subject drop-out after two visits would restrict variability in CDR-SB scores, only individuals who completed a minimum of three visits were examined in order to determine the association TBI may have on rate of cognitive decline from MCI to AD. In addition, since subject drop-out is extensive beyond six visits (i.e. ≥ 80%), the analysis included two models to examine the best fit to the data. In model 1, rate of decline in CDR-SB scores were assessed across five visits. In model 2 the 6^{th} visit was added. Each model included history of TBI and 10 other fixed effects predictors measured at time of MCI diagnosis: age at MCI diagnosis, sex, race, education, family history of dementia, number of Apoe4 alleles, cigarette smoking history (number of years smoking cigarettes), baseline CAIDE

risk score, and histories of depression and alcohol abuse. Time between study visits (number of days from initial visit) was modeled as a random intercept and slope to account for uneven follow-up intervals among the NACC subjects.

Although both amnestic and non-amnestic MCI subtypes are often considered transitional stages to AD, the amnestic type has been found to progress to AD more frequently than the non-amnestic type (Albert et al., 2011; Vos et al., 2013). As such, planned analyses initially included both MCI types combined in order to determine the possible magnitude of the effect TBI may have on the general progression from MCI to AD. Afterwards, analyses were performed again only for subjects diagnosed with amnestic MCI to assess whether associations remained between TBI and progression to AD. Assumptions for all tests were reviewed. All analyses were conducted using IBM© SPSS Statistics V22 (IBM Corp, SPSS Statistics V22, Armonk, NY, 2013) with a cutoff for significance set at $p < 0.05$.

RESULTS

Demographic Characteristics of MCI Groups

A total of 2,719 subjects diagnosed with MCI met inclusion criteria (See Figure 1). Among these, 248 reported a history of TBI with LOC ($n_{amnestic} = 197$) occurring more than one year prior to the initial visit and 2,471 subjects reported an absence of TBI ($n_{amnestic} = 2,038$). Baseline characteristics for the combined MCI group can be found in Table 1. The TBI+ and TBI− MCI groups did not

differ by race (p =.48), education (p =.87), CAIDE risk scores (p = .13), number of years smoking cigarettes (p =.13), family history of dementia (p =.58), or Apoe4 status (p =.79). Both groups were predominantly Caucasian (> 85%), well-educated (M_{years} > 14), had a median CAIDE score of 7 (TBI+ range = 3 ─ 8; TBI− range = 3 ─ 11), and those who smoked (n = 1,253) had an approximate mean of a 22 year smoking history (TBI+ Median = 20 year; TBI− Median = 20 years). A family history of dementia was reported in approximately 55% of both groups; likewise, nearly 40% of both groups had at least 1 Apoe4 allele. The MCI groups did differ significantly in terms of sex distribution and histories of depression and alcohol abuse (p's <.001). Compared to the TBI+ group, the TBI− group had a larger proportion of females (51% vs 33%) and fewer subjects with a history of depression (18% vs 31%) and alcohol abuse (3% vs 10%).

Clinical Characteristics of MCI Groups

At time of MCI diagnosis, CDR-SB scores were nearly equivalent for the TBI+ (M = 1.26; range = 0 ─ 4.5) and TBI− groups (M = 1.30; range = 0 ─ 8; $F_{(1, 2714)} = 2.00$, p =.16). However, MCI was diagnosed on average 2.6 years earlier in the TBI+ group (M = 71.68) relative to the TBI− sample (M = 74.33; $F_{(1, 2714)} = 16.81$, p <.001), controlling for sex and psychiatric comorbidities. Examining only subjects with amnestic MCI continued to show that CDR-SB scores did not significantly differ between those with and without a history of TBI ($M_{amnestic}$ TBI+ = 1.34; vs $M_{amnestic}$ TBI− = 1.37; $F_{(1, 2230)} = 0.67$, p =.41), but that diagnosis

of MCI was earlier for the TBI+ group ($M_{amnestic}$ TBI+ = 72.06; SD = 8.79) compared to the TBI− group ($M_{amnestic}$ TBI− = 74.71; SD = 8.46; $F_{(1, 2230)} = 13.58$, $p < .001$).

Progression from MCI to AD

The median duration of follow-up was 4 years (interquartile range = 2−5 years). A total of 1,016 subjects, out of 2,719, progressed from MCI to a diagnosis of AD over the course of 9 years, of whom 870 had amnestic MCI at baseline and 73 had a history of TBI (TBI+ amnestic MCI n = 67). Annual rates of progression from MCI to AD were 8% and 10% for the TBI+ and TBI− groups, respectively, during 5 years of follow-up (Figure 2). The average time for progression to AD was 2.6 years and did not significantly differ between the TBI+ (M = 2.48, SD =1.68) and TBI− groups (M = 2.57, SD = 1.61; $F_{(1, 1014)} = 0.18$, $p = .67$). Likewise, annual rates and average time for progression to AD were relatively similar for the amnestic MCI subjects with and without a history of TBI (annual rate = 10% vs 11%, respectively; M time to AD = 2.38 vs 2.51; $F_{(1, 932)} = 0.10$, $p = .75$).

History of TBI and Progression from MCI to AD

Hazard ratios, 95% confidence intervals for hazard ratios, and characteristics for survival analyses predicting progression from MCI to AD for the combined MCI sample can be found in Table 2. Kaplan-Meier survival analysis (unadjusted model) showed that a history of TBI alone was a significant

predictor but associated with *slower* progression from MCI to a diagnosis of AD (Figure 3; HR = 0.77; 95% CI = 0.61 to 0.97; Log rank χ^2 p = .02). However, in the Cox proportional model, adjusted for age of MCI diagnosis, sex, race, education, presence of Apoe4 alleles, family history of dementia, and the CAIDE risk score, history of TBI was a non-significant predictor for progression (HR = 0.84; 95% CI = 0.66 to 1.07; LR χ^2 p = .15). Individual adjustment for each covariate showed that a history of TBI remained a significant predictor for slower progression from MCI to AD (LR χ^2 *p's* < .04), except when the effect of age of MCI diagnosis was held constant (TBI model adjusted for age, LR χ^2 p = .15). Among subjects with amnestic MCI at baseline, history of TBI was a non-significant predictor for progression to AD in the unadjusted (HR = 0.81; 95% CI = 0.63 to 1.03; LR χ^2 p = .09) and adjusted (HR = 0.85; 95% CI = 0.66 to 1.09; LR χ^2 p = .19) models.

Overall Progression from MCI to AD

Progression from MCI to AD was significantly predicted by age of MCI diagnosis, race, Apoe4 status, and family history of dementia (LR χ^2 *p's* <.05; See Table 2). Specifically, aging, presence of APOE ε4 alleles, and a family history of dementia were associated with greater risk for progression from MCI to AD, while an African American background was protective (i.e., approximately 45% reduced risk). Similarly, age of MCI diagnosis (HR = 1.04; 95% CI = 1.03−1.04; LR χ^2 p < .001), race (African American HR = 0.57; 95% CI = 0.45−0.73; LR χ^2 p

< .001), and Apoe4 status (*1 allele* HR = 1.89; 95% CI = 1.64−2.18; LR χ^2 p < .001; *2 alleles* HR = 2.57; 95% CI = 2.08−3.17; LR χ^2 p < .001) predicted progression to AD among subjects with amnestic MCI, while family history of dementia was no longer a significant factor (HR = 1.13; 95% CI = 0.99−1.30; LR χ^2 p = .07). Cigarette smoking history (number of years smoked) and histories of depression and alcohol abuse were removed from the models due to the degree of non-significant prediction (LR χ^2 *p's* > 0.15).

Rate of Decline from MCI to AD

Among subjects progressing to an AD diagnosis (≥3 completed visits; TBI+ n = 62, TBI− n = 804), random regression showed that a history of TBI with LOC was a non-significant predictor for cognitive decline on CDR-SB (b = 0.15, T = 0.89, p = .38), while, sex, race, and history of depression were significant predictors (see Table 3). Because of the degree of non-significant predictions for age of MCI diagnosis (p = .28), family history of dementia (p = .56), Apoe4 status (p = .56), education (p = .15), cigarette smoking history (number of years smoked; p = .869), CAIDE score (p = .98), and history of alcohol abuse (p = .91), these variables were removed from the model. While CDR-SB scores across 5 visits provided the model of best fit (Akaike information criterion; Model 1 = 15,476 vs. Model 2 = 16,953), the results remained relatively unchanged when CDR-SB scores were examined across 6 visits (See Table 3). Examining only amnestic MCI subjects who progressed

to AD (TBI+ n = 55, TBI− n = 736) showed similar results, though history of depression became a non-significant predictor (see Table 4).

DISCUSSION

This study is the first to examine whether a history of TBI was associated with progression from MCI to AD. Despite a history of TBI with LOC being linked to an approximately 2.5 year earlier diagnosis of MCI, consistent with our previous study (LoBue et al., 2016), a TBI history was *not* associated with progression to AD over the course of 9 years (interquartile range = 2−5 years). Specifically, a history of TBI was initially associated with a 23% reduced risk for progression from MCI to AD (HR = 0.77; 95% CI = 0.61 to 0.97), with annual rates of progression being similar for subjects with a history of TBI (8%) relative to those without (10%). However, this association diminished further after adjusting for an earlier age of MCI diagnosis. These results were observed even when analyses focused only on subjects diagnosed with amnestic MCI at baseline.

One possible explanation for why a history of TBI was linked to a reduced risk and slower progression from MCI to AD may involve aging being the biggest risk factor for developing AD. Aβ deposition has been shown to accumulate with aging, likely reducing the threshold for cognitive/behavioral impairments to become clinically manifest. While a history of TBI with LOC is linked to an earlier onset of MCI, indicating that TBI might also accelerate the accumulation of AD-related pathology, doing so might actually offset the risk associated with

being older at time of MCI diagnosis, particularly since a history of TBI appears unrelated to progression to AD (See Figure 4). Thus, a history of TBI may be a risk factor for earlier development of MCI via contributing to the accumulation of tau and Aβ pathology found in AD, but once the neurodegenerative process for MCI to AD starts, TBI history appears unrelated to subsequent decline. These findings are similar to an association observed in other CNS insults with course of cognitive decline in AD, indicating that isolated cerebrovascular insults may lower the threshold for clinical expression of AD, but that progressive decline is related to the Alzheimer disease process only (Attems & Jellinger, 2014; Gorelick et al., 2011).

Although moderate-to-severe TBI is considered a significant risk factor for developing AD, a mechanistic link remains unclear. TBI is believed to initiate a neurodegenerative process, accelerate the expression of neurodegenerative diseases, or disrupt neuronal/cognitive reserve and interact with aging and other factors (Gardner et al., 2014). Previous neuroimaging studies have found that beyond the acute phase of injury (between 5 and 30 months), there is atrophy of frontal and temporal connections in small samples of moderate-to-severe TBI patients (Greenberg, Mikulis, Ng, DeSouza, & Green, 2008; Ng et al., 2008). It has also been reported that between 1 and 4 years after a moderate-to-severe injury, TBI patients show greater diffuse white matter atrophy compared to age-matched controls (Farbota et al., 2012). Damage to white matter tracts is believed

to initiate an accumulation of Aβ plaques and NFTs (Johnson et al., 2013), with findings from autopsy studies showing a presence of AD-related changes in some individuals several years after a single, moderate-to-severe TBI. Specifically, over 60% of patients surviving a moderate-to-severe TBI for longer than a year were found to have Aβ plaques present at autopsy that were more often fibrillary, similar to plaque formations seen in AD, and unlike the diffuse pattern observed in age-matched controls (Johnson et al., 2012). In addition, 33% of TBI patients in that sample also showed the presence of NFTs that were more abundant and at an earlier age compared to controls. Furthermore, a recent neuroimaging study found that several years after injury (1 to 17 years), Aβ plaques were present to a greater degree in-vivo in a small sample of moderate-to-severe TBI patients compared to an older cognitively normal group (nearly 20 years older), and that Aβ deposition was associated with greater white matter damage, partially overlapping the pattern seen in AD patients (Scott et al. 2016). Such findings support the notion, at the very least, that moderate-to-severe TBI can cause white matter degenerative changes that may initiate/accelerate AD-related pathology; however, what remains to be seen is whether such changes continue beyond a few years or eventually stabilize and whether similar changes occur in milder TBI severities.

In the present study, we did not find a link between a history of TBI and rate of cognitive progression from MCI to AD, as levels of impairment (i.e.,

CDR-SB scores) did not differ between the TBI+ and TBI− groups at time of MCI diagnosis, nor was a history of TBI associated with more rapid decline among subjects who progressed to AD. Given that greater AD-related pathology has been associated with accelerated aging and greater cognitive impairment (Rodrigue et al., 2012), these findings are contrary to what we might expect if TBI somehow triggers the progressive development of AD-related pathology. Notably, however, a majority of our TBI sample (65%) self-reported a history of mild TBI (< 5 mLOC) as opposed to more serious injuries that much of the evidence linking TBI to the development of AD stems from. Another issue is that TBIs occurring later in life may play an important role in rate of cognitive progression from MCI. For example, in an investigation that followed 325 individuals diagnosed with AD for up to 11 years (median of 1.5 years), a history of TBI (i.e., head injury resulting in LOC, medical attention, or post-traumatic amnesia) within 10 years of AD onset (n = 14) was found to be associated with more rapid decline on CDR-SB scores after dementia onset, while more remote TBIs were not (TBI history > 10 years prior to onset; n = 49) (Gilbert et al., 2014). While this study followed a limited number of TBI cases having trauma within 10 years of AD onset, the findings for remote TBI are consistent with those in the present study, indicating that a history of remote TBI does not appear to impact the course of cognitive decline from MCI to AD in many individuals. However, further investigation is needed, as the implications of TBI severity are unknown.

TBI, even at milder severities, produces white matter injury (Johnson et al., 2013), and in keeping with previous reports that white matter damage is linked to AD-related pathology (Scott et al., 2016), it would appear that TBI-related processes can accelerate the accumulation of pathological burden in MCI and AD in some individuals. Along these lines, a recent neuroimaging study examined 99 patients who reported a remote history of TBI resulting in LOC or posttraumatic amnesia (average > 50 years prior), and observed greater Aβ deposition among MCI patients (n = 25), but not cognitively normal individuals (n = 74), compared to those (MCI and cognitively normal) without any history of TBI (Mielke et al., 2014). Given this association, TBI may reduce the time needed to reach the threshold for clinical manifestation in these conditions and other neurodegenerative disorders, which is supported by emerging literature indicating that a history of TBI with LOC is associated with earlier diagnosis of neurodegenerative conditions such as MCI (LoBue et al., 2016), AD (LoBue et al. under review*), and frontotemporal dementia (LoBue et al., 2015). Although TBI has been associated with an accumulation of AD-related pathology and an earlier expression of MCI and AD, findings from the present study suggest that a history of TBI may not play a role in progression or rate of cognitive decline for many individuals at risk for dementia, indicating that aging and other factors are linked to why some individuals progress from MCI to AD at an accelerated rate.

Few background risk factors have been identified in previous studies that

predict progression from MCI to AD. In many cases, background factors are controlled, while clinical markers are utilized to predict those most likely to progress. In the present study, risk for progression from MCI to AD was greatest when individuals were older, Apoe4 carriers, and had a family history of dementia, whereas risk was reduced in subjects from an African American background (n = 348). It is not surprising that aging and presence of Apoe4 are associated with progression from MCI to AD since both are salient risk factors for developing MCI (LoBue et al., 2016) and AD (Corder et al., 1993; Lindsay et al., 2002; Visser, Kester, Jolles, & Verhey, 2006). Interestingly, we found African Americans to have a 40% reduced risk for progression to a diagnosis of AD when compared to Caucasians. Although cardiovascular and socioeconomic factors have been found to be largely associated with racial differences in risk for dementia (Plassman et al., 2007; Yaffe et al., 2013), we found African Americans had a reduced risk for progression even when many of these factors were taken into account (initial model with all covariates; $p < .001$). However, cognitive progression from MCI to AD was more rapid in individuals who were male, had a history of depression, and from an Asian/Pacific Islander/Native American background, though the association with race may be less reliable given the limited number of cases that progressed to AD (n = 17). It is possible we did not see a link with Apoe4 status and family history of dementia because our analyses were restricted to a subset of cases (i.e., those who completed > 2 visits and

progressed from MCI to AD). Since Apoe4 carriers were more likely to progress to a diagnosis of AD at a faster rate, a proportion of individuals may have shown rapid decline by their 2nd visit, and subsequently were less likely to continue follow-up beyond that period, which may have reduced our ability to detect differential change over time. On the other hand, our finding of a non-association with Apoe4 is consistent with a previous investigation examining neuropsychological decline over 4 years among MCI subjects who progressed to AD (Albert et al., 2007), suggesting that genetic factors such as Apoe4 status and a family history of dementia may not play a major role in rate of decline once the neurodegenerative process starts.

Among factors that may be linked to cognitive decline, rate of progression from MCI to AD was more rapid in males and those with a history of depression. The slower rate of decline observed in females is in line with a previous report that males who developed AD showed faster decline than females on the Mini Mental Status Examination over 4 years (Rosselli et al., 2009). In contrast, the association between rate of cognitive decline and history of depression is less clear. Depressive symptoms, but not a *history of depression*, have been shown to predict the development of dementia in older individuals within 5 years of evaluation (Mirza et al., 2014; Verdelho et al., 2013), even after taking potential confounding factors (e.g., vascular conditions and vascular brain-related changes) into account. There is evidence that risk for AD is increased among older persons

who develop depression symptoms within 10 years of AD onset, but that the association is attenuated for depression symptoms occurring earlier in life (Mirza et al., 2014).

Given that NACC's criteria for a history of depression is based on presence/absence of episodes occurring more than 2 years prior to baseline, "depression" in our sample could have been relatively more recent than remote, particularly since significant depression symptoms are common (nearly 20%) in MCI (Polyakova et al., 2014). Previous studies have suggested that a link between depression and the later development of AD may be related to the accumulation of Aβ. A recent investigation demonstrated that older, cognitively normal patients with high Aβ burden had an increased likelihood for later developing clinically significant depression symptoms over 5 years (Harrington et al., 2016). Another study revealed that among a small sample of patients with MCI and a history of depression, the age of onset of depression was linked to presence of Aβ; MCI subjects having Aβ pathology had an average age of onset of depression close to 70 years, which was 15 years older than those without Aβ (Tateno et al., 2015). These findings suggest that depression in older individuals may reflect the buildup of AD pathology, and thus, the earliest neurobehavioral symptoms of neurodegeneration. Alternatively, a history of depression could represent a response to having awareness of cognitive decline, as poorer memory performance predicted later development of depression symptoms, and not vice

versa, in a recent longitudinal study of older adults (N = 14,789) (Jajodia & Borders, 2011). Therefore, the finding that depression history was associated with faster cognitive decline among those that progressed from MCI to AD may actually reflect effects from the underlying neurodegeneration or having awareness of subtle neurobehavioral changes prior to a diagnosis of MCI.

Limitations

Limitations of the present study deserve mention. While follow-up was up to 9 years for some individuals, subject drop-out exceeded 75% at roughly 5 years (interquartile range = 2−5 years), which could restrict generalization of the findings at longer intervals. Another limitation relates to the lack of TBI details in the NACC dataset, as our ability to examine potentially important variables that could play a role in progression to AD was limited. NACC's cutoff of <5 and ≥5 mLOC for TBI includes a wide range of severities. As such, we could not examine TBI severity, which may have important implications given that moderate-to-severe TBI has been found to be a significant risk factor for developing AD. In addition, with the definition for remote TBI (i.e., >1 year), injuries may have occurred as recently as nearly one year prior to the initial ADC visit or decades earlier. It is possible subjects may have a >1 year time period between onset of symptoms of MCI and the age they arrived at an ADC for diagnosis; thus, an unknown proportion of TBIs in our sample may have occurred following onset of MCI or may have occurred in close temporal relationship to

MCI symptom onset. Further, although we did not examine medication use, it is possible that cholinesterase inhibitors were prescribed earlier for the TBI+ sample given the earlier age of MCI diagnosis, which may have moderated the risk of progressing to a diagnosis of AD. Lastly, NACC studies are not population-based. Subjects participating at ADC's are recruited through clinician referral or self-referral, and often are predominantly Caucasian, well-educated, and represent volunteers for dementia research. Despite these limitations, the present study included a large national sample whose cognitive status was well-characterized with extensive standard diagnostic evaluations, which might be more representative of U.S. citizens presenting for dementia assessment. In addition, this investigation overcomes a major limitation of many previous studies assessing the link between TBI and the later development of AD, namely, including individuals diagnosed with AD outside of specialized dementia clinics where diagnostic accuracy may be a concern.

Conclusions

A history of TBI with LOC was associated with an earlier age of diagnosis of MCI, but not progression to AD over the course of 9 years in this longitudinal investigation of a multicenter national database. Individuals with a history of TBI with LOC did *not* show faster progression from MCI to AD, higher annual rates of progression, or a greater rate of cognitive decline than those without a TBI history. These findings support emerging literature that TBI might accelerate the

accumulation of AD-related pathology, reducing the threshold for onset of MCI, but not hypotheses that TBI may activate a progressive neurodegenerative process. Rather, results from the present study demonstrate that aging, Apoe4 status, and other factors are associated with progression from MCI to AD. These findings underscore the need for further investigation as much is still unclear, including TBI's effects on the long-term development of AD-related pathology and its interactions with normal aging. Future studies with longitudinal neuroimaging after TBI, evaluation of neuropsychological patterns, and more detailed assessment of TBI features (e.g., severity and age of injury) in individuals presenting for dementia evaluation, are needed in order to further understand the implications of TBI on risk for later cognitive decline.

Table 1

Baseline Demographics and Medical History of Subjects With and Without a History of TBI

	TBI+ *(n=248)*	*TBI−* *(n=2471)*
Age of MCI diagnosis, *M (SD)*[*]	71.68 (9.05)	74.33 (8.50)
Education, *M (SD)*	15.17 (3.36)	15.20 (3.21)
Female[*], *n (%)*	82 (33)	1260 (51)
Race, *n (%)*		
Caucasian	203 (82)	1913 (78)
African American	25 (10)	323 (13)
Hispanic	14 (6)	158 (6)
Other, Non-white	6 (2)	70 (3)
Family History of Dementia, *n (%)*	143 (58)	1280 (56)
Apoe4 alleles, *n (%)*		
0 alleles	141 (57)	1388 (56)
1 allele	90 (36)	883 (36)
2 alleles	17 (7)	200 (8)
Cigarette Smokers, *n (%)*	51	46
# of Yrs Smoking Cigarettes, *M (SD)*	22.54 (15.23)	22.75 (14.97)

History of Depression*, *n (%)*	77 (31)	448 (18)
History of Alcohol Abuse*, *n (%)*	25 (10)	68 (3)
History of Other Substance Abuse, *n (%)*	6 (2)	12 (1)
CAIDE score, *M (SD)*	6.84 (1.78)	6.67 (1.81)
CDR−SB score, *M (SD)*	1.26 (1.02)	1.30 (1.08)

Note. * p <.05. MCI = mild cognitive impairment; TBI = traumatic brain injury with loss of consciousness; Other, Non-white = Asian/Pacific Islander/Native American background; CDR−SB = Clinical Dementia Rating Sum of Boxes; CAIDE = the Cardiovascular Risk Factors, Aging and Incidence of Dementia risk score; Apoe4 = apolipoprotein E-e4.

Table 2

Hazards Ratios, Confidence Intervals, and Statistics for Survival Analyses Predicting Progression from MCI to AD Among the Combined MCI Sample

	HR	*95% CI for HR*	LR χ^2 *p-value*
Unadjusted Model			
TBI history*	0.77	0.61 – 0.97	.02
Adjusted Model			
TBI history	0.84	0.66 – 1.07	.15
Age*	1.04	1.03 – 1.05	<.001
Family History of Dementia*	1.15	1.01 – 1.31	.03
Apoe4 alleles			
1 allele*	1.89	1.65 – 2.17	<.001
2 alleles*	2.83	2.31 – 3.47	<.001
Sex, Female	0.89	0.78 – 1.01	.08
Race			
African American*	0.57	0.45 – 0.71	<.001
Hispanic	0.80	0.58 – 1.09	.15
Other, Non-white	1.04	0.70 – 1.53	.86

Education	0.98	0.96 – 1.01	.14
CAIDE score	0.96	0.93 – 1.00	.05

Note. n = 2,719. * $p < .05$. HR = hazard ratio; CI = confidence interval; LR = log rank test; TBI = traumatic brain injury with loss of consciousness; Other, Non-white = Asian/Pacific Islander/Native American background; Apoe4 = apolipoprotein E-e4; CAIDE = the Cardiovascular Risk Factors, Aging and Incidence of Dementia risk score.

Table 3

Coefficients, Confidence Intervals, and Statistics for Predicting Decline on CDR-SB scores in the Combined MCI Sample who Progress to AD

	Model 1 (5 visits)			*Model 2 (6 visits)*		
	b	*95% CI*	*p*	*b*	*95% CI*	*p*
Sex, Female[* †]	-0.31	-0.48 – -0.13	.001	-0.34	-0.53 – -0.16	<.001
Education				-0.02	-0.06 – 0.01	.11
Race						
African American	-0.20	-0.51 – 0.12	.22	-0.25	-0.58 – 0.08	.14
Hispanic	0.12	-0.31 – 0.55	.58	0.06	-0.39 – 0.51	.81
Other, Non-white[* †]	0.91	0.29 – 1.53	.004	0.97	0.33 – 1.61	.003
History of Depression[*]	0.24	0.04 – 0.44	.02	0.25	0.00 – 0.50	.05
TBI History with LOC	0.15	-0.19 – 0.49	.38	0.21	-0.14 – 0.56	.24

Note. [*] $p < .05$ in Model 1. [†] $p < .05$ in Model 2. CI = confidence interval; *b* = coefficients.

Table 4

Coefficients, Confidence Intervals, and Statistics for Predicting Decline on CDR-SB scores in the Amnestic MCI Sample who Progress to AD

	Model 1 (5 visits)			*Model 2 (6 visits)*		
	b	*95% CI*	*p*	*b*	*95% CI*	*p*
Sex, Female[* †]	-0.30	-0.48 – -0.12	.001	-0.31	-0.50 – -0.13	.001
Race						
African American	-0.11	-0.45 – 0.23	.52	-0.11	-0.46 – 0.24	.55
Hispanic	0.06	-0.39 – 0.51	.80	0.07	-0.40 – 0.53	.77
Other, Non-white[* †]	0.84	0.20 – 1.48	.01	0.90	0.24 – 1.56	.007
History of Depression	0.23	-0.02 – 0.48	.07	0.21	-0.05 – 0.47	.11
TBI History with LOC	0.16	-0.20 – 0.52	.37	0.23	-0.14 – 0.60	.23

Note. [*] $p < .05$ in Model 1. [†] $p < .05$ in Model 2. CI = confidence interval; *b* = coefficients; MCI = mild cognitive impairment; Other, Non-white = Asian/Pacific Islander/Native American background.

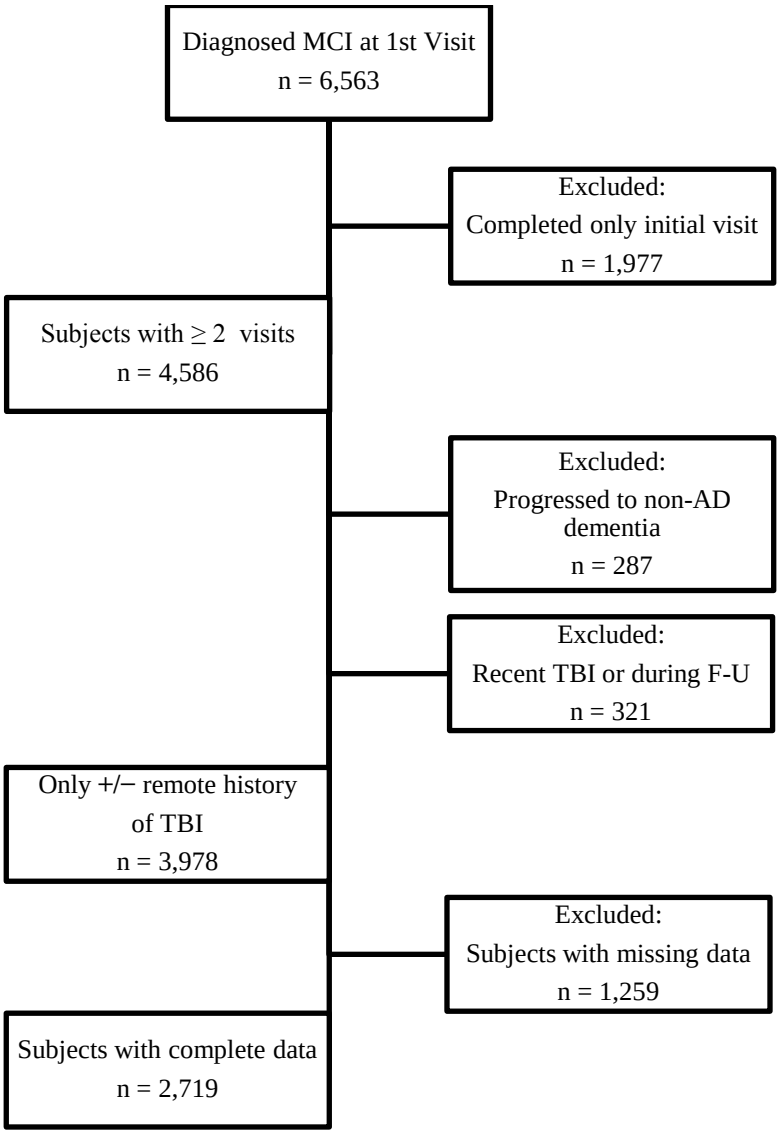


Figure 1. Flowchart of sample selection from NACC's UDS dataset. MCI = mild cognitive impairment; AD = Alzheimer disease; F-U = follow up visits; TBI = traumatic brain injury with loss of consciousness.

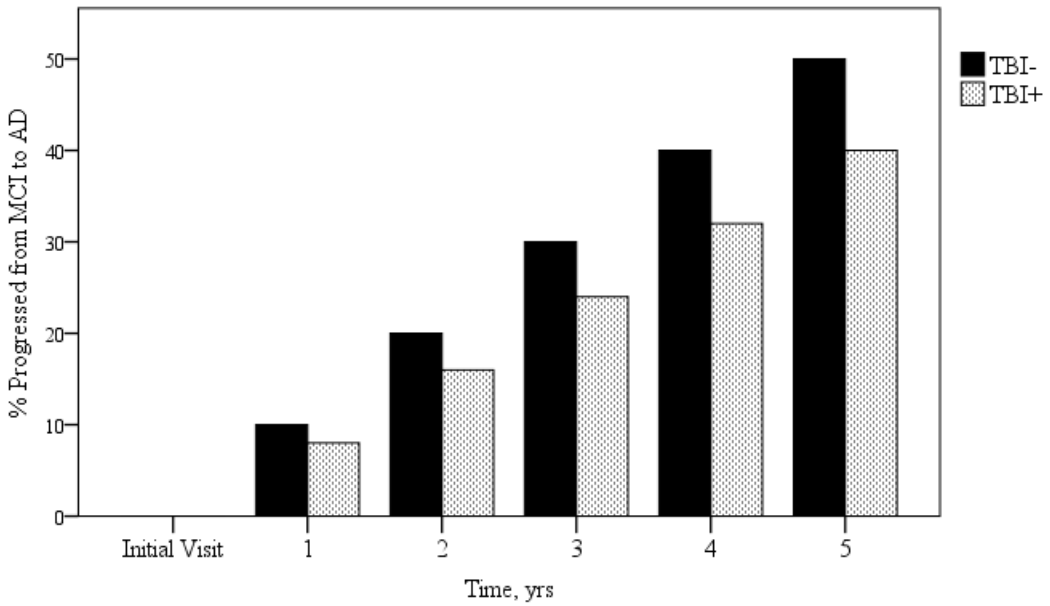
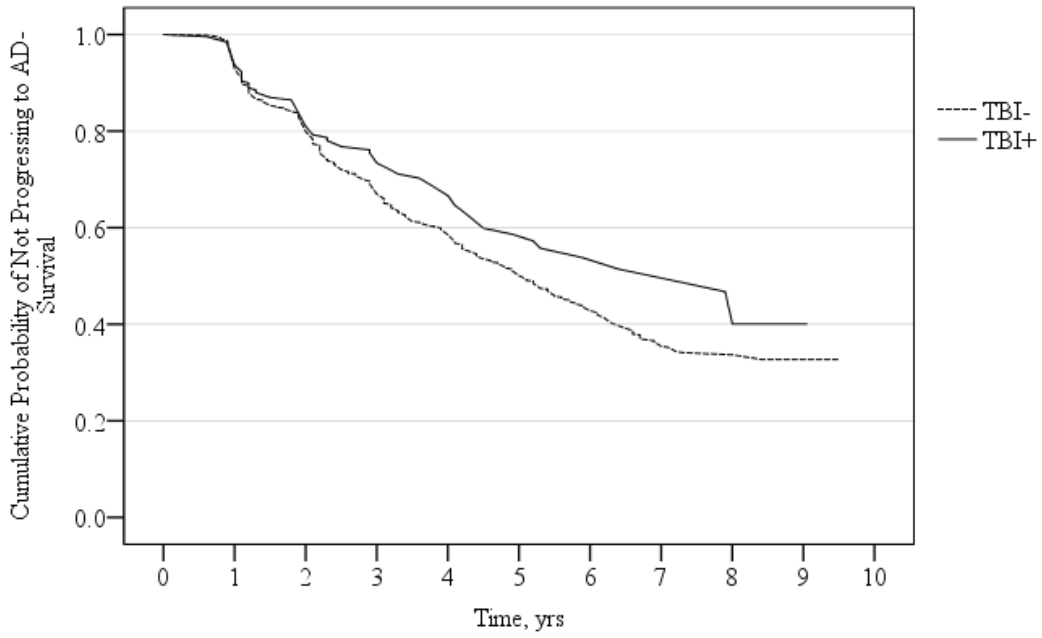


Figure 2. Annual rates of progression from MCI to AD in TBI−/+ subjects over 5 years. MCI = mild cognitive impairment; AD = Alzheimer disease; TBI−/+ = subjects without/with a history of traumatic brain injury with loss of consciousness.



TBI–	2471	2328	1601	1023	661	443	279	162	77	16	0
TBI+	248	227	158	109	75	46	27	18	7	1	0

Number of Subjects Alive at Each Time Interval

Figure 3. Survival rates for not progressing from MCI to AD in subjects with and without a history of TBI over 9 years. MCI = mild cognitive impairment; AD = Alzheimer disease; TBI+ = subjects with a history of traumatic brain injury with loss of consciousness.

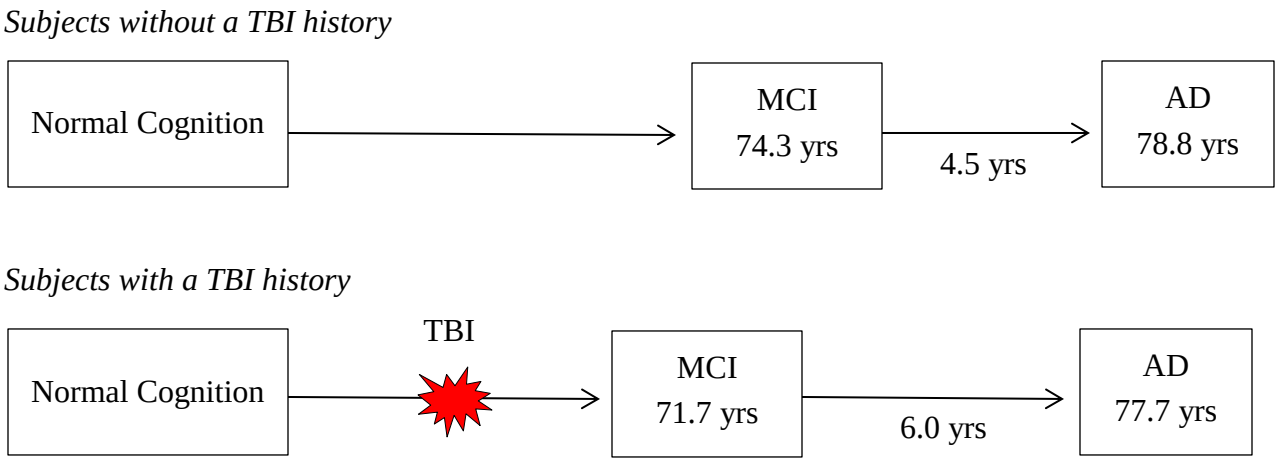


Figure 4. Timeline of progression from MCI to AD for subjects with and without a history of TBI. MCI = age of diagnosis of mild cognitive impairment; AD = age of diagnosis of Alzheimer disease; TBI = a history of traumatic brain injury with loss of consciousness.

SECTION IV

Additional Analyses

Additional analyses for Study 1 and Study 2 were carried out to further investigate if demographic characteristics, psychiatric comorbidities, Apoe4, and MCI subtype influenced the association between a history of TBI and development and progression from MCI. The results are presented here, and any implications are discussed in *SECTION V: Overview of Hypotheses and Summary of Conclusions*.

Study I

Effect of Education on the Association between a History of TBI and Age of Diagnosis of MCI and Estimated Age of Decline

Two-way ANCOVAs were used, controlling for sex differences, to explore whether an interaction between education level (i.e., <12, 12, and >12 years of education) and history of TBI had an effect on age of MCI diagnosis or estimated age of cognitive decline. Main effects and interaction for these analyses are displayed in Table 1. Results did not reveal a significant interaction effect for either age of diagnosis ($F_{(2, 3902)} = 0.15$, $p = .70$) or estimated age of cognitive decline ($F_{(2, 3902)} = 0.02$, $p = .12$).

Influence of Psychiatric Comorbidities on the Association between a History of TBI and Age of Diagnosis of MCI and Estimated Age of Decline

ANCOVAs were performed to examine if age at diagnosis and estimated age of cognitive decline onset were different between TBI+ and TBI− groups in the total MCI sample, after controlling for sex plus histories of depression and alcohol abuse. Age of diagnosis was significantly different, with the TBI+ group (M_{Age} = 72.22, SD = 10.03) being diagnosed with MCI on average 2.3 years earlier than the TBI− group (M_{Age} = 74.46, SD = 9.12; $F_{(1, 3182)} = 10.79, p < .001$). While clinician-estimated age of cognitive decline was similarly observed to be 1.7 years earlier for the TBI+ group (M_{Age} = 67.96, SD = 12.35) relative to the TBI− group (M_{Age} = 69.72, SD = 13.73), this difference was not significant ($F_{(1, 2807)} = 2.33, p = .13$).

Influence of Sex, Race, and Depression on History of TBI as a Predictor of MCI diagnosis

Two logistic regression models were performed to examine the utility of history of TBI as a predictor of a diagnosis of MCI (versus normal cognition), while serially controlling for additional factors that may have a link with cognitive decline (i.e., Model 1 added sex and race; Model 2 added histories of depression, alcohol abuse, and drug abuse). Odds ratios, 95% confidence intervals for odds ratios, and characteristics for each logistic regression model are provided in Table 2. The risk for MCI that was associated with a history of TBI with LOC

was attenuated by history of depression and, to a lesser extent, sex and race, which were significant predictors of MCI diagnosis. Risk for MCI was greatest when individuals were male, older, less educated, from a racial background other than Caucasian/African American, Apoe4 carriers, had several lifetime vascular conditions, and had a history of depression.

Comparison of Model Accuracies in Predicting MCI Diagnosis

Given that the risk for MCI that was associated with a history of TBI with LOC was attenuated by sex, race, and history of depression, ROC analyses were conducted to compare the accuracies of each adjusted model in predicting MCI diagnosis vs normal cognition. Results from these ROC analyses are displayed in Table 3. In brief, ROC results showed each of the adjusted models had similar sensitivities, specificities, and accuracies.

Incremental Value of Sex, Race, and History of Depression on Predicting MCI Diagnosis

The predictive value of the adjusted models was further evaluated using Net Reclassification Improvement (NRI) analyses in order to determine whether the models with additional predictors significantly improved classification accuracy for MCI diagnosis vs normal cognition. NRI analyses revealed that classification accuracies significantly improved when model predictions accounted for the additional predictors (Model 1 vs 2, NRI = 0.03; Model 2 vs Model 3, NRI = 0.01; *p*'s $\leq$.04), indicating that sex, race, and history of

depression significantly improved the classification accuracy for MCI diagnosis vs normal cognition.

Table 1

Main Effects and Interaction for Education Level and History of TBI on Age of Diagnosis of MCI and Estimated Age of Cognitive Decline

	Age of MCI Diagnosis				*Age of Cognitive Decline*			
	M	*SD*	*F*	*p*	*M*	*SD*	*F*	*p*
Main Effect for Education Level			6.35	.01*			2.53	.11
< 12 yrs	75.62	8.96			71.54	12.34		
> 12 yrs	74.17	8.942			69.84	12.04		
Main Effect for TBI Status			7.93	.005*			2.95	.09
TBI +	72.46	8.84			68.58	10.87		
TBI –	74.54	9.65			70.19	12.20		
Interaction for Education and TBI			0.15	.70			0.02	.89
< 12 yrs TBI −	75.77	8.33			71.74	12.59		
< 12 yrs TBI +	74.15	10.01			69.87	9.93		

> 12 yrs TBI −	74.37	8.79	70.00	12.14
> 12 yrs TBI +	72.24	9.58	68.41	10.99

Note. * $p < .05$. Yrs = years of education; TBI = traumatic brain injury with loss of consciousness.

Table 2

Odds Ratios, Confidence Intervals, and Fit statistics for Logistic Regression Models with Additional Predictors

	OR	*95% CI for OR*	*p-value*	*HL p*
Adjusted, Model 1				0.16
Age*	1.03	1.02 – 1.03	<.001	
Education*	0.92	0.91 – 0.94	<.001	
Composite vascular risk score*	1.16	1.11 – 1.20	<.001	
Apoe4 alleles				
1 allele*	1.94	1.73 – 2.17	<.001	
2 alleles*	5.28	4.00 – 6.97	<.001	
Sex, Female*	0.47	0.42 – 0.52	<.001	
Race				
African American	1.11	0.95 – 1.31	.19	
Other, Non-white*	2.10	1.50 – 2.94	<.001	
TBI history**	1.19	0.99 – 1.43	.07	
Adjusted, Model 2				0.11
Age*	1.03	1.02 – 1.04	<.001	

Education*	0.92	0.91 – 0.94	<.001
Composite vascular risk score*	1.15	1.11 – 1.19	<.001
Apoe4 alleles			
1 allele*	1.95	1.74 – 2.18	<.001
2 alleles*	5.39	4.08 – 7.11	<.001
Sex, Female*	0.45	0.41 – 0.51	<.001
Race			
African American**	1.16	0.99 – 1.37	.07
Other, Non-white*	2.19	1.56 – 3.08	<.001
History of Depression*	1.49	1.29 – 1.72	<.001
TBI history	1.14	0.94 – 1.37	.18

Note. * $p < .05$; ** Trend for significance. HL p = Hosmer-Lemeshow statistic p-value; TBI = traumatic brain injury with loss of consciousness; Apoe4 = apolipoprotein E-e4.

Table 3

Comparison of Model Accuracies in Predicting MCI Diagnosis

	AUC	*Cut Score*	*SS% / SP%*	*Accuracy %*
Adjusted, Model 1	0.66	0.486	62 / 63	62
Adjusted, Model 2	0.69	0.513	58 / 70	64
Adjusted, Model 3	0.69	0.495	62 / 67	65

Note. AUC = Area Under the Curve for model predictions; SS/SP = Sensitivity/Specificity for model predictions. Model 1 includes age, education, a composite vascular risk score, number of apolipoprotein E-e4 alleles, and history of traumatic brain injury with loss of consciousness as predictors. Model 2 includes predictors in Model 1 plus sex and race. Model 3 includes history of depression along with predictors in Models 1 and 2.

Study II

Non-Interaction between a History of TBI and History of Depression on Age of Diagnosis of MCI

A multivariate ANCOVA model was used to investigate whether there was an association between a history of TBI, history of depression, and an interaction of both factors on age of diagnosis of MCI. Means and SDs for groups are displayed in Table 4. There was a main effect for both history of TBI ($F_{(1, 2714)} = 10.78$, $p = .001$) and history of depression ($F_{(1, 2714)} = 11.39$, $p = .001$). Specifically, age of diagnosis remained 2.7 years earlier in the TBI+ group compared to the TBI− group. Likewise, subjects with a history of depression were diagnosed with MCI 2.9 years earlier than those without a depression history. However, the interaction of both factors was non-significant ($F_{(1, 2714)} = 1.84$, $p = .17$).

Association between History of TBI and Age of Diagnosis in Non-amnestic MCI subjects

An ANCOVA was performed, controlling for sex differences, to explore the relationship between a history of TBI and age of diagnosis of MCI in non-amnestic MCI subjects (TBI+ n = 51; TBI− n = 433). Results showed that age of diagnosis differed, with the TBI+ group ($M_{Age} = 70.20$, SD = 9.98) being diagnosed on average 2.5 years earlier than the TBI− group ($M_{Age} = 72.76$, SD = 8.55; $F_{(1, 569)} = 4.10$, $p = .04$).

Non-association between History of TBI and CDR-SB scores in Subjects with Non-amnestic MCI

An ANCOVA was performed, controlling for sex differences, to examine the relationship between a history of TBI and CDR-SB scores at time of MCI diagnosis in non-amnestic MCI subjects (TBI+ n = 51; TBI− n = 433). CDR-SB performance did not differ significantly between the TBI+ (M = 0.93, SD = 0.74) and TBI− groups (M = 1.02, SD = 1.01; $F_{(1, 569)} = 1.37$, $p = .24$).

Comparison of Change in CDR-SB scores in Subjects that Progress from Non-amnestic MCI to AD by History of TBI

A one-way mixed ANOVA was performed to explore the relationship between a history of TBI on change in CDR-SB scores across 3 visits in subjects that progressed from non-amnestic MCI to AD (TBI+ n = 11; TBI− n = 96). Mean CDR-SB scores for TBI+/− groups for each time point are displayed in Figure 1. Results revealed that CDR-SB scores significantly increased from the initial visit to visit 3 ($F_{(1.66, 174.61)} = 16.60$, $p < .001$); however, the interaction with history of TBI was non-significant ($F_{(1.66, 174.61)} = 0.46$, $p = .59$).

Associated Risk between History of TBI and Progression from MCI to AD by Sex

Kaplan Meier survival analyses were carried out to examine if a history of TBI predicted progression from MCI to AD when stratified by sex. Results are displayed in Figure 2. A history of TBI did not predict progression from MCI to

AD for females (HR = 0.67; 95% CI = 0.43−1.04; LR χ^2 p = .07) and males (HR = 0.79; 95% CI = 0.59−1.05; LR χ^2 p = .10).

History of Mild and More Serious TBI and Earlier Age of MCI Diagnosis

An ANCOVA was used to explore if age of MCI diagnosis was earlier for subjects with a history of mild (i.e., < 5 mLOC) and more serious (i.e., ≥ 5 mLOC) TBI compared to those without a TBI history, after controlling for sex plus histories of depression and alcohol abuse. Means and SDs for age of MCI diagnosis for the groups are presented in Table 4. Age of MCI diagnosis differed between the groups ($F_{(2, 2698)}$ = 6.11, p = .002), with subjects having a history of mild TBI and more serious injuries being diagnosed with MCI an average of 2.2 and 2.5 years earlier, respectively, than those without a TBI history. However, age of MCI diagnosis did not significantly differ between subjects having a history of mild TBI and those with a more serious injury.

History of Mild and More Serious TBI on Risk for Progressing from MCI to AD

Survival analyses were conducted to explore if there was a dosage effect for a history of mild TBI (i.e., < 5 mLOC) and more serious (i.e., ≥ 5 mLOC) injuries on risk for progressing from MCI to AD. Kaplan-Meier survival analysis revealed that a history of TBI alone was significantly associated with *reduced* risk for progressing from MCI to a diagnosis of AD, with a history of more serious TBI being associated with slower progression, but not a history of mild TBI.

However, adjustment for age of MCI diagnosis attenuated this association. Survival analysis results are displayed in Table 6.

Associated Risk between History of TBI and Progression from MCI to AD by Age Categories

Kaplan Meier survival analyses were performed to investigate whether a history of TBI predicted progression from MCI to AD when stratified by three age categories (i.e., 50−64, 65−80, and >80 years). Results are presented in Table 7. Across all age categories, a history of TBI was a non-significant predictor for progression from MCI to AD.

Associated Risk between History of TBI and Progression from MCI to AD by Education Level

Cox proportional hazard models were conducted to explore if a history of TBI, after adjustment for age of MCI diagnosis, predicted progression from MCI to AD when stratified by education level (i.e., <12, 12, and >12 years). Results are presented in Table 8. While age at MCI diagnosis predicted progression from MCI to AD across all education levels, a history of TBI was consistently a non-significant predictor.

Interaction Between Apoe4 and History of TBI on Progression from MCI to AD

A cox proportional hazard model was performed to examine whether an interaction between Apoe4 and a history of TBI was associated with increased risk for progression from MCI to AD, after adjustment for age of MCI diagnosis.

Results are displayed in Table 9. Age at MCI diagnosis and Apoe4 predicted progression from MCI to AD, but the interaction between Apoe4 and a history of TBI was a non-significant predictor.

Table 4

Main Effects and Interaction for History of TBI and History of Depression on Age of Diagnosis of MCI

	n	*M*	*SD*	*F*	*p*
Main Effect for Depression Status				11.39	.001
Depression −	2,194	74.66	8.46		
Depression +	525	71.72	8.71		
Main Effect for TBI Status				10.78	.001
TBI −	2,471	74.33	8.50		
TBI +	248	71.68	9.05		
Interaction for Education and TBI				1.85	.17
Depression − TBI −	2,023	74.88	8.39		
Depression − TBI +	171	72.09	8.83		
Depression + TBI −	448	71.88	8.56		
Depression + TBI +	77	70.75	9.51		

Table 5

History of Mild and More Serious TBI and Age of MCI Diagnosis

	n	*M*	*SD*
No TBI History	2,471	74.33	8.50
TBI < 5mLOC*	151	72.13	9.60
TBI ≥ 5mLOC*	82	71.75	7.96

Note. * Post-hoc tests between TBI < 5mLOC and ≥5 mLOC were significantly different from those without a history of TBI at $p < .05$. TBI = traumatic brain injury.

Table 6

Hazards Ratios, Confidence Intervals, and Statistics for Survival Analyses by History of Mild and More Serious TBI

	HR	*95% CI for HR*	LR χ^2 *p-value*
Unadjusted Model			
TBI History			.04
< 5 mLOC	0.78	0.58 – 1.05	.10
≥ 5 mLOC	0.64	0.41 – 0.99	.04
Adjusted Model			
Age of MCI Diagnosis	1.03	1.03 – 1.04	<.001
TBI History			.17
< 5 mLOC	0.84	0.62 – 1.12	.23
≥ 5 mLOC	0.71	0.46 – 1.11	.14

Note. HR = hazard ratio; CI = confidence interval; LR = log rank test; TBI = traumatic brain injury with loss of consciousness; mLOC = minutes of loss of consciousness

Table 7

Association between a History of TBI and Risk for Progression from MCI to AD by Age Categories

	n	*Events*	*HR*	*95% CI for HR*	LR χ^2 *p-value*
Aged 50–64 yrs	346	70			
TBI History	50	7	0.64	0.29 – 1.40	.26
Aged 65–80 yrs	1,628	602			
TBI History	136	41	0.82	0.60 – 1.13	.22
Aged >80 yrs	592	287			
TBI History	46	20	0.81	0.52 – 1.28	.38

Note. Events = number of subjects that progressed to AD; HR = hazard ratio; CI = confidence interval; LR = log rank test; TBI = traumatic brain injury with loss of consciousness.

Table 8

Association between a History of TBI and Risk for Progression from MCI to AD by Education Level

	n	*Events*	*HR*	*95% CI for HR*	LR χ^2 *p-value*
< 12 yrs of Education	190	65			
Age*	-	-	1.05	1.02 – 1.09	.001
TBI History	23	7	0.83	0.38 – 1.82	.64
12 yrs of Education	492	190			
Age*	-	-	1.03	1.01 – 1.04	.005
TBI History	34	10	0.90	0.48 – 1.71	.75
> 12 yrs of Education	2,037	761			
Age*	-	-	1.03	1.02 – 1.04	<.001
TBI History	191	56	0.84	0.64 – 1.10	.21

Note. * $p < .05$. Yrs = years; Events = number of subjects that progressed to AD; HR = hazard ratio; CI = confidence interval; LR = log rank test; Age = age at MCI diagnosis; TBI = traumatic brain injury with loss of consciousness.

Table 9

Interaction between Apoe4 and a History of TBI on Risk for Progression from MCI to AD

	n	*Events*	*HR*	*95% CI*	LR *p-value*
Age*	-	-	1.04	1.03 – 1.05	<.001
Apoe4 +*	1,190	564	2.05	1.80 – 2.34	<.001
TBI History	248	73	0.87	0.61 – 1.24	.64
Apoe4 and TBI Interaction	107	40	0.97	0.60 – 1.56	.89

Note. Total n = 2,719. Total events = 1,016. * $p < .05$. Events = number of subjects that progressed to AD; HR = hazard ratio; CI = confidence interval; LR = log rank test; Age = age at MCI diagnosis; Apoe4+ = presence of an apolipoprotein E-e4 Allele; TBI = traumatic brain injury with loss of consciousness.

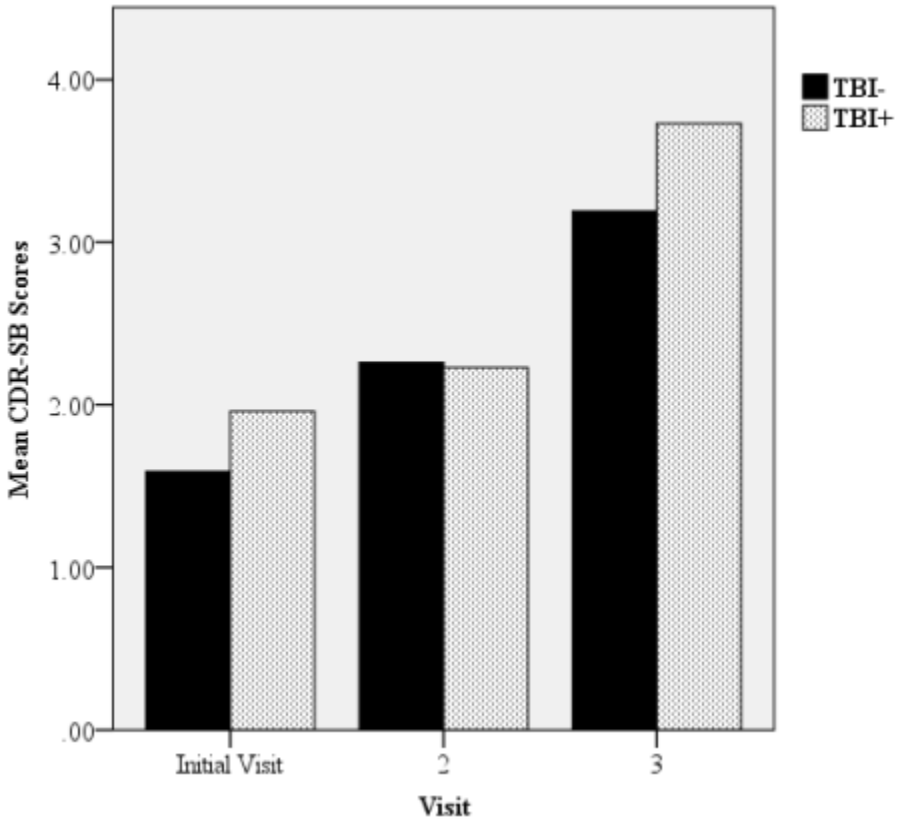
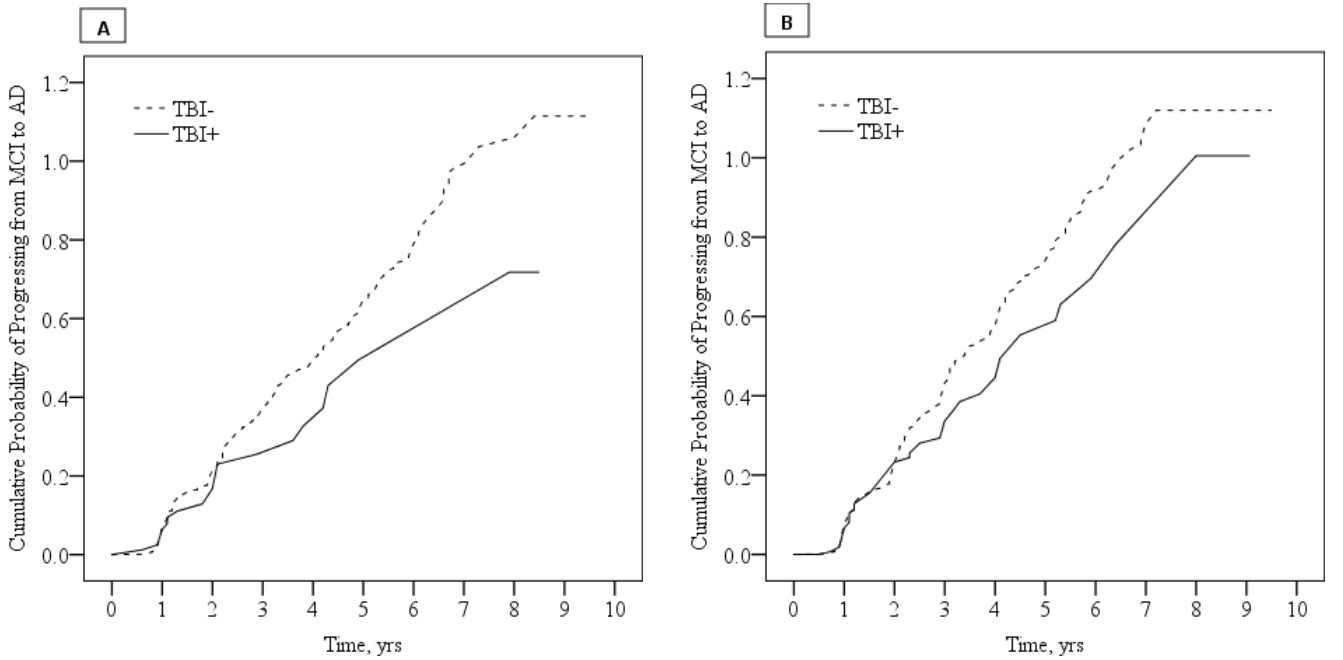


Figure 1. Mean CDR-SB scores across 3 visits in TBI+/− subjects that progressed from non-amnestic MCI to AD. TBI+ = subjects with a history of traumatic brain injury (TBI) with loss of consciousness; TBI− = subjects without a history of TBI.



Number of Female Subjects Alive at Each Time Interval

TBI-	1260	1187	827	535	358	242	152	87	43	9
TBI+	82	78	52	38	25	15	8	2	0	0
Time	0	1	2	3	4	5	6	7	8	9

Number of Male Subjects Alive at Each Time Interval

TBI-	1211	1141	774	488	303	201	127	75	33	7
TBI+	166	149	106	71	50	31	15	11	5	1
Time	0	1	2	3	4	5	6	7	8	9

Figure 2. Risk ratios for progressing from MCI to AD in female (A) and male (B) TBI−/+ subjects over 9 years. MCI = mild cognitive impairment; AD = Alzheimer disease.

SECTION V

Overview of Hypotheses and Summary of Conclusions

TBI has been identified as a risk factor for later development of neurodegenerative disorders, including Alzheimer disease. The mechanistic link between TBI and later cognitive decline is unknown, but it has been hypothesized that TBI triggers a progressive neurodegenerative process, accelerates an already present neurodegenerative disease, or disrupts neuronal/cognitive reserve and interacts with aging. This broad investigation consists of two studies examining the relationship between a history of TBI and the development and progression of MCI using a large national database.

Study I: Hypotheses

Study 1 investigated the hypotheses that a history of TBI would be associated with 1) an increased likelihood of MCI and 2) earlier age of diagnosis of MCI and estimated age of cognitive decline.

Study I: Conclusions

Study 1 results showed that a history of TBI with LOC occurring more than 1 year prior to diagnosis of MCI was associated with an increased risk of MCI, even after adjusting for other factors linked to cognitive decline that have been identified in the literature (e.g., age, education, Apoe4, vascular factors). Specifically, a history of TBI was associated with a 1.35 fold higher risk for a diagnosis of MCI. This increased risk is similar to findings reported in prior

studies with AD. In addition, the findings supported the hypothesis that a history of TBI with LOC would be associated with earlier onset of MCI, as MCI was diagnosed significantly earlier in TBI+ subjects (i.e., nearly 2 years) and a trend was observed for estimated age of cognitive decline. Although the degree of this association differs from a few smaller AD studies reporting that a history of TBI was associated with an approximately 7-9 year earlier onset (Nemetz et al., 1999; Sullivan et al., 1987), it is consistent with a recent large-sample investigation showing individuals with a history of TBI had a nearly 2.5 year earlier onset of AD (LoBue et al., under review). Interestingly, additional analyses revealed that history of depression and, to a lesser extent, basic sociodemographic factors (i.e., sex and race), attenuated the risk for MCI that was associated with a history of TBI. Also, prediction of MCI diagnosis was significantly improved when sex, race, and history of depression were taken into account. Furthermore, neuropsychiatric factors such as history of depression and alcohol abuse attenuated the trend for an earlier age of estimated onset. Therefore, the overall findings provided partial support for the hypotheses, as TBI was associated with an earlier diagnosis of MCI, but its associated risk for developing MCI may be influenced by other factors such as sex and depression.

Study II: Hypotheses

Study 2 examined the hypotheses that a history of TBI would be associated with 1) earlier diagnosis of MCI, 2) an increased risk for progression

from MCI to AD, 3) higher annual rates of progression from MCI to AD, 4) faster time to progression from MCI to AD, and 5) more severe decline on CDR-SB scores among subjects that progress to AD. A 6th hypothesis was also examined: that the strength of the above associations would be greater in subjects having amnestic MCI compared to nonamnestic MCI.

Study II: Conclusions

Study 2 found that a history of TBI with LOC was again linked to an earlier age of diagnosis of MCI, and exploratory analyses revealed this relationship to be independent of a history of depression (see additional analyses). However, a history of TBI was *not* associated with increased risk for progression from MCI to AD. Specifically, a history of TBI did not predict progression from MCI to AD, and annual rates of progression were similar in subjects with a history of TBI (8%) relative to those without (10%). The hypothesis that a history of TBI would be associated with faster progression from MCI to AD was also not supported, as time to progression was similar for TBI+/− subjects in survival analyses, and when examined cross-sectionally, average time to progression was nearly equivalent between TBI+ and TBI− groups. Furthermore, there was no relationship between a history of TBI and rate of cognitive decline among subjects who progressed to AD. The 6th hypothesis, that the strength of the above associations would be greater in subjects having amnestic MCI compared to nonamnestic MCI, could not be fully determined due to the limited number of

non-amnestic MCI cases with a TBI history. At a minimum, it appears that examination of both MCI types (amnestic and nonamnestic) converge on the same findings, i.e., that a history of TBI is associated with a nearly 2.5 year earlier age of diagnosis of MCI, but not greater decline (i.e., CDR-SB scores).

Integrated Conclusions

This two-part investigation shed light on what role TBI may play in later cognitive decline. A history of TBI with LOC does appear to be a risk factor for earlier development of MCI, similar to findings observed in AD. However, a history of TBI with LOC was not associated with *progression* from MCI to AD, suggesting that once the neurodegenerative process for MCI to AD starts, a history of TBI appears unrelated to subsequent decline. Taken together, these findings are consistent with literature studying the effects of other CNS insults on course of cognitive decline in AD, which indicates that cerebrovascular insults may lower the *threshold* for clinical *expression* of AD, but that progressive decline is related to the Alzheimer disease process (Attems & Jellinger, 2014; Gorelick et al., 2011). While this investigation provides evidence that TBI might contribute to a neurodegenerative process by slightly accelerating its *onset* for some individuals, the implications of various TBI characteristics (i.e., severity and time since injury) are unclear and deserve further investigation. Future studies that more comprehensively assess TBI features (e.g. severity, age of injury, repetitive

injuries, etc.) are needed to examine the potential role of these factors in the development and progression of later cognitive decline.

APPENDIX A

Aims and Hypotheses

Overall Aim: Investigate whether a history of TBI has an association with developing MCI and in progressing from MCI to AD.

Study 1

Aim 1: Determine if a history of TBI with LOC is associated with development of MCI.

Hypothesis 1: A history of TBI with LOC will be a significant predictor and associated with an increased risk for MCI diagnosis.

Aim 2: Determine if a history of TBI is associated with earlier onset of MCI.

Hypothesis 2: Age at diagnosis of MCI and estimated age of cognitive decline will be significantly earlier for TBI+ subjects compared to TBI− subjects.

Study 2

Aim 1: Determine if a history of TBI is associated with increased risk for progression from MCI to AD.

Hypothesis 1a: A history of TBI with LOC will be a significant predictor and associated with an increased risk for progression from MCI to a diagnosis of AD.

Hypothesis 1b: TBI+ subjects will have higher annual rates of

progression from MCI to AD than TBI− subjects.

Aim 2: Examine whether a history of TBI is associated with faster progression from MCI to AD.

Hypothesis 2a: Survival analyses will reveal that TBI+ subjects progress faster from MCI to a diagnosis of AD than TBI− subjects.

Hypothesis 2b: A history of TBI with LOC will predict more severe cognitive and functional decline on CDR-SB scores over time in subjects that progress to AD.

Aim 3: Determine if there are differences in the potential associations above based on type of MCI.

Hypothesis 3: TBI+ subjects with amnestic MCI will show a greater likelihood for and faster progression to AD compared to those with nonamnestic MCI.

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