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

Christian LoBue, MS^a, David Denney, MS^a, Linda S. Hynan, PhD^{a,b}, Heidi C. Rossetti, PhD^a, Laura H. Lacritz, PhD^{a,c}, John Hart Jr., MD^{a,c,d}, Kyle B. Womack, MD^{a,c,d}, Fu L. Woon, PhD^a, and DC. Munro Cullum, PhD^{a,c}

^aDepartment of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX

^bDepartment of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, TX

^cDepartment of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, TX

^dCenter for BrainHealth, School of Behavioral and Brain Sciences, University of Texas at Dallas, Dallas, TX

Abstract

This study examined whether history of traumatic brain injury (TBI) is associated with increased risk and earlier onset of mild cognitive impairment (MCI). Subjects with MCI ($n=3,187$) and normal cognition ($n=3,244$) 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 demographics, apolipoprotein E-e4 (ApoE4), a composite vascular risk score, and history of psychiatric factors. 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 ($OR=1.25$; 95% CI = 1.05 – 1.49) and adjusted models, accounting for age, education, ApoE4, and a composite vascular score ($OR=1.32$; 95% CI = 1.10 – 1.58). This association, however, was largely attenuated ($OR=1.14$; 95% CI = 0.94 – 1.37; $p=.18$) after adjustment for reported history of depression. MCI was diagnosed a mean of 2.3 years earlier ($p<.001$) in the TBI+ group, and although TBI+ subjects had an estimated mean of decline 1.7 years earlier, clinician-estimated age of onset failed to differ ($p=.13$) when sex and psychiatric factors were controlled. This is the first report of a possible role for TBI as a risk factor in MCI, but its association may be related to other factors such as sex and depression and requires further investigation.

*Corresponding Author: Christian LoBue, MS, 5323 Harry Hines Blvd., Dallas, TX 75208-8564, 214-422-3760 (cell); 214-648-5297 (fax), Christian.lobue@utsouthwestern.edu.

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Keywords

Traumatic Brain Injury (TBI); Mild Cognitive Impairment (MCI); Age of Onset; Risk Factors

Introduction

Each year, approximately 1.7 million persons sustain a traumatic brain injury (TBI) [1]. While many survive the initial insult, cognitive, psychiatric, and physiological dysfunction often follows and may be transient or persistent, depending in part on injury severity [2]. Whether full recovery is achieved or not, sustaining a TBI has been implicated as a risk factor for later development of neurodegenerative disorders,³ including Alzheimer disease (AD) [3,4], with evidence demonstrating that risk increases with greater length of loss of consciousness [5,6] and severity [7]. In addition, repetitive mild TBIs have been controversially linked to chronic traumatic encephalopathy (CTE) [8,9], and while this link remains in question, recent evidence has shown that mild TBI may invoke a higher risk for dementia [10].

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 neurodegenerative process [11] 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 [12]. As a consequence of diffuse axonal injury, amyloid precursor proteins are suspected of accumulating in the axon and forming amyloid- β (A β) plaques [12], while tau proteins aggregate into neurofibrillary tangles (NFT) [13], both believed to be involved in the pathogenesis of AD [14]. Previous studies have found that within hours of acquiring a single, severe TBI, A β plaques are present in up to a third of severely injured patients, even children [15]. It has also been noted that at autopsy, several years after the initial injury a significant proportion of TBI patients had A β plaques present that were fibrillary or a mixed diffuse/fibrillary pattern, unlike the predominantly diffuse plaques present in normal controls [16]. 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 [17] but were present when patients were examined after at least 1 year post-injury [16]. Additionally, persons who had sustained even a single TBI in that sample had more extensive NFTs and at a much earlier age relative to age-matched controls [16]. 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 A β 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 [18]. While previous research has emphasized the relationship between a history of TBI and AD [6,19,20], 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 of retired athletes [21]. In addition, a recent

finding showed that in a small sample of individuals diagnosed with MCI, those with a history of TBI and loss of consciousness showed greater amyloid deposition than those without, suggesting TBI may be associated with AD-related neuropathology [22]. Similarly, in a meta-analysis of 15 studies examining history of TBI as a risk factor for the later development of AD, Fleminger et al. (2002) found an odds ratio of 1.58, suggesting an increased risk, although the study is rather dated and does not include findings published over the last 12 years [6]. Furthermore, an earlier age of onset has been observed in some studies of patients with dementia [23], but these results have varied widely, ranging from 6 months to 8 years [3,20,24]. It is not known whether an increased risk for cognitive decline or an earlier age of onset may also be associated with 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.

Materials and Methods

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) [25] 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 amnesic or nonamnesic MCI (n = 3187) at the initial visit were selected for examination. Subjects with normal cognition were selected as a comparison group; however, in order to account for the possibility that some subjects may have progressed to MCI/dementia beyond the initial visit, only subjects with three or more visits completed (n = 3244) were included. Cognitive status and clinical diagnosis was determined by ADC clinicians using NINCDS/ADRDA guidelines. A clinical diagnosis of amnesic or nonamnesic 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 lack of neurocognitive impairment and failure to meet published clinical criteria of MCI, dementia, or other neurological conditions. For the present study only data obtained at the initial ADC visit were examined, as follows: age, education, sex, race, number of apolipoprotein E-e4 (ApoE4) alleles, and cigarette smoking history (number of years smoked and average number of packs/day). Age at initial visit corresponded with age of diagnosis for MCI subjects. In addition, clinician-estimated age of onset was examined, and was determined by ADC clinicians via subject/informant report for when cognitive abilities began declining.

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 no current treatment is underway), 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 of any duration and no chronic deficits were included. We attempted to limit potential confounding for cognitive decline that may be directly attributable to a TBI by excluding subjects who reported any history of TBI resulting in chronic deficit/dysfunction (n = 16) or a recent/active TBI (n = 65).

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 [26], and the use of composite vascular risk scores has proven useful in assessing the additive implications of multiple vascular factors on cognitive impairment [27]. 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.

NACC also contains some limited information about histories of depression and substance abuse as obtained via subject/informant report. Subjects are asked if they ever a) had a history of depression occurring >2 years prior to the initial visit and b) 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, taking antidepressant medication, or receiving a mood disorder diagnosis (i.e., major depression, dysthymia, bipolar)*. Like the TBI information, the alcohol and drug abuse questions were coded as absent, recent/active, remote/inactive, or unknown; only remote/inactive histories of alcohol and drug abuse were examined.

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. Four logistic regression models were used, serially controlling for different factors linked to cognitive decline, 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 six other covariates: age, years of education, number of Apoe4 alleles, cigarette smoking history (number of years smoked and average number of packs/day), and composite vascular risk score. Covariates remained in the model if $p < .15$. This was to include variables related to a MCI diagnosis, but to eliminate measures that potentially reduced the fit of the models. A third, adjusted model additionally included sex and race as covariates. A fourth model included all of the significant variables in previous models plus psychiatric conditions (i.e., histories of depression, alcohol abuse, and drug abuse).

The Hosmer-Lemeshow statistic was used to examine the fit of the models to the data. The criterion of an acceptable fit was defined as $p > .10$ and a good fit as $p > .40$.²⁸ Receiver operating characteristic (ROC) analyses compared the area under the curve between pairwise models using the predicted scores from each logistic regression model. 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 [29]. The added predictive value of the adjusted models was evaluated using Net Reclassification Improvement (NRI) analyses based on the ROC cut-scores [30]. This method was used to determine whether models with additional predictors significantly improved classification accuracy for MCI diagnosis vs normal cognition.

Two ANCOVAs 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, cigarette smoking history (number of years smoked and average number of packs/day), vascular risk factors, and histories of psychiatric conditions were compared between the TBI+ and TBI- groups using chi-square or independent samples t-tests. History of drug abuse was not compared due to the limited number of TBI cases reporting a positive history ($n = 9$). Because history of TBI is associated with later development of psychiatric conditions, especially depression [31], variables that differed between the groups were entered as covariates in a stepwise process, first controlling for relevant demographics and secondly, demographics plus medical/psychiatric factors. A Bonferroni correction of $p < .016$ was used to account for multiple comparisons.

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 in order to determine if unequal variances resulted in a Type I error.

Results

The MCI cohort included 3,187 subjects that were 51% female, well educated ($M_{\text{Educ}} = 15.0$, $SD = 3.3$), had a mean age of 74.4 years ($SD = 8.9$), were 84% Caucasian, and possessed approximately two vascular-related conditions on average (Median = 2.0, $SD = 1.5$, range = 0-10). History of TBI with LOC was reported in 10% of those with MCI. Forty-four percent of MCI subjects had no Apoe4 allele, 36% had only one Apoe4 allele, and 8% had two Apoe4 alleles. There were 3,244 normal cognition subjects who, like the MCI cohort, were 86% Caucasian, well educated ($M_{\text{Educ}} = 15.7$, $SD = 2.8$), and possessed approximately two vascular-related conditions on average (Median = 1.0, $SD = 1.3$, range = 0-9). The normal cognition subjects had a higher proportion of women (68%) and were slightly younger (mean age = 72.3 years, $SD = 8.9$) at the initial visit. History of TBI with LOC was reported in 8% of normal cognition subjects, 72% had no Apoe4 allele, 26% had only one Apoe4 allele, and 2% had two Apoe4 alleles. Demographic and psychiatric characteristics for the study samples can be found in Table 1.

Odds ratios, 95% confidence intervals for odds ratios, and characteristics for each logistic regression model can be found in Table 2.

Logistic regression for the unadjusted model showed that a history of TBI alone was a significant predictor for MCI diagnosis (OR = 1.25; 95% CI = 1.07 – 1.51; $p=.01$). However, ROC analysis revealed that TBI history alone did not discriminate between the two groups, as the area under the ROC curve (AUC) was .51 and non-significant ($p=.22$). In the second logistic regression model, age, education, number of Apoe4 alleles, composite vascular score, and history of TBI (OR = 1.32; 95% CI = 1.10 – 1.58) were all significant predictors ($p's <.01$) of diagnosis. Cigarette smoking history (number of years smoked and average number of packs/day) was removed from the model due to the degree of non-significant prediction ($p's = .75$ and $.81$, respectively). When sex and race were included in the third model, there was only a trend for history of TBI (OR = 1.19; 95% CI = .99 – 1.43; $p=.07$), while sex, race, and all of the previous covariates were significant predictors ($p's <.001$) of diagnosis. Further, history of TBI was a non-significant predictor of diagnosis in the fully adjusted model (OR = 1.14; 95% CI = .94 – 1.37; $p = .18$), while history of depression was a significant predictor along with sex, race, age, education, Apoe4 alleles, and a composite vascular score ($p's <.001$). Because of the degree of non-significant predictions for histories of alcohol and drug abuse ($p's = .34$ and $.86$ respectively), these variables were removed from the model. The Hosmer-Lemeshow statistic indicated that all of the adjusted models were an acceptable fit to the data ($p's = .11$; See Table 2). In addition, ROC results showed that for each of the adjusted models, AUCs were .66 and significantly ($p's <.001$) discriminated MCI from normal cognition subjects. Using the cut scores for the adjusted models (Model 2 = .486; Model 3 = .513; Model 4 = .495), the contribution of all the predictors included in each model provided sensitivities 58%, specificities 63%, and accuracies of 62%. NRI analyses revealed that classification accuracies significantly improved when model predictions accounted for additional predictors [Model 1 vs 2, NRI = 0.23; Model 2 vs 3, NRI = 0.03; Model 3 vs Model 4, NRI = 0.01; $p's = .04$], indicating that the fully adjusted model had the greatest classification accuracy.

TBI+ and TBI- groups did not differ by race ($p=.29$), education ($p=.86$), number of years smoking cigarettes ($p=.26$), average number of cigarette packs/day ($p=.06$), 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% vs 38%) and fewer subjects without a history of depression (17% vs 29%) and alcohol abuse (3% vs 9%) than the TBI+ group ($p's <.001$), sex and psychiatric conditions were used as covariates. Controlling for sex only, the TBI+ group ($M_{Age} = 72.2$, $SD = 10.0$) was diagnosed with MCI on average 2.3 years earlier ($p <.001$) than the TBI- group ($M_{Age} = 74.5$, $SD = 9.1$). When controlling for sex plus psychiatric conditions (depression and alcohol abuse), the difference remained statistically significant ($p=.001$). Based on Levene's test ($p's = .01$), the two groups had significantly unequal variances and a Welch's ANOVA was conducted to account 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 ($p <.001$) than the TBI- group. Clinician-estimated age of cognitive decline, controlling for sex, was on average 1.7 years earlier for the TBI+ group ($M_{Age} = 68.0$, $SD = 12.4$) compared to the TBI- group ($M_{Age} = 69.7$, $SD = 13.7$), although this was only a trend ($p=.05$). When sex and psychiatric conditions were controlled, estimated age of cognitive decline failed to differ between the TBI+ and TBI- groups ($p=.13$).

Discussion

A history of TBI with LOC was initially associated with increased odds of a diagnosis of MCI after adjusting for several variables that may have a causal link with cognitive decline; however, this risk was attenuated by history of depression and, to a lesser extent, basic sociodemographic factors (i.e., sex and race). Overall risk for MCI in the present study was greatest when individuals were 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. While previous studies have shown depression symptoms in early- and late- life to be associated with increased risk of cognitive decline and dementia [32], the nature of this relationship is unclear. Approximately 24% of TBI patients in general are found to later develop depression [31], and although a larger percentage of our TBI+ sample (29%) reported a depression history relative to the TBI- group (17%), we do not know if the depression was directly attributable, unrelated, or preceded the injury, since this information is based on a single question (i.e., presence/absence of depression episodes prior to 2 years of visit). In addition, depression symptoms are common in patients diagnosed with MCI and dementia (20-30%) [33,34]. Thus, whether or not depression is caused by other risk factors, a direct result of cognitive decline, the earliest symptoms of neurodegeneration, or is a true risk factor for cognitive decline is unclear and remains an area of investigation [32].

Age of diagnosis was found to be 2.3 years earlier for those with a TBI history among our MCI sample, and while clinician-estimated age of onset was similarly observed to be 1.7 years earlier for the TBI+ group, psychiatric comorbidities attenuated this trend. Late-life depression has been found to be associated with earlier onset of dementia [35], but the reasons for this association remain unclear, as discussed above. Therefore, the overall findings indicate that the risk for MCI that was associated with a history of TBI with LOC may be related to other factors such as sex and depression, though further investigation is needed, as the implications of depression in this equation are unclear and cannot be explored further in the NACC dataset.

Given that MCI is considered a prodromal phase of AD and dementia in general, one would anticipate that TBI history has a similar risk for and association with age of onset in both MCI and dementia. We did find that the level of risk for MCI associated with a history of TBI was comparable to dementia findings (95% CI odds ratios) [6, 7] prior to adjustment for depression and basic sociodemographic factors (i.e., sex and race). Interestingly, many previous dementia studies have not taken psychiatric comorbidities into account when examining TBI as a risk factor [5, 6, 7], suggesting that methodological differences across studies may account for mixed findings. In addition, among previous studies reporting on the association between TBI and earlier dementia onset, limited demographic factors were taken into account, and some reported no association [7,36], while others found that those with a history of TBI developed dementia approximately 6 months [20,37] or 8 years [24] earlier than those without. However, 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 [3], similar to our findings in MCI, even after adjusting for demographic and psychiatric factors such as depression. It follows then that

methodological differences in the literature likely account for a great deal of the mixed findings, including limited cases, reliance on medical records, different criteria for TBI classification, variation in ages at injury, variation in confounding factors, and dissimilar follow-up intervals.

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 [7]. 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, medical, and psychiatric factors [10]. 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 [19]. 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 [21,38]. 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, clinician-estimated age of onset of MCI is subjective, non-specific, and may suffer from biased recall. Moreover, 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 [39], 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 (66%) of those with MCI self-reported a history of mild TBI (i.e., LOC < 5 minutes), TBI severity could not be assessed for many, 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 history of TBI was associated with increased risk for an MCI diagnosis, although this association was attenuated by a reported history of depression. A TBI history was associated with approximately a 2.3 year earlier age of MCI diagnosis, but psychiatric comorbidities also attenuated the trend for an earlier age of clinician-estimated onset of MCI. These associations deserve further investigation as much is still unknown, including the implications of depression. Future research should incorporate tools that more

thoroughly assess TBI features (e.g. severity, age of injury, presence and duration of LOC, posttraumatic symptoms, etc.) and depression in order to identify which factors may be most associated with increased risk for or earlier onset of MCI.

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Table 1
Demographics and Medical History of MCI and Normal Cognition Groups

	<i>MCI (n=3187)</i>	<i>Normal Cognition (n=3244)</i>
Age, <i>M (SD)</i>	74.4 (8.9)	72.3 (8.9)
Education, <i>M (SD)</i>	15.0 (3.3)	15.7 (2.8)
% Female	51	68
% Caucasian	83	86
% APOE ε4 alleles		
0 ε4 alleles	56	72
1 ε4 allele	36	25
2 ε4 alleles	8	2
Composite Vascular Risk Score, <i>M (SD)</i>	1.7 (1.4)	1.3 (1.2)
% History of Vascular Conditions		
Heart Attack	7	4
Atrial Fibrillation	8	6
Angioplasty	8	5
Cardiac Bypass	6	3
Pacemaker	3	2
Congestive Heart Failure	3	2
Stroke	5	2
Transient Ischemic Attack	6	3
Hypertension	55	47
Hypercholesterolemia	55	46
Diabetes	14	9
Number of Years Smoking Cigarettes, <i>M (SD)</i>	10.3 (15.3)	10.1 (15.1)
Average Number of Cigarette Packs/Day		
% No Smoking History	56	55
% < Half Pack	14	16
% Half to 1 Pack	14	14
% 1 to 1.5 Packs	8	8
% 1.5 to 2 Packs	4	4
% 2 Packs	4	3
% History of Depression	18	15
% History of Alcohol Abuse	4	2
% History of Other Substance Abuse	1	1
% History of TBI	10	8

Note. MCI = mild cognitive impairment. TBI = traumatic brain injury with loss of consciousness.

APOE ε4 = apolipoprotein E-ε4.

Table 2
Odds Ratios, Confidence Intervals, and Fit statistics for Logistic Regression Models plus Results from Receiver Operating Characteristics using Model Predictions

<i>Unadjusted Model</i>	<i>OR</i>	<i>95% CI for OR</i>	<i>p-value</i>	<i>HL p</i>	<i>AUC</i>	<i>SS% / SP%</i>	<i>Accuracy %</i>
				---	0.51		
TBI history *	1.25	1.05 – 1.49	.01 *				
<i>Adjusted, Model 2</i>				0.13	0.66	62 / 63	62
Age *	1.03	1.02 – 1.03	<.001 *				
Education *	0.94	0.92 – 0.96	<.001 *				
Composite vascular risk score *	1.20	1.15 – 1.24	<.001 *				
APOE ε4 alleles							
1 ε4 allele *	1.93	1.72 – 2.16	<.001 *				
2 ε4 alleles *	5.26	4.00 – 6.91	<.001 *				
TBI history *	1.32	1.10 – 1.58	.003 *				
<i>Adjusted, Model 3</i>				0.16	0.69	58 / 70	64
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 *				
APOE ε4 alleles							
1 ε4 allele *	1.94	1.73 – 2.17	<.001 *				
2 ε4 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	0.19				
Other, Non-white *	2.10	1.50 – 2.94	<.001 *				
TBI history **	1.19	0.99 – 1.43	0.07 **				
<i>Adjusted, Model 4</i>				0.11	0.69	62 / 67	65

<i>Unadjusted Model</i>	<i>OR</i>	<i>95% CI for OR</i>	<i>p-value</i>	<i>HL p</i>	<i>AUC</i>	<i>SS% / SP%</i>	<i>Accuracy %</i>
				---			0.51
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 *				
APOE ε4 alleles							
1 ε4 allele *	1.95	1.74 – 2.18	<.001 *				
2 ε4 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	0.07 **				
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	0.18				

Note. HL p = Hosmer-Lemeshow statistic p-value. AUC = Area Under the Curve for model predictions. SS/SP = Sensitivity/Specificity for model predictions. TBI = traumatic brain injury with loss of consciousness. APOE ε4 = apolipoprotein E-ε4.

* $p < .05$.

** Trend for significance.

Table 3
Demographics, Age of Diagnosis, and Age of Cognitive Decline in MCI Subjects With and Without TBI

	<i>TBI+ (n=304)</i>	<i>TBI- (n=2883)</i>	<i>p</i>
MCI Age of Diagnosis, <i>M (SD)</i>	72.3 (9.8)	74.6 (8.8)	<.001 *
Estimated Age of Cognitive Decline, <i>M (SD)</i>	68.1 (12.2)	69.8 (13.6)	0.05
Education, <i>M (SD)</i>	15.0 (3.6)	15.0 (3.3)	0.86
% Female	40	52	<.001 *
% Caucasian	86	82	0.29
% APOE ε4 alleles			0.22
0 ε4 alleles	61	56	
1 ε4 allele	34	36	
2 ε4 alleles	6	8	
Composite Vascular Risk Score, <i>M (SD)</i>	1.7 (1.4)	1.7 (1.4)	0.70
% History of Vascular Conditions			
Heart Attack	6	7	
Atrial Fibrillation	11	7	
Angioplasty	8	8	
Cardiac Bypass	4	7	
Pacemaker	3	3	
Congestive Heart Failure	2	3	
Stroke	4	6	
Transient Ischemic Attack	9	5	
Hypertension	53	55	
Hypercholesterolemia	56	55	
Diabetes	14	14	
Number of Years Smoking Cigarettes, <i>M (SD)</i>	11.2 (16.1)	10.2 (15.2)	0.24
Average Number of Cigarette Packs/Day			0.07
% No Smoking History	50	56	
% < Half Pack	13	15	
% Half to 1 Pack	18	14	
% 1 to 1.5 Packs	8	8	
% 1.5 to 2 Packs	6	4	
% 2 Packs	6	4	
% History of Depression	29	17	<.001 *
% History of Alcohol Abuse	9	3	<.001 *
% History of Other Substance Abuse	3	1	--

Note. TBI+ are subjects with history of traumatic brain injury (TBI) with loss of consciousness; TBI- are subjects without TBI.

Age of Diagnosis reflects subjects' age in the initial visit when a diagnosis of MCI was received.

* $p < .05$