Association of self-reported traumatic brain injury with risk factors and brain MRI markers in the Multi-Ethnic Study of Atherosclerosis

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Abstract

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Background: This study sought to characterize patterns of traumatic brain injury (TBI) prevalence in a diverse community-based cohort of older adults, and to evaluate associations of TBI with five measures of interest on magnetic resonance imaging (MRI) of the brain.
Methods and Results: In 2000-2002, the Multi-Ethnic Study of Atherosclerosis enrolled 6814 participants from four race/ethnic groups who were 45-84 years of age and free of clinical cardiovascular disease. In a follow-up examination in 2018-2019 at a mean age of 73 years, 989 participants completed a head injury questionnaire and underwent brain magnetic resonance imaging (MRI). A total of 8.3% reported a history of TBI, defined as a head injury with loss of consciousness or feeling dazed or confused, with higher prevalence for men than for women. TBI prevalence was highest among Hispanic participants (11.6%), and lowest among Chinese-American participants (4.0%). In multivariable models, compared with those with no self-reported head injury, no significant associations were found between TBI and any of five brain MRI measures we evaluated (total white matter volume, total gray matter volume, white

matter hyperintensity volume, white matter fractional anisotropy, and presence of microbleeds) after adjusting for relevant demographic and cardiovascular risk factors.

Conclusions: Patterns of TBI prevalence in this diverse cohort of older adults are similar to those previously reported for White, and Black Americans, though overall prevalence was somewhat lower. The prevalence of reported TBI in Chinese-American participants was low, at 4%. This study did not find evidence of associations between TBI history and the five brain MRI measures of interest.

II. Background

Traumatic brain injury (TBI) is associated with a wide range of both acute and long-term adverse health outcomes (1,2). TBI is now widely considered a chronic condition and is recognized as a risk factor for dementia and Alzheimer's disease (1,3). It is also associated with elevated risk for a wide range of chronic medical conditions in both specialized and general populations, including cardiovascular disease (4), psychiatric conditions, metabolic dysregulation, neuroendocrine dysfunction, and certain chronic neurological conditions (1,5,6). TBI has the potential to both initiate and accelerate the progression of these conditions, with increasing severity of TBI (ranging from mild to moderate to severe) and increased number of events associated with increasing risk (1). Distinct from generalized head injury, TBI is defined as a blow to the head which results in altered mental status, including loss of consciousness (LOC) or a feeling of being dazed and confused (7).

TBI is relatively common in the US (1). According to 2011-2014 National Health and Nutrition Examination Survey (NHANES) data, a self-report of a blow to the head with LOC among adults above 40 years of age in the US had an overall prevalence of 15.7% (95% confidence interval 14.2, 17.2) and was higher among men than women (8). Differences were observed among racial and ethnic groups; TBI was highest among non-Hispanic White respondents, and lowest among non-Hispanic Black respondents (8).

Brain magnetic resonance imaging (MRI) is a useful tool to identify and characterize specific morphological and physiologic changes associated with TBI, and deep learning pipelines have opened up highly efficient avenues for detailed, quantitative reads of large sets of MRI images (9,10). In previous MRI studies, moderate to severe TBI in the chronic phase has been associated with volume loss in white matter (WM) regions in particular, though lower total gray matter (GM) volume was also observed (9,11). Measures of WM integrity are also associated

with TBI. Fractional anisotropy (FA) in the WM allows sensitive assessment of WM integrity, and provides a measure of diffuse axonal injury following TBI (12). Higher WM hyperintensity volume (WMH) has also been associated with chronic TBI in military populations (13). However, a study involving a population-based cohort found associations between TBI and lower WM volume, but found no association with WMH volume or brain microbleeds (14).

While many studies have examined associations between TBI and brain MRI measures, few have been conducted in racially and ethnically diverse community-based cohorts. This analysis leveraged data from the Multi-Ethnic Study of Atherosclerosis (MESA), a community-based cohort study that includes participants from four race/ethnic groups. Between 2018-2019, as part of the MESA Atrial Fibrillation ancillary study, participants were asked about their lifetime history of head injury and about LOC and being dazed or confused following head injury, and a total of 1062 brain MRIs were completed (15). MESA participants with a brain MRI self-identified as Black (25%), Chinese-American (15%), Hispanic (19%), or White (41%). Protocols for the characterization of numerous clinically relevant brain MRI metrics in MESA have been previously outlined (16,17).

The aim of this study was to characterize the prevalence of a self-reported history of TBI in this diverse MESA subpopulation, and to examine associations between such a history and a specified set of MRI measures: total WM volume, total GM volume, total WMH volume, WM FA, and brain microbleeds.

Finally, recent work has identified strong and consistent associations between cardiovascular risk factors (e.g. advanced age, elevated diastolic blood pressure (DBP), smoking) and MRI markers of WM injury (16). Since TBI is also associated with WM injury, we sought to examine

whether a history of TBI modifies established associations between age and brain MRI outcomes.

III. Methods

Participants

This project utilized a subset of data from MESA, a longitudinal cohort study. Data were collected as a part of the ongoing MESA cohort from 6 US field centers located in the following areas: Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota.

From 2000-2002 (baseline, Exam 1), 6814 individuals aged 45-84 who were free of clinically recognized cardiovascular disease were enrolled into MESA. Demographic data were collected at the baseline exam. Five subsequent follow-up exams were performed between 2000 and 2018.

From 2016 - 2018, 1557 MESA participants were recruited at Exam 6 to participate in the Atrial Fibrillation ancillary study. As a part of this study, participants completed a head injury questionnaire by phone, followed by a brain MRI for each eligible participant. A history of head injury was assessed based on questions from this phone interview. The demographic and cardiovascular risk factor data used in this analysis come from Exam 1 (2000-2002) and Exam 6 (2016 - 2018) at which participants were assessed at an in-person clinic visit.

Brain MRI scans for each consenting participant were collected according to the protocol described by Austin et al. (14). Automated deep learning models were applied to process the

scans and quantify the following measures: total and regional GM and WM volumes, total intracranial volume, WMH volume, total WM FA, and brain microbleed count.

Variable definition

The primary exposure of interest was a self-reported history of TBI based on an abbreviated version of a standardized telephone screening questionnaire, the Brain Injury Screening Questionnaire (BISQ) (7). TBI was defined as an answer *yes* to question 1 below, as well as an answer *yes* to either 2a or 2b. Non-TBI head injury was defined as an answer *yes* to question 1, with an answer *no* to 2a and 2b.

1. "In your lifetime, have you ever had a blow to the head in the following situations: in a car crash, hit by an object, due to a fall, in sports, while being assaulted or mugged, or during military service?"

2a. "Did you black out or lose consciousness with any of those head injuries?"

2b. "Were you ever dazed and confused after a blow to the head?"

The primary outcomes of interest were five different brain MRI measures: total WM volume, total GM volume, WMH volume, WM FA, and the presence of microbleeds.

Key covariates included race/ethnicity, sex, age at Exam 6, field center, educational attainment, and several cardiovascular risk factors known to be associated with the brain MRI outcomes: systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), diabetes status, use of hypertension medication, smoking status, and high-density lipoprotein (HDL), low-density lipoprotein (LDL), and diabetes status (16). At Exam 6, a certified technician measured SBP and DBP up to 3 times, and the 2nd and 3rd measurements were averaged. Trained personnel measured participants' height and weight, which were used to calculate BMI (in

kg/m^2). Participants' serum specimens were used to obtain measurements of HDL, and LDL was estimated using the Friedewald equation (18).

Analysis

We described the prevalence of self-reported TBI by demographic and other characteristics, including sex, race/ethnicity, age, highest educational attainment, family income, and certain cardiovascular risk factors including BMI, SBP, DBP, diabetes, smoking, and use of hypertension medication.

Multivariable logistic regression was used to estimate odds ratios for the association between several predictor variables (sex, age, race/ethnicity, and educational attainment) and a self-report of TBI (vs no head injury), treating TBI as the outcome in this model.

We used multivariable linear regression to assess the association of TBI history (vs no history of head injury) with brain MRI volumes and WM FA. All analyses involving volumetric brain measures were adjusted for total intracranial volume. Because the presence of microbleeds was common (present in about a third of MESA participants) and thus the odds ratio does not provide a good estimate of the risk ratio, the analysis of TBI history in relation to presence of microbleeds was conducted using multivariable Poisson relative risk regression with robust standard errors (17,19). A minimally adjusted model (Model 1) adjusted for age, sex, race/ethnicity, and MESA site. A second model (Model 2) additionally included adjustment for BMI, smoking status, SBP, DBP, use of antihypertensives, HDL, LDL, and diabetes status. A third model (Model 3) additionally included educational attainment. Family income was not utilized due to high missingness.

WM FA was reported as difference in SD units. Since WMH volume was highly right skewed, a natural log transformation was utilized for analysis. Regression results were expressed as the percent difference in WMH volume associated with the binary TBI exposure, based on the geometric mean ratio (16).

Finally, we assessed whether there was effect modification by history of TBI in the relationship between age and each of the MRI measures. Effect modification was assessed on the additive scale, using models containing the variables from model 3 above.

Power

Power calculations performed prior to the analysis estimated that this analysis had 82% power to find an association of TBI with a 23 mL difference in total GM volume. As a reference point, previous work in this MESA cohort identified a 17.6 mL difference in GM volume associated with 5-years older age (16).

IV. Results

During 2016-2018, 1557 participants enrolled in the MESA Atrial Fibrillation Ancillary study. The head injury questionnaire was completed and a total of 1062 brain MRIs were completed 1 to 2 years later. Of these, 26 were excluded due to image quality control issues, for a total of 1036 participants with complete MRI measures. We took a complete case analysis approach, additionally excluding 47 participants with missing head injury, demographic, or cardiovascular risk factor data for a total of 989 participants (Figure 1).

Association of TBI and non-TBI head injury with participant characteristics

Overall, 8.3% of the sample (N = 989) had a self-reported lifetime history of TBI. Differences were observed by both sex and race/ethnicity. Among males, 10.9% had a history of TBI, while among females the prevalence of TBI was 5.9%. TBI prevalence was highest among Hispanic participants (11.6%) and lowest for Chinese-American participants (4.0%). TBI prevalence was 5.8% for Black participants and 9.8% for White participants.

At the time of Exam 6, participants with TBI were on average 3 years younger (mean = 70 years) than those reporting a non-TBI head injury or no head injury. Among those with a head injury of any kind, the median age at first head injury was 20 years, and the median age of the most recent head injury was 36 years (Figure 2). The distribution of ages at head injury showed a peak in the teenage/young adult years and another peak at ages greater than 50 years. Among those with a head injury of any kind, 73% reported a single head injury, 17% reported two episodes of head injury, and 10% reported more than two episodes.

Across income groups, those reporting TBI were more likely to be in the high family income group (earning >$100,000), and less likely to be in the low income group (earning < $25,000) compared to those without TBI. Those with TBI were also more likely to have higher levels of educational attainment.

Cardiovascular risk factors were similar across head injury groups. Those with TBI had on average slightly lower systolic blood pressure (mean = 122 mmHg) compared to the non-head injury group (mean = 127 mmHg). Use of hypertension medication was on average slightly lower among those with TBI (54%) compared to those reporting no head injury (60%). Those with TBI also had a lower prevalence of diabetes (18%) compared to the no head injury group (22%). HDL was on average slightly lower for the TBI group compared with the non-head injury

group while LDL was slightly higher for the TBI group compared with the non-head injury group. Cigarette use, diastolic blood pressure, and BMI were similar across all groups.

In results from the logistic regression model for the association of demographic characteristics with TBI compared with no head injury, males had a higher odds of reporting TBI (vs no head injury) than females (OR = 2.05; 95% CI: 1.25, 3.37, p = 0.004) when adjusting for age, race/ethnicity, and education (Table 2). Chinese-American participants had lower odds of reporting TBI than White participants (OR = 0.35; 95% CI: 0.14, 0.87, p = 0.02).

Association of TBI with brain MRI measures

Summary statistics of the five MRI measures in the overall study population are shown in Table 3.

In our multivariable models, no significant associations were found between TBI (vs those without a self-reported head injury of any kind) and any of the five brain MRI measures, after adjusting for the demographic and cardiovascular risk factors described above (Table 4).

Effect modification analysis

As previously reported (16), age was significantly associated with each of the five MRI measures in our multivariable models. There was no evidence of effect modification by TBI status on the relationship between age and WM volume, GM volume, WMH volume, WM FA, or microbleed presence (in all models, p > 0.09 for interaction term).

V. Discussion

In this multiethnic cohort of nearly 1000 older adults, the overall prevalence of self-reported lifetime history of TBI was 8.3%. Prevalence of TBI was higher among males (10.9%) than

among females (5.9%), and was highest for Hispanic (11.6%) participants and lowest for Chinese-American participants (4.0%). Men had 2.1-fold higher odds of reporting TBI (vs no head injury) than females when adjusting for age, race/ethnicity, and education. In our multivariable models, no significant associations were found between TBI history and the five MRI measures of interest (total GM volume, total WM volume, MMH volume, WM FA, and microbleeds).

Strengths and limitations

Several important limitations should be considered when interpreting results. First, this study is subject to a strong selection bias. The subset of MESA participants who participated in the Atrial Fibrillation ancillary study and went on to have a brain MRI were generally healthy and excluded those who died prior to Exam 6. Among those who were a part of the ancillary study, 495 were unable to participate in the brain MRI due factors like poor health, having a metal implant, inability to lie flat, claustrophobia, death, or having moved from the study area (14). These selection pressures are essential to keep in mind when interpreting results. In general, patients with more health complications were less likely to participate in the brain MRI. Since such complications could potentially be associated with a history of head injury, participants with more severe complications from a history of TBI may not be included in our sample and results. This selection bias could affect our estimates of TBI prevalence and might attenuate associations between TBI and the five MRI measures.

The study is also limited by reliance on self-report for the head injury variable. Participants were part of an aging cohort (mean age 73), and recall may be limited, particularly for head injuries sustained at a young age. Different populations may remember or assign significance differently to TBI and other head injury events. Additionally, our methods of assessing lifetime history of TBI did not distinguish between severity of TBI (mild vs moderate vs severe). Associations

between TBI and brain MRI measures have been shown to vary substantially with changing TBI severity (20).

Of note, those reporting TBI in this analysis were on average several years younger than those reporting no head injury, and were correspondingly slightly healthier in terms of the cardiovascular risk factors examined. This could reflect differences in reporting rather than differences in true TBI prevalence for different age groups, potentially related to more recent awareness about the significance of head injury among younger participants, or generally better recall among younger participants.

Strengths of our analysis include the multiethnic nature of this population, which helps to support the generalizability of our findings. The use of a standardized head injury questionnaire lends validity to our measurement of TBI (7). Our use of automated detection for each brain MRI measure made possible the efficient analysis of a large set of images, and has been demonstrated to provide improved accuracy and precision compared to manual reads (10). This study adjusted for a comprehensive set of confounders, which were rigorously assessed in MESA.

Descriptive Analysis

Patterns of TBI were similar to those previously reported, with higher prevalence for men, and lower prevalence for Black participants compared with White participants (8). However, overall prevalence of TBI by self-report was substantially lower in our cohort than in previous work. In the 2011 – 2014 NHANES cohort, the prevalence of self-reported head injury meeting the definition for TBI among US adults 40 years of age or older was 15.7% (95% CI: 14.2 to 17.2). This is a marked difference from our estimate of 8.3% prevalence among a cohort of older adults. In the Health and Retirement Study, a longitudinal cohort of older adults, nearly 13%

experienced incident TBI during an 18-year study period (21). Compared to the 8.3% self-reported lifetime prevalence found in our study, those estimates are higher, possibly related to the selection bias discussed above. Of interest, TBI prevalence was higher in men than women in both MESA and NHANES, but TBI incidence in the Health and Retirement Study was somewhat higher for women than for men (21). In our analysis, we observed that those with TBI were more likely to have higher educational attainment and higher income, which is in alignment with findings from the Health and Retirement study (21).

Association of TBI with brain MRI measures

While smaller studies involving mild-moderate TBI have shown associations between TBI and total GM and total WM volume, these associations were not evident in our population-based study of older adults. In previous work, brain MRI has shown distinctive patterns of progressive brain atrophy following moderate to severe TBI in the chronic phase, distinct from both Alzheimer's disease and healthy brain aging (9). TBI has been associated with widespread progressive tissue volume loss, occurring in both the acute and chronic phase (11). TBI-specific changes involve atrophy of both WM and GM, though volume loss is most pronounced in WM regions, particularly central WM structures including the corpus callosum, internal capsule, and corticospinal tracts (9,11). Total WM volume, which is associated with axonal injury, had pronounced associations in previous work (11). Lower total GM volume was strongly associated with dementia but weakly associated with TBI (9). These associations were not captured in our findings, perhaps in part due to the limitations described, including the likelihood that the TBI events present in our cohort may have reflected predominantly mild TBI.

Other measures of WM tissue health similarly were not associated with TBI in this study. WMH volume - a measure of white matter injury burden - is strongly associated with vascular disease of the brain but findings have been mixed for associations with TBI (13,14). A previous

population-based cohort (3C Dijon) found associations between TBI and lower WM volume, but found no association with WMH or brain microbleeds (14). Another study among military members with TBI found a high incidence of WMH lesions, but relatively low incidence of brain microbleeds (13). In another study, those with TBI had higher WMH volume, and WMH volume increased with increasing severity of TBI (20).

We similarly found no significant associations with WM FA, a measure of white matter integrity which characterizes the degree to which water diffusion is constrained to a single dimension (12). Regional changes in FA have been previously associated with TBI in military populations, but findings have varied by brain region and population (22).

The presence of brain microbleeds is associated with cerebral small vessel disease, but is less strongly associated with TBI in past work (14,23). Our analysis found no significant associations between TBI history and brain microbleeds.

Clinical and research implications

TBI is a relatively widespread experience among diverse older adults, but this prevalence was lower in MESA compared to the prevalence reported in other studies. While the broad health consequences of TBI have been well-established, with the methods used in this study we did not detect significant associations between TBI history and the five brain MRI measures of interest.

VI. Figures and Tables

Figure 1. Analysis inclusion diagram

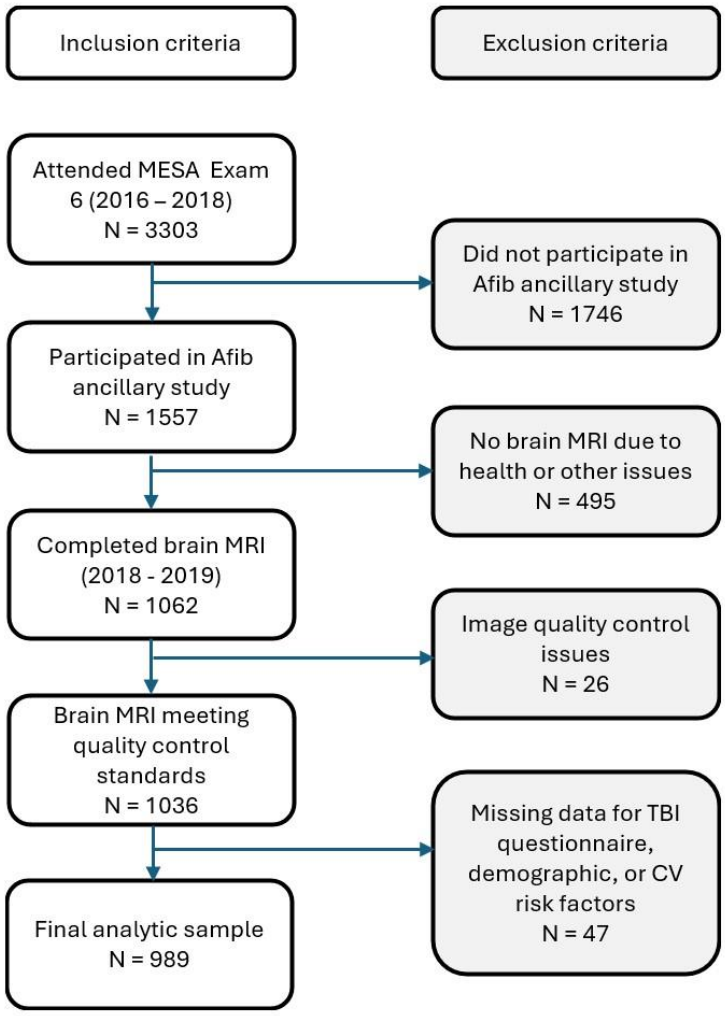

Figure 2. Histograms of age at first head injury and at most recent head injury, among participants reporting head injury of any kind

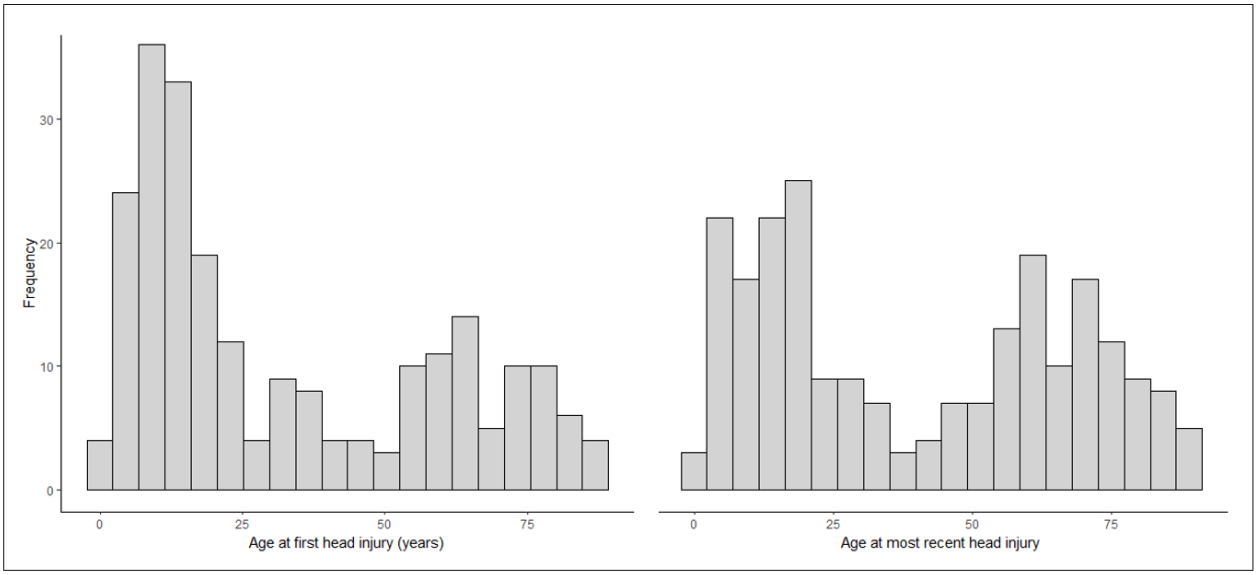

Table 1. Characteristics of MESA participants at Exam 6*

Characteristic	Exam 6, completed brain MRI							
	Total N = 989		TBI n = 82		Non-TBI head injury n = 148		No head injury n = 759	
Sex, n (%)								
Female	522	(53)	51	(38)	67	(45)	424	(56)
Male	467	(47)	31	(63)	81	(55)	335	(44)
Race/ethnicity, n(%)								
Black	243	(25)	14	(17)	25	(17)	204	(27)
Chinese-American	149	(15)	6	(7)	13	(9)	130	(17)
Hispanic	199	(20)	23	(28)	46	(31)	130	(17)
White	398	(40)	39	(48)	64	(43)	295	(39)
Age, years, mean (SD)	73	(8)	70	(7)	73	(8)	73	(8)
Income, n (%)**								
< $25,000	222	(23)	13	(16)	33	(23)	176	(24)
$25,000 - $49,999	236	(25)	19	(24)	37	(26)	180	(25)
$50,000 - $99,999	293	(31)	25	(31)	45	(32)	223	(31)
> $100,000	198	(21)	23	(29)	27	(19)	148	(20)
Education, n (%)								
< High school graduate	112	(11)	7	(9)	20	(14)	85	(11)
High school graduate	311	(31)	20	(24)	48	(32)	243	(32)
Technical school	79	(8)	8	(10)	14	(10)	57	(8)
College degree	262	(27)	24	(29)	36	(24)	202	(27)
Graduate degree	225	(23)	23	(28)	30	(20)	172	(23)
Cardiovascular risk factors								
Systolic BP, mm Hg, mean (SD)	127	(20)	122	(17)	126	(19)	127	(21)
Diastolic BP, mm Hg, mean (SD)	69	(10)	69	(11)	68	(10)	69	(10)
Cigarette use, n (%)								
Never	479	(48)	39	(48)	68	(46)	372	(49)
Former	456	(46)	41	(50)	76	(51)	339	(45)
Current	54	(6)	2	(2)	4	(3)	48	(6)
BMI, kg/m^2, mean (SD)	28.0	(5.4)	28.0	(5.2)	27.9	(5.1)	28.1	(5.4)
Antihypertensive use, n (%)	579	(59)	44	(54)	79	(53)	456	(60)
Diabetes, n (%)	212	(21)	15	(18)	31	(21)	166	(22)
HDL cholesterol, mg/dL, mean (SD)	61	(18)	57	(16)	61	(18)	60	(19)
LDL cholesterol, mg/dL, mean (SD)	107	(35)	113	(38)	103	(37)	107	(34)

*BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein

**Income values reflect 40 missing observations for this variable

Table 2. Multivariable associations between demographic characteristics and TBI in logistic regression model with participants reporting no head injury as the reference group

Characteristic	Odds ratio (95% CI)	p-value
Male sex	2.05 (1.25, 3.37)	0.004
Age (per 5 years older)	0.83 (0.71, 0.96)	0.01
Race/ethnicity		
White	ref	ref
Black	0.59 (0.30, 1.16)	0.13
Chinese-American	0.35 (0.14, 0.87)	0.02
Hispanic	1.68 (0.88, 3.19)	0.12
Education		
< High school graduate	ref	ref
High school graduate	1.18 (0.46, 3.00)	0.73
Technical school	1.97 (0.63, 6.19)	0.25
College degree	1.66 (0.64, 4.31)	0.29

Table 3. Summary statistics of brain MRI measures in MESA participants (N = 989)*

Brain MRI measure	
Total gray matter volume, mL, mean (SD)	596 (65)
Total white matter volume, mL, mean (SD)	495 (56)
Total WHM volume, mL, median (IQR)	2.8 (1.1, 7.5)
White matter fractional anisotropy, mean (SD)	0.39 (0.03)
Presence of microbleed(s), %	34

*WHM, white matter hyperintensity

Table 4. Associations between TBI and brain MRI measures in multivariable models*

Brain MRI measure	Model 1	Model 2	Model 3
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Total gray matter volume (mL difference)	2.1 (-4.7, 9.0)	1.3 (-5.4, 8.0)	1.1 (-5.7, 7.8)
Total white matter volume (mL difference)	0.48 (-4.6, 5.5)	0.31 (-4.7, 5.4)	0.34 (-4.8, 5.5)
Total white matter hyperintensity volume (% difference)	-6.2% (-29.9%, 25.6%)	-3.1% (-27.1%, 28.9%)	-2.5% (-26.8%, 29.7%)
White matter fractional anisotropy (SD units difference)	0.12 (-0.11, 0.34)	0.07 (-0.14, 0.28)	0.09 (-0.13, 0.31)
Microbleeds (risk ratio)	1.00 (0.69, 1.44)	1.02 (0.71, 1.48)	1.03 (0.72, 1.48)

*Model 1 adjusted for age, sex, race/ethnicity, total intracranial volume (for volumetric measures), and MESA site.
*Model 2 additionally adjusted for covariates in model 1 and BMI, smoking status, SBP, DBP, use of antihypertensives, LDL, HDL, and diabetes status.
*Model 3 additionally adjusted for covariates in model 2 and educational attainment

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