**ARIC Manuscript Proposal #3978**

**PC Reviewed: 12/14/21** **Status: _____** **Priority: 2**
**SC Reviewed: _____** **Status: _____** **Priority: ____**

**1.a. Full Title**: Associations between Head Injury and Mild Behavioral Impairment (MBI) Domains Across the Cognitive Spectrum

**b. Abbreviated Title (Length 26 characters)**: Cognition, Head Injury, and MBI

**2. Writing Group**:
Writing group members:

| | |
|---|---|
| Nicholas O. Daneshvari (co-first author) | Johns Hopkins University |
| Andrea L.C. Schneider (co-first author) | University of Pennsylvania |
| Lisa Richey | Johns Hopkins University |
| Michael J.C. Bray | Johns Hopkins University |
| Rebecca Gottesman | NIH/NINDS |
| Thomas Mosley | University of Mississippi |
| Keenan Walker | NIH/NIA |
| Matthew Peters (senior author; corresponding author) | Johns Hopkins University |

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __NOD___ **[please confirm with your initials electronically or in writing]**


**First author**: Nicholas Omid Daneshvari
Address: 5300 Alpha Commons Drive, Office 446
Baltimore, MD 21224

Phone: 818-454-2262
E-mail: ndanesh3@jhmi.edu


**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).


**Name:** Andrea L.C. Schneider, MD, PhD

**Address:** Department of Neurology, Division of Neurocritical Care
University of Pennsylvania Perelman School of Medicine
51 North 39th Street, Andrew Mutch Building 416
Philadelphia, Pennsylvania 19104

Phone: 443-827-2352
Fax: 215-662-9858
Email: Andrea.Schneider@pennmedicine.upenn.edu

**3. Timeline**:
Data for analyses are currently available. Data analysis, conference abstract submission, and manuscript preparation and submission will take place over one year from manuscript proposal acceptance (2021-2022).

**4. Rationale**:

A growing body of literature suggests that traumatic brain injury (TBI) may contribute to neuropathological changes consistent with dementia syndromes such as Alzheimer's disease (AD), frontotemporal dementia, Parkinson's disease, among others [1–3]. TBI may exert detrimental effects regardless of age, though it appears that TBI suffered during older adulthood may confer greater dementia risk [4]. With this context in mind, remote TBI may also stand to influence the progression from normal cognition to dementia, though the mechanism requires further study and remains an important area of ongoing investigation among the growing population of older adults.

TBI and its sequelae may contribute additional complexity to the clinical picture of dementia progression. Perhaps due to overlapping symptomatology, previous TBI may contribute to dementia misdiagnosis, with one study demonstrating that TBI history is associated with an elevated rate of false positives for clinician-diagnosed AD [5]. This complexity is further compounded by growing evidence that TBI alters the phenotype of neuropsychiatric symptoms (NPS) experienced by patients during the progression to all-cause dementia [6,7], though these NPS may further confound dementia diagnoses, particularly regarding chronic traumatic encephalopathy [8]. While a large proportion of patients experience NPS prior to dementia diagnoses [9], patients with prior TBI appear to have an elevated risk of apathy and motor disturbances, as well as earlier onset of anxiety symptoms compared to those patients without [6]. Collectively, these findings suggest TBI may introduce underlying vulnerabilities or functional disruption among underlying neural networks in some individuals. As such, the manner in which TBI affects neuropsychiatric symptomatology throughout dementia progression represents a strong priority for ongoing research and may help elucidate these underlying neuropathological changes.

The construct of mild behavioral impairment (MBI) may prove particularly useful in relating NPS to TBI which share underlying neural circuit disruption. MBI refers to the onset of persistent NPS emerging later in life that are not better explained by a common psychiatric disorder such as major depression, in the absence of dementia [10]. The MBI construct and associated diagnostic criteria were first addressed by the International Society to Advance Alzheimer's Research and Treatment in 2012, with the intent of more clearly defining the relationship between MBI, mild cognitive impairment (MCI), and subsequent dementia [10]. The culmination of these efforts in 2016 led to diagnostic criteria and division into five domains. The MBI checklist has been developed as a means of defining and quantifying MBI symptoms and improving case detection [11]. The five MBI domains include decreased motivation, affective dysregulation, impulse dyscontrol, social inappropriateness, and abnormal perception/thought content [11]. Each domain is associated with specific NPS. For example, agitation, irritability, and aberrant motor behavior fall under the impulse dyscontrol MBI domain. Although a construct originally developed for classification of pre-dementia symptomatology, given that the MBI domains link individual NPS to underlying neural circuit disruption, we believe these same domains have utility when looking at NPS across the course of dementia.

TBI may affect certain MBI domains more than others. Damage to the orbitomedial frontal circuit may lead to MBI characterized by social inappropriateness and impulse dyscontrol. Damage to the anterior cingulate circuit may result in MBI with decreased motivation. By contrast, damage to the dorsolateral prefrontal circuit may result in more cognitive symptoms and fewer behavioral ones. Hence, the relationship between TBI and MBI in all-cause dementia may be influenced by the specific disrupted pathway.

In Dr. Peters's previous work (currently under journal review) using National Alzheimer's Coordinating Center data, individuals progressing from normal cognition to all-cause dementia were studied to estimate MBI incidence and symptom domains in participants with prior TBI. TBI was associated with greater incidence of the impulse dyscontrol and social inappropriateness MBI domains prior to dementia onset, as well as greater incidence of MBI (any domain) and the decreased motivation domain looking across dementia progression. This writing group additionally has an existing ARIC MSP (#3916), which aims to examine NPS and MBI domains by head injury status within the ARIC cohort regardless of cognitive status to investigate associations of remote head injury with NPS and MBI domains. To expand on the growing literature and this previous work, in this proposal, we aim to examine NPS and MBI domains in ARIC participants with and without prior head injury across the cognitive spectrum (from normal cognition to MCI to dementia).

**5. Main Hypothesis/Study Questions**:

Aim 1 (Primary Analysis): To investigate the cross-sectional associations of prior head injury with NPS/MBI prevalence by cognitive status (i.e., normal cognition, MCI, and all-cause dementia).

Hypothesis 1: We hypothesize that prior head injury will be associated with certain MBI construct domains, namely decreased motivation, impulse dyscontrol, and social inappropriateness and that the associations of prior head injury with these MBI domains will strengthen across the cognitive spectrum (i.e., stronger association among individuals with MCI than normal and among individuals with dementia than among individuals with MCI).

Aim 2 (Secondary Analysis): To examine the prospective associations of prior head injury and NPS/MBI domain positivity with risk of dementia.

Hypothesis 2: We hypothesize that individuals with prior head injury with NPS/MBI domain positivity will have greater risk of dementia compared to individuals without head injury and to individuals with head injury and without NPS/MBI domain positivity.

**6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

***Study Design***.
Aim 1: Cross-sectional analysis using data from ARIC visit 5.
Aim 2: Prospective analysis using data from ARIC visits 5 to 7.

***Inclusion/Exclusion.***
In both aims, we will include White and Black participants (White participants from Minnesota, Maryland, North Carolina; Black participants from North Carolina, Mississippi) with non-missing data on head injury (defined below) whose informants completed the Neuropsychiatric Inventory Questionnaire (NPI-Q) in Stage 2 at Visit 5. We will exclude participants with missing information on cognitive status or covariate data (see below). In aim 2, participants with a diagnosis of dementia at ARIC visit 5 will additionally be excluded.

***Exposures.***

***Cognitive Status***. At in-person ARIC Visit 5, 6, and 7, cognitive status was categorized as normal, MCI, or dementia using information from proxy interviews, change in cognitive scores on 3 cognitive tests administered at prior study visits, the Mini-Mental State Examination, the Clinical Dementia Rating (CDR) form, the Functional Activities Questionnaire (FAQ), and *Z* scores from a full battery of 10 neuropsychological tests. An algorithmic diagnosis was assigned, and an expert committee reviewed the algorithmic diagnosis and assigned final cognitive status as normal cognition, MCI, or dementia. These definitions and questionnaire data have previously been used to study cognition in the ARIC cohort [12-13].

***Head Injury Occurring Prior to ARIC Visit 5***. Head Injury will be defined using a combination of self-reported data (from Visits 3, 4, 5, and the brain MRI visit) and ICD-9/10 code data from hospitalizations (ARIC hospitalization surveillance; Centers for Medicare and Medicaid Services [CMS] Fee-for-Service [FFS] data) and emergency department visits (CMS FFS data). As secondary exposures, we will also consider the number of prior head injuries (0; 1; 2+) and in the subset identified using ICD-9/10 code data, head injury severity (mild; moderate/severe). This definition has been used previously in the ARIC cohort (see below for self-reported questions and ICD-9/10 codes) [14-15]. At the time of ARIC Visit 5, approximately 25% of participants have a history of prior head injury.

Self-reported head injury questions.

| |
|---|
| **ARIC Visit 3 (1993-1995)**<br>1. Have you ever had a head injury which led you to see a physician or seek hospital care?<br>2. How many times has this happened?<br>3. How many of these head injuries resulted in your losing consciousness, no matter how briefly?<br>4.In what year was your head injury for which you sought medical care? |
| **ARIC Visit 4 (1996-1998)**<br>1. Have you ever had a major head injury? That is, one that resulted in your losing consciousness, no matter how briefly, or that led you to see a physician or seek hospital care?<br>2. How many times has this happened?<br>3. How many head injuries resulted in your losing consciousness, no matter how briefly?<br>4. In what year was your head injury for which you lost consciousness sought medical care? |
| **ARIC Brain MRI Visit (2004-2006)***<br>1. Have you ever had a head injury that resulted in loss of consciousness (knocked out)?<br>2. How many times?<br>3. In what year or how old were you when this first occurred? |

| |
|---|
| 4. In what year or how old were you when this last occurred? |
| **ARIC Visit 5 (2011-2013)*** |
| 1. Have you ever had a head injury that resulted in loss of consciousness? |
| 2. Have you had a head injury with extended loss of consciousness (>5 minutes)? |
| 3. Have you had a head injury that resulted in long-term problems or dysfunction? |
| **ARIC Visit 6-7+ (2016-2017 and 2018-2019)** |
| 1. Have you ever had a head injury that resulted in loss of consciousness? |
| 2. Have you had a head injury with extended loss of consciousness (>5 minutes)? |
| 3. Have you had a head injury that resulted in long-term problems or dysfunction? |

*Questions asked in a subgroup of ARIC participants selected for brain magnetic resonance imaging (MRI) scans.

ICD-9 and ICD-10 codes used to define head injury.

| **ICD-9 Codes** | |
|---|---|
| 800.xx | Fracture of vault of skull |
| 801.xx | Fracture of base of skull |
| 803.xx | Other and unqualified skull fractures |
| 804.xx | Multiple fractures involving skull or face with other bones |
| 850.xx | Concussion |
| 851.xx | Cerebral laceration and contusion |
| 852.xx | Subarachnoid, subdural, and extradural hemorrhage following injury |
| 853.xx | Other and unspecified intracranial hemorrhage following injury |
| 854.xx | Intracranial injury of other and unspecified nature |
| 959.01 | Head injury, unspecified |
| | |
| **ICD-10 Codes** | |
| S02.0 | Fracture of vault of skull |
| S02.1X | Fracture of base of skull |
| S02.8 | Fractures of other unspecified skull and facial bones |
| S02.91 | Unspecified fracture of skull |
| S04.02 | Injury of optic chiasm |
| S04.03X | Injury of optic tract and pathways |
| S04.04X | Injury of visual cortex |
| S06.X | Intracranial injuries, concussion, traumatic cerebral edema, diffuse and focal traumatic brain injury, traumatic epidural, subdural, and subarachnoid hemorrhage |
| S07.1 | Crushing injury of skull |

***Outcomes***.

*Neuropsychiatric Symptoms.* Late-life psychiatric and behavioral changes were measured using the Neuropsychiatric Inventory Questionnaire (NPI-Q). The NPI-Q was obtained via informant report from participants who were selected for Stage 2 Assessment at ARIC Visit 5. The NPI-Q measures the presence and severity of depression, apathy, agitation, delusion, hallucination,

anxiety, euphoria, disinhibition, irritability, aberrant motor behavior, sleep, and eating/appetite. NPS presence will be a binary variable (no symptom [0] versus yes symptom [1-3]); however, we will also look at the severity of each NPI-Q symptom (rated on scale of 0 to 3) and total NPI-Q symptom severity range (0-36).

***Mild Behavioral Impairment.*** NPI-Q symptoms will also be mapped to subdomains consistent with mild behavioral impairment (MBI) subdomains operationalized by the International Society to Advance Alzheimer's Research and Treatment-Alzheimer's Association (ISTAART-AA) research diagnostic criteria (see below) [10].

**TABLE 1. NPI Domain to MBI Domain Mapping**

| ISTAART MBI Domains | | | | | |
|---|---|---|---|---|---|
| | **Decreased Motivation** | **Affective Dysregulation** | **Impulse Dyscontrol** | **Social Inappropriateness** | **Abnormal Perception or Through Content** |
| **NPI Domains** | G. Apathy/Indifference | D. Depression/Dysphoria | C. Agitation/Aggression | H. Disinhibition | A. Delusions |
| | | E. Anxiety | I. Irritability/Lability | | B. Hallucinations |
| | | F. Elation/Euphoria | J. Aberrant Motor Behavior | | |

An MBI domain is considered present if at least one of the NPI domains is positive (binary variable). For example, presence of depression/dysphoria would map to presence of the MBI domain of affective dysregulation regardless of anxiety and elation/euphoria NPI domain.

***Covariates.***

Covariates included in statistical models will include: age, sex, race/field center (MN Whites; MD Whites; NC Whites; NC Blacks; MS Blacks), education (<high school; high school, GED, vocational school; college, graduate, or professional school), alcohol use (never; former; current), and apolipoprotein ε4 (APOE ε4) genotype (0 ε4 alleles; 1 or 2 ε4 alleles) (and in Aim 2 for cognitive status; normal cognition or MCI). We will also consider adjustment for global cognitive function (MMSE or global cognitive factor variable). All covariates will be measured at visit 5, except education and APOE ε4 genotype, which were measured at visit 1).These covariates were chosen *a priori* due to their known association with TBI, or their effect on neurodegeneration, neuropsychological outcomes of neurodegeneration, outcomes after TBI, or a combination of these factors.

***Statistical Analyses.***

Threshold for statistical significance for all tests will be set *a priori* as $\alpha$=0.05 (based on two-sided test). Baseline group differences will be presented overall and stratified by head injury (occurring by the time of Visit 5) and cognitive status (normal, MCI, dementia). Differences between will be assessed using Welch's T-tests (for continuous outcomes) and Chi-square tests with Yates' continuity correction applied (for categorical outcomes).

Aim 1: We will present unadjusted prevalence of scoring positive for each MBI domain by our 6 groups (1. no head injury and normal cognition; 2. head injury and normal cognition; 3. no head injury and MCI; 4. head injury and MCI; 5. no head injury and dementia; 6. head injury and

dementia). We will estimate prevalence ratios (PRs) and 95% confidence intervals (95% CIs) for associations of prior head injury/cognitive status with each positive MBI domain using adjusted generalized linear regression with a log link, Gaussian distribution, and robust variance estimator. We will also consider the use of adjusted logistic regression models. The reference group for analyses will change in order to determine if the association between head injury and MBI domain positivity differs between dementia and normal cognition, between MCI and normal cognition, and between dementia and MCI. Associations of head injury/cognitive status with NPI symptom severity (0-3 range for each symptom and 0-36 range divided into quartiles for overall) will be assessed using ordinal/multinomial logistic regression models. All statistical models will be adjusted for covariates described above. We will formally evaluate for interaction by age and sex.

Aim 2: Among visit 5 participants without baseline (visit 5) dementia, we will use unadjusted Kaplan Meier analyses and adjusted Cox proportional hazard models to evaluate associations of TBI and NPS/MBI domains with dementia risk (follow-up through visit 7). The proportional hazards assumption will be checked using -log(log) plots. We will create 4 groups: 1. no head injury and no NPS/MBI domain positivity; 2. no head injury and 1+ NPS/MBI domain positivity, 3. head injury and no NPS/MBI domain positivity; 4. head injury and 1+ NPS/MBI domain positivity. All statistical models will be adjusted for covariates described above. We will formally evaluate for interaction by age and sex. Due to the smaller sample sizes of participants in Aim 2 (i.e., patients without dementia at visit 5), we acknowledge that statistical power is limited. If sample size allows, we will incorporate a time-varying head injury and NPS/MBI domain that is updated using visit 6 data (but this may not be feasible due to the smaller number of individuals who had complete NPS data at visit 6).

**7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No**

**b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No**

(The file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

**8.a. Will the DNA data be used in this manuscript?__X__ Yes ____ No**

APOE ε4 genotype

**8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? __X__ Yes ____ No**

9. **The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.** ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

**_X_ Yes ____ No**

**10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?**

#2768: The Association of Head Injury and Cognition, Mild Cognitive Impairment, and Dementia in the ARIC Study (Andrea Schneider)
#3668: The Risk of Post-traumatic Epilepsy in the ARIC Study (Andrea Schneider)
#2767: The Association of Head Injury with Brain MR and Brain PET Amyloid Imaging in the ARIC Study (Andrea Schneider)
#2769: The Association of Head Injury with Risk of Stroke, Cardiovascular Disease, and Mortality in the ARIC Study (Andrea Schneider)
#3830: Association of Midlife Vascular Risk Factors with Late Life Neuropsychiatric Symptoms (Carla Rodriguez; Keenan Walker)
#3527: Hearing & Neuropsychiatric Symptoms among Older Adults with Cognitive Impairment (Carrie Nieman; Jennifer Deal)

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _X_ Yes ____ No**

**11.b. If yes, is the proposal**

**___ A. primarily the result of an ancillary study**
**_X_ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* Brain MRI Study 1999.01)**

*ancillary studies are listed by number https://sites.cscc.unc.edu/aric/approved-ancillary-studies

**12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.**

Understood.

**12b. The NIH instituted a Public Access Policy in April, 2008** which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

Understood.

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