ARIC Manuscript Proposal #4245

PC Reviewed: 5/09/23	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Trajectories of Blood-based Biomarkers of Neurodegeneration after Head Injury and Associations with Dementia Risk

b. Abbreviated Title (Length 26 characters): Head Injury Blood Biomarkers

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

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3. Timeline:

Blood-biomarker data proposed herein is currently measured and has undergone QC. Several papers led by Dr. Palta are currently underway to report the primary ARIC Study findings related to these biomarkers. We anticipate starting to work on the analyses proposed herein after these key papers are submitted/published. We anticipate submitting an abstract within 6 months to 1 year after starting data analysis and submitting the manuscript within 1-2 years after starting data analysis.

4. Rationale:

Traumatic brain injury (TBI; i.e., head injury) is a major public health burden and is a significant cause of death and disability. In the U.S., over 23 million adults aged 40 or older report a history of head injury with loss of consciousness at some point in their lives.[1] Annually, over 2.8 million people are diagnosed with a TBI in the U.S.,[2] with the highest incidence of TBI-related emergency department visits and hospitalizations occurring in older individuals, who are most susceptible to cognitive impairment and dementia.[3] TBI is heterogenous, and post-injury outcomes vary across time and between individuals. Much of the prior research on TBI outcomes has focused on the acute (days) to subacute (weeks-months) and chronic (usually within 5 years) post-injury time-periods and there is far less understanding of the sequelae of TBI in the remote (5 years to decades) post-injury time-period. More recently, it has become increasingly recognized that the sequelae from TBI are long-lasting and multiple studies have reported increased cognitive decline and higher rates of dementia among persons with TBI.[4–14]

The recent introduction of ultra-sensitive immunoassays has made possible measuring brain-derived protein biomarkers in peripheral blood, revolutionizing the TBI field. However, most studies have focused in the acute and subacute post-injury time-period. Only a few studies have examined the trajectories of blood-based biomarkers beyond 6 months,[15,16] and the trajectories of blood-based biomarkers in the remote post-injury time-period (i.e., 5 years to decades post-injury) remain less clear.

Several promising TBI and neurodegeneration-related biomarkers include neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), the ratio of amyloid-beta 40 and 42 ($A\beta_{40}/A\beta_{42}$) and phosphorylated tau proteins, including phosphorylated tau 181 (p-Tau181).[17–20] NfL is an intermediate filament protein expressed in long myelinated subcortical axons[21] and is found in circulation after injury.[20] After TBI, NfL levels peak around two weeks[15] and then decrease but remain elevated relative to individuals without TBI for up to 5 years.[22] GFAP is also an intermediate filament protein that is expressed by many cell types including astrocytes[23] and is released following neurotrauma where measurable increases after TBI have been reported,[24,25] peaking in the acute time-period and decreasing over time.[24] The $A\beta_{40}/A\beta_{42}$ ratio has been robustly studied in AD, where there is a decreased $A\beta_{40}/A\beta_{42}$ ratio.[26–28] In TBI, there are reports of a decreased $A\beta_{40}/A\beta_{42}$ ratio in military populations[29] as well as increases in plasma $A\beta_{42}$ levels in community-based populations.[30,31] Phosphorylated tau proteins, including p-tau181 are predominantly found in neurons and play a key role in the regulation of tau function, as well as stabilizing neuronal cytoskeleton and influencing axonal transport.[32] Few studies have

studied phosphorylated tau proteins in TBI, but one study found higher cerebrospinal fluid (CSF) p-tau 181 among individuals with a prior TBI compared to individuals without a TBI.[33]

The overall goal of this proposal is to investigate biomarkers of TBI-related neurodegeneration over decades post-injury. Using data from ARIC, we will characterize trajectories of blood-based biomarkers in the post-injury time-period and investigate associations of biomarker trajectories with dementia risk among individuals with a history of head injury. The overarching hypothesis of this proposal is that individuals with head injury, compared to those without a head injury, will have increasing burden of neurodegeneration over time (i.e., faster rates of change in blood-based biomarkers). Additionally, among individuals with prior head injury, individuals with greater increases in neurodegeneration (i.e., faster rates of change in blood-based biomarkers) will have greater risk of dementia compared to those with lesser increases in neurodegeneration (i.e., slower rates of change in blood-based biomarkers).

5. Main Hypothesis/Study Questions:

Aim 1: To determine if prior head injury (ascertained at the time of Visit 3) is associated with neurodegenerative blood-based biomarkers, both cross-sectionally and longitudinally. Specifically, we will investigate levels and trajectories of NfL, GFAP, p-tau181, and the $A\beta_{40}/A\beta_{42}$ ratio among individuals with and without head injury over a 26-year period (1993-2019).

Hypothesis 1A: In cross-sectional analyses (Visit 3), levels of NfL, GFAP, and p-tau181 will be higher and levels of $A\beta_{40}/A\beta_{42}$ will be lower among individuals with prior head injury compared to those without prior head injury.

- Additional cross-sectional analyses will also be conducted using Visit 5 and Visit 6/7 head injury and biomarker data.
- Sensitivity analyses will be conducted to examine biomarker levels by time since first head injury (head injury status ascertained over entire study duration).

Hypothesis 1B: In longitudinal analyses (Visit 3, Visit 5, Visit 6/7), the trajectories of NfL, GFAP, and p-tau181 will increase and the trajectory of $A\beta_{40}/A\beta_{42}$ will decrease over time, but there will be a faster rates of change (positive direction for NfL, GFAP, p-tau181; negative direction for $A\beta_{40}/A\beta_{42}$) in participants with head injury compared to participants without a prior head injury.

- Sensitivity analyses will be conducted operationalizing head injury as a time-varying exposure to incorporate information on head injuries occurring after Vist 3.

Aim 2: To evaluate associations of blood-based biomarker trajectories with incident dementia risk over time among individuals with a history of prior head injury.

Hypothesis 2*:* Among individuals with prior head injury, the risk of dementia will be higher among individuals with biomarker trajectories with faster rates of change (positive direction for NfL, GFAP, p-tau181; negative direction for $A\beta_{40}/A\beta_{42}$).

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).

Head injury definition. History of head injury (with or without loss of consciousness) in ARIC is defined using a combination of self-report questions and data from hospitalizations.[34,35] Self-report questions were asked to all participants at ARIC visit 3 (1993-1995), visit 4 (1996-1998), visit 6 (2016-2017), visit 7 (2018-2019), visit 8 (2019-2020), Visit 9 (2020-2021), and Visit 10 (ongoing 2021-2022) (and will be asked at upcoming visits) and to a subset of participants selected for brain MRI scans at an ancillary brain MRI visit (2004-06) and at visit 5 (2011-13). For this proposal, self-report data from Visit 3 will be primarily used and we will incorporate self-reported data up to Visit 7 in sensitivity analyses. Self-report questions inquired about prior head injury requiring physician/hospital care, loss of consciousness, number of prior head injuries, and date of head injury. Hospitalization records, including dates, were available from ARIC Study surveillance of all community hospitals. Head injury from medical records was defined using the Centers for Disease Control International Classification of Diseases (ICD)-9/10 code definitions. The primary exposure variable for head injury will be a binary variable categorized as yes or no history of prior head injury at the time of Visit 3. Secondary variables include number of prior head injuries (categorized as 0, 1, or 2+), and among head injury events identified using ICD codes, severity of injury (mild, moderate, severe/penetrating), as defined by the Defense and Veterans Brain Injury Center (DVBIC) TBI severity classifications. In sensitivity analyses, we will consider head injury events identified by self-report and by ICD codes separately and stratified by time since first head injury.

Blood-based biomarkers. Blood samples were collected at Visit 3 (1993-1995), Visit 5 (2011-2013), and Visits 6/7 (2017-2019). Samples were centrifuged at 3000g for 10 minutes and plasma was stored in microsample containers within 90 minutes of collection at -80°C until laboratory measurement. Using 250 µl of the stored frozen blood samples from a subset of participants, plasma biomarkers of neurodegeneration (Aβ40, Aβ42, NfL, GFAP, p-tau 181) were measured using commercially available ultrasensitive single-molecule array (Simoa™) assays from Quanterix. Compared to the more commonly used ELISA methods, the Simoa™ assays provide high sensitivity and precision, while minimizing the matrix interferences. $A\beta_{40}$, $A\beta_{42}$, NfL, and GFAP are being assayed together using a multiplex assay (Human Neurology 4-Plex E (N4PE)), and p-tau 181 using a singleplex assay.

Briefly, the selection criteria for the measurement of blood-based biomarkers included: 1) participants with available EDTA plasma specimens stored in the ARIC biorepository, 2) participants with brain MRI data at ARIC Visit 5. In total, the number of participants with available biomarker data is as follows: Visit 3 n~1,500, Visit 5 n~1,800, and Visit 6/7 n~600. Given these selection factors, we will consider sampling weights in our analyses.

Dementia Definition. There are 3 levels of dementia ascertainment in the ARIC Study, incorporating different levels of information. Level 1 is adjudicated dementia defined using comprehensive cognitive exams, the Functional Assessment Questionnaire (FAQ), the Clinical Dementia Rating (CDR) Scale, the Six-Item Screener (SIS), and the Ascertain Dementia 8-item Informant questionnaire (AD8) from in-person evaluations at ARIC visits. Level 2 adds telephone neurocognitive assessments, AD8, and SIS data from participants who were alive but did not attend ARIC visits and also adds data on CDR and FAQ from informants of participants who were alive but did not attend ARIC visits or who were deceased. Level 3, our main

outcome, adds dementia cases identified by hospitalization ICD codes or death certificate codes. Importantly, this level 3 outcome is not dependent on visit attendance and thus minimizes potential biases due to attrition and the competing risk of death. In sensitivity analyses, we will use Level 1 and Level 2 defined dementia.

Statistical Plan. In our primary analysis, prior head injury (yes/no) at the time of Visit 3 will be the exposure variable. Baseline characteristics (ARIC Visit 3) of the study population will be shown stratified by head injury status using means (SDs) for continuous variables and number and percentages for categorical variables. We will examine distributions of the blood-based biomarkers of NfL, GFAP, p-tau181, and the $A\beta_{40}/A\beta_{42}$ ratio by time since head injury and will use log transformations if distributions are non-normal. For all analyses using blood-based biomarker data we will consider sampling weights to account for the sampling strategy.

In cross-sectional analyses, we will investigate associations of each blood-based biomarker measured at Visit 3 with head injury status at the time of Visit 3 (in secondary analyses, we will perform additional cross-sectional analyses using Visit 5 and Visit 6/7 head injury and biomarker data) using adjusted linear regression models. In sensitivity analyses, we will examine biomarker levels by time since first head injury (with head injury status ascertained over entire study duration).

In longitudinal analyses, considering both complete case and incorporation of inverse probability of attrition weights and sampling weights, we will use a linear mixed effects model to investigate associations between head injury and biomarker trajectories over ~26 years. Time since baseline biomarker measurement and head injury ascertainment (Visit 3, 1993-1995) will be modeled using linear spline terms with knots at the median time between visits (Visit 5, 2011-2013 and Visit 6/7, 2017-2019). The coefficients of interest will be the interaction terms between our exposure variable and each time spline term, which represent differences in slopes in each biomarker over time by head injury status. Models will be adjusted for the following covariates: Model 1 will include age, sex, race, field center, and education level and Model 2 will include variables included in Model 1 plus military veteran status, smoking status, alcohol consumption, diabetes, hypertension, BMI, eGFR, physical activity, and cognitive status (yes/no dementia). In secondary and sensitivity analyses, we will also assess blood-based biomarker trajectories using the following alternate head injury exposure variables: time-varying head injury, number of prior head injuriess, head injury severity, time since first head injury, and head injury cases identified by self-report versus ICD codes.

From the models of biomarker trajectories, we will use the predicted individual biomarker slopes (e.g., categorized into quartiles or 1st quartile versus other 3 quartiles) for each participant and evaluate associations between biomarker trajectories with incident dementia risk among individuals with a prior head injury. Follow-up time will start at the time of last biomarker assessment (Visit 6/7, 2017-2019) and end at dementia onset, death, or censoring. We will also consider associations of biomarker trajectories defined between Visits 3 (1993-1995) and 5 (2011-2013) with dementia risk in order to expand follow-up time for dementia events to occur. We will perform Kaplan Meier analyses to show the cumulative incidence of dementia by category of biomarker slope. We will use adjusted Cox proportional hazards models employing Efron's approximation to handle ties to obtain adjusted hazard ratios (HRs) and 95% CIs for the

association of biomarker trajectory with incident dementia risk. The proportional hazards assumption will be assessed using Schoenfeld residuals. We will also consider Fine-Gray proportional hazards models to account for the competing risk of death. Models will be adjusted for the following covariates: Model 1 will include age, sex, race, field center, and education level and Model 2 will include variables included in Model 1 plus military veteran status, smoking status, alcohol consumption, diabetes, hypertension, BMI, eGFR, physical activity, and cognitive status (yes/no dementia). In secondary and sensitivity analyses we will also assess blood-based biomarker trajectories using the following alternate head injury exposure variables: time-varying head injury, number of prior head injuries, head injury severity, time since first head injury, and head injury cases identified by self-report versus ICD codes.

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

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)?

4041: Associations of Prior Head Injury with Physical Functioning, Frailty, and Falls in the Atherosclerosis Risk in Communities (ARIC) Study
4051: Associations of Prior Head Injury and Hearing in ARIC-NCS
3958: Associations of Prior Head Injury with Olfactory Functioning
2768: The Association of Head Injury and Cognition, Mild Cognitive Impairment, and Dementia in the ARIC Study
2769: The Association of Head Injury with Risk of Stroke, Cardiovascular Disease, and Mortality in the ARIC Study

3983: Late-life plasma biomarkers for Alzheimer's disease and related dementias in association with neurocognitive and MRI outcomes

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

_X_ A. primarily the result of an ancillary study (list number* 2015.07 - PI: Palta and 2022.19 - PIs: Walter/Schneider)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*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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