ARIC Manuscript Proposal #4298

PC Reviewed: 07/11/23	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Associations of Anger Proneness and Head Injury in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Anger Proneness and Head Injury

2. Writing Group:

Writing group members:

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Others welcome

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

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3. Timeline:
Data are currently available. Analyses and conference abstract and manuscript preparation will be performed over the next 6-12 months.

4. Rationale:

Traumatic brain injury (TBI), also referred to as head injury or concussion, is associated with significant short- and long-term morbidity and mortality[1–3]. Specifically, TBI is associated with psychiatric (depression and post-traumatic stress disorder), personality (impulsivity and affective instability), and cognitive (memory deficits and executive functioning) sequelae[4–6].

There is also evidence that TBI[7], can change an individual's propensity for anger. Anger was historically conceived of as a personality trait that remained relatively static over the life course[10]. In the past half century, anger has been viewed through the state-trait model, which splits the concept into the transitory emotional continuum of being annoyed, irritated, or otherwise angered (state anger), as well as an individual's stable temperamental vulnerability to becoming angered (trait anger or anger proneness)[8]. Additionally, more recent research provides evidence that there are effective interventions, such as cognitive behavioral therapy and training avoidance tendencies towards threatening situations, which can be used to improve anger proneness[9]. Trait anger has been associated with multiple negative health outcomes,[9] including: coronary heart disease[10] and diabetes[11], as well as almost a threefold increase in stroke[12]. Behaviorally, high trait anger is associated increased risk-taking behaviors[13,14] and impulsivity[8], as well as an impairment in effortful control[15].

Additionally, high trait anger is associated with an increased frequency in motor vehicle accidents[14] and is consistently associated with intimate partner violence and other types of assault;[16] all of which are common mechanisms for TBI. While prior literature has reported increases in anger proneness and other personality changes following TBI[17–20], less work has investigated anger proneness as a risk factor for TBI, particularly among middle-age and older individuals. Indeed, the highest incidence of TBI occurs among older individuals (i.e., aged 65+ years), with unintentional falls being the most common mechanism of injury in this age group, followed by motor vehicle traffic crashes[21,22].

The ARIC study presents a unique opportunity to utilize data both prior to and following TBI events, in order to explore a potential bidirectional relationship between head injury and anger proneness among community dwelling middle-age and older adults. We hypothesize both that prior head injury will be associated with higher trait anger and that greater anger proneness will be associated with increased risk of future head injury.

5. Main Hypothesis/Study Questions:

Aim 1: To examine associations between prior head injury (occurring before ARIC Visit 2) and anger proneness assessed at ARIC Visit 2.

> Hypothesis 1: Prior head injury will be associated with higher anger proneness at Visit 2 compared to no prior head injury. Furthermore, individuals with more severe head

injuries and with multiple (two or more) prior head injuries will have higher anger proneness compared to individuals with less severe head injuries and compared to individuals with one prior head injury.

Aim 2: To examine associations of interval head injury (occurring between ARIC Visits 2 and 4) and change in anger proneness from ARIC Visit 2 to ARIC Visit 4, among individuals with no history of head injury prior to ARIC Visit 2.

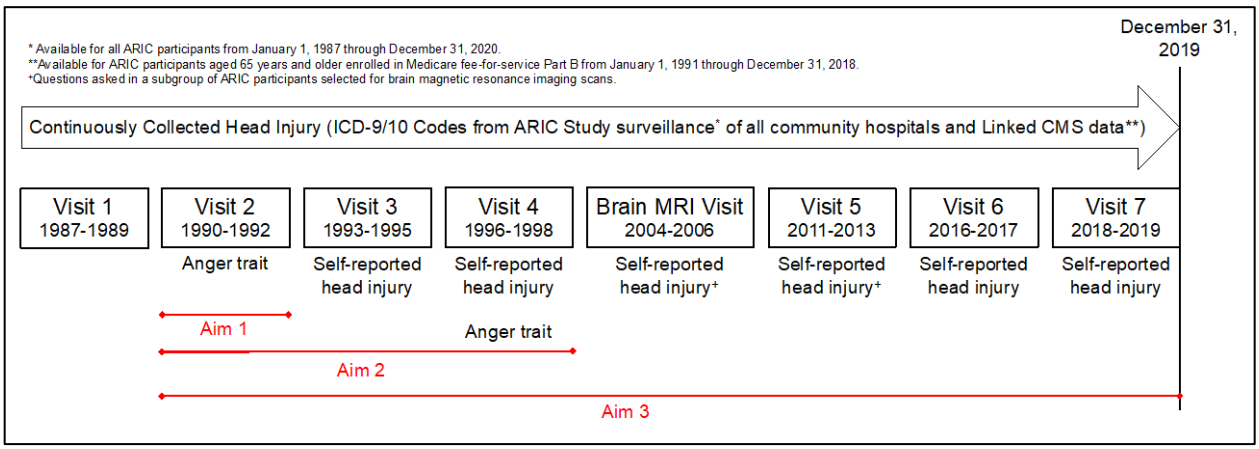
Hypothesis 2: Head injury occurring between ARIC Visits 2 and 4 will be associated with a greater increase in anger proneness from ARIC Visit 2 to ARIC Visit 4 compared to no prior head injury. Furthermore, individuals with more severe head injuries and multiple (two or more) prior head injuries will have greater increases in anger proneness than individuals with less severe head injuries and compared to individuals with one head injury.

Aim 3: To examine the association of anger proneness at Visit 2 (baseline) with risk of incident head injury over study follow-up (through 31 December 2020, or the most updated administrative censoring data at the time of journal submission), among individuals with no history of head injury prior to ARIC Visit 2.

Hypothesis 3: Higher baseline anger trait will be associated with increased risk of head injury compared to lower baseline anger trait. Furthermore, individuals with higher anger trait will be more likely to have more severe head injuries and multiple (two or more) head injuries compared to individuals with lower anger trait.

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/Study Population:
Study design and timing of head injury and anger trait data collection:



Aim 1:
Design: Cross-sectional.
Exposure: Head injury occurring prior to ARIC Visit 2.
Outcome: ARIC Visit 2 measure of trait anger.
Population: All participants with non-missing head injury, trait anger, and covariate data at ARIC visit 2 will be included.

Aim 2:
Design: Prospective analysis.
Exposure: Head injury occurring between ARIC Visit 2 and ARIC Visit 4.
Outcome: Change in anger proneness from ARIC Visit 2 to ARIC Visit 4.
Population: All participants without prior head injury at the time of Visit 2 with non-missing Visit 4 head injury data, Visit 2 and 4 trait anger data, and Visit 2 covariate data will be included.

Aim 3:
Design: Prospective analysis.
Exposure: ARIC Visit 2 measure of trait anger.
Outcome: Incident head injury occurring over study follow-up (through 31 December 2020, or the most updated administrative censoring data at the time of journal submission).
Population: All participants without prior head injury at the time of Visit 2 with non-missing subsequent head injury data, Visit 2 trait anger data, and Visit 2 covariate data will be included.

Head Injury Definition:
Consistent with previous work in ARIC,[23,24] indicator variables for head injury will be defined using a combination of self-reported data and diagnostic codes from the *International Classification of Diseases Ninth* (ICD-9) and *Tenth Revisions* (ICD-10) from emergency department visits and inpatient hospitalizations. From these data sources, variables for head injury status at the time of each ARIC visit will be derived based on dates of injury. For secondary analyses, we will define measures for the number of head injuries (0; 1; 2+) and in the subset of head injuries identified using diagnostic codes, we define a measure of head injury severity (mild; moderate/severe/penetrating) based on the department of defense (DOD) classification system. In sensitivity analyses, we will consider self-reported and hospital diagnosed head injuries separately. Questions used to identify self-reported head injury questions and diagnostic codes used to define head injury, which are consistent with the CDC TBI surveillance definition, are presented below:

Self-reported head injury:

ARIC Visit 3 (1993-1995)
1. Have you ever had a head injury which led you to see a physician or seek hospital care?
2. How many times has this happened?
3. How many of these head injuries resulted in your losing consciousness, no matter how briefly?
4.In what year was your head injury for which you sought medical care?
ARIC Visit 4 (1996-1998)

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? 2. How many times has this happened? 3. How many head injuries resulted in your losing consciousness, no matter how briefly? 4. In what year was your head injury for which you lost consciousness sought medical care?
ARIC Brain MRI Visit (2004-2006)*
1. Have you ever had a head injury that resulted in loss of consciousness (knocked out)? 2. How many times? 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),* Visit 6 (2016-2017), and Visit 7 (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 imagining (MRI) scans.

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

ICD-9 Codes (Prior to 9/30/2015)	
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 (Starting 10/1/2015)	
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

Anger Proneness:
Trait anger is measure of an individual's overall tendency to become angry (i.e., anger proneness)[9] and can be measured using the previously validated Spielberger Trait Anger Scale. The Spielberger Trait Anger Scale was performed at ARIC Visits 2 and 4. The Spielberger Trait Anger Scale is a 10-question assessment that uses a 4-point Likert scale (response choices: 1=almost never, 2=sometimes, 3=often, 4=almost always) to evaluate participants on two subscales: (1) anger-temperament and (2) anger-reaction. The former evaluates respondents' generalized sense of anger, while the latter focuses on situations where an individual may feel mistreated by others. Total scores range from a minimum of 10 to a maximum of 40 points.

We will consider modeling scores continuously in our primary analyses, as well as categorically as low anger proneness (score 10-14), moderate anger proneness (score 15-21), and high anger proneness (score 22-40) in our secondary analyses, consistent with prior studies[12,25]. Additionally, we will consider using splines to capture potential nonlinearity in analyses where the score is modeled continuously. The questions comprising the Spielberger Trait Anger Scale are presented below:

ARIC Visit 2 (1990-1992) and ARIC Visit 4 (1996-1998)

1	I am quick tempered.
2	I have a fiery temper.
3	I am a hotheaded person.
4	I get angry when I am slowed down by others' mistakes.
5	I feel annoyed when I am not given recognition for good work.
6	I fly off the handle.
7	When I get angry, I say nasty things.
8	It makes me furious when I am criticized in front of others.
9	When I get frustrated, I feel like hitting someone.
10	I feel infuriated when I do a god job and get a poor evaluation.

Covariates:
Covariates to be included in statistical models were assessed at ARIC Visit 2, unless otherwise specified, and will include: age (continuous), sex (male; female), race/center (Minnesota White; Maryland White; North Carolina White; North Carolina Black; Mississippi Blacks), education (assessed at ARIC Visit 1, <high school; high school, GED or vocational school; college, graduate, or professional school), military veteran status (yes; no), marital status (married; divorced; never married; separated); cigarette smoking status (current; former; never), alcohol consumption (current; former; never), and depression (measured by the Vital Exhaustion Questionnaire[26]).

Statistical Analysis:
Participant characteristics will be shown in two ways: 1) stratified by Visit 2 head injury status (yes; no) and 2) stratified by Visit 2 anger trait categories (low; medium; high).

Aim 1: We will use adjusted linear and multinomial logistic regression models to investigate associations between head injury status (at the time of Visit 2) with anger proneness modeled continuously and categorically, respectively. In secondary analyses, we will look at associations

of number of prior head injuries and head injury severity with anger proneness. In sensitivity analyses, we will consider associations for self-reported and hospital diagnosed injury separately. We will also consider time since first head injury (stratified as occurring within 10 years of Visit 2 versus greater than 10 years prior to Visit 2).

Aim 2: We will calculate change in anger proneness score from Visit 2 to Visit 4 and use adjusted linear regression models to estimate the association between interval head injury (occurring between Visit 2 to Visit 4) and change in anger proneness score. In secondary analyses we will look at associations of number of prior head injuries and head injury severity with change in anger proneness. In sensitivity analyses, we will consider associations of head injuries defined by self-report and defined by ICD-9/10 codes separately. We will consider the use of inverse probability of attrition weights to account for attrition and death occurring between ARIC visits 2 and 4.

Aim 3: We will use Cox proportional hazards regression models to estimate the HRs (95% CIs) for incident head injury risk associated with baseline (Visit 2) anger proneness. The proportional hazards assumption will be checked using Schoenfeld residuals and complementary log-log plots.

In all Aims, we will perform 2 nested statistical models. Model 1 will be adjusted for age, sex, race/center, education, military veteran status, and marital status. Model 2 will be adjusted for covariates from Model 1 plus cigarette smoking status, alcohol consumption, and depression.

All analyses will be performed using R (Version 4.2.3). A two-sided p-values of <0.05 will be considered statistically significant.

Limitations:

One limitation is the utilization of self-reported data and diagnostic codes to define head injury. As such, we will not have access to specific details about the type of head injury, injury location, imaging findings, or treatment. Although the Spielberger Trait Anger Scale has been shown to have good validity and reliability[27], it is based upon self-report. Self-reported data is subject to inherent biases, including recall bias, among others. Further trait anger was assessed using a single scale, which may not capture the full complexity of anger proneness. It is possible that Aim 2 will be underpowered if there are not enough head injury cases occurring between Visits 2 and 4. The timing between occurrence of head injury and measure of anger proneness will inherently differ between participants, which may result in measurements of different underlying constructs of anger depending on time since injury. Additionally, as with any observational study, there is the possibility of residual confounding.

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? ____ Yes __X__ 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"? ____ 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)?

Anger trait related proposals:
MSP 177: Components of trait anger and incident stroke risk: The ARIC Study (C.C. Patton)
MSP 508: Anger and the occurrence of CHD events (Janice Williams)
MSP 516: Association of anger and arterial stiffness (Janice Williams)
MSP 565: Anger-Vital Exhaustion and Metabolic Syndrome (Thomas Mosley)
MSP 610: Stability and change in trait anger and the relationship to CVD risk factors. The Atherosclerosis Risk in Communities (ARIC) Study (Janice Williams)
MSP 626: Differential prediction of CHD risk by trait anger subtype (Janice Williams)
MSP 691: The Moderating Effects of Social Support on the Association Between Negative Emotions and CHD Events, Carotid Arterial Wall Thickness, and Mortality (Thomas Mosley)
MSP 724: Trait anger and carotid atherosclerosis: Examination of a possible mechanism in cardiovascular disease (Janice Williams)
MSP 727: Anger confers risk of CHD to individuals who otherwise are at low risk of the disease (Janice Williams)
MSP 745: The role of anger and vital exhaustion in the relationship between alcohol consumption and risk of coronary heart disease (CHD) (Shaila Khan)
MSP 774: Anger proneness and markers of hemostatic function: Possible mechanisms for cardiovascular disease (Janice Williams)
MSP 854: Components of trait anger and incident stroke risk: The ARIC Study (Janice Williams)
MSP 1039: Negative Emotions and Subclinical Cerebrovascular Disease (Thomas Mosley)
MSP 1134: Associations of Negative Emotions with Retinal Microvascular Disease and Age-Related Maculopathy (Tien Wong)
MSP 1226: Psychosocial distress and risk for recurrent adverse cardiac events (Janice Williams)
MSP 1260: Association between exposure to combat-related stress and psychological health in aging men (Janice Williams)

MSP 1755: Anger proneness, heart failure risk, and hospital use (Anna Kucharska-Newton)
MSP 3135: Association of Anger, Depressive Symptoms, and Poor Social Support with the Risk of Incident Atrial Fibrillation (Parveen Garg)
MSP 4131: Associations of psychosocial factors and cardiovascular health measured by Life's Essential 8 (Kennedy Peter)

Head injury related proposals:
MSP 2767: The Association of Head Injury with Brain MR and Brain PET Amyloid Imaging in the ARIC Study (Andrea Schneider)
MSP 2768: The Association of Head Injury and Cognition, Mild Cognitive Impairment, and Dementia in the ARIC Study (Andrea Schneider)
MSP 2769: The Association of Head Injury with Risk of Stroke, Cardiovascular Disease, and Mortality in the ARIC Study (Andrea Schneider)
MSP 2978: Associations between Head Injury and Mild Behavioral Impairment (MBI) Domains Across the Cognitive Spectrum (Nicholas Daneshvari)
MSP 3668: The Risk of Post-traumatic Epilepsy in the ARIC Study (Andrea Schneider)
MSP 3958: Associations of Prior Head Injury with Olfactory Functioning (Andrea Schneider)
MSP 4041: Associations of Prior Head Injury with Physical Functioning, Frailty, and Falls in the Atherosclerosis Risk in Communities (ARIC) Study (Katie Hunzinger)

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

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)
___ 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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