ARIC Manuscript Proposal #3958

PC Reviewed: 11/9/21 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1a. Full Title: Associations of Prior Head Injury with Olfactory Functioning

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

2. Writing Group:

Writing group members (in alphabetical order by last name):

Honglei Chen MD PhD	Michigan State University
Rebecca F. Gottesman MD PhD	NIH/NINDS
Vidyulata Kamath PhD (Senior Author)	Johns Hopkins University
Thomas H. Mosley PhD	University of Mississippi
Nicholas Rowan MD	Johns Hopkins University
Andrea L.C. Schneider MD PhD (First Author)	University of Pennsylvania
A. Richey Sharrett MD DrPH	Johns Hopkins University
Others Welcome	

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

First author: 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

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 are currently available. Analyses and manuscript preparation will be performed over the next 6-12 months.

4. Rationale: The peripheral and central olfactory structures are centrally located in the medial forebrain, making it particularly vulnerable to injury following blunt force to the head, face and nose. Indeed, traumatic brain injury (TBI) represents a primary contributor of olfactory loss in adults, representing approximately 14 to 20% of patients with olfactory loss.[1] The magnitude of olfactory dysfunction following TBI can vary as a function of injury severity with incidence rates increasing from 0 to 13% in mild TBI to 15 to 30% following moderate to severe TBI.[2, 3] The proposed mechanisms for olfactory loss post-TBI are multifactorial and include shearing of the olfactory nerve fibers anchored to the bony cribriform plate and mechanical injury of the sinonasal tract, olfactory bulbs and olfactory-eloquent cortical brain regions.[4] Severe depression, post-traumatic epilepsy, and medications prescribed for TBI management may also contribute to the degree of olfactory dysfunction observed.[4]

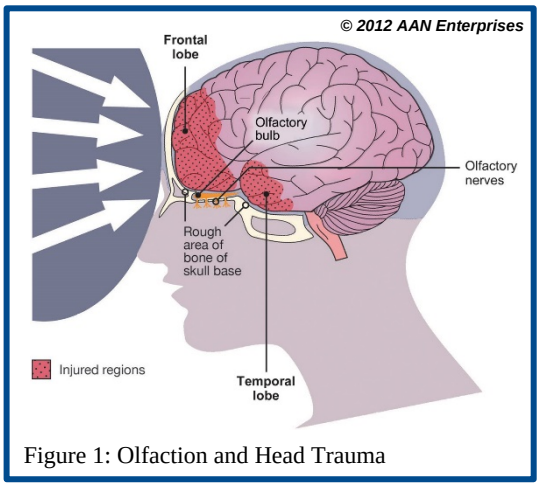

Figure 1: Olfaction and Head Trauma

Early case reports by Jackson and Ogle dating back to the late 1800s were among the first to propose a link between head injury and smell loss.[5, 6] Sumner (1964) followed up this work with the largest clinical case series of head injury patients (n=1,167) in which olfaction was assessed using self-report and non-standardized olfactory testing.[7] Approximately 5-7% of this sample were defined as anosmic and increased olfactory disturbance was observed in those with greater head injury severity. Since the publication of this large case series, the development of standardized olfactory psychophysical assessments and sophisticated neuroimaging and electrophysiological techniques have allowed for a more thorough understanding of this relationship. Compared to other senses, patients often underestimate or are unaware of olfactory loss, which has limited the use of self-report in capturing the prevalence of anosmia following TBI. When standardized testing is employed, significant differences between adult TBI patients and controls are reliably observed across measures of odor identification,[8-10] discrimination,[11-14] and detection threshold.[11-15] Initial work by Sumner (1964)[7] found that occipital impacts were associated with greater olfactory loss when compared to frontal and other sites of impact. Doty et al. (1997) later replicated and extended this work using quantitative MRI to capture the location and extent of head injury, along with standardized olfactory assessment.[16] In 268 patients with head trauma, 87.3% had olfactory difficulties in the hyposmia to anosmia range, with trauma severity and location of impact (occipital and side impacts) influencing the degree of olfactory loss. Olfactory loss in TBI is associated with damage to the olfactory bulbs, olfactory tracts, and frontotemporal regions of the brain,[13, 14] which likely result from bruising from blunt movement across the irregular skull base.[17] Olfactory event-related potentials (oERPs) are absent in approximately 33% of individuals with TBI-related olfactory loss with abnormal response latencies and amplitudes observed in the remaining 66% when compared to controls.[15]

Much of our understanding of the relationship between olfaction and head injury is based on studies plagued by selection bias, in which only those TBI patients complaining of smell loss undergo formal olfactory assessment. Prior studies are limited by small samples, lack of standardized olfactory assessment, incomplete information on injury characteristics and inadequate case-control design. The Atherosclerosis Risk in Communities Study provides a unique opportunity to examine the association between head injury and objective olfactory performance in a large community-based biracial cohort of older adults. Head injury information in ARIC is documented via self-report of head injuries requiring physician/hospital care, number of head injuries, and year of head injury. Additional head injury information is available from hospitalization records (ICD-9/10 codes) of all community hospitals through ARIC Study surveillance, allowing for additional analyses of TBI severity. Furthermore, olfactory performance is assessed formally using the 12-item Sniffin Sticks. In the current proposal, we will examine the cross-sectional and longitudinal relationship between head injury and olfactory performance and the influence of the number and severity of head injury on olfactory performance.

5. Main Hypothesis/Study Questions:

Aim 1: To examine the cross-sectional (Visit 5) relationship between prior head injury and olfactory performance.

Hypothesis 1: We hypothesize that prior head injury will be associated with increased olfactory dysfunction, and that individuals with multiple prior head injuries and more severe prior head injuries will have greater olfactory dysfunction.

Aim 2: To examine the prospective (Visit 5 to Visit 6) relationship between prior head injury and olfactory performance.

Hypothesis 2: We hypothesize that prior head injury will be associated with worsening olfactory function over time, and that individuals with multiple prior head injuries and more severe prior head injuries will have greater worsening in olfactory function over time.

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: Cross-sectional (Visit 5) and prospective (Visit 5 to Visit 6) analyses.

Inclusion/Exclusion Criteria: The cross-sectional analysis will include ARIC Visit 5 participants with non-missing head injury, olfaction, and covariate data. Participants self-identified as non-white or non-black race, black participants from the Minnesota and Maryland sites, will also be excluded from this analysis. We will additionally exclude individuals with prior brain tumor, skull/brain surgery or radiation. The prospective analyses will be restricted to the subpopulation who also underwent olfactory testing at ARIC Visit 6.

Exposure: Head injury occurring prior to Visit 5 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 look at number of prior head injuries (0; 1; 2+) and in the subset identified using ICD-9/10 code data, we will look by head injury severity (mild; moderate/severe). This definition has been used previously in the ARIC cohort[19, 20] (see below for self-reported questions and ICD-9/10 codes). 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) 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)* 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

Outcome: Olfaction was assessed using the 12-item Sniffin' Sticks[18] at ARIC Visits 5 and 6. Participants were asked to smell and identify 12 common odorants (orange, leather, cinnamon, peppermint, banana, lemon, licorice, coffee, cloves, pineapple, rose, and fish) in a multiple-choice format. Each correctly identified odorant was assigned one point, with a total possible score of 12. A score of ≤6 defines impaired olfaction (anosmia). Olfaction will be analyzed as a continuous variable and as a binary variable (>6 [normosmia] versus ≤6 [anosmia]) in our primary analyses. In secondary analyses, we will also consider categorization as >8 [normosmia] versus 7-8 [hyposmia] versus ≤6 [anosmia].

Covariates: Covariates were assessed at ARIC Visit 5, unless otherwise specified, and will include: age (continuous), sex (male; female), race/center (Minnesota whites; Maryland whites, North Carolina whites, North Carolina blacks, Mississippi blacks), education (assessed at ARIC Visit 1, <high school; high school, GED or vocational school; college, graduate, or professional school), cigarette smoking status (current; former; never), depression (defined by CES-D score ≥9), and cognitive status (normal; mild cognitive impairment; dementia).

Statistical Analyses: All analyses will be performed using Stata SE (Version 16, StataCorp, College Station, Texas) and a p-value <0.05 will be considered statistically significant. Participant characteristics will be shown overall and stratified by head injury status (at the time of ARIC Visit 5). Characteristics will be compared between head injury groups using t-tests for continuous variables and chi-square tests for categorical variables.

For cross-sectional analyses at Visit 5, we will use linear regression to examine associations between prior head injury, number of prior head injuries, and head injury severity with olfaction score (0-12 range). We additionally will use logistic regression to examine associations between

prior head injury, number of prior head injuries, and head injury severity with anosmia (defined as a Sniffin' Sticks score ≤6). Multinomial or ordinal logistic regression will be used to examine associations between head injury exposure variables with the 3-level secondary outcome variable consisting of normosmia (Sniffin' Sticks score >8), hyposmia (Sniffin' Sticks score 7-8, and anosmia (Sniffin' Sticks score ≤6). For prospective analyses between Visit 5 and Visit 6, we will use linear regression to examine associations between prior head injury, number of prior head injuries, and head injury severity with change in olfaction score. We additionally will use logistic regression to examine associations between prior head injury, number of prior head injuries, and head injury severity with incident anosmia (analysis restricted to those without anosmia at Visit 5). In our prospective analyses, we will consider the use of inverse probability of attrition weighting to account for study attrition between visits 5 and 6. We will perform testing for interaction by age, sex, and race. In supplemental analyses, we will also investigate the impact of time since first head injury on associations. In sensitivity analyses, we will exclude participants with a history of Parkinson's disease and with mild cognitive impairment or dementia at Visit 5.

Limitations: A limitation of this study is the use of self-reported and hospitalization ICD-9 codes to define head injury. We do not have details regarding the type of injury that occurred, location of injury, or details on treatment received. Additionally, we do not have specific dates for when olfaction impairment started as we only have the date of olfaction assessment (at visits 5 and 6). Additionally, as with any observational study, we will not be able to rule out the possibility of residual confounding in our analyses.

7a. Will the data be used for non-CVD analysis in this manuscript? __ Yes _X_ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? __ Yes __ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8a. Will the DNA data be used in this manuscript? __ Yes _X_ No

8b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 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/search.php
_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)?

Head Injury-related MSPs:

- 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 #3668: The Risk of Post-traumatic Epilepsy in the ARIC Study (Andrea Schneider)
- MSP 3916: Associations of Head Injury with Neuropsychiatric Symptoms (NPS) and Mild Behavioral Impairment (MBI) Domains (Lisa Richey)

Olfaction-related MSPs:

- MSP #2445: Prevalence and Associated actors of Anosmia (Honglei Chen)
- MSP #2841: Mid-life Biomarkers in Relation to Anosmia Late in Life (Honglei Chen)
- MSP #2872: Olfactory Impairment and Cognitive Function: the Atherosclerosis Risk in Communities Neurocognitive Study (Priya Palta)
- MSP #3423: Neural Correlates of Anosmia Among Persons With and Without Mild Cognitive Impairment: A Voxel-based Morphometry (VBM) Study (Vidyulata Kamath)
- MSP #3911: Olfactory Impairment and Relations to Microstructural Integrity of the Brain in the Atherosclerosis Risk in Communities Study (Srishti Shhrestha)

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

11b. If yes, is the proposal
X A. primarily the result of an ancillary study (list number* ARIC NCS 2008.06)
__ 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 at http://www.cscc.unc.edu/aric/forms/

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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