ARIC Manuscript Proposal #3993

PC Reviewed: 1/11/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Olfactory decline in older adults and its predictors: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Olfactory impairment and its predictors

2. Writing Group:

Writing group members: A. Richey Sharett, Andrea L.C. Schneider, B Gwen Windham, Jennifer Deal, Kevin Sullivan, Michael Griswold, Priya Palta, Rebecca Gottesman, Srishti Shrestha, Vidyulata Kamath, Xiaoqian Zhu, Thomas Mosley, Honglei Chen

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

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3. Timeline: Analysis will start immediately following proposal approval

4. Rationale:

Olfactory impairment (OI) has important health implications and can be an early manifestation of neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD) [1, 2]. OI affects nutrition, safety, social relationships, and mental health, diminishing overall quality of life [3-5] and is predictive of mortality, independent of chronic health conditions including neurodegenerative diseases [6]. Olfactory structures have been suggested to be one of the earliest brain structures to develop AD and PD-related neuropathology, decades before the onset of clinical symptoms.

OI is a common condition and can result from gradual or sudden damage to peripheral (e.g., olfactory epithelium) or central (e.g., olfactory bulb, entorhinal cortex) olfactory structures. However, little is known about factors associated with OI; some known predictors include increasing age, male sex, Black race, respiratory illnesses, head trauma, and certain toxicants. Studies have also linked factors including smoking, cardiovascular diseases and their risk factors, physical activity, and systemic inflammatory markers with poor olfaction, although these findings have not been consistent [7-11]. Further, most of the existing evidence comes from cross-sectional studies and only a few prospective studies have investigated such associations. Given the broad health implications of OI, research on its predictors is important. Specifically, this may help mitigate public health burden associated with OI. Further, identification of shared risk factors of OI and neurodegeneration may help understand early AD and PD pathophysiology.

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective cohort study of community-based US adults (enrolled 1987-1989). The ARIC study collected comprehensive information on socio-demographics, cardiovascular, and inflammatory risk profiles at enrollment and all follow-up surveys from study participants; the study measured olfaction at visit 5 (2011-2013) and visit 6 (2015-2016). Here we propose to identify factors associated with decline in olfactory ability. Previously, a cross-sectional investigation was conducted to identify factors related to OI using ARIC study data (i.e., using visit 5 exposure variables and visit 5 olfactory ability)[9]. Specifically, the study used pooled data from the ARIC study and the Health, Aging, and Body Composition study and found that increasing age, male sex, black race, higher education, lower cognitive score, *APOE ε4*, and lower body mass index were associated with higher prevalence of anosmia. Similar findings were observed in ARIC-specific analysis. Here, we extend the prior investigation by focusing on longitudinal decline in olfaction from visit 5 to visit 6.

5. Main Hypothesis/Study Questions:

Aim: To examine if visit 5 socio-demographic, cardiovascular, inflammatory, and genetic risk factors are associated with decline in olfaction from visit 5 to visit 6

Hypothesis: We hypothesize that increasing age, male sex, black race, lower education, poor cardiovascular and inflammatory risk factors, and presence of *APOE ε4* will be associated with decline in olfaction.

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: Prospective cohort study (ARIC visit 5 to visit 6)

Predictor variables of interest: Potential factors related to olfaction: Sociodemographic factors (e.g. age, sex, race, education), cardiovascular risk factors (physical activity, body mass index, cholesterol level, diabetes, hypertension), inflammatory risk profiles (C-reactive protein and urate measured at visit 5), head injury, and genetic risk factor (*APOE ε4* at visit 1). In our secondary analyses, we will consider available visit 1 exposure variables, measured at participants' midlife, to compare with findings for visit 5 (late-life) exposures.

Measures of olfaction: The 12-item Sniffin' Sticks screening test was used to measure olfaction at visits 5 and 6. We will use smell identification test score as a continuous olfaction variable; additionally, we will create a categorical outcome anosmia (defined using a conventional cut-off of score ≤ 6)[12].

Statistical analysis:

The analyses will be restricted to visit 5 participants with complete information on visit 5 olfaction, exposure variables, and covariates of interest. We will use linear mixed models with random slopes and random intercepts to examine the associations between visit 5 exposure variables and changes in continuous olfaction test scores over time adjusting for potential confounders. We will examine distributional assumptions of models and, when they are not met, we will consider other appropriate distribution/family in the generalized linear mixed model framework. Further, we will use mixed-effects logistic regression to examine longitudinal change in anosmia. Further, as only 57% of visit 5 participants completed olfaction test in visit 6, to address potential bias from cohort attrition, we will perform sensitivity analysis using shared parameter models; briefly, we will use two survival submodels (for dementia and death respectively) to inform longitudinal submodel examining decline in olfaction [13]. Separate sets of confounders will be considered for each exposure/predictor of interests.

In our secondary analyses, we will consider (i) examining cross-sectional associations between visit 5 risk factors and visit 5 olfaction for predictors that were not included in the prior ARIC investigation (for example, inflammatory markers) [9]); (iii) analysis excluding prevalent dementia, PD, and those with history of brain/skull surgery/radiation and reporting stuffy nose in the past 2 weeks; and (iii) examining visit 1 exposure variables, measured at participants' midlife, to compare with findings for visit 5 (late-life) exposures. Lastly, we will also consider using change/difference in score from visit 5 to visit 6 as the outcome variable.

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

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)?

- Dong, J., et al., The prevalence of anosmia and associated factors among U.S. black and white older adults. J Gerontol A Biol Sci Med Sci, 2017. 72(8): p. 1080-1086.
- Palta, P., et al., Olfactory function and neurocognitive outcomes in old age: The Atherosclerosis Risk in Communities Neurocognitive Study. Alzheimers Dement, 2018. 14(8): p. 1015-1021.
- ARIC Manuscript Proposal #2841 Mid-life biomarkers in relation to anosmia late in life
- ARIC Manuscript Proposal #3423: Neural correlates of anosmia among persons with and without mild cognitive impairment: A voxel-based morphometry (VBM) study (Kamath; Schneider)
- ARIC Manuscript Proposal #3911: Olfactory impairment and relations to microstructural integrity of the brain in the Atherosclerosis Risk in Communities Study
- ARIC Manuscript Proposal #3958: Associations of Prior Head Injury with Olfactory Functioning.

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 (list number* _2008.06, 2010.17, 2020.01_____)

___ 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.

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.

References

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2. Murphy, C., *Olfactory and other sensory impairments in Alzheimer disease.* Nat Rev Neurol, 2019. **15**(1): p. 11-24.
3. Mattes, R.D. and B.J. Cowart, *Dietary assessment of patients with chemosensory disorders.* J Am Diet Assoc, 1994. **94**(1): p. 50-6.
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5. Croy, I., S. Nordin, and T. Hummel, *Olfactory disorders and quality of life--an updated review.* Chem Senses, 2014. **39**(3): p. 185-94.
6. Liu, B., et al., *Relationship Between Poor Olfaction and Mortality Among Community-Dwelling Older Adults: A Cohort Study.* Ann Intern Med, 2019. **170**(10): p. 673-681.
7. Raff, A.C., et al., *Relationship of impaired olfactory function in ESRD to malnutrition and retained uremic molecules.* Am J Kidney Dis, 2008. **52**(1): p. 102-10.
8. Schubert, C.R., et al., *Inflammatory and vascular markers and olfactory impairment in older adults.* Age Ageing, 2015. **44**(5): p. 878-82.
9. Dong, J., et al., *The prevalence of anosmia and associated factors among U.S. black and white older adults.* J Gerontol A Biol Sci Med Sci, 2017. **72**(8): p. 1080-1086.
10. Bramerson, A., et al., *Prevalence of olfactory dysfunction: the skovde population-based study.* Laryngoscope, 2004. **114**(4): p. 733-7.
11. Schubert, C.R., et al., *Association of exercise with lower long-term risk of olfactory impairment in older adults.* JAMA Otolaryngol Head Neck Surg, 2013. **139**(10): p. 1061-6.
12. Hummel, T., et al., *Screening of olfactory function with a four-minute odor identification test: reliability, normative data, and investigations in patients with olfactory loss.* Ann Otol Rhinol Laryngol, 2001. **110**(10): p. 976-81.
13. Griswold, M.E., et al., *Reflection on modern methods: shared-parameter models for longitudinal studies with missing data.* Int J Epidemiol, 2021.