ARIC Manuscript Proposal #4078

PC Reviewed: 7/12/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Olfactory impairment and Chronic Diseases in Older Adults

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

2. Writing Group:

Writing group members (this project will lead to multiple papers, not necessarily all writing group members will be on each paper):

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

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3. Timeline: The funding period for the R01 supporting this work is 6/15/2022-2/28/2027. We expect the proposed work to be completed within this time frame.

4. Rationale:

Overview: Olfactory impairment affects 15-25%, or ~7.4-12.3 million, older US adults.[1-3] The estimate will only increase in the coming decades as population ages.[4] Although most afflicted people are unaware of this sensory deficit,[1-3] olfactory impairment may have significant implications for the health of older adults. We recently found that olfactory impairment likely signifies adverse health outcomes *beyond* its known relationships with neurodegenerative diseases.[5 6] Based on these findings and our pilot data, the present project aims to identify other adverse health outcomes that olfactory impairment may potentially herald, in addition to neurodegeneration.

Olfactory impairment and neurodegeneration: To date, olfactory impairment has been best studied as one of the earliest and most important prodromal symptoms of Parkinson's disease (PD) and dementia,[7-10] and as a robust predictor for total mortality.[5 11-15] Braak et al.[16] further posited that PD synucleinopathy might first develop within the olfactory structures years or decades before invading substantia nigra, suggesting that olfactory impairment is an integral part of PD prodromal development. Consistently, we[17] and others[18] found that olfactory impairment might precede PD clinical diagnosis by a decade or more. Similar roles of olfactory impairment in Alzheimer's disease (AD)[19-22] have also been established. Associations of olfactory impairment with other dementia subtypes (*e.g.*, Lewy body dementia,[23-26] vascular dementia[27 28]) are also reported, but less established.

Olfactory impairment and other diseases: In older adults, the prevalence of olfactory impairment is age-dependent. While olfactory impairment is a proven "canary in a coal mine" for impending dementia/PD, could it be a "miner's canary" for other age-related health issues as well? Our recent findings[5] support this idea. In the Health ABC Study, we analyzed potential pathways that connect olfactory impairment to increased mortality in older adults.[5] To our surprise, we found that only 22% of the excess 10-yr mortality associated with olfactory impairment was explained by dementia/PD.[5] Another 6% was explained by weight loss. Thus, approximately 70% of this excess mortality remains unexplained. Beyond neurodegenerative diseases and mortality, the health implications of olfactory impairment have been the subjects of wide speculation, for example, adverse effects on cardiovascular diseases, diabetes, depression, and declines in physical and mental functions; however, empirical evidence is limited and predominantly cross-sectional.

5. Main Hypothesis/Study Questions:

Aim 1: Examine the association of olfactory impairment among older adults with the incidence of dementia, PD, cardiovascular diseases, diabetes, pneumonia, and chronic lower respiratory diseases.

Aim 2: Examine the association of olfactory impairment among older adults with total and cause-specific mortality.

Sub-Aim 2a: Explore how much excess mortality observed among older adults with olfactory impairment can be explained by the aforementioned chronic diseases, assuming causal relationships.

This study will be conducted within two cohorts – the ARIC Study cohort and the Health ABC Study cohort. Manuscripts may be published as companion papers or in pooled/meta analyses.

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).

Exposure of interest: In ARIC-NCS, 6,093 participants completed a 12-item Sniffin' Stick (SS) test at V5 in 2011-2013 and 3,489 again at V6 in 2015-2016. We will use V5 olfaction data in the primary analysis because our main interest is to ascertain what a single smell test foretells about one's future health in aging. Our primary exposure measure is olfaction status at V5, and we will define *poor* olfaction as test scores ≤8, *moderate* as 9-10, and *good* as 11-12 (reference group), approximately corresponding to distribution tertiles and consistent with population norms.[41 42] We will conduct secondary analysis among ~3,400 ARIC-NCS participants with both V5/V6 olfaction data to assess olfactory change in association with various health outcomes.

Disease outcomes: The following disease outcomes will be ascertained from hospitalization and death surveillances, self-reported doctor diagnoses, symptomatic assessments, medication usages collected via periodical clinical visits or telephone interviews. We will consider Visit 5 as the study baseline and analyze outcome data ascertained through Dec. 31, 2021. For disease outcomes other than pneumonia, prevalent cases will be excluded from analyses.

1) Dementia: Analyses will be based on dementia ascertained at Visits 6, 7, 8 (via telephone) and 9. Proposed assessments (longitudinal), which will examine the association of olfaction with incident dementia (ascertained through Visit 9), will be distinct from and complement Dr. Priya Palta's published manuscript (ARIC MP#2872), in which she and co-authors examined the cross-sectional association of olfaction with cognitive function.

2) PD diagnosis in AIRC has adjudicated through Dec. 2015 according to a published protocol;[29 30] new cases, occurring during the period 2016-2021, will be adjudicated by the PI and his consultant, a movement disorder specialist (*X Huang from Penn State*) via a comprehensive review of self-reported physician-made diagnosis, medication uses, and hospitalization and death reports.

3) CVD includes coronary heart diseases, heart failure, and stroke, adjudicated by an expert panel of physicians with the assistance of computerized algorithms.[31-37]

4) Diabetes will be defined as elevated glucose at study visits (fasting glucose ≥7.0 mmol/l or non-fasting glucose ≥11.1 mmol/l), self-reported diabetes diagnosis or use of diabetes medication at study visits. Additionally, we will account for a self-report of a diabetes diagnosis of use of diabetes medication reported during the semi-annual telephone interviews.[38 39]

5) Pneumonia and ***chronic lower respiratory disease*** will be ascertained from hospitalization and death surveillance data using ICD codes.[40]

6) Death**:** Death events in ARIC have been identified from regular study contacts, hospitalization surveillance, regular NDI search, and local obituaries. The date and cause of death will be further verified by death certificate review.

We expect to analyze disease and mortality data through Dec. 31, 2021.

Statistical analyses: We will define the outcomes of interest as time from olfaction testing to new diagnosis of the above-referenced diseases. Except for pneumonia, we will examine individuals free of the disease at baseline. For pneumonia, because it is acute and may occur multiple times in life, we will not exclude participants with a history of pneumonia from the analysis**.** We will use hospitalization records in the ascertainment of pneumonia events. We will follow up eligible participants from the time of olfaction testing to disease diagnosis, last known contact, death, or

the end of follow-up, whichever occurs first. For each outcome, we will first conduct cohort-specific analysis (separately within ARIC and the Health ABC study), cross-validate findings, and then may analyze pooled data when appropriate. Both cohorts have established health surveillance infrastructures to identify disease diagnoses of participants, including those who did not actively participate in recent clinical visits or phone follow-ups. Due to the advanced age of our study participants, we will account for competing risk of death in the analysis[43] and for attrition due to non-participation. We will mainly use the absolute risk regression (ARR) model[44] to estimate the effect of olfaction on the cumulative incidence of the outcome of interest over time. This approach allows the effect of exposure to vary over time and provides 2 supremum tests for the null hypotheses of a constant effect and a zero effect respectively. Further, instead of hazard ratio, which is difficult to interpret,[45 46] ARR analysis directly quantifies the ratio of disease risk between olfaction groups given fixed values of other predictors. All analyses will account for age at olfaction testing, sex, and race-study site variables. Selection of other covariates *(e.g.,* education, marital status, smoking, coffee drinking, head injury, physical activity, body mass index, alcohol consumption, general health status, and chronic diseases*)* will be guided by literature. We will use the Bonferroni correction to account for multiple comparisons when analyzing multiple outcomes within the same analysis. We will repeat the analyses by sex and race/site to test potential effect modifications. To do so, we will apply a two-sample Z-test using subgroup effect estimates and corresponding standard errors, which is more robust than the interaction-term test because it does not assume that the effects of other covariates are the same across subgroups. If the associations of olfaction and disease we identify are time-varying in both subgroups, we will use an interaction term to test differential effects by subgroups. We will conduct secondary analysis to examine olfaction and its change from Visit 5 to Visit 6 in association with the various disease risks. The analysis plan is the same as above except that the categorized olfaction at *V5* will be replaced by the continuous B-SIT score at V5, the annual change rate of B-SIT score between V5-V6 (change/time gap), and their interaction. In sensitivity analyses, we will examine the robustness of results by excluding participants with prior sinus surgery, nasal polyps, or chronic rhinosinusitis as identified by hospitalization ICD-9 codes (22.x, 471.x, and 473.x) and participants with prior surgery/radiation involving the skull base or brain as noted in the V5 Neuro History Questionnaire.

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/aricproposals/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)?

- MP 2957 Harrison et al., Interrelationships of Olfaction, Brain Amyloid, and Cognitions: the ARIC-PET Study
- MS 2069 Chen, H et al., Genome-wide Meta-analysis on the Sense of Smell Among US Older Adults.
- MP 3993 Shrestha S., Olfactory decline in older adults and its predictors: the Atherosclerosis Risk in Communities Study
- MP3911 Shrestha S., Olfactory impairment and relations to microstructural integrity of the brain in the Atherosclerosis Risk in Communities Study
- MP 3958 Shneider A., Associations of Prior Head Injury with Olfactory Functioning
- MS 2872 Palta P., Olfactory function and neurocognitive outcomes in old age: The Atherosclerosis Risk in Communities Neurocognitive Study

Some of the lead authors of these proposals have been invited to this writing group, although not necessarily they will be on each individual manuscript.

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* #2020.01**)**
_X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s) 2010.17, 2014.25**)**

*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.

We expect multiple manuscripts from this proposal.

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.

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