ARIC Manuscript Proposal #4077

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

1.a. Full Title: Olfactory impairment, Functional Declines, and Frailty in Older Adults

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

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:

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]

In older adults, physiological functions decline with age. Such functional declines often develop insidiously and may elude detection at early stages. Frailty is a health construct representing the cumulative impacts of declines in multiple physiological systems and increased susceptibility to stressors. Both are common in older adults and affect health and daily life, sometimes in the absence of defined clinical comorbidity. Olfactory impairment among older adults can lead to reduced food intake and subsequent weight loss, which can lead to frailty and eventually higher mortality.[7] Recent data have linked olfactory impairment to poor physical[8] and mental[9] performance and frailty[10], but prospective evidence is largely lacking except for that related to cognitive function.

We will test the hypotheses that poor, as compared to age-normal, olfaction is associated with faster declines in physical and cognitive/mental functions, and with an elevated risk of frailty.

5. Main Hypothesis/Study Questions:

Aim 1: Examine the association of olfaction among older adults with change in physical and cognitive function

Aim 2: Examine the association of olfaction among older adults with frailty and change in frailty status.

We will ***test the hypothesis*** that poor, as compared to good, olfaction is associated with *faster* declines across multiple physiological systems, in physical, pulmonary, and cognitive/mental functions, and with a higher risk of frailty.

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: A total of 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. 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. 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.[9 11]

Outcomes of interest:

Frailty: We will examine two frailty constructs: the Fried frailty phenotype[12] and the Rockwood frailty index.[13] The frailty phenotype has 5 components, including weight loss, weakness, exhaustion, slowness, and physical inactivity, and is *conventionally* defined as *frailty (>2 items), pre-frailty (1-2), and robustness (0).*[12 14] We will examine associations of olfaction with the Fried frailty phenotype and with its individual components.

The frailty index is defined as the accumulation of age-related deficits across multiple physiological systems in a given individual, using ≥30 age-related health indicators of disease diagnosis, signs/symptoms, disability, and abnormal medical/biomarker test results.[13-15] Compared with the frailty phenotype, which focuses on assessing physical deficits, the frailty index quantifies the accumulation of age-related health deficits, supporting the concept of reduced homoeostatic reserve in frailty, and has been used as a proxy for accelerated aging.[16 17] As a proportion of accumulated deficits to the total number of deficits examined , the frailty index ranges from 0 to 1 and is often analyzed as a continuous variable to capture the varying degrees of frailty.

Both measures of frailty are available in ARIC at Visits 5, 6, and 7. We will examine the cross-sectional association of olfaction with frailty at Visit 5 and with its change from Visit 5 to Visits 6 and 7.

***Physical functions*:** We will define the primary outcome of physical functioning as the Short Physical Performance Battery (SPPB), used widely to assess lower-extremity physical functions of older adults. [18 19] The test includes series of balance tasks (side-by-side, semi-tandem, full-tandem stands for 10 sec. each), time to complete 5 repeated chair stands, & 6-meter walk. Each component scores from 0 (unable) to 4 (best performance), with a total score ranging from 0-12. SPPB was administered at ARIC Visits 5, 6 and Visit 7. In our analyses we will examine change in the SPPB score from Visit 5 to Visit 6 and 7.

***Cognitive & mental functions*:** The ARIC-NCS, designed to study cognitive decline and dementia,[20] has been conducting comprehensive cognitive assessments since V5**.** This battery of tests includes *delayed word recall, digit symbol substitution, and word fluency tests, incidental learning, animal naming, logical memory I & II, digit span backwards, trial making A & B,* and *Boston naming test*. Data are available for Visits 5-7. To study cognitive decline across visits, *ARIC-NCS* has developed factor scores for *global cognition* and *the domains of executive function, language, and memory*.[21] We will examine the association of olfaction with change in the global cognitive function factor scores from Visit 5 to Visits 6 and 7.

Statistical analyses: The analytic outcomes were repeatedly assessed as continuous (*e.g.,* cognitive function, *frailty index*) and ordinal (*e.g.,* frailty phenotype) measures. As these

assessments are only available for participants attending clinical visits, we will use inverse probability of attrition weighting to account for non-attendance at visits. We will also jointly model the longitudinal outcome of interest, death, and dropout[22] to estimate the effects of olfaction on longitudinal changes in functional measures in a mortal cohort.[23] Specifically, for each outcome, the joint model will include 2 sub-models: ***1)*** A linear mixed model to analyze repeatedly-assessed continuous measures or a generalized linear mixed model to analyze ordinal outcomes, where the fixed-effects part will include a flexible specification of follow-up time (determined based on LOESS curve[24]), the main effects of olfaction and carefully chosen confounders and interactions between the time terms and other covariates. The random-effects part will include an intercept and the time terms. ***2)*** A Cox-type cause-specific hazard model to account for non-participation and death. Specifically, this competing risk model incorporates covariates, including the concurrent functional and frailty constructs (the fixed-effects + random-effects parts), into the cause-specific hazards of non-participation and death in a multiplicative manner as the Cox model does. In this joint model, the cause-specific hazards of death and non-participation depend on the trajectory of the functional/frailty outcome. The coefficients of olfaction and its interaction with time in the longitudinal sub-model 1 can be interpreted as subject-level effects of olfaction on the trajectories of the outcome in the alive population,[22] which are our target parameters. Model fitting will be carried out using the R package 'JM'. We will use the likelihood ratio (LR) tests to test the effects of olfaction on outcome trajectories, by comparing a model with the main effect of olfaction and interactions between olfaction and time and a model without such terms in sub-model 1. When both the death and non-participation are random, the mixed model estimates are unbiased.[22] Even if either of the 2 processes is not random, the joint model will be unbiased when the correlation between the functioning measure and the non-random attrition process is modeled correctly.[25] Rate of change in physical and cognitive function will be examined over the entire time of follow-up from Visit 5 and as an annualized measure. 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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