ARIC Manuscript Proposal #2872

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SC Reviewed: _____	**Status: _____**	**Priority: ____**

1a. Full Title: Olfactory impairment and cognitive function: the Atherosclerosis Risk in Communities Neurocognitive Study

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

2. Writing Group:
Writing group members: Priya Palta (first), Jennifer Deal, Michael Griswold, David Knopman, Gerardo Heiss, Honglei Chen, Thomas H. Mosley, others welcome

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

First author: Priya Palta
Address: University of North Carolina at Chapel Hill
137 E. Franklin Street, Suite 306
Chapel Hill, NC 27514
Phone: (352) 219-4108
E-mail: priya_palta@unc.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: Thomas Mosley
Address: University of Mississippi Medical Center
The MIND Center
2500 N. State St.
Jackson, MS 39216
E-mail: tmosley@umc.edu

3. Timeline: Analyses to start upon approval of proposal. Submit for an abstract to AHA EPI/Lifestyle meeting due October 19th, 2016. Submit for publication within 9 months from proposal approval.

4. Rationale:

Olfactory impairment is characterized as the loss in sense of smell where an individual is no longer able to detect odors. The prevalence of olfactory impairment is almost 25% in individuals aged 53 years and older and increases to over 60% among individuals aged 80-97 years.[1] Impairments in olfaction can lead to decreases in quality of life (i.e. loss of pleasure in food) and increases in health hazards (i.e. inability to detect spoiled food and gas leaks). The most salient predictor for olfactory impairment among otherwise healthy adults is age. Other predictors include inflammation of the nasal passages, upper respiratory infections, viral infections, exposure to toxins, and head trauma.

Beyond the associated quality of life outcomes for olfactory impairment, it is hypothesized to be an early sign of neurodegenerative impairments leading to both Parkinson's disease and Alzheimer's disease.[2] Data from autopsy studies done in the Rush Memory and Aging Project show

that a greater loss in the sense of smell is associated with plaques and tangles in the central olfactory region of the brain,[3] which connects to the hippocampal region of the brain where neuropathologic changes related to dementia are first sited. Therefore, olfactory impairments may be an early marker for mild cognitive impairment (MCI) and/or dementia. A few population-based studies have examined the associations between olfaction and MCI/dementia and progression from MCI to dementia. Recent data from the Mayo Clinic Study of Aging found olfactory impairment to be associated with incident MCI and increased risk for progression from MCI to Alzheimer's dementia.[4] In a sample of 589 community-dwelling adults without cognitive impairment, a poorer odor identification score was predictive of the development of MCI.[5] In a multiethnic cohort of 1,037 participants from Northern Manhattan, those in the lowest quartile of smell test score had a higher risk of transitioning to Alzheimer's dementia compared to participants in the highest quartile of smell test score.[6]

An understanding of the associations of olfaction with cognitive function, whose changes are informative to the detection of clinically defined MCI and dementia, may elicit earlier diagnoses of these neurodegenerative conditions and prompt earlier preventive and/or intervention efforts. Also in the Mayo Clinic Study of Aging, researchers observed for every one-unit decrease in smell score (lower score=worse smell), a worse baseline and longitudinal performance in memory, executive function, language and global function. Similarly, findings from the Rush Memory and Aging Project showed a poorer smell score to be associated with lower baseline cognitive function and faster rates of decline in global cognition, memory, and processing speed.[7] More population-based studies of olfaction and cognitive function, and within specific domains of cognition, are needed to confirm these findings.

African Americans and Hispanics are observed to have significantly worse olfactory function,[8] which is even greater than the differences across gender groups.[9] Building on the prior literature on olfactory impairment and neurocognitive outcomes and related data on racial and gender differences in olfactory function, ARIC provides the exceptional opportunity to contribute to the existing literature by examining these associations in a well-characterized biracial sample of older adults with data on multidimensional cognition and adjudicated MCI/dementia outcomes and their etiologic diagnoses. Therefore, we propose to the test the hypothesis that poor sense of smell, as measured by 12-item Sniffin' Sticks' screening test, is associated with (1) lower cognitive function, and (2) increased odds of mild cognitive impairment (MCI) and dementia, with particular attention to examining differences in these associations by race and gender subgroups.

5. Main Hypothesis/Study Questions:

Aim 1.1: Characterize the cross-sectional relationship of olfactory impairment with domain-specific cognitive function in a sample of African-American and Caucasian older adults.

Aim 1.2: To test the hypothesis that olfactory impairment measured in older adulthood is associated with a greater decline in domain-specific cognition measured from mid- to late-life.

Aim 2: To test the hypothesis that olfactory impairment is cross-sectionally associated with higher odds of (a) mild cognitive impairment and (b) dementia.

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 analysis of olfactory impairment measured in older adulthood (Visit 5) and (1) domain-specific cognitive function and (2) odds of MCI and dementia. A subsidiary cross-temporal analysis of olfactory impairment measured in older adulthood with change in domain-specific cognition from mid- to late-life.

Odor identification data:			**n=6,063**
Neurocognition data:			
- Full neuro battery			**n=5,683**
- DWRT, DSST, WFT	n=5,525	n=5,164	n=5,264

Exclusions: Participants self-identified as Asian; and African American participants from the Minnesota and Maryland sites. For Aim 1.2, participants without a baseline (visit 2) neuropsychological assessment will be excluded.

Exposure(s):

Olfactory impairment measured by the 12-item Sniffin' Sticks screening test[10] to evaluate sense of smell

Participants are asked to smell 12 common odorants in a felt-tip pen (orange, leather, cinnamon, peppermint, banana, lemon, licorice, coffee, cloves, pineapple, rose, and fish), one at a time, and asked to identify each using a multiple choice format of 4 possible answer choices. One point is given to each correctly identified odorant, yielding a total possible score ranging from 0-12. Sense of smell will be analyzed (1) continuously and (2) dichotomized according the clinically defined cutpoint for olfactory impairment/anosmia (smell score ≤ 6).[11]

Outcomes- Neurocognitive outcomes

Aim 1.1. Cognition measured at visit 5 (cross-sectional)

The following tests were included in the comprehensive neuropsychological battery administered at ARIC visit 5:

- Delayed word recall test (DWRT)
- Digit symbol substitution test (DSST)
- Word fluency test (WFT)
- Logical Memory I and II
- Trail Making Test, Part A
- Trail Making Test, Part B
- Boston Naming Test
- Animal Naming
- Digit Span Backwards
- Incidental Learning

Tests will be examined individually and within domains. To facilitate relative comparisons across these tests, the raw test scores will be standardized to accommodate differences in scales. For each cognitive test at a visit, *z* scores will be calculated based on the means and standard deviations. Domain scores will be estimated by averaging the *z* scores for tests within a particular domain and then standardizing the averaged score using the mean and standard deviation. This ensures that each domain score is standardized to a mean=0 and standard deviation=1.

Aim 1.2 Secondary Analyses. Cognition measured at visits 2, 4 and 5 (longitudinal) Three cognitive tests were administered by trained interviewers using a standardized protocol at visits 2, 4 and 5: the Delayed Word Recall Test (DWRT), the Digit Symbol Substitution Test (DSST), and the Word Fluency Test (WFT). The *DWRT is a test of immediate verbal memory* where participants are asked to learn a 10-word list and then must recall as many words as possible after a 5-minute delay. The score is based on the total number of correctly recalled words. The *DSST is a test of executive function and psychomotor speed* where participants are asked to relate numbers to symbols using a key.[12] With a maximum score of 93, the participant's score is the number of correct symbol-number matches within 90 seconds. The *WFT is a test of language and executive function*.[13] Participants are asked to generate as many words as possible beginning with the letter, "F," "A," and "S" within one minute. The participant's score is the total number of correctly generated words from the three letters. To facilitate relative comparisons across these tests, the raw test scores will be standardized to accommodate differences in scales. For each cognitive test at a visit, *z* scores will be calculated based on the means and standard deviations at baseline (visit 2). The global cognition *z* score will be calculated by averaging the *z* scores across the three tests.

Aim 2. MCI and dementia as ascertained at the visit 5 examination[14]

Covariates: For Aims 1.1, and 2, time-varying covariates (smoking, diabetes, hypertension/blood pressure, anti-hypertensive medication use, stroke) are measured at visit 5.

For Aim 1.2, we will consider the following covariates measured at visit 2: age, educational attainment, smoking, diabetes, hypertension/blood pressure, anti-hypertensive medication use, stroke, and ApoE4.

Analysis: Sense of smell will be analyzed (1) continuously (score range: 0-12) and (2) dichotomized according to the clinically defined cutpoint for anosmia/olfactory impairment (smell identification score ≤ 6).

Aim 1.1: Multivariable linear regression models will be used to estimate the cross-sectional associations of olfaction with each cognitive test *z* score and cognitive domain score at visit 5.

Aim 1.2 Secondary Analyses: Using time on study, we will perform a longitudinal analysis using mixed effects models with a random intercept, a random slope for spline 1 and a random slope for spline 2.We will use an independence covariance matrix for the random effects. To account for the lapse in data collection in ARIC, a linear spline will be included at 6 years (visit 4) to estimate the change in cognition from (a) 0-6 years and (b) 6 years- end of study. An interaction term between continuous and categorical measures of olfaction and each time spline will be incorporated to estimate the change separately for years 0-6 and 6 years-end of study.

Aim 2: Multivariable logistic regression models will be used to estimate the odds of MCI and/or dementia per unit increase in continuous measures of olfaction and using the clinically defined cutpoint for anosmia/olfactory impairment at visit 5 (smell identification score ≤ 6). Models will be weighted to account for sampling probability. Vascular etiologies have been attributed to diagnoses of MCI and dementia in the ARIC cohort.[14] As a subsidiary analysis, we will examine the association between olfactory impairment and MCI/dementia among persons both with and without cerebrovascular features (e.g. history of stroke, infarcts on imaging, extensive WMH).

For the above analyses, we will examine effect modification by race, gender, and ApoE4.

Attrition and selection biases are of concern when using ARIC data since healthier individuals would have the greatest influence on associations when analyses are restricted to visit 5. At the time of the visit 5 examination (2011-2013), 33% (n=5,275) of participants had died and 38% (n=3,979) of those alive did not attend the examination. We will explore the use Heckman selection models to account for informative missingness for those participants who either died prior to visit 5 or were alive and did not attend visit 5.[15,16] The Heckman selection model is a type of joint model that allows for a two-stage estimation of submodels; Model 1: the probability of non-attendance at visit 5 due to either death or dropout, and Model 2: the exposure-outcome association accounting for the probability of non-attendance. We have previously identified several sociodemographic, clinical, and social risk factors associated with non-attendance to identify common predictors of both death and dropout. The following variables were identified as significant predictors of non-attendance: age, education, race-center, self-rated health, income, and functional status. In the first submodel, we will estimate the probability of not attending visit 5 using the above set of predictors. This estimated probability of non-attendance at visit 5 will then be included in the second submodel as an explanatory variable for the exposure-outcome associations described. Similar Heckman-type selection models have been used and validated in other epidemiologic studies to account for selection biases.[17,18]

Methodological limitations: The proposed longitudinal analyses in Aim 1.2 assumes that olfactory acuity measured in older adults is fixed and time-invariant since mid-life, which we know to be an important consideration given the changes in olfactory acuity expected with increasing age. Additionally, issues related to reverse causality will need to be addressed in the manuscript for the longitudinal aim 1.2. Therefore, we have proposed these analyses to be strictly secondary to the cross-sectional analyses of olfaction and cognition/MCI/dementia at Visit 5.

7.a. 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 ICTDER03 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 file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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)?

MS#2445 (lead: Honglei Chen) – Prevalence and associated factors of anosmia
MS#2841 (lead: Honglei Chen) – Mid-life biomarkers in relation to anosmia late in life

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* 1998.02-Life course SES, social context, and CVD (SESCVD)

___ 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. Agreed

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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