ARIC Manuscript Proposal #4074

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

1.a. Full Title: Normative Data for the 12-item Sniffin' Sticks Odor Identification Test in Older Adults from the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Olfaction Norms

2. Writing Group members: Vidya Kamath (first); Andrea L.C. Schneider (senior); Honglei Chen, Jennifer Deal; Dawn Mechanic-Hamilton, Thomas H. Mosley; Srishti Shrestha; others welcome

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

First author: Vidya (Vidyulata) Kamath, PhD
Address: 600 North Wolfe Street, Meyer 218, Baltimore, MD 21287
Phone: 410-614-6342 Fax: 410-955-0504
Email: vkamath@jhmi.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, Univ 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 olfactory system is a relatively neglected yet informative avenue for understanding neurodegenerative and neuropsychiatric conditions in late life.[1, 2] With only two synapses between sensory environment and cortical targets, olfactory probes provide direct environmental access to the orbitofrontal and limbic neurocircuitry implicated in many of these conditions. Accelerated olfactory loss is observed in multiple neurodegenerative diseases.[3, 4] In Parkinson's disease, hyposmia is an early pre-clinical risk marker that can predate clinical motor signs by up to ten years.[5] Smell loss is also observed in cognitively unimpaired older adults who ultimately transition to mild cognitive impairment or Alzheimer's dementia at longitudinal follow-up.[6-8] In addition, multiple reports have demonstrated that olfactory loss in late life is an independent predictor of all-cause mortality.[9-11] Due to the current COVID-19 pandemic, chronic olfactory loss has emerged as a major public health concern. It is estimated that 700,000 to 1.6

million people in the US may experience long-term olfactory dysfunction due to COVID-19.[12] As such, there is a need for comprehensive normative data for psychophysical olfactory tests in Black and White older adults.

The 12-item Sniffin Sticks Odor Identification Test (SSOIT-12) was initially developed in Germany and later normed in a cohort of 1,012 healthy subjects, 5 to 86 years of age, from Dresden, Germany.[13] The test is comprised of 12 common odors in which participants identify the odorant from four choices in a multiple-choice format. Although the test has since been normed in other populations across Europe, there is limited normative data for the 12-item version in older adults living in the United States. The absence of this data diminishes the clinical utility of the SSOIT-12 in the United States, where accurate assessment of olfactory functioning in older adults is useful for the evaluation of a range of neurologic, psychiatric and sinonasal conditions. Indeed, formal assessment of olfactory functioning has demonstrated utility in differentiating persons with Parkinson's disease and dementia with Lewy bodies from individuals with essential tremor and atypical forms of neurodegenerative parkinsonism (progressive supranuclear palsy, corticobasal syndrome).[14] Olfactory testing has been used in conjunction with neuropsychological measures to identify persons at risk for Alzheimer's disease. Olfactory assessment is also employed pre-post intervention for chronic sinusitis,[15] and is sensitive to the degree of orbitofrontal involvement or damage following traumatic brain injury or anterior communicating artery aneurysms.[16]

Psychophysical assessment of olfactory functioning allows clinicians to assess the degree of loss, establish concordance with a patient's reported difficulties and monitor changes over time. Prior work has demonstrated that healthy older adults show high rates of discordance between self-report and quantitative assessment and unawareness of olfactory loss can worsen with aging and medical co-morbidities.[17, 18] In a recent ARIC study, we found significant rates of discordance between self-ratings of olfactory abilities and psychophysical test scores in older adults with history of head injury.[19] Unawareness of olfactory loss can make it difficult to seek medical evaluation, delaying treatment and leading to adverse outcomes (e.g., eating spoiled food, inability to detect dangerous chemicals in one's environment).

The ARIC cohort will allow us to expand on existing work by developing normative data for the SSOIT-12 in a large, deeply phenotyped sample of Black and White older adults. We will use the existing Visit 5 normative sample (see exclusion criteria in table below). Odor identification performance may vary as a function of differences in region, odor exposure, socioeconomic status, and income level. As such, particular attention will be given to potential differences by age, sex, race, education, WRAT-3 performance, and area deprivation index.

5. Main Hypothesis/Study Questions: Using a subset of the ARIC V5 study population who are free of both clinical and subclinical neurological and sinonasal disease, we aim to develop normative data (separately for each age, sex, and education group - defined below) for the 12-item Sniffin Sticks Odor Identification Test (SSOIT-12).

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 study using V5 data (2011-2013).

Study Population (inclusion/exclusion criteria): We will use the existing V5 Normative Sample, which already has the following exclusion criteria applied:

Substantial cognitive decline prior to visit 5 Defined as **Normative sample exclusion criteria**	**N (not mutually exclusive)**	**Additive decrease in N from previous exclusion**
1. Stroke hospitalization as of Visit 5	267	6271
2. History of neurological disease	404	5979
3. Use of cholinomimetics at Visit 5	137	5887
4. Prorated MMSE < 22	374	5656
5. Self-report memory problems at Visit 5	1548	4474
6. Dementia discharge codes prior to Visit 5	81	4461
7. Dementia diagnosis at Visit 5	349	4414
8. Depression as of Visit 5	637	4135
9. APOE e4/4 allele carrier	144	4063
10. Decline in neurocognitive tests	1943	3094
11. MCI diagnosis or Unknown Diagnosis	1783	2739
12. Impairment identified in GEN	35	2738
13. Impairment identified in follow-up	864	2645
14. Race other than black or white	18	2639
15. Missing WRAT and/or Education, WRAT score <10	226	*2609

We will also exclude participants based on the following sinonasal-related criteria:

- History of surgery or radiation to brain/skull
- Chronic sinonasal disease or prior sinus surgery
- Nasal polyps

We will additionally perform three sensitivity analyses: 1) restricted to never smokers, 2) restricted to individuals without subjective olfactory impairment, 3) inclusion of individuals with depression and APOE e4/4 allele at Visit 5.

Olfaction was assessed using the 12-item Sniffin' Sticks (SSOIT-12[13]) at ARIC Visits 5. 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. We will examine the distribution of scores and consider exclusions for implausible scores (e.g., score of 0 that would be less likely than chance).

Statistical Analysis: To comprehensively characterize our analytic population, we will calculate means (standard deviations) and % for our covariates. Covariates to be included are demographic factors (age (years), sex (male; female), race (White; Black), field center [Minneapolis, MN; Washington County, MD; Jackson, MS; Forsyth County, NC], education [<high school; high

school or vocational school; college, graduate or professional school], income [<$35,000/year; ≥ $35,000/year; not reported], marital status, health insurance status), lifestyle factors (cigarette smoking, alcohol consumption), cardiovascular and genetic risk factors (diabetes, hypertension, history of coronary heart disease), Mini-Mental State Exam score, WRAT-score, ADI, and self-reported health status. We will also compare these among those participants included versus excluded from our analytic population.

In order to create SSOIT-12 norms, we will model the association between age and olfactory score and include terms for sex and education, and will consider interactions of education X sex. We plan to present the linear regression coefficients in tabular form (we will also consider negative binomial or quantile regression models and determine which model best fits the data). We will also present this data as figures (y-axis=SSOIT-12 score, x-axis=age), with mean, -1.5 SD, and -2 SD regression lines plotted for each age, sex, and education category. We also plan to present the summary data derived from our linear regressions tabular form giving mean, -1.5 SD, -2 SD scores for olfactory score stratified by 5-year age range (65-<70, 70-<75, 75-<80, 80-<85, 85-90), sex, and education. We will also evaluate for potential differences by race, WRAT-3 performance, and area deprivation index.

As a sensitivity analysis, we will also calculate normative values based on observed (not model-derived) SSOIT-12 scores by age group using methods, as was done in MOAANS[20], where norms are shown corresponding to the midpoint of the age group to represent individuals of that age, plus or minus 2.5 years (to get 5-year age groups), but the norm score will be derived from a subsample of all participants who are within five years of the midpoint age.

Limitations: Limitations of the current work include the single test of olfactory functioning and the limited age range of our population to older adults between 65 and 90 years of age. In addition, participants did not undergo a formal ENT evaluation to rule out peripheral causes to olfactory loss. Finally, the influence of medication use on SSOIT-12 is a limitation of the current work. Prior reviews[21, 22] note the complexities and few studies have systematically examined what medications influence quantitative olfactory assessment. We will consider sensitivity analyses for certain medication types, if feasible. The number of participants in certain cells stratified by age, sex, and education may be too small to generate norms. In these situations, we will consider collapsing categories. In order to increase numbers at the upper extremes of age, we will also consider using SSOIT-12 data from participants who completed this measure at V6 who meet criteria for the normative population and were not assessed at V5 (to exclude practice effects).

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 (APOE e4 genotype)

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)?

- 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.
- Schneider ALC, Sharrett AR, Gottesman RF, et al. Normative data for 8 neuropsychological tests in older blacks and whites from the Atherosclerosis Risk in Communities (ARIC) study. *Alzheimer's Disease and Associated Disorders.* 2015;29(1):32-44.
- Schneider, ALC, Gottesman, RF, Mosley, TH, Shrestha, S, Rowan, N, Sharrett, AR, Chen, H, Kamath, V. (in press). Associations of prior head injury with olfactory functioning: Results from the Atherosclerosis Risk in Communities (ARIC) Study. *JAMA Otolaryngology – Head & Neck Surgery*.
- Kamath, V, Senjem, ML, Spychalla, AJ, Chen, H, Palta, P, Mosley, TH, Windham, BG, Griswold, M, Knopman, DS, Gottesman, RF, Jack, CR, Sharrett, AR, Schneider, ALC. (in press). The neuroanatomic correlates of olfactory identification impairment in healthy older adults and persons with mild cognitive impairment. *Journal of Alzheimer's Disease*.
- #2841: Mid-life biomarkers in relation to anosmia late in life (Chen/Shrestha)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes _X_ No (ARIC-NCS)

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ 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.

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.

References:

1. Moberg PJ, Kamath V, Marchetto DM, et al. Meta-analysis of olfactory function in schizophrenia, first-degree family members, and youths at-risk for psychosis. *Schizophr Bull* Jan 2014;40(1):50-59.

2. Croy I, Hummel T. Olfaction as a marker for depression. *Journal of neurology* Apr 2017;264(4):631-638.

3. Daulatzai MA. Olfactory dysfunction: its early temporal relationship and neural correlates in the pathogenesis of Alzheimer's disease. *Journal of neural transmission* Oct 2015;122(10):1475-1497.

4. Doty RL, Kamath V. The influences of age on olfaction: A review. *Frontiers in psychology* 2014;5:20.

5. Chen H, Shrestha S, Huang X, et al. Olfaction and incident Parkinson disease in US white and black older adults. *Neurology* Oct 3 2017;89(14):1441-1447.

6. Devanand DP, Lee S, Manly J, et al. Olfactory deficits predict cognitive decline and Alzheimer dementia in an urban community. *Neurology* 2015/01/13/ 2015;84(2):182-189.

7. Schubert CR, Carmichael LL, Murphy C, Klein BEK, Klein R, Cruickshanks KJ. Olfaction and the 5-year incidence of cognitive impairment in an epidemiological study of older adults. *J Am Geriatr Soc* 2008/08// 2008;56(8):1517-1521.

8. Yaffe K, Freimer D, Chen H, et al. Olfaction and risk of dementia in a biracial cohort of older adults. *Neurology* 2017/01/31/ 2017;88(5):456-462.

9. Devanand DP, Lee S, Manly J, et al. Olfactory identification deficits and increased mortality in the community. *Ann Neurol* Sep 2015;78(3):401-411.

10. Pinto JM, Wroblewski KE, Kern DW, Schumm LP, McClintock MK. Olfactory dysfunction predicts 5-year mortality in older adults. *PloS one* 2014;9(10):e107541.

11. Liu B, Luo Z, Pinto JM, et al. Relationship Between Poor Olfaction and Mortality Among Community-Dwelling Older Adults: A Cohort Study. *Ann Intern Med* May 21 2019;170(10):673-681.

12. Khan AM, Kallogjeri D, Piccirillo JF. Growing Public Health Concern of COVID-19 Chronic Olfactory Dysfunction. *JAMA otolaryngology-- head & neck surgery* Nov 18 2021.

13. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' sticks': Olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chemical senses* Feb 1997;22(1):39-52.
14. Doty RL, Hawkes CH. Chemosensory dysfunction in neurodegenerative diseases. *Handbook of clinical neurology* 2019;164:325-360.
15. Haxel BR, Boessert P, Weyer-Elberich V, Fruth K. Course of olfaction after sinus surgery for chronic rhinosinusitis. *Laryngoscope investigative otolaryngology* Oct 2017;2(5):269-275.
16. Zald DH, Andreotti C. Neuropsychological assessment of the orbital and ventromedial prefrontal cortex. *Neuropsychologia* Oct 2010;48(12):3377-3391.
17. White TL, Kurtz DB. The relationship between metacognitive awareness of olfactory ability and age in people reporting chemosensory disturbances. *The American journal of psychology* Spring 2003;116(1):99-110.
18. Adams DR, Wroblewski KE, Kern DW, Kozloski MJ, Dale W, McClintock MK, Pinto JM. Factors Associated with Inaccurate Self-Reporting of Olfactory Dysfunction in Older US Adults. *Chemical senses* Mar 1 2017;42(3):223-231.
19. Schneider A, Gottesman R, Mosley T, Shrestha S, Rowan NR, Sharrett A, Chen H, Kamath V. Associations of prior head injury with olfactory functioning: Results from the Atherosclerosis Risk in Communities (ARIC) Study. *JAMA Otolaryngology – Head & Neck Surgery* in press.
20. Lucas JA, Ivnik RJ, Willis FB, Ferman TJ, Smith GE, Parfitt FC, Petersen RC, Graff-Radford NR. Mayo's Older African Americans Normative Studies: normative data for commonly used clinical neuropsychological measures. *Clin Neuropsychol* Jun 2005;19(2):162-183.
21. Schiffman SS. Influence of medications on taste and smell. *World journal of otorhinolaryngology - head and neck surgery* Mar 2018;4(1):84-91.
22. Lotsch J, Knothe C, Lippmann C, Ultsch A, Hummel T, Walter C. Olfactory drug effects approached from human-derived data. *Drug discovery today* Nov 2015;20(11):1398-1406.