ARIC Manuscript Proposal Form

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Publication Committee Review Date: **_12/12/23_**
ARIC Manuscript Proposal Number: **# 4374**

1.a. Full Title: Olfaction and blood-based biomarkers of Alzheimer's disease and neurodegeneration in the ARIC Study

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

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group members: Honglei Chen; Jennifer A. Deal; Michael E. Griswold; Rebecca Gottesman; Vidyulata Kamath (senior); Thomas H. Mosley Jr.; Priya Palta; Srishti Shrestha (first); Andrea L.C. Schneider; Kevin J. Sullivan; B. Gwen Windham; Xiaoqian Zhu (in an alphabetical order); others welcome
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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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

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3. Timeline: Blood-biomarkers proposed herein are measured and have undergone QC. Several papers led by Dr. Palta are underway to report primary ARIC Study findings related to these biomarkers. It is expected that analyses and manuscript preparation for this proposal will

be performed over the next year. We anticipate submitting the manuscript after Dr. Palta's key papers are submitted/published.

4. Rationale: Olfactory impairment appears early in the course of several neurodegenerative conditions, including Alzheimer's disease (AD) [1]. AD-related tau pathology is observed in the olfactory bulb and central olfactory regions years before the onset of clinical symptoms [1]. Though smell loss is observed in other neurodegenerative conditions, including Lewy body disease [2], olfactory performance, in combination with other AD-specific biomarkers, may have clinical utility in the early identification of individuals at high risk of progressing to AD. Thus, research on olfaction in the context of AD may have important implications for understanding early AD pathophysiology.

Prior studies have linked higher levels of blood amyloid-beta ($A\beta_{42}$ and $A\beta_{42}/A\beta_{40}$ ratio) levels (markers of brain amyloidopathy) and lower levels of blood phosphorylated-tau (p-tau) forms, glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL) (markers of tauopathy, reactive astrocytosis/astrocytic injury, and axonal degeneration, respectively) with lower risk of AD or dementia [3-7]. The potential utility of these novel blood-based biomarkers in AD diagnosis and prognosis has been of great interest due to their advantages over neuroimaging and cerebrospinal fluid (CSF) biomarkers, including low cost, MRI contraindications, and lower patient burden. The use of these blood-based biomarkers to characterize Aβ and tau pathology and neurodegeneration in research settings has risen in recent years [3,4]. To date, several studies examining imaging-based and CSF-based markers (mostly cross-sectional in nature) have linked olfactory impairment with pathophysiological hallmarks of AD, including tau and amyloid pathology, and diminished medial temporal and frontal lobes, regions known to be affected early in AD [8-12], although inconsistently [13]. Recent studies suggest that associations of olfaction with tau-pathology and neurodegeneration are stronger among amyloid-positive individuals compared to individuals with minimal brain amyloid burden [9,11,14,15]. For example, Klein et al. found an association between poor smell and tau burden in hippocampal and medial temporal cortex but only in the amyloid-positive subgroup [11], and Tian et al. found an association between accelerated olfactory decline and longitudinal increase in entorhinal tau burden, particularly in those individuals who were amyloid-positive [15]. Further, Lafaille-Magnan et al. reported an association of reduced odor identification with the CSF p-tau/ $A\beta_{42}$ ratio in healthy older adults with a family history of AD[14]. This ratio combines two AD pathological processes and may better characterize AD brain pathology compared to other individual biomarkers and may be useful to examine in blood-based biomarker studies [16-19].

Two prior studies have examined olfaction in relation to blood-based AD biomarkers. In the Beaver Dam Offspring Study (BOSS) of predominantly White adults (*n*=1,529, mean age: 49.2±10 years), olfactory functioning, measured by the 8-item San Diego Odor Identification Test, was not associated with baseline or changes in serum NfL, $A\beta_{42}/A\beta_{40}$ ratio, or total tau levels over the 10-year follow-up period [20]. In contrast, a study of rural-community dwelling Chinese adults (n=1,054, mean age: 70.9±4.6 years) found that higher olfaction score, measured using the 16-item Sniffin' Sticks test, was associated with concurrent lower plasma total tau and NfL concentrations, but not with $A\beta_{42}$, $A\beta_{40}$, or their ratio [21]. With these two studies failing to show consistent associations, the nature of the relationship between olfaction and blood-based

biomarkers remains unclear. Of note, the potential heterogeneity in the associations between olfaction and blood biomarkers of AD and neurodegeneration by amyloid status has not been explored. Thus, further investigations in populations that are large, diverse, and have better clinical characterization of cognitive phenotypes are warranted to better understand these relationships.

In prior ARIC investigations, we reported associations between olfactory impairment and smaller grey matter volumes in regions known to be the primary targets of AD pathogenic processes, including the olfactory cortex, amygdala, entorhinal cortex, and hippocampus in individuals with mild cognitive impairment (MCI) [12]. Poor olfaction was also associated with changes in brain microstructural integrity [22]. Here, utilizing repeated measures of blood biomarkers of AD and neurodegeneration available in a subset of ARIC study participants, we propose to examine associations of olfactory performance with concurrent levels and prospective changes of these biomarkers (namely, $A\beta_{42}$, $A\beta_{40}$, $A\beta_{42}/A\beta_{40}$, GFAP, NfL, p-tau181, and p-tau181/$A\beta_{42}$). We also propose to examine whether the blood $A\beta_{42}/A\beta_{40}$ ratio and brain Aβ deposition (as measured by ^{18}florbetapir positron emission tomography (PET)) modify the associations of olfaction with GFAP, NfL, and p-tau181. The association of olfaction with these biomarkers, if established, would support the potential clinical utility of assessing olfaction in individuals at high risk of dementia and neurodegeneration. Further, the findings may provide mechanistic insights into whether olfaction is indicative of AD-specific or other neurodegenerative pathology. As these blood biomarkers are intended to be convenient markers of AD-specific and other neurodegenerative brain changes, we are interested in evaluating whether any observed associations between olfaction and blood biomarkers are indeed accounted for by such brain changes. We will use available brain imaging data (for example, MRI brain volumes, PET amyloid data) as proposed markers of such brain neuropathology to examine if the associations of olfaction with concurrent and prospective blood-based biomarker levels can be explained by the available brain measures.

5. Main Hypothesis/Study Aims:

- Aim 1: To examine cross-sectional associations of olfaction measured at visit 5 with plasma $A\beta_{42}$, $A\beta_{40}$, $A\beta_{42}/A\beta_{40}$ ratio, GFAP, NfL, and p-tau181 at visit 5. We will also examine if the blood $A\beta_{42}/A\beta_{40}$ ratio and brain Aβ status modify the associations of olfaction with GFAP, NfL, and p-tau181.
    - Hypothesis: We hypothesize that lower olfaction score is associated with lower levels of $A\beta_{42}/A\beta_{40}$ ratio and higher levels of GFAP, NfL, p-tau 181, and p-tau 181/$A\beta_{42}$ ratio.
    - Hypothesis: We hypothesize that the associations of olfaction with GFAP, NfL, and p-tau181 are stronger among those with lower $A\beta_{42}/A\beta_{40}$ ratio and elevated brain Aβ deposition.

- Aim 2: To examine visit 5 olfaction in relation to prospective changes in plasma $A\beta_{42}$, $A\beta_{40}$, $A\beta_{42}/A\beta_{40}$ ratio, GFAP, NfL, and p-tau181 from visit 5 to visit 7. We will also examine if the blood $A\beta_{42}/A\beta_{40}$ ratio and brain Aβ status modify the associations of olfaction with GFAP, NfL, and p-tau181.

- Hypothesis: We hypothesize that lower baseline olfaction score is associated with a decrease in $A\beta_{42}/A\beta_{40}$ ratio and an increase in GFAP, NfL, p-tau 181, and p-tau $181/A\beta_{42}$ ratio levels over time.
- Hypothesis: We hypothesize that the associations of olfaction with GFAP, NfL, and p-tau181 are stronger among those with lower $A\beta_{42}/A\beta_{40}$ ratio and elevated brain Aβ deposition.

- Aim 3: To examine if the associations of visit 5 olfaction with visit 5 plasma biomarkers and prospective change in plasma biomarkers from visit 5 to visit 7 are explained by visit 5 brain imaging markers (namely, brain Aβ deposition as measured by PET and brain volume in medial temporal lobe regions as measured by MRI).
  - Hypothesis: We hypothesize that the associations of olfaction with concurrent and prospective plasma biomarker levels will be highly attenuated when including relevant imaging markers (for example, brain Aβ deposition and brain volume measures will explain the associations with the $A\beta_{42}/A\beta_{40}$ ratio and NfL, respectively).

6. Design and analysis - please address the following aspects:

a) Inclusion/exclusion: The analysis will be performed in a subset of participants with data on olfaction and blood-biomarkers of AD and neurodegeneration.

b) Study design: Cross-sectional (visit 5) and prospective (visits 5 and 7).

c) Outcome and other variables of interest with specific reference to the time of their collection

Blood-based biomarkers: Plasma biomarkers, including $A\beta_{42}$, $A\beta_{40}$, GFAP, NfL, and p-tau 181, were measured using commercially available ultrasensitive single-molecule array assays from Quanterix. Plasma biomarkers were measured in 1,829 visit 5 participants (those with MCI and brain MRI scans were oversampled) and in 521 visit 7 participants (those with at least one 3T MRI after visit 5 were considered).

Olfaction: The 12-item Sniffin' Sticks odor identification test [23] was used to measure olfaction at visit 5. Olfaction score will be modeled as a continuous variable. We will also create categorical outcome anosmia (defined using a conventional cut-off of score ≤ 6)[24]. In secondary analyses, we will consider categorization as >8 [normosmia] versus 7-8 [hyposmia] versus ≤6 [anosmia] if sample size permits.

Note: for our analytical purposes, we will consider olfaction as the independent variable and biomarkers as the dependent variables.

Brain MRI data: Brain MRI scans were performed at 3 Tesla at the visit 5 exam (n=1979). Brain volumes were measured on magnetization-prepared rapid acquisition gradient echo using Freesurfer version 5.1. We will mainly focus on the brain regions that are relevant to olfaction (for example, the temporal, frontal, and AD signature brain regions). We may also

consider using region-specific DTI measures (namely, those of the frontal, temporal, and medial temporal lobe regions) in our analysis. We will work with Dr. Palta to ensure that our analytic plan does not overlap with her proposal (ARIC proposal # 4235).

PET amyloid imaging data: As a part of the ARIC-PET Study, 346 participants from the three ARIC field centers (Maryland, North Carolina, and Mississippi) underwent Florbetapir PET scans within one year of the brain MRI [25]. For our analysis, we will consider a global cortical measure as well as region-specific measures of Aβ (as quantified by Standardized Uptake Volume Ratio (SUVR)). We will evaluate SUVRs as continuous and binary variables using SUVR > 1.2 as a cut-off [25].

Other covariates: age (years; continuous), sex (male; female), self-reported race (Black; White), field center (Minnesota; Maryland; North Carolina; Mississippi), education (<high school; high school/GED/vocational school; college/graduate/professional school, assessed at Visit 1), smoking (never; former; current; not reported), body mass index (kg/m^2), diabetes (yes; no; defined as fasting glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, hemoglobin A1c ≥6.5%, use of diabetes medications, or self-reported history of physician diagnosis), coronary heart disease (adjudicated)[26], hypertension (systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, use of medications, or self-report diagnosis), *APOE ε4* carrier status (0 versus ≥ 1 *ε4* alleles), physical activity (obtained using the Modified Baecke Physical Activity Questionnaire), total cholesterol (mg/dL, measured using enzymatic methods), global cognition factor score (derived from the ten neuropsychological tests using a latent variable approach), and estimated glomerular filtration rate (estimated from CKD-EPI creatinine 2009 equation). Total estimated intracranial volume will also be used for Aim 3. We will use visit 5 covariates as potential confounders for analyses examining cross-sectional associations and prospective changes.

d) Summary of data analysis

Aim 1: Cross-sectional associations between visit 5 olfaction and visit 5 plasma biomarkers of AD and neurodegeneration (n=1,829)

We will use linear regression models to examine the associations of continuous olfaction score and categorical olfaction variables with plasma $A\beta_{42}$, $A\beta_{40}$, $A\beta_{42}/A\beta_{40}$ ratio, GFAP, NfL, p-tau181, and p-tau $181/A\beta_{42}$ ratio adjusting for potential confounders. If the distributional assumptions for linear regression are not met, we will consider variable transformation (for example, log (base 2) transformation of plasma biomarkers). We will consider two sets of adjustment covariates: the first set will adjust for age, sex, race-center, smoking status, and *APOE ε4* carrier status; and the second set will additionally adjust for cardiovascular risk factors and estimated glomerular filtration rate.

In the primary analyses, we will include participants with dementia and stroke at visit 5. However, we will perform a sensitivity analysis excluding them. Further, we will perform a sensitivity analysis excluding individuals with prior sinus surgery, nasal polyps, or chronic rhinosinusitis (as identified by the following hospitalization ICD-9 codes: 22.x, 471.x, and 473.x).

Based on prior evidence that *APOE ε4* carriers and Black race are associated with higher burdens of olfactory impairment and dementia [27-30], we will also examine if these associations differ by *APOE ε4* status and race. Further, sample size permitting, we will examine associations stratified by cognitive status (i.e., if the associations differ among individuals with normal cognition, MCI, and dementia).

We will evaluate if the blood $A\beta_{42}/A\beta_{40}$ ratio and brain SUVRs modify the associations of olfaction with GFAP, NfL, and p-tau181 and test for interaction between olfaction and the continuous baseline (visit 5) $A\beta_{42}/A\beta_{40}$ ratio/SUVRs, adjusting for potential confounders. As with blood biomarkers, we will check the distribution of continuous SUVRs and consider variable transformation as deemed appropriate. We will also consider presenting the associations stratified by the dichotomized $A\beta_{42}/A\beta_{40}$ ratio and SUVR; we will select an appropriate cut-off for the $A\beta_{42}/A\beta_{40}$ ratio, based on our data and extant literature, and use SUVR > 1.2 as a cut-off (cite). The p-tau $181/A\beta_{42}$ ratio will also help address the potential joint associations between these markers, similar to prior work using CSF data [14].

Aim 2: Associations of visit 5 olfaction with changes in plasma biomarkers from visit 5 to visit 7.

We will use linear mixed models with random intercepts and slopes to examine associations of visit 5 olfaction (continuous olfaction score and categorical olfaction variable) with changes in plasma biomarkers from visit 5 to visit 7, adjusting for potential confounders. As in Aim 1, we will consider two sets of adjustment covariates. If the distributional assumptions of models are not met, we will consider variable transformation or use other appropriate distribution/family in the generalized linear model framework. We will also examine if these associations differ by *APOE ε4* carrier status, sex and race (sample size permitting).

As in Aim 1, we will evaluate if the blood $A\beta_{42}/A\beta_{40}$ ratio and brain SUVRs modify the associations of olfaction with GFAP, NfL, and p-tau181 and test for interaction between olfaction and the continuous baseline $A\beta_{42}/A\beta_{40}$ ratio/SUVRs. The p-tau $181/A\beta_{42}$ ratio will also help address the potential joint associations between these markers, similar to prior work using CSF data [14]. As only a subset of visit 5 participants had measured biomarkers in visit 7, we will use inverse probability weights or shared parameter models to account for potential bias due to attrition between visit 5 and visit 7.

Aim 3: To examine if the associations of visit 5 olfaction with visit 5 plasma markers and prospective change in plasma markers from visit 5 to visit 7 are explained by visit 5 brain imaging markers

This aim will be conditional on our Aim 1 and Aim 2 results and findings of the analyses examining (i) associations of visit 5 imaging markers (e.g. brain neurodegeneration as measured by brain volume and Aβ burden as measured by PET amyloid, etc.) with visit 5 plasma biomarker (e.g. NfL, $A\beta_{42}$, $A\beta_{40}$, etc.) levels and change in plasma biomarker levels from visit 5 to visit 7; and (ii) the association of visit 5 brain imaging markers with visit 5 olfaction. We will examine whether brain neuropathology (i.e., neurodegeneration, Aβ burden) lies on a "backdoor path" between olfaction and the plasma biomarkers by looking at a series of models, including:

1. Olfaction <- brain measure + adjustment covariates
2. Plasma biomarkers <- olfaction + adjustment covariates
3. Plasma biomarkers <- brain measure + adjustment covariates
4. Plasma biomarkers <- olfaction +brain measure + adjustment covariates

We expect associations found in model 2 (plasma biomarkers <- olfaction) to be highly attenuated in model 4 after including the imaging markers, if brain changes related to these markers are indeed causing both the olfaction and plasma biomarker levels to change. We may also use Generalized Structural Equation Modeling (GSEM) techniques to estimate percentages of the associations between olfaction and the plasma biomarkers explained by brain measures. We will consider adjusting for both model 1 and model 2 covariates.

e) Any anticipated methodologic limitations or challenges if present

Limitations of the current work include the single test of odor identification. In addition, participants did not undergo a formal ENT evaluation to rule out peripheral causes to olfactory loss, however, we will perform a sensitivity analysis excluding individuals with prior sinus surgery, nasal polyps, or chronic rhinosinusitis (as identified by the following hospitalization ICD-9 codes).

f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ Yes ☒ 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 is distributed to ARIC PIs annually, 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 ☐ 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"? ☒ Yes ☐ No

9. **The lead author or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□Publications□Proposal Search]

   ☒ 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, Chen H, Deal JA, Sharrett AR, Gross A, Knopman D, et al. (2018). Olfactory function and neurocognitive outcomes in old age: The Atherosclerosis Risk in Communities Neurocognitive Study. *Alzheimers Dement*, 14(8): 1015-1021.
- 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. (2022). The neuroanatomic correlates of olfactory identification impairment in healthy older adults and persons with mild cognitive impairment. *Journal of Alzheimer's Disease*. 89(1), 233-245.
- Shrestha, S., Zhu, X., Sullivan, K.J., Blackshear, C., Deal, J.A., Sharrett, A. R., Kamath, V., Schneider, A. L. C., Jack, C.R., Huang, J., Palta, P., Reid, R.I., Knopman, D.S., Gottesman, R.F., Chen, H., Windham, B.G., Griswold, M.E., Mosley, T.H. *(in press)* Olfactory impairment and relations to brain microstructural integrity in the Atherosclerosis Risk in Communities Study. *Neurology*.
- Schneider, ALC, Gottesman, RF, Mosley, TH, Shrestha, S, Rowan, N, Sharrett, AR, Chen, H, Kamath, V. (2022). Associations of prior head injury with olfactory functioning: Results from the Atherosclerosis Risk in Communities (ARIC) Study. *JAMA Otolaryngology – Head & Neck Surgery*. 148(9), 840-848.
- #4078: Olfactory impairment and chronic diseases in older adults (Chen/Kucharska-Newton)
- #4077: Olfactory impairment, functional declines, and frailty in older adults (Chen/ Kucharska-Newton)
- #2841: Mid-life biomarkers in relation to anosmia late in life (Chen/Shrestha)
- #3983: Late-life plasma biomarkers for Alzheimer's disease and related dementias in association with neurocognitive and MRI outcomes (Sullivan/Palta)
- #4235: Predictors of change in blood-based biomarkers of Alzheimer's disease pathology and neurodegeneration measured from mid- to late-life and their associations with late-life measures of brain health in the Atherosclerosis Risk in Communities (ARIC) Study (Palta)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☒ Yes ☐ No → Skip to question 12

11.b. If yes to 11.a., is the proposal

☒ **A. primarily the result of an ancillary study**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

11.c. If yes to 11.a., list number* 2010.17, 2020.27_

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website Ancillary Studies 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.

Acknowledged

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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website Publications Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

Acknowledged.

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