1.a. Full Title: Interrelationships of Olfaction, Brain Amyloid, and Cognition: the ARIC-PET Study

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

2. Writing Group: Lead and alphabetical order
Kimystian Harrison (first), Rebecca Gottesman, Michael Griswold, David Knopman, Seth Lirette, Thomas H. Mosley, Priya Palta, Dan Su, B. Gwen Windham, Dean F. Wong, Honglei Chen, others welcome

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

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3. Timeline: Writing and analysis to begin immediately. Submit for publication within 12 months from proposal approval.

4. Rationale:
Alzheimer’s disease is estimated to affect over 5 million people in the United States and continues to grow amongst the population of those age 65 years and older.1 With the rising costs of healthcare due to the debilitating disease, more research is needed to target prevention and to identify at-risk persons earlier in the course of cognitive decline with the expectation that earlier treatment may be effective in preventing progression of the disease. It is hypothesized that the accumulation of a protein in the
brain, amyloid beta, is largely responsible for the pathogenesis of Alzheimer’s disease. However, clinical symptoms do not become apparent until the disease process is irreversible.

More recently, researchers have focused on evaluating the use of imaging studies to detect amyloid beta in older adults prior to clinical presentation. Some studies support use of florbetapir-positron emission tomography (PET) imaging to detect amyloid beta in the brain.\(^2,^3,^4\) Furthermore, increased uptake of florbetapir-PET in the brain has been shown to correlate with decline in cognitive function in patients with and without Alzheimer’s dementia.\(^5,^6\) Genetic tests for carriers of ApoE genotype ε4 have also yielded strong associations with dementia.\(^7,^8,^9\) Although the neuropathology of lesions found in Alzheimer’s disease appears to be similar across race and sex, blacks have been found to have a greater risk of dementia and higher levels of brain amyloid compared to whites.\(^10,^11,^12\) More research is needed on factors that may predict and/or prevent progression of the disease in at risk populations.

Olfactory impairment, or loss of smell, has been identified as a clinical predictor of neurodegenerative disease.\(^13\) Prior evidence suggests associations between protein aggregation, including amyloid, and loss of smell.\(^14\) Our group and others have shown associations between poorer olfaction and poorer cognition (Palta et al, MS proposal 2872). Additionally, studies have shown that olfactory impairment is associated with a higher incidence of mild cognitive impairment, dementia, and decline in global cognition.\(^15,^16,^17\) These findings suggest that sense of smell may provide a low cost, noninvasive practical tool for clinicians and scientists to predict dementia risk.

Separately, data from olfaction and imaging studies may inform potential predictors of cognitive decline in the elderly. However, it is unknown whether the associations of olfaction with cognition could be explained by amyloid beta. If brain amyloid is a mediator of the olfaction-cognition relationship, this may support use of olfaction as a clinical risk screening instrument. This study seeks to examine the association between olfactory impairment and brain amyloid beta deposition as determined by PET imaging in the biracial ARIC Study cohort.

5. **Main Hypothesis/Study Questions:**

1. We hypothesize that poorer smell will be associated with higher amyloid beta deposition.
   
   **Aim 1:** Determine whether poorer smell is associated with higher global and region-specific amyloid burden.

2. We hypothesize that amyloid burden will explain the association between poor smell and cognitive function.
   
   **Aim 2:** Determine if amyloid burden explains the association between poor smell and cognitive function.

3. We hypothesize that relationships in Aims 1 and 2 will be similar in blacks and whites.
   
   **Aim 3:** Determine whether there are differences in the above findings by race.
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**: This will be a cross-sectional analysis of olfaction and amyloid burden, both measured at Visit 5, as well as mediation analysis of the effect of brain amyloid on the relationship between olfaction and cognition.

**Predictor**: Sense of smell was measured by the 12-item Sniffin’ Sticks screening test. ARIC participants were 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 then asked to identify each odorant 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 continuously.

**Outcomes**: Amyloid burden to be measured by Standardized Uptake Volume Ratio (SUVR) from ARIC-PET, in pre-specified regions of interest. Focus for this analysis is on: global mean cortical SUVR, precuneus SUVR, orbitofrontal cortex SUVR, and posterior cingulate SUVR. The SUVR’s will be evaluated as continuous variables as well as a binary variable based on a hypothetical cut-point explored in prior literature of an SUVR of 1.2. Cognition will be measured by the use of a composite global z score, which accounts for 3 cognitive tests: Delayed Word Recall (DWR), Digit Symbol Substitution (DSS), and Word Fluency (WF).

**Inclusion(s)/Exclusion(s):**
Inclusion/exclusion criteria are as follows from the original ARIC-PET study:

**Inclusion criteria**: persons with a CDR of 3 or lower, and also with a FAQ of 5 or lower, and with a brain MRI (from ARIC-NCS) within 12 months of recruitment. MMSE cannot be “low” (<19 for African-Americans and <21 for Caucasians) at the time of visit 5/ NCS. All participants were required to be able to give their own consent. **Exclusion criteria for involvement in ARIC-PET:** We excluded individuals with history of: (1) radiation therapy, chemotherapy, or surgery in the 6 weeks preceding the ARIC-PET visit; or (2) clinically significant liver or renal dysfunction; (3) prolonged QT interval; (4) drug or alcohol abuse. We will allow use of anticholinergic medications or memantine if the dose has been stable for ≥3 months preceding the PET scan.

**Other variables of interest**: Age, sex, race, site, education information from ARIC baseline and Visit 5, as well as apoE genotype from prior ARIC measurement. We will examine additional models with covariate adjustment for hypertension, diabetes, smoking, stroke, white matter hyperintensities (WMH), total intracranial volume (TIV), and infarcts.
Summary of data analysis: Descriptive statistics and generalized linear models will be employed for the analysis. Olfaction will be analyzed continuously in our primary analysis. We will also consider a categorical olfactory impairment using a clinically validated threshold of ≤6, as previously used in ARIC. We will explore the SUVR data for skewedness to determine if transformation or quintile analysis of the values should be considered. Linear regression or ordinal logistic regression models, respectively, will be used for these analyses. Models will be run separately for the global measure and region-specific measures, as described. We will also use logistic regression models to examine the association between olfaction and the binary SUVR>1.2 cutpoint. Race, age, sex, and number of ApoE ε4 alleles will be included as independent variables. Additional models will be stratified by race and ApoE to evaluate for interactions between race and ApoE, as well as cognition and ApoE. Cognition will be examined through the use of a global z score, which will be calculated by averaging the z scores of 3 cognitive tests: Delayed Word Recall (DWR) for immediate verbal memory, Digit Symbol Substitution (DSS) for executive function/psychomotor speed, and Word Fluency (WF) for language. Finally, a mediation model of the effect of brain amyloid on the relationship between olfaction and cognition will be constructed. To examine potential bias from attrition or missing PET data on our findings, we will conduct sensitivity analyses to account for missing data using MICE, IPAW, joint models, and the Heckman correction as appropriate.

7.a. Will the data be used for non-CVD analysis in this manuscript? ___ x__ Yes ___ 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? ___ x__ Yes ___ No
(This 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? _____ 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

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.cscce.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#2872 (lead: Priya Palta) – Olfactory impairment and cognitive function: the Atherosclerosis Risk in Communities Neurocognitive Study

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

MS#2466 (lead: Rebecca Gottesman) – The ARIC-PET Amyloid Imaging Study: Differences in Brain Amyloid deposition by Age, Race, Sex, and ApoE genotype

MS#2511 (lead: Rebecca Gottesman) – Vascular risk factors and brain amyloid deposition: The ARIC-PET Study

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* 2009.29 PET-Amyloid study; 2008.06 Neurocognitive study)

   ___      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.

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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References:


