ARIC Manuscript Proposal #3746

PC Reviewed: 12/8/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The association between criteria air pollutant exposure and late-life amyloid burden

b. Abbreviated Title (Length 26 characters): Air pollutants and amyloid

2. Writing Group: Erin E. Bennett, Melinda C. Power, Jingkai Wei, Xiaohui Xu, Eun Sug Park, Qi Ying, Eric A. Whitsel, Richard Smith, James Stewart, Jeff D. Yanosky, Rebecca Gottesman, Dean Wong

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

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3. Timeline: 12 months following completion of both air pollution estimation and Visit 7 availability

4. Rationale:

Identifying modifiable risk factors for Alzheimer's disease and related dementias (ADRD) is a top priority for dementia-related research as the failure rate for clinical trials remains staggeringly high.[1] However, only one-third of Alzheimer's disease cases worldwide

can be explained by commonly recognized modifiable risk factors[2,3], highlighting the need to investigate novel exposures as potential causative agents. The detrimental effects of short- and long-term exposure to air pollution on mortality and health status have been well-established[4-13]. More recently, the literature linking long-term, ambient air pollution to Alzheimer's disease and related dementias has grown dramatically, with evidence that suggests associations between criteria air pollutants and cognitive level[14-21], cognitive decline[22,23], incident dementia[24-26], and MRI-based measures of brain morphology[27-30] and cerebrovascular disease[30].

Despite this growing body of evidence, the primary mechanisms by which air pollution impacts cognition and brain health remain unclear. One commonly cited theory linking air pollution to aging-related disease is that the accumulation of reactive oxygen species (ROS), which can be produced by components of particulate matter (PM), oxides of nitrogen (NOx), and ozone (O_3), overwhelm the body's antioxidant defense system and inflict damage on cellular structures.[31] Over time, sustained oxidative stress contributes to aging and disease[32], especially neurodegenerative disease.[33] Importantly, the beta-amyloid plaque accumulation that is characteristic in Alzheimer's disease patients has been proposed as a possible response to sustained oxidative stress.[34]

Despite this plausible mechanism, there is little epidemiologic literature regarding the association between air pollution and brain amyloid accumulation in adults. Additionally, though most studies of air pollution and brain health have focused on associations with particulate matter, other criteria air pollutants, such as nitrogen dioxide (NO_2), have oxidative potential[31], and thus are equally important to consider as possible neurotoxins.

Therefore, we propose to study the association between cumulative mid- to late-life exposure to criteria air pollutants (specifically PM_{10}, $PM_{2.5}$, O_3, and NO_x) and late-life amyloid accumulation in the ARIC-Amyloid PET cohort.

5. Main Hypothesis/Study Questions:

1. Is exposure to PM_{10}, $PM_{2.5}$, ozone, and NO_x associated with elevated late-life amyloid burden?
    a. We hypothesize that long-term cumulative exposure to ambient PM_{10}, $PM_{2.5}$, ozone, and NO_x is associated with elevated late-life amyloid burden.
2. Are there factors that modify the association between cumulative exposure to ambient air pollution and late-life amyloid burden?
    a. We hypothesize that the association between long-term exposure to PM_{10}, $PM_{2.5}$, ozone, and NO_x and late-life amyloid burden will be stronger in those with at least one APOE e4 allele compared to those with no APOE e4 alleles.

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).

<u>Study Design:</u>

Cross-temporal evaluation of the association between past air pollution exposure and amyloid-beta positivity on PET neuroimaging at Visit 5.

Inclusion/Exclusion Criteria:

We will exclude participants without amyloid-PET data at visit 5. The ARIC-PET imaging study had specific exclusion criteria: contraindication to MRI, heavy alcohol use, renal failure, or a clinical diagnosis of dementia (one participant who was retroactively diagnosed with dementia underwent a PET scan, and will be excluded from all analyses). Only participants from the Jackson, MS; Forsyth County, NC; and Washington County, MD field centers were enrolled.

We will also exclude participants whose addresses could not be geocoded, because we use participant geocoded addresses to assign air pollution exposures. We will also exclude participants who are otherwise missing air pollution exposure data.

Finally, we will exclude participants missing important covariate data (such as education and APOE e4 genotype). If this results in substantial missingness, we will consider multiple imputation to overcome this issue.

Outcome of Interest

Our outcome of interest is a florbetapir PET scan-derived global cortical measure of amyloid, calculated as a weighted average of standardized update value ratios (SUVRs) in various regions of the brain, as described elsewhere, with cerebellar gray matter as the reference.[35] Elevated amyloid uptake will be defined as global SUVR>1.2 and treated as a dichotomous variable. PET scans were conducted on a subset of ARIC participants at visit 5 (2011-2013).

Independent Variables of Interest

We will consider long-term exposure to PM_{10}, $PM_{2.5}$, ozone, and NO_x as our potential predictors of interest. Our primary air pollution modeling approach uses two air pollution emissions inventories and two chemical transport models to estimate PM_{10}, $PM_{2.5}$, ozone, and NO_x exposures at ARIC residential locations. Estimates are then weighted based on measured air pollution levels at EPA monitoring stations to create ensemble predictions, and observation-data fusing is used to correct biases in estimation. We will quantify prediction errors using a leave-one-out cross-validation approach and will only use estimates passing QA/QC standards. Air pollution estimates will be linked with ARIC addresses geocoded by Dr. Whitsel's team to produce residential address-level estimates of exposure. Note that we have generated new geocode data at the time of each participant AFU call or Visit for the period of Visit 4 through Visit 7.

Because amyloid accumulation appears to begin 10 to 20 years before the onset of clinical symptoms, long-term exposures in midlife are most likely to be etiologically relevant for amyloid accumulation in late life.[36] Therefore, we will average estimated air pollutant exposure at participants' geocoded residential addresses from 2000 to 2010.

In sensitivity analyses, we will compare associations of amyloid burden with our air pollution estimates to those with alternate estimates of air pollution exposures at ARIC

participant residential locations. Two of these alternate approaches were produced in the context of ARIC Ancillary Study #2009.08 at geocoded addresses of participants using (1) national-scale, lognormal ordinary kriging and national-scale, lognormal measurement error kriging and (2) land use regression / spatial smoothing. We are also linking additional estimates produced using (3) observation-fused aerosol optical depth and chemical transport model modelling approach[37], and (4) spatiotemporal modeling apporach[38]. Note that not all models generate estimates for all pollutants.

Covariates of Interest

We will consider the following covariates in our analyses:

- Demographics: sex, race, ARIC center, and visit 5 age
- SES: education, pre-retirement occupation, and pre-retirement health insurance status
- Health status at Visit 4: self-rated health, alcohol intake, smoking status, physical activity, BMI
- Cumulative census tract measures of SES during exposure period: area deprivation index (ADI) based on census data. We may also consider specific census-related SES measures if they provide information different from the ADI, including median household income; median value of owner-occupied homes; percent of households receiving interest, dividends, or net rental income; proportion of adults with high school and college degrees; proportion of individuals in professional, managerial, and executive occupations; proportion of families below the poverty line; unemployment; and population density.
- Effect modifiers: age, APOE e4, cognitive status

Statistical Analyses

We will use logistic regression to estimate the association between cumulative PM_{10}, $PM_{2.5}$, ozone, and NO_x exposure and late-life elevated brain amyloid burden, defined as a global SUVR > 1.2. Exposures will be modeled per 5 ug/m^3 increase[39] for PM_{10} and $PM_{2.5}$ and per 1 ppb increase for ozone and NO_x. All analyses will be adjusted for sex, race, ARIC center, visit 5 age, and education. We will further adjust for pre-retirement occupation, pre-retirement health insurance status, cumulative census tract-level ADI, and Visit 4 measures of self-rated health, alcohol intake, smoking status, physical activity, BMI, , and APOE e4 status. We will assess potential effect modification by APOE e4 genotype and visit 5 cognitive status by including multiplicative interaction terms in our models.

Sensitivity analyses will consider whether effect estimates are sensitive to the choice of modeling approach. We will also conduct analyses stratified by study site to consider the possibility of intractable confounding by site. Finally, we will consider an alternate parameterizations of amyloid status, as a continuous variable

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/aric/mantrack/maintain/search/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)?

#2412: Association of particulate matter air pollution with MRI outcomes (Power)

#3348: Ambient air pollution and late-life cognition and dementia (Power)

#2957: Interrelationships of Olfaction, Brain Amyloid, and Cognition: the ARIC-PET Study (Harrison)

#3441: Associations among Ambient Air Pollution, Genetic Risk Factors and Age-related Macular Degeneration in the Atherosclerosis Risk in Communities (ARIC) Study (Lin)

#3460: Accounting for exposure measurement error in assessment of the effects of air pollution on dementia (Park)

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

#2822: Subclinical cerebrovascular disease and brain amyloid deposition: The ARIC-PET Study (Gottesman)

#3011: Systemic inflammation and brain amyloid deposition: The ARIC-PET Study (Walker)

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

#3502: The associations of dietary copper with neurocognitive outcomes: The ARIC Study (Wei)

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* _2020.09, 2016.20, 2009.29___)

___ 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.

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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8. Liu C, Chen R, Sera F, et al. Ambient Particulate Air Pollution and Daily Mortality in 652 Cities. *N Engl J Med.* 2019;381(8):705-715.
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