ARIC Manuscript Proposal #4001

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1.a. Full Title: Association of gaseous ambient air pollution with brain MRI outcomes in the ARIC cohort

b. Abbreviated Title (Length 28 characters): Air Pollution and MRI outcomes

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **_[KL]**

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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 (this must be an ARIC investigator).

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3. Timeline:

The brain MRI and neurocognitive testing data at visit 5 and ARIC variables are now available. We plan to complete the work within 1 year of generating final air pollution exposure data.

4. Rationale:

There is growing evidence linking air pollution to late-life cognitive health. Currently, the strongest evidence supports an effect of particulate matter air pollution;[1] however, gaseous pollutants deserve further attention, as they may impact brain health through a variety of mechanisms.

First, exposure to ozone (O_3) or nitrogen dioxide (NO_2) may induce processes related to inflammation and oxidative stress that impact brain health and lead to cognitive impairment. Ozone (O_3), nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) have been linked to oxidative stress responses and systemic inflammation in a limited number of animal studies[2-8] (although results are not universal, e.g., one study did not find evidence of lipid peroxidation from O_3 exposure in rats[9]). Oxidative stress, in turn, can promote neuroinflammation and lipid and protein peroxidation which can damage cells, and can lead to the production of toxic compounds that can result in neuronal apoptosis.[10] Similarly, systemic inflammation could also contribute to neuroinflammatory processes because proinflammatory cytokines can cross the blood-brain barrier.[11] Studies of rodents have specifically found exposure to O_3 leads to brain inflammation and oxidative stress in several areas of the brain, including the hippocampus, cerebral cortex and substantia nigra. [12-19] Some of these studies also found signs of damage to cells in parts of the brain, including increased apoptosis,[15, 16, 18] and damage to mitochondria,[17] after exposure to O_3. Similar results have been obtained after controlled exposure to NO_2. For example, a study of NO_2 exposure in rats that found signs of oxidative stress also found neuronal apoptosis.[7] Supporting potential for translation from animal to human studies, systemic inflammation has also been found to be associated with cognitive deficits and increased white matter disease in epidemiologic studies.[20, 21]

Second, gaseous air pollutants have been shown to affect brain amyloid levels – a hallmark of Alzheimer's disease - in animal studies. Studies of rodents have found effects of O_3 exposure on β amyloid processes in the brain, including increased accumulation,[22-24] which is also seen in Alzheimer's disease in humans.[25] Additionally, a study of mice exposed to NO_2 found increased neuropathological processes such as aggravated amyloid β_{42} accumulation; these mice also exhibited cognitive effects found in Alzheimer's disease such as decline in spatial learning and memory.[26] The impact of gaseous air pollutants on Alzheimer's disease-related pathology in rodents appears to be related to the potential for these pollutants to produce inflammation and oxidative stress, as discussed above. The authors determined that the processes underlying the impact of NO_2 exposure on amyloid β_{42} accumulation and cognitive deficits likely involved Cox-2 mediated arachidonic acid (AA) metabolism including AA-derived prostaglandin E2, a prostaglandin that has been implicated in β-amyloid formation and can promote neuroinflammation.[26]

Third, some studies suggest that exposure to certain gaseous pollutants may also promote atherosclerosis development. For example, studies have found that a 10-ppb increase in NO_2 contributes to 33.6 mm^2 increase in total plaque area, and that NO_2 was associated with coronary artery calcium severity.[27, 28] Atherosclerosis can contribute to thromboembolic events and ischemic strokes, which can harm neurons through lack of

blood and oxygen, and inflammatory processes, leading to neuronal loss,[29] and which are commonly part of the pathophysiological process underlying vascular dementia.[30]

Although potential pathophysiological connections to brain health exist, relatively few studies have considered the impact of NO_2/NO_x or O_3 on late-life cognitive health. While some study results have shown significantly decreased cognitive global and/or domain-specific scores (e.g. memory, executive function) with increased exposure to NO_2 or NO_X,[31-34] other results have not been significant or even showed increased scores.[31, 35-38] Of the limited studies of NO_2/NO_X and cognitive change, one study found a statistically significant decrease in cognitive scores with increased exposure to NO_2 for one of their two cohorts,[31] but results for the other cohort and from other studies were null.[31, 39, 40] Studies on NO_2/NO_X and dementia outcomes found a mix of positive, negative and null associations.[40, 41] Data linking O_3 to cognition is even more limited. For O_3, a couple of studies found increased exposure to O_3 was associated with both significantly increased and decreased cognitive test scores, as well as non-significant results.[34, 37]

While carbon monoxide (CO) poisoning is known to cause central nervous system effects, including headaches, dizziness, cognitive effects, and even comas, less is known about the effects of ambient levels of CO exposure on cognitive health or dementia risk.[42] One study found increased exposure to CO was associated with decreased global cognition, attention and executive function scores.[37] Two other studies found mixed, but sometimes significant results for the association between vascular dementia risk and increased exposure to CO.[43, 44] In limited studies that considered the effects of SO_2 on cognition/dementia, SO_2 was associated with decreased global cognition and memory function,[37] but was not associated with the risk of vascular dementia.[43] Overall, the research linking gaseous pollutants to late-late cognitive health is limited, and study results are mixed.

MRI biomarkers provide a window into pathogenic change. The argument that air pollution is causally related to cognitive change would be strengthened by evidence linking air pollution to pathogenic change associated with dementia and visible on MRI. Currently there is very little research on whether gaseous air pollutants are associated with brain changes visible on MRI. One such study in the 1000Brains Cohort considered the effects of both NO_2 and NO_x exposure on local gyrification indices (markers of local brain atrophy) from brain MRIs found an association with lower right posterior cingulate cortex and precuneus indices for both pollutants.[38] Related analyses in the UK Biobank found no statistically significant associations between NO_2 or NO_x and region of interest brain volumes, with the exception of marginally significant association between NO_2 and decreased thickness in the Alzheimer's disease (AD) signature brain areas ($p=0.05$).[36] However, analyses leveraging the Northern Manhattan Study (NOMAS) cohort found no significant associations between NO_2, NO_x or O_3 and measures of brain volume, or presence of subclinical brain infarcts.[45] We are not aware of any studies that have looked at the association between CO and MRI biomarkers. As the results of these MRI studies are mixed, and only limited types of gaseous pollutants were included, further research is clearly needed.

For this reason, we aim to build up prior work in the ARIC study by Power et al, 2018,[46] which analyzed associations between $PM_{2.5}$ and PM_{10} exposures and several MRI markers of neurodegeneration and cerebrovascular disease measured at Visit 5. We propose to use a similar process to analyze associations of the MRI findings with the gaseous pollutants NO_2/NO_x, SO_2, O_3 and CO.

5. Main Hypothesis/Study Questions:

Hypothesis 1: Higher long-term exposure to specific gaseous air pollutants--NO_2/NO_x, SO_2, O_3, and CO-- will be associated with smaller total and regional brain volumes.

Hypothesis 2: Higher long-term exposure to specific gaseous air pollutants--NO_2/NO_x, SO_2, O_3, and CO-- will be associated with greater burden of markers of cerebrovascular disease: infarcts, microbleeds, lacunes, and white matter hyperintensities.

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).

Exclusions:

We will exclude persons in small race-center categories including not white in Washington County or Minnesota; not Black in Jackson; not white or Black in North Carolina; presence of tumor, surgery, or radiation to the head; missing primary covariates; missing air pollution data; having no valid MRI data.

Independent variables:

We will use an ensemble/observation data-fusing approach to generate monthly NO_2/NO_x, SO_2, O_3, CO component concentrations at each participant's residential address from 1990-2012. The approach includes generating exposure estimates from the Community Multiscale Air Quality (CMAQ) model (a chemical transport model) using two different emission inventories, the U.S. EPA's National Emission inventory and the European Union's Emission Database for Global Atmospheric Research (EDGAR) emissions inventory. The resulting estimates are combined through calculation of a weighted average and adjusting the resulting concentrations with an observation data fusing technique.

For the ARIC dataset, the estimates will be linked with geocoded addresses from 1990-2012 to produce residential-level exposure estimates. We will initially focus on estimates within the ten years prior to Visit 5 (2001-2010), but may also consider alternate lag periods. In sensitivity analyses we may also consider alternate exposure estimates created using other modelling or estimation approaches (i.e., inverse distance weighting, nearest neighbor, and models that use log-normal ordinary and log-normal measurement error kriging[47], universal kriging with land-use regression and partial least

squares regression,[48, 49] and a chemical-transport model based approach with satellite and ground observations.[50, 51]) to understand the impact of model choice on effect estimates.

Dependent variables:

MRI data at Visit 5:

- Microhemorrhages
- White matter hyperintensities
- Cortical infarcts
- Lacunar infarcts
- Brain volumes (total, hippocampal, Alzheimer's disease (AD) signature region[52], lobar, white matter hyperintensity)
- Diffusion tensor imaging measures, including mean diffusivity, fractional anisotrophy

Covariates:

All analyses will be adjusted for a set of variables, determined a priori: age, race, gender, education level, smoking status, intracranial volume, and measures of cumulative, area-level SES. We will use penalized splines to assess the functional form of the continuous variables. In sensitivity analyses, we may consider adjustment for additional covariates (e.g., rural vs. urban residence, additional measures of health, APOE e4). We will also explore whether there is confounding by PM2.5 or other co-pollutants, using two-pollutant models.

Effect modifiers:

We will consider study site as an effect modifier because of the possibility that variables related to location, such as variation in pollutants by site, could impact the effect of air pollution on MRI outcomes. We will also use two-pollutant models to explore whether there is effect modification by PM2.5 or other co-pollutants.

Statistical Analyses:

Due to possibility of variation in pollutants by site, site-specific analyses will be performed and then meta-analyzed using a random-effects model to produce entire cohort effect. We will evaluate heterogeneity of effect using the I^2 test. If no heterogeneity across sites is found, we will perform the analysis with the entire ARIC population as a single sample.

To analyze the associations between NO_2/NO_x, SO_2, O_3, CO and continuous MRI markers (white matter hyperintensities, volumes) we will use linear regression. For dichotomous markers (cortical infarcts, lacunes, and microbleeds) we will use logistic regression. We will also explore multivariate regression due to concerns about power.

Data on white matter hyperintensities may be log-transformed prior to use as an outcome in our models because previous analyses found this variable was highly skewed; additional transformations may be considered. To account for the Visit 5 Stage 3 MRI sampling strategy and refusals, coordinating-center derived weights will be used in the analyses. We will treat exposure as a linear term or categories of exposure depending on the shape of the dose-response curve as evaluated by penalized splines. As mentioned above, we will include covariates in the analysis as potential confounders and may consider additional potential confounders in the sensitivity analyses. In additional sensitivity analyses, we will account for attrition using inverse probability weights (IPW), and may compute limits of the association using different assumptions about attrition to address selection issues.

Limitations/Challenges:

Our analysis has several limitations. First, the analysis looks at outcomes from one time period, Visit 5, and does not look at within-individual change in MRI functioning or cognition. Additionally, despite adjustment for *a priori*-specified confounders and sensitivity analyses considering additional confounders, the potential for bias from confounding remains. Further, the possibility of selection bias exists, although we will attempt to address any concerns in sensitivity analyses. While some misclassification of air pollution exposure and MRI outcomes is expected, we expect misclassification to be non-differential and for resulting bias to be towards the null. We are also limited by a relatively small sample size for the MRI outcomes; however, this is one of the larger community-dwelling MRI samples currently available.

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 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 file ICTDER03 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/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)?

#3762 Association of ambient particulate matter components with MRI outcome (Power)

#3825 Comparison of Air Pollution Exposure Assessment Methods and Their Impacts on Associations with Cognition and Neuroimaging Outcomes: the Atherosclerosis Risk in Communities (ARIC) Cohort (Lynch)

#3746 The association between criteria air pollutant exposure and late-life amyloid burden (Bennett)

#2351 Association of blood pressure with neurodegenerative and cerebrovascular changes on brain MRI (Power)

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

#3813 Air pollutants, Cardiovascular Risk, and Mortality: Investigating Exposure Thresholds with Pooled Cohorts (Kaufman)

#3829 Ambient Air Pollution, Incident dementia and 25-Year Cognitive Change (Power)

#3652 Exposure to PM2.5 is Associated with Incident Atrial Fibrillation (Kshirsagar)

#3613 Response to a Request to Contribute to a Methylome-wide Association Study of Ambient Particulate Matter Air Pollution and Roadway Proximity (Collins)

#2876 Particulate Matter Air Pollution and DNA Methylation (Gondalia)

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

#2315 Association of Diabetes with Brain Magnetic Resonance Imaging (Schneider)

#2288 Associations of Brain Imaging with Cognitive Change over 20 Years (Knopman)

#2266 Associations Between Brain Vascular Imaging Features and Regional Volumetrics (Graff-Radford/Knopman)

#1553 Associations Between Vascular Risk Factors and Longitudinal Changes in Ventricular Size: a 14-Year Longitudinal Study (Knopman)

#1387 Temporal changes in blood pressure and cerebral white matter lesions in a biethnic sample: The ARIC MRI Study (Gottesman) -- Gottesman, R. F., et al. (2010). "Blood Pressure and White-Matter Disease Progression in a Biethnic Cohort: Atherosclerosis Risk in Communities (ARIC) Study." Stroke **41**(1): 3-8.

#1894 Retinal microvascular abnormalities predict progression of white matter disease and incident lacunar infarcts: The ARIC MRI study

#2909 Particulate Matter-Gene Interactions and QT Interval Duration (ARIC AS#2009.08)

#2321 Genome-wide Association Study of Particulate Matter and Supraventricular Ectopy (ARIC AS#2009.08)

#2078 Genome-wide Association Study of Particulate Matter and Ventricular Ectopy (ARIC AS#2009.08)

#1310 Role of air pollution measured as particulate matter concentration on the association between HFE gene mutations and heart rate variability. (Agarwal)

#760 Association between air pollution and hemostatic/inflammation factors (Liao)

#860 Association between air pollution and cardiac autonomic control (Liao)

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) AS# 2016.20

___ 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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