ARIC Manuscript Proposal #3829

PC Reviewed: 4/13/21 **Status: _____** **Priority: 2**

SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Ambient Air Pollution, Incident dementia and 25-Year Cognitive Change

b. Abbreviated Title (Length 26 characters): Air pollution & cognition

2. Writing Group: Melinda C. Power, Xiaohui Xu, Eric A. Whitsel, Richard Smith, James D. Stewart, Eun Sug Park, Qi Ying, Erin E. Bennett, Katie M. Lynch, Jeff Yanosky, Naa Adoley Parker-Allotay

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

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3. Timeline:

Analyses will be complete within 1 year of air pollution data availability and manuscript proposal approval.

4. Rationale:

With increasing life expectancies and decreasing birth rates, the U.S. is undergoing a historic demographic shift in which the population of older adults is projected to surpass that of children [1]. As of 2014, there were more than 46 million American adults over the age of 65, and this number could potentially double by 2060 [2]. As older adults begin to make up a greater percentage of the total population, diseases that predominantly affect older adults will have a more significant impact on public health and require additional investigation [2].

Alzheimer's disease and related dementias (ADRDs) are a set of neurodegenerative disorders that primarily affect adults over the age of 65 [3]. Increased prevalence of ADRD has placed growing burden on health systems globally [4]. In 2019, estimated health care expenditures dedicated to caring for ADRD exceeded $290 billion, and this figure is expected to surpass $1 trillion by 2050.[5] Since there is currently no cure or effective disease-altering treatment for ADRD [6], interventions on risk factors to delay or prevent dementia may be our best hope for reducing economic and social burdens associated with ADRD [7].

Air pollution is a leading cause of global morbidity and mortality, with over 90% of the world's population living in areas with air pollution that exceeds the WHO guideline limits [8]. Exposure to chronic air pollution is presumed to be a causal agent for many chronic diseases, including lung and cardiovascular diseases [9-11]. Air pollution may also contribute to the pathogenesis of dementia through a variety of mechanisms. To begin, cardiovascular health has been linked to risk of ADRD; thus, ambient air pollution exposures may contribute to cognitive impairment and ADRD through effects on cardiovascular health.[12-16] Animal toxicologic studies have shown that air pollution can contribute to oxidative stress and neuroinflammation, which may promote the neurodegenerative processes present in ADRD [17-21]. Furthermore, it appears that ultrafine particulate matter can enter the brain through the olfactory bulb, crossing the blood brain barrier, where it may effectively operate as a neurotoxin [22,23]. Supporting a role of air pollution on brain health through this mechanism, diminished olfactory bulb function is a known antecedent to the development of ADRD [24-26]. Recent epidemiologic studies of air pollution exposure and neuroimaging biomarkers of ADRD also suggest a link between air pollution and structural changes to the brain, although the literature is mixed [27-30].

Recent epidemiologic studies suggest that ambient air pollution may be a risk factor for cognitive decline and incident dementia [31-34]. However, there is substantial heterogeneity across studies -- which consider a wide range of pollutants and outcomes -- in both associations considered and findings [31,32,35]. Most studies consider particulate matter with an aerodynamic diameter <2.5 microns ($PM_{2.5}$); studies of

other air pollutants, such as oxides of nitrogen (NO_x/NO_2) or ozone (O_3), are less common. Similarly, the majority of existing studies focus on associations with cognitive level, assessed as cognitive test performance at a single time point. Fewer studies report on associations with cognitive change or incident dementia.

In addition to issues of sparsity and heterogeneity of findings in the literature, we also note two common limitations in the existing studies. First, most studies of incident dementia ascertain dementia diagnoses utilizing either claims, death certificates, or medical records (e.g., [36-38]). Use of this data increases the potential for systematic bias in calculated effect estimates due to differential misclassification. For example, the sensitivity and specificity of Medicare-based dementia ascertainment differs substantially by a number of participant characteristics [39]. As many of these factors vary spatially, and differences in provider norms around dementia diagnosis also likely vary spatially, it is likely that there is also differential misclassification of dementia status with respect to spatially-varying air pollution exposure levels. Studies with standard dementia ascertainment procedures, including criterion-standard dementia diagnoses, are needed to determine the extent to which such misclassification impacts effect estimates. Second, most existing studies rely on exposure estimates in late-life, close to the timing of cognitive assessment or the timing of dementia diagnosis. As dementia pathogenesis is hypothesized to have a long latent period and begin decades before diagnosis, it is likely that earlier exposures are more relevant to dementia risk. This appears true for a variety of dementia risk factors, where we see that midlife exposures are more relevant to dementia risk than late life exposures[40-44]. Thus, while likely correlated with exposures in the more distant past, recent exposure summaries may not reflect exposures during the most likely etiologically relevant time period.

To expand the evidence base and to address these limitations in the existing literature, we propose to address the association between midlife ambient air pollution exposures with cognitive change and incident dementia over ~25 years of follow-up. The ARIC cohort provides decades of clinical cognitive follow-up and individual exposure assessment which will strengthen quality of results and derived associations. As the global burden of ADRD continues to rise, this investigation will not only be of critical importance to understanding the antecedent risk factors of dementia, but it also has the potential to meaningfully inform environmental policy decisions which can have lasting and profound public health implications.

Please note that we have an approved ancillary study (#2016.20) and funded R01 (R01 ES029509) to investigate the relationship between air pollution and late-life cognitive health in the ARIC cohort. We also recently received an administrative supplement to our R01 (approved ancillary study #2020.09) to expand the number of air pollution exposure estimates available to us, allowing comparison of findings using multiple air pollution estimation approaches. Broadly, our goal is to investigate the association of ambient exposure to air pollutants with cognitive decline, incident cognitive impairment, and neuroimaging biomarkers of dementia-related pathology in the ARIC study. This manuscript proposal is one of several we anticipate submitting in this context.

5. Main Hypothesis/Study Questions:

We hypothesize that exposures to ambient air pollution in midlife, specifically $PM_{2.5}$, NO_x, and O_3, is associated with accelerated cognitive decline and higher incidence of dementia over the following 25 years.

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 is a cohort study. Our exposure will be midlife residential air pollution exposures, and our outcomes will be cognitive decline and incident dementia.

Exclusions:

We will restrict our sample to those who participated at Visit 2 and provided complete cognitive data. Participants will be excluded if we are unable to generate air pollution exposure data (e.g., due to a lack of geocoded address data). Based on low participant counts in certain race groups by ARIC field center, we will also exclude those who are non-white and non-Black in NC, those who were non-white in MD or MN, and those who were non-Black in MS. Lastly, any participants missing necessary covariate data may be excluded as well; if this exclusion results in substantial loss in sample size, we will consider performing multiple imputation for covariates.

Exposure estimates: Monthly ambient air pollution exposure estimates for particulate matter with an aerodynamic diameter of less than 2.5 microns ($PM_{2.5}$) and less than 10 microns (PM_{10}), oxides of nitrogen (NO_2/NO_x), and O_3 in the areas where ARIC participants live will be generated by Qi Ying as part of our grant activities. These use an ensemble chemical transport model (CTM)/observation data-fusing approach for air pollution estimation.[45] We will quantify prediction errors using a cross-validation approach and will only use estimates passing QA/QC standards. Air pollution estimates will be linked with geocoded ARIC addresses generated by Dr. Whitsel's team to produce residential address level estimates of exposure; note that existing geocodes have high demonstrated accuracy and precision,[46,47] and that we have since geocoded participant addresses at the time of AFU calls and Visits from Visit 4 through Visit 7.

For our primary analysis, we'll consider average exposures from 1990-1995 as a measure of long-term, midlife exposure, given our expectation that long-term cumulative exposures in midlife are most relevant to dementia pathogenesis.

Dependent Variables:

For our analyses of cognitive change, we will quantify the association between air pollution and overall and domain-specific cognitive change (i.e., memory, executive functioning, etc.) at Visits 2, 4, 5, 6, and 7[48]. In secondary analyses, we will also consider associations with change in the z-scores for individual cognitive tests administered consistently across all study visits (DWRT – delayed word recall, DSST – digit symbol substitution, WFT – word fluency test) and a summary z-score calculated as the average z-score across these tests, as done for prior analyses of Visit 2-5 cognitive change (e.g. [49,50]).

For our analyses of incident dementia, we will define incident dementia using Level 3 dementia ascertainment. This classification is based on all information available to the ARIC cohort, including: algorithmic diagnosis of dementia at visits 5-7, telephone interview for cognitive status, proxy interview, and dementia codes from the cohort eligibility form or death records. In secondary analyses, we will use Level 1 dementia diagnosis, and explore whether differential misclassification in Level 3 ascertainment could bias our results.

Covariates:

All models will be adjusted for a common set of baseline (visit 2) covariates: demographics (age, sex, race), personal SES (education, pre-retirement health insurance status), self-rated health, alcohol use, smoking status, leisure time physical activity [51], and area-level SES (% of residential census tract below the poverty line, and a summary measure of neighborhood wealth/income, education and occupation)[52].

Effect Modifiers:

First, we will examine whether our effects differ by study site. If so, all analyses will be conducted by site and summary estimates will be combined using meta-analyses as in our prior analysis of PM2.5 and visit 5 MRI outcomes (PMID: 29467108, ARIC MP: 2412).

We will conduct exploratory analyses to determine whether the observed associations differ by APOE e4 status, gender, education, age at baseline, and area-level SES.

Statistical Analyses:

For our primary analyses of cognitive change, we will use linear mixed effects models. For our primary analyses of incident dementia, we will use Cox proportional hazards models.

We will conduct several sensitivity analyses. We will consider analyses restricting to white participants or those who did not move during follow-up, censoring persons at time of stroke, and adjusting for vascular risk factors and cardiovascular disease. If air pollution predicts attrition, we will use inverse probability weighting[53,54] or MICE to address potential selection bias due to informative attrition [55,56]. If we determine that measurement errors have a significant impact on exposure estimates, we will account for that by a Bayesian hierarchical models analysis. [57,58] We will also consider robustness of our analysis by restricting to persons who reside within the 1km domain used for fine-scale exposure estimation.

In sensitivity analyses, we will also compare associations between our air pollution estimates with incident dementia and cognitive change to those produced using alternate air pollution exposures estimated for 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) spatiotemporal land-use regression model. Both estimation methods have been validated.[59-63] We are also linking additional estimates produced using (3) observation-fused aerosol optical depth and chemical transport model modelling approach [64], and (4) spatiotemporal monitoring approach[65] as part of Ancillary Study #2020.09, and will consider these as well. Note that not all models generate estimates for all pollutants.

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? __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/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)?

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

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

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

3417; "Novel Estimation of Inverse Probability Weights Accounting for Attrition" (Smith)

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

3762; "

Association of ambient particulate matter components with MRI outcomes

" (Power)

"Life-Course Individual and Neighborhood Socioeconomic Status and Risk of Dementia in the Atherosclerosis Risk in Communities Neurocognitive Study" (George)

3241; "Association between particulate matter and chronic kidney disease" (Blum)

2412; "Association of particulate matter air pollution with MRI outcomes" (Power)

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

2876; "Particulate Matter Air Pollution and DNA Methylation" (Gondalia)

2924; "Particulate Matter Air Pollution and Leukocyte Traits" (Gondalia)

2078; "Genome-wide Association Study of Particulate Matter and Ventricular Ectopy" (Napier)

1146; "Ambient air pollution is associated with the onset of acute events –The ARIC Study" (Liao)

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

2321; "Genome-wide Association Study of Particulate Matter and Supraventricular Ectopy" (Fransceschini)

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* 2016.20, 2020.09**_)**

___ 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 https://www2.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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