

ARIC Manuscript Proposal #3348 (Amended)

PC Reviewed: 11/16/20	Status: _____	Priority: 2
SC Reviewed: _____	Status: _____	Priority: _____

1.a. Full Title: Ambient air pollution and late-life cognition and dementia

b. Abbreviated Title (Length 26 characters): Air pollution and dementia

2. Writing Group: Melinda C. Power, Xiaohui Xu, Eric A. Whitsel, Richard Smith, Jay Stewart, Eun Sug Park, Qi Ying, Erin Bennett, Jingkai Wei, Jeff Yanosky, others welcome

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

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3. Timeline: 6-9 months following completion of both air pollution estimation and Visit 7 availability

4. Rationale:

The burden of Alzheimer's disease and related dementia (ADRD) is substantial and growing. While the age-specific incidence of ADRD may be declining,¹⁻³ the absolute number of persons affected will continue to grow as the population ages.⁴ As existing treatments do nothing to alter the course of the most common dementia types,⁵ and Alzheimer's disease recent treatment trials have been

disappointing,⁶⁻⁹ identifying ways to prevent or delay ADRD may be our best option for reducing disease burden.^{10,11}

Air pollution presents well-known dangers to health, particularly cardiovascular and respiratory health.¹²⁻¹⁶ Emerging evidence suggests that air pollution exposures may also impact risk of ADRD. Experimental and postmortem studies report that high air pollution exposures are related to multiple indicators of ADRD pathogenesis, including levels of amyloid- β .¹⁷⁻³⁰ Several mechanisms are plausible. Exposure to particulate matter (PM) appears to promote cardio-metabolic risk factors, cardiovascular disease, and cerebrovascular disease,³¹⁻³⁶ which likely contribute to cognitive decline and ADRD.³⁷⁻³⁹ Similarly, multiple air pollutants induce pro-inflammatory signals that can lead to neuroinflammation,⁴⁰⁻⁴⁴ a standard feature of ADRD pathogenesis.⁴⁵⁻⁵⁰ Animal data also indicates that PM or adsorbed compounds can reach the brain, after travelling through the systemic circulation and crossing the blood-brain barrier or through translocation up the olfactory nerve,⁵¹⁻⁵³ their presence in the brain is associated with oxidative stress and neuroinflammation.^{17-22,24,54,55}

While the existing epidemiologic studies of the association between air pollution and late-life cognitive or brain health are suggestive, they are insufficient to justify action.^{56,57} Most prior studies examine the association between air pollution and cognitive test scores at a single time point,⁵⁸⁻⁶⁷ yet evidence of associations with cognitive change, neuropathology, and incident dementia diagnosed systematically using research criteria are needed to make the case for intervention. Most prior studies also consider the impact of recent exposures,⁵⁶ for example, in the year prior to cognitive testing.^{36,58-60,62,65,68}

However, the most relevant exposure windows for effects on initiation and progression of dementia are likely in the distant past, as dementia pathogenesis takes years to decades, and recent exposures may not adequately reflect past exposures. Reliance on measures of recent exposures also raises concerns about reverse causation leading to spurious findings, a pervasive issue in dementia epidemiology.⁶⁹⁻⁷¹ Therefore, findings of associations with time-appropriate exposures are also needed to infer causality.

Finally, it is unclear how model choice for estimating individual air pollution exposures impacts effect estimates for cognitive outcomes. Many air pollution models including geographic information system (GIS)-based statistical models, air dispersion and chemical transport models, geo-statistical interpolation approaches, and hybrid models have been developed to derive outdoor air pollution concentrations for use in epidemiologic research, and each approach has unique strengths and weaknesses.^{72,73} While some studies have found that modeling approach did not markedly impact effect estimates for overall mortality⁷⁴, ischemic heart disease, and circulatory system disease⁷⁵, it is unclear whether this is true for cognitive and brain-related outcomes. Ensuring results are robust to modeling approach choice would strengthen our confidence that observed associations are not attributable to air pollution modeling assumptions.

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 the first of several we anticipate submitting in this context.

In this manuscript proposal, we propose to begin by addressing the association of ambient exposure to particulate matter (PM) and ozone at varying lags and averaging periods prior to baseline with late-life cognitive decline and incident dementia from Visit 5 through Visit 7.

5. Main Hypothesis/Study Questions:

We hypothesize that higher long-term cumulative exposures to PM_{2.5}, NO₂, and ozone (O₃) are associated with incident AD/DRD and accelerated cognitive decline.

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:

Non-white/non-black, black in MN or MD.

Missing relevant exposure, outcome, or covariate data.

Analyses of incident cognitive impairment will be restricted to those who are cognitively normal at Visit 5.

Independent variables:

Monthly ambient air pollution exposure estimates for particulate matter with an aerodynamic diameter of less than 2.5 microns (PM_{2.5}), or 10 microns (PM₁₀), oxides of nitrogen (NO₂/NO_x), and O₃ in the areas where ARIC participants live will be generated by Qi Ying as part of our grant activities. We will use an ensemble chemical transport model (CTM)/observation data-fusing approach for air pollution estimation, which is an extension of methods previously used successfully to estimate exposures for other epidemiologic studies.⁷⁶⁻⁸³ We will quantify prediction errors using a hold-out monitor out approach and will only use estimates passing QA/QC standards. Air pollution estimates will be linked with geocoded ARIC addresses generated by Eric Whitsel by Dr. Whitsel's team to produce residential address level estimates of exposure; note that we are generating new geocode data at the time of each participant AFU call or Visit for the period of Visit 4 through Visit 7.

In primary analyses, we'll consider various exposure windows –2005-2010, 2000-2004, 1995-1999, and 1990-1994, as well as a cumulative average over the entire period (1990-2010).

Dependent variables:

Domain-specific cognitive function at visits 5, 6, and 7

Level I and III dementia status at visits 6, and 7

Covariates:

All models will be adjusted for a common set of covariates: demographics (age, sex, race), personal SES (education, pre-retirement health insurance status), self-rated health, alcohol use, smoking status,

leisure time physical activity ⁸⁴), and area-level SES (% of residential census tract below the poverty line, a summary measure of neighborhood wealth/income, education and occupation ⁸⁵).

Effect modifiers:

APOE e4, sex, smoking status, physical activity, obesity, SES, and co-exposures

Statistical Analyses:

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

We will conduct sensitivity analyses including multiple averaging periods in a single model if more than 1 appears related to subsequent cognition. We will conduct several sensitivity analyses to address the potential impact of confounding, missing data, and selection bias. 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. We will also conduct formal bias analyses to determine the characteristics of an un-accounted for confounder or selection process that would be necessary to produce our findings ^{86,87} We will consider use of inverse probability weighting for attrition ⁸⁸ or MICE to address potential selection bias due to informative attrition.

To address the issue of measurement errors and uncertainties associated with use of modelled exposure, we will employ Bayesian hierarchical modeling (BHM) to model the impact of air pollution exposure on our cognitive and neuroimaging outcomes. Here, our Bayesian model consists of two levels: (Level 1) a measurement model that links predicted air pollution concentrations with the unobserved true ambient exposure, and (Level 2) a health model that links the ADRD-related outcomes with true ambient exposure. The error terms are included in both models. Dr. Park and Dr. Smith bring substantial expertise with Bayesian approaches and statistical methods to deal with measurement error and uncertainty in air pollution modelling ⁸⁹⁻⁹⁷

In sensitivity analyses, we will 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) land use regression / spatial smoothing. Both estimation methods have been validated. ⁹⁸⁻¹⁰¹ We are also linking additional estimates produced using (3) observation-fused aerosol optical depth and chemical transport model modelling approach ¹⁰², and (4) spatiotemporal monitoring approach ¹⁰³. Note that not all models generate estimates for all pollutants.

7.a. Will the data be used for non-CVD analysis in this manuscript? ☒ 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? ☒ 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 ☐ 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.csc.unc.edu/aric/mantrack/maintain/search/dtSearch.html>

☒ 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)?**

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" (Franseschini)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ☒ Yes ☐ No

11.b. If yes, is the proposal

☒ **A. primarily the result of an ancillary study (list number* 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 <https://www2.csc.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.csc.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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