ARIC Manuscript Proposal #3825

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

1.a. Full Title: Comparison of Air Pollution Exposure Assessment Methods and Their Impacts on Associations with Cognition and Neuroimaging Outcomes: the Atherosclerosis Risk in Communities (ARIC) Cohort

b. Abbreviated Title (Length 26 characters): Air Pollution Method Impact

2. Writing Group:

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

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3. Timeline:

We expect analyses to be completed within 6 months after manuscript proposal approval.

4. Rationale:

We have acquired, or are in the process of acquiring, air pollution exposure estimates from several modeling groups. A recent administrative supplement to our R01 (approved ancillary study #2020.09) has allowed us to expand the number of air pollution exposure estimates available to us. This proposal aims to explain how we plan to use the data produced by the different groups to compare estimates of annual-average air pollution exposures, and to quantify whether choice of modelling approach influences estimated associations with cognition and related neuroimaging outcomes. It will also discuss the importance of this analysis.

Ambient air pollution (AAP) has become one of the greatest environmental health risk factors due to both its ubiquitous nature and its adverse toxicological effects on human health [1-3]. Globally, over 90% of the world's population living in areas with AAP that exceeds WHO attainment limits. In 2019, an estimated 4.1 million deaths (118 million Disability Adjusted Life Years (DALYs)) were attributable to ambient $PM_{2.5}$ and 365,000 deaths (6.2 million DALYs) to ozone [3]. Particularly, low and middle income countries are disproportionately impacted [3, 4]. Furthermore, AAP exposure can impact a wide range of health outcomes across the lifespan. Prenatal exposure to air pollution is associated with low birth weight [5, 6], worse childhood cognitive function [7-9], and reduced lung function [10-12]. AAP exposure can also impact respiratory health among children, for example by exacerbating asthma [13], and recent studies suggest mental health effects [14, 15]. Among adults, AAP exposure has been associated with cardiovascular and respiratory morbidity and mortality [16-22], hypertension [23-25], cancer [26-30], and adverse neurological outcomes such as dementia [31-33].

While air pollution epidemiology is a rapidly expanding field that has allowed for examining associations between ambient air pollution and several health outcomes, more work is needed to close knowledge gaps and mitigate health burden associated with AAP. Accurate exposure assessment is necessary and critical to understand health impacts of environmental exposures in environmental epidemiology. Air pollution exposure assessment is particularly challenging due its nature of spatial and temporal variations. For some outcomes of interest, such as dementia, the relevant exposure period may precede disease development by decades. Therefore, accurately measuring long-term human air pollution exposure is an extremely difficult endeavor. However, accurate assessment of long-term ambient air pollution exposure, over long periods in the past, both on the individual and population scale, is a crucial step towards advancing the evidence base.

Traditional methods of estimating such exposures, e.g. by assigning concentrations measured at the nearest central site monitor, often make data collection easier and cheaper, and are generally readily available and reliable; however, they do not effectively capture within-community spatial variation, which may be important, especially for spatially heterogenous pollutants (e.g., CO and NO_2) [34-36]. Additionally, this direct form of exposure estimation may be impossible if distant past exposures are of interest, given insufficient monitor density in such time periods and areas of interest. Studies relying on air pollution concentrations measured at central-site monitors may therefore introduce exposure misclassification by assuming spatial and even temporal homogeneity (e.g. when missing days are imputed) of air pollutant exposures where it did not or does not exist, which can bias health effect estimates [34, 35].

Air pollution exposure modeling methods have been developed to estimate exposures where ground monitors are sparse, data is missing, or spatial misalignment is present between monitors

and locations of interest [36, 37]. Methods include geo-statistical interpolation approaches, geographic information system (GIS)-based statistical models, air dispersion and chemical transport models, satellite models, and hybrid models [36-38]. Interpolation approaches such as inverse-distance weighting and kriging interpolate exposures measured at monitors to unmeasured locations using deterministic and stochastic geostatistical techniques, respectively [36]. GIS-based statistical models, such as land use regression and spatiotemporal models, predict spatial and temporal patterns of air pollution concentrations using geographic variables, including topographic, emissions, land use, and traffic data [36, 39]. Dispersion and chemical transport models, such as the Community Multiscale Air Quality (CMAQ) model, combine meteorological and emission data to predict AAP concentrations using deterministic processes over time and space [38]. Lastly, other studies rely on complex hybrid models that combine and integrate outputs from multiple environmental data sources and air pollution models [37].

Each air pollution modelling method has its own advantages and disadvantages. Dispersion and chemical transport models can be applied to generate spatially distributed and temporally rich exposure estimates, and do not rely on a dense network of monitoring stations. However, they are computationally intensive, obtaining input data can be costly, emissions inventories are incomplete and may be inaccurate, dispersion pattern assumptions may be unrealistic or limited to local environments, and they do not provide high spatial resolution over large domains[36]. Interpolation and GIS-based statistical models rely on the availability of data from monitoring stations, and may be less accurate when such data is unavailable or when pollutant concentrations vary significantly over small scales [36, 38]. Additionally, interpolation approaches do not take into account external environmental factors (i.e. meteorology, wind speed, traffic density, and land use) that could impact exposure estimation [36]. Land use regression models may not be generalizable to other locations [38]. Hybrid approaches that combine outputs may share these limitations, and also require additional assumptions for validity.

The potential impact of air pollution modelling approaches on epidemiologic findings remains unclear. Unlike other areas of measurement, there is no gold standard for assessment of air pollution exposures. While epidemiologic studies often report exposure model cross-validation statistics comparing estimates to measured air pollution at monitoring sites [40-45], this form of comparison can be difficult to evaluate given the heterogeneity in the choice of validation statistics, variable spatiotemporal resolution of models, and differences in geographic areas covered by air pollution models. Additionally, cross-validation using monitoring sites may not adequately represent residences or other prediction locations, so comparisons of modelled data against that from monitoring stations may not be an appropriate validation approach [46, 47] Finally, independent set of monitor data external to the modeling process are seldom available.

Few studies have directly compared air pollution exposures across multiple methods or quantified the impact of air pollution estimation approaches on health effects estimates. In one example, Yu et al. compared 14 different methods for modeling daily concentrations of a variety of air pollutants in the Atlanta, Georgia region, ultimately demonstrating that any of the methods considered (besides raw CMAQ output) may be appropriate for certain applications [48]. Another study by McGuinn et al. used five air pollution exposure methods, including both monitored and modeled data (from satellite- and CMAQ-based models), to estimate associations between $PM_{2.5}$ exposure and odds of coronary artery disease and myocardial infarction [49]. They found that choice of modeling approach did not substantially affect associations with those health outcomes [49]. In a study of the effects of air pollution exposure on lung function of

children, correlations between LUR and dispersion models were high for NO_2, $PM_{2.5}$ and $PM_{2.5}$ soot, but lower for PM_{10} [50]. Associations were generally similar across models, but for $PM_{2.5}$ and PM_{10} they were stronger with wider confidence intervals for exposures based on the LUR model compared to the dispersion model [50]. Another study on the effects of 3-year estimated average $PM_{2.5}$ on mortality from circulatory diseases and ischemic heart disease found significant associations for each of the seven included exposure models, but effect estimates were typically larger from models that incorporated ground-based information compared to those that only used remote sensing [47]. Overall, these studies seem to suggest that effect estimates may differ slightly, but still result in the same direction of association for different exposure models. However, to date, few studies have compared long-term average exposures using modelling approaches developed by different groups or considered whether modelling approach impacts associations with late-life cognitive health. The latter is of particular interest given substantial, yet unexplained heterogeneity in the current literature [51].

The Atherosclerosis Risk In Communities (ARIC) cohort [52] is a unique dataset in which we can compare individual air pollution exposure estimates from different modelling approaches employed by different research groups and assess whether choice of air pollution modelling approach influence its associations with late-life cognitive health including cognition and related neuroimaging outcomes.

Therefore, our goal is to compare estimates of annual-average air pollution exposures produced by different groups, and quantify whether choice of modelling approach influences estimated associations with cognition and related neuroimaging outcomes using the ARIC cohort data.

5. Main Hypothesis/Study Questions:

Aim 1: To assess the consistency and agreement of the air pollution exposure estimates from various air pollution models within the ARIC cohort, identifying any modeling approaches that do not produce similar estimates. We hypothesize that air pollution estimates from different modeling approaches will be similar; however, if there are any that do not have similar estimates this is important to determine as this difference could impact effect estimates for outcomes.

Aim 2: To determine whether choice of air pollution model influences the associations between air pollution exposures with Visit 5 MRI outcomes (total and regional brain volumes, and presence of lacunes, microbleeds, and white matter hyperintensities) and Visit 5 cognitive status. We hypothesize that associations with Visit 5 MRI and cognitive outcomes will be similar regardless of choice of air pollution model.

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 cohort study will compare estimates of long-term air pollution exposure generated from different models and estimate the association between air pollution exposure and MRI outcomes and cognitive status.

Exclusions:

For all analyses, we will restrict to participants who attended Visit 5 and have Visit 5 cognitive data. We will exclude participants who do not have a full geocoded residential history available for 2000 through 2007 or for whom we are unable to estimate air pollution exposures for this period. We will also exclude participants in small race-center categories: non-white participants in Minneapolis, MN and Washington County, MD; non-Black participants in Jackson, MS; and non-white or non-Black participants in Forsyth County, NC. Finally, we will exclude participants missing relevant covariate data.

For analyses of long-term air pollution exposure and Visit 5 MRI outcomes, we will further restrict to participants who have non-missing Visit 5 MRI data, no stroke prior to Visit 5, and no presence of tumor, surgery, or radiation to the head, or an implausible intracranial volume.

Independent Variables:

Our primary exposure of interest will be annual $PM_{2.5}$ at ARIC geocoded residential locations; in secondary analyses we may consider other pollutants, including PM_{10}, NO_2, ozone, and PM components. Geocoding efforts in the ARIC cohort have previously been validated, and have high accuracy[53, 54].

We will be comparing estimated air pollution exposures generated from multiple modeling approaches. The different approaches and their temporal resolution are summarized in **Table 1.** To date, ARIC investigators have used two different methods [42, 55](the approaches generated by Yanosky and Liao) to estimate air pollution exposures for participants using geocoded address-specific AAP concentrations. We are also working to link exposure estimates from models developed by three separate groups of investigators to the ARIC cohort: the Atmospheric Composition Analysis Group of Dalhousie University [56, 57], the Kaufman group at University of Washington [58, 59], and Dr. Qi Ying at Texas A&M University (in progress) as part of AS2016.20 and AS2020.09. We may also add nearest-neighbor or inverse-distance weighted exposure assessment as well.

Table 1: Air Pollution Modelling Approaches

Modeling Approach	**Type of Modeling Approach**	**Pollutants Available**	**Temporal Resolution Available to ARIC**
Yanosky [55]	Generalized Additive Mixed Model with Land Use Regression	$PM_{2.5}$, PM_{10}	Monthly
Liao [42]	National Log-Normal	$PM_{2.5}$, PM_{10}, O_3, NO_2, NO_x, SO_2	Daily

	Measurement-Error Kriging Model		
Liao [42]	National Log-Normal Ordinary Kriging	$PM_{2.5}$, PM_{10}, O_3, NO_2, SO_2, CO	Daily
Dalhousie [56, 60]	Chemical Transport-based Approach with Satellite and Ground Observations	$PM_{2.5}$, $PM_{2.5}$ components	Annual
Kaufman [59]	Universal Kriging with LUR & PLSR - Historical $PM_{2.5}$ Model	$PM_{2.5}$	Annual
Kaufman [58]	Regionalized Universal Kriging with LUR & PLSR - Biweekly Models	$PM_{2.5}$, NO_x, NO_2, Ozone	Monthly
Ying	CMAQ-NEI/CMAQ-EDGAR + Fusing + Near Roadway	$PM_{2.5}$ and $PM_{2.5}$ components, ozone, NO_2, SO_2, and CO	Monthly and annual

We will focus on comparing annual $PM_{2.5}$ exposures for 2000 through 2007, as all models under consideration generated estimates for this pollutant and time period and long-term exposures are likely most relevant for cognitive outcomes. In sensitivity analyses, we may also consider comparing estimates for PM_{10}, O_3, NO_2, and $PM_{2.5}$ components (note that not all of the aforementioned models generated exposure estimates for ozone, NO_2, and $PM_{2.5}$ components).

Dependent Variables:

Our primary outcomes are Visit 5 cognitive status and Visit 5 MRI outcomes. All ARIC participants were administered an extensive battery of cognitive tests at Visit 5: delayed word recall (DWR), logical memory I and II, incremental learning, trail making test parts A and B, digit symbol substitution test, digit span backwards, animal naming, Boston naming, word fluency, and clock time. In primary analyses we will focus on the global factor score. In sensitivity analyses, we will also explore associations with domain-specific cognitive test scores.

MRI outcomes include the following: brain volumes (total, hippocampus, Alzheimer's disease signature region, regional), presence of lacunar and cortical infarcts, white matter hyperintensity volume, presence of severe white matter hyperintensities, and presence of

microbleeds. Brain volumes and white matter hyperintensity volume will be continuous measures (white matter hyperintensity volume will likely be log-transformed, as previous analyses demonstrate that this variable is largely skewed). All other outcomes will be dichotomous.

Covariates:

All analyses will be adjusted for a set of variables determined a priori: age, education, gender, BMI, smoking status, and area-level socioeconomic status. Analyses with MRI outcomes will also be adjusted for total intracranial volume. In a secondary analysis, we might further adjust for physical activity and occupational category.

Statistical Analysis

Aim 1: Air Pollution Comparison

We will first use descriptive statistics and plots to assess agreement between the air pollution estimates. These will include calculation of means, standard deviations, ranges, minima, maxima, and percentiles for average air pollution exposures for each air pollution model as well as plots including boxplots and density plots. We will also create dot maps representing air pollution estimations at each ARIC participant location for each air pollution modeling method to aid understanding of how well air pollution estimates agree with each other across space. Dots will be of a sufficient resolution or jittered such that there are not identifiability issues.

Figure 1. Equations for assessing absolute differences between pairs of air pollution models *(equations adapted from the US EPA Air Quality Model Performance Metric Definitions document):*

$$\text{Mean Bias} = \frac{1}{n}\sum_{1}^{n}(M - O)$$

$$\text{Mean Error} = \frac{1}{n}\sum_{1}^{n}|M - O|$$

$$\text{Root Mean Square Error} = \sqrt{\frac{\sum_{1}^{n}(M - O)^2}{n}}$$

Absolute differences between air pollution estimates will explored by calculating the mean bias, mean error, and root mean square error between all possible pairs of air pollution models (equations in **Figure 1)** Because no one model represents "true" exposures, these statistics will represent absolute differences between modeled air pollution estimates rather than how well the models predict true air pollution exposures. We will also consider completing a clustering analysis (multidimensional scaling), which is a visualization technique that groups models into clusters based on correlation [61].

To visually represent and compare both the absolute and relative differences between pairs of air pollution models, we will construct Bland-Altman plots[62]. With these plots, we will be able to determine the average difference between estimates generated by each pair of air pollution models. We will also determine whether estimates tend to agree or disagree more as the average air pollution estimate increases, further generating suggestions for when pollution estimation methods are comparable and when they produce substantially different estimates.

Agreement between air pollution estimates will also be assessed using Deming regression. If there is no systematic difference between air pollution estimates, the slope of the estimated regression line should be close to 1 and the intercept close to 0. A deviation from the slope of 1 indicates a proportional discrepancy between air pollution estimates. A non-zero intercept represents an absolute discrepancy between air pollution estimates. We will also visually assess correlations using scatterplots as well as examining Pearson and Spearman correlation coefficients.

We will repeat all of these analyses stratified by study site, in order to investigate spatial variability of agreement.

Aim 2: Associations between $PM_{2.5}$ and Cognitive- as well as MRI-Related Outcomes

Given concerns that between-site variation in PM will be large in comparison to within-site variation and known regional differences in $PM_{2.5}$ composition, we will initially perform all analyses separately by site. Site-specific analyses will be meta-analyzed using a random-effects model to produce an effect for the entire cohort, as done previously in analyses of air pollution and MRI outcomes [62, 63]. Heterogeneity of effect will be evaluated using the I^2 test[64]; if this test suggests no heterogeneity across sites, we will examine models considering the entire ARIC population as a single sample.

We propose to use linear (for outcomes white matter hyperintensities, volumes, cognitive factors cores) and logistic regression (for outcomes cortical infarcts, lacunes, and microbleeds) to assess the association between $PM_{2.5}$ with cognitive status and MRI markers. All analyses with MRI markers will be weighted using coordinating center derived weights to account for the sampling strategy for Visit 5 stage 3 MRI and refusals. We will appropriately adjust for known confounders detailed above.

We will calculate the association between air pollution exposure and each outcome using exposures from each of the models to see how variations in air pollution estimates may influence health effect estimates. We will also plot each air pollution model's associated effect estimates (betas and odds ratios) and 95% confidence intervals in a forest plot to visually represent whether effect estimates tend to agree, and whether precision in health effect estimates between air pollution methods is comparable.

Limitations and Challenges

We recognize the constraints of our chosen approach. Primarily, our study will not tell us which air pollution model performs the best; rather, our intention is to characterize the absolute and relative agreement between models as a first step towards understanding why these differences occur. We will only consider air pollution exposures between 2000 and 2007 because this period gives us the most overlap between models. It is possible that exposures in the more distant past are more predictive of late-life cognition and MRI-related outcomes. It is also possible that there is residual confounding that cannot be accounted for with available data. However, our goal here is to determine whether associations are markedly different depending on the air pollution model used to assign $PM_{2.5}$ exposures. We will emphasize interpreting the differences between effect estimates rather than interpreting the magnitude of singular effect estimates.

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"? __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 et al.
#3348, Ambient air pollution and late-life cognition and dementia, Power et al.
#3746, The association between criteria air pollutant exposure and late-life amyloid burden, Bennett et al.
#3460, Accounting for exposure measurement error in assessment of the effects of air pollution on dementia, Park et al.
#3762, Association of ambient particulate matter components with MRI outcomes, Power et al.

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.

Okay.

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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