ARIC Manuscript Proposal #2412

PC Reviewed: 8/12/14 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Association of particulate matter air pollution with MRI outcomes

b. Abbreviated Title (Length 26 characters): Particulate matter and MRI

2. Writing Group:

Writing group members: Rebecca Gottesman (senior), Cliff Jack, Duanping Liao, Thomas Mosley, Melinda Power (first), James D. Stewart, Eric A. Whitsel, Jeff D. Yanosky, others welcome

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

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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 visit 5 brain MRI data and an initial set of derived variables are now available; we plan to submit for publication within 12 months.

4. Rationale:

Exposure to particulate air pollution may promote cognitive decline and dementia. A direct neurotoxic effect of particulate matter on brain health is plausible given that particulates, primarily fine and ultrafine particulates, and their adsorbed compounds, can reach the brain.[1-3] Particulate matter, especially fine or ultrafine particulates, may also have indirect impact on cognitive function through effects on blood-brain barrier function[4] or promotion of cardiovascular or cerebrovascular disease.[5-9]

Experimental and ecologic literature suggests an effect of particulate air pollution on brain health and function, including cognitive and neurodegenerative changes. For example, experimental studies show an impact of ultrafine particulate matter exposure on brain activity indicative of a cortical stress response,[10] exercise-induced hippocampal brain-derived neurotrophic factor expression,[11] neuroinflammation,[12, 13] and cortical neuronal loss.[14] Moreover, mice exposed to fine particulate matter for ten months showed decrements in spatial learning and memory as well as pro-inflammatory cytokine expression in the hippocampus compared to those exposed to filtered air.[15] Further support from autopsy studies of animals and persons exposed to high versus low air pollution has shown evidence of increased oxidative damage, inflammation, and amyloid-beta 42 in the brain related to air pollution exposure level.[16-20]

There is a growing body of epidemiologic literature suggesting an association between long-term markers of air pollution exposure and cognitive status at a single point in time. Multiple studies report a link between exposure to traffic-related air pollution, which contains a high proportion of ultrafine particulate matter, and cognition. Among older German women with a stable residential address over many years, those who lived within 50 meters of a major road, a marker of high exposure to traffic-related air pollution, had significantly worse performance on neuropsychological testing and a test of olfaction.[21] Similarly, within a cohort of older men in the greater Boston area, the Normative Aging Study, higher estimated exposure to black carbon, a marker of traffic related pollution, was associated with worse cognitive performance on a battery of cognitive tests.[22] In a second Boston-based cohort, MOBILIZE Boston, decreasing distance to a major road was associated with relatively poor performance on several cognitive tests covering many domains, including verbal learning and memory, executive function, psychomotor speed, and language.[23] Several other studies report associations between cognitive status and other measures of air pollution, including ozone or particulate matter with an aerodynamic diameter less than 2.5 (PM2.5) or 10 (PM10) microns. Analyses in the Health and Retirement Study, a U.S. nationally representative sample, suggest a cross-sectional association between PM2.5 and cognitive function, particularly in the domain of episodic memory.[24] Similarly, higher air pollution increased the odds of cognitive impairment in a large sample of Chinese elders,[25] and in data from the National Health and Nutrition Examination, ozone, but not PM10, was associated with cognitive performance after adjustment for sociodemographic factors.[26] Although higher ozone, NO2, and PM2.5 were not cross-sectionally associated with global cognition or most cognitive domains in a cohort of cognitively intact residents of Los Angeles, some pollutants were marginally associated with worse performance on specific cognitive

domains.[27] Finally, two studies have considered the association of air pollution and cognitive trajectories. Despite the findings of the REGARDS study that PM2.5 was not reliably associated with incident cognitive impairment,[28] in the Nurses' Health Study, long-term exposure, but not short-term exposure, to PM2.5 and PM10 were both associated with decline in overall cognitive performance.[29]

Despite this growing body of literature suggesting adverse consequences of particulate matter exposure on cognitive outcomes in older adults, studies of the association between particulate matter air pollution and MRI markers of neurodegeneration or cerebrovascular disease are lacking. Such studies are critical to promote understanding of how particulate matter exposures, especially repeated exposures over long time perios, may impact brain health. For example, cerebrovascular injury is associated with cognition.[30] As particulate matter is unarguably associated with cardiovascular disease,[5, 6] and also appears associated with risk of stroke,[7-9] it is reasonable to hypothesize that particulate matter acts on cognition through promotion of cerebrovascular insult. However, hypotheses linking particulate matter directly to Alzheimer's pathology are also reasonable, given some evidence linking particulate matter exposure to neurofibrillary tangles and neuronal amyloid-beta levels in dogs.[16, 31]

Therefore, we propose to evaluate the association between particulate matter exposure and markers of neurodegenerative and cerebrovascular disease using data from the ARIC cohort. (*Please note that we intend to submit a separate proposal considering the association between particulate matter and cognitive/dementia outcomes; including both in the same proposal was unwieldy*). This manuscript proposal specifically outlines two sets of analyses, with the expectation of two manuscripts. The first will evaluate the association between long-term exposure to particulate matter with an aerodynamic diameter less than 2.5 microns (PM2.5) and particulate matter with an aerodynamic diameter less than 10 microns (PM10) with several MRI markers of neurodegeneration and cerebrovascular disease measured at Visit 5. The second will evaluate whether PM2.5 and PM10 are associated with greater within-person change in white matter hyperintensities (WMH), infarct burden, or atrophy measures between assessments at Visit 3 and the Brain MRI visit.

5. Main Hypothesis/Study Questions:

Hypothesis 1a: Higher long-term exposure to particulate matter, specifically PM2.5, will be associated with smaller total and regional brain volumes.

Hypothesis 1b: Higher long-term exposure to particulate matter, specifically PM2.5, will be associated with greater burden of subclinical cerebrovascular disease, including microbleeds, lacunes, and white matter hyperintensities.

Hypothesis 2: Higher long-term exposure to particulate matter, specifically PM2.5, will be associated with greater progression of white matter hyperintensities, burden of infarcts, and measures of atrophy.

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).

We outline the design and analyses for Hypotheses 1a and 1b separately from that evaluating Hypothesis 2, as we intend each to be a separate manuscript.

HYPOTHESIS 1a/b

Hypothesis 1a: Higher exposure to particulate matter, specifically PM2.5, will be associated with smaller total and regional brain volumes.

Hypothesis 1b: Higher exposure to particulate matter, specifically PM2.5, will be associated with greater burden of subclinical cerebrovascular disease, including microbleeds, lacunes, and white matter hyperintensities.

Exclusions:

Not white in Washington County or Minnesota; not African-American in Jackson; not white or African American in North Carolina; stroke prior to visit 5; presence of tumor, surgery, or radiation to the head; missing education, or having no valid MRI data.

Independent variables:

Analyses will rely on mean concentrations ($\mu g/m^3$) of PM2.5 and PM10 previously estimated in the context of ARIC Ancillary Study #2009.08 at geocoded addresses of participants using (1) national-scale, lognormal ordinary kriging and (2) land use regression / spatial smoothing. The aforementioned estimation[32-36] and geocoding[37, 38] methods have been validated. For this study, we anticipate averaging will be performed over three time periods, although we may consider other averaging periods as well in either primary or sensitivity analyses:

- The year 1999
- The year 2010
- Average exposure from 1999-2010

Long-term cumulative exposure is likely most relevant to the development of neurodegenerative and cerebrovascular disease. Therefore, we use three measures of long-term cumulative past exposure to PM2.5 and PM10: the average exposure over the calendar year 1999, average exposure in the calendar year prior to the Visit 5 MRI, and the average exposure from 1999-2010. Yearly air pollution levels are highly correlated from year to year, although there has been a downward trend in absolute levels over time and air pollution levels vary in somewhat predictable ways within a year according to variations in the seasons and weather. Use of these three measures of long-term exposure allow us to test hypotheses about whether recent cumulative exposure, distant

cumulative exposure, or total cumulative exposure are more relevant to differences in MRI outcomes.

Dependent variables:

Visit 5 MRI data;

- Microhemorrhages
- White matter hyperintensities
- Cortical infarcts
- Lacunar infarcts
- Brain volumes (hippocampal, Alzheimer's disease (AD) signature region[39], regional, total).

Covariates:

All analyses will be adjusted for a set of variables, determined a priori: total intracranial volume, age, education, gender, BMI, smoking status, and measures of regional SES. Appropriate functional form of continuous covariates will be assessed using penalized splines. We will update time-varying covariates according to the exposure of interest, allowing for appropriate control for confounding. Sensitivity analyses will consider additional adjustment for meteorological covariates, rural/urban residential location, additional indirect measures of socio-demographic status, and potential intermediates, including hypertension and diabetes status.

Effect modifiers:

Gender, race, age, and anthropomorphic measures (BMI, waist-circumference) at baseline.

Statistical Analyses:

Final analytical methods will be coordinated with the NCS MRI workgroup.

Given concerns that between-site variation in PM will be large in comparison to within-site variation and known regional differences in PM 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. Heterogeneity of effect will be evaluated using the I^2 test; 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 (white matter hyperintensities, volumes) and logistic regression (cortical infarcts, lacunes, and microbleeds) to assess the association between PM2.5 and PM10 with MRI markers. Data on white matter hyperintensities is approximately log-normal and will be transformed prior to use as an outcome in our models. We will use

multiplicative interaction terms, likelihood ratio tests, and stratified analyses to assess effect modification. All analyses will be weighted using coordinating-center derived weights to account for the sampling strategy for Visit 5 stage 3 MRI and refusals. We will use penalized splines to evaluate the appropriate shape of the dose response curve and will provide analyses with exposure treated as a linear term or in quartiles of exposure, as appropriate. In sensitivity analyses, we will develop and apply inverse probability weights (IPW) to account for attrition prior to Visit 5 and may conduct sensitivity analyses to compute bounds on the potential association under a range of assumptions about differential attrition to address issues of selection. Similarly, we will conduct sensitivity analyses adjusting for additional variables, as described above, to address concerns about residual confounding. If available, we may also incorporate analyses considering an additional exposure variable, distance-to-road, a commonly used proxy of traffic-related air pollution exposures.

Limitations/Challenges: Our analysis has several limitations. First, we will not consider within-individual change in these specific analyses, incorporating data from Visit 5 (however we do consider examining within-individual changes using data from Visit 3 and the Brain MRI sub-study in Hypothesis 2). Prior scans differed from current scans in terms of pulse sequences, field strength, and image processing, and we currently do not understand whether differences detected across scans with different protocols reflect true biological change or artifacts of different scanning and processing protocols. While we will adjust for *a priori*-specified confounders and conduct sensitivity analyses to address concerns about selection and confounding, the potential for bias due to confounding or selection remains. Some misclassification of particulate matter exposure and MRI markers is expected; however, we expect misclassification to be non-differential and for resulting bias to be towards the null. We are limited by a relatively small sample size with the expectation of modest effects; however, this study is relatively large by MRI standards and of similar sample size to prior studies of particulate matter and cognition, which do show an association despite similar limitations.

HYPOTHESIS 2

Hypothesis 2: Higher exposure to particulate matter, specifically PM2.5, will be associated with greater progression of white matter hyperintensities, burden of infarcts, and measures of atrophy.

Exclusions:
Not white in Forsyth County; not African-American in Jackson; presence of tumor, surgery, or radiation to the head; missing education, or having no valid MRI data at Visit 3 and Brain MRI.

Independent variables:

We propose to use estimates of PM2.5 and PM10 at the residential address of each eligible ARIC participant, derived as described above. For this analyses, we anticipate that we will use the average exposure to PM10 and PM2.5 at the residential address of

each eligible participant in the calendar year of 1999 (the first year for which PM2.5 data are available), and PM10 in the calendar year of 1993; however, we may also consider alternate averaging periods.

Dependent variables:

Change in:

- White matter hyperintensities (WMH)
- Ventricular size
- Sulcal widening
- Burden of infarcts

All measures were assessed at both Visit 3 and the Brain MRI study in 2004-2006.

WMH, ventricular size, and sulcal widening were quantified using a 0 to 9 scale at both scans. At the Brain MRI study, standardized volumetric measurements of WMH were obtained in addition to the ordinal scale. As such, we should be able to convert WMH grade to volumes at Visit 3, using calibration data from Brain MRI. Given the possibility of inducing differential misclassification with a simple regression calibration approach, we will use a multiple imputation approach including all the covariates listed below to inform the imputation. Using categorical WMH, ventricular size, and sulcal widening measurements, progression will be defined as an increase of 2 or more in score from visit 3 to the Brain MRI study, although we will consider alternate cut-offs in sensitivity analyses. Increasing infarct burden will be defined as any incident infarct. We will also consider change in WMH volume, using derived volumes at Visit 3 as described above, as an indication of progression.

Effect modifiers:

Gender, race, age, and anthropomorphic measures (BMI, waist-circumference) at baseline.

Covariates:

All analyses will be adjusted for a set of variables, determined a priori: total intracranial volume, age, education, gender, BMI, smoking status, and measures of regional SES. Appropriate functional form of continuous covariates will be assessed using penalized splines. Sensitivity analyses will consider additional adjustment for meteorological covariates, rural/urban residential location, additional indirect measures of socio-demographic status, and potential intermediates, including diabetes and hypertension.

Statistical Analyses:

Given concerns that between-site variation in PM will be large in comparison to within-site variation and known regional differences in PM composition, we will consider the

results from the prior analyses to determine if it is necessary to perform all analyses separately by site.

We will use logistic regression for analyses of progression of WMH, sulcal size, and ventricular size, based on the 0-9 scale scores, and incident infarcts. For analyses considering change in WMH volume, we will use linear regression. We will use penalized splines to evaluate the shape of the dose response curve and will report analyses with linear, transformed, or quantiles of exposure as appropriate. We will use multiplicative interaction terms, likelihood ratio tests, and stratified analyses to assess effect modification.

In sensitivity analyses, we will develop and apply inverse probability weights (IPW) to account for attrition prior to Visit 5 and may compute bounds on the potential association under a range of assumptions about differential attrition to address issues of selection. Similarly, we will conduct sensitivity analyses adjusting for additional variables, as described above, to address concerns about residual confounding, and will evaluate the impact of alternate cut-offs for progression. If available, we may also incorporate analyses considering an additional exposure: distance-to-road, a commonly used proxy of traffic-related air pollution exposures in additional analyses.

If issues regarding differences in scanner technology and processing can be overcome, we may also consider associations with change in MRI measures from Visit 3 or Brain MRI through Visit 5.

Limitations/Challenges: Our analysis has several limitations. While we will adjust for *a priori*-specified confounders and conduct sensitivity analyses to address concerns about selection and confounding, the potential for bias due to confounding or selection remains. Some misclassification of particulate matter exposure and MRI measures is expected; however, we expect misclassification to be non-differential and for resulting bias to be towards the null. We are limited by a relatively small sample size in with the expectation of modest effects; however, this study is relatively large by MRI standards and of similar sample size to prior studies of particulate matter and cognition, which do show an association despite similar difficulties.

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?
___ 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/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)?

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

#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

___ A. primarily the result of an ancillary study (list number)
ARIC Brain MRI: 1999.01, ARIC NCS: 2008.06; Modification of PM-Mediated Arrhythmogenesis in Populations: 2009.08

___ 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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