

**ARIC Manuscript Proposal # 3241**

**PC Reviewed:** 10/8/19  
**SC Reviewed:** \_\_\_\_\_

**Status:** \_\_\_\_\_  
**Status:** \_\_\_\_\_

**Priority:** 2  
**Priority:** \_\_\_\_\_

**1.a. Full Title:** Association between particulate matter and chronic kidney disease

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

**2. Writing Group:**

Writing group members: Matthew Blum, Eric Whitsel, Duanpin Liao, , Morgan E. Grams, Melinda C. Power (co-last authors) *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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**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:** Analysis will begin upon receipt of the data and approval of the manuscript proposal. Manuscript will be written and submitted for ARIC Publications Committee review within one year of manuscript proposal approval.

**4. Rationale:**

Particulate matter (PM), is a heterogenous mixture of solid and liquid particles from various sources including fossil fuel combustion, road dust, industrial processes, and natural sources. It is characterized by particle diameter, with PM10 and PM2.5 being 10 and 2.5 micrometers in diameter or smaller, respectively. It is a principal component of air pollution

that contributes to a wide array of health effects including increased hospital admissions,<sup>1</sup> cardiovascular disease mortality,<sup>2</sup> impaired lung function,<sup>3</sup> and diabetes prevalence.<sup>1,4</sup>

While exposure to nephrotoxic metals can contribute to both acute and chronic kidney injury,<sup>5,6</sup> few studies have explored the link between PM exposures and kidney disease. A pair of mechanistic studies have linked respiratory exposure to diesel exhaust to exacerbation of acute and chronic kidney disease in mice.<sup>7,8</sup> Epidemiologically, relatively few studies exist on this topic. A pair of cross-sectional studies relating air pollution to eGFR in Korea and Taiwanese adults have shown higher PM<sub>10</sub> to be associated with lower eGFR.<sup>9,10</sup> A recent analysis of a large VA cohort that demonstrated an association between county-wide exposure to PM<sub>2.5</sub> and CKD incidence and progression.<sup>11</sup> The effect of ambient PM exposure on CKD progression deserves further study.

We will take an approach similar to that used in a recent ARIC study on the association between PM exposure and brain MRI findings.<sup>12</sup> By linking results of a spatiotemporal model to residential addresses, individual-level PM estimates were developed for a subset of ARIC participants. Using PM estimates for the entire ARIC cohort, our analyses will estimate the association between exposure to ambient PM and the development of CKD, GFR decline, and ESRD.

## 5. Main Hypothesis/Study Questions:

Aim 1: Evaluate the associations of ambient PM<sub>10</sub> and PM<sub>2.5</sub> exposure in adults with the development of CKD, GFR decline, and ESRD.

Hypothesis 1: Exposure to higher levels of long-term cumulative past exposure to PM<sub>2.5</sub> and PM<sub>10</sub> is associated with an increased hazard of kidney outcomes, independent of covariates.

Aim 2: Evaluate the associations of ambient PM<sub>10</sub> and PM<sub>2.5</sub> exposure in adults with the development of CKD, GFR decline, and ESRD in meta-analyses including ARIC and WHI, if available.

Hypothesis 2: Associations will be similar across cohorts and study sites.

## 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:** We will conduct a prospective analysis of the ARIC cohort, using study visit 4 as baseline with follow-up through December 31, 2016 (or the most recent surveillance year).

**Study Population:** The study population will include all members of the ARIC cohort with available creatinine at visit 4 and measures of PM exposure generated with the same methods as the previously mentioned study of PM and brain MRI features. Individuals will be excluded if they are missing follow up information on CKD outcomes. Incident CKD analysis will exclude those with eGFR < 60 ml/min per 1.73 m<sup>2</sup> at visit 4. In meta-analyses with WHI, we will align the baseline visit and associated PM exposure measures to most closely align with temporal and exposure history in the other cohorts (likely visit 1).

**Exposure:** We will consider mean PM<sub>2.5</sub> and PM<sub>10</sub> exposures from 1990-1998 at the residential address of each participant, generated using a validated spatiotemporal land-use regression model.<sup>13-15</sup> In meta-analyses, we will align exposure averaging periods so that they are similar in length to those that can be calculated in WHI.

### **Outcomes:**

The main outcomes are incident chronic kidney disease and incident end-stage renal disease. Estimated glomerular filtration rate (eGFR) will be calculated using the creatinine-based Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation, incorporating serum creatinine measurements at visit 4, visit 5 and visit 6.<sup>16</sup> Incident chronic kidney disease will be defined as meeting any of the following criteria: 1) development of eGFR < 60 mL/min/1.73 m<sup>2</sup> at follow-up accompanied by ≥ 25% eGFR decline relative to baseline; 2) chronic kidney disease-related hospitalization or death based on ICD-9/10 codes; 3) development of end-stage renal disease, as defined below.<sup>17</sup> We will also investigate the decline in eGFR associated with PM exposure using mixed models to estimate slopes as a sensitivity analysis.

Incident end-stage renal disease will be defined as the initiation of renal replacement therapy (either dialysis or transplant) and cases will be defined through linkage of the ARIC study with the United States Renal Data System (USRDS) registry. As a sensitivity analysis, we will use a composite outcome of kidney failure defined as meeting any of the following criteria: 1) USRDS-identified end-stage renal disease; 2) eGFR < 15 mL/min/1.73 m<sup>2</sup> at follow-up (visit 5); or 3) ICD-9/10 code for a kidney failure-related hospitalization or death.<sup>18</sup>

### **Statistical Analysis:**

Descriptive statistics (means, proportions, etc.) will be used to examine baseline characteristics of the study participants according to quantiles of PM<sub>2.5</sub> and PM<sub>10</sub> and test for differences using  $\chi^2$  tests and linear regression. The cross-sectional association between eGFR and albuminuria and PM<sub>2.5</sub> and PM<sub>10</sub> will be investigated using scatterplots and correlation coefficients.

Cox proportional hazards regression will be used to estimate the association (hazard ratios, 95% confidence intervals) between PM<sub>2.5</sub> and PM<sub>10</sub> and risk of kidney disease during follow-up, incorporating time to the development of kidney disease and accounting for censoring. Cubic splines will be used to visually depict the association between PM<sub>2.5</sub> and PM<sub>10</sub> and kidney disease risk, and nonlinear transformations of PM exposure will be used if needed. Because of the known heterogeneity in PM exposure across study sites, site-specific models will be performed and combined using random effects meta-analysis as done previously.<sup>12</sup>

Potential covariates for multivariable regression models include: age, sex, race (for North Carolina), body mass index, systolic blood pressure, anti-hypertensive medication use, hypertension status, hemoglobin A1c, diabetes status, history of cardiovascular disease, cigarette smoking status, eGFR, albuminuria, and average ambient temperature. In a second model we will also adjust for area-level socioeconomic measures and individual-level measures including

income and education. Multiple imputation will be explored for imputation of missing covariate values. We will test interactions between PM exposure and gender as well as socioeconomic status, diabetes and hypertension.

To test of our models, will perform Cox proportional hazards regression analyses for additional outcomes that will serve as a positive control and a negative control. For a positive control, we will estimate the association between particulate matter and mortality, which is a well-established association<sup>19</sup> but has not previously shown in ARIC. As a negative control, we will estimate the association between particulate matter exposure and incident motor vehicle accidents, which have no plausible relation.

**Limitations:**

Geographic exposures are limited to home address. PM2.5 exposure will be estimated as done previously. PM is inherently non-specific in the absence of speciated pollution data. There is the potential for additional unmeasured geographic confounders.

**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”?** \_\_\_ 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/search.php>**

\_\_\_\_\_ 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)?**

2183 - Progression of CKD focusing on kidney function (Coresh)

2412 - Association of particulate matter air pollution with MRI outcomes (Gottesman)

**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\* 2013.21)**  
 **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.csc.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.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.

**13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication.** Approved manuscripts should be sent to Pingping Wu at CC, at [pingping\\_wu@unc.edu](mailto:pingping_wu@unc.edu). I will be using CMS data in my manuscript  Yes  No.

## References

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