

Particulate Matter and Albuminuria, Glomerular Filtration Rate, and Incident CKD

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Abstract

Background and objectives Exposure to particulate matter (PM) <2.5 μm in aerodynamic diameter (PM_{2.5}) has been linked to detrimental health effects. This study aimed to describe the relationship between long-term PM_{2.5} exposure and kidney disease, including eGFR, level of albuminuria, and incident CKD.

Design, setting, participants, & measurements The study included 10,997 participants from the Atherosclerosis Risk in Communities cohort who were followed from 1996–1998 through 2016. Monthly mean PM_{2.5} concentrations ($\mu\text{g}/\text{m}^3$) were estimated at geocoded participant addresses using geographic information system–based, spatiotemporal generalized additive mixed models—including geospatial covariates such as land use—and then averaged over the 12-month period preceding participant examination. Covariate-adjusted, cross-sectional associations of PM_{2.5}, baseline eGFR, and urinary albumin-creatinine ratio (UACR) were estimated using linear regression. PM_{2.5} and incident CKD (defined as follow-up eGFR <60 ml/min per 1.73 m² with $\geq 25\%$ eGFR decline relative to baseline, CKD-related hospitalization or death based on International Classification of Diseases 9/10 codes, or development of ESKD) associations were estimated using Cox proportional hazards regression. Modeling was stratified by study site, and stratum-specific estimates were combined using random-effects meta-analyses.

Results Baseline mean participant age was 63 (± 6) years and eGFR was 86 (± 16) ml/min per 1.73 m². There was no significant PM_{2.5}-eGFR association at baseline. Each 1- $\mu\text{g}/\text{m}^3$ higher annual average PM_{2.5} was associated with higher UACR after adjusting for demographics, socioeconomic status, and clinical covariates (percentage difference, 6.6%; 95% confidence interval [95% CI], 2.6% to 10.7%). Each 1- $\mu\text{g}/\text{m}^3$ higher annual average PM_{2.5} was associated with a significantly higher risk of incident CKD (hazard ratio, 1.05; 95% CI, 1.01 to 1.10).

Conclusions Exposure to higher annual average PM_{2.5} concentrations was associated with a higher level of albuminuria and higher risk for incident CKD in a community-based cohort.

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Introduction

Particulate matter (PM) air pollution is a heterogeneous mixture of solid and liquid particles from various sources including fossil fuel combustion, road dust, industrial processes, and natural sources. Major components include sulfates, nitrates, ammonium, chloride, elemental and organic carbon, crustal and biologic materials, and trace metals; specific components vary by place and time (1–3). Fine particulate matter, which consists of particles <2.5 μm in aerodynamic diameter (PM_{2.5}), is thought to be particularly harmful, because these small particles reach distal airways and alveoli where they may trigger a systemic inflammatory response and potentially enter the systemic vasculature (4). PM_{2.5} exposure has been linked to various adverse health outcomes including cardiovascular disease (5,6), respiratory disease (7), diabetes mellitus (8,9), and mortality (10–12).

Air pollution may also affect kidneys, which participate in the excretion of many systemically absorbed PM

components. For example, heavy-metal components of PM_{2.5} such as lead, cadmium, and mercury may promote kidney injury through oxidative damage, causing tubular dysfunction and subsequent interstitial fibrosis (13,14). PM_{2.5}-induced systemic inflammatory and dysautonomic effects (4) may affect kidneys as well (15). These effects may occur both acutely and through long-term exposure. A few studies have linked higher 1-year (16–18) or 2-year (19) PM_{2.5} exposure to higher prevalence of CKD (16), longitudinal eGFR decline (17,18), and higher incidence of eGFR <60 ml/min per 1.73 m² (18,19), although the relationship between PM_{2.5} and prevalent eGFR has been mixed (17,20). One study has explored the association between PM exposure and albuminuria but found no relationship, despite the theoretic vulnerability of kidneys to toxin-mediated glomerular, tubulointerstitial, and vascular injury (21).

Featuring participants from the Atherosclerosis Risk in Communities study, a community-based cohort of adults, this study aimed to build upon previous work

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and examine the associations of PM_{2.5} exposure with kidney function, albuminuria, and incident CKD. We hypothesized that higher exposure to PM would be associated with higher burden of kidney disease, and that associations would be consistent across demographics and underlying comorbidities. As negative and positive cross-sectional controls, we evaluated the association of PM_{2.5} exposure with height and area deprivation index, respectively. As a negative and positive longitudinal control, we evaluated the association of PM_{2.5} exposure with incident cellulitis and mortality.

Materials and Methods

Study Population

The Atherosclerosis Risk in Communities study is a prospective community-based cohort following 15,792 adults across four sites in the United States: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland. There have been six study visits: the first visit (1987–1990) was followed by triennial visits through visit 4 (1996–1998) and then, after a hiatus, visit 5 (2011–2013) and visit 6 (outcomes available through 2016). During follow-up, participant hospitalizations were tracked by active review of local hospital-discharge lists, and also through patient report in telephone surveys (initially annual, increased to semiannual in 2012), after which records of all reported hospitalizations were requested. The study was approved by the Institutional Review Boards of the University of North Carolina, Wake Forest University, the University of Mississippi Medical Center, the University of Texas Health Sciences Center at Houston, the University of Minnesota, and the Johns Hopkins University. Written informed consent was obtained. Further details about the Atherosclerosis Risk in Communities study have been published (22).

The study population included all participants in the Atherosclerosis Risk in Communities study with available plasma creatinine at visit 4 ($n=11,560$), which served as the baseline visit for this study. Individuals were excluded if they were missing annual PM_{2.5} exposures ($n=476$; Supplemental Table 1) or had ESKD at baseline ($n=20$). Black participants from Minneapolis ($n=11$) and Washington County ($n=26$) and nonblack, nonwhite individuals from all sites ($n=30$) were excluded due to small numbers (Supplemental Table 2). The final cohort consisted of 10,997 participants. For analyses of incident CKD, participants with eGFR <60 ml/min per 1.73 m² at visit 4 also were excluded (final $n=10,302$).

Exposure

Monthly mean PM_{2.5} concentrations ($\mu\text{g}/\text{m}^3$) were estimated (1988–2007) using a geographic information system-based, spatiotemporal generalized additive mixed model, which included meteorologic and geospatial covariates such as land use; this model had high predictive accuracy (crossvalidation R^2 of 0.68–0.77 across regions). The exposure model was used to predict PM_{2.5} levels at accurately geocoded participant addresses, which were updated at visits 1 through 4 (23,24), and was based on US Environmental Protection Agency's Air Quality System PM_{2.5} (25) and other

monitoring data (26–28). Estimation before 1999 involved using the log-transformed ratio of PM_{2.5} to predicted PM₁₀ (PM with aerodynamic diameter <10 μm) because PM_{2.5} monitoring data were not widely available until 1999. Before 1988, monthly concentrations were imputed using concentrations from corresponding months in 1988, given substantial correlation of monthly means over years. Monthly means were subsequently averaged over the 12-month period (annual average) ending on the visit 4 examination month, but only when data were available for $\geq 75\%$ of months in the period. Annual average PM_{2.5} concentrations were missing in 4.1% of participants. In sensitivity analyses, we evaluated 60- and 120-month averaging periods, which had slightly higher missing data, up to 5.5% for the 120-month exposure.

Outcomes

Three outcomes were assessed: visit 4 eGFR, visit 4 albuminuria, and incident CKD after visit 4. eGFR was calculated using the creatinine-based CKD Epidemiology Collaboration equation and plasma creatinine measured at visit 4 (29). Creatinine was measured using the modified kinetic Jaffé method in plasma and urine specimens from visit 4 and measured using the Roche enzymatic method in serum specimens from visit 5 (Roche-Hitachi Modular P chemistry analyzer with Roche Creatininase Plus assay; Hoffman-La Roche) and visit 6 (Roche Cobas 6000 chemistry analyzer with Roche Creatininase Plus assay). Albumin was measured in urine specimens from visit 4 by a nephelometric method (Dade Behring BN100 or Beckman Image Nephelometer). Urinary albumin-creatinine ratio (UACR) was calculated at visit 4 and log-transformed to obtain a normal distribution. Incident CKD was a composite outcome defined as meeting any of the following: (1) development of eGFR <60 ml/min per 1.73 m² at follow-up visit 5 or visit 6 accompanied by $\geq 25\%$ eGFR decline relative to baseline; (2) CKD-related hospitalization or death based on International Classification of Diseases 9/10 (ICD-9/10) codes; or (3) development of ESKD, which was defined as United States Renal Data Systems-identified ESKD, eGFR <15 ml/min per 1.73 m² at follow-up, or ICD-9/10 code for a kidney failure-related hospitalization or death (30,31). Participants were censored if lost to follow-up or death from a cause not related to CKD or ESKD (Supplemental Table 3).

Covariate Selection

Baseline covariate data were derived from visit 4. Demographic data included sex, age, and race along with socioeconomic factors including neighborhood socioeconomic score (32), family income, and education level. Clinical covariates included body mass index; smoking status; eGFR; UACR; C-reactive protein; systolic BP; and the presence of comorbid conditions including diabetes mellitus (defined as random blood glucose ≥ 200 mg/dl, fasting blood glucose ≥ 126 mg/dl, reported history of diabetes mellitus, or taking medications for diabetes mellitus), hypertension (defined as average of first two systolic BPs ≥ 140 mm Hg or diastolic BPs ≥ 90 mm Hg or taking antihypertensive medications), and a composite cardiovascular-disease covariate to reflect the presence

of any prevalent coronary heart disease, stroke, heart failure, or peripheral artery disease (Supplemental Table 4). UACR and C-reactive protein were log-transformed. Daily mean ambient temperature (°C) across all National Climatic Data Center (33) monitoring stations ≤ 50 km from geocoded participant address was averaged over the same averaging periods used for PM_{2.5}.

Statistical Analyses

Baseline characteristics were stratified above and below site-specific median annual average PM_{2.5} concentrations and pooled for comparison. Linear regression was used to estimate cross-sectional associations of PM_{2.5} with eGFR and UACR. Linear regressions were performed using log-transformed UACR; coefficients were expressed as a percentage difference $[(e^{\beta} - 1) \times 100\%]$ to aid interpretation. Cox proportional hazards regression was used to estimate associations between PM_{2.5} and incident CKD. All regressions were performed per 1- $\mu\text{g}/\text{m}^3$ higher PM_{2.5}.

Given the heterogeneity of PM_{2.5} concentrations among sites, analyses were stratified by site, and stratum-specific results were combined in random-effects meta-analyses with testing for heterogeneity of effect (34). Regressions were performed for the annual average PM_{2.5} exposures and sequentially adjusted using two models. The first model adjusted for sex, age, race, neighborhood socioeconomic score, family income, and education level. The second model incorporated the covariates of the first model and additionally included body mass index, diabetes mellitus, hypertension, systolic BP, composite cardiovascular disease, cigarette smoking, C-reactive protein, eGFR, UACR, and temperature. Linear splines were used for body mass index with a knot at 30 kg/m² and systolic BP with a knot at 120 mm Hg. Multiple imputation was performed for missing covariate values, excluding eGFR and UACR. Models were stratified by sex, age, diabetes, hypertension, and site-specific median income, and tested for effect modification in the full model with interaction terms.

Exposure-control analyses for linear-regression models were performed using area deprivation index (35) and participant height as positive and negative controls, respectively, and for Cox proportional hazards models with mortality and cellulitis as positive and negative controls, respectively. Sensitivity analyses were performed excluding those with baseline UACR of at least 30 mg/g; excluding Jackson; in the full population using 60- and 120-month average PM_{2.5} exposures; and a competing risk analysis (modeling the competing event of non-CKD death). Analysis of the between- and within-site effects was performed for incident CKD using a Cox proportional hazards model for the association of incident CKD with the site mean PM_{2.5} as the exposure variable to assess between-site effect; another Cox proportional hazards model using both the site mean and individual PM_{2.5} exposure minus the site mean PM_{2.5} was used to assess within-site effect (36). Values were considered significant when P was < 0.05 . A Bonferroni-corrected P value of 0.01 was applied to the five interaction analyses. Statistical analysis was performed

using Stata SE version 15.0 (StataCorp LLC, College Station, TX).

Results

Study Population

A total of 10,997 participants were included across the four sites. The population was 56% female. At visit 4 baseline, mean age was 63 (± 6) years and mean eGFR was 86 (± 16) ml/min per 1.73 m². Table 1 shows demographic characteristics of participants stratified by site-specific annual average PM_{2.5}. Missing covariates are listed in Supplemental Table 5. PM_{2.5} was highest in Forsyth County and lowest in Minneapolis (Figure 1).

Cross-Sectional Associations between Fine Particulate Matter and Estimated Glomerular Filtration Rate and Urinary Albumin-Creatinine Ratio

There was no statistically significant cross-sectional association between PM_{2.5} and eGFR in either adjustment model, nor across any stratifying variable (Table 2). In contrast, a 1- $\mu\text{g}/\text{m}^3$ higher annual average PM_{2.5} was significantly associated with higher UACR when adjusting for demographics and socioeconomic status in model 1 (percentage difference, 8.5%; 95% confidence interval [95% CI], 3.6% to 13.7%) and when additionally adjusting for clinical covariates in model 2 (percentage difference, 6.6%; 95% CI, 2.6% to 10.7%). There were no significant interactions for any eGFR or UACR subgroup analysis. Associations between PM_{2.5} and UACR were significant at each site except Jackson in models 1 and 2 (Supplemental Figure 1), and the overall I^2 was 50.4% ($P=0.11$; Supplemental Table 6), indicating possible heterogeneity. Results were consistent in analyses excluding Jackson (Supplemental Table 7) with a lower I^2 (Supplemental Table 8), and were weaker when using longer averaging periods.

Associations between Fine Particulate Matter and Incident CKD

Out of 10,302 participants with eGFR ≥ 60 ml/min per 1.73 m², there were 2816 cases of incident CKD over a median 17.7 years follow-up through visit 6 (Table 3). The overall CKD incidence was 17.8 events per 1000 person-years (Supplemental Table 9). Annual average PM_{2.5} was significantly associated with increased risk of CKD in model 1 (hazard ratio per 1- $\mu\text{g}/\text{m}^3$ higher PM_{2.5}, 1.07; 95% CI, 1.03 to 1.11) and model 2 (hazard ratio, 1.05; 95% CI, 1.01 to 1.10). Figure 2 shows the model 2 exposure response function. There were no significant interactions for any subgroup. There was no significant heterogeneity ($I^2=6.8\%$, $P=0.36$). Supplemental Table 10 describes the within- and between-site effects. Results were directionally similar but weaker when excluding Jackson or using longer averaging periods (Supplemental Figures 2 and 3), and consistent when excluding participants with UACR ≥ 30 mg/g at baseline (Supplemental Table 11). In the competing risk analysis, annual average PM_{2.5} was significantly associated with incident CKD in model 1 but not model 2 (Supplemental Table 12).

Table 1. Baseline characteristics of the Atherosclerosis Risk in Communities study population, stratified above and below site-specific median annual average PM_{2.5} concentration

Characteristic	Annual Average PM _{2.5} (μg/m ³)	
	≤Site-Specific Median	>Site-Specific Median
Number of participants	5499	5498
Age, mean (SD), yr	63 (6)	63 (6)
Female, <i>n</i>	3033 (55%)	3128 (57%)
Black, <i>n</i>	1177 (21%)	1231 (22%)
Smoker, <i>n</i>		
Never	2332 (43%)	2211 (41%)
Former	2362 (43%)	2420 (44%)
Current	790 (14%)	822 (15%)
eGFR, mean (SD), ml/min per 1.73 m ²	86 (16)	86 (16)
eGFR<60 ml/min per 1.73 m ² , <i>n</i>	346 (6%)	349 (6%)
UACR, median (IQR), mg/g	3.4 (5.8)	4.0 (6.4)
C-reactive protein, median (IQR), mg/L	2.5 (4.4)	2.5 (4.4)
Body mass index, mean (SD), kg/m ²	28.8 (5.5)	28.8 (5.7)
Systolic BP, mean (SD), mm Hg	127 (19)	128 (19)
Hypertension, <i>n</i>	2546 (46%)	2678 (49%)
Diabetes mellitus, <i>n</i>	872 (16%)	943 (17%)
Composite cardiovascular disease, <i>n</i>	1026 (19%)	1090 (20%)
Neighborhood socioeconomic score (SD)	0.4 (5.4)	−0.3 (5.5)
Annual household income, <i>n</i>		
<\$25,000	1591 (30%)	1699 (32%)
≥\$25,000	3676 (68%)	3536 (66%)
Refused	124 (2%)	126 (2%)
Education, <i>n</i>		
≤11 yr	1045 (19%)	1042 (19%)
12–16 yr	2273 (41%)	2358 (43%)
17–21 yr	2171 (40%)	2091 (38%)
Temperature, mean (SD), °C	12.4 (4.3)	13.0 (4.0)

Median annual average PM_{2.5} concentration for each site: Forsyth County, 15.3 μg/m³; Jackson, 12.2 μg/m³; Minneapolis, 9.4 μg/m³; and Washington County, 14.6 μg/m³. PM_{2.5}, particulate matter <2.5 μm in aerodynamic diameter; UACR, urinary albumin-creatinine ratio; IQR, interquartile range.

Control Analyses

In analyses of negative cross-sectional and longitudinal controls, there was no association between PM_{2.5} and

baseline height or between PM_{2.5} and incident cellulitis (Supplemental Table 13). In analyses of positive cross-sectional and longitudinal controls, higher PM_{2.5} was

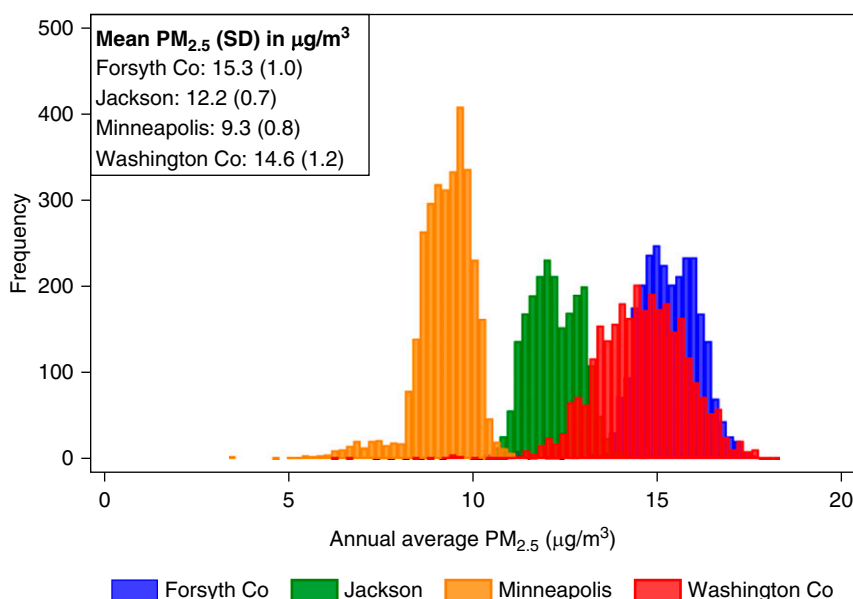


Figure 1. | Annual average PM_{2.5} concentration varies across sites. Co, county; PM_{2.5}, particulate matter <2.5 μm in aerodynamic diameter.

Table 2. Associations of annual average PM_{2.5} with baseline eGFR and urinary albumin-creatinine ratio

Characteristic	Number of Eligible Participants	eGFR			UACR ^a		
		ml/min per 1.73 m ² (95% CI)	P Value	Interaction P Value	% Difference (95% CI)	P Value	Interaction P Value
Overall							
Model 1 ^b	10,997	0.14 (−0.32 to 0.60)	0.55		8.5 (3.6 to 13.7)	<0.001	
Model 2 ^c		0.07 (−0.28 to 0.41)	0.71		6.6 (2.6 to 10.7)	0.001	
Sex							
Male	4836	0.16 (−0.25 to 0.56)	0.46	0.56	10.3 (5.9 to 14.9)	<0.001	0.09
Female	6161	−0.00 (−0.52 to 0.52)	1.00		3.7 (−1.7 to 9.4)	0.18	
Age, yr							
<65	6597	0.03 (−0.40 to 0.46)	0.90	0.95	7.0 (0.8 to 13.7)	0.03	0.32
≥65	4400	0.17 (−0.26 to 0.60)	0.44		5.9 (1.7 to 10.3)	0.005	
History of diabetes							
No	9135	0.06 (−0.36 to 0.48)	0.78	0.67	6.0 (2.8 to 9.4)	<0.001	0.44
Yes	1815	0.46 (−0.43 to 1.35)	0.31		7.6 (−8.6 to 26.7)	0.38	
History of hypertension							
No	5729	−0.05 (−0.49 to 0.39)	0.81	0.61	7.5 (1.0 to 14.4)	0.02	0.75
Yes	5224	0.24 (−0.21 to 0.70)	0.29		5.2 (−0.3 to 11.1)	0.07	
Income above median^d							
No	6043	0.09 (−0.28 to 0.47)	0.64	0.90	6.5 (1.4 to 11.8)	0.01	0.80
Yes	4459	0.03 (−0.55 to 0.60)	0.93		7.5 (3.5 to 11.8)	<0.001	

PM_{2.5}, particulate matter <2.5 μm in aerodynamic diameter; UACR, urinary albumin-creatinine ratio.
^aUACR coefficient underwent exponentiation using the formula ($e^{\beta}-1$)×100%.
^bModel 1: sex, age, race, neighborhood socioeconomic score, family income, education level.
^cModel 2: model 1 plus body mass index, diabetes mellitus, hypertension, systolic BP, composite cardiovascular disease, cigarette smoking, eGFR,* UACR,** C-reactive protein, temperature. Covariate omitted for eGFR analyses (*) and UACR analyses (**). Model 2 adjustment used for stratified analyses. Analyses performed per 1-μg/m³ higher PM_{2.5}.
^dMedian income was \$16,000–\$24,999 for Jackson, \$25,000–\$34,999 for Washington County, and \$35,000–\$49,999 for Forsyth County and Minneapolis.

significantly associated with higher area deprivation index and increased mortality.

Discussion

In this study of older adults at four sites followed for a median 17.7 years, higher annual average PM_{2.5} exposure was associated with increased albuminuria and a higher risk of CKD. There were no associations between PM_{2.5} and baseline eGFR. These findings support the role of PM_{2.5} exposure as a potential risk factor for CKD and suggest PM_{2.5} mitigation efforts as a potential avenue for reducing CKD burden.

Animal models support a causal link between PM_{2.5} exposure and kidney injury. Healthy rats exposed to 8 weeks of PM_{2.5} experienced a variety of physiologic changes including increased BP, increased levels of angiotensin-converting enzyme and angiotensin II receptor type 1, a depleted antioxidant response, hematuria, and reduced GFR, but no change in urinary albumin (15). Histologic changes after PM_{2.5} exposure included increased kidney fibrosis, mesangial expansion, and reduced glomerular and tubular lumen volumes (37). TNF-α signaling

pathways may be important contributors to PM_{2.5}-induced oxidative kidney injury. Prolonged PM_{2.5} exposure may promote sodium retention by reducing expression of the D₁ receptor, contributing to hypertension (38). A study of rats exposed to PM_{2.5} showed a direct relationship between the concentrations of metals measured in the air and those measured in kidney tissue, supporting the hypothesis that systemically absorbed PM_{2.5} components directly damage kidney tissue (37). Overall, these mechanistic studies suggest the presence of a complex, multifaceted response to PM_{2.5}, which is likely affected by the timing, duration, and specific components of exposure.

This study adds to the current body of literature by providing further support for the link between long-term PM_{2.5} exposure and CKD incidence and by demonstrating an association between PM_{2.5} and albuminuria. A previous study in a large Veterans Affairs (VA) cohort found 10-μg/m³ higher PM_{2.5} averaged over 1 year to be associated with a 27% (95% CI, 17%–38%) higher risk of incident CKD (18). A Taiwanese study in the general population showed a smaller magnitude of association, with a 10-μg/m³ higher PM_{2.5} averaged over 2 years

Table 3. Association of annual average PM_{2.5} with incident CKD in participants with eGFR ≥ 60 ml/min per 1.73 m² at baseline

Characteristic	Number of Eligible Participants	Number of CKD Events	Person-Years	CKD Incidence per 1000 Person-Years (95% CI)	Incident CKD, HR (95% CI)	P Value	Interaction P Value
Overall							
Model 1 ^a	10,302	2816	158,199	17.8 (17.2 to 18.5)	1.07 (1.03 to 1.11)	0.001	
Model 2 ^b					1.05 (1.01 to 1.10)	0.03	
Sex							
Male	4518	1359	65,511	20.7 (19.7 to 21.9)	1.04 (0.98 to 1.10)	0.20	0.54
Female	5784	1457	92,687	15.7 (14.9 to 16.5)	1.10 (1.00 to 1.21)	0.05	
Age, yr							
<65	6385	1559	104,501	14.9 (14.2 to 15.7)	1.03 (0.97 to 1.10)	0.31	0.63
≥ 65	3917	1257	53,697	23.4 (22.2 to 24.7)	1.09 (0.99 to 1.20)	0.07	
History of diabetes							
No	8623	2105	136,223	15.5 (14.8 to 16.1)	1.08 (1.01 to 1.16)	0.02	0.13
Yes	1635	698	21,387	32.6 (30.3 to 35.2)	0.98 (0.89 to 1.08)	0.73	
History of hypertension							
No	5536	1177	89,278	13.2 (12.5 to 14.0)	1.02 (0.96 to 1.09)	0.55	0.15
Yes	4726	1629	68,339	23.8 (22.7 to 25.0)	1.09 (1.02 to 1.16)	0.02	
Income above median^c							
No	5581	1616	81,926	19.7 (18.8 to 20.7)	1.05 (0.98 to 1.12)	0.21	0.58
Yes	4253	1072	69,603	15.4 (14.5 to 16.4)	1.06 (0.99 to 1.14)	0.07	

PM_{2.5}, particulate matter <2.5 μm in aerodynamic diameter; HR, hazard ratio.

^aModel 1: sex, age, race, neighborhood socioeconomic score, family income, education level.

^bModel 2: model 1 plus body mass index, diabetes mellitus, hypertension, systolic BP, composite cardiovascular disease, cigarette smoking, eGFR, urinary albumin-creatinine ratio, C-reactive protein, temperature. Model 2 adjustment used for stratified analyses.

Analyses performed per 1- $\mu\text{g}/\text{m}^3$ higher PM_{2.5}.

^cMedian income was \$16,000–\$24,999 for Jackson, \$25,000–\$34,999 for Washington County, and \$35,000–\$49,999 for Forsyth County and Minneapolis.

associated with a 6% (95% CI, 2%–10%) higher risk of CKD (19). The overall PM_{2.5} concentration was much higher in the Taiwanese study (mean, 27.1 $\mu\text{g}/\text{m}^3$) compared with the VA study (median, 11.8 $\mu\text{g}/\text{m}^3$) and the cohorts differed in study design: the Taiwanese population was younger (38.9 versus 62.5 years old), had higher baseline eGFR (87.0 versus 76.3 ml/min per 1.73 m²), was followed at standardized medical exam rather than clinically, and had lower incidence of CKD (6 versus 41 events per 1000 person-years). In the single previous study of PM exposure and UACR, neither short-term (1- and 2-month) nor long-term (20-year) PM_{2.5} exposure period was associated with cross-sectional UACR or change in UACR over time in the Multi-Ethnic Study of Atherosclerosis cohort (21). In our study, we found an association when looking at different length exposures (12- and 60-month). These time frames, which are long enough to account for seasonal variations, were not previously used in UACR analyses and may account for our distinct findings, as could the lower baseline

cardiovascular disease burden in the Multi-Ethnic Study of Atherosclerosis cohort.

Interestingly, previous cross-sectional studies between PM_{2.5} and eGFR have yielded variable results. In an analysis of the Medicare population, higher PM_{2.5} was associated with higher CKD prevalence defined by ICD-9, Clinical Modification diagnosis codes (16), consistent with a VA study in which PM_{2.5} exposure was associated with lower eGFR (17). Our results, and those of a large Taiwanese cohort, showed no association between PM_{2.5} and eGFR (20). Potential reasons underlying these distinct findings include differences in baseline eGFR, albuminuria, or racial makeup of these populations. Furthermore, PM_{2.5} components vary by region, with certain regions containing concentrations of components that could be more detrimental to glomerular or proximal tubular function (39).

Study strengths include the use of cohort data with exposures and outcomes measured in a research setting with active ascertainment, the high percentage of patients with UACR measurement, and sensitivity analyses using

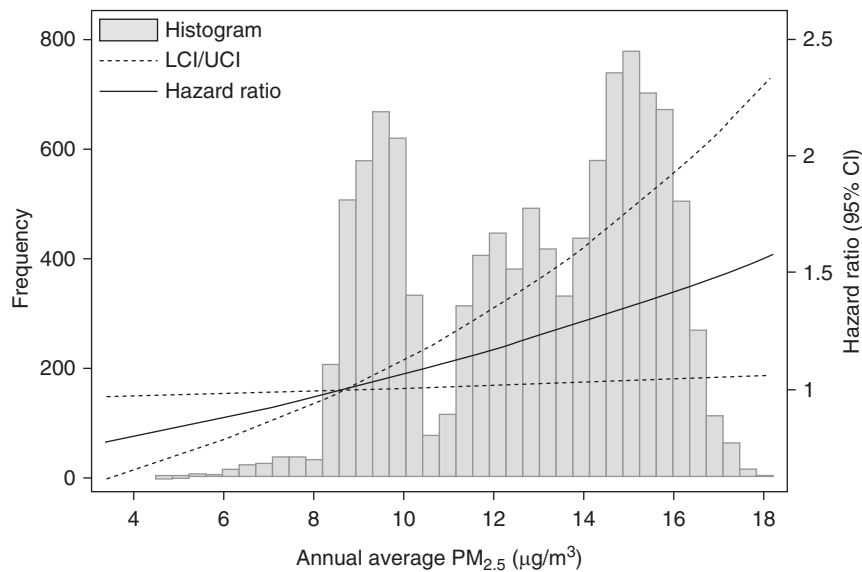


Figure 2. | Higher annual average $PM_{2.5}$ concentration associates with higher risk of incident CKD. Exposure response function created using model 2. The fifth percentile $PM_{2.5}$ value of $8.7 \mu g/m^3$ was selected as the reference. CI, confidence interval; LCI, lower CI; $PM_{2.5}$, particulate matter $<2.5 \mu m$ in aerodynamic diameter; UCI, upper CI.

various $PM_{2.5}$ averaging periods. Weaknesses include the prolonged period of time between visits 4 and 5, limiting the ability to trend biomarker changes over time; absence of dietary data; use of spot UACR instead of first morning void or 24-hour urine albumin collections; absence of indoor air pollution exposure; lack of hemoglobin A1C as an available covariate for visit 4; analysis limited to one pollutant; and the possibility of residual confounding. The relatively small cohort size reduced analytical power resulting in wide CIs. All but one site predominantly enrolled a single race, precluding tests of interaction by race. The relatively advanced cohort age may reflect a selection bias in which the highest risk participants may not have survived to the baseline visit (40). There was substantial heterogeneity in the eGFR and UACR models, which was driven by Jackson, Mississippi. In the most highly adjusted models, $PM_{2.5}$ was not associated with incident CKD in the analysis that excluded Jackson, although this may reflect a lack of power. Assigning $PM_{2.5}$ by home address provided an incomplete characterization of the participants' true exposure.

In summary, this study found that exposure to higher annual average concentration of $PM_{2.5}$ was associated with increased albuminuria and increased risk of incident CKD. This finding may be especially important for parts of the world with higher air pollution burden, such as China and India, where $PM_{2.5}$ concentrations are five to ten times higher than in the United States (41). Future work should quantify whether efforts to improve air quality yield health benefits, including reducing the burden of CKD.

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Supplemental Material

This article contains the following supplemental material online at <http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.08350719/-/DCSupplemental>.

Supplemental Table 1. Missing $PM_{2.5}$.

Supplemental Table 2. Excluded participants.

Supplemental Table 3. Participants censored.

Supplemental Table 4. Variable parameterization.

Supplemental Table 5. Missing covariates.

Supplemental Table 6. Heterogeneity of effect (I^2) for associations of annual average $PM_{2.5}$ with baseline eGFR, urinary albumin to creatinine ratio, and incident CKD.

Supplemental Table 7. Sensitivity analyses for associations of annual average $PM_{2.5}$ with baseline eGFR, urinary albumin to creatinine ratio, and incident CKD when omitting Jackson and testing 60- and 120-month $PM_{2.5}$ exposures.

Supplemental Table 8. Heterogeneity of effect for associations of annual average PM_{2.5} with baseline eGFR, urinary albumin to creatinine ratio, and incident CKD when excluding Jackson.

Supplemental Table 9. CKD incidence in participants with eGFR ≥ 60 ml/min per 1.73 m² at baseline by site, stratified by median annual average PM_{2.5}.

Supplemental Table 10. Between and within site effects for Cox proportional hazards models of annual average PM_{2.5} and incident CKD.

Supplemental Table 11. Sensitivity analyses for association of annual average PM_{2.5} with incident CKD when excluding those with urinary albumin to creatinine ratio ≥ 30 mg/g.

Supplemental Table 12. Competing risk analysis for association of annual average PM_{2.5} with incident CKD with a competing risk of non-CKD death.

Supplemental Table 13. Positive and negative control models for the associations of annual average PM_{2.5} with height, area deprivation index, incident cellulitis, and incident mortality.

Supplemental Figure 1. Forest plots describing overall and site-specific associations of annual average PM_{2.5} with baseline eGFR, urinary albumin to creatinine ratio, and incident CKD.

Supplemental Figure 2. Forest plots describing overall and site-specific associations of 60-month PM_{2.5} with baseline eGFR, urinary albumin to creatinine ratio, and incident CKD.

Supplemental Figure 3. Forest plots describing overall and site-specific associations of 120-month PM_{2.5} with baseline eGFR, urinary albumin to creatinine ratio, and incident CKD.

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