

Particulate Matter Air Pollution and the Risk of Incident CKD and Progression to ESRD

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ABSTRACT

Elevated levels of fine particulate matter $<2.5 \mu\text{m}$ in aerodynamic diameter ($\text{PM}_{2.5}$) are associated with increased risk of cardiovascular outcomes and death, but their association with risk of CKD and ESRD is unknown. We linked the Environmental Protection Agency and the Department of Veterans Affairs databases to build an observational cohort of 2,482,737 United States veterans, and used survival models to evaluate the association of $\text{PM}_{2.5}$ concentrations and risk of incident $\text{eGFR} < 60 \text{ ml/min per } 1.73 \text{ m}^2$, incident CKD, eGFR decline $\geq 30\%$, and ESRD over a median follow-up of 8.52 years. County-level exposure was defined at baseline as the annual average $\text{PM}_{2.5}$ concentrations in 2004, and separately as time-varying where it was updated annually and as cohort participants moved. In analyses of baseline exposure (median, 11.8 [interquartile range, 10.1–13.7] $\mu\text{g}/\text{m}^3$), a 10- $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration was associated with increased risk of $\text{eGFR} < 60 \text{ ml/min per } 1.73 \text{ m}^2$ (hazard ratio [HR], 1.21; 95% confidence interval [95% CI], 1.14 to 1.29), CKD (HR, 1.27; 95% CI, 1.17 to 1.38), eGFR decline $\geq 30\%$ (HR, 1.28; 95% CI, 1.18 to 1.39), and ESRD (HR, 1.26; 95% CI, 1.17 to 1.35). In time-varying analyses, a 10- $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration was associated with similarly increased risk of $\text{eGFR} < 60 \text{ ml/min per } 1.73 \text{ m}^2$, CKD, eGFR decline $\geq 30\%$, and ESRD. Spline analyses showed a linear relationship between $\text{PM}_{2.5}$ concentrations and risk of kidney outcomes. Exposure estimates derived from National Aeronautics and Space Administration satellite data yielded consistent results. Our findings demonstrate a significant association between exposure to $\text{PM}_{2.5}$ and risk of incident CKD, eGFR decline, and ESRD.

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Elevated levels of fine particulate matter of $<2.5 \mu\text{m}$ in aerodynamic diameter ($\text{PM}_{2.5}$) are associated with increased risk of death, reduced life expectancy, increased risk of cardiovascular disease, and stroke, as well as a host of other adverse health outcomes.^{1–13} Studies on the relationship of $\text{PM}_{2.5}$ and the kidney are limited.

Experimental laboratory evidence suggests that exposure to deep exhaust particles leads to disturbances in renal hemodynamics, promotes oxidative stress, inflammation, and DNA damage in renal tissue, exacerbates AKI, and further promulgates chronic renal injury in murine models^{14,15}

Data on the relationship of air pollution and kidney disease in humans is very scarce. Hendryx described higher kidney disease mortality in coal mining

Appalachian areas in the United States and suggested that this increase in kidney disease mortality burden may reflect environmental exposure to particulate matter.¹⁶ In a cross-sectional analysis of 1103 Boston-area patients hospitalized for ischemic stroke,

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Lue *et al.*¹⁷ showed that residential proximity to major roads is associated with reduced eGFR. In seminal findings, Mehta *et al.*¹⁸ examined the relationship between long-term exposure to PM_{2.5} and longitudinal changes in eGFR in a regional cohort of 669 older men who were participants in the Boston-based Veterans Administration Normative Aging Study, and found that higher 1-year PM_{2.5} exposure was associated with lower eGFR and an additional annual decrease in eGFR. In a large Chinese study, Xu *et al.*¹⁹ examined an 11-year (for indication) renal biopsy series of 71,151 native kidney biopsies and reported that long-term exposure to high levels of PM_{2.5} was associated with increased odds of membranous nephropathy, but not other glomerular diseases.

The sum of the experimental and clinical findings provides biologic plausibility and supports the hypothesis that environmental exposure to elevated levels of PM_{2.5} is associated with increased risk of kidney disease. However, whether exposure to elevated levels of PM_{2.5} is associated with increased risk of development of CKD and CKD progression has not been examined in large national longitudinal epidemiologic studies. Identification of air pollution as a potential contributor to kidney disease will inform national and global burden of disease estimates, stimulate further policy discussions on the importance of curbing air pollution on health and disease, and inform the public about the hazards of air pollution. In this work, we built a longitudinal national cohort of 2,482,737 United States veterans and characterized the relationship of PM_{2.5} and risk of incident CKD, and progression to ESRD.

RESULTS

There were 2,482,737 cohort participants followed for a median of 8.52 years (interquartile range, 8.04–8.80). PM_{2.5} concentrations ranged from 5.0 to 9.1 $\mu\text{g}/\text{m}^3$, 9.2 to 11.0 $\mu\text{g}/\text{m}^3$, 11.1 to 12.6, and 12.7 to 22.1 $\mu\text{g}/\text{m}^3$ in quartiles 1, 2, 3, and 4, respectively. Overall cohort participants were mostly white men (Table 1). Cohort participants living in counties in the highest quartile of PM_{2.5} concentrations were more likely to be black, more likely to have hypertension, diabetes mellitus, cardiovascular disease, and higher eGFR at time of cohort entry (Table 1). They were also more likely to be current or former smokers (Table 1). Counties in the highest quartile of PM_{2.5} concentrations had significantly higher population density. There was a gradual increase in incident rate of eGFR <60 ml/min per 1.73 m², CKD, eGFR decline $\geq 30\%$, and ESRD across quartiles of county level PM_{2.5} concentrations (Table 2). Adjusted survival curves by PM_{2.5} quartiles are presented in Figure 1, A–D.

Exposure to Ambient Fine Particulate Matter and the Risk of Incident eGFR <60 ml/min per 1.73 m² and Incident CKD

We examined the association of PM_{2.5} concentrations and the risk of incident eGFR <60 ml/min per 1.73 m² among those who had no history of eGFR <60 ml/min per 1.73 m² before time of cohort entry. Where exposure was defined at baseline

Significance Statement

Exposure to fine particulate matter air pollution (<2.5 μm) is associated with increased risk of cardiovascular disease and death, but its impact on CKD and ESRD is not known. Analyses of data from a large cohort of United States Veterans demonstrate a linear relationship between exposure to fine particulate matter air pollution and risk of incident CKD or progression to ESRD. The study provides a quantitative assessment of the US burden of CKD and ESRD attributable to air pollution and establishes air pollution as an important risk factor. The findings contribute to understanding the geographic variation in burden of CKD in the US and globally. Further study is needed to understand the mechanisms by which small particulate air-borne pollutants effect the progression of CKD.

as the annual average PM_{2.5} concentrations in 2004, a 10- $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} concentration was associated with increased risk of incident eGFR <60 ml/min per 1.73 m² (hazard ratio [HR], 1.21; 95% confidence interval [95% CI], 1.14 to 1.29) (Table 3). In analyses where exposure was time-varying throughout duration in the cohort (exposure for each cohort participant was matched with his/her county of residence at a given time and the county's average annual particulate matter concentration for that year), the risk was also increased (HR, 1.25; 95% CI, 1.17 to 1.34) (Table 3). In analyses where exposure was considered in quartiles, compared with cohort participants in the lowest quartile (quartile 1) of PM_{2.5} concentrations, those in quartile 2, 3, and 4 had graded increased risk of incident eGFR <60 ml/min per 1.73 m² in analyses considering baseline 2004 exposure and time-varying exposure (Supplemental Table 1). Spline analyses suggested a linear relationship between PM_{2.5} concentrations and risk incident eGFR <60 ml/min per 1.73 m² (*P* for nonlinearity = 0.90); the linear representation of the association of PM_{2.5} concentrations and risk is depicted in Figure 2A.

We evaluated the risk of incident CKD (defined as two eGFR measurements <60 ml/min per 1.73 m² at least 90 days apart) in a subcohort of people with at least two eGFR measurements separated by at least 90 days during follow-up and who had no history of eGFR <60 ml/min per 1.73 m² before time of cohort entry. The results were consistent (Figure 2B, Supplemental Table 1, Table 3).

Exposure to Ambient Fine Particulate Matter and the Risk of eGFR Decline and Progression to ESRD

In the overall cohort, an increase in PM_{2.5} of 10 $\mu\text{g}/\text{m}^3$ was associated with increased risk of eGFR decline $\geq 30\%$ in analyses considering baseline exposure (HR, 1.28; 95% CI, 1.18 to 1.39), and time-varying exposure (HR, 1.36; 95% CI, 1.26 to 1.46) (Table 3). Compared with the lowest quartile (quartile 1) of PM_{2.5} concentrations, quartiles 2, 3, and 4 exhibited a graded increase in risk of eGFR decline $\geq 30\%$ (Supplemental Table 1). There was a linear relationship between PM_{2.5} concentrations and risk of eGFR decline $\geq 30\%$ (Figure 2C) (*P* for nonlinearity = 0.84). The results were consistent in analyses considering the outcome of ESRD (Figure 2D, Supplemental Table 1, Table 3).

Table 1. Demographic and health characteristics of overall study cohort and according to quartiles of annual average county PM_{2.5} concentrations

Characteristic	Overall Cohort	PM _{2.5} Quartile 1, 5.0–9.1 $\mu\text{g}/\text{m}^3$	PM _{2.5} Quartile 2, 9.2–11.0 $\mu\text{g}/\text{m}^3$	PM _{2.5} Quartile 3, 11.1–12.6 $\mu\text{g}/\text{m}^3$	PM _{2.5} Quartile 4, 12.7–22.1 $\mu\text{g}/\text{m}^3$
No. of counties	3108	791 (25.45)	771 (24.81)	789 (25.39)	757 (24.36)
No. of cohort participants	2,482,737	322,251 (12.98)	598,370 (24.10)	621,155 (25.02)	940,961 (37.90)
Median age (IQR)	62.46 (54.68–71.78)	64.03 (55.81–72.38)	62.65 (54.89–71.64)	62.42 (54.76–71.74)	61.80 (54.06–71.69)
Race					
White	2,036,361 (82.02)	290,924 (90.28)	523,520 (87.49)	517,474 (83.31)	704,443 (74.86)
Black	362,583 (14.60)	11,755 (3.65)	50,665 (8.47)	90,869 (14.63)	209,294 (22.24)
Other	83,793 (3.38)	19,572 (6.07)	24,185 (4.04)	12,812 (2.06)	27,224 (2.89)
Men	2,363,311 (95.19)	307,776 (95.51)	567,783 (94.89)	592,247 (95.35)	895,505 (95.17)
Cancer	289,110 (11.64)	38,174 (11.85)	67,854 (11.34)	71,682 (11.54)	111,400 (11.84)
Cardiovascular disease	741,249 (29.86)	94,163 (29.22)	173,534 (29.00)	189,752 (30.55)	283,800 (30.16)
Chronic lung disease	483,502 (19.47)	65,050 (20.19)	121,479 (20.30)	122,786 (19.77)	174,187 (18.51)
Diabetes mellitus	690,144 (27.80)	81,115 (25.17)	161,374 (26.97)	172,679 (27.80)	274,976 (29.22)
Hyperlipidemia	1,416,616 (57.06)	185,645 (57.61)	346,339 (57.88)	356,589 (57.41)	528,043 (56.12)
Hypertension	1,669,922 (67.26)	208,108 (64.58)	390,968 (65.34)	422,939 (68.09)	647,907 (68.86)
Peripheral artery disease	66,596 (2.68)	8169 (2.53)	16,649 (2.78)	16,047 (2.58)	25,731 (2.73)
Smoking status					
Current	632,049 (25.46)	73,416 (22.78)	143,482 (23.98)	161,417 (25.99)	253,734 (26.97)
Former	522,016 (21.03)	55,268 (17.15)	120,328 (20.11)	140,116 (22.56)	206,304 (21.92)
Never	1,328,672 (53.52)	193,567 (60.07)	334,560 (55.91)	319,622 (51.46)	480,923 (51.11)
BMI					
Underweight	25,691 (1.03)	2901 (0.90)	5738 (0.96)	6415 (1.03)	10,637 (1.13)
Normal weight	487,974 (19.65)	62,600 (19.43)	112,829 (18.86)	120,285 (19.36)	192,260 (20.43)
Overweight	977,236 (39.36)	130,877 (40.61)	234,486 (39.19)	244,086 (39.30)	367,787 (39.09)
Obese	911,836 (39.95)	125,873 (39.06)	245,317 (41.00)	250,369 (40.31)	370,277 (39.35)
ACEI/ARB use	1,165,940 (46.96)	146,774 (45.55)	280,308 (46.85)	295,063 (47.50)	443,795 (47.16)
Median county particulate matter 2.5 (IQR), $\mu\text{g}/\text{m}^3$	11.8 (10.1–13.7)	8.3 (7.5–8.8)	10.1 (9.8–10.6)	11.8 (11.3–12.2)	14.3 (13.4–15.6)
Median air sodium ^a (IQR), $\mu\text{g}/\text{m}^3$		0.04 (0.03–0.05)	0.06 (0.03–0.11)	0.06 (0.04–0.11)	0.05 (0.04–0.8)
Median follow-up time (IQR), yr	8.52 (8.04–8.80)	8.54 (8.07–8.80)	8.52 (8.05–8.80)	8.52 (8.04–8.80)	8.52 (8.03–8.79)
Death during follow-up	598,728 (24.12)	75,821 (23.53)	142,130 (23.75)	151,109 (24.33)	229,668 (24.41)
Average eGFR at T ₀ (SD), ml/min per 1.73 m ²	76.26 (19.88)	73.20 (18.20)	76.09 (19.25)	76.00 (19.80)	77.60 (20.74)
Mean eGFR slope (SD), ml/min per 1.73 m ² per yr	–0.79 (3.26)	–0.46 (3.08)	–0.72 (3.16)	–0.74 (3.27)	–0.97 (3.37)
eGFR slope category,					
ml/min per 1.73 m ² per yr					
No decline, ≥ 0	905,033 (36.45)	139,925 (43.42)	223,319 (37.32)	231,448 (37.26)	310,341 (32.98)
Stable decline, <0 to ≥ -1	632,381 (25.47)	80,837 (25.09)	157,018 (26.24)	158,807 (25.57)	235,719 (25.05)

Table 1. Continued

Characteristic	Overall Cohort	PM _{2.5} Quartile 1, 5.0–9.1 $\mu\text{g}/\text{m}^3$	PM _{2.5} Quartile 2, 9.2–11.0 $\mu\text{g}/\text{m}^3$	PM _{2.5} Quartile 3, 11.1–12.6 $\mu\text{g}/\text{m}^3$	PM _{2.5} Quartile 4, 12.7–22.1 $\mu\text{g}/\text{m}^3$
Moderate decline, <–1 to \geq –5	757,720 (30.52)	82,208 (25.51)	176,639 (29.52)	184,731 (29.74)	314,142 (33.39)
Rapid decline, <–5	187,603 (7.56)	19,281 (5.98)	41,394 (6.92)	46,169 (7.43)	80,759 (8.58)
Median no. of outpatient eGFR measures before T ₀ (IQR)	4 (2–8)	5 (2–8)	4 (2–8)	4 (2–7)	4 (2–7)
Median no. of outpatient eGFR measures after T ₀ (IQR)	13 (8–20)	13 (8–19)	13 (8–20)	13 (8–20)	13 (7–20)
Median no. of hospitalizations (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
One or more hospitalizations	411,318 (16.57)	49,900 (15.48)	96,800 (16.18)	101,241 (16.30)	163,377 (17.36)
Myocardial infarction	90,019 (3.63)	10,729 (3.33)	20,998 (3.51)	22,851 (3.68)	35,411 (3.77)
Median county percent in poverty (IQR), %	13.0 (10.2–15.6)	12.1 (10.1–15.4)	12.6 (10.5–15.2)	13.1 (10.3–16.6)	13.4 (10.5–15.9)
Median population density (IQR) per square mile	254.9 (74.4–931.4)	39.5 (15.0–224.4)	166.1 (50.7–399.1)	238.4 (78.0–803.0)	529.7 (198.0–1801.2)

Data are presented as n (%) unless otherwise indicated. Covariates as measured at T₀. IQR, interquartile range; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

^aIn a subcohort within 30 miles of an air monitoring station that measures sodium (n=1,368,122).

PM_{2.5} and Risk of Adverse Kidney Outcomes Using National Aeronautics and Space Administration Data

We additionally considered PM_{2.5} estimates derived from the National Aeronautics and Space Administration (NASA) space-borne satellite sensors as an alternative data source to define ambient PM_{2.5} exposure levels. Analyses considering the NASA satellites remote sensing data yielded results consistent with those shown using exposure data obtained from ground-based air monitoring stations (Table 4).

Population Attributable Fraction

Population attributable fraction (PAF) represents the proportional reduction in population disease that would occur if exposure to PM_{2.5} was reduced to the Environmental Protection Agency's (EPA) recommended levels of 12 $\mu\text{g}/\text{m}^3$. PAF for incident eGFR <60 ml/min per 1.73 m² and incident CKD were 1.51% (95% CI, 1.44 to 1.58), and 2.06% (95% CI, 1.96 to 2.17), respectively. PAF for eGFR decline \geq 30%, and ESRD were 2.21% (95% CI, 2.14 to 2.30), and 2.31% (95% CI, 1.86 to 2.75), respectively. Our estimate of the national burden of CKD attributable to elevated levels of PM_{2.5} exceeding the EPA standard (where the theoretical minimum risk exposure level [TMREL] was set at the EPA standard of 12 $\mu\text{g}/\text{m}^3$) in the contiguous United States was 44,793 incident cases per year (95% uncertainty interval [95% UI], 42,716 to 46,869). The national burden of ESRD attributable to PM_{2.5} levels in excess of EPA standards was 2438 incident cases per year (95% UI, 1963 to 2902). We conducted analyses where we defined TMREL on the basis of the methodologies of the Global Burden of Disease (GBD) studies; this TMREL was assigned on the basis of a uniform distribution of PM_{2.5} from 2.4 to 5.9 $\mu\text{g}/\text{m}^3$ representing exposure values between the minimum and fifth percentiles of exposure distributions from outdoor air pollution cohort studies.^{20–22} Using the GBD definition of TMREL, the estimate of the national burden of incident CKD attributable to air pollution was 337,032 (95% UI, 207,976 to 466,087) and the national burden of incident ESRD attributable to air pollution was 13,537 (95% UI, 8377 to 18,696).

Maps depicting the geographic distribution of the burden of incident CKD where the theoretical minimum was set at the EPA standard, and according to the GBD methodologies are presented in Figures 3, A and B, respectively.

Sensitivity Analyses

In order to test different distance thresholds (and spatial resolutions) for exposure definition, we assigned PM_{2.5} exposure levels to each cohort participant on the basis of the nearest air monitoring station in those who were within 30, 10, and 5 miles of an air monitoring station (Supplemental Table 2); the results were consistent and yielded slightly higher risk estimates in time-varying analyses where the maximum distance from an air monitoring station was <5 miles (Supplemental Table 2). In order to evaluate the robustness of study findings in the most populated counties in the United States, the analyses were restricted to the 100 counties with highest numbers

Table 2. Incident rate of renal outcomes in overall study cohort and according to quartiles of annual average county PM_{2.5} concentrations

Outcome	Overall Cohort	PM _{2.5} Quartile 1, 5.0–9.1 $\mu\text{g}/\text{m}^3$	PM _{2.5} Quartile 2, 9.2–11.0 $\mu\text{g}/\text{m}^3$	PM _{2.5} Quartile 3, 11.1–12.6 $\mu\text{g}/\text{m}^3$	PM _{2.5} Quartile 4, 12.7–22.1 $\mu\text{g}/\text{m}^3$
Incident rate (95% CI) of incident eGFR <60 ml/min per 1.73 m ² ^a	7813.22 (7811.62 to 7814.82)	6751.90 (6747.88 to 6755.91)	7493.88 (7490.48 to 7497.28)	7734.59 (7730.88 to 7738.30)	8376.30 (8373.60 to 8379.01)
Incident rate (95% CI) of incident CKD ^b	4118.50 (4117.43 to 4119.57)	3430.86 (3427.65 to 3434.07)	3888.67 (3886.47 to 3890.86)	4052.62 (4050.81 to 4054.42)	4516.87 (4514.78 to 4518.97)
Incident rate (95% CI) of $\geq 30\%$ decline in eGFR	4740.79 (4739.87 to 4741.71)	3876.58 (3874.16 to 3879.00)	4504.68 (4503.00 to 4506.35)	4684.52 (4682.84 to 4686.20)	5191.62 (5190.32 to 5192.92)
Incident rate (95% CI) of ESRD	44.36 (44.27 to 44.45)	26.71 (26.55 to 26.87)	36.91 (36.75 to 37.07)	43.53 (43.36 to 43.71)	55.60 (55.44 to 55.75)

Incident rates are adjusted for age, race, sex, and T₀ eGFR, and standardized to the overall cohort. Incident rate is per every 100,000 person years.

^aIncident eGFR <60 ml/min per 1.73 m² was evaluated in a subcohort of people with no prior history of eGFR ≤ 60 ml/min per 1.73 m² at time of cohort entry.

^bIncident CKD was evaluated in a subcohort of people with at least two eGFR measurements separated by at least 90 days who had no prior history of eGFR ≤ 60 ml/min per 1.73 m² at time of cohort entry.

of population, and results were consistent in terms of direction and magnitude of risk estimates (Supplemental Table 3). Because variation in regional characteristics may confound the association of PM_{2.5} and kidney disease, we developed strategies to evaluate the association in analyses, considering city-adjusted and within-city models (as described in Supplemental Material); the results suggest that within metropolitan areas (city-adjusted or within-city models), higher PM_{2.5} concentrations were associated with higher risk of renal outcomes (Supplemental Table 4). Between-city risk estimates were slightly higher than within-city estimates (Supplemental Table 4). Because characteristics of geographies might confound the association between PM_{2.5} and risk of kidney outcomes,²³ we curated the County Health Rankings datasets^{24,25} and built analyses additionally controlling for 55 United States county-level variables in six domains, including demographics, physical environment, social and economic factors, health behaviors, clinical care, and health outcomes; the results remained consistent (Supplemental Table 5). We repeated the analyses using expanded and more sensitive definitions of hypertension and diabetes: the definition of hypertension included relevant diagnostic codes and average systolic BP (treated as a continuous variable) in the year before time zero (T₀); the definition of diabetes included relevant diagnostic codes as well as use of diabetic medications (including oral hypoglycemic agents and insulin) and hemoglobin A1c levels $>6.4\%$. The results remained stable to this challenge of using expanded definitions of key drivers of kidney disease (Supplemental Table 6). The results were reproduced in analyses considering alternative renal outcomes, including odds of rapid eGFR decline (eGFR slope < -5 ml/min per 1.73 m² per year), and risk of ESRD or eGFR decline $\geq 50\%$ (Supplemental Table 7). As a measure of calibration, we examined the association of PM_{2.5} and risk of death where *a priori* observations suggest that an association is expected (positive control).^{6,10} Our results show a significant association between PM_{2.5} concentrations and risk of death (Supplemental Table 8). We also considered the outcome of myocardial infarction as an additional positive control^{3,26}; the results were consistent with published literature^{6,10} in that an increase in PM_{2.5} was associated with increased risk of myocardial infarction (Supplemental Table 9). Results of sensitivity analyses for the competing risk of death were consistent with those shown in primary analyses²⁷ (Supplemental Table 10).

Negative control is a valuable complement to other epidemiologic methods and serves to identify and resolve both suspected and unsuspected sources of spurious causal inference, including confounding, mismeasurements, and other biases, design, or analytic flaws.²⁸ Ambient air sodium concentration is one of the parameters measured by air monitoring stations. There is no biologic basis to support an association between levels of sodium concentrations in the air and risk of adverse renal outcomes; this renders ambient air sodium a suitable negative control.²⁸ We therefore, as a negative exposure control, tested the association between ambient air sodium levels and the risk of renal outcomes, and the results show a vanishingly weak or non-significant association in models, considering baseline exposure

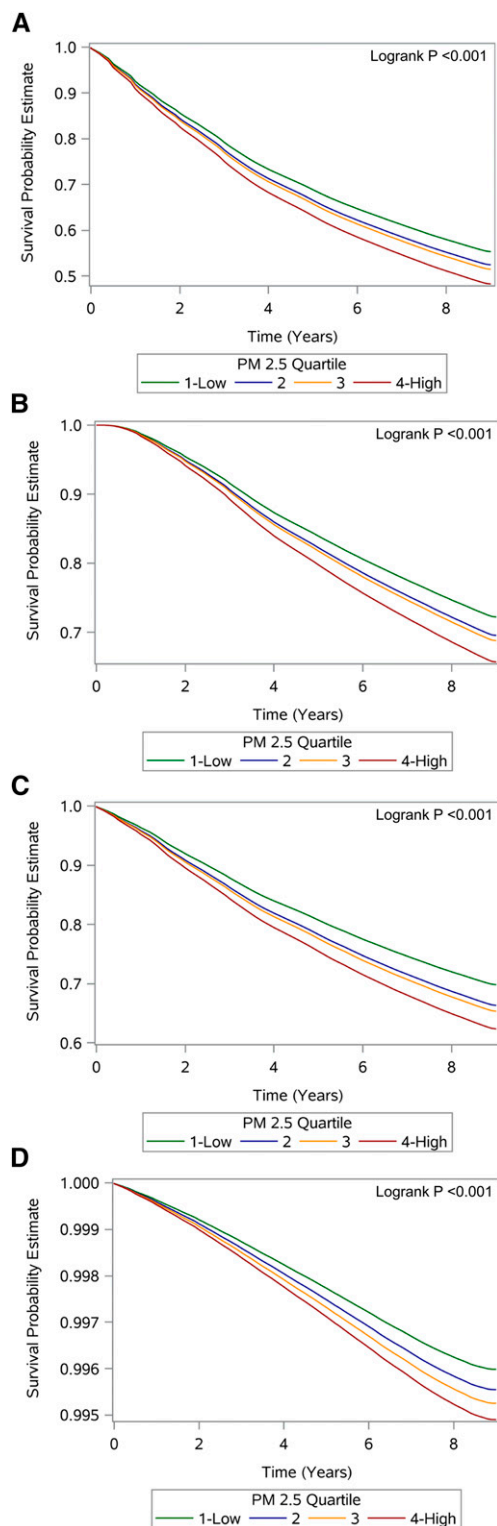


Figure 1. Adjusted survival curves by PM_{2.5} quartiles. (A) Incident eGFR <60 ml/min per 1.73 m², (B) incident CKD, (C) eGFR decline ≥30%, and (D) ESRD. Survival curves are adjusted for age, race, sex, and T₀ eGFR.

in the year 2004 and time-varying exposure (Supplemental Table 11). An analysis considering the association between air sodium levels and risk of death also shows no association in models considering baseline exposure (HR, 1.00; 95% CI, 1.00 to 1.01) and those considering time-varying exposure (HR, 1.00; 95% CI, 0.99 to 1.00) (Supplemental Table 11). Additional details on sensitivity analyses are presented in Supplemental Material.

In formal interaction analyses, race did not modify the association of PM_{2.5} and risk of kidney outcomes; the association was more pronounced among women and in those below the median age and in those below the median body mass index (BMI) of the overall cohort (Supplemental Figure 1).

DISCUSSION

In a large national cohort of United States veterans, we observed a linear relationship between PM_{2.5} concentrations and risk of incident CKD and progression to ESRD. The results were consistent where baseline exposure was defined as the annual average PM_{2.5} concentrations in the year 2004, and where exposure was time-varying to reflect movement of cohort participants and changes in PM_{2.5} concentrations over the years. Furthermore, we examined a range of kidney outcomes including development of kidney disease, kidney function decline (eGFR decline ≥30%), and the terminal outcome of ESRD. The results consistently showed a linear relationship between PM_{2.5} levels and risk of kidney outcomes. The results were robust in sensitivity analyses including the examination of different distance thresholds from an air monitoring station, and analyses evaluating the association within metropolitan areas. The results were also consistent in analyses using ambient PM_{2.5} estimates derived from NASA's satellite data. Ambient air sodium concentrations (used as a negative control) were not associated with increased risk of adverse renal outcomes. The constellation of findings suggests that chronic exposure to fine particulate matter air pollution is a significant risk factor for the development and progression of kidney disease.

Although air quality has significantly improved in the United States over the past several decades, air quality remains suboptimal in many parts of the country and in multiple geographies around the world. In our analyses, the risk of CKD and its progression was most pronounced at the highest levels of fine particulate matter concentrations. However, analyses where PM_{2.5} concentrations were categorized in quartiles suggest a graded relationship; spline analyses (and tests of nonlinearity) endorse a linear relationship where risk starts to increase at relatively low concentrations of particulate matter that are well below the recommended levels by the World Health Organization (10 μg/m³) and the EPA (12 μg/m³). We used a conservative approach to estimate the attributable burden of CKD and ESRD in the contiguous United States, and our results suggest a small but significant number of incident cases of CKD (44,793 per year) and ESRD (2438 per year) are attributable to levels of particulate matter air pollution exceeding the EPA

Table 3. Risk of renal outcomes for every 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentrations:

$\text{PM}_{2.5}$ Exposure	Measure	Incident eGFR <60 ml/min per 1.73 m^2 ^a	Incident CKD ^b	≥30% Decline in eGFR	ESRD
Year 2004 annual average	N	1,709,761	1,644,351	2,482,737	2,482,737
	Events, n %	590,799 (34.55)	358,923 (21.83)	758,342 (30.54)	31,904 (1.29)
	HR (95% CI)	1.21 (1.14 to 1.29)	1.27 (1.17 to 1.38)	1.28 (1.18 to 1.39)	1.26 (1.17 to 1.35)
Time varying	N	1,702,923	1,637,643	2,473,531	2,473,531
	Events, n %	588,557 (34.56)	357,600 (21.84)	755,378 (30.54)	31,790 (1.29)
	HR (95% CI)	1.25 (1.17 to 1.34)	1.37 (1.26 to 1.48)	1.36 (1.26 to 1.46)	1.31 (1.21 to 1.43)

Models adjusted for age, race, sex, cancer, cardiovascular disease, chronic lung disease, diabetes mellitus, hyperlipidemia, hypertension, T_0 eGFR, BMI, smoking status, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, county population density, number of outpatient eGFR measurements, number of hospitalizations, and county percent in poverty.

^aIncident eGFR <60 ml/min per 1.73 m^2 was evaluated in a subcohort of people with no prior history of eGFR ≤60 ml/min per 1.73 m^2 at time of cohort entry.

^bIncident CKD was evaluated in a subcohort of people with at least two eGFR measurements separated by at least 90 days who had no prior history eGFR ≤60 ml/min per 1.73 m^2 at time of cohort entry.

recommended level of 12 $\mu\text{g}/\text{m}^3$. A lower and more stringent TMREL of $\text{PM}_{2.5}$ between 2.4 and 5.9 $\mu\text{g}/\text{m}^3$ yielded a higher estimate of incident CKD (337,032 per year) and incident ESRD (13,537 per year). The findings provide a quantitative assessment of the potential reduction in burden of CKD that is achievable with improvement in air quality in the United States, and suggest the need for a broader assessment of the global burden of kidney disease attributable to air pollution.

Multiple studies reported substantial geographic variation in the burden of CKD and ESRD in the United States and globally; the variation was persistent after accounting for diabetes, hypertension, and obesity conditions generally considered to be major drivers of kidney disease, suggesting that variation in burden of disease is likely due to factors other than these traditional drivers.^{23,29} It has been hypothesized that some of the geographic variation in kidney disease burden may be due to environmental factors.²³ Our study results suggest that particulate matter air pollution is an important, but yet unrecognized risk factor for kidney disease and its progression, which may explain some of the geographic variation in kidney disease burden in the United States. Examination of the effect of particulate matter on risk of incident kidney disease and its progression outside the United States, and particularly in areas with much higher levels of particulate matter air pollution is warranted.

Three distinct hypotheses have been proposed to explain the epidemiologic observations of a relationship between $\text{PM}_{2.5}$ and cardiovascular outcomes; these may also be pertinent in the evaluation of renal outcomes.³⁰ The first suggests that inhaled particles provoke pulmonary inflammation which may then lead to systemic inflammation.³⁰ The second suggests that the mechanism involves pollutant-induced disturbances in the lung autonomic nervous system.³⁰ The third (and most plausible hypothesis) is predicated on the premise that airborne particulates enter the bloodstream where they may then interact with tissue components to promote the observed pathologic effects^{30,31}; the latter is supported by emerging evidence suggesting that inhaled inert gold nanoparticles not only enter the bloodstream of healthy adult volunteers, but are detected in the urine within minutes after exposure, providing a proof of concept that inhaled nanoparticles get filtered

and excreted by the kidney.³¹ These three hypotheses provide contextual background to evaluate the experimental and clinical findings describing the extrapulmonary effect of particulate matter air pollution, where it has been reported that exposure to elevated levels of $\text{PM}_{2.5}$ is associated with increased inflammatory mediators (including TNF- α , IL-6, and plasminogen activator inhibitor-1), oxidative stress,^{32–34} increased atherosclerotic plaque area, and exaggerated vasoconstrictor responses to phenylephrine and serotonin.³⁵ Evidence suggests that increased $\text{PM}_{2.5}$ concentrations are associated with significant decrease in flow-mediated dilatation,^{36,37} increases in systolic BP and pulse pressure,^{38–40} and disturbances in the hypothalamic-pituitary-adrenal axis.⁴¹ Emerging evidence also suggests that exposure to ambient air pollutants can lead to metabolic disturbances, including glucose intolerance, decreased insulin sensitivity, higher blood lipid concentrations, weight gain, and increased risk of diabetes mellitus.^{42–44} It is plausible that one or more of these mechanistic pathways may explain the association described here.

This study has several limitations. Cohort participants were United States veterans and mostly older white men; therefore, the findings may not be generalizable to other populations. Although we accounted for known confounders, the possibility of residual confounding due to either unknown or unmeasured confounders cannot be completely excluded. We specifically note that the counties with the highest measures of $\text{PM}_{2.5}$ had higher population density and greater percentage of citizens living in poverty. Although we took care to develop analyses for the 100 most populated counties, built city-adjusted and within-city analyses, and also accounted for United States county-level characteristics²³ in domains including demographics, physical environment, social and economic conditions, health behaviors, clinical care, and health outcomes, it is possible that individual differences in genomic makeup, dietary habits, physical activity, other environmental or occupational attributes, variation in exposure to heavy metals, or other factors not captured in our analyses might explain the described results. To define covariates we relied on VA administrative databases, and although we used comorbidity definitions validated for use in administrative datasets, misclassification or inaccurate measurement of predictor variable

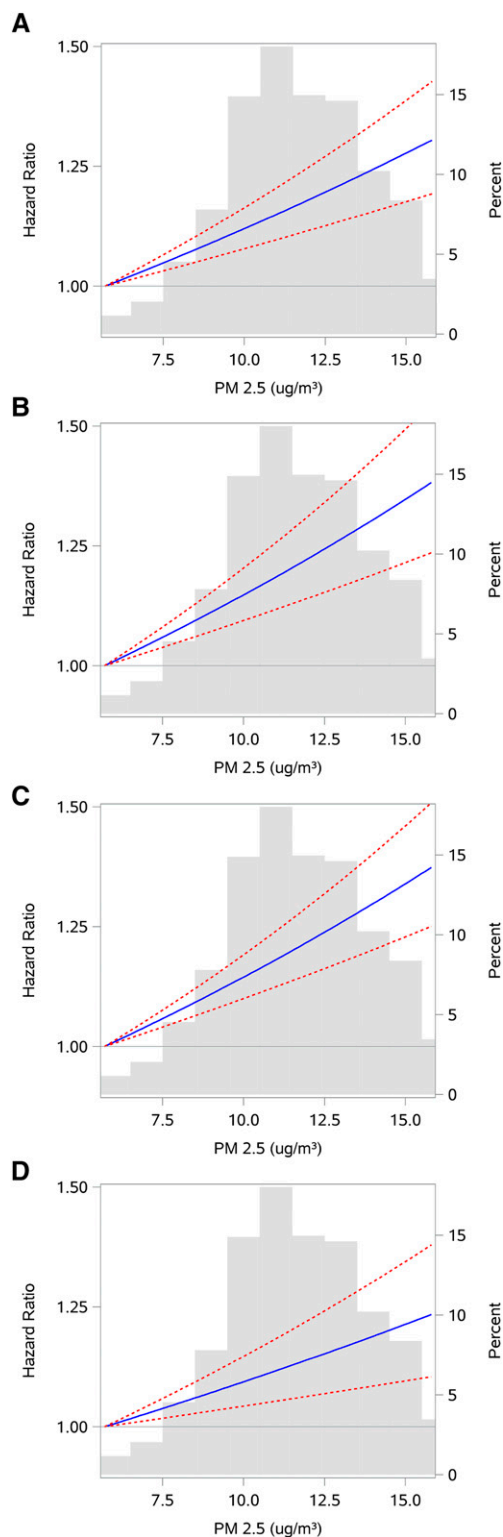


Figure 2. Analyses of risk of renal outcomes by $\text{PM}_{2.5}$ concentrations ($\text{PM}_{2.5}$ of $5.7 \mu\text{g}/\text{m}^3$ served as a reference) with $\text{PM}_{2.5}$ probability distribution in the background. (A) Risk of incident $\text{eGFR} < 60 \text{ ml}/\text{min}/1.73 \text{ m}^2$ (P for nonlinearity = 0.90). (B) Risk of incident CKD (P for nonlinearity = 0.90). (C) Risk of eGFR decline $\geq 30\%$ (P for nonlinearity = 0.84). (D) Risk ESRD (P for nonlinearity = 0.47). Models

is not impossible. Our analyses did not consider the composition of $\text{PM}_{2.5}$, which may vary by region and over time; however, estimates using nonspecific $\text{PM}_{2.5}$ mass alone may underestimate the total effect of $\text{PM}_{2.5}$ on health outcomes and bias the results toward the null hypothesis.¹⁰ Our datasets did not contain information on time spent in traffic or outdoors, and did not include information on potential exposure to indoor air pollutants, which may result in misclassification of exposure. The study has a number of strengths, including the large national cohort of veterans who are recipients of care in a single integrated network of health care systems designed to reduce variation in care practices, and the analyses benefited from the merging of large databases including those of the VA, EPA, Census Bureau, and other data sources. We followed our cohort participants for a median of 8.52 years (interquartile range, 8.04–8.80), designed analytic strategies using time-varying exposure (to capture updated exposure levels as participants moved over the years), and evaluated a range of well defined chronic kidney outcomes, including development of kidney disease, CKD progression, and the terminal outcome of ESRD. Our analytic approach to examine within-city and city-adjusted effect reduces concern about confounding due to variation in regional characteristics, and potential geographic variation in composition and toxic content of $\text{PM}_{2.5}$. The analyses also considered NASA's satellite data as alternative data source to define $\text{PM}_{2.5}$ exposure. The analytic strategies also included the development and testing of positive and negative controls to detect possible hidden bias. In summary, our results demonstrate a significant association between $\text{PM}_{2.5}$ concentrations and risk of development of kidney disease, and its progression to ESRD. Effort to improve air quality might ease the burden of kidney disease in the United States and globally.

CONCISE METHODS

Cohort Participants

We selected users of the Veterans Affairs (VA) Healthcare System, using data from the US Department of Veterans Affairs, who had at least one outpatient eGFR measurement between October 1, 2003 and September 30, 2004 and no prior history of ESRD, and designated the date of last eGFR measurement in this time period as T_0 ($n=2,751,717$). Patients were further chosen on having at least one eGFR measurement after T_0 ($n=2,680,431$), and were followed until September 30, 2012 or death. Participants were then limited to those who had data on $\text{PM}_{2.5}$ ($n=2,628,465$) and data on all covariates, yielding an analytic cohort

adjusted for age, race, sex, cancer, cardiovascular disease, chronic lung disease, diabetes mellitus, hyperlipidemia, hypertension, T_0 eGFR , BMI, smoking status, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, county population density, number of outpatient eGFR measurements, number of hospitalizations, and county percent in poverty.

Table 4. Risk of renal outcomes for every 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration using NASA Socioeconomic Data and Applications Center data for exposure levels

$\text{PM}_{2.5}$ Exposure	Measure	Incident eGFR <60 ml/min per 1.73 m^2 ^a	Incident CKD ^b	$\geq 30\%$ Decline in eGFR	ESRD
Year 2004 annual average	N	1,649,148	1,585,827	2,398,318	2,398,318
	HR (95% CI)	1.19 (1.17 to 1.21)	1.24 (1.22 to 1.27)	1.23 (1.21 to 1.25)	1.18 (1.14 to 1.23)
Time varying	N	1,648,772	1,585,517	2,397,912	2,397,912
	HR (95% CI)	1.18 (1.16 to 1.21)	1.25 (1.22 to 1.28)	1.25 (1.23 to 1.28)	1.24 (1.18 to 1.30)

Models adjusted for age, race, sex, cancer, cardiovascular disease, chronic lung disease, diabetes mellitus, hyperlipidemia, hypertension, T_0 eGFR, BMI smoking status, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, county population density, number of outpatient eGFR measurements, number of hospitalizations, and county percent in poverty.

^aIncident eGFR <60 ml/min per 1.73 m^2 was evaluated in a subcohort of people with no prior history of eGFR ≤ 60 ml/min per 1.73 m^2 at time of cohort entry.

^bIncident CKD was evaluated in a subcohort of people with at least two eGFR measurements separated by at least 90 days who had no prior history eGFR ≤ 60 ml/min per 1.73 m^2 at time of cohort entry.

of 2,482,737 (Figure 4). The study was approved by the Institutional Review Board of the VA Saint Louis Health Care System (Saint Louis, MO).

Data Sources

Department of Veterans Affairs datasets were used to obtain patient demographics, inpatient and outpatient data, laboratory information, vital signs, and medications.^{45,46} Details on the VA datasets used are provided in

Supplemental Material.^{47–51} Data from the US Renal Database System (USRDS) was used to supplement ESRD status information. The Center for Disease Control's (CDC) National Environmental Public Health Tracking Network furnished annual particulate matter estimates for the contiguous United States that originate from Community Multiscale Air Quality modeled output.^{52,53} The Community Multiscale Air Quality System uses, for counties with air monitoring stations, the measures from the EPA's Air

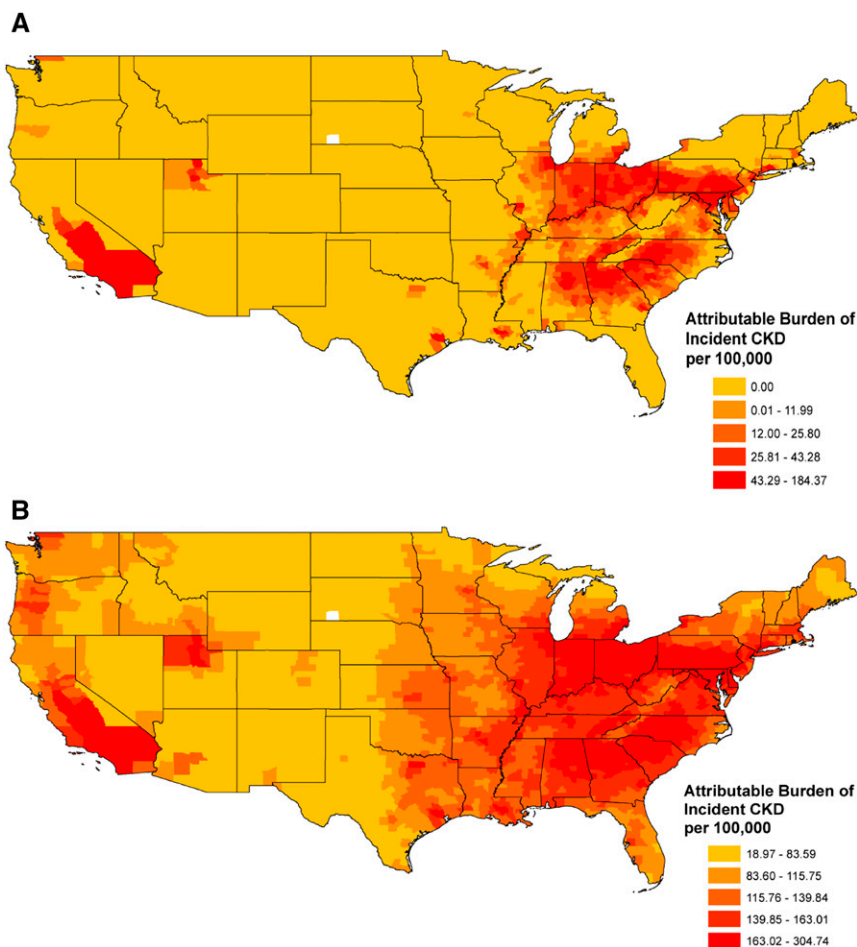


Figure 3. Geographic distribution of the national burden of incident CKD attributable to air pollution in the United States. (A) Risk attributable to exposure levels of $\text{PM}_{2.5}$ above the EPA recommended concentration of $12 \mu\text{g}/\text{m}^3$. (B) Risk attributable to exposure levels of $\text{PM}_{2.5}$ above a uniform distribution between 2.4 and $5.9 \mu\text{g}/\text{m}^3$. Burden is per 100,000 population.

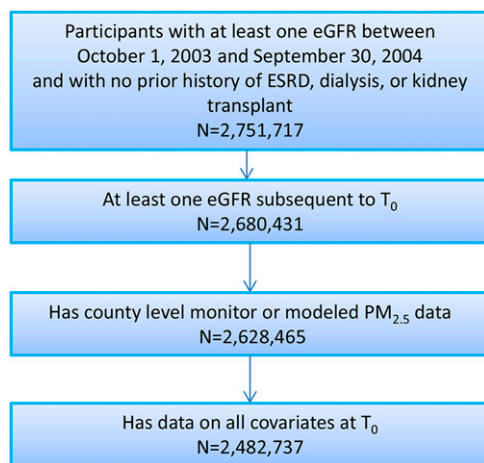


Figure 4. Flow diagram of cohort participant inclusion.

Quality System. EPA data also provided information on sodium levels, as well as the latitude and longitude of said monitoring stations.⁵⁴ The NASA Socioeconomic Data and Applications Center Global Annual PM_{2.5} grids from Moderate Resolution Imaging Spectroradiometer, Multi-angle Imaging Spectroradiometer, and Sea-Viewing Wide Field-of-View Sensor aerosol optical depth remote space-borne satellite sensing data provided an additional source of ambient PM_{2.5} estimates at the 10×10 km resolution.^{55,56} National United States–based estimates of incident rates of CKD and treated ESRD were obtained from the CDC CKD Surveillance Project and the 2016 USRDS Annual Data Report, respectively.^{57,58} Data on county-level poverty, population, population density, metropolitan statistical areas, and zip code centroid were obtained from the US Census Bureau. More detailed description of data sources is provided in Supplemental Material.

Exposure Assessment

The primary predictor variable for analyses was PM_{2.5} concentrations. Cohort participants were assigned geographic location, which may have varied over time, on the basis of their county information contained in outpatient or inpatient data closest to but before a given time point. Using annual monitor and modeled data, exposure (in micrograms per cubic meter) was defined as (1) the annual average in year 2004, where a patient's geographic location was designated as location at T₀ (used in baseline models); and (2) time varying where geographic location was updated as cohort participants moved (and average annual exposure was matched to their updated geographic location at any specific time). In all primary analyses, unless otherwise indicated, measures correspond to a 10-μg/m³ increase in PM_{2.5}.⁹ PM_{2.5} exposure was additionally categorized into quartiles defined by the county-level distribution. In the time-varying model, quartiles were independently defined by exposure distributions among the counties in each given year. PM_{2.5} was alternatively defined by NASA's SEDAC Global Annual PM_{2.5} grids from MODIS, MISR and SeaWiFS aerosol optical depth data through linkage to participant's zip code of residence.^{55,56} Further details are provided in Supplemental Material.

Ascertainment of Outcomes

Outcomes evaluated included the risk of incident eGFR <60 ml/min per 1.73 m², the risk of incident CKD where CKD was defined as two

eGFR measurements <60 ml/min per 1.73 m² at least 90 days apart,⁴⁷ time until ≥30% decline in eGFR from eGFR at T₀, and time until ESRD.⁵⁹ Patients were censored after onset of ESRD, for all outcomes other than ESRD, and at time of death or end of study follow-up. The date of first ESRD services was ascertained through linkage of VA and USRDS databases. Outpatient eGFR was used in the assessment of all outcomes except for ESRD. eGFR was calculated using the four-variable abbreviated CKD Epidemiology Collaboration equation on the basis of age, race, sex, and serum creatinine.⁶⁰

Covariates

Covariate selection was on the basis of factors that could potentially confound the association of PM_{2.5} and kidney disease outcomes, and was informed by prior studies.^{3,23,47,61–64} Baseline covariates were ascertained from October 1, 1999 until cohort entry (T₀). Covariates included age, race, sex, cancer, cardiovascular disease, chronic lung disease, diabetes mellitus, hyperlipidemia, hypertension, T₀ eGFR, BMI, smoking status, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, county population density, number of outpatient eGFR measurements, number of hospitalizations, and county percent in poverty. Details of covariate definitions are provided in Supplemental Material. Covariates were treated as continuous variables where appropriate, unless otherwise indicated.

Statistical Analyses

Demographic and clinical characteristics of the overall cohort and by county PM_{2.5} quartile are presented as frequency (percent) for categorical variables, and as mean (standard deviation) or median (interquartile range) for continuous variables if normally or non-normally distributed, respectively. PM_{2.5} quartiles for Table 1 and baseline models were derived from the distribution of 2004 monitor and modeled PM_{2.5} among counties. Age, race, sex, and eGFR adjusted incident rates are presented, and were standardized to the distribution of these variables in the overall cohort. Survival curves for PM_{2.5} quartiles, adjusted for age, race, sex, and eGFR, are presented. Cox proportional hazard models were adjusted for covariates as described. In order to account for intracounty correlation, a robust sandwich estimator was used. Analyses were performed in baseline models and time varying models, where PM_{2.5} exposure was treated as time varying. Patients were excluded from time-varying analyses if their county of residence had missing data at any time during follow-up. The inclusion of time-varying models in the analytic strategies was in consideration of the fact that cohort participants may have moved over time, but also importantly in recognition of the fact that the Clean Air Act and other environmental policies at state and local levels have resulted in reduction in PM_{2.5} over the years.⁶⁵ The primary analyses were repeated utilizing PM_{2.5} exposures derived from NASA satellite data. Effect modification of the association between PM_{2.5} exposure and renal outcomes by age, race, sex, and BMI was examined through the addition of interaction terms in separate baseline models using above and below median age, black and nonblack, men and women, and above and below median BMI interactions.

Cubic spline analyses were performed.⁶⁶ A Wald chi-squared test for nonlinearity of spline terms indicated that, for all outcomes, there was no statistical evidence of deviation from linearity. Further information on the spline analysis is provided in Supplemental Material. A representation of the linear relationship of PM_{2.5} and the HRs from

proportional hazard regression models are provided, where the PM_{2.5} concentration of 5.7 $\mu\text{g}/\text{m}^3$ was used as the reference. Distribution histograms of PM_{2.5} are included in the background of these graphs.

PAF is presented as a measure of the proportion of the outcome in the population attributable to PM_{2.5} exposure above the EPA standard of 12 $\mu\text{g}/\text{m}^3$. Further details on calculation of PAF and attributable burden of disease are provided in Supplemental Material.

Missing data were not imputed. In analyses, a 95% CI of an HR that does not include unity was considered statistically significant. In all analyses, a *P* value ≤ 0.05 was considered statistically significant. All statistical analyses were done using SAS Enterprise Guide version 7.1 and SAS 9.4 (SAS Institute, Cary, NC).

Sensitivity Analyses

To test robustness of study findings, we undertook a number of sensitivity analyses as described in Supplemental Material.

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DISCLOSURES

None.

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