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Air Pollution and Acute Kidney Injury in the U.S. Medicare Population: A Longitudinal Cohort Study

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Background: Recent studies have reported the association between air pollution exposure and reduced kidney function. However, it is unclear whether air pollution is associated with an increased risk of acute kidney injury (AKI).

Objectives: To address this gap in knowledge, we investigated the effect estimates of long-term exposures to fine particulate matter [PM $\leq$2.5 μm in aerodynamic diameter ($PM_{2.5}$)], nitrogen dioxide (NO_2), and ozone (O_3) on the risk of first hospital admission for AKI using nationwide Medicare data.

Methods: This nationwide population-based longitudinal cohort study included 61,300,754 beneficiaries enrolled in Medicare Part A fee-for-service (FFS) who were ≥65 years of age and resided in the continental United States from the years 2000 through 2016. We applied Cox-equivalent Poisson models to estimate the association between air pollution and first hospital admission for AKI.

Results: Exposure to $PM_{2.5}$, NO_2, and O_3 was associated with increased risk for first hospital admission for AKI, with hazard ratios (HRs) of 1.17 (95% CI: 1.16, 1.19) for a 5-$\mu g/m^3$ increase in $PM_{2.5}$, 1.12 (95% CI: 1.11, 1.13) for a 10-ppb increase in NO_2, and 1.03 (95% CI: 1.02, 1.04) for a 10-ppb increase in summer-period O_3 (June to September). The associations persisted at annual exposures lower than the current National Ambient Air Quality Standard.

Discussion: This study found an association between exposures to air pollution and the risk of the first hospital admission with AKI, and this association persisted even at low concentrations of air pollution. Our findings provide beneficial implications for public health policies and air pollution guidelines to alleviate health care expenditures and the disease burden attributable to AKI. https://doi.org/10.1289/EHP10729

Introduction

Acute kidney injury (AKI), formerly known as acute renal failure, is a clinical syndrome characterized by a sudden decrease in renal excretory function.[1] AKI is common (50.8 admissions per 1,000 persons in 2018) in the United State Medicare population[2] and is more common among intensive care unit admissions. A previous review study reported that the incidence of AKI ranges from 20% to 50% during intensive care unit admissions, based on 51 individual studies published between 2006 and 2012.[3] Furthermore, AKI is closely related to the incidence and progression of chronic kidney disease (CKD) and end-stage renal disease[2,4] and is also associated with greater likelihood of long-term care, higher health care costs, and increased mortality.[2,5] The incidence of dialysis-treated AKI has increased during the last decades.[2,6] The cumulative 1-y incidence of death after initiation of outpatient hemodialysis for AKI treatment was >31.6% in Medicare beneficiaries (2017–2018).[2]

Despite its importance, studies on the effect estimates of environmental stressors on AKI are scarce. There are several biological mechanisms that can link air pollution exposure and kidney disease. Inhaled air pollution can directly lead to a decrease in renal function, oxidative stress, DNA damage in renal tissue, and AKI exacerbation.[7,8] In addition, long-term exposure to fine particulate matter [PM $\leq$2.5 μm in aerodynamic diameter ($PM_{2.5}$)] and nitrogen oxide (NO_x) can prematurely age blood vessels and gradually restrict blood flow to the heart and other major blood vessels over time. The long-term exposure to air pollution also gradually increases the likelihood of incident cardiovascular events, such as stroke and cardiac infarction,[9] which are the major triggers of AKI.[1] Long-term exposure to air pollution is also closely related to gradual deteriorations in respiratory, urinary tract, and pulmonary function that can develop into sepsis,[10–12] and a previous study has shown that ~60% of patients with septic shock developed AKI.[13]

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The findings from the previous studies provide biological plausibility supporting the hypothesis of an association between air pollution and AKI. Therefore, in this study, we aimed to estimate the association between air pollution and the first hospital admissions associated with AKI, using a nationwide longitudinal cohort study covering >61 million Medicare Part A FFS beneficiaries from 2000 through 2016, with 451.3 million person-years of follow-up.

Materials and Methods

Ethics Considerations

This study was conducted under a protocol approved by the Yale Institutional Review Board. The need to obtain informed consent was waived because this study used existing anonymous data sources. This study followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guideline (see the Supplemental Material, "A. STROBE Statement").

Data Sharing Information

Data were collected by the Yale–Harvard Medicare collaboration under a data user agreement with Centers for Medicare and Medicaid Services (CMS). The data cannot be made publicly available.

Study Design and Participants

We constructed a longitudinal Medicare cohort that included beneficiaries who were enrolled in Medicare Part A FFS Medicare (≥65 years of age) in the contiguous United States from 1 January 2000 to 31 December 2016. The Medicare inpatient hospital claims were obtained from the Medicare Provider and Analysis Review (MedPAR) files that contain one record per hospital admission. For each beneficiary, we extracted the first admission date for AKI, age, sex, race, ZIP code of residence, and Medicaid eligibility (as a proxy for low socioeconomic status; hereafter "dual" refers to Medicaid beneficiaries who were also eligible for Medicaid, and "non-dual," to Medicare beneficiaries who were not eligible for Medicaid)[14] in each follow-up year. Beneficiaries become eligible to enter Medicare when they turn 65 years of age. For our study, the follow-up for each beneficiary started on 1 January 2000, or 1 January of the year following their entry into the cohort, and individuals were followed-up through the first admission with diagnosis codes for AKI, death, or the end of the study period, whichever came first. We used primary or secondary discharge diagnosis codes categorized according to the *International Statistical Classification of Diseases, Ninth Revision*[15] (ICD 9; WHO 1978) or the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*[16] (ICD-10; WHO 2016), namely, ICD-9 code 584; ICD-10 code N17 to address any inpatient hospital admissions with any AKI onsets. We used the first 10 diagnosis fields to define the primary (the first diagnosis field) and secondary (as the diseases from the 2nd to the 10th diagnosis fields) diagnosis codes for AKI. The directed acyclic graph (DAG) for this study is displayed in the Supplemental Material, "B. DAG for this study."

Air Pollution Data

A nationwide air pollution data set including high-resolution $PM_{2.5}$, NO_2, and ozone (O_3) estimates obtained from prediction models was used. Specifically, predicted daily concentrations of ambient levels of $PM_{2.5}$, NO_2, and O_3 (daily maximum 8-h O_3) at 1-km^2 spatial resolution across the contiguous United States were obtained from well-validated published models.[17–19] These predictions were estimated using hybrid ensemble models incorporating random forest, gradient boosting, and neural networks. Multiple predictor variables from monitoring data, satellite data, meteorological conditions, land-use variables, and chemical transport models were used. The technical details of the prediction models have been previously published[17–20] with excellent performance: cross-validated R^2s of 0.89 for annual $PM_{2.5}$, 0.84 for annual NO_2, and 0.88 for summer-season O_3 across the continental United States. Daily concentration predictions at 1 km^2 were aggregated to each ZIP code by averaging the predictions at grid cells with centroid points inside the boundary of that ZIP code.[14,20,21] For each calendar year, we assigned the annual ($PM_{2.5}$ and NO_2) and summer-season (June to September: O_3) ZIP code-level average concentrations to Medicare Part A enrollees according to their residential ZIP code as the main exposures.[14,20–22] Ground-level O_3 is formed by chemical reactions from precursor pollutants, such as fuel combustion, road transport, and vegetation, and the reactions are catalyzed by heat and sunlight. Thus, the summer-season O_3 was used in this study to assess the long-term effect estimates of O_3.[22,23] To examine the correlation among pollutants, we calculated Pearson's correlation coefficients.

Confounders

We considered confounding variables that could affect the associations between long-term exposure to air pollution and hospital admissions for AKI. First, we collected four individual-level variables from Medicare files: age at cohort entry in 2-y categories (65–66, 67–68, …, ≥85 y old), sex, race [self-reported; White, Black, and other (Asian, Hispanic, American Indian or Alaskan Native, and unknown)],[14,21] and Medicaid eligibility. This racial categorization was for stable statistical estimation, and further divisions of race were not possible owing to the structure of the data provided from the CMS.

In addition, we collected 10 neighborhood-level socioeconomic status indicators that have been associated with both kidney disease and air pollution exposures,[24–26] that is, eight ZIP code-level indicators and two county-level indicators, as well as indicator variables indicating geographical regions. The eight indicators available at ZIP Code Tabulation Areas (ZCTA) level were derived from the 2000 U.S. Census, the 2010 U.S. Census (https://www.census.gov/), and the American Community Survey (https://www.census.gov/programs-surveys/acs) from 2005–2016. If indicators were missing for a year, we linearly interpolated or extrapolated their values using available data. The ZCTA indicators included the percentage of the population below the poverty level, population density (persons per kilometer squared), median home value (in USD), percentage of the population that is Black, percentage of the population that is Hispanic, median household income (in USD), percentage of homes with owner-occupied housing, and percentage of the population without a high school education. These ZCTA data were matched to ZIP code. In addition, two county-level indicators [average body mass index (BMI) and percentage of the population that had ever smoked] were collected from the Behavioral Risk Factor Surveillance System (BRFSS; https://www.cdc.gov/brfss/) for the period of 2000–2016. These county-level indicators were matched to ZIP code if the ZIP code centroids fell within the country boundary. Finally, we included indicator variables for the region (Northeast, Southeast, Midwest, Southwest, and West) and calendar year in the main model to adjust for potential residual confounding by spatial and temporal trends.

Statistical Analysis

We used a Cox-equivalent reparameterized Poisson model to address the computational challenges of the conventional Cox proportional hazard model.[21] This Poisson model is mathematically

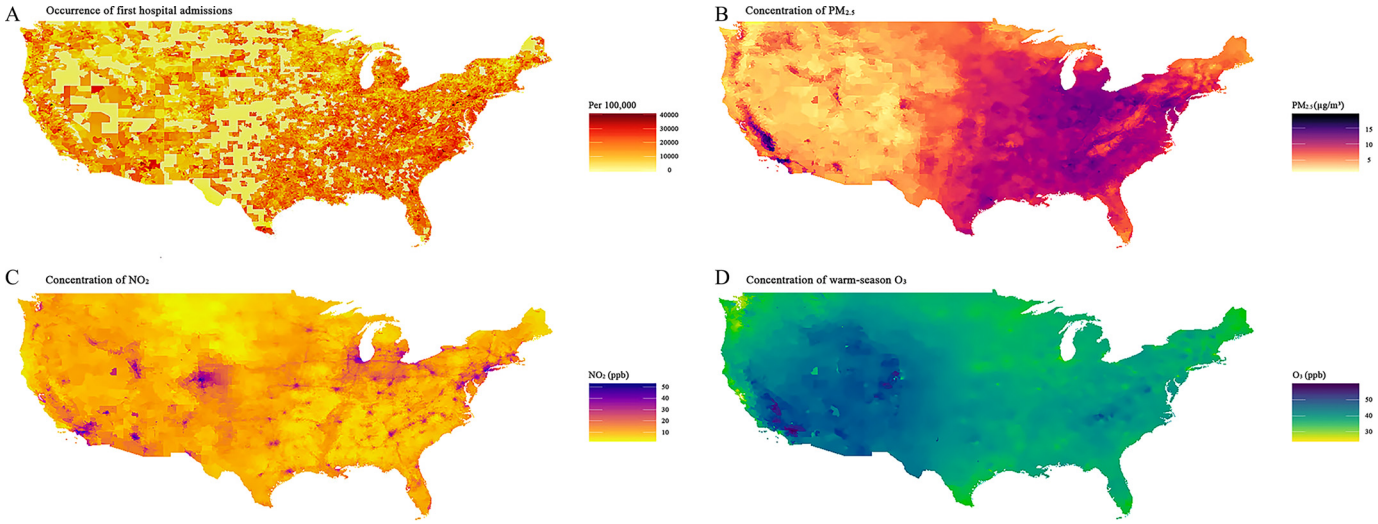

Figure 1. Nationwide first hospital admissions for the acute kidney injury (AKI) and concentrations of air pollution across the contiguous United States (2000–2016). (A) Occurrence of first hospital admissions per 100,000 Medicare Part A fee-for-service beneficiaries (≥65 years of age), (B) 17-y average concentration of annual fine particulate matter ($PM_{2.5}$), (C) concentration of nitrogen dioxide (NO_2), and (D) concentration of warm-season ozone (O_3) (June to September O_3).

identical to a time-varying Cox hazard model under an Anderson–Gill representation.[21,27] Specifically, for each pollutant (i.e., single-pollutant model), a stratified Poisson model was fit to estimate the association between time-varying (current year) annual air pollution and the first hospital admissions with AKI diagnosis code. The dependent variable was the count of the first hospital admissions in each follow-up year, (time-varying) calendar year, and ZIP code within strata specified by individual-level variables, namely: age at study entry in 2-y categories (65–66, 67–68, . . ., ≥85 y old), sex, race, and Medicaid eligibility. The total person-time of Medicare Part A FFS beneficiaries within each stratum was used as the offset. We adjusted for neighborhood-level indicators as covariates and indicator variables for region in the model. This study performed a complete-case analysis and did not consider missing-data imputation. The m-out-of-n bootstrap method with ZIP code units was applied to calculate empirical confidence intervals (CIs).[28] The mathematical equation on the equivalence between the Cox proportional hazard model and the stratified Poisson model that we used is as follows:

$$h^{c,z}(a,t) = h_0^c(a)\exp(\beta_1 W_{z,t} + \beta_2 C_{z,t}), \quad (1)$$

where $h^{c,z}(a,t)$ indicates the hazard of hospitalization at follow-up year a, calendar year t, and ZIP code z for individual-level strata c (age group, sex, race, and Medicaid eligibility), and $h_0^c(a)$ is a baseline hazard function. $W_{z,t}$ denotes the annual average air pollutants in ZIP code z in year t. $C_{z,t}$ indicates time-varying covariates. Model 1 can be written as follows:

$$\frac{E\left(Y_{a,t}^{c,z}\right)}{T_{a,t}^{c,z}} = h_0^c(a)\exp(\beta_1 W_{z,t} + \beta_2 C_{z,t}), \quad (2)$$

where $E\left(Y_{a,t}^{c,z}\right)$ denotes the expected number of events for each stratum c, and $T_{a,t}^{c,z}$ is the corresponding total person-time in that stratum. Taking the log of both sides, model 2 can be written as

$$\log\left(\mathrm{E}\left(Y_{a,t}^{c,z}\right)\right) = \log\left(T_{a,t}^{c,z}\right) + \log\left(h_0^c(a)\right) + \beta_1 W_{z,t} + \beta_2 C_{z,t}. \quad (3)$$

Model 3 is the equation for the stratified Poisson model, which is equivalent to model 1. We used R software (version 4.0.3; R Development Core Team) to perform statistical analyses with the package *gnm*.[29]

In addition, to examine whether the effect estimate of air pollution on AKI exists at low concentrations (hereafter referred to as the low-pollution cohort), we repeated the main analysis but restricted it to the subset of the cohort with annual exposures lower than $<12\,\mu g/m^3$ $PM_{2.5}$; based on the current National Ambient Air Quality Standard (NAAQS), 20 ppb NO_2, and 50 ppb warm-season O_3 during the entire study period given that such analysis is highly important to inform future policy decisions. Finally, to assess any potential deviations from linearity in the concentration–response curves, we replaced the linear term of air pollution in the main model with a B-spine function with three equally distributed internal knots (at the 25th, 50th, and 75th percentiles of the air pollution concentrations) for each pollutant.[30] To draw the maps in Figure 1, we used a shapefile provided from the Environmental Systems Research Institute, Inc. (ESRI), with used R software (version 4.0.3). The attributes of this file included the five-digit ZIP code, the two-letter abbreviation for the state in which the ZIP code point was located, the area of the ZIP code area based on in square miles Albers Equal Area Projection, and the Federal Information Processing Standard publication (FIPS) code for the county in which the ZIP code was located.

Subpopulation Analysis

To identify subpopulations who showed higher or lower vulnerability, we repeated the same analyses stratified by race (White, Black, and other), age group (65–74 and ≥75 y old), sex, and Medicaid eligibility (as a proxy of low socioeconomic status). In addition, we repeated the analysis by region to consider potential heterogeneity among regions caused by differing chemical compositions, environmental factors, climatic conditions, and population characteristics.

CKD Status and Primary Diseases Accompanied by AKI

We examined the potential difference in the association between air pollution and AKI by CKD status prior to the first hospital admission for AKI and primary diseases accompanied by AKI. The main analysis was repeated with data stratified by *a*) the hospital admission for CKD (inpatient hospital admissions) with

Table 1. Descriptive cohort characteristics [*n* (%) or mean ± SD] for U.S. Medicare Part A beneficiaries (≥65 years of age), 2000–2016.

Characteristics	Full cohort ($N = 61,390,754$)	Low-pollution cohort		
		$PM_{2.5}$ <12 μg/m³ ($n = 19,456,404$)	NO_2 <20 ppb ($n = 16,671,751$)	O_3 <50 ppb ($n = 12,982,688$)
Age at entry (y)				
65–74	47,086,254 (76.7)	14,992,132 (77.1)	12,976,559 (77.8)	11,754,531 (76.6)
75–84	10,494,944 (17.1)	3,273,073 (16.8)	2,717,030 (16.3)	2,634,673 (17.2)
≥85	3,809,556 (6.2)	1,191,199 (6.1)	978,162 (5.9)	964,484 (6.3)
Sex				
Men	27,545,251 (44.9)	8,984,178 (46.2)	7,612,285 (45.7)	7,027,957 (45.8)
Women	33,845,503 (55.1)	10,472,226 (53.8)	9,059,466 (54.3)	8,325,731 (54.2)
Race				
White	51,731,626 (84.3)	17,475,710 (89.8)	14,976,507 (89.8)	12,939,265 (84.3)
Black	5,391,156 (8.8)	576,461 (3)	1,088,577 (6.5)	942,711 (6.1)
Other[a]	3,598,102 (5.9)	1,182,646 (6.1)	480,830 (2.9)	1,288,161 (8.4)
Medicaid eligibility				
Not eligible	53,793,102 (87.6)	17,388,739 (89.4)	14,691,420 (88.1)	13,318,146 (86.7)
Eligible	7,597,652 (12.4)	2,067,665 (10.6)	1,980,331 (11.9)	2,035,542 (13.3)
Air pollution concentration				
Annual $PM_{2.5}$ (μg/m³)	9.8 ± 3.1	7.2 ± 2.2	9.1 ± 2.8	8.5 ± 2.7
Annual NO_2 (ppb)	18.9 ± 10.1	15.4 ± 8.4	9.8 ± 3.4	16.1 ± 8
Summer-period O_3 (ppb)	45.2 ± 8.5	42.7 ± 9.9	43.3 ± 7.1	36 ± 6.3
Potential confounder (neighborhood-level characteristic)				
Below poverty level (%)	10.5 ± 8.1	9.4 ± 7.5	11.1 ± 8	10.4 ± 7.8
Population density (persons per km²)	3,269.8 ± 8,519	1,411.4 ± 2,376.4	256.5 ± 662.1	2,775 ± 4,562.1
Median home value ($1,000)	203,912.7 ± 167,755.5	201,364 ± 157,472.9	134,910.8 ± 106,900.5	232,379.7 ± 194,675.2
Black (%)	11.9 ± 18.4	5 ± 9.9	9.5 ± 16.1	9.4 ± 14.9
Hispanic (%)	7.2 ± 8.8	6.8 ± 7.6	4.2 ± 6.3	7.9 ± 8.6
Median household income ($1,000)	52,689 ± 23,079	52,418.1 ± 20,871.4	44,573.1 ± 15,620.5	53,696.4 ± 22,725.5
Owner-occupied housing (%)	67.4 ± 17.7	70.7 ± 14.7	75.1 ± 11.4	66.6 ± 17.3
Below high school education (%)	26.9 ± 16.1	22.6 ± 14.9	29.4 ± 16.2	24.8 ± 15.8
Ever smoked (%)	46 ± 7.3	47.4 ± 7.9	48.3 ± 8.3	46 ± 8.1
BMI (kg/m²)	27.5 ± 1	27.3 ± 1	27.8 ± 1.1	27.3 ± 1

Note: Table 1 consists of complete data without missing variables. BMI, body mass index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, fine particulate matter; SD, standard deviation.
[a]Race of other included Asian, Hispanic, American Indian or Alaskan Native, and unknown. Further divisions of race were not possible owing to the structure of the data.

primary or secondary ICD discharge diagnosis codes (ICD-9 code 585; ICD-10 code N18) prior to the first hospital admission for AKI, *b*) the primary diseases of the first hospital admission with a secondary AKI diagnosis code: circulatory system disease (ICD-9 codes 390–458; ICD-10 codes I00–I99), ischemic heart disease (ICD-9 codes 410–414; ICD-10 codes I20–I25), heart failure (ICD-9 code 428; ICD-10 code I50), acute myocardial infarction (ICD-9 code 410; ICD-10 code I21), cerebrovascular disease (ICD-9 codes 430–438; ICD-10 codes I60–I69), pneumonia (ICD-9 codes 480–486; ICD-10 codes J12–J18), diabetes mellitus (ICD-9 code 250; ICD-10 codes E08–E14), and urinary tract infection (ICD-9 code 599.0; ICD-10 code N39.0).

Sensitivity Analysis

We performed sensitivity analyses to examine whether our main results were robust to the selection of confounders (we examined the risk estimates with or without neighborhood-level indicator or region indicators adjustments in the analytic procedures). We also applied 1-y lag period exposures as an alternative exposure window and conducted a sensitivity analysis restricting kidney outcomes to only those with primary diagnoses codes. Moreover, to exclude potentially prevented cases, we repeated the analyses using data excluding beneficiaries who had the first hospital admission for these outcomes in their first 2 y of follow-up. Finally, we fit two-pollutant models for all combinations of air pollutants to examine the effect estimate of each pollutant by including the other pollutant as a potential confounder.

Results

The full cohort data set included 61,390,754 beneficiaries living in 34,918 ZIP codes. Descriptive information on the beneficiaries is displayed in Table 1. There were 451.3 million person-years of follow-up for AKI, and the total number of first admissions with AKI primary or secondary diagnosis code was ∼9.3 million (Table 2). Of those first AKI admissions, 23.5% (2,180,045 cases) of hospitalizations were identified as the primary discharge diagnosis code, and the median follow-up was 6 y. The low-pollution cohort included 126.9–145.3 million person-years of follow-up depending on pollutant. The correlations among air pollutants were as follows: $PM_{2.5}$ and NO_2, 0.4; NO_2 and summer-season O_3, 0.3; and $PM_{2.5}$ and summer O_3, 0.2.

The geographical distributions of first hospital admission occurrences with AKI and air pollution concentrations are displayed in Figure 1. The Southeast Region showed the most frequent occurrence of first AKI hospital admissions. The average annual concentrations of air pollution over the study period were 9.7 μg/m³ for annual $PM_{2.5}$, 23 ppb for annual NO_2, and 25 ppb for summer-period O_3. $PM_{2.5}$ concentrations were highest in California and in the Eastern and Southeastern Regions of the United States. The highest NO_2 concentrations were generally in metropolitan areas (New York, Los Angeles, and Chicago), and the highest O_3 concentrations were observed in California.

The estimated concentration–response curves for all pollutants (Figure 2; see Table S1 for corresponding numeric data) suggest an approximately linear association between air pollution concentrations and the first hospital admission for AKI, and results from the linear model are shown in Table 2. In the full cohort (i.e., considering all levels of air pollution), air pollution was positively associated with AKI for all pollutants, with hazard ratios (HRs) of 1.17 (95% CI: 1.16, 1.19) for a 5-μg/m³ increase in $PM_{2.5}$, 1.12 (95% CI: 1.11, 1.13) for a 10-ppb increase in NO_2, and 1.03 (95% CI: 1.02, 1.04) for a 10-ppb increase in warm-season O_3. In the low-pollution cohort (i.e., considering air

Table 2. Admissions for acute kidney injury (AKI) and association between air pollution and the first hospital admission for AKI for the United States.

Cohort/category	$PM_{2.5}$	NO_2	O_3
Full cohort			
Admissions (*n*)	9,272,274	9,272,274	9,272,274
Total person-years	451,305,627	451,305,627	451,305,627
Median follow-up (y)	6	6	6
Hazard ratio (95% CI)	1.17 (1.16, 1.19)	1.12 (1.11, 1.13)	1.03 (1.02, 1.04)
Low-pollution cohort			
Admissions (*n*)	2,582,170	2,379,401	2,757,486
Total person-years	145,327,939	126,903,255	135,797,051
Median follow-up (y)	6	6	6
Hazard ratio (95% CI)	1.20 (1.17, 1.22)	1.07 (1.05, 1.09)	1.03 (1.01, 1.04)

Note: The low-pollution cohort includes the subset of the cohort with annual average levels below NAAQS levels for the entire follow-up duration. Hazard ratio: $PM_{2.5}$ (per 5 $\mu g/m^3$, annual), NO_2 (per 10 ppb, annual), and O_3 (per 10 ppb, summer-season). Individual-level confounders (age, sex, race, Medicaid eligibility), neighborhood-level indicators [percentage of the population below the poverty level, population density (persons per kilometer squared), median home value (USD), percentage of the population that is Black, percentage of the population that is Hispanic, median household income (USD), percentage of homes with owner-occupied housing, percentage of the population without a high school education, average BMI, percentage of the population that had ever smoked], calendar year, and indicator variables for the region (Northeast, Southeast, Midwest, Southwest, and West) were adjusted in the results. Study population: Medicare Part A fee-for-service beneficiaries (≥65 years of age) from 2000 to 2016. A Cox-equivalent reparameterized Poisson model was used to estimate the hazard ratios. BMI, body mass index; CI, confidence interval; NAAQS, National Ambient Air Quality Standard; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, fine particulate matter.

pollution levels below the NAAQS levels), positive associations were still observed with HRs of 1.20 (95% CI: 1.17, 1.22) for a 5-$\mu g/m^3$ increase in $PM_{2.5}$, 1.07 (95% CI: 1.05, 1.09) for a 10-ppb increase in NO_2, and 1.03 (95% CI: 1.01, 1.04) for a 10-ppb increase in summer-season O_3.

In general, a positive association between air pollution and AKI was observed across all subpopulations (Figure 3; see Table S2 for corresponding numeric data). Those who were White or not eligible for Medicaid generally showed higher air pollution effect estimates compared with those who were Black and other populations and people who were eligible for Medicaid. These patterns were also observed in race–Medicaid eligibility stratified analysis (Table S3). Furthermore, for $PM_{2.5}$ and NO_2, people ≥75 years of age showed more pronounced impacts of air pollution than people 65–74 years of age. In addition, the positive associations with air pollution were observed across all regions (except for the association with O_3 in the Southwest Region), although the effect sizes varied by region; the highest effect estimates were observed in the Midwest and Northeast Regions (Table S4).

Table 3 displays the association between air pollution and AKI differ by CKD hospitalization prior to the hospital admission for AKI and primary diseases of the first hospital admission with AKI secondary diagnosis code. Beneficiaries who had the hospital admission for CKD prior to the first AKI hospital admission showed lower air pollution effect estimates compared with the total population. Meanwhile, for $PM_{2.5}$ and NO_2, the association between air pollution and AKI was more pronounced in hospitalized beneficiaries for AKI with heart failure, cerebrovascular disease, pneumonia, and urinary tract infection as a primary disease compared with the total population. For O_3, the association between air pollution and AKI was more pronounced in hospitalized beneficiaries for AKI with cerebrovascular disease and pneumonia as a primary disease.

Finally, the results of our sensitivity analysis were generally consistent with the main results, except for several of the O_3 results. Our results were robust to confounder adjustments, removal of prevalent cases, and use of a different lag period. In addition, the exclusion of cases identified by secondary diagnostic codes did not change the main results (Table S5). Two-pollutant models showed that estimates were consistent with those from the single-pollutant models, although effect sizes slightly decreased (Table S6).

Discussion

This study investigated the association between air pollution and the first hospital admission for AKI using a nationwide large prospective cohort covering >61 million Medicare Part A FFS beneficiaries from 2000 to 2016. Annual exposures to $PM_{2.5}$, NO_2, and summer-period O_3 were associated with an increased risk of the first hospital admission for AKI, and the associations existed even at levels below the current annual NAAQS levels for $PM_{2.5}$ (12 $\mu g/m^3$) and NO_2 (53 ppb). These findings suggest that improving air quality may lead to public health benefits and reduce the risk of AKI. To the best of our knowledge, this is the first and largest epidemiological study to investigate the association between long-term exposure to air pollution and AKI development using nationwide Medicare cohort data.

The findings of this study are consistent with previous studies examining the association between exposure to long-term air pollution and a decrease in renal function. Three U.S. military

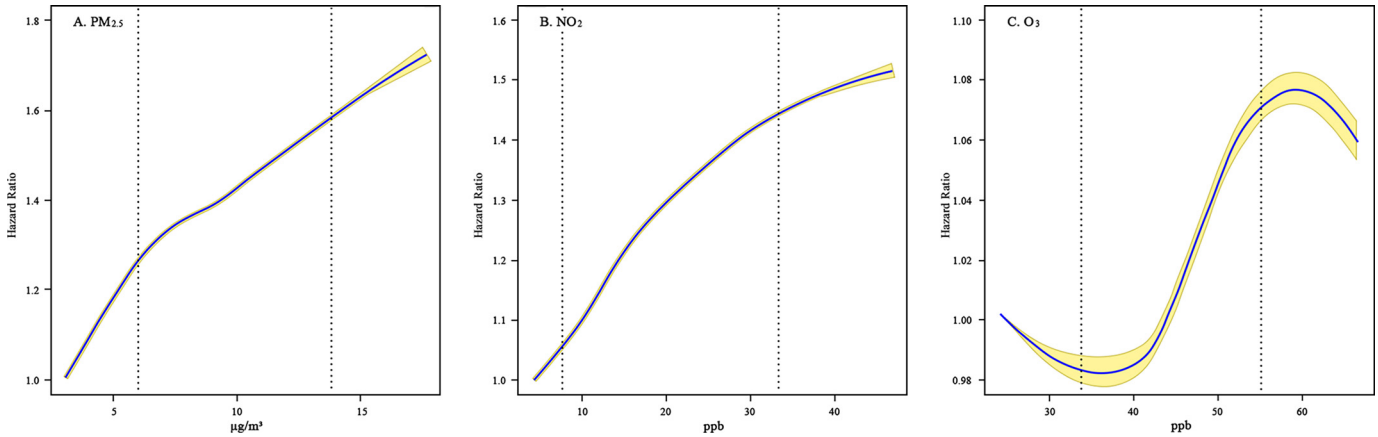

Figure 2. Concentration–response curves for the association between long-term air pollution exposure and kidney diseases: (A) $PM_{2.5}$, (B) NO_2, and (C) O_3. Dotted vertical lines: 10th and 90th percentiles of each air pollution concentration. Shaded areas: 95% CIs. Reference exposure points: 0 $\mu g/m^3$ for $PM_{2.5}$ and 0 ppb for NO_2 and O_3. Individual-level confounders (age, sex, race, Medicaid eligibility) and neighborhood-level socioeconomic status indicators were adjusted in the results. Study population: Medicare Part A fee-for-service beneficiaries (≥65 years of age) from 2000 to 2016. See Table S1 for corresponding numeric data. A Cox-equivalent reparameterized Poisson model was used to estimate the hazard ratios. Note: CI: confidence interval; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, fine particulate matter.

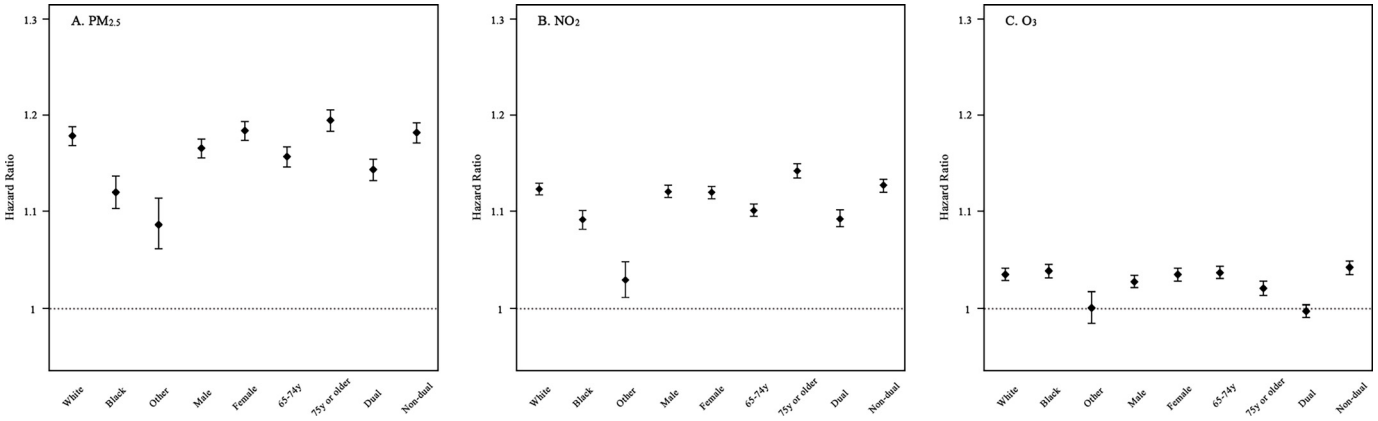

Figure 3. Subpopulation-specific association between air pollution and first hospital admission for acute kidney disease (AKI). Hazard ratio: (A) $PM_{2.5}$ (per 5 $\mu g/m^3$), (B) NO_2 (per 10 ppb), and (C) O_3 (per 10 ppb). Dual: Eligible for Medicaid, Non-dual: Noneligible for Medicaid. Individual-level confounders (age, sex, race, Medicaid eligibility), neighborhood-level indicators (percentage of the population below the poverty level, population density (persons per kilometers squared), median home value (USD), percentage of the population that is Black, percentage of the population that is Hispanic, median household income (USD), percentage of homes with owner-occupied housing, percentage of the population without a high school education, average BMI, percentage of the population that had ever smoked), calendar year, and indicator variables for the region (Northeast, Southeast, Midwest, Southwest, and West) were adjusted in the results. Study population: Medicare Part A fee-for-service beneficiaries (≥65 years of age) from 2000 to 2016. See Table S2 for corresponding numeric data. A Cox-equivalent reparameterized Poisson model was used to estimate the hazard ratios. Note: BMI, body mass index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, fine particulate matter.

veteran cohort studies reported that long-term (annual average) exposure to higher concentrations of air pollution [$PM_{2.5}$,[31–33] PM_{10}, NO_2, and carbon monoxide (CO)[34]] is associated with a reduced estimated glomerular filtration rate (eGFR). Another cohort study conducted in four U.S. counties reported that higher annual average $PM_{2.5}$ was associated with a higher urinary albumin–creatinine ratio.[35] A Taiwanese cohort study also showed that an increased concentration of $PM_{2.5}$ was associated with an increased risk of CKD development, which was defined by an eGRF of <60 mL/min per 1.73 m^2.[36] A recent cohort study in South Korea revealed a positive long-term effect estimate of $PM_{2.5}$ on the mortality of CKD patients.[37] In addition, a recent time-stratified case-crossover study reported a positive association between short-term exposure to $PM_{2.5}$ (lag 0–1 d) and risk of urgent or emergent hospital admissions for AKI in the U.S. Medicare population,[11] and another population-based time-series study in South Korea also showed a positive short-term effect estimate of air pollution on emergency department visits due to AKI.[38]

This study provides scientific evidence that the public health benefits of stricter air pollution standards may alleviate the potential risk of AKI. The concentration–response curves (Figure 2) indicate no evidence of a threshold value for pollution for the development of AKI, although the O_3 curve that showed fluctuations should be interpreted carefully because of its uncertain estimates at very low and high values. Furthermore, the results from low-pollution cohorts showed that the effect estimate of exposure to air pollution on the first hospital admission for AKI persisted at the low concentrations across all air pollutants. The results indicate that the health-benefit-per-unit decrease in the concentration of these air pollutants are consistent across concentrations that are below the current NAAQS levels.

Nevertheless, this study had several limitations. First, although we performed stratified analyses, the Medicare Part A data we used in this study is an administrative database for Medicare FFS claims, thus we were limited in assessing the confounding and interactive effects of medication and underlying medical conditions, such as sepsis, CKD, heart diseases, diabetes

Table 3. Association between air pollution and the first hospital admission for acute kidney injury (AKI) by chronic kidney disease admission record prior to AKI and primary disease of the first hospital admission with a secondary AKI diagnosis code (full cohort, $N = 61{,}390{,}754$).

		$PM_{2.5}$	NO_2	O_3
Hospital admission/disease	*N* (%)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Prior to the hospital admission for AKI				
Chronic kidney disease	3,189,290 (34.4)	1.07 (1.05, 1.08)	0.98 (0.97, 0.99)	0.98 (0.98, 0.99)
Primary disease of the first hospital admission with a secondary AKI diagnostic code				
Circulatory system disease	2,880,526 (31.1)	1.18 (1.16, 1.20)	1.13 (1.12, 1.14)	1.02 (1.01, 1.03)
Ischemic heart disease	782,960 (8.4)	1.17 (1.15, 1.19)	1.12 (1.11, 1.14)	1.02 (1.01, 1.03)
Heart failure	935,738 (10.1)	1.23 (1.21, 1.26)	1.15 (1.13, 1.17)	1.01 (1.00, 1.02)
Acute myocardial infarction	574,103 (6.2)	1.16 (1.14, 1.18)	1.01 (0.99, 1.02)	1.01 (1.00, 1.02)
Cerebrovascular disease	321,819 (3.5)	1.27 (1.24, 1.30)	1.16 (1.14, 1.19)	1.06 (1.05, 1.07)
Pneumonia	618,543 (6.7)	1.25 (1.22, 1.27)	1.12 (1.10, 1.13)	1.06 (1.05, 1.07)
Diabetes mellitus	194,903 (2.1)	1.17 (1.13, 1.20)	1.16 (1.14, 1.18)	1.03 (1.01, 1.04)
Urinary tract infection	335,871 (3.6)	1.28 (1.24, 1.32)	1.16 (1.13, 1.18)	1.02 (1.01, 1.04)

Note: Hazard ratio: $PM_{2.5}$ (per 5 $\mu g/m^3$, annual), NO_2 (per 10 ppb, annual), and O_3 (per 10 ppb, summer-season). Individual-level confounders (age, sex, race, Medicaid eligibility), neighborhood-level indicators [percentage of the population below the poverty level, population density (persons per kilometer squared), median home value (USD), percentage of the population that is Black, percentage of the population that is Hispanic, median household income (USD), percentage of homes with owner-occupied housing, percentage of the population without a high school education, average BMI, percentage of the population that had ever smoked], calendar year, and indicator variables for the region (Northeast, Southeast, Midwest, Southwest, and West) were adjusted in the results. Study population: Medicare Part A fee-for-service beneficiaries (≥65 years of age) from 2000 to 2016. A Cox-equivalent reparameterized Poisson model was used to estimate the hazard ratios. BMI, body mass index; CI, confidence interval; HR, hazard ratio; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, fine particulate matter.

mellitus, and hypertension, which are identified risk factors associated with AKI.[1,39] In addition, like previous studies based on health insurance claim data,[38,40,41] we had a limitation in identifying the complex pathways and mediating diseases of AKI that were affected by exposure to air pollution. Further, we were not able to collect detailed information on mortality (e.g., causes of death) that were sufficiently informative to consider the competing risk models between mortality and the first hospital admission for AKI; thus, our estimates on the association between air pollution and hospital admissions for AKI should be interpreted as the overall effect of air pollution on any inpatient hospitalizations associated with AKI irrespective of causative medical conditions. This limitation is important and should be addressed carefully in future studies.

Second, because the Medicare cohort includes only individuals who were ≥65 y old, our results are limited in their ability to represent the entire U.S. population. Our results represent only the Medicare Part A FFS population, which does not include all Medicare beneficiaries (the Medicare FFS population covers up to ∼65.8% of the Medicare population in 2016) or persons ≥65 years of age.[21] Because we had no information on Medicare–HMO (managed care) claims and younger Medicare-eligible population with disabilities or end-stage renal diseases, we were unable to cover the entire Medicare population. Third, the first hospital admission with an ICD-diagnosis code for AKI has limitations when interpreting it as the onset of AKI. AKI is generally diagnosed through laboratory tests (e.g., the accumulation of end products of nitrogen metabolism or decrease urine outputs).[1] A previous study in Scotland and a systematic review including 25 studies in four counties (United States, Canada, Australia, and Spain) reported that the incidence of AKI was substantially underestimated when ICD diagnostic codes were used to define AKI[42,43]: A median of positive predictive values (PPVs) was ∼67%–70%. (A study by Logan et al.[42] was performed at acute hospitals in two Scottish Health Boards, and a review study by Vlasschaert[43] included 8 U.S. studies based on the California Hospital Discharge Abstract Database, the Partners Health Care System Research Patient Data Registry, and the Veterans Affairs Patient Treatment File). In addition, hospital admissions can occur at more advanced stages of the disease or for treating complications attributed to AKI, such as volume overload, electrolyte, and acid–base disturbances.[44] Thus, hospital admission records cannot adequately represent the incidence of AKI, and our cohort could undercount AKI onset. In addition, although this study includes multiple neighborhood-level indicators as the potential confounders, Medicare claims do not include extensive individual-level data on behavioral and socioeconomic risk factors, which could be crucial confounders. Therefore, the potential effects of unmeasured confounders should be considered in depth in future studies.

Together with the aforementioned limitations, several points should be addressed further. With the large study size of the Medicare data set, we were able to estimate differences in the air pollution–AKI risks among subpopulations: the older (≥75 y old), White, and Medicaid-noneligible beneficiaries generally showed higher effect estimates of air pollution on the first hospital admission for AKI. Nevertheless, the results corresponding to those of White and Medicaid-noneligible persons should be investigated further because they are seemingly different from results of previous U.S. studies that revealed a higher air pollution–mortality risk in non-White and Medicaid-eligible populations, albeit for different health outcomes.[14,45] There are several plausible explanations. First, there may have been underdiagnosis. In general, despite Medicare, low-income individuals and racial minorities can have lower accessibility to medical facilities,[46] which could result in underdiagnosis. Particularly, based on a recent U.S. national study, the hospitalization for AKI was associated with an increase in excess hospitalization costs of $1,800–$7,900 compared with patients without AKI, and the excess costs were generally higher than those of other acute medical conditions.[47] Thus, we postulate that the high economic burden of AKI might be considerably associated with the underdiagnosis problem, especially in socially marginalized populations. Although we considered Medicaid eligibility and neighborhood-level socioeconomic variables, additional variables that reflect individual-level disparities in accessibility to medical resources (e.g., income level, medical expenditure, and accessibility to nephrologists) should be addressed in future studies because these variables do not fully capture factors related to disparities.

Second, there may be confounding effects. A cohort study in Korea reported that CKD patients with healthy lifestyles (normal weight, nonsmokers, and nondrinkers) showed a higher air pollution–mortality risk than CKD patients with less-healthy lifestyles.[37] A study in Taiwan also reported that cohort participants with comorbidities showed a lower risk of $PM_{2.5}$ on CKD incidence.[36] These results imply the possibility of confounding effects between air pollution and behavior or biological factors on the development of kidney disease. Especially, in the United States, high-income White individuals generally have lower prevalence of hypertension, obesity, and diabetes, as well as better health behaviors[46] than the general population. Therefore, the results of this study could be influenced by the potential confounding effects of underlying health behaviors and other biological conditions.

Finally, future research could also address the complex air pollution mixture and should disentangle the association with short- and long-term exposure to air pollution. We focused on annual average air pollutant levels of $PM_{2.5}$, NO_2, and O_3 individually although the actual air pollution mixture is complex, with simultaneous exposure to these and other pollutants, as well as relationships among these pollutants (e.g., NO_2 and a precursor of O_3) and different chemical structures of $PM_{2.5}$. In addition, based on these complex chemical compositions and seasonality of air pollutants, seemingly inconsistent sensitivity analysis results of O_3 should be interpreted carefully and examined in depth in future studies using data with higher temporal resolution.

In summary, we found an association between exposures to air pollution and the risk of the first hospital admission for AKI, and this association persisted even at low concentrations of air pollution. Our findings suggest beneficial implications for public health policies to alleviate health care expenditures and disease burden attributable to AKI and also provide epidemiological evidence on the value of air pollution guidelines for potential AKI patients.

Acknowledgments

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